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A Histological Study on the Response of Transplanted Mandibles and Teeth in Syrian Hamsters and Rats

Frank Maximilian Kneussl

Loyola University Chicago

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A HISTOLOGICAL STUDY ON THE RESPONSE OF TRANSPLANTED
MANDIBLES AND TEETH IN SYRIAN HAMSTERS AND RATS

by

Frank Maximilian Kneussl

A Dissertation Submitted to the Faculty of the Graduate School
of Loyola University of Chicago in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy

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BIOGRAPHY

Frank Maximilian Kneussl was born on November 3, 1939, in Ottawa, Illinois.

He was graduated from the Ottawa Township High School, Ottawa, Illinois, in June, 1957. After attending the University of Chicago and Shimer College, Mount Carroll, Illinois, he received the degree of Bachelor of Science in Natural Sciences, from Shimer College in June of 1962.

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TABLE OF CONTENTS

ABSTRACT..................................................................................................................xvi

I. INTRODUCTION.......................................................................................................1

II. LITERATURE REVIEW.............................................................................................6
   A. Tooth Transplants in Animals Other Than Rat and Hamster...............................6
      1. Sites.....................................................................................................................6
         a. Anterior Eye Chamber....................................................................................6
         b. Brain...............................................................................................................9
         c. Subcutaneous.................................................................................................10
         d. Abdominal Wall and Ovary...........................................................................13
         e. Bone..............................................................................................................16
         f. Sockets of Teeth............................................................................................16
      2. Immunological Properties................................................................................17
         a. Rabbit............................................................................................................17
         b. Guinea Pig......................................................................................................20
         c. Mouse...........................................................................................................22

   B. Tooth Transplants in Rat.....................................................................................23
      1. Sites...................................................................................................................23
         a. Sockets of Teeth............................................................................................23
         b. Subcutaneouse and Submucous....................................................................24
         c. Bone..............................................................................................................31
      2. Immunological Properties................................................................................33

   C. Tooth Transplants in Hamster............................................................................39
      1. Sites...................................................................................................................39
a. Reimplantation .......................................................... 39
b. Sockets of Teeth ....................................................... 40
c. Subcutaneous ............................................................ 42
d. Bone ........................................................................ 44
e. Intramuscular ............................................................. 45
f. Cheek Pouch ............................................................... 46

2. Immunological Properties ........................................... 47

D. Effect of Hormones ..................................................... 49
   1. Cortisone ................................................................. 49
   2. Estrogens and Androgens ......................................... 51

E. Effect of Immunosuppressive Drugs .............................. 54
   1. 6-Mercaptopurine .................................................... 54
   2. Methotrexate ........................................................... 55

F. Mandible Transplantation Sites .................................... 56
   1. Brain ........................................................................ 56
   2. Intramuscular .......................................................... 57
   3. Subcutaneous ........................................................... 57
   4. Cheek Pouch ............................................................ 60
   5. Spleen ...................................................................... 61

G. Effect of Immunosuppressive Drugs on
   Transplants of Other Tissues ........................................ 61
   1. 6-Mercaptopurine .................................................... 61
      a. Rabbit .................................................................... 61
      b. Mouse .................................................................... 67
      c. Guinea Pig ............................................................ 75
d. Rat ............................................................................ 75
2. Imuran
   a. Rabbit
   b. Mouse
   c. Rat
   d. Dog

III. MATERIALS AND METHODS
   A. Materials
   B. Experimental Procedures
   C. Microscopic Examination

IV. RESULTS
   A. Neonatal Hamster Transplants
   1. Ear Site Transplants
   a. First Mandibular Molars
   b. Half-Mandibles
   c. Half-Mandibles with Partly Excised Incisor
   d. Molars in Part of Mandibles
   2. Transplants in Back
   a. Half-Mandibles
   b. Half-Mandibles with Partly Excised Incisor
   3. Half-Mandibles in Uterine Horn
   4. Half-Mandibles in Testis
   5. Half-Mandibles in Kidney
   B. Hamster Rib Autografts in Ear
   C. Neonatal Rat Half-Mandible Transplants
1. In Ear......................................................... 164
2. In Kidney..................................................... 175
D. Neonatal Half-Mandible Transplants in 6-Mercaptopurine and Vehicle Treated Hamsters................................. 179
1. In Back......................................................... 179
2. In Ear......................................................... 189
E. Neonatal Half-Mandible Transplants in Imuran and Vehicle Treated Hamsters......................................................... 208
1. In Ear......................................................... 208
2. In Cheek Pouch............................................... 223
V. DISCUSSION.................................................. 229
A. Half-Mandibles.............................................. 229
B. Incisors......................................................... 246
C. Molars.......................................................... 250
D. Effects of Immunosuppressive Drugs.............................. 285
  1. 6-Mercaptopurine........................................... 285
  2. Imuran......................................................... 294
VI. SUMMARY AND CONCLUSIONS................................. 303
VII. LITERATURE CITED......................................... 309
VIII. TABLES....................................................... 318
IX. FIGURES AND PLATES......................................... 372
X. GLOSSARY..................................................... 410
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Experiments on Neonatal Hamster Teeth and Half-Mandibles Transplanted into Normal Adults</td>
</tr>
<tr>
<td>2. Experiments on Rib Autotransplants in Ear of Adult Hamsters</td>
</tr>
<tr>
<td>3. Experiments on Neonatal Rat Half-Mandible Transplants in Normal Adults</td>
</tr>
<tr>
<td>4. Experiments on Neonatal Hamster Half-Mandible Transplants in 6-Mercaptopurine Treated Adults</td>
</tr>
<tr>
<td>5. Experiments on Neonatal Hamster Half-Mandible Transplants in Imuran Treated Adults</td>
</tr>
<tr>
<td>6. Experiment IA: Neonatal Hamster First Mandibular Molar Transplants in Ear of Adults</td>
</tr>
<tr>
<td>7. Experiment IB: Neonatal Hamster Half-Mandible Transplants in Ear of Adults</td>
</tr>
<tr>
<td>8. Experiment IC: Neonatal Hamster Half-Mandible Transplants in Ear of Adults</td>
</tr>
<tr>
<td>9. Experiment ID: Neonatal Hamster Half-Mandible Transplants in Ear of Adults</td>
</tr>
<tr>
<td>10. Experiment IE: Neonatal Hamster Half-Mandible Transplants with Partly Excised Incisor in Ear of Adults</td>
</tr>
<tr>
<td>11. Experiment IF: Neonatal Hamster Molar Transplants with Adjacent Mandible in Ear of Adults</td>
</tr>
<tr>
<td>12. Experiment IIA: Neonatal Hamster Half-Mandible Transplants in Back of Adults</td>
</tr>
<tr>
<td>13. Experiment IIB: Neonatal Hamster Half-Mandible Transplants with Partly Excised Incisor in Back of Adults</td>
</tr>
<tr>
<td>14. Experiment III: Neonatal Hamster Half-Mandible Transplants in Uterine Horn of Adults</td>
</tr>
<tr>
<td>15. Experiment IV: Neonatal Hamster Half-Mandible Transplants in Testis of Adults</td>
</tr>
</tbody>
</table>
LIST OF TABLES (cont'd)

16. Experiment V: Neonatal Hamster Half-Mandible Transplants in Kidney of Adults .................................................... 341
17. Experiment VI: Rib Autografts in Ear of Adult Hamsters .......... 343
18. Experiment VII: Neonatal Rat Half-Mandible Transplants in Ear of Adults ............................................................. 344
19. Experiment VIII: Neonatal Rat Half-Mandible Transplants in Kidney of Adults ......................................................... 347
20. Experiment IXA: Neonatal Hamster Half-Mandible Transplants in Back of 6-Mercaptopurine Treated Adults ....................... 349
21. Experiment IXB: Neonatal Hamster Half-Mandible Transplants in Back of 6-Mercaptopurine Treated Adults ....................... 352
22. Experiment XA: Neonatal Hamster Half-Mandible Transplants in Ear of 6-Mercaptopurine Treated Adults .......................... 354
23. Experiment XB: Neonatal Hamster Half-Mandible Transplants in Ear of 6-Mercaptopurine Treated Adults .......................... 356
24. Experiment XC: Neonatal Hamster Half-Mandible Transplants in Ear of 6-Mercaptopurine Treated Adults .......................... 360
25. Experiment XIA: Neonatal Hamster Half-Mandible Transplants in Ear of Imuran Treated Adults ...................................... 362
26. Experiment XIB: Neonatal Hamster Half-Mandible Transplants in Ear of Imuran Treated Adults ...................................... 366
27. Experiment XII: Neonatal Hamster Half-Mandible Transplants in Cheek Pouch of Imuran Treated Adults ........................... 369
LIST OF FIGURES

FIGURES

1. A Sagittal Section of a Normal Neonatal First and Second Mandibular Molar in a Hamster Mandible......................... 372
2. A Sagittal Section of a Normal Neonatal Hamster First Mandibular Molar................................................................. 372
3. A Sagittal Section of a Normal Neonatal Hamster Second Mandibular Molar................................................................. 373
4. A Sagittal Section through the Crown of a Normal Hamster First Mandibular Molar......................................................... 373
5. A Sagittal Section through the Roots of the First Mandibular Molar Shown in Figure 4................................................. 374
6. A Sagittal Section through the Crown of a Normal Hamster Second Mandibular Molar......................................................... 374
7. A Sagittal Section through the Roots of the Second Mandibular Molar Shown in Figure 6................................................. 375
8. A Sagittal Section through the Crown of a Hamster First Mandibular Molar Transplant in the Ear............................... 375
9. A Section through the Root of the Molar Shown in Figure 8.............................................................. 376
10. A Section through Part of the Crown and Root of a Hamster First Mandibular Molar Transplant in the Ear.................... 376
11. A Section through the Crown and Part of Root of the Molar Shown in Figure 10............................................................ 377
12. A Sagittal Section through the Crown of a Hamster First Mandibular Molar Transplant in the Ear..................................... 377
13. A Sagittal Section through the Crown and Root of a Hamster First Mandibular Molar Transplant in the Ear..................... 378
14. A Section through the Crown of the Molar Shown in Figure 13.............................................................. 378
15. A Section through the Root and Part of the Crown of a Hamster First Mandibular Molar Transplant in the Ear................... 379
LIST OF FIGURES (cont'd)

16. A Section through the Molar Shown in Figure 15......................... 379

17. A Section through the Crown of a Hamster First Mandibular Molar Transplant in the Ear................................. 380

18. A Section through the Crown of the Molar Shown in Figure 17.......... 380

19. A Section through the Crown and Root of a Hamster First Mandibular Molar Transplant in the Ear................................. 381

20. A Section through the Crown of a Hamster First Mandibular Molar from a Mandibular Transplant in the Ear................... 381

21. A Sagittal Section through a Hamster Second Mandibular Molar from a Mandibular Transplant in the Ear................................. 382

22. A Section through the Crown of a Hamster First Mandibular Molar from a Mandibular Transplant in the Ear................... 382

23. A Sagittal Section through the Crown of a Hamster Second Mandibular Molar from the Mandibular Transplant Shown in Figure 22................................. 383


25. A Sagittal Section through a Hamster Second Mandibular Molar from a Mandibular Transplant in the Ear................................. 384

26. A Section through the Molar Shown in Figure 25.......................... 384

27. A Sagittal Section through a Hamster Second Mandibular Molar from a Mandibular Transplant in the Ear................................. 385

28. A Sagittal Section through a Hamster Second Mandibular Molar from a Mandibular Transplant in the Ear................................. 385

29. A Sagittal Section through a Hamster Second Mandibular Molar from a Mandibular Transplant in the Ear................................. 386

30. A Sagittal Section through a Hamster Second Mandibular Molar from a Mandibular Transplant in the Ear................................. 386

31. A Section through the Crown of a Hamster First Mandibular Molar from a Mandibular Transplant in the Ear................................. 387

32. A Section through a Hamster Second Mandibular Molar from a Mandibular Transplant in the Ear................................. 387
LIST OF FIGURES (cont'd)

33. A Section through a Hamster Second Mandibular Molar from a Mandibular Transplant in the Ear.........................................................388
34. A Section through a Hamster Second Mandibular Molar from a Mandible, with Partly Excised Incisor, Transplanted in the Ear.........................................................388
35. A Section through a Hamster Second Mandibular Molar from a Mandible, with Partly Excised Incisor, Transplanted in the Ear.........................................................389
36. A Sagittal Section through a Hamster Second Mandibular Molar from a Mandible, with Partly Excised Incisor, Transplanted in the Ear.........................................................389
37. A Sagittal Section through a Hamster Second Mandibular Molar from a Transplant in the Ear of Molars with Part of Adjacent Mandible.........................................................390
38. A Sagittal Section through a Hamster Second Mandibular Molar from a Transplant in the Ear of Molars with Part of Adjacent Mandible.........................................................390
39. A Section through a Hamster Second Mandibular Molar from a Transplant in the Ear of Molars with Part of Adjacent Mandible.........................................................391
40. A Section through a Hamster Second Mandibular Molar from a Transplant in the Ear of Molars with Part of Adjacent Mandible.........................................................391
41. A Sagittal Section through a Hamster Second Mandibular Molar from a Mandible Transplanted into the Lumen of the Uterine Horn.........................................................392
42. A Section through Part of the Crown of a Hamster First Mandibular Molar from a Mandible Transplanted into the Kidney.........................................................392
43. A Section through the Crown of the Molar Shown in Figure 42.........................................................393
44. A Section through a Rat First Mandibular Molar from a Mandibular Transplant in the Ear.........................................................393
45. A Section through Part of the Crown and Root of a Rat First Mandibular Molar from a Mandibular Transplant in the Ear.........................................................394
46. A Section through a Second Mandibular Molar Found in the Transplant Shown in Figure 45.........................................................394
LIST OF FIGURES (cont'd)

47. A Section through a Rat Second Mandibular Molar from a Mandibular Transplant in the Ear ................................................................. 395

48. A Section through a Rat Second Mandibular Molar from a Mandibular Transplant in the Ear ................................................................. 395

49. A Section through a Rat First Mandibular Molar from a Mandibular Transplant in the Ear ................................................................. 396

50. A Section through a Second Mandibular Molar from the Same Transplant Shown in Figure 49 ................................................................. 396

51. A Section through a Rat First Mandibular Molar from a Mandibular Transplant in the Kidney ................................................................. 397

52. A Section through the Root of the Molar Shown in Figure 51 ................................................................. 397

53. A Possible Second Mandibular Molar Found in the Transplant Shown in Figure 51 ........................................................................ 398

54. A Section through a Hamster Second Mandibular Molar from a Mandible Transplanted in the Back of a 6-MP Treated Hamster ....................................................................... 398

55. A Sagittal Section through a Hamster Second Mandibular Molar from a Mandible Transplanted in the Ear of a 6-MP Treated Hamster ....................................................................... 399

56. A Section through a Hamster Second Mandibular Molar from a Mandible Transplanted in the Ear of a 6-MP Treated Hamster ....................................................................... 399

57. A Section through the Crown of a Hamster Second Mandibular Molar from a Mandible Transplanted in the Ear of a 6-MP Treated Hamster ....................................................................... 400

58. A Section through Hamster Mandibular Bone from a Mandible Transplanted in the Ear of a 6-MP Treated Hamster ....................................................................... 400

59. A Section through Hamster Mandibular Bone from a Mandible Transplanted in the Ear of a Control Hamster ....................................................................... 401

60. A Sagittal Section through a Hamster Second Mandibular Molar from a Mandible Transplanted in the Ear of a Control Hamster ....................................................................... 401

61. A Section through Hamster Mandibular Bone from a Mandible Transplanted in the Ear of a 6-MP Treated Hamster ....................................................................... 402
A Section through Hamster Mandibular Bone from a Mandible Transplanted in the Ear of a Control Hamster
A Sagittal Section through a Hamster Second Mandibular Molar from a Mandible Transplanted in the Ear of a Control Hamster
A Sagittal Section through a Hamster Second Mandibular Molar from a Mandible Transplanted in the Ear of an Imuran Treated Hamster
A Sagittal Section through a Hamster Second Mandibular Molar from a Mandible Transplanted in the Ear of an Imuran Treated Hamster
A Section through a Hamster Second Mandibular Molar from a Mandible Transplanted in the Ear of an Imuran Treated Hamster
A Section through Hamster Mandibular Bone from a Mandible Transplanted in the Ear of an Imuran Treated Hamster
A Section through Hamster Mandibular Bone from a Mandible Transplanted in the Ear of a Control Hamster
A Section through Part of the Crown of a Hamster Second Mandibular Molar from a Mandible Transplanted in the Ear of an Imuran Treated Hamster
A Section through the Molar Shown in Figure 69
A Section through Hamster Mandibular Bone from a Mandible Transplanted in the Ear of an Imuran Treated Hamster
A Section through Hamster Mandibular Bone from a Mandible Transplanted in the Ear of a Control Hamster
A Section through a Hamster Second Mandibular Molar from a Mandible Transplanted into the Cheek Pouch of an Imuran Treated Hamster
A Section through a Hamster Second Mandibular Molar from a Mandible Transplanted into the Cheek Pouch of an Imuran Treated Hamster
LIST OF FIGURES (cont'd)

75. A Section through Hamster Mandibular Bone from a Mandible Transplanted into the Cheek Pouch of an Imuran Treated Hamster.................................................. 409

76. A Section through Hamster Mandibular Bone from a Mandible Transplanted into the Cheek Pouch of a Control Hamster................................................................. 409
ABSTRACT

Half-mandibles and teeth from neonatal hamsters were homotransplanted subcutaneously into the dorsal surface of the ear, the back, between the scapulae, and into the cortex of the kidney, lumen of the uterine horn and into the testis of adults. Other half-mandibles, with incisors partly excised, were homografted into the ear and back of hamsters. Parts of half-mandibles with molars, and first mandibular molars alone, were similarly homografted into the ears of adults. Half-mandibles of neonatal rats were also homografted into the ear and kidney of adults.

Additional half-mandibles from neonatal hamsters were homografted into the ear and back and into the cheek pouches of Imuran or 6-mercaptopurine (6-MP) treated adults. When treated with a daily dosage of 10 mg/100 gm of 6-MP, reduced to 5 mg after four days, grafts in the ear showed a retarded revascularization and attachment at six days. Those in the back, treated with 10 mg for 10 or 12 days, revealed only one viable molar. At the daily dosage of 5 mg/100 gm, grafts in the ear, showed a trend toward increased molar viability at 15 days, not found where the dosage had been only 2 mg. The daily dosage of 2 mg of Imuran was not so effective as the 5 mg dosage since the latter revealed an increase in molar viability and growth in ear grafts. Grafts in cheek pouches of hosts treated with Imuran (5 mg/100 gm/day) disclosed an improvement in molar viability but not in growth. At daily doses of 5 mg and lower, Imuran and 6-MP reduced the intensity of the immune reaction.

Half-mandible grafts did not increase in size in either rats or hamsters; however, more bone formation occurred after immunosuppressive therapy, the greatest amount having developed following the 5 mg dosages.
The ear was found to be the most successful site for half-mandible grafts and the most growth occurred where molars had been implanted alone. Viable teeth were few in kidneys, but most implants disclosed some bone formation. All implants in the testis were resorbed. No viable teeth were found in uterine implants.

No surviving incisors were found in any of the homografts. The severely retarded growth of molars, as revealed by a reduction in size, was enhanced by Imuran treatment. The dentin formed immediately after grafting was frequently abnormal, but by 15 days, it was usually more normal. Enamel formation was severely inhibited. Ameloblasts were the most susceptible cell type and were often transformed into squamous cell cords. Second mandibular molars were more viable especially after immunosuppressive therapy and survived more frequently than first molars.

The variable success of grafts in this experiments can be ascribed to a number of factors. The reduction in size of teeth was attributed to a retarded development believed to be caused by a delay in the re-establishment and revascularization of grafts. The immune reaction was a factor in determining the viability of teeth, since immunosuppressive therapy partly suppresses this reaction. The implantation site played a role in the fate of teeth and bone in heterotopically grafted half-mandibles. The failure of incisors and molars to survive in greater numbers may be attributed to delays in revascularization believed to be retarded by the osseous nature of the mandibular bone.
I. INTRODUCTION

The possibility of replacing injured or destroyed tissues and organs by means of transplantation has intrigued man for many centuries. Some of the earliest reported transplantations were carried out several hundred years B.C. by Hindus who developed a technique for the reconstruction of missing facial features, such as the nose, by the transposition of attached flaps of forehead or cheek skin with their partially attached blood supply. This reconstructive surgical procedure is now called "pedicle-grafting" (Billingham, 1963). It is now generally assumed that these Hindus also employed "free-skin" autografts in their reconstructions. Although autografts of parts of limbs and other structures of the human body were occasionally successful, it was not until about 1870 that success was achieved by Reverdin in "free-skin" grafting.

During the first decade of the twentieth century, Alexis Carrel (1873-1944) developed a surgical technique for anastomosis of blood vessels which enabled him to perform successful kidney autografts. In addition, Carrel and other investigators recognized differences in survival and function, between auto- and allografts, which were recognized as being due to biological differences between host and donor.

In the 1940's, P.B. Medawar clearly demonstrated that the rejection of skin allografts was an immunological phenomenon and F.M. Burnet formulated his "Clonal Selection" theory of immunity. It was these significant studies, in addition to other early investigations on the genetic relationships of tumor transplants, which led to the present concepts of transplant acceptance and rejection.

Transplantation techniques have been improved and extended in the inter-
vening years, but despite modern advances we may safely assert that, with the exception of autografts, completely successful transplants are still the exception rather than the rule.

In recent years, experimental and clinical observations on the transplantation of skin, bone and cartilage, as well as organs such as the kidney, heart and endocrine glands have yielded encouraging results. Considerable interest has also been shown in the transplantation of teeth, and this procedure has been employed in studies on the growth and development of these structures. In most instances, tooth germs or the developing teeth of laboratory animals were employed, and the sites of implantation were usually outside the oral cavity. In these experiments virtually every available laboratory animal has been used and a variety of sites, including such areas as muscle, spleen, ovaries, the marrow cavities of long bones and prepared cavities in bone, jaws and alveolar sockets, as well as kidneys, eyes, the brain, and the peritoneal cavity have been utilized.

In general, the conditions necessary for the successful transplantation of teeth are largely unknown and despite the number and variety of studies involved, the degree of success attained has been highly variable and disappointing, except possibly in cases where the anterior chamber of the eye and the brain were the sites of choice.

A number of investigators have transplanted mandibles, and parts of mandibles containing teeth, to various sites, and with varying degrees of success, in different laboratory animals. Mandibles obtained from fetal rats, three days before birth, and transplanted into the leg muscles of mothers, revealed a significant increase in size when recovered 40 days later (Baker, '36). Kostecka ('38) reported that parts of jaws containing tooth germs,
from one and one-half month old dogs, transplanted subcutaneously and intramuscularly into eight month old dogs, had shown no further development on recovery. However, he found that parts of fetal mouse jaws, of differing ages, when implanted into adult mice, disclosed significant growth and development of teeth. Traux ('60) likewise observed that mandibular halves from two day old postnatal mice, when transplanted subcutaneously into immature mice of the same strain, revealed osteogenesis but no growth or development of teeth. On the other hand, Jones ('63) observed eruption of both incisors and molars in mandibles transplanted from newborn mice and rats into the spleens of adults of the same strains.

That developing teeth may survive and grow following transplantation is born out by other reports in the literature. Utilizing the anterior chamber of the eye and brain of adult rabbits, mice and guinea pigs, and various subcutaneous spaces in mice, Fleming ('52, '53a, '53b, '56a, '56b, '58), Nagai and Yoshioka ('62) and Goldman and Gould ('65a and '65b) reported that transplanted tooth germs may undergo relatively normal growth and differentiation.

That the undifferentiated teeth of the Syrian hamster may survive and grow when transplanted has been reported by several investigators. Myers and co-workers ('54) removed second mandibular molars from 36 day old hamsters and successfully re-implanted them into their original sockets. Hoek and co-workers ('58) transplanted developing second molars from six day old hamsters into the second molar sockets of two month old hamsters and 75 days later found that eight of 20 grafts had developed vital connective tissue in root canals. Reece ('59) bilaterally transplanted third mandibular molars, between four to eight week old hamsters and, on recovery, found that
one of eight hosts had retained both grafts and that these showed normal periodontal reattachment and normal pulps. Hoffman ('60) reported that of 23 newborn molars transplanted subcutaneously into 30 day old hamsters, 12 had shown development and growth 28 days later. Utilizing the diaphysis of the femur as a transplantation site, this investigator ('66) noted growth and development of crowns, roots, and periodontal membranes, as well as vascularized pulps, in seven of 24 first maxillary molars, when recovered 28 days later. In another series, ('67) he found that, eight of 12 newborn hamster first maxillary molars, transplanted into the trapezius muscle of 30 day old hamsters, revealed development of roots, crowns and periodontal membranes on recovery 28 days later. However, although normal dentin formation had occurred in these experiments, enamel formation was retarded. These studies clearly show that, despite a great deal of investigative work, the degree of success attained in transplantations on hamster teeth has been highly variable. Consequently, it was felt that the problem warranted further investigative work.

We are unaware of any previous studies in the hamster where mandibles or teeth were transplanted into the uterus, kidney, or testis, or into the subcutaneous space in the ear. Furthermore, we know of no studies on the effects of an immunosuppressive drug on the survival and growth of transplants in the hamster.

The purpose of our investigation was to conduct a study on the influence of different transplantation sites, on the survival, growth and differentiation of neonatal teeth, and parts of mandibles with teeth intact, and to evaluate histologically the effect of the host-graft response as revealed by the growth and differentiation of such grafts. In addition, we were inter-
ested in studying the effects of immunosuppressive drugs on the survival and growth of these structures in the sites under investigation.
II. LITERATURE REVIEW

A. Tooth Transplants in Animals other than Rat and Hamster

1. Sites

   a. Anterior Eye Chamber

   The anterior chamber of the eye of guinea pigs, rabbits and mice was utilized for the homologous and heterologous transplantation of tooth germs from mice, cats, guinea pigs and man (Fleming, '52). Of 40 intact tooth germs from 15 to 30 day old fetal guinea pigs, transplanted to the anterior eye chamber of other guinea pigs, for postoperative intervals of six to 300 days, 26 revealed good growth and differentiation whereas only scar tissue or total resorption was seen in the others. Hard tissues of long term transplants appeared to be replaced by bone. Eighteen and 21 days fetal rabbit tooth germs transplanted into the anterior eye chamber of both eyes for periods of seven to 31 days, were also successful while 18, 21, and 25 day old fetal rabbit tooth germs heterotransplanted into the eye chamber of guinea pigs also grew and differentiated but some of these had shown progressive regression and resorption. Some growth had occurred in 30 day fetal cat tooth germs when heterotransplanted into the anterior eye chambers of rabbits and guinea pigs. Tooth germs from four and five month old human fetuses heterotransplanted into the anterior eye chamber of rabbits and guinea pigs usually revealed growth but resorption was also seen. Fourteen day old fetal mouse tooth germs in the anterior eye chamber of other mice failed to grow after an initial period, subsequently resorbed or in a few cases only osteodentin or bone was found.

Fleming reported that the best retention of normal form in developing teeth was seen where tooth germs had been transplanted into the anterior eye
chamber. Once vascularized, such transplants usually showed rapid growth and development until calcified teeth had formed. These teeth also revealed a more compact pulp and supporting tissues, as well as more dentin and enamel, than was seen in the surviving grafts from other sites. All transplants of three or more weeks duration had undergone changes with most of the dentin being replaced by osteodentin. Where enamel had failed to form in anterior eye chamber transplants, the ameloblasts had degenerated and formed cords or groups of epithelial cells, epithelial pearls, keratinized material and sometimes cysts. Whenever ameloblasts failed to survive, the normal form of the tooth was lost.

In fetal rabbit and guinea pig tooth germs homologously transplanted into the anterior eye chamber of rabbits and guinea pigs, most of the dentin became modified into an osteoid-like tissue or osteodentin during postoperative intervals of 13 days to one year and in some cases these formation ultimately obliterated pulp cavities (Fleming, '53a). Twenty-five guinea pigs and 14 rabbits received anterior eye chamber tooth germ transplants. Subsequent histological study showed that the extent and rate of change in pulps was variable and that many teeth had lost the normal arrangement of odontoblasts resulting in their ultimate disappearance in many of the transplants. Fleming felt that pulp cells had the potential to form osteoid and that formation of this tissue in transplants was the result of induction by the transplant. The blood supply of transplants was observed to decrease after an initial period of growth. It was concluded that the odontoblasts did not form the osteoid tissue seen in transplants but that this was formed by the other cells of the pulp.

Fleming ('55a) heterotransplanted tooth germs and blocks of jaws with
intact tooth germs, from eight to 21 week old human embryos and fetuses, into the anterior eye chamber of guinea pigs. Tooth germs were also implanted into the anterior eye chamber of rabbits. Transplants were recovered at intervals of up to 60 days. Generally, transplants in the anterior eye chambers of guinea pigs and rabbits revealed initial revascularization, differentiation, and pre-enamel and predentin formation followed by mineralization and maturation. It appeared that the most successful transplants were those of teeth from four to five month old fetuses. Tooth germs from younger donors were less satisfactory showing less survival and a slower rate of development. Observations indicated that the ultimate fate of grafts depended on stromatization and vascularization during the first four to five days. Some transplants appeared to remain static in that they were neither accepted nor rejected by the host while others formed normal dentin and enamel. Connective tissue encapsulation and attachment of grafts to host tissues was seen and whenever pulps were injured, they were invaded by connective tissue. In some cases the enamel epithelium of transplants had formed cords and clusters of epithelial cells, and in others bone had formed in pulp chambers.

Fleming ('55b), in a review of his previous work, reported that homologous and heterologous transplants of tooth germs from guinea pigs, rabbits, mice and rats, when transplanted into anterior eye chambers, as well as other sites, showed the best growth when pulps were intact. Such grafts revealed better vascularization and the cellular changes observed in pulps more closely resembled those of normal teeth. Whenever the pulps were disrupted, fewer and smaller blood vessels, coarser collagen fibrils, dis-
organized odontoblasts, and pulpal osteoid tissue were seen. Pulpal revision occurred more slowly in grafts with intact pulps. Grafts with disrupted pulps also showed less dentin and enamel formation. Osteoid formations progressively obliterated pulp cavities and in some cases plasma cells and lymphocytes were found in pulps.

Goldman and Gould (’65a) homologously transplanted incisor and molar tooth germs, from 40 to 50 day old guinea pig fetuses, into the anterior eye chamber of guinea pigs maintained on a scorbutogenic diet for six days before transplantation. At 35 days postoperatively, transplanted incisors revealed normal development while the host incisors revealed the characteristic signs of vitamin deficiency. A wide predentin zone had developed and bone had formed in such grafts. The investigators concluded that developing embryonic tissues such as bone and teeth may not have the same ascorbic acid requirements as does collagen for repair since corneal healing and collagen formation in would healing did not take place in ascorbic acid-deficient hosts.

Boyle and Lustig (’67) transplanted tooth germs from 14 day old fetal mice into the anterior eye chambers of other mice. At postoperative intervals of 12 to 60 days, grafts undamaged during transplantation, revealed revascularization, growth and differentiation, normal dentin and cementum formation and enamel covering crowns. Hypoplastic enamel was seen in the less-well vascularized grafts. Tubular dentin of normal thickness occurred and the capillaries in pulps were observed to penetrate to the predentin border. Alveolar bone containing marrow was seen in 25 day old grafts as well as root and periodontal membrane formation.

b. Brain

Fleming (’52) utilized the brains of mice as transplantation sites for
tooth germs from 14 days old fetal mice. The grafts showed growth and differ­
entiation during post-transplantation intervals of seven to 50 days.
Tooth germs were found to grow better in the brain than in any other site
utilized in the mouse.

In fetal guinea pig tooth germs homologously transplanted into the
brain of guinea pigs, most of the dentin became modified into an osteoid or
osteodentin-like tissue, during postoperative intervals of 13 days to one
year, which in some cases completely obliterated the pulp (Fleming, '53a).
Histological study of grafts showed that the extent and rate of change in
pulps was variable and that many of the teeth had lost the normal arrange­
ment of odontoblasts during early stages resulting in their ultimate disap­
pearance. Contrary to what had been observed in anterior eye chamber grafts,
no bone was found in brains believed to be the result of induction by the
transplant. It was further noted that in such implants of long standing,
the osteodentin tended to become acellular in nature and that the blood
supply of grafts deceased after an initial period of growth.

Fleming ('55a) heterotransplanted tooth germs and blocks of jaws with
intact tooth germs, from eight to 21 week old human embryos and fetuses, into
the brains of the guinea pigs. These implants were unsuccessful and the
transplants were usually completely resorbed after periods through 60 days.
Masses of red blood corpuscles were usually seen at implantation sites and a
few grafts showed small areas of osteoid.

c. Subcutaneous

Fleming ('52) reported growth and differentiation in 14 day old fetal
mouse tooth germs following homotransplantation into the axilla and abdomen.
Tooth germs from a four month old human fetus transplanted into the axillae of mice usually revealed growth. Grafts recovered from the axilla and abdomen showed more connective tissues, bone and cartilage than had been seen in anterior eye chamber implants, but the overall size of teeth was generally the same. In all transplants in excess of three weeks' duration, change and regression had occurred with most of the dentin being replaced by osteodentin. When enamel failed to form, ameloblasts degenerated and formed cords or groups of epithelial cells, epithelial pearls, keratinized material and not infrequently cysts. When the ameloblasts failed to survive, the normal form of the tooth was lost.

Fleming ('55a) heterotransplanted tooth germs and sections of jaws with intact tooth germs from eight to 21 week old human embryos and fetuses into the axillae of mice. Transplants were recovered at intervals up to 60 days. In general, such transplants revealed early revascularization, differentiation and pre-enamel and pre-dentin formation followed by mineralization and maturation. Grafts which had not revealed development of teeth showed nonviable tissues, or connective tissue containing some spicules of bone. The ultimate fate of surviving transplants depended on an initial stromatization and vascularization during the first four to five days. When pulps were disrupted, connective tissue invasion occurred. The outer enamel epithelium formed clusters and cords of epithelial cells in some cases. In cases where grafts were not accepted the situation was attributed either to the occurrence of an inflammatory reaction or to the fact that they had remained static and were gradually resorbed without first having undergone an inflammatory reaction or being incorporated into the host.
Fleming ('56a) reported that tooth buds transplanted into subcutaneous areas tended to elicit a more vigorous connective tissue response than when transplanted to other sites. When transplanted tooth buds were damaged, the connective tissue surrounding the implant appeared to invade the graft and retard its development. However, fully formed teeth were recovered when non-damaged tooth germs had been implanted subcutaneously, into the anterior eye chamber or into the brain. When the normal anatomical relationships were maintained between the different tissues of the tooth germ, particularly the epithelial tissues, the normal form of the tooth was retained. A human deciduous mandibular cuspid and a molar tooth germ, retained in the axilla of a hamster for 106 days, showed calcification and maturation of the cuspid. The molar, on the other hand, showed immature enamel and dentin but normal cellular structures. It was noted that the thickness of the connective tissue capsule surrounding these grafts was greatly reduced when compared with that seen in the mouse. The investigator concluded that tooth germ transplants evoked less of a connective tissue response in the hamster, and that the hamster axilla was a more favorable transplantation site than the axilla of the mouse. Success of transplants was associated with the age of donor tissues since it was observed that tooth germs could be successfully transplanted before calcification had begun, whereas those already calcified or partly calcified elicited an inflammatory reaction which ultimately contributed to the destruction of the graft.

Edblom and Felts ('66) subcutaneously transplanted first, second and third mandibular molars, obtained from 19 to 21 day old fetal mice, into inbred BALB/c adult mice. Thirty-two of 120 sets of first, second and third mandibular molars revealed growth, differentiation, and development. Cusp and
root formation had occurred; however, bifurcation of roots was not evident. Most failures were attributed to excisional trauma. Third molars, which had shown the least development when transplanted, also revealed the least success. However, when development had occurred, their growth was greater than that of other transplanted molars and was found to be closer to normal size. Grafts of first molars had developed more frequently than those of other molars but they also showed the greatest discrepancy in size. The growth of second molars was intermediate between that of first and third molars. A developmental lag of three to six days, with an average of five days for the first molars, was attributed to the time necessary for revascularization. These investigators concluded that the change in environment was responsible for the abnormal shape of teeth which revealed a tendency towards compression or elongation more evident in second than in first molars.

d. Abdominal Wall and Ovary

Huggins and co-workers (‘34) autologously transplanted, isolated enamel epithelium, odontoblasts and pulp, odontoblasts and pulp with ameloblast layer, ameloblasts and odontoblast pulp with preservation of their normal relationships, central pulp and peripheral pulp and oral gingival epithelium from three to six week old dogs, into the connective tissue between the internal and external oblique muscles. The tissues were obtained from non-erupted, permanent, canine teeth from which the dentin and enamel had been removed. Transplanted, isolated enamel epithelium revealed neither ameloblasts nor enamel formation. The enamel epithelium survived as a stratified squamous epithelium composed of cords or islands without cyst formation. Transplanted, isolated pulp and odontoblasts showed formation of small masses of dentin when removed from 14 to 26 days post-operatively.
The dentin occurred at the junction of the pulp and fibroblasts of the graft capsule. Some dentin showed a tubular structure; however, most of it was found to be osteodentin or osteoid. Transplants of pulp, odontoblasts and enamel epithelium in a relatively normal anatomical relationship, revealed preservation of cylindrical ameloblasts while new dentin and enamel occurred in large amounts in a normal relationship between these layers. Hertwig's sheath had survived, but where odontoblasts were absent, no ameloblasts were seen. Transplants of enamel epithelium and odontoblast pulp, where the normal relationships between the cell layers had not been preserved, showed dentin formation and stratified squamous epithelium in some while others revealed survival of Hertwig's sheath. Transplants of central pulp without odontoblasts, showed no dentin formation and only stellate cells were seen, whereas transplants of the odontoblastic layer showed islands of dentin surrounded by odontoblasts. Transplants of gingival oral epithelium formed cysts which revealed no formation of calcified material. The investigators concluded that the mesodermal connective tissue derivatives (odontoblasts) had an influence on the form and function of the enamel epithelium since no enamel had formed in their absence; however, odontoblasts survived transplantation and formed dentin while central stellate pulp cells alone did not induce calcification.

Hahn (141) autologously transplanted pulp with intact odontoblasts, isolated enamel epithelium, and pulp minus odontoblasts but the enamel epithelium, from six week old dog, non-erupted, maxillary canine teeth, into ovaries or into the abdominal wall. In the first series 18 grafts of pulp with odontoblasts, transplanted into ovaries for seven days, showed a calcifying osteoid tissue between the ovarian connective tissue and the pulp graft;
however, typical odontoblasts were not identified. Fifteen days later, normal tubular dentin with an outer irregular layer was seen and a fibrous dentin layer, possibly corresponding to the predentin of a normal tooth, had developed. Odontoblasts were found in all grafts 15 to 30 days after transplantation. In a second series comprised of 16 grafts, of isolated enamel epithelium transplanted into ovaries, the enamel organ had lost its characteristic form and had reverted into a stratified epithelium when examined seven days later, while at ten days, epithelial lined cysts had appeared. Inflammatory processes were also noticeable in host tissues which were attributed to infection or to the presence of partially calcified enamel rods adhering to the transplanted enamel epithelium. No new enamel had formed. No organizing effect on teeth by the connective tissue of the ovary was seen. Odontoblasts, with enamel epithelium but free of pulp, transplanted into the fascia of the abdominal wall, revealed changes similar to those seen in enamel epithelium transplants at seven days in the first series, but no cysts formed. The pulp appeared to be normal having retained its reticular appearance and stellate cells. Grafts of 14 to 21 days revealed pulp, more closely approaching the structure of the surrounding connective tissue, and several areas of amorphous material. Hahn contends that the amorphous material represents an initial stage of degeneration. Cysts, which were similar to those found when only enamel epithelium had been transplanted, were seen after 14 days. No evidence, suggesting the formation of odontoblasts, was encountered up to 21 days after transplantation, and no enamel or dentin had been formed. The authors concluded that enamel epithelium was not essential for the maintenance of normal dentin once a calcified layer formed.
e. Bone

Sutro and Pomerantz (139) autologously transplanted halved, non-erupted, tooth germs of canines of kittens, from which the calcified dentin and enamel had been removed, into the marrow cavity in the upper third of tibias. The grafts were recovered at post-operative intervals of three to 180 days. At three days no evidence of either dentin or enamel formation was seen. However, 21 days later, hypertrophy of pulpal cells and active dentin formation had occurred although no enamel or ameloblasts were seen. At 31 days, considerable dentin was found and Hertwig's sheath and nests of ameloblasts were noted. In another graft recovered after 31 days, several large epithelial nests were observed, and where epithelial nests were not in contact with pulp enamel formation was seemingly absent. Dentin formation had progressed at this time, but pulp tissues were replaced by bone and osteodentin in some grafts. Furthermore, where ameloblasts were not present, odontoblasts failed to form regular dentin, pulpal cells also failed to differentiate into odontoblasts and isolated ameloblasts, without adjacent pulp cells, were transformed into epithelial islands.

f. Sockets of Teeth

Grewe and Felts (168) transplanted mandibular incisors, from five day old inbred mice, into the mandibular incisor sockets of seven day old mice of the same strain. In a second experiment incisors, from five day old inbred mice, were removed and re-implanted into the sockets of the same animals. Transplanted and re-implanted incisors were recovered at intervals of from one hour to 35 days. Histological study showed that all transplanted incisors (40) had failed to grow, that all showed resorption and that approxi-
mately one-third had been shed. Those that had been in their sockets revealed
cysts and abscesses and different degrees of inflammation. Thirty of 40 re-
implanted incisors, recovered seven to 35 days postoperatively, showed some
growth. The remaining ones had either been shed or were found to be necrotic.
The latter also revealed inflammation, osteodentin formation, and an irregular
formation of dentin, enamel and cementum as well as abnormal periodontal tis-
sues. It was concluded that the difference between transplanted and reim-
planted incisors could be a consequence of surgical trauma. Transplants were
subjected to additional trauma during reinsertion into sockets. Since the
grafts were exchanged between members of an inbred strain, these investigators
assumed that such transplants were not subject to immunological rejection.

2. Immunological Properties

a. Rabbit

Shulman ('64) studied the antigenicity of tooth homografts in rabbits.
Sixteen rabbits were paired and two molars removed from each. After the pulps
were excised and the apices sealed, one molar was autologously, and the other
homologously, subcutaneously transplanted. After three weeks, ear skin homo-
grafts were exchanged between the same pairs of hosts and a control, skin
autograft carried out on each rabbit. Local swelling at the site of homo-
graft teeth was greater than that at the site of autografts. Abscesses had
formed and the capsules enclosing homologous transplants were infiltrated with
plasma cells while these cells were absent in autografts. Skin autografts
were accepted, but skin homografts were rejected revealing an accelerated re-
jection where such grafts had followed tooth transplants. In a second experi-
ment, both first central incisors, with intact pulps and unsealed apices,
were homologously exchanged between pairs of rabbits. Homografts of skin exchanged between the pairs showed an accelerated rate of rejection. In a third experiment, skin homografts, biopsied at four, six and eight days after tooth transplantation, revealed an accelerated rejection. It was concluded that, since accelerated skin graft rejection from the same donor followed homologous tooth transplantation, homologous teeth sensitized the recipients and that teeth and skin probably shares the same transplantation antigens. Shulman also suggested that the transplantation antigenicity observed in this experiment may have been brought about by tissues of the tooth other than cementum, dentin or enamel.

To examine the antigenicity of soft and hard tissue of teeth for their ability to initiate or stimulate an immune response, as evaluated by accelerated rejection of skin grafts, White and Rogers ('67) carried out the following experiments in the rabbit: Controls received primary skin allografts which were normally rejected. Three weeks later, a second skin graft was performed in this group and an accelerated rate of rejection was observed. The rabbits in the second experiment received autologous reimplanted incisors followed by autografts and allografts of skin three weeks later. Normal rejection times of skin allografts were noted. The third group received intraperitoneal injections of a suspension of pulp and periodontal membrane, removed from allogenic teeth, and three weeks later, skin allografts from the same donors. These skin allografts also revealed an accelerated rejection in all cases. The fourth group of hosts received implants, of the remaining hard parts of the teeth used in the third experiment, into alveolar sockets followed three weeks later by a skin allograft from the same donors. An accelerated skin
allograft rejection was also noted in this group. In a fifth experiment, allogenic teeth were treated with trypsin prior to transplantation into alveolar sockets, and these were also followed three weeks later by skin allografts. These skin allografts were also rejected in an accelerated fashion. In the final experiment, an accelerated rejection was seen in skin allografts applied three weeks after an intraperitoneal injection of a powdered suspension of hard tooth structures. In all these experiments, skin allografts revealed accelerated rejection in a manner similar to that seen in skin grafts on rabbits which had been given a primary skin transplant. These results led the investigators to conclude that teeth do possess transplantation antigens and that their observations confirm evidence from previous experiments of other investigators who found that teeth possess the same transplantation antigens as those associated with skin. They also concluded that the hard tooth structures were as capable of sensitizing an animal to these antigens as were pulp and periodontal membrane.

In order to study the immunizing properties of allogenic tooth pulp transplants in rabbits, Zaleski and co-workers ('67) subcutaneously transplanted pulps from the incisor of adult rabbits into pockets formed on the dorsal surface of the ears of other adults. Each graft consisted of the pulp from two incisors. The cytological changes occurring in the regional lymph nodes (blastic reaction) were selected as indicators of host immunization. The first group of 30 recipients and the second of five received only dental pulp. The third group of four were each given a second pulp transplant 21 days following the first. The fourth group of ten each received a skin allograft 21 days after the first pulp transplant. The fifth and sixth groups of four hosts each were pre-immunized with injections of bone marrow and 21 days
later they also received pulp grafts. Groups seven and eight, consisting of four recipients each, were given immunizing injections of spleen cells and 21 days later the hosts in group seven were given pulp grafts. In group eight pulp grafts were carried out seven days after spleen cell injections.

Following allogenic pulp grafts, an increase in the percentage of blast cells was seen in the regional lymph nodes, in the ears, and an acceleration in the rejection of skin grafts, applied three weeks after pulp transplantation, occurred, showing that tooth pulps were capable of evoking a state of sensitization in hosts. Five days after transplantation, all pulp grafts revealed foci of osteodentin; however, beginning on the tenth day this tissue was gradually destroyed. Four of eight pulp grafts, in the group where tooth pulp had been transplanted seven days after the initial spleen cell injections, also showed osteodentin formation. As a result of these observations the investigators concluded that the development of osteodentin was most likely the result of growth and differentiation of the pulp grafts. They also theorized that allogenic dental pulp transplants had the capacity of provoking an immunological response, though somewhat delayed, which they believed was due to a smaller amount of antigen, the character of the pulp, or to the temporary isolation of the graft from the host tissues. It was also believed that the accelerated rejection of skin grafts following pulp transplants showed the probability that at least some antigens are shared between skin and pulp, and that pulp grafts can immunize the recipient against skin grafts.

b. Guinea Pig

Fleming and Soni ('65) subcutaneously, heterotransplanted, tooth germs from 30 day old fetal guinea pigs into young adult Swiss mice. Additional hosts received two or three intraperitoneal injections of either guinea pig
serum or guinea pig embryonic tissue extract prior to transplantation. Transplants were recovered weekly through the eighth postoperative week. Histological observations showed that the immune response to heterotransplanted tooth germs was most vigorous in untreated controls which revealed prominent accumulations of chronic inflammatory cells around grafts. Very little growth or development was observed within five weeks after transplantation. The formation of enamel was severely affected and degeneration of pulps, revealing a strong inflammatory response, was also noted. Resorption of grafts gradually became complete usually within three to four weeks. A decrease in the graft inflammatory response was seen in hosts treated with embryonic tissue extract. In hosts treated with guinea pig serum, the inflammatory reaction was also greatly reduced, but the reaction was greater than that seen in hosts treated with extracts of embryos. Accumulations of inflammatory cells were significantly fewer in these grafts and in some cases in older transplants were practically absent. Growth and development of grafts had increased significantly in serum treated hosts revealing enamel and dentin formation, as well as cellular tooth elements, which appeared to be closer to normal than that seen in other experimental groups. Microradiography showed that the dentin of transplants was more uniformly mineralized in serum treated hosts although, in general, these teeth revealed a greater degree of mineralization in enamel than in dentin.

Haley and Costich (1967) evaluated the immune response, elicited by allografts of guinea pig molars subcutaneously implanted into the right dorsolateral thorax by means of histological observations on changes in the lymphoid cell populations in the cortices of right and left axillary lymph nodes. Grafts were recovered at intervals of 22 hours and 6.5, 8, and 9.5
days after transplantation. Many large pyroninophilic cells were found in the cortex and medulla of node germinal centers by 6.5 days after transplantation. Only a slight decrease in the number of these cells was recorded at 8 days, and by 9.5 days, only a few large pyroninophilic cells and mitoses were seen in the cortices of nodes. The cortices of nodes draining grafts revealed an increase in thickness, when compared with contralateral nodes, and these contained a larger number of pyroninophilic cells. These investigators suggested that since the lymph nodes showed increases in the number of these cells, guinea pig teeth were antigenic.

c. Mouse

Utilizing two inbred strains of mice, Valente and co-workers (164) homologously subcutaneously, transplanted teeth which were later followed by skin grafts from the same donor strain. Control groups received autologous tooth grafts followed by skin homografts. In both groups skin grafts were recovered after six days for histological examination. In excess of 50% survival of epithelial cells was seen in controls and less than 5% in experimentals. Parts of teeth, free of pulp and cementum, were autologously and homologously, subcutaneously transplanted followed by homologous skin grafts. Skin transplants were recovered after six days. Epithelial cell survival scores were recorded as 52.9% for controls and 11.6% for experimentals. The investigators concluded that skin grafts in experimental groups showed a second set, homograft, immune rejection response while tooth homografts evoked an immunological reaction and were antigenic.

Valente and Shulman (166) subcutaneously homologously transplanted intact lower incisors from inbred BALB/c mice into the flanks of inbred C57 mice in order to evaluate the onset, intensity and duration of the immunity
developed by such transplants. Groups of ten hosts each were challenged with donor skin allografts at 2, 5, 6, 7, 8, 9, 10, 12 and 16 weeks after transplantation of the incisors. Histological observations on recovered skin grafts revealed transplantation immunity two weeks after transplantation which had disappeared by the fifth week, and reappeared during the sixth through eighth weeks. The authors concluded that the stronger initial reaction was against the soft tissues whereas the weaker subsequent reaction was brought about by the less antigenic hard structures.

B. Tooth Transplants in Rat

1. Sites

   a. Sockets of Teeth

   In a study to determine the capacity of developing tooth germs to grow and differentiate when transplanted into the alveolus of rats, Shapiro and Johnson (1958) transplanted second molar tooth buds, from five to 10 day rats, into the third molar sockets of 24 to 28 day old rats. Tooth buds of the third molar, from 15 to 18 day old rats, were transplanted in the same manner, into hosts of the same age as the above. Grafts were recovered at intervals of from one week to two months. Seven days after transplantation, they revealed pulpal revascularization and normal pulps showing a small amount of new dentin while at 23 days, considerable dentin formation as well as growth of roots had occurred. By 28 days the teeth were still well established and dentin had continued to form. Transplanted teeth generally showed growth, retention of form, cusp elongation, root formation, considerable dentin formation and a partial eruption into the oral cavity. These results led the investigators to conclude that the third molar socket was an excellent site for the transplantation of developing teeth.
b. Subcutaneous and Submucous

Lefkowitz ('61) isologously transplanted 19 day old fetal rat first molar buds into adult inbred male rats of the same strain. Two grafts were transplanted into each of 12 hosts, one beneath the submucosa anterior to the first maxillary molar, the other subcutaneously into the dorsum. The remaining three hosts received a single subcutaneous transplant. Only eight submucous and five subcutaneous grafts were recovered at postoperative intervals of three hours to 13 weeks. In a second series, 15 tooth buds were cultured in vitro for 12 days before transplantation into sites identical to those of the first series. Here, each of seven rats received one submucous and one subcutaneous graft and an additional rat received only a submucous graft. In this series only two subcutaneous and six submucous grafts were recovered, between one and 13 weeks subsequently.

It was found that subcutaneously transplanted, uncultured tooth germs were vascularized at one week. These revealed differentiation of odontoblasts and ameloblasts as well as a layer of calcified dentin and an enamel matrix, however, a dense infiltration of lymphoid cells into dental sacs revealed evidence of rejection. Such grafts at two weeks, showed further growth but at three weeks the dental papilla had degenerated, although the already existing dentin and enamel did not appear to be affected. Uncultured submucous grafts at one week revealed loss of normal form, no revascularization, and development was considered to be slower than that of subcutaneous grafts. At two weeks, only very thin layers of dentin and enamel were seen; the general form of teeth did not resemble normal molars, and degeneration was evident. At three weeks none of the original soft tissues had remained and resorption of enamel and dentin had occurred. It appeared that rejection of the sub-
cutaneous grafts had progressed more slowly than the submucous grafts. Cultured subcutaneous transplants showed normal development, cusp formation, and absence of lymphoid cell infiltrations at one week. However, at two weeks, these grafts were revascularized and only slightly more growth was seen although the tissues were normal. Cultured submucous grafts on the other hand, revealed growth, development and revascularization at one week, and at six weeks no evidence of rejection was seen. Roots had formed, but their growth was less than normal. Crowns were covered with enamel, cementum had formed and the grafts were surrounded by a bony crypt. In all cases, regardless of site or pretreatment, the enamel had remained in a matrix-like site.

Ivanyi and Vacek (164) carried out subcutaneous, homologous and isologous transplantations of newborn rat first maxillary and mandibular tooth germs into the tops of heads of newborn and adult non-inbred and inbred three month old rats. Each host received one transplant and these were recovered at postoperative intervals of 24 hours to 50 days. Where newborn tooth buds had been transplanted into 30 newborn and 11 adults of the same strain, histological examination revealed growth and development with no signs of rejection. Homologously transplanted tooth germs between 44 newborn non-inbred siblings also showed no evidence of round cell infiltration or rejection; however, grafts exchanged between different litters of 52 non-inbred rats did show some evidence of rejection. Evidence of rejection was most frequently seen where newborn tooth germs had been grafted into 50 adults of a non-inbred strain.

Histological study revealed no significant difference between surviving homo- and isografts. The teeth showed growth and differentiation after a period of pulpal regeneration, but growth was not so rapid as that
seen in normal, intact teeth. Development of roots and a bony alveolus were observed in surviving teeth although many roots were distorted, a condition believed to be due to compression of tooth germs or damage to Hertwig's sheath during transplantation. Development of primary and secondary cementum as well as periodontal ligament formation had also occurred. The study indicated that the onset of the transplantation rejection reaction had occurred at different intervals following transplantation. The degree of lymphocytic infiltration of tissues surrounding grafts, infiltration of pulps, tooth degeneration, and the degree of development, as well as the amount of hard tissue formed, were criteria employed in evaluating the onset of graft rejection. Ivanyi and Vacek stated that they were unable to support the conclusions of other investigators that immunological principles did not apply to transplanted tooth germs, since they were able to demonstrate rejection of teeth, with accompanying round cell infiltration. They asserted, however, that there were some inherent peculiarities in the behavior of transplanted tooth germs.

Zussman (1966) homologously, subcutaneously transplanted enamel organs from the incisors of adult W/Fu and Sprague-Dawley rats into the necks of three day old rats of the same strain. Some enamel organs were also grafted into three day old rats which had been thymectomized at birth. Each host received two subcutaneous transplants. Successful grafts of enamel organs revealed growth and proliferation up to 14 days. Between one and two days after transplantation eosinophilia and swelling of the cytoplasm of cells of enamel organs were seen as well as a reduction in nuclear size and nuclear hyperchromasia. At three days epithelial cells in contact with subcutaneous tissues were necrotic and other epithelial cells had become flattened, elongated and showed prominent nuclei. At five days, epithelial proliferations in the form
of clusters were observed, while at six days epithelial cords appeared although no normal cells of the enamel organ other than epithelial cells were seen. In the basal areas of epithelial cords a PAS positive material was seen separating cords from the adjacent connective tissue.

Calcified foci were seen in grafts which were not related to the epithelial cells or to the formation of bone or enamel which were compared to epithelial rest calcifications. At seven days, a clustering of epithelial cells in parts of cords and a dense PAS positive and eosinophilic material was found around the epithelial cells. By the twelfth day, the epithelial cells were arranged around an intense PAS positive fibrillar substance, and by the fourteenth day plump, closely packed, enlarged cells were clustered around coarsened PAS positive fibers. After 14 days the transplants had become necrotic revealing lymphocytic infiltrations which were interpreted as evidence of a sudden rejection.

Zussman (1966) concluded that transplanted enamel epithelium had survived and that it grew without any specific degeneration of specialized cells which were able to organize into cords and nests. The author also felt that the PAS positive material formed by these cells served a protective function and that it was not associated with enamel formation. The failure of enamel formation was attributed to the absence of already formed dentin which appears to be necessary for the formation and survival of enamel.

Zussman (1966b) subcutaneously transplanted pulps and enamel organs from the incisors of adult rats, into three day old rats thymectomized at birth. Preliminary studies had indicated that the transplantation inflammatory response was deceased when hosts had been thymectomized at birth and grafts carried out three days later. Each host received two grafts which
were recovered at intervals of three to 40 days. When only enamel organs were transplanted, epithelial cells proliferated as cords during the first week and later formed nests. After two weeks, no further growth occurred and destruction with lymphoid infiltration was seen. When pulps were transplanted alone, local calcification and elongation of cells occurred during the first week, while during the second week the formation of spicules of compact and later spongy bone was seen. After three weeks, odontoblast-like cells were observed along a layer of compact bone.

When enamel organs and pulps had been transplanted together, calcification within pulps occurred rapidly which was not the same as that seen when pulps were transplanted alone. After one week, epithelial cords had proliferated from the enamel organ but these were separated from the surrounding stroma by a PAS positive material. Pulpal cells were surrounded by a granular and in some cases a fibrillar calcified material. After two weeks such grafts revealed a calcified tissue surrounded by epithelium, a marked lymphocyte response and inflammation. After three weeks the calcified mass had become surrounded by giant cells.

This investigator reported that whenever enamel had formed an inflammatory reaction and destruction followed. He also noted that when ameloblasts were present odontoblasts initially formed a dentin-like substance, but when transplanted alone, odontoblasts formed bone which was later modified after which a dentin-like material appeared. The author observed that odontoblasts were able to remain active in the absence of ameloblasts and concluded that when enamel forming epithelium is transplanted with odontoblasts, a more advanced development occurs than when odontoblasts are transplanted alone.

Zussman ('66c) subcutaneously homologously transplanted intact dental
pulps, with hard tissues removed, from adult rats into littermate rats, ranging in age from newborn to three days, and into one group of hosts thymectomized at birth. Each of 138 hosts, received two subcutaneous grafts in the right and left groins, in the right and left sides of the neck, and some in the groin and neck.

Pulps showed degeneration of odontoblasts between one and two days after transplantation. Three days later, accumulations of basophilic calcium granules were seen at the basal ends of the odontoblasts. One week after transplantation, an increase in fibroblasts was identified in the undifferentiated parts of the pulp. At eight to nine days, calcification had occurred in the outer region of the pulp, and giant cells were present, while the fibrous central region contained capillaries. At ten to 11 days a uniform calcified material was noticeable in the odontoblast region and resorption of the calcified material had occurred. Calcification had also occurred around large blood vessels and calcified material was present in the dense fibrous parts of the central pulp. By two weeks, the pulps showed bony spicules surrounded by elongated cells whereas other areas revealed larger, spongy, bony masses granularly calcified with a tubular structure surrounded by irregularly shaped cells.

Replacement of dental pulps by spicules of lamellated bone with odontoblasts at their periphery and fibrous tissue containing large blood vessels between the spicules was seen at 17 days. During the next one or two days, a dense fibrous peripheral region, was a vascularized, fibrous central part, with odontoblast cells located between the boarders of the fibrous and calcified parts had appeared. Within the following 24 days, the graft decreased in size and odontoblasts with nuclei adjacent to the calcified material were
The peripheral calcified material was tubular and spongy but appeared to be homogeneous centrally.

Transplants in non-thymectomized rats revealed necrosis and neutrophilic infiltration which persisted longer (eight to ten days) although by 19 days their appearance was similar to grafts in thymectomized rats. No transplants were rejected in either thymectomized or normal hosts, and no differences were seen between subcutaneous groin or neck grafts. Dentin appeared only after bone formation whenever grafts were not in contact with other oral tissues. The enamel organ was found to be unnecessary for the calcification and function of the odontoblasts. The investigator concluded that the odontoblasts have the potential to form both bone and dentin.

Weinreb and co-workers ('67a) autologously transplanted 120 maxillary first molar tooth buds into the dorsal subcutaneous tissues of 100 ten day old rats. Grafts were recovered between two and 180 days subsequently. Two days after implantation, the pulp and odontoblasts revealed small round cell infiltration and degeneration. At five days, further degeneration of pulps, atypical odontoblasts, and a decrease in pulpal cellularity was seen. Further progressive degeneration had occurred at seven days when pulps showed edema, however, by 14 days the pulps revealed an increase in cellularity and some dentin formation had occurred while the cells adjacent to the dentin had remained atypical in form. By 21 days the pulp had regained a normal appearance and new dentin had formed which became more regular in formation with the increasing age of the graft. Thus, these investigators concluded that the pulp had the potential to recover from a severely degenerated state, produce new dentin, and develop normal staining reactions.

Molar tooth buds from 10 day old rats were homologously, subcutaneously
transplanted into 34 rats, 14 days of age, which had been thymectomized within
the first 24 hours after birth (Oprisiu et al., '68). Graft rejections were
observed in two of the 34 hosts, and one died. Nine of the survivors had re­
ceived fragments of alveolar processes containing tooth buds, but all were
rejected believed to be the result of infection. Grafts were regarded as
successful when teeth remained vital and developed into calcified structures.
After ten days grafts showed formation of dentin and enamel and minimal
development of dental follicles occurred. Radiological examination disclosed
crown development comparable to normal age. However, roots had not developed
presumably because the connective tissues from which the roots form was not
transplanted with the epithelial dental sac. At 65 days grafts revealed well
developed pulps showing viable odontoblasts and well formed dentin and enamel.
A slight leukocyte infiltration into the dental sac was observed; however,
evidence of suppuration or a foreign body reaction was not found. Transplants
recovered at 75 days revealed significant development of crowns and layers of
dentin and enamel. The dentin of transplants in immunologically incompetent
(thymectomized) rats was irregularly mineralized, not homogeneous and roots
showed poor development as well as a lack of cementum; however, follicles
were viable and inflammatory, and foreign body reactions appeared to be absent.
These investigators attribute a large part of their unusual success to a lack
of injury to the dental follicle during transplantation.

c. Bone

Weinreb and co-workers ('67b) autotransplanted 100 first maxillary
molar buds into a total of 92 ten day old rats. In the first experiment,
tooth buds were transplanted into the dorsal subcutaneous tissues. These, one
week later, were surrounded by an inflammatory reaction. The enamel organ
had undergone destruction and only remnants of stratified epithelium were found. Degeneration of odontoblasts was evident; however, the dentin appeared to be normal. By two weeks, there was less inflammation and dentin formation had continued although it appeared to be irregular in some areas. Some osteodentin was also found. Between three and six months, an enamel matrix had formed but no secondary calcification of enamel was seen. Pulps appeared to be normal and dentin formation was more regular in nature with the exception of that found in the apical part of the tooth where osteodentin and bone had formed.

In the second experiment performed by Weinreb and co-workers, the transplants were blocks of maxillary alveolar bone with intrinsic tooth bud and supporting structures intact. These were autologously grafted into the dorsal subcutaneous connective tissues. An inflammatory reaction, similar to that in the first experiment, and the formation of epidermoid cysts occurred. During the first week, the enamel epithelium underwent destruction and pulps contained degeneration, but after two weeks the pulps were normal in appearance. Some pulpal bone developed and more irregular dentin formation as well as some loss of its tubular character had occurred. In a second part of this experiment, first maxillary buds were removed from blocks of maxillary alveolar bone, the alveolus was cleaned, and the bud was replaced. These blocks were then transplanted into the dorsal connective tissue. No significant differences in growth or differentiation were seen.

In the third experiment by Weinreb and associates, a piece of tibia was excised, the marrow removed, and an autologous first maxillary molar inserted base downward into the medullary cavity thus simulating an artificial socket. The piece of tibia was then transplanted into the dorsal connective tissues.
When later examined, the odontogenic epithelium appeared to be similar to that seen in the other experimental groups with the exception that postoperative dentin formation was more irregular. At 14 days, some resorption had occurred and pulps revealed bone and/or bone marrow gradually replacing most of the pulps. At 90 days, resorption was more evident, but normal pulp showing odontoblasts and dentin formation was seen in areas where the pulp had not been replaced.

In a final series, first maxillary molar buds were autologously transplanted into the marrow cavity of tibias. Thirty days after implantation, the grafts were surrounded by marrow and bone and in some cases they were ankylosed to the tibial bone. The dentin was similar in appearance to that seen in the third experiment, but signs of dentin resorption were seen earlier at seven days. Resorption continued so that by 60 to 90 days most of the tooth bud had disappeared.

In summary, Weinreb et al. reported that all transplants, regardless of the experiment, became revascularized and continued to develop following an initial period during which some degenerative changes had occurred. The fate of tooth buds differed depending on the types of bone into which they had been transplanted. Resorption had not occurred when associated with alveolar bone, but massive resorption did occur in tibial bone. The authors concluded that alveolar bone seemed to have different inductive and protective properties than tibial bone with respect to the development of grafted teeth and that alveolar bone appeared to be a more normal physiologic site for tooth development.

2. Immunological Properties

To investigate the immunological properties of tooth germs Ivanyi
(65a) isologously and homologously, subcutaneously transplanted first molar tooth germs from newborn inbred rats, to the crowns of heads of inbred and outbred newborn and adult rats. The transplants were recovered daily through 50 days after implantation and histologically examined. Of 43 grafts exchanged between newborn, nonrelated, rats only three showed evidence of an immune reaction. No rejections occurred when transplants were carried out between newborn littermate rats (36) or between newborn rats (27) from the same inbred strain. However, of 42 homologous transplants into adult rats, 23 were rejected, whereas isologous control grafts in adults did not reveal rejection. Newborn rat tooth germs transplanted between newborn littermates and recovered three months later showed a host reaction in only one of 21 grafts, whereas 13 of 19 grafts between newborn of different litters were rejected. All but one, of 25 tooth germs in rats which had been immunized with spleen cells 10 days preoperatively, disclosed rejection within four days following implantation.

These observations led to the conclusion that survival of tooth germ transplants depends on an immunogenetic relationship between host and donor. Furthermore, since prolonged survival was seen in a large number of transplants in newborn rats and only occasionally in the adult, it was concluded that tooth germs may have some special characteristics, and it was believed that there did not appear to be any essential, immunological, behavioral difference between tooth germ transplants and transplants of other tissues.

To further investigate the immunological properties of tooth germs Ivanyi (65b) homologously, subcutaneously transplanted molar tooth germs into the tops of heads of littermates and unrelated newborn rats. All grafts were recovered at three months. Of 21 transplants between newborn littermates,
only one showed a rejection reaction. However, this tooth was well-developed and still showed surviving odontoblasts. The remaining 20 teeth showed thick layers of dentin with no evidence of an immunological reaction. Two of these were seen in the initial stages of piercing the skin and revealed roots connected with the subcutaneous connective tissue. In a second experiment, tooth germs were transplanted between newborn litters of nonrelated rats and here only three of 19 teeth showed survival three months later while rejection was seen in the remaining 16 teeth. In general, the majority of these rejected teeth showed that the onset of a homograft reaction had occurred a considerable period after transplantation since the grafts had developed considerable hard tissue. The investigator concluded that a study of three months' duration revealed a greater dependency on the genetic relationship between host and donor for graft survival than did shorter periods. This investigator felt that tooth germs, as other embryonic tissues, probably were less antigenic than tissues such as skin and therefore survived for a longer period.

To investigate the histocompatibility requirements of developing teeth, Ivanyi (166) subcutaneously homologously transplanted tooth germs from newborn inbred Lewis rats into (BN x Lewis) F2 hybrid adult rats. Histological examination of grafts was carried out 100 days after implantation. Twenty-eight of 58 grafts were considered successful since they were well developed, showing tubular dentin, secondary cementum and pulp containing odontoblasts. No signs of an immune reaction were seen. Only five of 318 skin homografts exchanged between members of the same strains were successful. In a second experiment, tooth germs from inbred newborn Wistar rats were transplanted into 29 newborn random bred Wistar rats. Twenty days later, the
hosts were divided into three groups. Fifteen received injections of inbred Wistar spleen cells and later a skin graft. Only two of 15 grafts showed round cell infiltration nine days later; the remaining 13 revealed no signs of rejection. The second group of seven hosts, each of which had received only a skin graft following the original tooth germ transplant, revealed no rejected teeth while the seven controls showed only one partly rejected tooth. It was concluded that perhaps only strong transplantation antigens influence survival of tooth germ transplants and that only two or three histocompatibility loci are responsible for their survival.

To further evaluate the immunogenetic relationships between donors and recipients of tooth germ grafts, Ivanyi (‘68) subcutaneously homologously transplanted first molars of newborn, inbred Lewis rats into six week old (Lewis x BN) F₂ hybrid rats. Grafts were recovered 100 days later and recipients serologically typed for compatibility at the H-1 locus. Of 47 hosts with serologically compatible grafts, 31 revealed survival of transplants; however, 10 of these had undergone late and six early rejection. Fourteen hosts were found to be serologically incompatible grafts at the H-1 locus and of these only two were surviving and 12 had undergone early rejection as revealed by their very small growth. Of 36 grafts under observation for 200 days only 14 were successful.

These results led the author to conclude that compatibility at the H-1 locus, between the donor and the host, was necessary but was not an entirely sufficient condition to ensure progressive growth since compatible grafts were also rejected. The author theorized that the H-1 histocompatibility locus is the only strong locus responsible for tooth transplant rejection and the synergistic activity of a number of relatively weaker histocompatibility loci is
responsible for rejection in hosts with compatible grafts at the H-1 locus.

To investigate the antigenicity of the transplanted developing tooth bud, Weinreb and co-workers (1968) allotransplanted first maxillary molar buds. They took these from 10 day old random bred rats and transplanted them into the dorsal subcutaneous tissues of adult rats from the same colony. Sixty-one of a total of 106 transplants displayed acceptance during an interval of 28 and 150 days; 31 revealed no growth or dentin formation and were rejected shortly after implantation; while fourteen transplants manifested initial acceptance with some growth and dentin formation, but were later rejected. Histological examination of accepted grafts revealed formation of dentin, normal pulp and an absence of small round cell infiltration. In a second experiment, pieces of spleen were transplanted simultaneously with 37 molars and of these only one tooth revealed acceptance and growth by the end of six weeks. Eighteen were rejected disclosing no growth but eight had been initially accepted but were later rejected. The authors concluded that when tooth buds are transplanted with spleen, immunological rejection occurs earlier than when teeth are transplanted alone since in the latter, there was a wider range in the onset of reactions. They also concluded that the tooth bud was either a tissue with a low antigenicity or that its antigens were too weak to elicit an immune response.

Sharav and co-workers (1969) subcutaneously allografted first maxillary molar tooth buds from 10 day old random bred rats into the dorsal connective tissue of 12 week old rats from the same colony to determine if established tooth bud allografts would become progressively less susceptible to immunological destruction. To determine the immunogenetic relationship between members of the random bred rat colony, skin grafts were carried out which
revealed a median survival time of 11 days (range of 9 to 20 days). In the first experiment, 96 tooth buds were allografted. Histological assessment revealed that 20 of 34 such grafts after 10 weeks, 13 of 31 after 14 weeks, and 10 of 31 after 20 weeks appeared to have been successfully accepted. In a second experiment, 26 tooth buds were transplanted concurrently with spleens from the same donors. Ten weeks after grafting, histological examination showed that all teeth were rejected.

In a third experiment by Sharav and associates, 72 tooth buds were transplanted, and at four and 10 weeks subsequently, spleens from donors of teeth were also grafted. On histological examination only seven of 43 tooth grafts which had been challenged at four weeks after grafting were found ten weeks later to have been accepted. However, six of 29 teeth in hosts which had received challenges of splenic transplants at 10 weeks following tooth grafting and recovered 10 weeks later showed acceptance.

These results led Sharav and co-workers to conclude that developing teeth showed a high incidence of acceptance, but their success decreased with the increasing transplant age, and that teeth were invariably rejected when transplanted concurrently with spleen. However, when the teeth had been allografted four to 10 weeks before host challenge with spleen, a higher incidence of successful grafts occurred. The gradual decrease in graft acceptance was attributed to a continuous process of host sensitization whereas the acceptance of established implants after antigenic challenge was attributed to gradual transplant adaptation. They felt that the tooth bud was a "privileged" organ in its relatively weak ability to elicit an immune reaction. They postulated that survival of the tooth germ graft would appear to be determined by a delicate balance between the rate and strength of concurrent processes of
sensitization and adaptation.

C. Tooth Transplants in Hamster

1. Sites

a. Re-Implantation

Bilateral extraction and re-implantation of second and third mandibular molars in 36 day old hamsters was studied by Meyers and co-workers ('54) in eight hamster littermates. On histological examination, three of four teeth recovered after five days revealed degeneration of periodontal membranes while cementum and alveolar bone showed some resorption. Normal pulp tissue and odontoblasts were present, but in three of six root canals some pulpal necrosis was seen. One tooth revealed a completely necrotic pulp. At ten days, three of four reimplants showed excellent periodontal re-attachment, viable pulp and odontoblasts. Four teeth from 19 and 21 day old implants showed periodontal re-attachment, but the pulps of two were partially or completely necrotic while viable pulp was seen in the other two. Two implants recovered at 30 days revealed periodontal attachments; nevertheless, the pulp was completely necrotic in one, while the other showed viable pulp and dentin undergoing repair. Regions of resorption occurred but cementum undergoing repair was also seen. The investigators concluded that successful reimplantation of teeth is possible in hamsters, and that such teeth may remain viable and achieve a successful periodontal attachment.

Lower right, second molars from 16 male and 13 female, 21 day old hamsters were removed and reimplanted into their original sockets and recovered at intervals between 14 days and three months postoperatively (Costich et al., '58). Three of 29 teeth were lost. Histological study indicated that four of the remaining teeth had been perforated during re-implantation and had
necrotic pulps. Of the remaining 22, seven also showed pulpal necrosis but in most cases viable pulps were seen in root canals. Four teeth disclosed root canals mostly filled with osteodentin. Although teeth recovered early in the experiment did not reveal an organized arrangement of fibroblasts in the periodontal membrane, a normal arrangement in relation to the roots and the alveolus was seen on later recoveries. All but one tooth showed evidence of some degree of resorption and about half of them revealed ankylosis.

b. Sockets of Teeth

Hoek and co-workers (158) transplanted homologously right and left second mandibular molars, from six day old hamsters. These were grafted into the sockets of right and left second mandibular molars in seven female and 12 male hamsters approximately two months of age. Two of the hosts had only one graft each and three died during the course of the experiment. At 75 days, gross examination revealed that ten teeth had been sloughed, 16 were loose and four were firmly attached. Histological study of 20 recovered teeth revealed necrotic pulps in 13, while viable connective tissue was seen in the root canals of eight. Three teeth showed good periodontal re-attachment and two only fair, while re-attachment in the remainder was poor; however, no ankylosis was encountered and only five teeth revealed evidence of resorption.

A comparison between transplantation and reimplantation of bilateral second molars, from 30 day old hamsters, exchanged between pairs of hamsters, was carried out by Myers and Flanagan (158). Of 30 transplants recovered at 30 days, seven were considered good and 23 poor takes. In no case did periodontal membrane fibers show a total absence of re-growth. Root resorption was widespread, but was not serious enough to hinder tooth function. Perfect
takes revealed revascularization, a regular arrangement of odontoblasts and appeared to be histologically identical to normal teeth. Necrosis of pulps without inflammation was seen in some grafts; in others, inflammation of pulps occurred in apical regions and some showed stages of repair. Some teeth revealed replacement of pulp with osteoid. Six of 30 teeth reimplanted into the original site in the mandible were considered successful.

In a later series, Myers and Flanagan ('59) bilaterally exchanged second mandibular molars between 30 day old littermate hamsters. These homologously transplanted teeth were recovered at intervals of 30 and 60 days and 18 months after implantation. Histological evaluations on 20 grafts recovered at 30 days revealed five as having been successful. Sixteen of 28 grafts were evaluated as successful at 60 days, seven of 33 at 18 months, three of which were considered perfect and one nearly so and eight were missing entirely. Some grafts revealed complete regeneration of pulps. Good regeneration, however, was seen less frequently in the pulp than in any of the other dental tissues. Transplants with poor pulp regeneration showed acellular pulps, inflammed pulps or formation of osteodentin. Except in regions of inflammation periodontal membrane formation was good. Root resorption was seen in all grafts, but was minimal in successful grafts and excessive when inflammation occurred in adjacent tissues. Little evidence of tissue incompatibility was found.

Reece ('59) bilaterally, homotransplanted third mandibular molars into third mandibular sockets, between pairs of four to eight week old hamsters, to determine the best age and technique for the transplantation of erupted teeth. Thirty days later, only one of 12 hamsters in the eight week group had survived and it had retained both molar transplants. These revealed
regions of normal periodontal re-attachment and normal pulps; however, excessive predentin formation was seen and some root resorption had occurred. Ten of 12 hosts, in the six week group survived the 30 day postoperative interval. Only one of these transplants was found among the survivors, and it showed necrosis and inflammation of the pulp and only a small area of periodontal re-attachment, but some normal odontoblasts were found. Within 10 days, nine of the four week old hosts which had received penicillin had died and only one graft was found in the surviving host 30 days after transplantation. A decrease in pulpal cellularity, absence of odontoblasts, some predentin formation and a region of normal periodontal re-attachment were seen in this graft. The investigator concluded that infection of the mandible was the major cause of death of the hosts.

Maxillary incisors from adult inbred hamsters of the LSH and MHA strains were iso-, allo-, and autotransplanted, and re-implanted into their intra-oral sites (Coburn and Henriques, '66). Those which had attained occlusion were considered successful. Four of five reimplants revealed occlusion 10 days later whereas only three of six autografts, which had been transplanted to opposite sides of the jaw, showed occlusion 16 days later. Retarded growth and development were seen, in five of six isografts, and only two of eight allografts showed growth, none of which had attained occlusion. It was concluded that the allografts had undergone immunological rejection which was responsible for their retarded growth and failure to reach occlusion.

c. Subcutaneous

To investigate the origin of the stimulus for the formation of periodontal tissues, Hoffman ('59) subcutaneously and homologously transplanted
molar tooth germs from 13, 14 and 15 day old hamster fetuses, and molar teeth from newborn and five day old hamsters into 30 day old hamster hosts. The grafts comprised the dental papilla and enamel organ without the dental sac. Of 112 transplants allowed to develop for 28 days, 59 were recovered of which 42 had formed alveolar bone and a periodontal ligament. Thus, it was concluded that the stimulus for the formation of periodontal tissues was present in the developing tooth possibly associated with the proliferating Hertwig's epithelial sheath or the enamel epithelium.

Hoffman ('60) studied the formation of the periodontal tissues in newborn hamster maxillary first molars, subcutaneously transplanted into the backs of 30 day old, random bred, hamsters of both sexes. Gross observations at the time of recovery of surviving grafts revealed vascularization, in the form of large vessels originating in the host, and a capillary network on the surface of grafts. Of 23 transplants, 12 revealed growth and viable tissues 28 days later. Five were not recovered and were believed to have been re­sorbed while four were found to be small, non-vascularized, hard masses of nonviable tissue. Histological study of two grafts revealed little growth and no root formation; however, they had developed a periodontal ligament, showed alveolar bone formation and bone was also found in the pulps. Surviving grafts revealed little enamel formation although the general size and form of the molars was relatively normal. Cementum covered the enamel-free parts of crowns and fibrous connective tissue adjacent to the tooth had the appearance of periodontal ligament with its fibers embedded in cementum. Some cusps revealed tips which had the appearance of osteodentin. The roots contained normal vascularized pulps and had attained normal lengths. The pulps were more cellular and more highly vascularized than those of controls.
An irregular formation of predentin and areas of interglobular dentin were seen. Cellular cementum was found on the sides of roots. Recovered grafts also revealed a thin shell of bone on outer root surfaces and interradicular bone occurred between roots. Fiber groups of the periodontal ligament were narrower and more randomly oriented than corresponding ligaments in the controls. The alveolar bone of transplants was not so compact as that of the controls. It was concluded that genetic differences between donors and hosts were the cause of the immunological rejection of grafts and the most likely factor responsible for the loss of grafts.

Keenan and Barton (1967) subcutaneously homologously transplanted mandibular second molars from one day old newborn to 30 day old hamsters. Thirty-four of 62 transplants manifested growth and development when recovered at intervals of 14, 18, 22, 26, and 42 days later. Histological study revealed normal cementoblast activity although odontoblast activity, associated with dental sacks, was not seen until 14 days after transplantation and in some cases not at all. Between 18 and 21 days postoperatively, collagenous fibers, between alveolar bone and cementum, took on a functional orientation but grafts which did not show bone growth also failed to reveal orientation of these fibers until 26 days after transplantation. The authors concluded that periodontal fiber orientation was not predetermined in grafts but that bone growth initiated the arrangement of these fibers.

d. Bone

Twenty-four first maxillary, newborn, hamster molars were transplanted into crypts prepared in the medial aspect of right femurs of 30 day old hamsters (Hoffman, 1966). At 28 days after implantation, seven of 24 showed growth and development of crowns and roots. Although grafts were oriented
in the femur so that eruption could occur, such did not take place. In
general, surviving teeth revealed vascularized pulps and normal appearing
odontoblasts and ameloblasts; however, in some regions of crowns, the amelo-
blasts did not survive and enamel failed to form. Although some irregularly
wide predentin was seen in the pulps of roots and some osteodentin occurred
in the cusps of crowns, the odontoblasts had continued to form dentin in both
crowns and roots. Resorption of dentin had occurred in the enamel-free areas
of cusps. Alveolar bone and periodontal ligaments had developed around the
roots of all surviving molars. Alveolar bone was found to be continuous with
that of the femur, with bony trabeculae extending from the femur to the
alveolus. Resorption of femoral diaphyseal bone was seen around growing roots
while in other areas growing femoral bone had joined with the bony alveolus
of the transplant. It appeared that the form of the roots was influenced by
the femoral bone since their direction of growth was diverted through contact
with this bone. Eight transplants showing no root growth disclosed only
limited overall growth or none at all. Some revealed no survival of pulps
and no further dentin formation. In two such teeth viable pulp was seen in
one cusp while the pulp of the other cusps contained fibrous connective tis-
sue and bone formation.

e. Intramuscular

Twelve newborn hamster, maxillary molars were transplanted into the
trapezius muscle of 30 day old hamsters (Hoffman, '67). Twenty-eight days
later, eight of the transplants were recovered. Six of these were found with-
in the muscle while the other two had been displaced and were found in the
connective tissue covering the muscle. All recovered grafts were vascularized
and encapsulated. Histological study revealed crown and root development, the presence of periodontal ligaments, and alveolar bone surrounding the roots. The molars were one-third smaller than those of controls. The crowns showed some distortion in form, and a pronounced distortion of roots which was in sharp deviation from the normal course of root growth. Enamel formation varied, most of the molars showing enamel covering only one-third to one-half of the crown area. A reduction in thickness of existing enamel was also noted.

Ameloblasts were seen and these showed greater survival, and greater enamel formation in the intramuscular sites and in the femur, than had occurred in subcutaneous sites in previous studies by Hoffman. Intramuscular transplants revealed normal dentin formation in crowns. The dentin also showed osteodentin-like tissue in cusp tips and was fibrous in character. Odontoblasts were seen adjacent to thin predentin. The roots revealed no osteodentin, root dentin appeared to be irregular, and predentin formation was also irregular but showed a greater thickness than that of controls. Very thick layers of cellular and acellular cementum were also observable on roots. All grafts had developed periodontal ligament fibers with a normal orientation such as seen in functional molars. Hoffman believed that the absence of enamel formation in some crown areas, revealing irregular survival and function of ameloblasts, was partly due to the stage of development at time of transplantation. Modifications in dentin formation were attributed to disturbed nutrition of functional cells as a consequence of transplantation.

f. Check Pouch

Barton and Keenan ('67) subcutaneously transplanted 16 lower second molar tooth buds, from two day old hamsters, into the check pouches, of four through six week old female hamsters, by means of an extra-oral procedure.
Each host received a single graft and were recovered 28 days later. Controls were obtained from 14 and 28 day old hamsters. At 28 days after implantation five teeth had been lost, four resorbed, and seven were found to be histologically normal. The teeth had grown approximately five times their size at grafting and had attained the size of the controls. Histological examination of grafts revealed a connective tissue capsule around each transplant, normal crown and root formation, normal pulps, periodontal ligaments, cementum and a shell of alveolar bone. Enamel formation had been retarded and was found only on the tips of cusps while cementum had formed in regions of crowns where enamel normally forms. Osteodentin had begun to form on the tips of some cusps and at apices, but other dentin was normal. The cementum was as thick as that seen in 28 day old controls and was acellular with the exception of that seen in the inter-radicular and apical areas. Sharpey's fibers inserting into the cementum were continuous with the periodontal ligament. Both bone and cementum had formed in the apical and inter-radicular areas. Of interest was the observation that periodontal ligament and Sharpey's fibers showed greater development on mesial root surface of grafts than on others, but this was also seen in controls. The most significant difference between control and transplanted teeth was the retarded formation of enamel. Barton and Keenan concluded that Sharpey's fibers form under non-stress and nonfunctional conditions, and are not completely dependent on external forces for their formation.

2. Immunological Properties

Haley and Costich ('68) used two immunological methods to assess the immunological reaction provoked by allografts of hamster teeth. Nineteen inbred MHA strain hamsters received allografts from inbred CB strain donors; however, two isografts and four autografts were also performed in MHA hosts.
Each graft consisted of two molars which had been immersed in an aqueous solution of thimersol for two and one-half hours before subcutaneous transplantation into the right dorsolateral thoracic region. Grafts were recovered at postoperative intervals up to 14 days. Histological sections were obtained from the right and left axillary and brachial lymph nodes of hosts bearing allografts, and isografts, and from one intact and three sham operated controls. On recovery all nodes of controls showed large numbers of pyroninophilic lymphoid cells whereas none of those from transplant carrying hosts revealed a greater increase in the number of these cells when compared with controls. No cutaneous reactions were seen when graft bearing hamsters were intradermally injected with CB strain, cheek pouch, epithelial cells or (CB x MHA) F1 hybrid lymph node cells. Histological examination of allografts revealed no infiltration of transplants or graft beds by excessive numbers of lymphocytes, as is usually seen in the classical immune rejection. Haley and Costich concluded that allografts of hamster teeth do not elicit a host immune response. Haley and Costick also concluded that the allograft cells were not viable, since transplants had been immersed for two and one-half hours in a thimersol solution prior to grafting, hence only the antigenicity of the hard tissues was being assessed.

Two through six month old inbred male MHA hamsters received subcutaneously, just below the axilla, allografts, isografts and autografts of two molars each from adult hamsters (Haley and Costich, '69). The allotransplant molars were obtained from inbred CB hamsters. All grafts, with the exception of four allografts, were treated for two and one-half hours in an aqueous solution of merthiolate and were considered to be nonviable when transplanted. Grafts were recovered between one and 84 days. Axillary and brachial lymph-
nodes were recovered from all hosts. Histological observations on axillary and brachial nodes draining allografts revealed no significant difference in the number of large pyroninophilic lymphoid cells, in the paracortical regions of nodes, between hosts and controls. Intradermal injections of viable allogenic (CB x MHA) F₁ hybrid lymph node cells, into hosts bearing allografts, did not elicit a cutaneous reaction.

Histological examination of recovered transplants, including viable allografts, revealed no evidence of rejection. Only a few lymphocytes were observed in the fibrous tissue surrounding transplants of long duration which indicated a chronic inflammatory response rather than the classical immune reaction. The inflammation observed in grafts consisted of polymorphonuclear cells and macrophages and not the lymphocyte infiltration of grafts as would be seen during a typical immune rejection response. Furthermore, this response subsided by 14 days and was regarded as minimal at eight weeks. The necrotic pulp of grafts had been replaced by granulation tissue. It should be pointed out that no signs of rejection of alveolar bone fragments which had been transplanted with the teeth were evident. Haley and Costich felt that no resorption had taken place following transplantation. The authors concluded that the hard tissues of the hamster are either not antigenic, or so weakly antigenic, that the means of detection employed could not reveal the response. It was suggested that incompatibility of only one strong histocompatibility factor might not be sufficient to elicit a response to hamster teeth. The investigators felt that the histocompatibility requirements for survival of the hard tissues of mature teeth can be lower than those for skin.

D. Effect of Hormones

1. Cortisone
The effect of cortisone was studied on tooth germs from 20 day old guinea pig fetuses transplanted into the anterior eye chamber of young adults of both sexes (Fleming, '53b). Following transplantation, 24 of 48 hosts each received 2.5 mg of cortisone acetate intramuscularly for eight successive days. Injections were discontinued after eight days due to severe loss of weight and poor appetite. Grafts in cortisone treated hosts appeared to be vascularized within 24 hours, whereas control grafts required four to five days. The initial growth of transplants in cortisone treated animals was enhanced, but after those in controls had become revascularized, their growth surpassed that of treated animals. The cortisone treated animals also revealed prominent masses of red blood corpuscles, in large vascular spaces surrounding grafts which were notably absent in controls.

When compared with controls, cortisone treated grafts did not reveal as early an attachment to the iris. An absence of lymphocytes was noted for the duration of hormone treatment; however, immediately following cessation of treatment, the grafts revealed a lymphocytic attack and an inhibition of growth. Many cortisone treated grafts were ultimately resorbed. Osteodentin formation observed in non-treated transplants was absent in hormone treated transplants and calcification was retarded.

In a later review Fleming ('55b) reported that his cortisone treated hosts showed tooth germ transplants with pulpal capillaries generally engorged with red blood corpuscles, but neither the presence of endothelial cells nor additional capillary growth was detected. The pulps also contained larger than normal numbers of cells which appeared to be immature.

Thirteen and 14 day old fetal and one to 12 hour old newborn hamster half-mandibles were transplanted into the cheek pouches of treated and non-
treated young adult hamsters receiving subcutaneous injections of cortisone at a daily dosage of 2 mg/100 gm body weight (Kneussl, '66). Cortisone administration was begun on the day of, and one or two days prior to, transplantation and continued until the end of the experiment.

Fetal and newborn mandibles did not grow in either cortisone treated or control hosts. Incisors of grafts also did not reveal growth in treated or control animals. Only one molar revealed growth and differentiation in a treated host. In this tooth, the formation of enamel and dentin apparently was not affected by cortisone treatment. Vascularization of transplants was not enhanced by cortisone treatment, nor did such treatment prevent connective tissue invasion or replacement of grafts in most cases. A decrease in vascularization, increased resorption and more severe necrosis were seen in all but one of the cortisone treated transplants.

2. Estrogens and Androgens

Fleming ('56b) reported that tooth germs from 25 to 35 day old fetal guinea pigs, homologously transplanted into the anterior eye chamber and brain of ovariectomized guinea pigs, matured more slowly but epithelial and mesenchymal tissues were more functionally active, and for longer periods, than in similar grafts in intact female hosts. Growth of transplants was enhanced in ovariectomized females and more pre-enamel and predentin formation was seen in both brain and eye transplants. Frequently, such teeth were larger on recovery than were comparable intact teeth in host jaws. Some ovariectomized females received intramuscular injections of 1.0 mg of diethylstilbesterol, three to five times weekly, for four weeks. Growth of grafts in such hosts was greater than that seen in normal hosts, but usually not as great as that seen in non-treated ovariectomized hosts.
Maximum vascularization of transplants was maintained for longer periods in ovariectomized females and the pulps of grafts in non-treated and hormone treated hosts showed more blood vessels than were seen in normal controls. The blood vessels of transplants in hormone treated hosts were engorged with red blood corpuscles and small hemorrhages were often seen in pulps. A greater pulpal cellularity, which persisted for longer intervals, was seen in non-treated and hormone treated ovariectomized hosts than in normals. The dentin formed in the transplants of castrates was of a regular tubular nature; however, calcification was retarded. Fleming concluded that castrated hosts revealed a decreased antagonistic graft response since connective tissue reactions and lymphocyte accumulations were less pronounced.

Fleming ('58) homologously transplanted guinea pig tooth germs into the anterior eye chamber and brain of castrated male and female guinea pigs. Stilbesterol was administered intramuscularly to female castrates and testosterone to male hosts in a dosage of 1.0 mg per injection three times weekly. Histological observations showed that vascularization of transplants in such hosts was maintained longer than in normals. The administration of hormones increased vascularization. As the injections were continued, the small vessels in the pulps of transplants increased in both size and number, ultimately crowding out odontoblasts and other pulpal cells with the resultant interruption of normal growth and development of teeth. A significant increase in the number of red blood corpuscles in the connective tissue vessels surrounding grafts was also seen.

Zussman ('65) subcutaneously transplanted tooth pulps of incisors minus enamel organs, recovered from W/Fu adult rats, into 14 entire litters (130 animals) of two to three day old W/Fu rats. Two subcutaneous transplants
were placed in the neck of each host. Seven litters received subcutaneous implants of pellets containing 0.5 gm of diethylstilbestrol in cholesterol at time of transplantation. Grafts were recovered at two day intervals between one and 145 days. From 68 hormone treated hosts, 124 pulp transplants were recovered while from 62 controls, 120 grafts were recovered.

At five days, histological examination of non-treated control grafts showed columnar cells arranged around a loose fibrous connective tissue of the pulp. The latter revealed lymphocytic infiltration, plasma cells and multinucleated giant cells. At ten days, capillaries had appeared in the increasingly larger core of loose fibrous tissues surrounded by hyperchromatic nucleated columnar cells. An amorphous, eosinophilic material was seen about these cells as well as a central adjacent PAS positive fibrillar network. By three weeks the amount of fibrillar material had decreased but the amount of eosinophilic, amorphous material, representing a newly formed matrix, had increased. After four weeks, cells now identified as the original odontoblasts, had replaced the central fibrous core of the graft, and were arranged adjacent to the amorphous material.

At five days following transplantation, the hormone treated grafts showed a greater cellular distortion than was seen in non-treated grafts, and odontoblasts had undergone replacement with a fibrillar tissue. Multinucleated giant cells, which were seen at five days in controls, were not observed in grafts in treated prior to 10 days. The junction between host and graft tissues seen in treated animals revealed a more extensive fibrillar and tubular network. Increased fibrosis of the central core was seen. At two weeks the hyperchromatic nuclear cells were smaller than those of non-treated grafts. At two weeks the hyperchromatic nuclear cells were smaller than those of non-
treated grafts. At four weeks, the central fibrous region showed reorganization and a scant amount of amorphous, eosinophilic matrix surrounding clusters of cells. A greater host-graft tissue reaction was detected in treated grafts. Older treated grafts showed small cells oriented along thick, almost lamellated, layers of an amorphous eosinophilic substance surrounded by an intensely staining tubular and fibrillar material.

Zussman concluded that the increase in fibrous tissue formation, and the delayed cellular restoration in hormone treated grafts, resulted from an initially delayed matrix formation which later was greater in amount and more fibrous than that of controls. The odontoblasts in hormone treated and control grafts formed osteodentin rather than tubular dentin. The author also concluded that the increased fibrosis and PAS positive fibrillar material, seen in treated hosts, could have been due to the increased vascularization observed following hormone administration.

E. Effect of Immunosuppressive Drugs

1. 6-Mercaptopurine

Morris ('62) investigated the effect of 6-mercaptopurine (6-MP) on the Rhesus monkey and its effectiveness in reducing the immune reaction as measured by the suppression of circulating antibodies to bovine serum albumin. A solution of 6-MP in a 1 N base and honey was fed in daily doses of 12 mg/kg for 14 consecutive days. The decreased reaction of 6-MP treated monkeys to bovine serum albumin showed that such a dosage prevented antibody formation against a foreign protein.

Morris ('63) administered 6-MP for two weeks, beginning at time of transplantation, to monkeys that had received autologous and homologous transplants of unerupted central incisors. Controls were non-treated monkeys which
had undergone the same transplantation procedure. Histological observations on control grafts revealed a rapid degeneration of pulps into a fibrous tissue showing flattened and sparse pulpo-dentinal cells. The homologous transplant in the 6-MP treated host on the other hand, revealed a normal appearing pulp showing elaboration of a secondary dentin during the three to six week interval following transplantation. The autologous graft in the same treated host showed a greater quantity of secondary dentin. At eight to 12 weeks after transplantation, the homologous graft had pulp which revealed degenerative fibrous tissue, cessation of secondary dentin formation and osteogenic tissue in the apex. Secondary dentin had continued to form in the treated autograft during the same eight to 12 week interval, but the pulp was not fibrous in appearance. The author concluded that if rejection had occurred, it was not typical since no round cell infiltration or necrosis were seen in any of the transplants from treated animals and vascularization of pulps appeared to be normal.

2. Methotrexate

To investigate the immunosuppressive effect of methotrexate on tooth transplants, Broughton ('67) homologously transplanted mandibular and maxillary tooth buds, from a 50 day old fetal guinea pig, into the subcutaneous space in the axilla of 10 adult inbred guinea pigs. Five hosts received 5 mg of methotrexate intraperitoneally beginning one day before transplantation and continued daily for three weeks and then once every other day until host was sacrificed. A second group of five non-treated hosts served as normal controls. Grafts were recovered beginning on the fifteenth postoperative day and weekly thereafter. Two methotrexate treated hosts were lost through death. Histological examination of grafts, recovered from methotrexate treated hosts,
showed normal dentin, predentin and enamel formation; nevertheless, some areas of the pulp had been replaced by osteodentin. The rejection reaction usually associated with transplanted teeth was found to have had little effect on the growth and development of teeth in grafts from treated animals and was considered to be negligible. Control grafts in non-treated animals revealed a severe host-graft inflammatory response, dentin resorption and an irregular formation of enamel. Broughton concluded that the administration of methotrexate had suppressed the inflammatory response usually associated with transplanted teeth.

F. Mandible Transplantation Sites

1. Brain

In a study utilizing the brain and cervical subcutaneous space in the neck as transplantation sites, in two to four week old albino rats, Willis ('35) reported growth and differentiation of molars and incisors in transplanted fetal intact heads, lower jaws, upper and lower jaws together, and upper jaws, recovered between four and 13 weeks after implantation. Only one incisor was found in three implants of fetal heads 13 weeks later. Two of six lower jaw transplants into brains each revealed one well formed tooth while another showed only a part of a tooth; however, two teeth were found in lower jaws grafted into the necks of the same hosts four weeks after transplantation. Only two teeth were observed in transplants of upper jaws into the brains of six hosts while none were recovered from subcutaneous jaw grafts three to seven weeks later. Five teeth were revealed in nine hosts where combined upper and lower jaws had been implanted into brains. Only one incomplete tooth disclosed growth and differentiation where near term fetal heads had been transplanted both intracerebrally and subcutaneously in nine rats.
In summary, the series of subcutaneous cervical transplants showed 13 of 23 surviving grafts while the intracerebral series showed 21 of 23 recovered within 13 weeks following transplantation. Surviving epidermis, cartilage, bone and skeletal muscle were also found in transplants, but salivary gland tissue, adipose tissue and smooth muscle were less frequently seen.

2. Intramuscular

Fetal rat mandibles, three days before birth, were transplanted into the anterior eye chamber, leg muscle, and brains of young female rats (Baker, 136). Successful grafts were recovered from all three sites; although, the most successful ones were found in leg muscle. Forty days later the transplant in this site had grown one-third larger but was only half the size of the intact control mandible. The bone in these transplants had undergone resorption, which always occurred at the sites of muscle attachment at the ramus, while the body of the mandible had revealed little resorption after 60 days.

3. Subcutaneous

Kostecka (138) reported results on the transplantation of mashed parts of jaws from 11 mm fetal mice into adult mice. Two of eight such grafts showed survival and growth of four teeth which were smaller than controls but revealed normal dentin and enamel and atrophic pulps. The cartilage and bone of these grafts revealed growth. Parts of subcutaneously transplanted mandibles containing teeth, from 20 mm fetal mice, did not reveal growth of teeth. When parts of upper and lower jaws from 24 mm fetal mice were subcutaneously transplanted into 26 adult mice, growth and normal differentiation, but atrophic pulps, were obvious in ten of 18 recovered teeth. Two of four grafts of jaws from newborn mice, subcutaneously transplanted into the thighs of adults, disclosed growth of teeth. In these experiments, the author reported that trans-
plants of older fetal parts of jaws more frequently showed growth of bone, cartilage and teeth, however, surviving teeth were smaller than normal teeth. It should be noted that in all experiments except the last series, the epithelial cyst formation was frequently encountered.

Ostergren (1958) reported the results of subcutaneous transplantations of 14 day old, fetal, mouse half-mandibles, into adult mice of the same inbred strain. He observed vital periosteum and thickened bony walls around marrow spaces in grafts recovered at intervals up to 40 days after implantation. In less than half the mandibular transplants, one or two molars had developed in each and these were less than half normal size. No evidence of further growth or development of incisors was seen. The mandibles were smaller than normal and had not undergone morphogenesis since most of them were thin and greatly distorted. A simple bony alveolus had formed around surviving molars.

Traux (1958) subcutaneously transplanted half-mandibles from two day old mice into adults of the same strain. Transplants recovered within a 100 day interval revealed no growth or eruption of teeth although growth of bone had occurred.

Flem (1959) subcutaneously transplanted half-mandibles from newborn mice into adults of the same inbred strain. He reported smaller than normal and malformed molars in grafts recovered up to 50 days subsequently. A well formed incisor was found in one of the grafts.

Half-mandibles from two day old mice were subcutaneously transplanted into the dorsolateral lumber region of 28 immature females of the same strain (Truax, '60). Eighteen mice with intact mandibles served as controls. Transplants were recovered at intervals between two and 102 days. Bone formation had occurred whenever transplants were revascularized. Growth and development
of teeth was not seen nor did mandibles reveal normal size or shape. Bone formation occurred at the surface of grafts but gonion and condylar cartilages were replaced by bone. Resorption was first disclosed at 20 days and was seen in all grafts by 35 days after transplantation.

Soni and Hayden ('66) subcutaneously, heterotransplanted parts of mandibles and maxillae with intact tooth germs, from 30 day old fetal guinea pigs, into the axillae of adult mice. A group of 15 normal non-treated hosts received grafts which served as controls. All transplants were recovered at the end of three weeks. Histological study on control grafts revealed a very severe host rejection response and distortion of the gross form of the teeth. First and second molars revealed retarded development and growth although some formation of dentin and of enamel had occurred.

In another series, teeth from 15 transplants in hosts pretreated with three successive injections of guinea pig serum, showed greatly decreased host rejection responses when compared with controls. Development, growth and survival of such teeth appeared significantly superior to that of controls. The teeth from pretreated hosts also showed more dentin and enamel formation. In a third series, grafts in hosts pre-treated with three successive injections of pooled, guinea pig, embryonic tissue extract, revealed growth, differentiation and development comparable to that seen in the serum treated hosts. A decreased host inflammatory response was also noted. Normal enamel and dentin formation had also occurred and there appeared to be no interference with tooth formation in this series. Soni and Hayden concluded that guinea pig serum, or embryonic tissue extract, administered prior to transplantation modified the immune reaction thus rendering the host more tolerant to transplants. They also felt that the histocompatibility response
elicited when a jaw with intact teeth was heterotransplanted, was more favorable than that seen in previously reported studies from the same laboratory where tooth germs had been heterotransplanted alone.

Abrams and co-workers ('66) transplanted jaws with teeth intact, from 28 day old fetal guinea pigs, into both axillary regions of 24 adult guinea pigs. Twelve hosts each received two injections of guinea pig embryo extract before transplantation while the remaining 12 hosts served as non-treated controls. Grafts were recovered at two, four and eight weeks postoperatively. Histological examination revealed a decreased inflammatory reaction and an increase in survival, growth and development of grafts in extract treated hosts. Controls revealed osteodentin in pulps and an altered dentinogenesis. Polarizing microscopy and microradiography showed a dissolution of enamel, and in some instances also of dentin in controls. The formation of both dentin and enamel was superior in extract-treated grafts.

4. Cheek Pouch

Thirteen of 18 newborn hamster half-mandibles, transplanted into the cheek pouches of young adults by means of an intraoral procedure, were recovered at intervals of five to 113 days after surgery (Kneussl, '66). Five of the grafts were not recovered, either due to death of the hosts, resorption, or loss before recovery. Only three of the recovered grafts revealed one molar each, all of which showed growth and differentiation. In a second series, four of 17 newborn half-mandibles, transplanted into the cheek pouches of adults by an extraoral procedure, showed survival and differentiation of only one molar each on recovery at 15, 18, 20 and 22 days later. In a third series, three of five 13 day old fetal mandibles transplanted into the cheek pouches of adults intraorally were recovered from
seven to 20 days later. Surviving teeth were not found in this series. In experiments where molars survived, growth was normal but retarded as indicated by their small size. The molars revealed formation of dentin and enamel and were surrounded by a bony alveolus. Incisors did not survive in any of these experiments; most of them were avascular and necrotic, while others revealed intensive inflammation. Neither fetal nor newborn mandibular grafts showed normal growth although regions of limited bone formation were observed. The absence of surviving teeth was attributed to insufficient revascularization, probably a consequence of the osseous barrier and involvement of the graft in an immunological reaction.

5. Spleen

Jones ('63) isologously transplanted mandibular-halves obtained from newborn rats and mice, into the spleens of adult rats and mice of the same strains. Although disturbances in normal mandibular growth were seen, bone formation had nevertheless occurred. Both incisors and molars survived and revealed growth, differentiation and eruption.

G. Effect of Immunosuppressive Drugs on Transplants of Other Tissues

1. 6-Mercaptopurine

a. Rabbit

Meeker and co-workers ('59) reciprocally exchanged full thickness skin homografts on abdomens between New Zealand and black and white Dutch rabbits. In the first experiment 6 mg/kg/day was administered intravenously at time of transplantation and was continued until the grafts were sloughed. The mean slough time on 10 treated hosts was 17.5 days postoperatively as compared with 14.4 days for 10 non-treated controls. Four of the treated animals with viable grafts died at 5, 12, 15, and 27 days after treatment.
respectively. Intensive round cell infiltration was seen in histological sections of homografts.

In a second experiment, 12 mg/kg/day was given intravenously from the day of transplantation until the transplants sloughed. Seven of 10 treated hosts with viable grafts died during the course of treatment at an average of 18.4 days subsequent to transplantation. The three surviving treated animals revealed a mean slough time of 22 days for homografts. Nine non-treated controls showed mean slough times of 14.1 days. All but one of the treated hosts revealed progressive weight loss and all showed a decrease in the number of circulating white blood cells.

In the third experiment, 10 hosts received 12/mg/kg/day of the drug beginning at the time of grafting and continued for 14 days. One of the 10 treated hosts with a viable graft died 23 days after transplantation. The nine remaining hosts disclosed a mean homograft slough time of 24.3 days as compared with 14.1 days for the non-treated controls. All treated homografts in this experiment were rejected between 26 and 28 days after grafting, from which it was concluded that additional treatment would have been required to maintain suppression of the homograft response.

The results of these experiments revealed that 6-MP in the doses employed, suppressed the homograft response to skin grafts in rabbits, but it was also shown that this treatment may be lethal in many instances. The toxicity of the drug was not attributed to bone marrow suppression since a large number of other hosts had died prior to the appearance of leukopenia.

Hubay and co-workers (160) undertook a series of experiments on the effect of 6-MP on the survival of split thickness, skin homografts on rabbits. Five non-treated control rabbits rejected skin homografts at a mean survival
time of 11.2 ± 2.0 days while 14 received 12 mg of 6-MP/kg/day intravenously, and another group of 12 the same dosage intraperitoneally, rejected their grafts at 9.6 ± 0.5 and at 10.5 ± 1.5 days respectively. They were unable to confirm the observations of Meeker and co-workers ('59), that dosages of 12 mg/kg/day, given intravenously, prolonged survival of skin homografts in rabbits.

Schwartz and co-workers ('60) observed as much as a three-fold increase in survival of skin homografts on the ears of rabbits when treated with 6-MP. Sixteen controls revealed a mean rejection time of 6.8 days whereas nine treated hosts, given subcutaneous injections of 6 mg/kg/day of the drug for two weeks, disclosed a mean skin homograft rejection time of 10.0 days. Skin homografts in a second group of seven rabbits receiving injections of 10.0 mg/kg/day for two weeks, and then the same dose on alternate days, revealed mean graft rejection times of 13.9 days. Seventeen hosts given 12 mg/kg/day for an identical period showed mean rejection times of 17.8 days. A final group of four hosts given oral doses of 12 mg/kg/daily for two weeks and then on alternate days rejected grafts at 14.0 days. Rejection of grafts in drug treated hosts was frequently slower and required several days for completion whereas the onset of rejection in controls was acute and was usually completed within one day.

To evaluate the effect of 6-MP on survival of second set skin homografts, a second skin homograft was exchanged between the same pairs of rabbits two weeks after rejection of the first set. Doses of 6, 10, and 12 mg/kg/day did not affect graft rejection while rejection times were comparable with second set grafts on non-treated controls.

The histological study on homografts retained in drug treated hosts
before rejection revealed no significant differences from autografts carried out on the same animals. Drug treatment did not appear to retard healing of skin homografts since neither vascular nor fibroblastic proliferation were impaired. It was noted that where rejection of homografts had begun, it continued with no evidence of a partial suppression. Schwartz and co-workers concluded that the onset of the reaction was delayed when effective doses of 6-MP were given; however, no permanent tolerance occurred since second set rejection times, at all the dosages employed, were similar to those of non-treated controls.

Meeker and co-workers (160) observed the effects of 6-MP, on full thickness skin homografts, on abdomens, exchanged between albino New Zealand and black and white Dutch rabbits. Four drug regimens were employed in the first experiment. Non-treated control skin homografts showed mean graft rejection values of 14.7 and 14.1 days. The first group of seven 6-MP treated rabbits received 6 mg/kg/day beginning at time of grafting and continued until time of rejection which occurred at 18.4 days. A second group of seven animals given 12 mg/kg/day, initiated at time of transplantation, revealed a mean transplant slough of 23.3 days. The third group of 10 hosts received 12 mg/kg/day for 14 days and showed a mean slough time of 24.3 days. The fourth group of six hosts received 25 mg/kg/day for three days before grafting and an additional 12 mg/kg/day for nine days thereafter. This series revealed a mean slough time of 20.7 days. An increase in graft survival time occurred in all 6-MP treated rabbits, but those receiving 12 mg/kg/day for 14 consecutive days were the most successful. These grafts continued to survive for a period following discontinuation of drug administration. The results led the investigators to conclude that suppression of the immune
response occurred during the period of drug treatment.

To evaluate the effects of 6-MP pretreatment on skin homografts in rabbits, ten prospective hosts received daily doses of 12 mg/kg for 14 days prior to grafting. Only three of these survived treatment and they revealed a mean graft survival of 14 days. A second group of 11 rabbits received 10 mg/kg/day for 14 days prior to grafting and only three of these survived the treatment. These showed a graft survival range of 15 to 20 days. In a third group, eight rabbits were given 10 mg/kg/day for a two-week period; of these only three survived treatment, and grafts were rejected between seven and 14 days later. Non-treated control grafts showed mean survival times of 14.5 days. The results of these experiments clearly indicated that 6-MP pretreatment did not significantly increase graft survival and that the greatly increased host mortality indicated an inability to tolerate dosages administered.

In another experiment, eight rabbits received 10 mg/kg/day of 6-MP beginning seven days after skin homografts. Injections were continued until grafts were rejected. In this experiment only three hosts survived showing a mean graft survival time of 14.1 days whereas in eight non-treated controls it was 13.6 days.

To investigate the effects of 6-MP on the rejection of second set skin homografts, 14 rabbits each received a second skin homograft two weeks after rejection of the first. Eight of these received 18 mg/kg/day beginning on the day they received the second graft. Injections were continued through rejection. In this experiment mean graft survival times of only 9.2 and 10.2 days were seen in treated and control animals respectively. The investigators concluded that 6-MP had no effect on second set skin homografts.
Andre and co-workers ('62) carried out skin homografts between rabbits which had received daily subcutaneous doses of 12.0 mg/kg of 6-MP from time of transplantation until grafts were either rejected or recovered. In successful cases, only minimal enlargement of germinal centers and lymphoid follicles of lymph nodes was seen between five and seven days subsequently. Atrophy of nodes occurred as treatment was continued revealing depletion of lymphoblasts and medium sized lymphocytes. All treated hosts with successful grafts disclosed moderate weight loss, anemia and leukopenia.

In another experiment on rabbits, Andre and co-workers administered daily doses of 12 mg/kg of 6-MP seven days prior to skin grafting. All treated hosts rejected grafts within the same time interval as seen in non-treated controls. The reaction in lymph nodes and spleens of treated animals was as vigorous as that seen in non-treated controls. When injections were delayed for two, three, or four days after transplantation, grafts were rejected within the normal non-treated control limits. The lymph nodes and grafts of treated hosts were found to reveal all the signs of rejection. No increase in graft survival time was noted when second set skin homografts were carried out in 6-MP treated hosts. Observations on lymph nodes and spleens in treated and non-treated hosts were comparable although the number of hemocytoblasts was reduced in the former. Pretreatment of hosts bearing second set skin homografts also did not prolong survival of grafts.

Permanent survival of grafts was not encountered in any of these experiments. Lymph follicles and germinal centers were observed to enlarge during the process of graft rejection and large primitive cells, called hemocytoblasts by these investigators, proliferated in untreated rabbits rejecting skin homografts. None of these changes were seen in 6-MP treated
rabbits with successful homografts. Extensive lymphoid atrophy, in lymph nodes draining grafts, and an almost exclusive cell population of small lymphocytes was observed in treated animals. Hemocytes were not seen where homograft rejection failed to occur. The authors concluded that retardation of the homograft response in these experiments was the result of an inhibition of growth of the nodular hemocytes. Since 6-MP administration before or after grafting was not effective in retarding graft rejection, Andre and co-workers concluded that administration of the drug in relation to the timing of antigen (grafting) administration was crucial because it appeared to inhibit the formation of hemocytes. Furthermore, it was seen that once the reaction had begun, 6-MP failed to suppress the formation of hemocytes and subsequently failed to suppress graft rejection. The investigators also believed that the hosts probably were able to form some immunologically competent cells that were resistant to the suppressive effect of 6-MP.

Powell and co-workers ('62) studied the effects of 6-MP on skin homograft survival in rabbits. The drug was administered intravenously in daily doses of 12 mg/kg or 120 mg/kg beginning on the day of grafting. Grafts in treated hosts did not reveal greater survival than those of non-treated controls. The higher dosage was toxic to hosts. A daily dosage of 12 mg/kg of 6-MP also did not increase survival of second set skin homografts.

b. Mouse

Employing three inbred strains of mice, two of which are similar at the H-2 locus and the third differing at this locus, McLaren ('61) observed that total daily doses of 0.30 mg and 0.60 mg of 6-MP per mouse given intramuscularly for 14 consecutive days resulted in prolonged survival of skin
grafs exchanged between these strains, but no permanent graft survival was seen. Surviving mice that had received 6-MP therapy, concurrent with a primary skin graft, showed an accelerated rejection response when given second grafts. When spleen cells were injected concurrently with 6-MP therapy, into hosts differing at the H-2 locus, and after an interval of 9 weeks following cessation of drug therapy skin homografts were carried out, survival times of grafts were not prolonged when compared with control groups. Injection of bone marrow cells into similarly 6-MP treated hosts also did not result in a prolonged survival of skin grafts. A state of persisting immunity was disclosed by "white" graft rejection. These studies revealed that in mice the survival of skin grafts could be prolonged by 6-MP therapy, but even when the donors and hosts shared the same H-2 locus characteristics, grafts were rejected when drug administration was discontinued. In another experiment a massive injection of spleen cells, from donors sharing similar H-2 histocompatibility locus characteristics, was given after 14 daily 6-MP injections and tolerance to skin homografts from the donor strain was established. When the H-2 locus characteristics of the donor and host differed, identical treatment did not produce tolerance. It was concluded that the weaker the genetic difference between donor and host, the more easily tolerance can be induced.

Sutton and co-workers (1963) observed a significant increase in the survival time of skin homografts, from female mice of one inbred strain transplanted into females of another inbred strain, when 6-MP was administered in six daily 20 mg/kg doses. Noticeable increase in graft survival time occurred also when the drug was given in six or 12 daily 50 mg/kg doses.

Kimball and co-workers (1965) observed a two day increase in survival
time of skin homografts from female C3H/Hej mice to adult female AKR/j mice which had received daily 10 and 15 mg/kg doses of 6-MP beginning one day before transplantation and continued until the graft had sloughed. Donor mice had also received 6-MP treatment before transplantation. Drugs were administered daily in two equal doses. In another experiment AKR/j mice received injections of tanned sheep blood cells concurrent with injections of 15 mg/kg/day of 6-MP. A reduction in the hemagglutination response was noted on the fifth day. In another series a toxic dose of 60 mg/kg/day was begun the day before challenge with sheep cells and continued for four days thereafter. These mice revealed hemagglutinin titers about one-fourth of that seen in non-treated controls at five days. These investigators felt that 15 mg/kg/day was the highest dosage which could be employed for extended therapy, but this dose had only a minimal effect on transplant survival in experiments employing strains of mice which did not have great H-2 histocompatibility differences.

Utilizing inbred strains of female mice, Kimball and co-workers (167) observed a median survival time of 17.0±0.7 days of skin grafts on tails of hosts which had received daily doses of 75 mg/kg of 6-PM for three days after grafting. Controls on the other hand had rejected transplants at 14.0±1.0 days. When other mice of the same host strain were injected with tanned sheep blood cells and treated with 6-MP at the same dosage, and under the same conditions, inhibition of hemagglutinin formation against the sheep cells was observed within five days. When Swiss mice were used and tanned sheep cells were injected, 60 mg/kg given for four days beginning on the day of antigenic stimulation revealed only partial inhibition of 19S antibody formation and preferential inhibition in the formation of 7S antibodies.
Kimball and co-workers concluded that 6-MP produced a minimal increase in skin homograft survival time and a strong inhibition in hemagglutinin response involving humoral antibody.

Other investigators have observed that host treatment with 6-MP produced only a slight, if any, increase, and in some cases a shortening of graft survival time in mice.

Studies on the effect of 6-MP on survival of skin homografts between strains of inbred mice were made by Meeker and co-workers (160). Reciprocal grafts between strains B1 to C and C to B1 were performed in each experimental group. In the first experiment, doses of 72 mg/kg/day of 6-MP administered beginning on the day of grafting, showed a mean rejection time of 12 days in both strain combinations, whereas controls showed transplant sloughs at seven and eight days. In a second experiment, 100/mg/kg/day was given beginning at time of grafting and survivals of 9 and 12 days were noted compared with seven and 11 days in control groups. In the third experiment, 150 mg/kg/day was administered beginning at time of transplantation and survival times of grafts in two strain combinations were seven and eight days, whereas those of both controls were seven days. These results indicated that large doses of 6-MP failed to produce an increase in survival time of grafts.

In another experiment by Meeker and associates, single massive doses of 600 mg/kg, given on the day of grafting, failed to show an increase in graft survival time; however, only two of 20 hosts had survived until grafts were rejected. Different doses of 6-MP, accompanied by donor strain spleen cell injections, failed to increase graft survival, but there was some improvement in the survival of hosts.

Six-mercaptopurine was not as effective in prolonging survival of skin
grafts in the mouse as was observed in the rabbit during experiments carried out by Meeker and co-workers (1960). The effect of the drug was found to vary according to the species involved. Meeker and co-workers believed that maximum survival time of skin homografts was not attained due to the toxicity induced by the excessive doses administered. A large number of hosts had died while retaining viable skin transplants after control grafts had been rejected. Also of significance were the observations that pretreatment of hosts increased host mortality which was attributed to increased toxicity of the drug. Meeker and associates suggested that the significant decrease in drug toxicity in graft bearing hosts may be due to a nonspecific stimulation of the reticuloendothelial, lymphoid and hematopoetic systems by the homografts, as the protective mechanism, rather than stimulation of the adrenal cortex as a result of surgery and anesthesia. The authors concluded that to be effective 6-MP treatment must begin at the time of grafting and must be continued thereafter, and that the effect of the drug appeared to be dependent on the dosage employed. The investigators theorized that increased graft survival was the result of 6-MP inhibiting the metabolic processes essential for development and expression of the host immune response.

Hubay and co-workers (1960) undertook a series of experiments on the effect of 6-MP on the survival of full thickness skin homografts in the mouse. Fifty-eight control mice rejected skin homografts at 11.0 ± 0.7 days whereas those receiving a daily dose of 12.0 mg/kg rejected grafts at 10.9 ± 1.8 days. No increase in survival time of skin homografts was observed.

In initial experiments, Dineen and Szenberg (1961) evaluated the possibility of inducing immunological tolerance to skin grafts, exchanged between strains of inbred mice, by utilizing injections of 6-MP in doses of
0.25, 0.50, 1.0, 1.5, and 2.0 mg given daily for seven to 10 days before and for several days following transplantation. Several groups of 6-MP treated hosts were also injected with spleen cells from the graft donor strain during the period of drug treatment. Mean survival times of skin grafts from C57Bl mice to C3H mice were only extended beyond that of controls by three days. This occurred only in those hosts showing the greatest degree of lymphoid tissue involution attributed to the more toxic doses of 6-MP. When C3H skin was transferred to C57Bl mice, an increase in survival time was not observed in hosts which had undergone identical treatment. No increase in survival time occurred where skin grafts were exchanged between closely related mice of the inbred AKR and C3H strains when hosts were treated with 6-MP.

Rubin and Lewis ('61) observed that maximum tolerated doses of 6-MP, administered intraperitoneally in adult mice, did not produce any increase in tolerance to skin homografts.

Powell and co-workers ('62) studied the effects of 6-MP on survival of skin homografts in mice. Daily intraperitoneal doses of 12 mg/kg, begun at time of grafting and continued until time of rejection, did not prolong the period of survival of transplants beyond that observed in non-treated controls.

Amiel and co-workers ('64) studied the effects of 6-MP on survival of allogenic skin transplants on tails of inbred mice. Six-mercaptopurine was given in doses of 24 mg/kg for six days and then 12 mg/kg on alternate days for an additional 14 days. Grafts of DBA/2 skin were placed on (CBA x C57Br) F1 hybrid hosts. Controls consisted of skin homografts on non-treated mice. Several different groups of hosts were employed: (a) treated before trans-
plantation, (b) treated before and after, and (c) those only treated after grafting. Treated groups revealed positive but not statistically significant increases in survival time, of AKR skin on (CBA x C57Br)F₁ hosts receiving identical doses of 6-MP, treated before, treated after and treated both before and after transplantation, was prolonged; however, the differences in survival time, although not statistically significant, did indicate a slightly increased tolerance. On the other hand, mice receiving identical drug treatment showed an inhibition in response to Poliomyelitis virus when treatment was carried out before stimulus, before and after the introduction of the virus. This was believed to illustrate the importance of the type of antigenic stimulus on which the suppressive drug is treated, since identical studies by these investigators on suppression of the response to human albumin indicated that 6-MP had no effect. The authors concluded that 6-MP was only slightly effective in the mouse against the rejection of allogenic skin homografts, not effective in suppressing the response against human albumin, but was highly effective against the immune response to Poliomyelitis virus. Thus, they theorized that 6-MP had maximum activity when administered before the antigenic stimulus.

Nouza ('66) utilized inbred strains of mice differing only at the relatively weak H-3 locus, and observed that 40 mg/kg of 6-MP administered intramuscularly for 10 days before transplantation, and 10, 20, and 40 mg/kg given for 20 days after transplantation, had adverse effects on the survival of grafts since all grafts of ear skin were rejected by 20 days after grafting. Non-treated control grafts were rejected by 30 days. The mean rejection time, the time from the first signs of transplant damage to rejection in treated animals, was shorter than that seen in untreated controls.
Nouza concluded that the use of inbred strains of mice, differing only at the H-3 locus, revealed a greater sensitivity to the suppressive activity of a drug than would be observed in grafts exchanged between strains differing at the much stronger H-2 histocompatibility locus. The results of this experiment did not confirm the effectiveness of 6-MP as an immunosuppressive agent as has been reported by other investigators. Six-mercaptopurine in the doses employed had actually shortened the survival times of skin homografts in mice.

Utilizing inbred strains of mice, Stewart ('69) devised a series of experiments, employing models of decreasing histocompatibility differences, to evaluate the suppressive activity of 6-MP on cell-mediated immunity as revealed by survival of skin allografts. Six-mercaptopurine was administered in a short course of 50 mg/kg for five days beginning at time of transplantation, or in a lower daily dose of 15 mg/kg beginning from the day before to 14 days postoperatively. Neither dosage had revealed any significant increase in skin graft survival time, between strains incompatible at the H-2 locus, when compared with non-treated controls. Similar results were observed where the host and donor combinations were compatible at the H-2 locus. When strain combinations which had even weaker histocompatibility differences were employed, drug treatment also did not reveal any significant increase in graft survival time when both dosages of the drug were administered in the same manner as described above.

Stewart concluded that 6-MP did not significantly prolong skin allograft survival, even when histocompatibility differences between host and donor were decreased, and that 6-MP had little or no effect on cell mediated immunity, despite the fact that in the mouse this drug selectively suppresses
formation of humoral antibody.

c. Guinea Pig

Hubay and co-workers (1960) undertook a series of experiments on the effect of 6-MP on the survival of split thickness skin homografts in guinea pigs. Sixteen control guinea pigs had rejected skin homografts at 9.3±1.2 days. Ten which had received 6 mg/kg/day of 6-MP rejected grafts at 9.6±1.0 days while 12 which had received 12 mg/kg/day rejected transplants at 9.4±0.4 days. In another series, 12 hosts were given 48 mg/kg/day and these were found to have rejected grafts at 11.8±4.1 days. With the exception of the largest dosage, no significant increase in skin homograft survival time was observed in guinea pigs treated with 6-MP. These investigators observed that prolonged treatment was lethal to hosts and concluded that death did not appear to be due to a suppression of the function of bone marrow.

Powell and co-workers (1962) also studied the effects of 6-MP on skin homograft survival in guinea pigs. The drug was administered intraperitoneally beginning on the day of grafting and continued daily until time of rejection. Daily doses of 6, 12, and 24 mg/kg failed to prolong graft survival time; in fact grafts in experimentals were rejected earlier than those of controls. However, when 48 mg/kg/day was given on an identical schedule there was an approximate two day increase in survival time. Eight of 12 hosts had died during the course of the experiment attributed to the toxicity of the drug.

d. Rat

Thomas and co-workers (1961) reported only a brief increase in mean survival time of full thickness skin homografts on 241 Long Evans rats given various doses of 6-MP. Injections were initiated at intervals from time of
transplantation to 174 days before transplantation and treatment was continued until grafts had rejected. Twelve groups of rats, 14 to 42 animals each, received doses of the drug ranging from 20 to 350 mg/kg three times weekly. Homografts in controls revealed mean survival times of 11 days. The greatest survival time in experimentals was only five days beyond that seen in controls. High doses of 6-MP and long-term administration were not consistently effective in suppressing the homograft reaction although a few treated hosts receiving the higher dosages showed long graft survivals. Rejection of transplants within the survival range observed in controls occurred in most of the animals in the experimental groups. Pre-treatment with 6-MP also did not extend transplant survival time.

Santos and Owens (1'65) investigated the effects of 6-MP on the first-set response, in female Sprague Dawley rats, to skin homografts from female Lewis and BN rats. Six-mercaptopurine was injected once daily for five consecutive days or administered in a single dose. Single doses were approximately half of the previously determined LD50 and the dosage was 175 mg/kg. Single injections of 6-MP at two days before grafting and at five and two days after grafting showed median survival times for BN skin of 11.7±1.2, 12.6±1.5, and 12.5±1.6 days respectively as compared with controls of 11.0±0.2 days. On the other hand single identical doses of 6-MP given at identical times produced survival times of 13.5±1.2, 15.1±1.6 and 13.1±1.3 when skin from the Lewis strain of rats was grafted onto Sprague Dawley rats.

In a second experiment multiple doses of 6-MP (100 mg/kg/day) were administered intraperitoneally for five consecutive days. Drug administration was begun two and five days after grafting and four hours, two days and four days before transplantation. The longest mean survival time of the skin of
BN rats on Sprague Dawley rats in the series where the drug was given seven days after transplantation was 13.0±1.5 days, whereas non-treated controls showed mean survival times of 10.5±0.5 days. Utilizing an identical drug dosage and timing, but skin from Lewis strain rats grafted on Sprague Dawley rats, the median survival time of grafts, when the drug was given seven days after transplantation, was 16.4±1.5 days while in untreated controls it was 11.3±1.1 days.

Six-mercaptopurine was more effective in the rat when given at five and seven days after grafting than when given at other times; however, the time difference did not appear to have any great influence on survival of transplants. Weight loss, diarrhea, and depression of peripheral blood cell counts were observed in all animals and were signs of toxicity since dose levels of the drug were near the maximum tolerated. Single doses of 6-MP did not have much of an effect on the survival of first set skin homografts. Control homografts of BN and Lewis skin showed similar survival times in normal Sprague Dawley rats, but when immunosuppressive drugs were administered, skin grafts from Lewis strain rats on Sprague Dawley rats almost always showed longer survival times than grafts of skin from BN strain rats on Sprague Dawley strain rats. Santos and Owens suggested that there may be a closer genetic relationship between Lewis and Sprague Dawley rats than between the BN and Sprague Dawley combination, and that genetic differences may be enhanced through immunosuppressive therapy.

Hubay and co-workers (160) undertook a series of experiments on the effect of 6-MP on the survival of split thickness skin homografts in rats. Daily injections of 6-MP were given beginning at the time of transplantation. Fifty-eight control grafts in normal rats were rejected at 10.0±0.54 days
whereas 14 receiving 6 mg/kg/day were rejected at 9.0±0.9 days, 12 receiving 12 mg/kg/day revealed rejection at 8.2±1.3 days while in 16 receiving 24 mg/kg/day grafts were rejected at 10.6±1.0 days. Hence, no increase in survival time of skin homografts in rats was seen in these experiments. The investigators also reported that 6-MP when given for prolonged periods may be lethal and that death of hosts is not necessarily due to a depression in bone marrow function. The investigators concluded that the general debilitating effect of nearly lethal doses of 6-MP could account for the inconsistent suppression of immune responses to homografts observed by other investigators and should indicate caution in the interpretation of findings when utilizing this drug.

Powell and co-workers (162) also studied the effects of 6-MP on skin homograft survival in rats. Drugs were administered intraperitoneally beginning on the day of grafting and were continued daily until grafts were rejected. Daily doses of 3, 12, and 24 mg/kg did not prolong survival of skin homografts. Nevertheless, the investigators reported that dosages of 12 mg/kg did prolong the survival of second set skin homografts to a mean survival time of 9.2 days compared with a non-treated control second set survival time of 6.0 days.

2. **Imuran**
   
   a. **Rabbit**

   Polack (166) observed the effects of Imuran (Azathioprine) on the rejection of partially penetrating corneal homografts in adult rabbits. Two weeks after the corneal grafts were made, skin was transplanted on the abdomens of the same pairs of rabbits. Imuran in daily doses of 10 mg/kg was injected intramuscularly for 30 consecutive days subsequent to the skin
grafting. The corneal transplants showed no evidence of the hosts for periods of four to five weeks after the skin transplants. Twelve to 14 days following cessation of the Imuran therapy, five of the corneal transplants became vascularized and opaque. Corneal grafts in non-treated controls were usually rejected between 14 and 16 days after skin grafting.

In a second experiment, daily intramuscular doses of 10 mg/kg of Imuran were begun at three to four days following skin grafting on seven rabbits which had received corneal grafts two weeks previously. Drug administration was continued for at least two weeks. Opacity of the corneal transplants occurred in all seven of the grafts which were completely rejected.

In a third experiment, seven rabbits received 20 mg/kg/day of Imuran intramuscularly from the day of the first signs of rejection of the corneal grafts which had been carried out two weeks prior to skin homografting. Drug injections were continued for at least one week. Corneal graft rejection was not prevented, but opacification of the grafts was delayed and appeared to be less severe in nature than that seen in non-treated controls. One of the animals died and two others developed skin abcesses. Polack considered this dosage to be too toxic. Corneal grafts revealing opacity during drug treatment also disclosed cellular infiltration consisting primarily of lymphocytes and plasma cells. The corneal endothelium was destroyed, and a round cell infiltrate was seen in the limbus of eyes of treated hosts; nevertheless the degree of infiltration was less than that of controls.

In a fourth experiment, rabbits received both corneal and skin grafts in a manner identical to that described for the first. These animals were given subconjunctival injections of a suspension containing 0.1 mg of Imuran every second day for at least four weeks beginning on the day of skin graft-
ing. Observations were continued for five to seven weeks. Three corneal grafts where drug had been injected three days subsequent to skin grafting were opaque 16 to 17 days later. One transplant, in which therapy had been discontinued due to eye inflammation, became opaque at 14 days. This graft was rejected despite resumption of injections. Two transplants remained clear and were recovered at four weeks. Between the third and fourth week of Imuran therapy, seven of the corneal grafts showed initial stages of rejection, although opacification progressed slowly requiring three to four weeks as compared to three to four days in untreated controls. Two other grafts began to opacify at the end of the fourth week so the drug was discontinued, but an additional 12 days were required before they became totally cloudy. No evidence of drug toxicity was seen in this experiment. Thus, in 11 of 15 grafts, rejection was delayed for an average of two weeks beyond the usual two to three weeks seen in controls.

Polack found that when Imuran was injected within three days following a skin graft, from the donor supplying the corneal transplant, graft rejection was prevented without exception. He observed that the immune reaction could be modified with the use of drugs; hence, he concluded that a combination of local treatment in addition to a short interval of systemic immunosuppressive therapy might be effective in maintaining graft survival.

b. Mouse

McKneally and co-workers (164) observed that neither a daily dose of 50 or 100 mg/kg of Imuran injected intraperitoneally, for three days prior to and for three days following grafting, prolonged survival of skin homografts in mice. However, when liver antigen, prepared from minced fresh liver in Ringer's lactate solution and disrupted by alternate freezing and thawing
was injected as a single dose concurrently with the drug, a high incidence of
tolerance to skin grafts was seen. Mice were considered tolerant to grafts,
when hair growth was observed at ten weeks after transplantation.

Optimal immunosuppressive effects were seen when Imuran (azathioprine)
was administered to inbred mice bearing ear skin allografts from another in-
bred strain differing from the recipients only at the H-3 locus (Nouza '66).
Control grafts on non-treated mice had rejected all transplants by 30 days
(range 17 to 29 days). The mean rejection times (time required for actual
rejection) of such grafts was $8 \pm 3$ days. Pretreatment of hosts for 10 con-
secutive days with 150 mg/kg given intraperitoneally, was effective in pro-
longing transplant survival time to 60 days; however, the same dosage begun
at time of grafting and continued for 10 consecutive days showed survival,
in perfect condition, beyond six months, in eight of 10 grafts. In the first
group, 8% mortality occurred whereas no mortality was seen when treatment was
begun at time of transplantation. The mean rejection time in this group was
$18.4 \pm 6.1$ days whereas in the second group the mean rejection time was $2.0 \pm
0$ days. When the initial dose of 150 mg/kg was delayed until the tenth day
after grafting and then was administered for the next ten days, all grafts
had survived at 30 days and half of them at 45 days, but such a ten day post-
operative delay was not so effective in prolonging survival as when the drug
was started soon after transplantation. Optimal results of long term sur-
vival where employing Imuran were obtained; yet, complete immunological
tolerance was not induced, since second set skin grafts from the same donors
rejected within 42 days, and rejection had begun earlier than in controls,
ranging from ten days to beyond two months. The first set grafts were still
retained despite rejection of the second set grafts. It was felt that some
form of graft adaptation may have occurred. Nouza concluded that even with every weak genetic differences between donor and recipient, immunological tolerance could not be induced merely by drug therapy.

c. Rat

Significant increases in survival of kidney allografts between highly inbred strains of rats was seen when Imuran was administered in daily non-toxic doses (Tinbergen '68). The mean survival time in control, non-treated, kidney allografts, exchanged between the two inbred strains, was 14 days post-operatively (range 9 to 55 days). The majority of the kidneys had been rejected by 14 days. Imuran administration, in daily 8 mg/kg intraperitoneal doses, was begun at time of transplantation. The group of 15 rats revealed a mean survival time of 105 days with a range of 13 to 273 days. In four of these hosts, therapy was discontinued at 138, 139, 160, and 161 days and the rats survived an additional 30, 34, 74, and 135 days respectively. Nine hosts received Imuran in daily doses of 4 mg/kg beginning at time of grafting and these revealed a mean survival time of 44 days (range 11 to 76 days). Histological observations showed that transplant rejection, usually attributed to vascular necrosis and thrombosis, was completely prevented by Imuran therapy. Severe glomerular damage was seen in all animals receiving Imuran which may account for the death of hosts. Tinbergen thus concluded that the responses of rats to kidney allografts were analogous to those of dogs and were similar in rejection times. This immunosuppressive agent had significant and comparable effects in the rat to those in the dog. Histological examination of transplanted kidneys suggested that host death was due to a process of chronic rejection, as revealed by every severe glomerular changes in grafts, and was not the result of drug toxicity.
d. Dog

Sabet-Payman and co-workers (64) found that pieces of homologous rib transplanted into the spleens of dogs, receiving daily oral doses 5 mg/kg of Imuran beginning two days before transplantation and continuing for eight weeks subsequently, showed growth and proliferation of homologous marrow at eight weeks. The growth of marrow in these grafts was comparable to that seen in rib autografts in the spleens of the same hosts. Homologous transplants revealed proliferation of erythrocytic, myelocytic and platelet elements.

Hechtman and co-workers (62) observed a three to six day increase in survival time beyond that of controls, in skin homografts exchanged between randomly selected dogs when treated with BW 57-322 (Imuran). Oral doses of 2.5, 10 and 15 mg/kg were begun on the day of grafting, given for the first two post-operative days and continued three times weekly thereafter. The relatively wide ranges in survival times of transplants were attributed to varying degrees of histocompatibility between donors and hosts.

Utilizing adult mongrel dogs, Kiskin (66) bilaterally allotransplanted, skin on the necks of dogs receiving 10 mg/kg of Imuran orally the day before and on the day of grafting. From then on 5 mg/kg/day were administered for the next five days and 2.5 mg/kg/day thereafter. Nine such dogs showed average skin graft survivals of 18.8 days as compared to 10.3 in non-treated controls. Eleven dogs, thymectomized at two to four weeks before skin transplantation, showed average survivals of 12.8 days whereas 14 thymectomized dogs receiving an identical drug regimen revealed an average graft survival of 24.6 days. Depression of white blood cells or alterations in differential blood counts did not appear to be related to the survival of
Calne ('61) homologously transplanted kidneys in dogs and studied the effects of Imuran on their survival. Seventeen dogs received renal homografts following removal of both kidneys and these were given BW 57-322 (Imuran) orally in maximally tolerated doses (10 to 12 mg/kg) beginning on the day of transplantation and for two to three days thereafter. The dosage was then reduced to 2.5 to 5 mg/kg/day. Some of these hosts had also received doses of 6-MP at grafting. In addition, three of the hosts daily received 5 to 10 mg/kg of cortisone orally, two of these beginning at time of transplantation and the third for eight days beginning when rejection first became evident. Two dogs died during the first week and another two at 26 and 32 days. None of these revealed rejection of grafts. However, at 16, 20, 23 and 28 days four dogs died from infection and also showed graft rejection. After four months one dog manifested normal kidney function. At 29 days one host was removed from chemotherapy, but 10 days later rejection had commenced and despite resumption of therapy, it died after 42 days showing rejection. The one host treated with cortisone beginning at the appearance of rejection, died at 37 days without disclosing a reversal. Both dogs, treated with cortisone and Imuran at grafting, died at seven and 12 days showing rejecting kidneys. One dog with a littermate graft was still alive at eight weeks; another died at 13 days with a normal kidney, and the third died at 31 days and revealed rejection.

Calne concluded that Imuran was less toxic to bone marrow than 6-MP, but its effects on transplant survival were inconsistent. It was believed that the differences in the effect of Imuran on graft rejection may have been due to chance variance in the genetic relationship between donors and
recipients. Imuran was at least as effective in prolonging kidney homograft survival as was 6-MP; however, a tolerant state was not attained since grafts were rejected within 10 days after cessation of drug administration. Large doses of Imuran also did not reverse established graft rejection.

Zukoski and co-workers (1963) bilaterally nephrectomized adult mongrel dogs and homotransplanted a kidney into each. All medications were administered orally and begun on the day of transplantation. A group of 10 bilaterally nephrectomized dogs with renal homografts received no therapy and served as controls. These dogs survived an average of 15 days (range 9 to 25 days) subsequent to transplantation. In one experiment, seven dogs with renal homografts received 10 mg/kg/day of Imuran for the first two days following grafting, 5 mg/kg/day for the next four days and 2.5 mg/kg/day thereafter. In this experiment, six of seven dogs survived for an average of 23 days (range 15 to 148 days) after grafting. None of the Imuran treated dogs showed white blood cell suppression. A marked decrease in the number of lymphoid cells in mesenteric lymph nodes and spleens was seen after a few days of drug therapy. It was concluded that the administration of Imuran significantly diminished the host immune response.

Moseley and co-workers (1966) studied the effect of azathioprine (Imuran) on skin and kidney homografts in non-related mongrel dogs. Full thickness skin homografts were placed on the recipient thorax. Azathioprine was administered orally in daily doses of 5 mg/kg. In addition, azaserine was given in 0.5 mg/kg/day doses intravenously. Subsequent drug dosage was reduced when toxic manifestations began to appear. Usually on about the tenth day azaserine was discontinued and azathioprine was reduced to 2.5 mg/kg/day if drug toxicity continued. However, when transplant rejection began to
appear, the daily dosage of azathioprine was increased to 5 mg/kg ad
initially administered. Three dogs rejected skin grafts at an average of 14
days when the drug dosage was reduced. Three, in which the drug dosage had
not been reduced, died of drug toxicity at an average of 17 days, but the
skin homografts appeared to be still intact. Microscopic observations
showed minimal cellular infiltration in two grafts but active rejection in
the third. Five dogs revealed survival of grafts for an average of 25 days
when the drug dosage was reduced and later increased when signs of rejection
were seen. Increased drug administration revealed marked reversal or re­
jection and skin transplant epithelium grew accompanied by healing. However,
all five hosts died due to the toxic effects of the drug. Histological
preparations of these grafts at the time of host death disclosed minimal
mononuclear cellular infiltration in three grafts and active rejection in two.

In a second experiment, utilizing identical drug treatment, eight of
nine bilaterally nephrectomized dogs with renal homografts survived more than
50 days. Five were alive between 175 and 375 days. Moseley and co-workers
believed minor but continued immunologic damage to kidneys occurred in all
hosts.

In a third experiment, seven dogs were bilaterally nephrectomized and
each was simultaneously given a renal and a skin homograft from the same
donor. Drug regimens were identical to those employed in the first experi­
ment. Significant increases in the survival of skin homografts were observed
but the survival of renal transplants was markedly decreased. Skin grafts
survived an average of 39 days. Rejected kidneys contained a mononuclear
cellular infiltration.

In a fourth experiment, simultaneous skin and renal homografts from
different donors were studied in bilaterally nephrectomized dogs receiving 
drug treatment identical to those in the first series. Two of five dogs had 
still survived at 135 and 160 days following grafting; however, they had 
begun rejecting the skin homografts at 58 and 81 days respectively. Three 
of the dogs died between 18 and 34 days post-operatively.

Moseley and co-workers concluded that the chemotherapy employed had 
increased the survival time of skin homografts two to three times that of 
non-treated controls. Identically drug treated animals also showed increased 
survival times of renal homografts. The differences between the relatively 
short increases in survival time of skin homografts and the much greater 
increases in kidney survival was attributed to antigenic differences between 
the two tissues. The greatly increased survival time of skin when accom­
panied by a renal homograft which in consequence revealed a decrease in sur­
vival time, appeared to be specifically related to the presence of the kidney 
homograft. Thus, they concluded that the skin grafts stimulated the host 
immune system to produce specific antibodies, and that kidney destruction 
resulted from the elimination of such antibodies from the circulation and 
consequently preservation of the skin homografts.

Kirchheim and co-workers (167) observed different degrees of sup­
pression of the rejection of kidneys subcutaneously transplanted into pouches 
in necks of dogs, which were treated with daily doses of 2 to 4 mg/kg of 
Imuran. Kidney biopsies were obtained between five and 30 days post­
operatively and grafts recovered between 15 and 30 days. Non-treated con­
trols revealed a rejection reaction within the first five to none days which 
was characterized principally by local mononuclear cellular infiltrates.
Histochemical studies disclosed a reduction in acid and alkaline phosphatase,
esterases, succinic dehydrogenase and other enzyme activities in tissues of the kidney in regions of focal cellular infiltrate. Cellular infiltration in controls increased daily until a diffuse mononuclear infiltrate was seen throughout the renal cortex accompanied by necrosis of the graft. This cellular infiltrate continued to increase and contained polymorphonuclear leukocytes and macrophages as well as the original mononuclear cells. The peritubular capillaries were first affected, appearing ruptured, and fibrinoid necrosis of the tunica media of small arteries also occurred. Later, most of the small arteries and arterioles were obstructed, and these changes were soon extended to the larger blood vessels.

In Imuran treated transplants, the inflammatory changes were generally markedly reduced and were mostly proliferative fibrosis, focal cellular infiltrations and vascular in character. Increases in the amount of collagen in the interstitial spaces were seen and the focal cellular infiltrates were found to consist mostly of mononuclear cells. At 26 days, fewer of these cells were found to be pyronin-positive in the treated than in the untreated controls. Blood vessels were more normal in appearance with the exception of some thickening of the media and swelling of the intimal. Normal enzyme activity was less severely affected than in non-treated except in some of the areas of focal cellular infiltration.

Almgard and co-workers ('67) found significant increases in survival of kidney homografts exchanged between 14 mongrel dogs when given 5 to 8 mg/kg/day of Imuran at time of grafting and 2 to 4 mg/kg/day thereafter. Eight of these hosts were given 5 to 10 mg/kg of prednisolone (11β, 17α, 21 trihydroxypregna - 1,4-diene-3,20-dione) daily begun at time of grafting. Arteriographic examinations and parallel needle biopsies were taken
regularly during the first month following transplantation. Transplants were recovered from 13 to 140 days generally when transplant impairment or loss of function were observed. Untreated renal allografts were usually rejected at six to 14 days after grafting. The range of graft survival time was found to extend from no observable effect at all to maintaining radiographic function and morphologic condition for 20 to 59 days and in two grafts for as long as 140 days. One graft removed 49 days post-operatively revealed no histological evidence of graft rejection. Two grafts recovered at 20 to 26 days showed sparse to moderate cellular infiltrations located perivascularly and periglomerularly. Two kidney grafts recovered at 14 and 21 days showed impaired renal function, marked lymphocyte infiltration, intravascular thrombi, focal necrosis and fibrinoid lesions in the walls of small arteries and arterioles. These grafts had undergone advanced rejection. One kidney, histologically examined at 45 days, also disclosed advanced rejection, pronounced cellular infiltration, hemorrhagic necrosis, increased interstitial connective tissue and extensive fibrinoid vascular lesions. Two kidneys recovered at 15 and 19 days revealed no radiographic evidence of function. These kidneys were totally necrotic, showed local perivascular cellular infiltration, dispersed hemorrhages and intravascular thrombi. At 70 days, they still functioned, and after 140 days they revealed some radiological evidence of impaired renal function. At 115 days, histological examination of biopsy specimens revealed no cellular infiltration and at 140 days, when the grafts were recovered, the cortices were found to be extensively fibrosed with the subcapsular region showing greatest involvement. A more focal fibrosis was found in the inner cortical areas, but normal tubular-glomerular areas were also seen. Cellular infiltration was found to be mild and focal
in these fibrotic areas. One graft recovered after 98 days showed sclerotic scar tissue in the cortex which was continuous with fibrous perirenal tissue. The medullary region consisted of scar tissue and was devoid of tubules. This area also showed necrosis of cellular infiltration. Three kidneys were completely degenerated and mostly reabsorbed at recovery at 91, 96 and 97 days. Calcification and conversion to connective tissue was found.

Almgard and co-workers concluded that the effect of Imuran on survival of kidney allografts varies. They found that the action of the drug was most effective where histocompatibility differences between donors and recipients were weak. Since donors and hosts were randomly selected they felt that there was likely to be some variation in incompatibility and that this was the reason for the variations in therapeutic effects seen in these experiments.
III. MATERIALS AND METHODS

A. Materials

The Syrian hamster, *Mesocricetus auratus*, was the animal of choice throughout these experiments. Eight randomly bred, pregnant females were originally purchased, and the litters of these were subsequently inbred to provide necessary donors and hosts. A strain of inbred hamsters LSH/SsLAK was later secured and the litters of these were also inbred to supply additional animals. These two lines were not interbred and were maintained throughout the period of our investigation.

All animals were housed in stainless steel, wire-bottomed cages throughout. Pregnant animals were always placed into solid-bottomed cages with sawdust bedding a few days before they were due to litter. The animals were maintained on Teklad Hamster Diet and tap water *ad libitum* and were periodically supplemented with lettuce.

A limited series in which young male, albino rats, *Rattus rattus*, were employed was also undertaken. The rats likewise were housed in wire-bottomed cages and, as in the case of the hamsters, pregnant animals were always placed in solid-bottomed cages with sawdust bedding prior to littering. The rats were provided with Rockland Rat and Mouse Diet and tap water *ad libitum*.

1-Purchased from Abrams Small Stock Farm, Chicago, Illinois.
2-Purchased from Lakeview Hamster Colony, Newfield, New Jersey.
4-Purchased from Hormone Assay Laboratories, Chicago, Illinois.
5-Manufactured by Teklad, Inc., Winfield, Iowa.
Two immunosuppressive drugs six-mercaptopurine $^6$ (6-MP) (Purinethol) and azathioprine $^7$ (Imuran) were employed. In the first 6-MP, a stock solution of 100 mg of the drug dissolved in one milliter of 1 N sodium hydroxide and diluted in sterile distilled water to a concentration of 50 mg/ml was employed in several experiments. In other experiments the stock solution was diluted in sterile distilled water to a concentration of 25 mg/ml. Fresh solutions were prepared each day as required. In the case of the second, Imuran, a stock solution of 500 mg was prepared daily as follows: To a suspension of 500 mg of Imuran in 20 ml of saline, 1.81 ml of 1 N sodium hydroxide was added and the solution diluted in saline to 250 ml giving a final concentration of 2 mg/ml.

The immunosuppressive drugs were administered intraperitoneally in all experiments, once daily, and as close to the same time each day as possible. Injections and operative procedures were carried out under as nearly aseptic conditions as circumstances permitted.

In experiments where six mercaptopurine was employed the daily dosages were 2, 5, and 10 mg/100gm body weight, and in the Imuran experiments the daily dosages were 2 and 5 mg/100gm body weight. Both drugs were administered intraperitoneally beginning at the time of transplantation. Injections were continued until termination of the experiment or until signs of severe drug toxicity, such as marked daily weight loss, the most readily available criterion, became manifest. In both studies, controls consisted of hosts carry-

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ing grafts which received an equivalent volume of vehicle per 100 gm body weight with pH adjusted to that of administered drug. The vehicle was administered at the same time, manner, and for the same duration as the drug.

B. Experimental Procedures

Inbred, male hamsters, 30 to 100 days of age were employed as hosts. In the majority of cases donor mandibles and teeth were obtained from newborn hamsters one to 20 hours old. In one series, however, donors were 40 hours and in another three days of age. Donors and hosts always belonged to the same inbred line. Grafts were never exchanged between inbred lines.

In the series employing rats, donor mandibles were obtained from newborn rats 6 to 14 hours of age of both sexes while the hosts were young 30 to 60 day old male rats.

In those series where the effects of an immunosuppressive drug were to be studied, one graft from each littermate donor was implanted into a drug treated host, the other into a control host receiving only vehicle. From each litter of donors, the mandibles of two littermates served as controls. In the experiments where drugs were not used, the half-mandible not transplanted was fixed and served as a control to show degree of development at time of transplantation. Littermate donors not used, were sacrificed at the termination of experiments and the mandibles fixed to serve as controls showing degree of normal development at this time.

Mandibles of newborn and 3 day olds were prepared for transplantation in the following manner: Following decapitation, mandibles were separated from skulls in the region of the temporomandibular joint, by the insertion of the tips of a pair of scissors above the angle of the mandible and cutting upwards and posteriorly. The mandible was then placed in sterile saline,
separated at the mandibular symphysis, and soft tissues carefully excised. In experiments where only a part of a half-mandible was used, everything except the section containing teeth was removed. In series where developing molars were to be transplanted, the half-mandible was obtained in the manner described above, the overlying bony lingual plate removed, and the molar shelled out. Donor tissues were always placed into a sterile saline solution as soon as possible.

Hosts were anesthetized by the intraperitoneal administration of pentobarbital sodium (Nembutal, Abbott) at a dosage of 7 mg/100gm body weight (hamsters) and 3.0 to 3.5 mg/100gm body weight in rats. Hosts were immobilized on a dissecting board, surface hair clipped in the operative region and the integument cleansed with 70% alcohol and sterilized with tincture of Iodine. Every effort was made to maintain strict asepsis in operative procedures as far as conditions permitted.

In series where hamsters and rats received intra-kidney transplants of half-mandibles, the procedure was as follows: A transverse incision was made on the left side below the last rib and carried through the peritoneum. The kidney was then visualized, the overlying peritoneum incised and the organ gently immobilized with cotton and forceps. An incision was now carried through the renal capsule and with a pair of fine pointed forceps a pocket was formed in the kidney substance. The graft was then inserted into this pocket and the capsular incision closed by suture or cauterization. The viscera were now returned to their normal position and the layers of the

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8-Ambott Laboratories, North Chicago, Illinois.
abdominal wall and skin sutured separately and discontinuously with silk.

In the procedure where hamsters were to receive intrauterine transplants, an incision was made through the abdominal wall in the left inguinal region exposing the peritoneum. The peritoneum was then incised and a small transverse incision carried through the uterine horn into the lumen. The transplant was now inserted into the uterine lumen, manipulated distally, and the incision closed by means of discontinuous sutures. Finally, the abdominal wall and integument were separately closed by discontinuous sutures.

In another procedure, hosts to receive intra-testicular transplants were prepared as follows: A longitudinal incision was made through the scrotum and extended to the testicular capsule. The testis was then removed and the capsule incised near the inferior pole. A pocket was now formed and the graft inserted with fine pointed forceps in the testicular tissue. The capsule was then sutured, the testis returned to the scrotum, and the incision through the scrotum and integument separately sutured. All sutures were silk and were discontinuous.

Two subcutaneous sites were utilized in the hamster and one in the rat. In one the dorsal subcutaneous space between the scapulae was employed. This was used only in the hamster and was prepared as follows: An incision was made through the integument between the scapulae and with a pair of scissors a pocket was formed in the subcutaneous tissues. The graft was then inserted into this pocket, manipulated distally and the integument sutured. The other subcutaneous site was the space on the dorsal surface of the ear. This site was utilized in both the hamster and the rat. Here, a transverse incision was made through the integument, a pocket formed with a pair of scissors and the graft inserted and manipulated away from the incision. The skin incision
was then closed discontinuous by with silk sutures.

In another series, grafts were inserted into the cheek poich of the hamster in the following manner: A lucite trans-illumination rod was positioned against the exterior surface of the pouch. The mouth of the host was then opened and a pair of elastic holders placed over the maxillary and mandibular incisors to ensure full retraction of the jaws. Access to the interior of the pouch was attained by passing an elastic retractor through a prepared opening in the periphery of the lip and evertting the pouch over the lucite rod. The interior of the pouch was then cleaned with sterile saline to remove any stray food particles. A small incision was now made in the oral epithelium overlying the pouch, care being taken to avoid injuring the underlying vascular bed. The points of a pair of iridectomy scissors, were then inserted into the incision, directed toward the area of the lip and spread so as to form a pocket. The mandibular graft was now inserted into this pocket and manipulated distally. The incision was then closed with a continuous silk suture.

The grafts were examined at regular intervals whenever their location permitted the use of trans-illumination. Grafts readily available for such examinations were those located either in the cheek pouch or subcutaneously on the ear. Grafts were also examined at weekly intervals with the aid of a dissecting scope. Graft position, vascularity, mobility, evidence of infection (excessive redness, swelling, etc.) and general progress were studied and recorded. In cases where grafts became partially exteriorized through openings in the incision, they were re-inserted whenever their condition warranted.

Grafts were generally recovered at 10, 15, 20, 26, and 30 days following
transplantation. In exceptional cases hosts were anesthetized and kodachrome pictures of grafts in situ taken before recovery. On recovery, grafts were immediately placed into a solution of 2.0% calcium acetate, 1.0% saline and 10.0% formalin and allowed to fix for at least four days. They were then decalcified in a solution of 50gm sodium citrate, 125 cc of 90.0% formic acid and 375 cc distilled water, usually for a period of one to four days prior to dehydration and embedding in paraffin in vacuo. Grafts were serially sectioned at 8 u and stained with Harris hematoxylin and eosin.

C. Microscopic Examination

Transplants were carefully studied in search of evidence for growth and differentiation. The general appearance of the graft and its associated teeth was ascertained and the characteristics of its tissues compared with those of controls. The degree and character of vascularization received special attention. Where evidence of an immunological reaction indicated by the presence of multinucleated giant cells, lymphocytes, neutrophils, and plasma cells occurred, areas of resorption and cellular types were carefully evaluated. In cases of partial or complete encystment, the contents and relationships to the graft were examined and the findings recorded.

The following cells and tissues were studied: (1) the cells of the odontoblastic and ameloblastic layers, stratum intermedium, stellate reticulum and pulp, (2) the pre-enamel, enamel, predentin, dentin and cementum, (3) the periodontal membrane and bony alveolus, (4) irregularities and zones of disturbed formation were noted in all tissues.

In order to present a better picture of the results the following scale was devised: The symbol (+++) designates teeth showing maximum growth. The symbol (++) was assigned to grafts showing viable teeth but less growth than
that seen in category (+++). The symbol (+) was used to designate viable teeth having vascularized pulps but showing only small amount of growth. The symbol (±) was assigned to teeth which still revealed viable tissues but were undergoing a weak rejection and degeneration. These teeth usually showed vascularized areas of pulp, some viable odontoblasts and some predentin formation, however, evidence of round cell infiltration showed that rejection was underway. The symbol (-) was employed in grafts where an unmistakable rejection reaction had developed. This category ranged from cases showing tooth grafts in the later stages of regression to those in which only fragments of dentin remained.
IV. RESULTS

A. Neonatal Hamster Transplants

1. Ear Site Transplants

   a. First Mandibular Molars (Experiment IA)

   Nine of 11 subcutaneous transplants, of first mandibular molars and follicles, from eight to 15 hour old neonatal hamsters (fig. 2) transplanted into the dorsal surface of the ear of inbred males, were recovered 15 days later (table 1). Two transplants had been completely resorbed, whereas a third showed resorption of the tooth and only a small ossicle of bone was observed. Another was necrotic and had been completely rejected. Of the remaining seven, each showed one surviving tooth revealing considerable growth and differentiation. Nevertheless, only two of these were free of lymphoid cell infiltrations or other signs of rejection (table 6).

   The first mandibular molars in all intact newborn controls showed differentiated ameloblasts on all three cusps (figs. 1,2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. Root formation had not yet begun.

   All the surviving teeth showed considerable growth and differentiation. One of these revealed a great deal of growth and formation of osteodentin (table 6; animal #1). Most of the growth seen in this tooth was disorganized (fig. 8). Root formation had begun, but their direction deviated from the normal and were seen to be corrugated and had turned towards the pulp (fig. 9). Enamel formation was greatly retarded. Crowns and cusps were largely enamel-free except for a very small enamel space on one cusp which was bordered by cuboidal cells rather than tall columnar ameloblasts.
Other parts of the crown were mostly free of pre-enameled and were covered with a stratified squamous epithelium which may have had its origin from the ameloblasts (fig. 8). A small amount of regular tubular dentin had formed but most of the dentin in the cusps was in the form of osteodentin showing many cellular and vascular inclusions. The dentinal matrix closest to the pulp chamber consisted of a thin irregular layer of tubular dentin. An irregularly formed layer of normal pre-dentin lined most of the pulp chamber. Tall, normal appearing odontoblasts were seen in all bordering parts of the pulp chamber where pre-dentin formation had occurred. Pulpal cells appeared to be normal and the pulp was non-fibrous in appearance. No lymphoid cell infiltrate was seen in the pulp nor was there evidence of any pulpal degeneration. The pulp was well-vascularized showing numerous large blood vessels and capillaries were observed to extend into the odontoblastic layer. A cellular osteocementum was noted on the outer dentinal surface of the tooth, in the lower crown and on the forming roots, to which a dense connective tissue was attached. Dense connective tissue fibers, forming a partially developed periodontal ligament, were seen between alveolar bone and the osteocemental matrix on the tooth surface. The remaining dense connective tissue surrounding the tooth was more randomly arranged. Portions of the squamous epithelium covering parts of the surface of the cusps appeared to be continuous with a cyst adjacent to the crown. Gross observations at the time of recovery did not reveal any cyst formation and the graft was tightly attached to the connective tissue of the host bed overlying the cartilage of the ear. A few blood vessels originating from the graft bed were seen coursing over the surface of the graft.

The second first mandibular molar recovered 15 days after grafting re-
vealed more growth and development than was seen in the one just described (table 6; animal #2). This tooth showed a readily recognizable development of three cusps had been disorganized and distorted since most of them consisted primarily of osteodentin. One root had deviated at right angles to its normal course of development (fig. 10). Enamel formation was absent on cusps. A small region of pre-enamel was seen on the middle cusp which revealed small areas of short, cuboidal ameloblasts. Other parts of the crown, normally showing enamel, were covered with a squamous epithelium (fig. 11). The bulk of the tooth consisted of a cellular osteodentin while more recent formation of dentin matrix was an irregularly formed tubular dentin. The roots, however, revealed mostly a tubular dentin. Inner surfaces of the pulp chamber showed an irregular deposition of the regular tubular type of pre-dentin. Pulpal cells were normal in appearance, showed no signs of degeneration and no fibrosis of the pulp tissues. Tall and normal appearing odontoblasts, revealing no signs of degeneration, lined the pulp. Numerous large blood vessels and capillaries, extending to and into the odontoblastic layer, were seen throughout the pulp. No lymphoid cell infiltration was seen in the pulp. Some parts of the roots had formed regular acellular cementum. Between the tooth and a partially complete bony alveolus, well-vascularized, dense connective tissue was seen embedded in the cemento-osteoid on the surface of the molar and oriented toward the viable bone of the alveolus in the manner of a periodontal membrane. No ankylosis between the tooth and the alveolus was seen. Adjacent to the crown of the molar a small cyst was seen, the epithelium of which appeared to be continuous with that on the outer surface of the molar. It had replaced the ameloblasts on the crown of the tooth. Gross observations at 15 days showed many small blood vessels on the surface of the
graft and no evidence of cyst formation. The graft was tightly bound to
the connective tissue overlying the ear cartilage.

Five of the seven viable teeth revealed some pulpal degeneration as well
as a small amount of pulpal lymphoid cell infiltration (table 6). One of
these grafts had developed three cusps, and partial formation of one root
(table 6; animal #3). Considerable disorganization and distortion of the
normal shape of the tooth had occurred and only one root had developed.
Enamel formation was retarded to the extent that only a thin layer of pre-
enamel was seen covering each of the three cusps and only part of one of
these showed viable ameloblasts. The latter appeared to be continuous with
the squamous epithelium tangential to the remainder of the crown surface
(fig. 12). The three cusps each revealed large amounts of osteodentin,
which almost obliterated the pulps, and showed both cellular and vascular
inclusions within the matrix (fig. 12). On the pulpal surface of the
osteodentin in two of the three cusps, there was a thick but irregular
layer of tubular dentin. The formation of pre-dentin in two of the cusps
was also irregular in thickness and was absent in the third. The pulps of
two cusps and the root showed borders of viable, tall, normal appearing
odontoblasts; however, some regions of the pulp revealed degeneration of
odontoblasts as indicated by a reduction in the height of these cells. The
pulps in two of the cusps were more condensed than normal while that of the
third was necrotic and avascular and consisted entirely of cellular debris
and inflammatory cells. The two pulps showing an absence of necrosis, re-
vealed little inflammatory cell infiltration in the form of lymphoid cells
and were well vascularized. The root also showed viable odontoblasts, con-
sisting mostly of normal tubular dentin with a wide layer of pre-dentin.
Both non-cellular and cellular cementum were found on the outer surface of the root; but most of the cementum was cellular in nature. Connective tissue fibers embedded in the cementum continued as a vascular dense connective tissue attaching to adjacent bone on one side of the tooth in the form of a primitive periodontal ligament. The bone-free side of the tooth was covered with a dense connective tissue which was not so orderly in arrangement as a normal periodontal ligament. The bone which had formed only on one side of the molar was very vascular and showed osteogenic tissue and viable osteocytes. Gross observations at recovery did not disclose cyst formation.

Another surviving tooth showed development of two cusps and one root (table 6; animal #4). Most of the crown was enamel-free but the cusps revealed several large enamel spaces which were lined with tall to cuboidal ameloblasts (figs. 13, 14). Other areas of the crown, normally covered with enamel revealed revealed replacement of the ameloblasts with squamous epithelium. Very little pre-enamel was found on any cusp. Osteodentin, showing vascular and cellular inclusions, had formed in both cusps. The tubular dentin was found toward the pulpal surface which was irregular in formation in cusps but became more regularly formed in the root. An irregular formation of pre-dentin was seen in cusps, but it was more regular in nature in the root. The pulps showed a low degree of lymphoid cell infiltration and these cells were also seen in the pulp as small perivascular accumulations. Although most of the pulp cells appeared to be normal, some areas of the pulp, where lymphoid infiltration was observed, showed signs of degeneration. No pulpal osteodentin formation was seen. Normal appearing, tall columnar odontoblasts were seen lining the pulps of cusps and the root; yet, in the regions of lymphoid cell infiltration, the odontoblasts were shorter and
some appeared to have undergone degeneration. The pulp tissues were found to be much more dense than normal. Numerous large blood vessels were seen throughout the pulp and capillaries occurred in the odontoblast layer. The outer surface of the root manifested some normal acellular cementum while other parts of the root surface revealed the formation of a cellular cemento-osteoid. Dense connective tissue fibers were attached to the cementum and cemento-osteoid surfaces. Dense connective tissue enclosed most of the tooth. In areas between the tooth and the surrounding bone, connective tissue fibers were found to attach to the cemental surface of the molar and were oriented towards bone in the fashion of a periodontal ligament (fig. 13). Other fibers from the tooth to the bone were more randomly arranged. The periodontal tissues showed some lymphoid cell infiltration, but no necrosis was seen and they were very vascular. Only part of a bony alveolus had formed about the molar. This was vascular, but the intertrabecular spaces showed accumulations of lymphoid cells. Parts of the molar crown were adjacent to a cyst and areas of squamous epithelium were seen where ameloblasts would normally have been found. This epithelium appeared to be continuous with that of the cysts. Gross observations at time of recovery showed the graft to be tightly attached to the subcutaneous part of the graft bed. No cyst formation could be detected at this time and blood vessels, which originated from the subcutaneous part of the transplant bed, were seen coursing over the surface of the transplant.

Another transplant showed growth and differentiation of a molar which revealed a poorly developed crown formed by two malformed cusps (table 6; animal #5). Development of only one root was seen and this had deviated at right angles from its normal course of development (fig. 15). This molar was
smaller and showed less development and growth than most of the molars in this series. Most of the crown surface was devoid of pre-enamel and enamel except for a small area of pre-enamel showing a border of very short ameloblasts. The crown consisted of osteodentin and irregularly formed tubular dentin was seen toward the pulp; however, the root was largely composed of tubular dentin (fig. 15). A thin layer of pre-dentin lined most regions of the pulp chamber (fig. 16). The pulps disclosed a small amount of small round cell infiltration indicating the presence of a rejection reaction. The pulp was noticeably much more condensed and fibrous than normal. The odontoblasts seemed to be much shorter than those of other grafts in this series. They were missing from some parts of the pulp. Other areas of odontoblasts appeared to have undergone some degeneration and some multinucleated giant cells were seen in the odontoblastic layer. A decrease in vascularity of the pulp was noticed in this molar when compared with others in the same series. Blood vessels were smaller and less numerous than normal, but small capillaries were found to reach and course through the odontoblastic layer. Lower crown and root surfaces were covered with a cemento-osteoid to which some cartilage from the host graft bed was attached. Dense connective tissue, which was attached to the cemento-osteoid, enclosed most of the tooth. Very little bone had formed and no bony alveolus was seen. Gross observations on recovery showed the graft to be well incorporated into the graft bed and to be very vascular, as judged by the many small blood vessels covering the surface of the transplant.

The fourth surviving tooth appeared to have been undergoing the early stages of rejection as revealed by a lymphoid cell invasion and some degeneration. This molar revealed considerable disorganization in growth (table 6;
animal #6). Three cusps and two roots had formed (figs. 17, 18). It seemed as though the original graft had broken, with the result that two cusps and one root had developed from one fragment and one cusp and one root from the other. Both fragments showed much growth and differentiation, but considerable gross distortion of the tooth had also occurred. Only one cusp showed a large and some smaller enamel spaces. These spaces revealed borders consisting of short columnar to cuboidal ameloblasts while the enamel-free regions of the cusp were covered with squamous epithelium (fig. 18). The other cusps were devoid of epithelium and were covered with a dense connective tissue. All cusps revealed large amounts of osteodentin showing cellular and vascular inclusions. Tubular dentin, very irregular in thickness, had formed near the pulp chamber. Most areas of this chamber revealed an irregularly formed pre-dentin. The roots were composed mostly of regular tubular dentin and pre-dentin although some osteodentin was seen. The pulp chambers were large and the pulps appeared to be more dense than normal and they were also more fibrous in the second fragment where a lymphoid cell infiltration had occurred. Nevertheless, very little degeneration of pulp cells was seen in this cusp and root. The odontoblasts forming the borders of the pulp were tall columnar cells. The pulp was well-vascularized and revealed numerous large blood vessels and capillaries within the odontoblastic layer. The surfaces of roots and parts of crowns disclosed a cemento-osteoid showing embedded cells and considerable matrix formation as well as an attachment of dense connective tissue fibers. Such dense connective tissue surrounded both fragments of the tooth in areas not covered with either squamous epithelium or ameloblasts. Where bone was found adjacent to the tooth, dense connective tissue fibers were oriented between the bone and the surface on the
tooth. Bone formation about the molar was largely in the form of isolated ossicles which did not constitute a complete alveolus. Several small cysts were noted adjacent to the squamous epithelium on the cusps. Gross observations at time of recovery showed the graft to be tightly attached to the connective tissue over-lying the ear cartilage. No cysts were detected and the graft seemed to be well-vascularized by vessels originating in the graft bed.

The last surviving tooth of this series showed a disorganized and distorted development of two cusps and one root (table 6; animal #7). The crown and cusps were free of enamel except for a part of the side of one cusp which revealed a small enamel space showing a border of cuboidal ameloblasts. Squamous epithelium covered the other areas of the crown normally covered with enamel (fig. 19). The cusps consisted mostly of osteodentin revealing cellular and vascular inclusions. Some areas of the cusps and the root showed thick formations of tubular dentin; however, these were usually very irregular in thickness. A thin layer of pre-dentin was seen throughout the wall of the pulp chamber. Viable, but shortened, odontoblasts formed the border of the pulp, and some of these cells appeared to have undergone degeneration. A lymphoid cell infiltration of the pulp was more extensive in this than in the other surviving grafts of this series. The pulp tissue was more dense and fibrous than that normally found; yet the pulps showed good vascularization as revealed by the large number of prominent blood vessels. Cemento-osteoid was found on most of the root surface and very little normal acellular cementum was seen. Only very small ossicles were scattered about the tooth and a complete alveolus had not formed. Dense connective tissue fibers were found between the bone and cemento-osteoid of the tooth.
One tooth in this series showed that total rejection had occurred prior to recovery (table 6; animal #8). Only fragments of cusps remained and no roots had developed. Pre-enamel covered parts of the cusps, but no ameloblasts were seen. Osteoid had formed on the dentin. The surfaces of the pulp chamber in cusps showed a formation of osteoid on the dentin but very little predentin had formed prior to the deposition of osteoid. Pulp had been replaced by a vascular marrow-like tissue and no odontoblasts were found. The pulps of the cusps also showed a formation of bony trabeculae with viable osteocytes. The cusps had become ankylosed to adjacent bone. Some lymphoid infiltration had occurred within the pulp and about the remnants of the tooth. The molar had been undergoing resorption as indicated by the presence of multinucleated giant cells within and resorption lacunae on its surfaces.

One graft on recovery at 15 days, revealed only a small piece of osteoid surrounded by a dense connective tissue and squamous cells (table 6; animal #9). No remnants of the molar itself were found. In two of the hosts no transplant tissue was found at time of recovery (table 6; animal L0, 11). Since the incisions had remained closed it was assumed that these transplants had been resorbed and had not escaped from the transplantation site.

No viable molar transplant in this series disclosed the growth seen in an intact 15 day old control first mandibular molar (figs. 4, 5).

b. Half-Mandibles

1. Experiment IB

Half-mandibles from two to 15 hour old neonatal hamsters were transplanted subcutaneously into the dorsal surface of the ear in adult males of an inbred strain. All grafts (12) were recovered 15 days subsequent to
implantation (table 1). No graft had been completely resorbed. Seven of the 12 showed surviving teeth (tables 1, 7). In six of the seven grafts showing viable teeth, only one molar, revealing growth and differentiation, was found in each while in the seventh two molars were encountered. No evidence of surviving incisors was seen in any of the transplants in this series.

The incisors in all eight to 15 hour newborn intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps, but had not yet begun to form dentin (figs. 1, 3).

One graft showed survival of only a first molar (table 7; animal #1). Two cusps had developed in this molar and only part of the crown was covered with enamel. The enamel spaces were lined with short ameloblasts (fig. 20). No roots had formed. The remainder of the hard tissues were dentin and predentin. Some osteodentin showing cellular inclusions was also seen. The dentin was very irregularly formed. The layers of predentin, denoting the limits of the pulp chamber, also showed many irregularities. A few vascular inclusions were seen in the layer of dentin. The pulp revealed some perivascular and focal accumulations of lymphoid cells, but this infiltration was not extensive. The pulp was very vascular and showed many blood vessels. Tall normal appearing odontoblasts were observed in most areas of the pulp, although they were absent in a few, and here dense connective tissue had replaced the pulp. Portions of the outer dentin surfaced showed a cellular cemento-osteoid. The tooth was surrounded by a dense connective tissue
showing fibers oriented from the surface of the tooth to the adjacent bone. Some foci of lymphoid cells were manifested in the surrounding connective tissue. The tooth was encased for about three fourths of its perimeter by a thin-walled bony alveolus. The second molar in this graft had been completely resorbed.

The non-viable incisor remnant in this graft was found to consist largely of a dentin shell which was undergoing resorption. The pulp revealed a very vascular, dense connective tissue and considerable bone. The lingual alveolus of the incisor was ankylosed to its dentin surface. No surviving odontoblasts or ameloblasts were found. The central areas of the mandible were largely hollow, showing that some bony necrosis and resorption had occurred. The bone in the posterior part of the mandible had also undergone resorption, but a considerable amount of vascular marrow was obvious. Formation and growth of bone was observed mainly in the peripheral areas. A large cyst was located on the lingual aspect of the graft, but it did not contain any graft tissues. Lymphoid cell infiltration was minimal throughout the graft. Gross observations at the time of recovery showed what appeared to be a cyst on the mandible in the region of the molars. Small blood vessels arising from the graft bed covered the graft surface.

A second graft revealed the survival of a second mandibular molar (table 7; animal #2). Not much growth and development had occurred in this tooth. One cusp and part of another had developed, but no enamel had formed. The crown of the developing tooth was covered with tall, columnar, normal appearing ameloblasts and a normal stratum intermedium and stellate reticulum were observed (fig. 21). Dentin had formed as a thin layer on only one cusp, but it was tubular and regular in nature. Seemingly normal, but
immature odontoblasts were seen lining the pulp chamber. The papilla was vascularized, showed normal pulpal cells, and disclosed no inflammatory cell infiltration. The tooth was encased within an alveolus of viable bone.

The incisor in the above transplant was merely a partially resorbed dentin remnant with no surviving odontoblasts or ameloblasts. The vascular pulp showed considerable bone and marrow formation as well as in-growths of dense connective tissue. The first molar in this transplant had been completely resorbed at the time of recovery. The bone in the remainder of the mandible showed growth, but a large number of osteoclasts were seen in the other bony areas indicating that resorption had been underway. Very noticeable increments in trabecular diameter were also evident. Much marrow had been replaced by a dense connective tissue and these areas also revealed an inflammatory cell infiltration. A large cyst was seen extending the length of the lingual aspect of the mandible and within the first molar alveolus. No encysted graft tissue was found. A relatively dense lymphoid cell infiltration was apparent throughout the graft and surrounding connective tissue. Gross observations on the transplant at the time of recovery showed encystment of the graft, swelling of the graft bed and engorgment of the blood vessels on the surface of the graft. The transplant was very tightly attached to the connective tissue of the graft bed.

One graft showed survival of a first and a second mandibular molar (table 7; animal #3). The first molar revealed much growth and development; however, development of the crown was greatly distorted (fig. 22). Small perivascular accumulations of lymphoid cells were seen in the pulp. One root had formed, but no bifurcation of the root had occurred. One large cusp and a smaller second one were also seen. The crown showed many enamel-free areas;
yet approximately half of its surface showed some enamel formation. Large enamel spaces were seen and a fibrous pre-enamel was seen adjacent to them (fig. 22). Cords of squamous cells appeared to merge with the ameloblasts. Dense connective tissue was immediately tangential to the dentin crown surface where the ameloblasts or squamous cells were absent. No stratum intermediate or stellate reticulum was observed. The second cusp revealed no enamel spaces but some irregular pre-enamel was seen. Most of the dentin seemed to be regularly formed and tubular in nature, although some irregularities occurred at the junction of the root and crown. Here, the irregularly formed dentin was very thick and some parts of the root also showed some similarly formed dentin. Osteodentin, which showed both cellular and vascular inclusions was seen. Pre-dentin formation was noticeable on the pulpal surface of the dentin throughout the pulp chamber and the pulp cells appeared to be normal. Dense connective tissue invasion of the pulp was not apparent. A lymphoid cell infiltration was confined mainly to perivascular areas. The pulp was very vascular and showed numerous large blood vessels. The crown pulp revealed the highest degree of vascularity. Tall columnar odontoblasts, showing no degenerative changes, lined the entire pulp chamber and root. The outer root surfaces revealed a thin layer of cemento-osteoid showing cellular inclusions. Connective tissue fibers were attached to this layer, and these fibers were part of the dense connective tissue which extended to the adjacent alveolar bone in the manner of a primitive periodontal ligament. The molar was enclosed within a viable alveolus which was incomplete in the region of the crown.

This transplant also revealed a second mandibular molar showing a low degree of growth and development (fig. 23). Two cusps were in the process
of formation, one being larger than the other. No roots had developed and enamel had not appeared. Tall, columnar ameloblasts covered the crown. A normal stellate reticulum and stratum intermedium were seen. A regular layer of tubular dentin was present on the largest cusp. No osteodentin was seen. Pulpal cells were normal and no lymphoid cell infiltration was in the pulp. Tall odontoblasts lined the entire vascular pulp. The molar was encased within a viable bony alveolus.

The incisor in the above graft was a non-viable dentin shell which had undergone some resorption and showed no surviving odontoblasts or ameloblasts. The dentin remnant was partly ankylosed to the adjacent mandibular bone. The pulp had been replaced by bone, marrow and a dense connective tissue. The remainder of the mandible revealed a considerable amount of bone formation evident as an increase in trabecular thickness. Nevertheless, a great deal of the graft bone was necrotic in appearance. Although the marrow appeared to be vascular, a lymphoid cell infiltration and a dense connective tissue invasion were extensive. Most of the peripherally located bone had remained viable. Most of the resorption and necrosis seemed to be centrally located. Two cysts were found but neither of them showed any inclusion of transplant tissues. Gross observations at the time of recovery revealed a firm attachment to the host bed. A cyst was found in the area of the molars.

The fourth transplant of this series showed a viable second mandibular molar revealing considerable growth and development (table 7; animal #4). The crown showed only one cusp and only one root had formed (fig. 24). Growth on one side of the tooth was retarded as indicated by incomplete and distorted formation of the crown and that side of the root. A thick layer
of enamel had formed on most of the crown and tall, columnar ameloblasts, revealing no signs of degeneration, were found on all surfaces of the enamel. Cells of the stratum intermedium were seen. Hertwig's sheath was intact in this molar, but its cells showed some degenerative changes and a reduction in height. A wide pre-enamel layer was present. Dentin had formed in a regular fashion and was tubular in nature, except where the crown and root had become distorted in shape. Calcification of the dentin layer was irregular. Small peripheral area of osteodentin had formed, showed cellular and vascular inclusions and were seen primarily in areas where the crown and root were distorted. The remainder of the dentin showed a wide layer of normal appearing pre-dentin. The cells of the pulp appeared to be normal and no lymphoid cell infiltration was seen in the pulp. The pulp manifested many large blood vessels ramifying into a large number of capillaries within the odontoblastic layer. Tall and normal appearing odontoblasts were seen along the entire pulp. On the dentin surface of the root a thin layer of matrix, showing cellular inclusions, and to which fibers from the adjacent connective tissue were attached was seen. The molar was surrounded by dense connective tissue some of whose fibers were attached to the tooth surface and the alveolar bone in the fashion of a periodontal membrane. These fibers were not arranged in discrete bundles. A bony alveolus encased the molar.

The incisor in the above transplant was a dentin remnant which had undergone some resorption. Part of the distal half was encysted. The pulp, although vascular, revealed dense connective tissue and bone. No odontoblasts or ameloblasts were seen. Ankylosis and bone formation had occurred on the outer surface of the tooth.

The first mandibular molar in this graft consisted of distorted dentin
fragments, embedded in a dense connective tissue and surrounded by a lymphoid cell infiltration. The pulp revealed a generalized necrosis and cellular debris. No bony alveolus had formed around the dentin fragments. The remainder of the transplant showed considerable bone formation and growth. A coalescence of trabeculae in the peripheral areas of the mandible was observed. Resorption, accompanied by a dense connective tissue invasion and lymphoid cell infiltration was seen in the central parts of the mandible. Nevertheless, new spongy bone had formed. Gross observations at the time of recovery revealed a probable encystment of the part of the mandible as well as a great deal of swelling of the graft bed. Some engorgement of blood vessels on the connective tissue capsule was apparent.

The fifth graft revealed survival and growth of a second mandibular molar (table 7; animal #5). Three cusps had formed, but no roots had developed. The central and largest cusp showed formation of enamel while the other cusps appeared to be in the early stages of enamel formation (fig. 25). Pre-enamel was found on all three of the cusps. Tall columnar, ameloblasts showing no degenerative signs, covered the entire crown surface. The stratum intermedium and stellate reticulum seemed to be normal. An intact Hertwig's root sheath, which manifested no signs of atrophy, was seen. Regularly formed dentin was seen on all cusps, but no osteodentin had developed. Pre-dentin was present as the innermost layer of dentin. The pulp cells appeared to be normal and no lymphoid cell infiltration occurred in the highly vascular pulp. Tall columnar odontoblasts lined the pulp chamber and displayed no indication of degeneration. The molar was contained within an alveolus of viable bone. The dental lamina of the molar was continuous with the epithelium of an adjacent cyst (fig. 26).
The incisor of the above transplant was a non-viable dentin shell revealing an ingrowth of dense connective tissue, lymphoid cell infiltration, bone formation in the pulp and no viable odontoblasts or ameloblasts. All that remained of the first molar in this graft was some dentin fragments of cusps containing no surviving odontoblasts or ameloblasts. One cusp was enclosed in squamous epithelium while the others were embedded in dense connective tissue. The pulps showed ingrowths of dense connective tissue and an infiltration of giant cells as well as other inflammatory cells. The remaining parts of the mandible itself showed considerable bone formation; yet much of it was necrotic and an extensive dense connective tissue substitution of resorbed bone had occurred which was most conspicuous in the central part of the mandible. The greatest degree of growth and formation of bone appeared to have taken place peripherally. Areas of the mandible normally showing marrow had been replaced by a dense connective tissue. Inflammatory cells were seen throughout the transplant which formed dense accumulations while the surrounding tissues manifested an even greater accumulation of these cells. Gross observations on recovery disclosed a thickened connective tissue capsule surrounding the graft and possibly an initial encystment. Some swelling was noted in the graft bed while the transplant was found to be tightly attached to the host bed.

The sixth transplant showed survival and growth of a second mandibular molar which had developed two cusps but no roots (table 7; animal #6). Although no calcified enamel had formed, a thin layer of fibrous pre-enamel was obvious on one cusp. The entire crown revealed tall, normal appearing ameloblasts and a viable, intact Hertwig's root sheath was also noted (fig. 27). The stratum intermedium and stellate reticulum seemed to be normal.
The cusp, showing the formation of pre-enamel, also revealed the development of regular layers of tubular dentin as well as pre-dentin. Formation of dentin had begun on the second cusp. Osteodentin was not encountered. No abnormalities were observed in the cells of the pulp which disclosed no lymphoid cell infiltration. Tall, normalodontoblasts, showing no degeneration, were noted in the pulp of the larger cusp, but, these cells were not so tall in the smaller, less developed cusp. The molar was enclosed in a alveolus of predominantly viable bone.

In this transplant, all that remained of the incisor was a fragment of dentin surrounded by dense connective tissue. Other parts of the incisor had been resorbed. Three cusps and a few dentin fragments, showing some pre-enamel of their outer surfaces, constituted the remains of the first mandibular molar. Some of the cusps and fragments were encysted, while others were surrounded by dense connective tissue. The remainder of the mandible had undergone an intensive reaction, since part of the bone had been encysted and other parts were necrotic. Lymphoid cell infiltration was extensive throughout the graft tissues and a dense connective tissue substitution of resorbed bone was also extensive. Gross observations at the time of recovery revealed the graft to be contained within a vascular cyst.

The seventh graft showed a surviving second molar (table 7; animal #7). Three cusps had developed, but no roots had formed. No enamel-free areas were seen on the crown. The layer of enamel, which disclosed very few irregularities, was approximately three times that of the dentin. A layer of pre-enamel adjacent to the tall, normal appearing ameloblasts, revealing no degenerative changes, covered the entire surface of the crown (fig. 28). The thick layer of dentin showed some uneven calcification, however, the
tubular dentin had formed normally. No osteodentin had developed. A regular layer of pre-dentin, which revealed no zones of disturbed formation, was apparent on all three cusps. The cells in the pulp appeared to be normal with no evident lymphoid cell infiltrate. Numerous pulpal blood vessels were present and many capillaries were seen within the odontoblastic layer. Tall, normal appearing odontoblasts lined the entire pulp chamber with no evidence of degenerative changes or disturbed function. The tooth was partly encased within a bony alveolus.

The only part of the incisor found in this transplant was an encysted dentin remnant surrounded by cellular infiltrate. The tooth was necrotic in appearance and showed no odontoblasts or ameloblasts. The cusps of the first mandibular molar were disorganized and distorted dentin remnants with no apparent surviving dental cells. The remnants were surrounded by dense connective tissue and lymphoid cells. The remainder of the mandible was almost completely encysted. Other non-encysted parts were necrotic and manifested a very intensive inflammatory cell infiltration as well as a large number of multinucleated giant cells. A small amount of viable bone was seen in the posterior part of the mandible although extensive resorption of graft bone had occurred. Gross observations at time of recovery revealed a partly encysted graft tightly attached to the graft bed, thus indicating incorporation of graft into the host.

The remaining grafts in this series showed no survival of teeth. Usually all that remained of the teeth were nonviable dentin shells of the cusps. Some of these disclosed a small layer of unresorbed pre-enamel. Although none of them showed survival of normal ameloblasts, some cusp fragments revealed squamous epithelial cords tangential to the outer surface of the cusps.
Many of the remnants disclosed bone and marrow in the pulps while others revealed either degenerated cells and cellular debris, or dense connective tissue. In general, with the exception of those indicating pulpal marrow formation, lymphoid cells were found about and within pulps of the remnants. Resorption lacunae were observed in the dentin of all the teeth and most of them had already undergone varying degrees of resorption. In only one case had the molar been entirely resorbed. Some ankylosis of fragments to adjacent bone was noted.

In all cases of viable molars in transplants in this series, none of the teeth approached the degree of growth found in molars in intact 15 day control mandibles (figs. 4, 5, 6, 7).

In no case had the incisor survived in transplanted mandibles. These, like the other rejected teeth of this series, usually persisted as non-viable dentin remnants showing no survival of either odontoblasts or ameloblasts. Usually, the proximal portion of the incisor remnant displayed invasion of the pulps by dense connective tissue and inflammatory cells. Others disclosed pulpal bone formation in some areas and still others the presence of marrow. The pulps in the distal parts of incisor remnants usually showed degenerated cells and cellular debris. Those grafts in which the incisor had been perforated or broken, showed a dense connective tissue invasion into the distal pulp.

All of the transplants in this series revealed some viable mandibular bone. The amount of new bone in those not disclosing surviving teeth was highly variable. In one graft the central mandibular areas were mostly necrotic with only small areas of viable bony trabeculae. Very little osteogenic tissue was found and large numbers of osteoclasts were seen. The
marrow revealed mostly lymphoid cells wherever fibrous connective tissue had not replaced it. Very little bone growth had occurred in this graft. In a second graft, several areas of calcified cartilage were observed. Much new spongy bone had formed and trabecular growth had occurred as manifested by increases in the diameters of trabeculae. The peripheral mandibular parts showed a coalescence of trabeculae to form compact bone. Vascular marrow was observed throughout the graft; nevertheless, in a few areas connective tissue had replaced the marrow. More formation than resorption of bone had occurred in this graft.

In another transplant considerable new bone had developed; yet, necrosis was widespread. Marrow spaces revealed much lymphoid cell infiltration and a dense connective tissue replacement of both bone and marrow. Resorption had occurred, but was seen to be concomitant with bone formation. Another graft manifested extensive bone formation throughout. The bone was very vascular and little inflammatory cell infiltration was observed. The amount of bone which had been resorbed appeared to be small when compared with the newly formed bone. Vascular marrow was found throughout bone of the transplant. Most of the newly formed bone had the appearance of spongy bone and showed trabecular growth. The final graft, which had not revealed survival of teeth, showed new bone formation and a vascular marrow. Resorption in this graft was minimal.

Cyst formation had occurred in every graft of this series. Four of 12 showed encystment of the distal part of the incisor while a fifth revealed encystment of the first mandibular molar. In two of the transplants, the dental lamina of second mandibular molars were continuous with the squamous epithelium of an adjacent cyst. The remaining grafts disclosed cysts, but
these did not include graft tissues. Seven of 12 grafts showed very intense lymphoid cell infiltrations and the largest areas of necrotic tissues, but five disclosed lesser degrees of infiltrations. However, the grafts of both categories displayed varying amounts of viable tissue, some showing an intensive reaction, also disclosed mostly viable tissues, while still others, revealing a relatively mild cell infiltration, showed considerable tissue necrosis. In all cases the greatest concentrations of inflammatory and giant cells were observed in the tissues neighboring cysts and within and about teeth undergoing rejection. The latter usually showed a greater degree of lymphoid cell infiltration than other regions of the transplant, although this was not always the case.

2. Experiment IC

Half-mandibles from 12 to 14 hour old neonatal hamsters were transplanted subcutaneously into the dorsal surface of the ear of inbred adult males. Nine of 10 such grafts were recovered 15 days later (table 1). One host died before the termination of the experiment; hence, its graft was not recovered. Of the remaining nine grafts, only three showed surviving teeth, none of which were incisors (table 8). Of the three grafts disclosing surviving teeth only one molar revealing growth and differentiation was found in each (table 8).

The incisors in all newborn intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs. 1, 3).
One of these grafts showed a surviving second molar (table 8; animal #1). This molar had two cusps revealing dentin formation, but no roots or enamel were seen (fig. 29). Tall, normal appearing ameloblasts and some showing degeneration were seen. An intact stratum intermedium and stellate reticulum were encountered, although small peripheral regions of the latter showed foci of early small lymphocyte infiltration. The outer enamel epithelium was vascular and seemed to be normal except in one area where it was continuous with the stratified squamous epithelium of an adjacent cyst. A layer of normal tubular dentin was seen on one cusp, but the dentin on the second cusp was much less abundant. The pulp in the largest cusp was lined with tall odontoblasts, but these cells appeared to be shorter in the second cusp. The odontoblastic layer revealed capillaries between and beneath the cells. The pulp was more condensed than normal and showed a low degree of lymphoid cell infiltration. Some parts of the dental sac manifested foci of lymphoid cell infiltration. The molar was encased within a bony alveolus except in the region of the upper crown where a band of dense connective tissue had separated the tooth from an adjacent cyst. Most of the alveolar bone was viable and had shown growth; however, some parts of it disclosed pyknotic osteocytes.

The first mandibular molar in the above graft had shown very little growth on recovery and only dentin remnants of two cusps and part of a third were found. These remnants were distorted and fragmented. No surviving ameloblasts or pre-enamel were found, but in the position of the ameloblasts, a stratified squamous epithelium was seen which appeared to be continuous with the epithelium of an adjacent cyst. Only a small amount of dentin had formed, and this layer was thickest on the middle cusp. Bone
formation had occurred on the pulp surfaces of the cusps. No odontoblasts were found. A sparsely vascular, dense, connective tissue, containing multinucleated giant and lymphoid cells as well as bony trabeculae, had replaced the normal pulpal tissues. No bony alveolus had formed around the remnants of this molar which were partly embedded within a cyst. The non-encysted cusps were embedded in a dense connective tissue.

The incisor of this graft had broken near the tip and had become partly resorbed. The remaining dentin remnant showed osteoid formation on the outer and pulpal surfaces and was ankylosed to the surrounding bone. No surviving ameloblasts or odontoblasts were found. Bony trabeculae, accumulations of lymphoid cells and a dense connective tissue invasion were observed in the pulp. The distal half of the incisor pulp revealed some degenerated odontoblast and pulpal cells. The pulp was vascular, but the distal parts were mostly avascular. The mandible revealed much viable bone peripherally, yet the central areas showed degeneration of osteogenic tissue and a considerable dense connective tissue replacement of resorbed bone and marrow had occurred throughout. Although the central parts of the mandible showed necrosis and resorption, the peripheral areas manifested growth and viable bone. The most intensive inflammation and resorption occurred in the areas surrounding the remnants of the first molar and the incisor. Most areas of the mandible and the surrounding host tissues disclosed an intensive inflammatory cell infiltration. The posterior part of the mandible showed cartilage which had undergone calcification. Bone formation had occurred about this cartilage. Gross observations at the time of recovery revealed no encystment of the graft which was firmly attached to the subcutaneous part of the transplant bed. Many small blood vessels which originated from the host tissues covered the sur-
face of the graft.

The second graft contained a surviving molar which revealed a higher degree of growth and development than the one just described (table 8; animal #2). Three greatly distorted cusps had developed and root formation had begun (fig. 30). Enamel showing retarded calcification, which was approximately one and one-half times thicker than the dentin layer, had formed on all cusps. The enamel was evenly formed and showed no hypoplastic areas except for one small area on the side of the crown. A layer of fibrous pre-enamel was seen adjacent to the enamel. Tall, normal appearing ameloblasts bordered the pre-enamel and covered the entire outer surface of the molar. Regularly formed tubular dentin had developed with only a very few areas of disturbed formation. A layer of pre-dentin lined the pulp chamber. No osteodentin was seen. A normal appearing, intact Hertwig's root sheath was observed and root formation had been underway. Tall odontoblasts lined the pulp. The pulp was not fibrous and showed no lymphoid cell infiltration. The pulp was very vascular and small blood vessels, in addition to capillaries, were noted between the odontoblasts. The tooth was surrounded by a vascular, loose periodontal connective tissue revealing some small foci of lymphoid cells. A bony alveolus enclosed the molar, but was incomplete in the area of the upper crown where a cap of dense connective tissue completed the alveolus and separated the tooth from an adjacent cyst. The alveolus was vascular and revealed much bony trabecular formation; still, some inter-trabecular spaces showed lymphoid cell infiltration.

The first mandibular molar in the same transplant was merely a dentin remnant showing three cusps and very little growth. One cusp had become encysted whereas the other two were embedded in dense connective tissue.
The latter revealed no odontoblasts or ameloblasts while the pulps were sparsely vascular and showed some osteoid. The pulps consisted primarily of fibrous dense connective tissue containing inflammatory cells. Numerous giant cells were also seen about the cusps. The adjacent cyst occupied the necrotic and almost completely non-viable bony alveolus of this molar. The incisor in this graft was a dentin remnant evidencing osteoid formation on the outer and pulpal surfaces of the remaining dentin. No surviving odontoblasts or ameloblasts were found. The cells of the pulp had been replaced by a dense, fibrous, but well-vascularized connective tissue. An inflammatory cell infiltration, consisting primarily of small lymphoid cells, was observed in the pulp and a large number of multinucleated giant cells were noted adjacent to the dentin. Bone had formed in the pulp. The tip of the incisor was enclosed within a cyst that extended most of the length of the lingual aspect of the mandible and invaded the alveolus of the first molar. The bone of the mandible was vascular and considerable bone growth had occurred as revealed by the increase in trabecular thickness, especially peripherally. Many of the trabeculae revealed flattened osteoblasts lining the intrabecular spaces while some lacunar osteocytes were shrunken and displayed pyknotic nuclei. The marrow disclosed a considerable degree of small round cell inflammatory infiltration, but was highly vascular. Much dense connective tissue replacement of marrow was also observed. The bone of the transplant also appeared to have been undergoing resorption since large numbers of multinucleated giant cells were seen in numerous resorption lacunae on the trabeculae. Gross observations on the graft at the time of recovery revealed a fluid filled cyst containing about half of the graft, and small blood vessels were seen ramifying over the surface of the nonencysted
part. The graft was firmly attached to the graft bed.

The third surviving tooth was a first mandibular molar which showed one partly encysted cusp, a second undergoing degeneration, and a third, though disorganized and distorted, disclosing viable bone and a small amount of growth (table 8; animal #3). The cusps had broken off and had separated from each other. Two of them contained some surviving ameloblasts although most of their surfaces were free of ameloblasts and enamel (fig. 31). A large enamel space which revealed greatly shortened to cuboidal shaped ameloblasts was seen on one side of a cusp. Other small enamel spaces were seen on the other side of the same cusp. At the extremities of the enamel spaces, the ameloblasts appeared to merge with adjacent stratified squamous epithelium, while in other areas they were separated from other cells by the stratum intermedium. Pre-enamel formation on cusps, which did not cover their entire surface, had been retarded since only thin layers were occasionally seen. The pulp of one cusp was sparsely vascular, degenerated and no surviving odontoblasts were found. An infiltration of lymphoid cells into the pulp was also discerned. A large amount of osteodentin, displaying cellular and vascular inclusions, had formed on one cusp; nevertheless, a more normal appearing tubular dentin had developed nearer the pulp although the dentin was very irregularly in formed. Lining the vascular pulp of this cusp were tall and short odontoblasts. Only a small amount of pre-dentin was seen. The pulp was condensed in character but was not fibrous, and it showed some foci of small round cell inflammatory infiltration. The pulp of the other cusp was fibrous in nature, manifested cellular degeneration, was sparsely vascular, and revealed an lymphoid cell infiltration. No surviving odontoblasts were observed. The tooth was surrounded by a dense fibrous
connective tissue. Only fragments of a bony alveolus remained; most of the bone had been resorbed.

The second mandibular molar of this graft had been entirely resorbed. The incisor which had been broken off at the tip showed a necrotic distal pulp. A part of the distal half of the incisor had become encysted. Viable odontoblasts were not seen in the more proximal areas of the pulp. Bone had formed in the vascular, basal pulp and dense connective tissue had replaced the pulpal cells. Much osteoid had formed on the outer surface of the incisor and ankylosis to the alveolar bone had also occurred. Considerable growth of bone had taken place in the mandible as revealed by an increase in thickness and the number of bony trabeculae. This new bone was very vascular. Some resorption was observed; also areas of bone and marrow replacement by dense connective tissue were noticeable. Calcification of cartilage had occurred in the posterior part of the mandible as well as the formation of new bone. Lymphoid cell infiltration was not so extensive as that observed in other grafts of this series. A large cyst involving the tip of the incisor and the first molar was obvious adjacent to the lingual aspect of the mandibular graft. Gross observations on the transplant at the time of recovery disclosed a firm attachment of the graft to the host bed. The surface of the graft revealed many small blood vessels originating from the surrounding host tissues.

None of the transplants in this series revealed evidence of survival of any of the incisors. The proximal halves of most incisor pulps were vascular, but they failed to show survival of odontoblasts or pulpal cells. In cases where these cells could be identified, they were found to be in various stages of degeneration. Many of the pulps also showed extensive
lymphoid cell infiltration as well as many multinucleated giant cells. The formation of bone on the dentin pulpal surfaces of the incisors was detected in most of the pulps and additional bony trabeculae had formed in the basal pulps of many. The distal areas of the incisor pulps were largely avascular and in general, revealed degenerated, necrotic, cellular material and a poorly staining loose connective tissue. Ameloblasts were absent in most of the incisors or only a few pyknotic nuclei remained. Most of these teeth showed bone on the outer surfaces and ankylosis to the adjacent alveolar bone. In most instances, a dense connective tissue containing numerous multinucleated giant and inflammatory cells was seen around these teeth.

One incisor (table 8; animal #6) was practically intact for its entire length. Some parts of this tooth had been resorbed and some dense connective tissue replacement had occurred while other parts seemed to have undergone resorption as revealed by accumulations of giant cells adjacent to the dentinal surfaces. Ameloblasts were not found. However, the basal part of the incisor showed some cords of squamous cells which may have resulted from dedifferentiation of the basal ameloblasts. This area also disclosed the presence of shortened cells adjacent to the pulpal surface of the dentin. These cells may have been odontoblasts which had undergone some degeneration. A very irregular formation of dentin was seen underlying an irregular thin layer of pre-dentin. The shortened odontoblast-like cells were also located adjacent to the pre-dentin. Other parts of the surface of the pulp chamber showed an osteoid similar to that seen on the outer surface of the tooth. Bony trabeculae were also observed in the vascular pulp of this tooth.

With the exception of one surviving first mandibular molar, revealing growth and differentiation, first mandibular molars had not survived trans-
plantation in this series (table 8). In the remaining eight grafts, two first molars had been entirely resorbed, while all that remained of the other six were thin dentin shells partly resorbed. Some molar remnants were embedded in a dense connective tissue, whereas others had become ankylosed to adjacent spongy mandibular bone. Pulps disclosed dense connective tissue containing lymphoid and giant cells or spongy bone showing marrow. The pulps of other first molar remnants manifested degenerated cells, cellular debris, and lymphoid cells. In most instances, odontoblasts or ameloblasts were not seen, or they occurred as degenerated cellular skeletons.

Except in those cases where second mandibular molars had shown growth and differentiation, they were almost completely resorbed. In one instance, a small irregularly formed, distorted, dentin mass, partly encysted and partly embedded in dense connective tissue was encountered. The pulp revealed no odontoblasts and was invaded by connective tissue and inflammatory cells. A part of the outer surface was covered with squamous epithelium continuous with that of an adjacent cyst. Normal ameloblasts were not found.

In cases where neither molar had survived, a molar alveolus failed to form. In several instances of molar encystment, the cyst occupied a necrotic and resorbing alveolus. The presence of a viable molar appeared to be necessary for the formation of a bony alveolus. In cases where the second mandibular molar had survived, it was contained within an incompletely formed alveolus, separate from the first molar regardless of the fate of the latter or the remainder of the graft.

The mandibular transplants appeared to undergo the most vigorous resorptive reactions in areas where teeth had not survived. These sites disclosed the highest degree of lymphoid cell infiltration as well as bone re-
sorption and dense connective tissue replacement of resorbed bone. Peripheral parts of the mandible generally showed viable bone, an increase in size of trabeculae and vascularity. These areas usually did not show an intensive lymphoid cell infiltration. In some cases, the grafts did reveal a fairly intense peripheral reaction. Most of the transplants in this series also showed a tendency for bone resorption, in central parts of the mandible, concurrent with dense connective tissue replacement of thin centrally located bony trabeculae. Growth of bone was not uniform and large areas of bone growth were only infrequently observed. Most grafts were vascular showing many large and small blood vessels usually extending into the central parts of the mandible.

In general, although three molars were found to have survived and shown growth and differentiation, growth, nevertheless, had been severely retarded as revealed by size when compared with molars in normal intact control jaws (figs. 4, 5, 6, 7). The formation and calcification of enamel was inhibited in all transplants and disturbances in the formation of dentin were also seen in some cases. Viable teeth in these transplants did not reveal the normal amount of dentin or enamel.

3. Experiment Id.

The mandible halves from 14 to 18 hour old neonatal hamsters were transplanted subcutaneously into the dorsal surface in the ear in adult males of an inbred strain. Ten days later all 14 of the implants were recovered (table 1). None of the transplants had been totally resorbed. Of the 14 grafts recovered, only two showed surviving teeth, none of which were incisors (table 9), and of these two, only one molar in each revealed growth and differentiation.
The incisors in all 14 to 18 hour old newborn intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs. 1, 3).

One of the above grafts showed a surviving second mandibular molar (table 9; animal #1). A very small degree of growth and differentiation and development of only one cusp had occurred (fig. 32). Viable ameloblasts covered the cusp, but no enamel had developed. The molar was partly encased within a viable bony alveolus; however, a portion of the alveolus was encysted. An intact stratum intermedium and stellate reticulum were seen. Odontoblasts had differentiated but were immature, as revealed by their very short columnar appearance, and dentin was observed only on the tip of the cusp. The papilla was vascularized and the pulp cells appeared to be normal. No evidence of a lymphoid cell infiltration was detected in the papilla. The growth of this molar was severely retarded as indicated by its small size (figs. 32, 6).

All that remained of the first mandibular molar in this graft were dentin and pre-enamel remnants of cusps embedded in bone. No ameloblasts or odontoblasts were found. Bony trabeculae had formed in the pulp, but no bony alveolus was seen about the tooth. All that remained of the incisor was a dentin remnant which had undergone some resorption. No ameloblasts or odontoblasts were found. The pulp was vascular and consisted primarily of dense connective tissue showing formation of bony trabeculae. The distal quarter of the pulp was avascular and revealed a generalized necrosis and degenerated cells. The tip of the incisor was partly encysted. Most of the
bone in the remainder of the mandible was viable, vascular and normal in appearance disclosing areas of extensive new trabecular formation as well as increase in thickness of other trabeculae. Some calcified cartilage was noted. The center of the mandible appeared to be hollow showing resorption of bone and a dense connective tissue replacement of bone. A cyst with a squamous epithelium lining its cavity was continuous with the dental lamina of the surviving second molar. No lymphoid cell infiltration was observed in this graft. Gross observations on the graft at the time of recovery revealed some swelling in the graft bed and a small fluid filled cyst. The transplant was tightly bound to the subcutaneous part of the graft bed and numerous small blood vessels were detected on the graft surface originating from the surrounding host tissues.

The second graft in this series showed a surviving second mandibular molar (table 9; animal #2). Two developing cusps were revealed, but no dentin or enamel had appeared (fig. 33). Ameloblasts were found on the developing crown and a normal stratum intermedium as well as a stellate reticulum were seen. Odontoblasts had been undergoing differentiation in the vascular and normal appearing papilla. Small capillaries were encountered in the odontoblastic layer. No lymphoid cell infiltration was evident in the papilla. The developing tooth was partly enclosed within a bony alveolus.

All that remained of the incisor in this graft was a dentin shell embedded in dense connective tissue manifesting no surviving ameloblasts or odontoblasts. Dense connective tissue and giant and lymphoid cells were observed in the pulp. No bone was seen in the pulp of this dentin shell; the distal part of which had become encysted.

All that remained of the first mandibular molar were the remnants of
three cusps which had undergone some resorption. These showed pulps containing dense connective tissues and lymphoid cells but revealed no surviving ameloblasts or odontoblasts. The parts of the cusps that were not ankylosed to adjacent bone were embedded in dense fibrous connective tissue. Two cusp surfaces were tangential to the squamous epithelium of an adjacent cyst. Some bone had formed in the pulp of one cusp. The tooth was enclosed within an incomplete bony alveolus. The remainder of the transplant was very vascular and calcified cartilage was seen adjacent to newly formed bone. Extensive lymphoid cell infiltration was observed throughout the graft and considerable dense connective tissue had replaced the marrow as well as the resorbed bone. Small amounts of new bone were seen in peripheral areas of the graft and it seemed that the rate of resorption exceeded new bone formation. Gross observations on the graft at the time of recovery showed a small cyst on one side of the graft. The graft seemed to be fairly vascular and was tightly attached to the subcutaneous part of the graft bed.

The incisors did not survive in all grafts. In the 14 grafts recovered, one incisor had been totally resorbed, while in the rest they revealed degeneration and different degrees of resorption. Some incisors showed pulps with degenerated odontoblasts and pulp cells, in addition to bone formation in the basal regions and a vascular connective tissue invasion. The distal parts of the pulps were usually necrotic and avascular. No ameloblasts were found in any of the incisors. Some ankylosis to the alveolar bone was observed in most of the incisors. In general, the incisors appeared to be the focus of an intensive rejection reaction as indicated by the accumulations of lymphoid and giant cells.

No first mandibular molars survived transplantation in this series.
Although none had been completely resorbed, all revealed varying degrees of resorption. Most of them showed only remnants of cusps disclosing no viable ameloblasts; the latter had degenerated and disappeared in most of the teeth. Several molars were partly or wholly encysted whereas others were surrounded by a dense connective tissue. The pulps frequently showed dense connective tissue, lymphoid and giant cells, or degenerated cells and cellular debris. Some revealed bone in pulps and ankylosis to adjacent bone and a few disclosed marrow in pulps. Several first mandibular molars showed the squamous epithelium of a cyst arranged tangentially to the dentinal surface of the cusps. Squamous epithelial cords were seen in the basal parts of some molar remnants and may have developed from ameloblasts. Differences in the degree of growth, as determined by the amount of dentin matrix remaining at recovery, had occurred, but none appeared to have developed for more than a few days subsequent to grafting before rejection began. No root formation was observed and growth following grafting seemed to be greatly disorganized since the shape of many molars was grossly distorted.

Only two second mandibular molars survived, while the others had either been resorbed or had persisted as the thin dentin shells of cusps. No odontoblasts or ameloblasts were found in any of the molar remnants. These remnants were usually avascular except where dense connective tissue had invaded the pulp chambers. Several showed squamous epithelial cords adjacent to the cusps. Some of the pulps consisted mainly of dense connective tissue and lymphoid cell infiltrations. In one such molar growth and development of two cusps had occurred. The necrotic molar was embedded in dense connective tissue. A few degenerated remnants of ameloblasts were found on the surface of the pre-enamel. Dentin and pulpal osteoid had formed. Some
degenerated cells were seen in the region of the odontoblasts, but degenerated pulp cells were also seen. The pulp had been mostly replaced by inflammatory cells and connective tissue.

In no instance did a viable second molar in a graft reveal the degree of growth and differentiation seen in an intact 15 day control (figs. 6, 7).

In cases where the molars did not survive, no alveolus was seen except in those instances where a cyst occupied the alveolus. The surviving molars in this series were enclosed within an incomplete bony alveolus. It would therefore appear, that the presence of a surviving molar is necessary for the development and retention of a complete alveolus.

All of the grafts showed at least a small amount of viable, vascular bone. Four grafts revealed extensive resorption of the mandible, while six showed much new bone which appeared in the form of new trabeculae and as increases in trabecular thickness. Most of the mandibles revealed resorption centrally and bone formation in peripheral and posterior areas of the mandible. These mandibles disclosing extensive resorption of bone also revealed ossicles with centrally located trabeculae and marrow surrounded by a rim of viable bone. Vascularization of grafts had occurred, and some dense connective tissue replacement of resorbed bone was seen in all grafts. A vascular marrow was usually found in grafts manifesting the least resorption and the most bone formation. However, these also disclosed some areas where the marrow had been replaced with connective tissue.

The majority of the transplants in this series revealed a fairly intensive, mostly small lymphocyte inflammatory infiltration. These cells usually occurred in dense accumulations about teeth in the process of rejection and within necrotic areas of bone. However, in a few instances, dense con-
Centrations of these cells were distributed throughout the graft, and in these cases many macrophages as well as multinucleated giant cells were seen. Such grafts also revealed considerable bone resorption and dense connective tissue invasion. Those grafts showing the most active bone formation also usually showed a less intensive inflammatory cell infiltration. The dense connective tissue surrounding grafts showed foci of these cells in some whereas in others these cells were distributed throughout the surrounding tissue.

Cysts located in the lingual aspect of the mandible were found in all but one transplant. Twelve grafts revealed partial encystment of the distal parts of the incisor and of one or more of the molars. In most cases involving the molars the epithelium of the cyst was found to be tangential to the cusps. In no cases were the mandibles entirely encysted. The cysts appeared to involve only teeth and were usually separated from the remainder of the graft by a dense connective tissue.

c. Half-Mandibles with Partly Excised Incisor (Experiment 15.)

Half-mandibles, from 15 to 17 hour neonatal hamsters, from which most of the incisor had been excised, were transplanted subcutaneously into the dorsal surface of the ear of inbred male adults. All grafts (10) were recovered 15 days following transplantation (tables 1, 10). None were lost or completely resorbed. Only three of the grafts showed surviving teeth and only one molar in each of these had shown growth and differentiation (table 10).

Differentiated ameloblasts were found on all three cusps of the first mandibular molar in all 15 to 17 hour old newborn intact control mandibles (figs. 1, 2). The central cusps had developed dentin and some enamel.
Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs. 1, 3).

The surviving mandibular molars showed varying degrees of growth and differentiation following grafting. In one surviving second molar (table 10; animal #1), two malformed cusps showed pre-enamel on some of the cusp surfaces. A small amount of normal appearing tubular dentin was seen while the remainder of the hard matrix was osteodentin which had formed on the pulpal surface of the tubular dentin which had developed before transplantation (fig. 34). No surviving ameloblasts were seen. Adjacent to the pre-enamel surfaces, small squamous cell cords were seen which may have represented dedifferentiated ameloblasts. Hertwig's epithelial root sheath was not intact and no roots had formed prior to recovery. Several areas of the pulp showed viable, though somewhat shortened, odontoblasts adjacent to a well-vascularized pulp tissue; however, other areas appeared to be devoid of odontoblasts and contained a dense connective tissue which was less vascular and showed a lymphoid cell infiltration. Several areas on the outer surface of the tooth revealed resorption lacunae containing multinucleated giant cells presumably carrying out resorptive functions. The molar was surrounded by a dense connective tissue and was partly encased within a bony alveolus.

Only fragments of several cusps, which had undergone some degree of resorption, were all that remained of the first mandibular molar in the above transplant. Small amounts of tubular dentin, osteodentin, and fibrous pre-enamel were seen, but ameloblasts were entirely absent. Some squamous epithelial cords were seen adjacent to the tooth but no odontoblasts were found. Parts of the cusps were ankylosed to the spongy bone. The tooth apparently was undergoing resorption as indicated by the presence of numerous giant cells.
on the tooth surface. Considerable formation of new bone had occurred in the
mandible in the form of additional trabeculae and growth as revealed by in-
creases in thickness of the trabeculae. Most bony areas disclosed osteogenic
tissue as well as well vascularized marrow, although a few areas showed a con-
nective tissue replacement of the marrow. Viable cartilage, which had under-
gone calcification was seen in the posterior aspect of the mandible. A cyst
had formed adjacent to the first molar which occupied the alveolus of this
tooth. The transplant was generally vascular, but a low degree of lymphoid
cell infiltration prevailed except in the connective tissue between the graft
and the cyst. Gross observations at the time of recovery revealed no evidence
of encystment.

The second graft in this series revealed a surviving second molar, show-
ing considerable growth and differentiation, but it was also distorted and
abnormal in form (table 10; animal #2). Two cusps had developed, but they had
become fused into a mass of osteodentin. No roots were seen. No enamel forma-
tion had occurred and no ameloblasts were observed, although many squamous
cell cords were found adjacent to the outer surface of the tooth. Hertwig's
sheath did not survive intact; nevertheless, several squamous cell cords were
seen in the area suspected to be its normal location. On the pulpal surface
of the tubular dentin a large amount of osteodentin had formed which disclosed
cellular and vascular inclusions. A small pulp chamber remained which was
lined with odontoblasts (fig. 35). Some of these cells revealed signs of
degeneration and appeared to be shorter than normal. Pre-dentin had formed
adjacent to the more normal appearing odontoblasts. Although the pulp was
generally vascular, showing large blood vessels and capillaries within the
odontoblastic layer, its cells seemed to have undergone degeneration since
focal and perivascular accumulations of lymphoid cells were obvious within the pulp. The entire tooth was surrounded by a very dense connective tissue showing focal accumulations of lymphoid cells. Some of the connective tissue fibers attached to the surface of the tooth and to the adjacent, partially complete, viable bony alveolus.

In this graft, two cusps and part of a third were all that remained of the non-viable first mandibular molar. This remnant was partly formed by tubular dentin which showed some fibrous pre-enamel on its outer surface. The pre-enamel surface was tangential to the squamous epithelium of an adjacent cyst and no ameloblasts were found. The pulp revealed a dense connective tissue, sparse vascularity and lymphoid cell infiltration but no odontoblasts. Much of the tooth had been resorbed. It was not encased within a bony alveolus and inflammatory small round cell infiltration was intense about the remnant. The remainder of the graft showed viable bone with much new trabecular bone formation and considerable growth of other trabeculae. On the lingual aspect of the mandible adjacent to the cyst, necrotic bony trabeculae were seen, however, most of the intertrabecular spaces revealed vascular marrow and osteogenic tissue even where the bone had a necrotic appearance. Small bony areas of the mandible showed signs of resorption with a dense connective tissue replacement of resorbed bone. Most of the spongy bone revealed vascular marrow. The graft showed only a moderate degree of lymphoid cell infiltration. The cyst located on the lingual aspect of the mandible occupied the alveolus of the first molar and involved the outer surfaces of the cusps of the same tooth. Gross observations on the graft at the time of recovery disclosed a small cyst in the molar area of the mandible. The transplant revealed many small blood vessels
on its surface and was tightly attached to the graft bed by a dense connective tissue.

A third graft revealed growth and differentiation of a second molar (table 10; animal #3). This tooth showed a more normal growth and differentiation than either of the other two surviving molars described above. Three cusps had developed, but no roots had appeared. The central cusp revealed formation of a thin layer of fibrous pre-enamel but the remaining two cusps were devoid of enamel. Tall, normal appearing ameloblasts covered the entire surface of the crown, and a intact and viable Hertwig's root sheath was seen (fig. 36). Normal tubular dentin had formed on all cusps, but the highest degree of dentin matrix formation was observed on the middle cusp. A layer of predentin had formed on the pulpal aspect of the dentin, but no osteodentin was found. The pulp was vascular and was lined by tall, normal appearing odontoblasts; no degenerative changes were detected in these cells. The pulp cells appeared to be normal with no evidence of lymphoid cell infiltration. The tooth was surrounded by a bony alveolus. The squamous epithelium of a cyst appeared to be continuous with the dental lamina and the outer enamel epithelium of the molar. The cyst had not incorporated any part of the tooth or its alveolus.

The remnant of the first molar in the above graft was found in the form of a roughly spherical mass of osteodentin showing cellular and vascular inclusions but no tubular dentin. Cords of squamous cells were seen tangential to the outer surface of this mass, but no ameloblasts were found. A pulp chamber was not found; consequently no odontoblasts were seen. The mass of osteodentin was encased in dense connective tissue, showed some lymphoid cell infiltration and was partly surrounded by a bony alveolus. Most of the bone
in this transplant had not undergone resorption; however, there seemed to be very little new bone formation. Most of the trabeculae were thin but viable in appearance; nevertheless, some necrotic appearing ones were centrally located while others were seen adjacent to the cyst. A very vascular marrow was observed throughout the graft. Small areas of bony resorption occurred but osteoclasts were not numerous. Resorption seemed most pronounced in the central areas of the mandible where fewer trabeculae were seen than in the more peripheral areas. Lymphoid cell invasion was not extensive throughout the graft; the highest degree of invasion being seen in the tissues adjacent to the cysts. Gross observations on the transplant at the time of recovery did not disclose any cyst formation. The transplant seemed quite vascular and was firmly attached to the graft bed.

None of the first mandibular molars revealed survival in this series (table 10). The molar in one graft had been completely resorbed. The remaining grafts showed non-viable dentin and pre-enamel remnants of the molars. These usually occurred as shells of cusps. Some were totally necrotic, in which case the pulps disclosed only cellular debris and degenerated and inflammatory cells. Other pulps showed either bone or an invasion of dense connective tissue. Several of the first molars revealed the stratified squamous epithelium of a cyst adjacent to the outer surfaces of the remnants. A few showed the dentin shells of cusps embedded in bone and in these cases bone and marrow were found in the pulp. The ameloblasts had not survived transplantation in any of the first mandibular molars in this series. They seemed to have degenerated and were absent except in the few cases where epithelial cords were seen adjacent the tooth remnants. Enamel was usually lacking except on parts of the cusps where the pre-enamel
had not been completely resorbed. In most cases, the ameloblasts, stratum intermedium and the stellate reticulum were replaced by either dense connective tissue, debris and inflammatory cells or bone. Marrow occurred in the pulp in some teeth. The dentin in molar remnants was usually irregular in appearance and showed resorption lacunae.

The second mandibular molars, with the exception of the three surviving molars, were completely resorbed in four of the grafts (table 10). In the remaining cases, all that was seen was the dentin shell of a cusp showing pulps containing dense connective tissue, some lymphoid cells but no odontoblasts. Ameloblasts were also absent. These remnants were usually embedded in dense connective tissue and lacked a bony alveolus. Some small areas of osteodentin were observed in several of the grafts, but resorption of parts of each of the remnants were seen. A rejection reaction, as indicated by the presence of numerous lymphoid cells in the tissues around the molars, was seen to varying degrees in all of the cases. The pulps of all second mandibular molars were avascular except in those cases where a connective tissue invasion had occurred.

In no instance did a viable molar in a transplant reveal the degree of growth seen in an intact 15 day old control (figs. 6, 7).

In those cases where the molars did not survive, the remaining part of the mandible did not reveal a molar alveolus. The formation and retention of a complete alveolus appeared to require the presence of a surviving tooth.

All of the mandibular transplants revealed some viable bone. Most of the grafts showed large amounts of bone and new bone formation, largely as trabecular growth, although new spongy bone was also seen. Intertrabecular spaces revealed viable and vascular osteogenic tissue, but in many cases,
trabeculae adjacent to cysts were necrotic in appearance. Some transplants showed a higher degree of new bone peripherally, while centrally, areas of the mandible had undergone resorption and connective tissue invasion of varying degrees of bony necrosis. Most transplants also revealed a vascular marrow even where most of the graft had been resorbed. A few showed only a few ossicles of bone, and these revealed high degrees of dense connective tissue invasion and replacement of resorbed bone. Thin, lacy, bony trabeculae were found in a few grafts, and these had not undergone extensive remodeling or new bone formation, but dense connective tissue replacement and resorption were seen. Calcified cartilage encased by spongy bone was observed in many of the mandibles. The mandibular grafts in all instances were very vascular but this vascularity was noticeably reduced in areas of intensive inflammation and where dense connective tissue had replaced resorbed bone.

Approximately half of the grafts revealed moderate degrees of inflammatory cell infiltration consisting primarily of small lymphoid and multinucleated giant cells. In these cases the greatest accumulations of such infiltrates were located about the teeth or adjacent to cysts. The remainder of the transplants showed a much more intensive inflammatory infiltration and also larger and more extensive areas of infiltration. With the exception of a few grafts in this series, undergoing massive inflammatory cell infiltrations, most of the transplants revealed considerable viable graft tissue.

Only one of the transplants did not reveal any formation of squamous epithelium lined cysts. Three grafts showed cysts located adjacent to the lingual aspect of the mandible and none of these contained graft tissues. In the remaining five grafts, only one revealed encystment of some graft bone,
while the others showed some epithelium of the cyst to be tangential to or include cusps of the first mandibular molars.

d. Molars in Part of Mandibles (Experiment IF)

The molar containing parts of half-mandibles from neonatal hamsters age 12 to 14 hours were subcutaneously transplanted into the dorsal surface of the ear in male adults of an inbred strain. All grafts (10) were recovered 15 days later (table 1). None had been either totally resorbed or lost. However, one was irreparably damaged during the course of processing; hence the results could not be evaluated. Of the remaining nine grafts, four showed surviving teeth with only one molar revealing growth and differentiation in each (table 1, 11).

The first mandibular molars in all 12 to 14 hour old newborn intact controls showed differentiated ameloblasts on all three cusps at the time of transplantation (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs. 1, 3).

Of the grafts with surviving teeth, one graft had a surviving second mandibular molar which disclosed development of two cusps (table 11; animal #1). However, one cusp was observed to be more advanced in development than the other (fig. 37). The former also showed that root formation on that side of the tooth had begun. Growth of the molar had been severely retarded as indicated by the small size of the tooth (fig. 6). A thick layer of pre-enamel and enamel had formed on the better developed cusp, while enamel was absent on the other. The surface of the crown was covered with tall, normal appearing ameloblasts. An intact Hertwig's root sheath was seen. The stratum intermedium appeared to be normal and the stellate reticulum vascular.
The dentin appeared to be regularly formed, tubular in nature and was thickest on the more mature cusp. A layer of pre-dentin lined the pulp chamber and no osteodentin was found. The pulp cells seemed to be normal in appearance and the pulp was vascular and showed capillaries within the odontoblastic layer. No lymphoid cell infiltration or degeneration were seen in the pulp. Normal appearing odontoblasts with no degenerative signs were seen; nevertheless, these cells were taller on the cusp showing the highest degree of dentin formation. The molar was contained within an incomplete alveolus of viable bone. The squamous epithelium of an adjacent cyst appeared to be continuous with the cells of the dental lamina of this molar; yet, the tooth was not encysted.

Only a few dentin and pre-enamel fragments remained of the first mandibular molar in the above graft. Bone had formed on the surfaces of the fragments which were ankylosed to adjacent spongy bone. No ameloblasts or odontoblasts were seen and the remnants were surrounded by bone and marrow. The remainder of the mandible revealed considerable growth of spongy bone as indicated by the increase in thickness of trabeculae. Most of the bone was viable although there were some areas in which dense connective tissue had replaced the resorbed bone. The rate of new bone formation appeared to exceed bone resorption. Lymphoid cell infiltration was minimal throughout the graft. Usually these were found in discrete foci about a few necrotic areas. A second cyst was located adjacent to the lingual surface of the mandible, but it did not include any graft tissue. Gross observations on the graft at the time of recovery showed a small cyst adjacent to the seemingly highly vascular graft. The transplant was firmly attached to the connective tissues of the graft bed.
The second graft showed a surviving second molar with two developing cusps and root formation (table 11; animal #2). A third immature cusp was seen, but it did not disclose enamel formation, whereas the other two had been covered with enamel. Tall, normal appearing ameloblasts were observed to cover the entire surface of the crown (fig. 38). The dental lamina of the molar appeared to be continuous with the squamous epithelium of a cyst, however, the cyst did not include any portion of the tooth. The layer of enamel seemed normal in thickness but calcification was very irregular. Approximately one-third to one-fourth of the layer was composed of fibrous pre-enamel. Regularly formed dentin was present. It showed a normal tubular character, however, a stratification in calcification had occurred. Zones of disturbed formation of dentin-osteodentin were not found. A layer of regularly formed pre-dentin had developed. The pulp chamber was lined by normal appearing, tall, columnar odontoblasts disclosing no degenerative changes. The cells of the pulp appeared to be normal with no evidence of lymphoid cell infiltration. Many large pulpal blood vessels were seen and capillaries had developed within the odontoblastic layer. The molar was partly surrounded by a bony alveolus, composed of thin but viable trabeculae.

The dentin fragments of four cusps were all that was found of the first mandibular molar in this graft. These were embedded in dense connective tissue, showed lymphoid cell infiltration and were located adjacent to a cyst. The pulp contained fibrous connective tissue and lymphoid cells. No ameloblasts or odontoblasts were seen. The molar was not surrounded by a bony alveolus and many giant cells were found adjacent to its outer surface and within the pulp, indicating that active resorption had been underway. The remaining parts of the mandible showed viable bone although some
necrotic bone was seen adjacent to the cyst. The bony trabeculae were usually thin, nevertheless, some new spongy bone had appeared. Small areas of connective tissue replacement of resorbed bone were seen, but the rate of resorption seemed to be less than that of many other grafts in this series. The marrow was very vascular and lymphoid cell infiltration appeared to be minimal except in the tissues adjacent to the cyst. Gross observations on the graft at the time of recovery did not disclose any cyst formation. The transplant was firmly attached to the graft bed and appeared to be vascular.

A third graft showed a second molar in which some growth and differentiation had occurred (table 11; animal #3). A distortion in the formation of the crown was observed although three cusps had developed. Two of the cusps disclosed pre-enamel, but this layer was absent from the third more immature cusp. Tall, normal appearing ameloblasts, revealing no degenerative signs, covered the surface of the crown (fig. 39). Hertwig's root sheath had differentiated, but no root formation was seen. Although a thin layer of fibrous pre-enamel had formed on two of the three cusps no enamel had appeared. A regular tubular dentin was found on two of the cusps, but none was evident on the third. No disturbances were observed in dentin formation and no osteodentin was detected. The pulp revealed normal appearing pulpal cells and an absence of lymphoid cell infiltration. The pulp was vascular and capillaries were seen in the layer of tall, normal appearing odontoblasts forming the outer limits of the pulp. The odontoblasts in the least well developed cusp appeared to be shorter than normal presumably due to their immaturity. About half of the molar was encased in a bony alveolus composed of viable but resorbing bone. The squamous epithelium of a neighboring cyst
appeared to be continuous with the dental lamina of the molar; however, no part of the tooth was encysted.

Only fragments of cusps were found of the first mandibular molar of the above graft. These had become ankylosed to the adjacent spongy bone. Bone formation had occurred in the pulp and no ameloblasts or odontoblasts were seen. The remaining parts of the mandible showed mostly viable bone; nevertheless, the marrow revealed considerable lymphoid cell infiltration and a dense connective tissue invasion of about half of the transplant. An increase in thickness of trabeculae and a coalescence of peripheral trabeculae to form a compacta indicated that some bone growth had occurred. The formation of new spongy bone did not appear to be so great as that of some other grafts. A large cyst which did not contain any graft tissues was located on the lingual aspect of the graft. Gross observations on the graft at the time of recovery showed a firm attachment and vascularization originating from the host tissues.

The fourth transplant to reveal a surviving tooth showed a second molar which had developed two large cusps and a smaller more immature cusp (table 11 animal #4). No roots had developed. The largest cusp showed a layer of pre-enamel but this layer was absent on the others. Tall, normal appearing ameloblasts covered the crown and a viable, intact Hertwig's root sheath was seen (fig. 40). The central and largest cusp showed a layer of regular tubular dentin, but the dentin layer was not so thick on the other cusps. No osteodentin had developed. The pulp chamber revealed a layer of predentin. The pulp cells appeared to be normal and no lymphoid cell infiltration was seen in the pulp. The pulp was very vascular and capillaries were observed within the odontoblast layer. Normal appearing odontoblasts
formed the border of the pulp of the central cusp, but these cells were somewhat shorter in the pulps of the other cusps which also disclosed less dentin. No degeneration was seen in the odontoblastic layer. The tooth was enclosed within an incomplete alveolus of viable bone. The squamous epithelium of a cyst seemed to be continuous with the dental lamina of the molar; still, no part of the tooth was encysted.

All that remained of the first mandibular molar in the above graft were the dentin fragments of four cusps. Bone had formed in the pulps, and degenerated, giant and lymphoid cells were seen in the pulp. The squamous epithelium of a cyst was located tangential to the outer dentin surface of the fragments. Other fragments were embedded in dense connective tissue or ankylosed to spongy bone. No surviving odontoblasts or ameloblasts were observed. The remainder of the graft revealed viable, vascular bone showing considerable new spongy bone and some calcified cartilage. Considerable growth of bone had also occurred as indicated by increases in trabecular thickness, although some resorption had also occurred as manifested by a dense connective tissue substitution in limited areas, particularly centrally. A viable vascular marrow was seen; but most of the intertrabecular spaces had been filled with osteogenic tissue. Although a lymphoid cell infiltration was generally minimal, a rather dense accumulation of these cells was seen in tissues surrounding the transplant. Gross observations at the time of recovery revealed a seemingly vascular graft and an absence of cysts.

None of the first mandibular molars in this series revealed survival and growth (table 11); however, only one graft revealed complete resorption of this molar. Some grafts showed fragments of molar cusps on which bone had formed and pulps also showed bone and marrow. Ankylosis of the remnants
to adjacent mandibular bone was frequently observed. In others the remnants were embedded in dense connective tissue and showed fibrous connective tissue invasions into the pulp. These also usually revealed accumulations of lymphoid cells within the pulps and about the remnants. Some grafts disclosed a partial encystment of some of the cusps while the remainder of the cusps were usually embedded in a dense connective tissue. The pulps of these teeth usually contained degenerated cells, lymphoid and giant cells and some fibrous connective tissue. Some molars had formed some pre-enamel before rejection. All molar remnants revealed resorption lacunae, containing giant cells, indicating that resorption had been underway. In no cases were viable odontoblasts or ameloblasts observed. The first mandibular molars were not encased in a bony alveolus in a single graft in this series.

The second mandibular molars, with the exception of the four survivors, had been resorbed (table 11). In no instance did a viable molar in a transplant show the degree of growth seen in an intact 15 day old control (figs. 6, 7).

In cases where neither the first nor second mandibular molar had survived, a molar alveolus was never found. A surviving molar appeared to be necessary for the continued development of an alveolus.

The remaining parts of the mandible revealed at least some viable bone and new bone formation. Most of the bone formation had occurred in the form of trabecular growth, and this was seen mainly in the peripheral parts of the graft while in others bone formation had occurred throughout. A few mandibles showed only small amounts of new bone and this had usually occurred as new spongy bone. New spongy bone was however revealed in almost all transplants. Several grafts disclosed large amounts of peripheral compact
bone formed through a coalescence of trabeculae. Central resorption, and a dense connective tissue replacement of resorbed bone, was observed in such grafts. Some necrotic appearing bone was found adjacent to cysts, but viable and vascular osteogenic tissue was also observed in these regions. All of the transplants showed some degree of dense connective tissue invasion and replacement of bone, but a replacement of large areas of grafts was rarely seen. Calcified cartilage was seen in most of the grafts and spongy bone formation had occurred about the cartilage in many. Most of the grafts disclosed a vascular marrow showing only limited degrees of dense connective tissue substitution, but in a few cases substitution of almost all of the marrow was seen. A few grafts had undergone more resorption than bone formation. Widespread necrosis was observed in only a few cases.

Five of nine transplants revealed only a low degree of lymphoid and accompanying giant cell infiltration. In the remaining four, strong reactions, disclosing dense accumulations of these cells, were observed in both transplant and connective tissues surrounding the grafts. Usually, the highest degree of lymphoid cell infiltration was noted about rejected teeth or in bone and other tissues adjacent to cysts. In areas of bony necrosis, large accumulations of these cells were also seen.

The formation of one or more cysts had occurred in each of the grafts. All four showing viable molars disclosed cysts in which the squamous epithelium of the cyst appeared to be continuous with the cells of the dental lamina of the molar. One of these revealed the epithelium of the cyst to be tangential to the surfaces of the cusp remnants of the first mandibular molar. The cysts in these cases did not enclose any of the transplant tissues. In the remaining five, only one showed a part of the first molar
encased within a cyst and a second revealed cyst formation tangential to the remnants of the cusp. In the other three, no graft tissues were involved in any part of the cysts. In most instances cysts were also found in what had formerly been the alveolus of the first mandibular molar.

2. Transplants in Back

a. Half-Mandibles (Experiment IIA)

Half-mandibles from three to 15 hour old neonatal hamsters were transplanted subcutaneously between the scapulae of male adults of an inbred strain. Ten of 11 mandibular transplants were recovered 15 days subsequently (table 1). One graft had been resorbed. Of the remaining 10, none had revealed survival of molars or incisors (table 12).

The incisors in all three to 15 hour old newborn intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1,2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs. 1,3).

The incisors in all of the transplants were necrotic and consisted largely of avascular dentin and pre-enamel shells (table 12). Pulps showed degenerated odontoblasts and pulp cells as well as large amounts of cellular debris. In two cases, the incisor had been completely resorbed. Two others showed some bone formation in the pulps; but in most cases remnants of the incisors were located in areas of necrotic and degenerated graft tissues. No viable ameloblasts were seen in the remains of incisors.

None of the molars revealed any evidence of survival, growth or differentiation in any of the transplants (table 12). Most of them were
found to be necrotic dentin shells of cusps with small areas of pre-enamel, and pulps containing necrotic and degenerated remnants of odontoblasts and pulpal cells and much cellular debris. Very little if any growth of molars had occurred. Some of the molars had been completely resorbed, while others showed varying degrees of resorption. However, the main feature with respect to the molars in this series was the complete or almost complete degeneration of all constituent cells.

The second mandibular molars, except in one case, where a piece of osteodentin still remained, had not formed any dentin and were seen as degenerated cells (table 12).

The remainder of the mandible in most cases was necrotic and largely non-viable. These grafts were also practically avascular in bony areas. A few of the grafts showed some new bone in the mandible, but bone had been undergoing active resorption as indicated by the very large number of osteoclasts. One graft revealed a large amount of new spongy bone throughout; nevertheless, considerable dense connective tissue replacement of resorbed bone and marrow had also occurred. Areas of necrotic bony trabeculae were also seen, but this graft was very vascular when compared with others of this series. Histological examination of another graft disclosed only two ossicles of viable looking bone and these showed that resorption had been underway at the time of recovery. Most of the bony parts of this graft had already been resorbed. In another graft, viable bone was only seen in the posterior part of the mandible. The remainder of the graft was non-viable and necrotic. Extensive resorption had been underway at time of recovery. The rest of the transplants were sparsely vascular and showed non-viable appearing bone; most with extensive necrosis.
The grafts revealing survival and growth of some bone also disclosed an intensive infiltration of lymphoid cells with exception of one case. Those which showed mostly necrotic bone and widespread necrosis of other graft tissues, revealed much less inflammatory cell infiltration, but they usually showed degeneration and cellular debris.

Squamous, epithelial lined cysts were associated with all the grafts. Eight grafts revealed cysts enclosing varying degrees of the incisor whereas only three revealed encystment of parts of molars. However, six grafts showed first mandibular molars separated from cysts on the lingual surface of the mandible by walls of dense connective tissues. One graft revealed the formation of a cyst located lingually in relation to the mandible and this cyst did not encase any transplant tissues.

Gross observations on transplants at the time of recovery showed that all the grafts were very loosely attached to the subcutaneous tissues of hosts. In most instances, mobility of grafts was very pronounced. Usually these grafts showed a meager vascularity as revealed by very small numbers of tiny blood vessels on transplant surfaces.

b. Half-Mandibles with Partly Excised Incisor (Experiment IIB)

Mandibular halves, from three day old neonatal hamsters, with most of incisor and adjacent mandible excised, were transplanted subcutaneously between the scapulæ of inbred male adults. All 10 grafts were recovered 30 days later (tables 1, 13). In none of the grafts was there any evidence of surviving molars (table 13).

The first mandibular molar in three day old neonatal controls showed a thick layer of enamel on all three cusps at time of grafting. The thickness of the enamel was approximately three times that of the dentin. Tall
columnar ameloblasts and odontoblasts covered the crown and lined the pulp chamber of the tooth respectively. Roots had not yet begun to form. The second mandibular molar revealed dentin on all cusps and a layer of pre-enamel was seen. Columnar ameloblasts, but shorter than those seen on the first molar, covered the crown and odontoblasts lined the pulp.

The first mandibular molars did not survive in any of the grafts of this series (table 13). Three of the 10 showed that molars had been completely resorbed. Seven showed non-viable dentin fragments of cusps, some with only a little pre-enamel, which had been undergoing resorption at time of recovery. None of the first molars disclosed viable ameloblasts. The remnants of the teeth were either surrounded by lymphoid cells and cellular debris or were embedded in a dense connective tissue in a few of the cases. The remnants also revealed varying degrees of resorption. The pulps were necrotic and contained some lymphoid cells. Remnants of degenerated odontoblasts lining the pulps at the tips of cusps were observed in several grafts. Small amounts of dense connective tissue were seen in those showing a less intensive reaction. Pulps were either very sparsely vascularized or were avascular. A few pulps showed a small amount of osteodentin. Only two of the first molars showed complete or partial encystment.

Three of the grafts showed total resorption of second molars; however, no viable second molars were observed in the others. The remnants of the second molars usually consisted of one or more dentin shells of cusps showing various degrees of resorption. Viable ameloblasts and odontoblasts were not seen in any of the second molars. Most of the molar remnants were necrotic and were surrounded by lymphoid cells and other cellular debris. The pulps showed remnants of degenerated cells and cellular debris and were
mostly avascular. No growth of second molars seems to have occurred following grafting.

Although no transplant in this series had been completely resorbed, most of the mandibles revealed only small ossicles of viable bone. These were usually spongy in nature. Most of the bone remaining in these grafts consisted primarily of non-viable, necrotic trabeculae and these areas were largely avascular except where dense connective tissue invasions had occurred. Two of the grafts showed no viable bone at all and consisted entirely of necrotic bone. One of these was completely encysted.

Most of the transplants revealed a very intense lymphoid cell infiltration indicative of a strong rejection reaction. These cells were usually seen in dense accumulations throughout the transplants and particularly about rejected teeth. Dense, small, round lymphoid, other inflammatory and giant cell accumulations were disclosed in the host connective tissues surrounding the grafts.

Although the formation of squamous, epithelial lined cysts was encountered, six of these grafts showed no cysts. Only one graft had been completely encysted, whereas another revealed encystment of only the tips of the cusps of the first molar including a small amount of bone. Three others disclosed cyst formation adjacent to the lingual aspect of the mandible, but these were separated from the graft by a wall of dense connective tissue. Gross observations on transplants at the time of recovery showed that most of them were loosely attached to the subcutaneous tissues of the host, and hence, were very mobile. The capsule of connective tissue encasing the grafts was usually thin and the grafts seemed to be moderately vascular although in a few vascularity was noticeably sparse.
3. **Half-Mandibles in Uterine Horn (Experiment III)**

The halves of mandibles from 18 to 40 hour old neonatal hamsters were transplanted into the lumina of uterine horns of adult females. Nine of 10 grafts were recovered at 26 days following transplantation (table 1). In only one host had total resorption of the graft occurred. Histological examination revealed only dense connective tissue and foci of inflammation in another host. None of the remaining eight grafts disclosed survival of incisors or molars (table 14).

The incisors in all 18 to 40 hour old newborn intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time, showed differentiated ameloblasts on all three cusps, but more dentin and enamel had formed than shown in Figures 1 and 2. The second mandibular molars also showed more development and dentin formation than that seen in Figure 3.

One graft recovered at 26 days showed a second mandibular molar revealing considerable growth and differentiation as well as almost complete degeneration of its tissues (table 14; animal #1). Two cusps had developed, but no roots had appeared (fig. 41). The crown was covered with a thick layer of fibrous pre-enamel approximately twice that of the underlying dentin. Except for the area between the cusps, which showed deficient enamel formation, there were no enamel-free areas. On the outer surface of the enamel, only a few groups of ameloblasts still remained. These were tall degenerated cells with pyknotic appearing nuclei. Hertwig's root sheath was almost totally degenerated and was not intact. A thick layer of regular tubular dentin was seen and a thin layer of pre-dentin was found on the surface of the pulp chamber. Only a few tall odontoblasts were found adjacent to the
pre-dentin, but these also revealed signs of advanced degeneration as indicated by their pyknotic nuclei and partial dissolution of cell membranes. Most areas of the pulp revealed total degeneration and a diffuse inflammatory infiltration of lymphoid and some polymorphonuclear leukocytes were seen throughout the pulp. Large and small blood vessels were seen in the pulp, but these were usually empty although some still revealed a few erythrocytes. The tissues around the molar still showed some vascularity, but generally they had degenerated revealing necrotic debris as well as a lymphoid cell infiltration. The incomplete bony alveolus encasing the tooth, showed osteocytes with pyknotic nuclei and acellular trabeculae were observed in parts of the alveolus. Only a part of the distal end of the incisor was found. The rest of the tooth had been resorbed.

The first mandibular molar in this graft had been entirely resorbed. The remainder of the mandible showed mostly non-viable, necrotic appearing bone. Considerable trabecular growth had occurred as revealed by the greatly increased trabecular diameter, however, the lacunae usually contained degenerated osteocytes or were empty. Osteogenic tissue was absent throughout the bony areas and it appeared as though considerable resorption had also occurred. The absence of new spongy bone was particularly noticeable. A diffuse infiltration of mostly lymphoid cells, but some polymorphonuclear leukocytes, was observed throughout the graft. Gross observations at the time of recovery revealed no signs of inflammation or of blood vessels entering the transplant. No cyst formation was seen either on histological or gross examination.

In the remaining eight transplants, five had been resorbed and the others revealed only necrotic, non-viable shells of dentin and some pre-enamel.
The teeth were devoid of odontoblasts and ameloblasts and had undergone varying degrees of resorption.

With the exception of two transplants, all first mandibular molars were completely resorbed (table 14). One graft showed an acellular, avascular dentin fragment of a cusp surrounded by a lymphoid cell infiltration. No odontoblasts or ameloblasts were seen. The second graft showed a piece of a dentin cusp which was also devoid of its constituent cells. All second mandibular molars, with the exception of the one revealing growth and differentiation, were resorbed (table 14).

Only two grafts in this series showed any viable bone at time of recovery. One of these revealed some normal appearing bone which was very vascular, but most of the graft had been resorbed. The viable, vascular, part disclosed growth and osteogenic tissue. The second graft showed a few small ossicles of viable bone while the remainder of the graft was necrotic and largely acellular showing much lymphoid cell infiltration. The remaining grafts all showed necrotic bone, which in one case had become encysted. In the others, most of the original graft had been resorbed. All of the graft revealed widespread necrosis. An intensive inflammatory cell infiltration had occurred in all but one case. Gross observations at the time of recovery usually revealed a failure of the grafts to become incorporated into the wall of the uterine horn. Some grafts appeared to be well attached especially were granulation tissue had occurred.

4. Half-Mandibles in Testis (Experiment IV)

Half-mandibles from one to 12 hour old neonatal hamsters were transplanted into the testis of inbred male adults. Four of five grafts were recovered at 20 days after transplantation (table 1). One graft was lost due
to the death of the host. In none of the remaining four was there any evidence of surviving incisors or molars (table 15). All of four grafts revealed complete resorption.

The incisors in all one to 12 hour old newborn intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs. 1, 3).

Histological examination of the transplantation sites revealed an intense inflammatory activity as revealed by dense foci of lymphoid cells. These foci were surrounded by a dense and degenerating connective tissue forming the wall of a pseudo-cyst-like cavity. No squamous epithelium lined these cavities. Interspersed between the inflammatory cells were large amounts of cellular debris and degenerating cells but no graft tissues. Most of the inflammatory foci also showed considerable necrosis and appeared to be avascular since no blood vessels were seen. The connective tissue surrounding the foci was poorly vascularized. The inflammatory cellular infiltration was observed to extend into the surrounding host tissues although the degree of infiltration into these tissues was less than observed at the focus.

5. Half-Mandibles in Kidney (Experiment V)

Seven of seven, eight to 13 hour old newborn hamster half-mandibles, transplanted into the left kidney of adult males, were recovered 20 days later (table 1). Only one of the seven grafts revealed a surviving molar while another showed a part of a first molar which had undergone a very small amount of growth, but the molar had been rejected (table 16).
The incisors in all eight to 13 hour old newborn intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs. 1, 3).

None of the transplants revealed survival of an incisor (table 16) and only three of the seven grafts showed fragments of incisors which were dentin shells showing lymphoid cells and necrosis of pulps. No viable odontoblasts or ameloblasts were seen. In remaining grafts the areas of the grafts where incisors are normally seen revealed a dense connective tissue replacement of the resorbed teeth.

The surviving first mandibular molar in this series showed considerable growth and development (table 16; animal #1) but less than seen in a 15 day old control (figs. 4, 5). Enamel covered only one side of the crown while the other crown surfaces were enamel-free (figs. 42, 43). A large amount of normal appearing tubular dentin had formed and a thick layer of pre-dentin was also seen. Small areas of osteodentin, revealing cellular inclusions, were seen in the crown while others were observed in the apical portion of the developing root. A normal appearing calcification of dentin was disclosed throughout most of the tooth. Tall odontoblasts were present which in some areas were shorter than normal. The exceptionally vascular pulp was more compact than normal while the pulp cells revealed no disruption and appeared to be normal. An intact and viable Hertwig's root sheath was seen. A dense connective tissue was attached to the enamel-free surface of the crown and to the adjacent bone in the manner of a periodontal ligament (fig. 43).
molar was partly enclosed within a bony alveolus and osteogenic tissue was seen in the intertrabecular spaces of the alveolar bone. Some parts of the alveolus appeared to have undergone resorption.

The incisor and the second mandibular molar had been resorbed in this graft. The remaining parts of the mandible showed mostly viable bone with normal appearing osteocytes and vascular osteogenic tissue about trabeculae. Many regions revealed trabecular growth, but resorption of bone had also occurred, since less bone was found on recovery than had originally been implanted. A cyst was found adjacent to the graft which was separated from it by a thin band of dense connective tissue. No transplant tissues were seen in the cyst. Only a low degree of lymphoid cell infiltration was observed in this graft.

Only fragments of the first mandibular molars were encountered in the remaining grafts of this series (table 16). These revealed no survival of odontoblasts although a few degenerated remnants of these cells were occasionally seen. The ameloblasts had degenerated and were completely absent in most. The pulps disclosed either dense connective tissue or lymphoid cells or they contained only degenerated cells. The molars had been partly resorbed and the remnants showed many resorption lacunae. Lymphoid cells were seen surrounding the remnants of the teeth.

The second mandibular molars had been resorbed in all but one transplant (table 16). This transplant revealed a dentin remnant of one cusp and was located within a cyst. No viable odontoblasts or ameloblasts were observed in the avascular shell.

Some bone growth occurred in all of the grafts although much resorption of bone was also observed. Most of the grafts showed viable osteocytes and
osteogenic tissue was seen adjacent to bony surfaces. The grafts usually were very vascular disclosing numerous blood vessels in the intertrabecular spaces. A normal appearing vascular marrow was present in several transplants, but these also showed varying degrees of replacement of the marrow with connective tissue and some lymphoid cell infiltration. Several of the grafts also revealed hollow ossicles showing resorption centrally and bone formation peripherally. A dense connective tissue replacement of resorbed bone was not infrequently observed in all of the transplants.

Lymphoid cell infiltration of grafts was seen in all; however, those revealing survival of teeth or a large amount of bone revealed the least intensive infiltration. Cyst formation had occurred in all but one graft.

B. Hamster Rib Autografts in Ear (Experiment VI)

Segments of rib from adult male hamsters were subcutaneously autotransplanted into the dorsal surface of the ear. Eight autografts were performed and all were recovered 15 days later (table 2). None of them had been completely resorbed prior to recovery (table 17). Only one of the grafts showed some inflammation and a small cyst. Nevertheless, this transplant showed much viable cartilage and bone. The cartilage had undergone calcification as well as growth. Some chondrocytes appeared to have undergone degeneration. Bone formation was observed and only a small degree of resorption had occurred. The cyst revealed no inclusion of transplant tissues.

None of the other seven grafts revealed any signs of inflammation; calcified cartilage was seen and endochondral ossification had occurred in most of them (table 17). Adjacent to the cartilage surfaces new spongy bone had formed, sometimes in the form of an osteoid rather than in the form of trabeculae. Active resorption of transplants was not observed except in
regions of remodeling and in areas where bone was forming on cartilage. In cases where graft bone revealed a necrotic appearance, new bone had been deposited on the old. In none of these cases had any inflammatory cell infiltration occurred. All of the grafts were very vascular. Gross observations on the transplants at the time of recovery showed that the grafts were very firmly attached to the host tissues on the ear. All of the graft surfaces seemed to be highly vascular.

C. Neonatal Rat Half-Mandible Transplants

1. In Ear (Experiment VII)

Half-mandibles from 12 to 14 hour old neonatal rats were transplanted subcutaneously into the dorsal part of the ears of adult males. Sixteen grafts were carried out in this series and 15 were recovered 15 days later (table 3). One transplant had been lost due to the death of the host prior to recovery. In the 15 remaining grafts, seven surviving teeth were found (table 18). Two of the grafts showed survival of two molars each and three others, survival of only one each. None of the grafts revealed any evidence of surviving incisors.

The incisors in 12 to 14 hour old newborn controls had not erupted. The first mandibular molars of these controls showed formation of three cusps with ameloblast and odontoblast differentiation on all of them. Layers of dentin were seen on all of the cusps with the greatest thickness on the central one. In some cases a very thin layer of pre-enamel was seen adjacent to the tall ameloblasts. The second mandibular molars were developing cusps, but in most of them differentiation of odontoblasts was in its very early stages or had not yet occurred. In both instances the second molars had not formed dentin.
All of the surviving molars in transplants showed growth and differentiation. In one graft a first molar revealed considerable growth of osteodentin, showing cellular and vascular inclusions, which obliterated the normal shape of the tooth (table 18; animal #1). This growth was disorganized in such a way that the original cusps had become embedded in osteodentin. The molar appeared to be a solid block, with a pulp cavity showing several pulpal horns, and part of it had become inverted in such a manner that odontoblasts appeared on the outer surface of the mass in many parts (fig.44). The entire surface of the tooth was enamel-free and no ameloblasts were found. Very little tubular dentin was seen. This had been very irregularly formed disclosing an uneven layer on the pulpal aspect of the osteodentin. The pulp seemed to be fibrous in nature in some parts and was very vascular. The pulpal cells showed many signs of degeneration and a lymphoid cell infiltration was seen throughout the pulp. The pulp was lined with short odontoblasts some of which had undergone degeneration. One side of the outer surface of this molar also showed some short odontoblasts and a thin layer of pre-dentin. No odontoblasts could be found in some regions of the pulp. Pulpal pre-dentin formation was usually seen in the form of a thin and very irregular layer. The tooth was embedded in dense connective tissue and showed a very intense lymphoid cell infiltration and a large number of giant cells. Only part of the molar was surrounded with a bony alveolus most of which had been resorbed.

All that remained of the second mandibular molar in this transplant was a small crescent-shaped piece of dentin with osteoid formation on its outer surface. No ameloblasts were found. The pulp revealed short osteoblast-like cells but normal columnar odontoblasts were not seen nor were normal pulpal
cells found. The tooth was surrounded by a dense connective tissue containing a very intensive lymphoid cell infiltration. It was encased within a bony alveolus.

Remnants of the incisor in this transplant consisted of a broken shell of dentin partly ankylosed to adjacent spongy bone. The pulp revealed a few degenerated cells, but its basal parts showed bone formation and an ingrowth of dense connective tissue. Considerable trabecular growth had occurred in the remainder of the mandible. A peripheral coalescence of trabeculae to form a compacta was noted. A dense connective tissue replacement of much of the resorbed bone was observed and marrow had been replaced by connective tissue. A dense lymphoid cell infiltration was seen throughout the graft and around the remaining parts of the teeth. Cyst formation had occurred but the graft tissues had not been involved. Gross observations on the transplant at the time of recovery disclosed a vascular graft firmly attached to the subcutaneous tissues of the host.

A second graft revealed survival of a first and second molar (table 18; animal #2). Considerable distortion of growth and development was seen in the first molar. Three cusps had developed and some root formation had occurred. The distorted crown was enamel-free except for one small area which showed an enamel space lined with cuboidal ameloblasts. The enamel-free area of the crown was composed of osteodentin and tubular dentin and was covered with a cellular cemento-osteoid. Fibers from the surrounding dense connective tissue were attached to its matrix. Most of the tooth was composed of osteodentin showing both cellular and vascular inclusions (fig. 45). More internally a large amount of irregular tubular dentin was observed. A layer of irregular pre-dentin was seen throughout most of the tooth adjacent
to the pulp chamber. The pulp revealed many large blood vessels and capillaries; however, the pulp cells seemed to have degenerated in some areas, but most of the pulp was more fibrous than normal. Some parts of the pulp disclosed ingrowths of dense connective tissue. A low degree of lymphoid cell infiltration was seen throughout the pulp. These cells were observed mainly as perivascular foci of lymphoid cells. In some areas a very diffuse distribution of these cells was also seen. Other areas of the pulp appeared to be free of these cells. Odontoblasts were found in most of the pulp, but many of them appeared to have been undergoing degeneration as indicated by a decrease in their height when compared with normals. The partly developed root of this molar was greatly deformed and showed some perforations. Part of Hertwig's root sheath was seen, but most of it had degenerated. The tooth was encased within a bony alveolus which seemed to have undergone some resorption and showed an intense lymphoid cell infiltration into the marrow.

A small cyst was located adjacent to the surface of one cusp and part of the epithelium of the cyst was tangential to the cusp surface; yet no part of the tooth had become encysted.

The second molar of this graft showed considerable growth, which appeared largely as osteodentin formation (table 18). The shape of the molar resembled a bell with greatly thickened walls formed primarily by cellular osteodentin peripherally and a very irregularly deposited dentin adjacent to the pulp (fig. 46). Very little pre-dentin was seen. The entire tooth was devoid of enamel and no ameloblasts were found. The outer surface of the molar revealed a cellular osteoid and dense connective tissue fibers were attached to it. The pulp manifested small perivascular accumulations of lymphoid cells, but the pulp cells seemed to be normal although the pulp appeared to be fibrous
in areas adjacent to the connective tissue surrounding the tooth. Odonto-
blasts lined the pulp, but they were absent in some areas. These cells
were less numerous than in normal teeth and in some cases were more cuboidal
than columnar. Some degenerative signs were also noted. The very vas-
cular pulp revealed numerous large blood vessels and capillaries were seen
within the odontoblastic layer. The tooth was embedded in dense connective
tissue showing foci of lymphoid cells. Some bundles of connective tissue
fibers were attached to the tooth surface and extended to the bony alveolus.
The tooth was surrounded by an incomplete bony alveolus. A small cyst was
seen adjacent to the tooth, but no part of it had become encysted.

The incisor in this graft had been almost completely resorbed and
only a few dentin fragments ankylosed to bone remained. No ameloblasts
were seen. The remainder of the mandible revealed growth of trabeculae
and a coalescence of peripheral trabeculae to form compacta. Most of the
bone formation appeared to have occurred as an enlargement of trabeculae
rather than as a formation of new spongy bone. Viable and calcified
cartilage was also present. An intensive lymphoid cell infiltration was
observed which was seen within the graft and neighboring host connective
tissues. Gross observations on this transplant at the time of recovery
disclosed a firm attachment of the graft to the subcutaneous tissue capsule
surrounding the graft. The transplant seemed to be very vascular and a
small cyst had formed at the angle of the mandible.

In a third transplant, a surviving second mandibular molar was found
which revealed considerable growth and development (table 18; animal #3).
Some root formation had occurred (fig. 47). Two cusps had developed, but
the crown of the molar had become flattened. A thick layer of enamel
covered the entire crown surface and an enamel space was observed adjacent to the dentin. A few areas of hypoplastic enamel formation were seen. Enamel calcification had been retarded since most of it was fibrous in nature. Ameloblasts covered most of the surface of the enamel; however, in a few areas these cells seemed to have undergone some degeneration. The stratum intermedium had largely disappeared and only a few degenerated cells could be found. The stellate reticulum had been infiltrated by a dense accumulation of lymphoid cells. Hertwig's root sheath, though still identifiable, revealed many degenerated cells. Small capillaries were seen adjacent to the ameloblastic layer. A thick layer of irregularly formed tubular dentin was seen beneath the enamel. One cusp showed osteodentin, but the matrix which had formed later was tubular in nature. A layer of regularly formed predentin was also disclosed. The pulp revealed normal appearing cells except in the regions of inflammation where some degeneration had occurred. A large number of blood vessels were seen in the pulp and capillaries were recognized within the odontoblastic layer. Small lymphoid cells were found in perivascular accumulations in most areas of the pulp, but in some areas these cells were more diffusely distributed. Tall odontoblasts lined the pulp, but these cells seemed to have undergone some degeneration. Some cemento-osteoid had formed where root development had occurred. The tooth was surrounded by a dense connective tissue showing an intensive lymphoid cell infiltration. An alveolus, which had been partly resorbed, encased only part of the molar. Adjacent to the molar, but separated from it by a dense connective tissue, a cyst was seen.

The incisor of this graft had been almost completely resorbed and disclosed only a dentin fragment ankylosed to adjacent bone. The pulp revealed
bony trabeculae and a small amount of osteodentin. A dense connective
tissue ingrowth had occurred, but no odontoblasts or ameloblasts were seen.
The first mandibular molar of this graft had been resorbed. A growth of
bony trabeculae was observed in the remainder of this graft as well as a
small amount of new spongy bone. A coalescence of trabeculae to form a
compacta had occurred in the periphery of the transplant. Some resorption
had occurred and a considerable replacement of resorbed bone with con-
nective tissue, and a dense connective tissue invasion into the marrow
had taken place. Although cyst formation had occurred, the graft tissues
were not encysted. In general, a very intense lymphoid cell infiltration
was seen in all of the graft tissues and within the surrounding connective
tissues of the host. Gross observations on the transplant at time of re-
covery disclosed a vascularized graft firmly attached to the subcutaneous
tissues of the host.

A fourth graft revealed survival of a single molar (table 18; animal
4). This tooth, a second mandibular molar, revealed a high degree of
disorganized and distorted growth and development. The tooth seemed to
have undergone some degeneration. Root formation had begun. The cusps had
fused into masses of osteodentin. Most of the crown was enamel-free and
only two enamel spaces were seen. These showed cuboidal to short columnar
ameloblastic lining cells. A large amount of osteodentin disclosing many
cellular and vascular inclusions had formed but some irregularly formed
tubular dentin was seen in the pulpal aspect (fig. 48). The formation of
pre-dentin was seen adjacent to the vascular pulp. The pulp chamber re-
vealed short odontoblasts, most of which seemed to have undergone some
degree of degeneration. The pulp cells also showed some degeneration and
the pulp revealed an intense lymphoid cell infiltration. Regions of the crown, not covered with enamel, revealed a cellular cemento-osteoid in which were embedded connective tissue fibers originating from the connective tissue surrounding the tooth. The molar was partly enclosed with a bony alveolus which had undergone resorption.

All that remained of the incisor in this graft was a dentin shell. The pulp revealed mostly necrotic, degenerated cells and debris. A small amount of osteoid formation had occurred in the basal pulp. No viable odontoblasts or ameloblasts were observed. A distorted dentin remnant is all that was found of the first mandibular molar. The pulp had been invaded by dense connective tissue and the remnants of the tooth were embedded in dense connective tissue disclosing an intensive lymphoid cell infiltration. Although much bony resorption had occurred in the mandible itself, many of the bony trabeculae had increased in thickness and viable osteocytes were seen. Cyst formation had occurred but no graft tissues were found within it. A lymphoid cell infiltration of the graft and the surrounding host tissues was very intense and was indicative of a strong rejection reaction. Gross observations on the graft at the time of recovery revealed a vascular graft that was firmly attached to the host connective tissue. A cyst was seen on the surface on the graft.

The fifth graft to reveal viable teeth, showed survival of a second mandibular molar (table 18; animal #5). The first molar disclosed development of two cusps. Considerable osteodentin was also seen (fig. 49). The shape of the tooth was greatly distorted and growth was disorganized. Only a small area of the crown showed any pre-enamel while the rest of the crown was devoid of enamel and pre-enamel. Only one cusp revealed an intact Hertwig's root
sheath. The area of the crown showing pre-enamel also showed some tall ameloblasts. In the absence of enamel, a cellular cemento-osteoid had formed on the outer dentin surface. The molar consisted primarily of a thick but irregularly formed layer of tubular dentin but external to the tubular dentin there was a large amount of osteodentin showing numerous cellular and vascular inclusions. Yet, the formation of dentin seemed to be more regular in areas nearest the pulp and pre-dentin lined parts of the surface of the pulp chamber. The pulp was vascular but revealed some degeneration as well as foci of lymphoid cells. Tall odontoblasts lined most of the pulp chamber, but some of these cells also appeared to have been undergoing degeneration. The nature of the pulp seemed to be somewhat more fibrous than that of normals. Attached to the cemento-osteoid, on the outer surface of the molar, connective tissue fibers appeared to radiate outward into the dense connective tissue surrounding the molar. Some of these fibers were observed to attach to the bone of a partly formed bony alveolus. A large cyst was seen adjacent to the molar. As in most of the teeth in this series, the dense connective tissue enclosing the molar revealed an intense infiltration of lymphoid cells.

The second mandibular molar of this graft had also survived but it showed distorted growth and development (table 18). This tooth was smaller than the adjacent first mandibular molar and disclosed that enamel had formed only on one surface of its malformed crown (fig. 50). It appeared that one cusp of this tooth had continued to develop while the other had become detached and had degenerated. Only one necrotic dentin remnant of the second cusp was found. Considerable osteodentin formation had occurred. Only part of a Hertwig's root sheath was seen. Root formation had not occurred. Tall columnar ameloblasts were observed on the crown adjacent to enamel, but these
cells were absent on the remainder of the crown (fig. 50). The stellate reticulum and stratum intermedium had degenerated. Although a regular tubular dentin was seen, much of the tooth was comprised of osteodentin. Most of the tubular dentin was located nearest the pulp. Degeneration of pulp cells had occurred in some parts of the pulp and a lymphoid cell infiltration was also seen, but the greatest accumulations of lymphoid cells were perivascular. The vascular pulp revealed large blood vessels and capillaries were apparent within the layer of odontoblasts. Although some areas of the odontoblasts showed degeneration and were located adjacent to areas of disturbed dentin formation, most of the odontoblasts seemed to be normal. The tooth was surrounded by a dense connective tissue revealing a dense lymphoid cell infiltration. The bony alveolus had been practically completely resorbed. Gross observations at the time of recovery revealed a vascular graft firmly attached to the subcutaneous tissues of the host.

The incisor had been completely resorbed in this transplant. The remainder of the mandible showed some viable bone although lymphoid cell infiltration was extensive and considerable resorption and connective tissue substitution of resorbed tissue had occurred. The remaining bony trabeculae had increased in diameter. Much of the marrow had also been replaced with a dense connective tissue and revealed lymphoid cell infiltration although cyst formation had occurred, no graft tissues were involved.

In the remaining 11 grafts, the incisors had either been resorbed or all that remained of them was necrotic dentin shells which in some cases disclosed some pre-enamel. No viable odontoblasts or ameloblasts were seen. Some pulps showed bone formation while in others dense connective tissue had replaced all pulp tissues. Varying degrees of resorption and a cellular
lymphoid infiltration were observed in all incisors.

In 12 of the grafts, no first mandibular molars had survived. In four grafts, they had been completely resorbed, while in the remaining eight, only non-viable, dentin remnants of cusps were seen. None of the latter revealed viable odontoblasts or ameloblasts. Two showed a mass of osteodentin without pulp chambers, while the remainder were dentin remnants showing dense connective tissue, bone or cellular debris and lymphoid cells in the pulp. None of the molars were enclosed within a bony alveolus with the exception of the two osteodentin masses which were embedded in a dense connective tissue. Some ankylosis of the fragments of cusps to adjacent spongy bone was seen.

The second mandibular molars had also been resorbed in seven of the transplants. Another five were found to be viable and were described above. The others revealed dentin fragments of cusps, none of which showed viable odontoblasts or ameloblasts. These remnants usually revealed degenerated cells in the pulps and a dense connective tissue invasion. One remnant disclosed an encysted cusp, but none of the others showed total encystment of the teeth. These molars in all instances were located within foci of lymphoid cells.

All of the mandibles in this series showed varying amounts of viable bone. Most of them revealed an increase in the diameter of trabeculae and some formation of new spongy bone. Some resorption of bone and dense connective tissue substitution were also observed in all of these mandibles, but in several of them most of the bone was necrotic with a high degree of graft bone already resorbed.

Eleven of the 15 transplants revealed a very strong rejection reaction
disclosing dense accumulations of lymphoid and giant cells. Although some marrow was usually observed, most of the grafts manifested varying degrees of connective tissue invasion of the marrow accompanied by such inflammation. Two of the grafts revealed a moderate reaction and two others displayed a relatively light infiltration. Although all of the grafts revealed cysts, only one graft showed a molar and the tip of the incisor incorporated within a cyst. The remainder did not show encystment of graft tissues.

Gross observations on the transplants at the time of recovery showed that the majority of them were very firmly attached to the subcutaneous tissues of the hosts. Most of the grafts also disclosed many small blood vessels on the surface of the mandibles.

2. In Kidney (Experiment VIII)

Half-mandibles secured from six to 10 hour old neonatal rats were transplanted into the kidney of male adults. All grafts (12) were recovered 15 days after transplantation. None had been lost or resorbed prior to recovery. Only one of the grafts revealed a surviving tooth (table 19) and in no case was there any evidence of surviving incisors.

The incisors in six to ten hour old newborn controls had not erupted. The first mandibular molars of these controls showed formation of three cusps with ameloblast and odontoblast differentiation on all of them. Layers of dentin were seen on all of the cusps with the greatest thickness on the central one. In some cases a very thin layer of pre-enamel was seen adjacent to the tall ameloblasts. The second mandibular molars were developing cusps but in most of them differentiation of odontoblasts were in very early stages or had not yet occurred. In both instances the second molars had not formed dentin.
The first mandibular molar was the only viable tooth in this series and it revealed considerable distortion in growth and development (table 19; animal #1). One cusp had formed, but it was free of enamel (fig. 51). A low degree of root development had also occurred, but the root appeared to have broken away from the molar (figs. 52, 53). No enamel was found on the crown; however, some spaces lined with tall columnar cells were seen adjacent to the dentin. Most of the crown was composed of osteodentin revealing many cellular and vascular inclusions; nevertheless some areas of tubular dentin were also seen (fig. 51). Some of the tubular dentin had been deposited over osteodentin and seemed to have been more recently formed. The tubular dentin also showed an irregular pre-dentin formation. Some of the outer surfaces of the molar disclosed pre-dentin formation in areas were enamel would normally have been found. Most areas of the pulp showed viable odontoblasts, but some of these cells were shorter than normal. Odontoblasts lined most of the pulp and pre-dentin was seen adjacent to them. The pulp, though somewhat more fibrous than normal, revealed large blood vessels. Capillaries were found within the odontoblastic layer. A noticeable absence of lymphoid cell infiltration was seen in the pulp while only a few such cells were seen in the tissues encasing the molar. Parts of the outer surface of the molar showed a matrix containing some flattened, small cells to which a fibrous connective tissue was attached. The molar was encased within an incomplete alveolus of viable bone containing marrow.

A fragment, in the shape of a cusp, was found in this graft, but it could not be positively identified as a part of the first molar or a developing second molar (fig. 53). The fragment showed considerable enamel formation but also areas of hypoplastic calcification. A layer of pre-enamel was seen
adjacent to an uninterrupted row of tall ameloblasts which extended to the base of the cusp to form a Hertwig's root sheath. The tubular dentin was regularly formed. On the pulpal dentin surface a layer of pre-dentin was observed. Tall odontoblasts were seen in the very vascular pulp. The pulp also showed normal appearing pulp cells but it did not reveal any lymphoid cell infiltration. The tooth fragment was surrounded by dense connective tissue and part of a bony alveolus was noted. The incisor of this transplant had been resorbed. The remainder of the mandible in this graft occurred in the form of a large, almost hollow ossicle containing the parts of the tooth and centrally it showed trabeculae and a vascular marrow. Peripherally portions of more compact bone were observed showing greatly thickened trabeculae. Lymphoid cell infiltration seemed to be minimal and very few areas of necrotic tissue were seen. However, some dense connective tissue substitution of resorbed bone had occurred. A squamous epithelium lined cyst was found adjacent to the first molar, but no graft tissue was encased in it.

One transplant disclosed only a remnant of a tooth (table 19; animal #2). Some areas of this graft had been damaged during processing and were lost. The remaining tubular structure was comprised of dentin and pre-dentin. Some cuboidal odontoblasts were seen adjacent to the outer pre-dentin surface. Centrally, the pulp-like chamber disclosed a basophilic matrix and a fibrous material associated with some tall, columnar ameloblast-like cells. The fragment had become partly ankylosed to adjacent spongy bone.

Another graft revealed a large osteoid and osteodentin mass which apparently was the remnant of the first mandibular molar but was not conclusively identified as such (table 19; animal #3). This mass disclosed several internal cavities which were lined with cuboidal cells. Many cellular
inclusions were seen in the matrix which was mostly fibrous and non-tubular in nature and comprised the bulk of the tooth. The outer osteoid surface was covered primarily by osteoblast-like cells and bony trabeculae.

In none of the grafts was there any evidence of the survival of an incisor. Four of the grafts revealed complete resorption of the incisors. The remaining eight showed only dentin shells which had undergone varying degrees of resorption. In none of them were viable odontoblasts, ameloblasts or pulp cells seen. Usually some osteoid and bone were observed in some of the pulps, while in other pulps, only dense connective tissue, cellular debris, degenerated cells and lymphoid cell infiltrations were seen. A vascular pulp was usually seen where pulpal bone formation or connective tissue ingrowths had occurred.

No first molars, other than those already described, survived in this series. Eight had been resorbed. One showed a small fragment of dentin added embedded in dense connective tissue containing a lymphoid cell infiltrate. This tooth had been practically resorbed while the fragment remaining was undergoing resorption.

In eleven of the 12 grafts resorption of the second mandibular molar had occurred. Only one disclosed a possible surviving tooth and that was described above.

All of the transplants in this series revealed at least a small amount of viable bone. Nevertheless, several displayed considerable bone formation. Without exception, grafts revealed active bone resorption as indicated by the small amount of bone remaining and the large number of osteoclast observed throughout the grafts. Several grafts manifested mostly necrotic, non-viable appearing bone and some encystment of bone. Whenever vascular marrow was not
seen, a dense connective tissue or a lymphoid cell infiltration was noticed in the intertrabecular spaces. Hollow ossicles occurred in most grafts in which the central cavity disclosed some trabeculae surrounded by either marrow or dense connective tissue.

All but one of the grafts revealed one or more cysts. In one case, part of the distal half of the incisor had become encysted, but the cyst did not include other graft tissues. Two other grafts disclosed encystment of part of the transplanted mandibular bone which was found to be necrotic and non-viable. The remaining eight grafts revealed cysts, but none of these involved graft tissues.

Ten of 12 transplants revealed intense reactions as revealed by the degree of lymphoid cell infiltration. These grafts disclosed dense accumulations of these cells throughout the entire transplant. Still, some of these also showed a large amount of viable bone. Two grafts showed a mild lymphoid cell infiltration with considerable bone growth. A surviving molar was found in one of these.

D. Neonatal Half-Mandible Transplants in 6-Mercaptopurine and Vehicle Treated Hamsters

1. In Back
   a. Experiment IXA

Six of eight half-mandibles from 12 to 20 hour old, neonatal hamsters, transplanted subcutaneously between the scapulae, were recovered 15 days later from inbred male adult hamsters which had received daily intraperitoneal injections of 10 mg/100 gm body weight of 6-mercaptopurine (6-mP), beginning at time of grafting and continued for 12 consecutive days (table 4). Two grafts in treated hamsters were not recovered since one host had died and one
graft had been totally resorbed before termination of the experiment. Eight control hamsters received identical transplants and treatment with vehicle, but only six of the eight were recovered at 15 days (table 4). Two of the controls had died before the termination of the experiment and consequently, transplants were not recovered. Only one of the grafts in the 6-MP treated hosts had survived and shown growth of a molar (table 20). None of the remaining grafts from either the 6-MP or the vehicle treated controls disclosed viable teeth.

The incisors in all one to 20 hour old newborn intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs. 1, 3).

The surviving tooth, in the graft in the 6-MP treated host was a second mandibular molar which showed only a small amount of growth and differentiation (table 20; animal #1). The degree of growth of this molar did not approach that of a 15 day control (figs. 6, 7). Two cusps had developed, but only one of these revealed pre-enamel formation and this layer was only about half to one third as thick as the dentin layer. However, dentin had formed on both cusps (fig. 54). Root formation had not yet begun. Tall, normal appearing ameloblasts covered the entire surface of the crown, but one small area at the tip of one cusp, disclosed ameloblasts showing signs of degeneration. A small cyst was seen within an otherwise viable and vascular stellate reticulum. Another larger cyst was found adjacent to the molar and its dental lamina seemed to be continuous with the squamous epithelium of this cyst.
A layer of dentin had formed on both cusps, but it was thickest on the cusp on which pre-enamel formation had occurred. The formation of dentin was apparently not disturbed and no osteodentin was seen. A layer of pre-dentin lined the pulp chamber throughout the tooth. A continuous layer of tall, normal odontoblasts lined the pulp and revealed no degenerative changes. These cells were shorter than normal in the pulp of the less well developed cusp. The pulp cells appeared to be normal, and no pulpal lymphoid cell infiltration was observed. The pulp showed capillaries within the odontoblastic layer, but no connective tissue invasion had occurred. For the most part, the molar was surrounded by a dense connective tissue and the tooth was partly encased within a bony alveolus.

The incisor of the above graft consisted of a dentin shell. The outer surface of the shell was ankylosed to bone and no viable ameloblasts were observed. The tip of the incisor was encysted. The basal part of the pulp was very vascular showing bone formation and some dense connective tissue. However, more distally, the pulp revealed degenerated odontoblasts and pulp cells as well as some cellular debris and necrosis. Only a small number of lymphoid cells was observed in the pulp. The first mandibular molar of this transplant showed remnants of three cusps which had become separated by a cyst. The cusp that remained in its relatively normal position, had become ankylosed to bone, had broken and showed no viable odontoblasts or ameloblasts. The other two cusps had been displaced towards the incisor remnant and were mostly encysted. The non-encysted parts were embedded in a dense connective tissue containing giant and inflammatory cells. The pulps revealed similar cells and dense connective tissue. All of the cusps had undergone some resorption and none were encased within an alveolus.
Much of the mandible in this graft had been resorbed; however, new spongy bone had also formed in peripheral and central areas. Most of the remaining bone appeared to be viable and vascular and considerable marrow had been replaced by osteogenic tissue. A high degree of trabecular growth, as shown by an increase in thickness, had occurred and areas of resorbed bone had been replaced by a dense connective tissue. Only parts of the incisor and first molar had been encysted. A cellular inflammatory infiltration, which was relatively minor, consisted predominantly of polymorphonuclear and some lymphoid cells. Gross observations at the time of recovery showed numerous large blood vessels on the surface of the graft which was firmly attached to the graft bed of the host. The transplant had become encased in a dense connective tissue capsule but not encysted.

The graft in the control host, on the other hand, revealed rejection of the incisor, the first molar and complete resorption of the second molar (table 20; animal #2). Only a dentin shell, with some pre-enamel but no ameloblasts, remained of the incisor. The largely avascular pulp showed little lymphoid cell infiltration except basally, but revealed necrosis. The pulpal cells and odontoblasts had degenerated. The distal part of the tooth and a portion of its bony alveolus were encysted. The first mandibular molar was observed to consist of three separated dentin remnants of cusps, two showing a small amount of pre-enamel. These remnants were embedded in a dense connective tissue containing lymphoid cells. The pulps were avascular and contained degenerated cells, cellular debris and lymphoid cells.

More than half of this graft in the control had been resorbed and most of the remaining bone was either encysted and necrotic, or embedded in dense connective tissue. Most of the marrow had been replaced by a dense connective
A much more intense rejection reaction was observed in this graft, as compared to the 6-MP treated graft, when evaluated by the degree of infiltration with mostly lymphoid cells and some polymorphonuclear cells and macrophages. Furthermore, much less bone had survived in the control. The absence of bone formation was particularly evident. Widespread necrosis as well as active resorption were also evident in the control graft. Gross observations at time of recovery showed more swelling and tissue edema at the site of this graft than was noted in the experimental graft. Many small blood vessels were seen on the surface of the control but numerous small cysts were also seen.

In transplants in neither the 6-HP treated nor the control hosts had the incisors survived. One graft in a treated host revealed total resorption of the incisor while one in a control host showed only a few fragments of dentin remaining. In most cases, the incisor in grafts in treated and control hosts was a mere dentin shell which had undergone varying degrees of resorption. However, more bone formation was seen in the pulps in grafts in control hosts than in those of treated hosts. Most of the grafts in treated hosts showed a more intense lymphoid cell infiltration about the incisor than was observed in grafts in control hosts while encystment of incisors had frequently occurred in both groups. None of the incisors in the grafts of either 6-HP treated or control hosts revealed survival of ameloblasts, odontoblasts or pulp cells.

The first mandibular molars did not survive in 6-HP treated or control animals. One graft in each group showed total resorption of these molars. Although more of the molar dentin remnants appeared to remain in the treated than in control groups, neither revealed survival of this tooth, and all of
them had undergone some resorption. Most of the molars consisted of one or more cusps surrounded by lymphoid cell infiltrations and a few revealed partial encystment. In none of them were any surviving odontoblasts or ameloblasts seen. The rejection reaction was usually greater around the molars than in any other area with the exception of the incisors. In no case had a molar alveolus survived except in cases where the molar had been encysted and the alveolus was occupied by that cyst.

Second mandibular molars were resorbed in grafts in both 6-HP treated and control hamsters with the exception of the one surviving molar and a dentin fragment in another host. This fragment was located adjacent to a cyst. The pulp revealed degenerated cells and no surviving odontoblasts or ameloblasts were observed.

In general, the grafts in both treated and control hosts manifested varying degrees of bone resorption as well as bone formation. The rate of bone resorption seemed greater than that of formation in most transplants of both series. The viable bone was usually highly vascular.

The inflammatory rejection reaction in general appeared to be of about equal intensity in both 6-MP treated and control groups. There was no consistent pattern with respect to a decrease in the reaction intensity of the treated group. The most intense lymphoid cell infiltration was usually observed in the areas of rejected teeth and necrotic bone. Cyst formation was evident in grafts in all treated hosts and in all but one of the controls. Complete encystment of the transplant was observed in only one graft and this occurred in a treated animal. The remaining grafts in both treated and control hosts showed cyst formation involving the distal part of the incisor and in some cases the first molar. Treatment of hosts with 6-MP did not
seem to reduce the incidence of cyst formation in grafts.

b. **Experiment IXB**

Three of four half-mandibles from 12 to 13 hour old, neonatal hamsters were recovered from the subcutaneous area between the scapulae of inbred adult male hamsters having received intraperitoneal injections of 10 mg 6-HP daily/100 gm body weight beginning at time of implantation and continued for 10 days at the end of which time the grafts were recovered (table 4). Four of four grafts in control hosts were recovered from hosts having received an identical treatment with the aqueous vehicle (table 4). The transplant in one treated host was lost owing to the death of the host. One graft in a 6-HP treated and one in a control host were recovered at six days subsequent to grafting, due to the toxic effects of the drug on the treated host (table 4).

The incisors in all 12 to 13 hour old newborn intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs. 1, 3).

No evidence of survival of molars or incisors was found in grafts in either the 6-HP treated or control series (table 21). The treated host, from which the graft had been removed at six days, had shown a weight loss of 32 gm during the post-transplantation interval. This animal revealed a severe diarrhea, a scabby appearing mouth, and a shabby, dull looking fur. A very low respiration rate was noted when compared with others in the treated group. Eyes were partly closed, crusted and runny. The posture was hunched
and movements were inhibited. Many of these symptoms were also detected in the animals of other experiments utilizing this drug. Gross observations on the transplant in this animal, at time of recovery, showed encystment of the transplant and a larger number of small blood vessels were seen in the connective tissue capsule of the graft than were seen in the graft in the control host of the same age.

Histological examination of the graft in the treated host showed the incisor to consist of a non-viable dentin shell with an avascular pulp showing degenerated pulp cells and odontoblasts. Ameloblasts were not found. The first mandibular molar consisted of three non-viable dentin shells of cusps disclosing degenerated pulps and no surviving ameloblasts. The second molar consisted of a disrupted mass of degenerated cells with no evidence of dentin formation. The remainder of the mandible in this transplant was a mass of avascular, necrotic bone and cartilage; all of which appeared to be non-viable. However, the graft was not encysted and was separated from a pus filled sac by dense connective tissue. A minimal amount of lymphoid cell infiltration had occurred.

The transplant in the control host recovered at the same time, also showed an incisor remnant which was a necrotic dentin shell in which all the cellular constituents of the tooth had degenerated (table 21). The first mandibular molar of this graft revealed remnants of dentin cusps, but all of the ameloblasts, odontoblasts and pulpal cells had degenerated. The second mandibular molar revealed disruption and had degenerated. No dentin had formed. More resorption of bone had occurred in this control than was seen in the transplant in the treated host. Most of the remaining bone and cartilage showed widespread necrosis though a few small regions of viable osteoid were seen.
Inflammatory cell infiltration also appeared to be greater in this control than in the treated and consisted primarily of lymphoid and some polymorphonuclear cells and numerous macrophages.

The incisors of the remaining, three grafts in 6-MP treated hamsters were necrotic dentin shells in which no surviving odontoblasts, ameloblasts or pulpal cells were seen. Encystment of a part of the incisor had occurred in each case and the teeth were avascular and necrotic. Some showed lymphoid cell infiltrations within necrotic pulps and all showed an intense inflammation about the entire incisor area. The remnants of the incisors in grafts in the three controls were also encysted and the initial stages of cyst formation were evident in the fourth. The incisor remnants were dentin shells showing only degenerated cells. Intensive inflammation, consisting primarily of polymorphonuclear cells accompanied by macrophages and multinucleated giant cells was seen in grafts in both control and treated hosts. One graft in a control host revealed an incisor showing pulpal bone formation and vascular connective tissue in the basal part of the pulp.

The first mandibular molars also did not survive in the grafts in 6-MP treated and control hamsters; nevertheless, none had been completely resorbed. The grafts in treated hosts disclosed dentin shells of molar cusps showing no viable odontoblasts, ameloblasts or pulpal cells. The molars were usually surrounded by inflammatory cells and macrophages. These molars in grafts in control hosts revealed a similar appearance, but one molar disclosed some loose connective tissue in the pulp and the parts of the cusps not encysted, were embedded in dense connective tissue containing inflammatory cells. The remnants of first molars, regardless of treatment were generally avascular. In general, the first molars from grafts in treated hamsters disclosed no
superior viability when examined at recovery 10 days following grafting.

The second mandibular molars likewise did not survive transplantation. At 10 days following grafting, one of three molars from treated animals and two of four from control hosts had been resorbed. Only one molar in a graft in a control host had formed dentin, but it had degenerated and was encysted. None of the second molars in the remaining treated or control groups had formed dentin and the pulps revealed degenerated cells and cellular debris. None of these appeared to have grown or differentiated following grafting and all of them were necrotic and avascular.

Extensive necrosis of parts of the mandibular grafts, other than the teeth, was a feature common to transplants in experimental and control hosts. Most of the grafts from treated hamsters in this series showed less bone resorption than was seen in controls; however, resorption of bone was generally less except in a graft in one control hamster which had become partly encysted. The latter disclosed considerable resorption of both the encysted and non-encysted bone. Very little normal appearing bone was observed in any grafts in the treated hosts, but viable bone was usually seen in the form of a few small ossicles while the remainder of the transplant seemed to be necrotic and non-viable. Grafts in control hosts, on the other hand, generally showed more resorption, more dense connective tissue invasion of the graft, and in some cases, a greater amount of viable bone. However, one of the grafts in a control revealed considerable osteoid and new spongy bone formation and was the only graft to disclose any significant amount of bone formation.

All transplants, with the exception of the graft in a 6-MP treated hamster recovered at six days, showed cyst formation. These squamous
epithelial lined sacks contained varying amounts of transplant tissues, ranging from only the distal part of the incisor to most of the transplant, in grafts in both treated and control hosts. The administration of 6-MP did not seem to inhibit the formation of cysts. The cellular inflammatory infiltrations in grafts in treated hamsters recovered at 10 days, appeared to be as intense as those in controls and consisted primarily of a very dense accumulation of polymorphonuclear and lymphoid cells as well as large numbers of macrophages and multinucleated giant cells. Only one graft showed a mild cellular infiltration and this was seen in that control which also revealed new bone formation. It appeared that there was little difference between grafts in treated and control hamsters and that treatment with 6-MP did not noticeably diminish the degree of inflammatory cell infiltration; nevertheless, the graft in a treated host recovered at six days did reveal a significantly lower degree of infiltration when compared with that of its control.

2. In Ear

a. Experiment XA

Four of seven half-mandible transplants from eight to ten hour old, neonatal hamsters were recovered from the subcutaneous area in the dorsal surface of the ear in hamsters having received intraperitoneal injections of 10 mg 6-MP daily/100 gm body weight. Six-MP injections were begun at grafting and continued for four days and then reduced to daily injections of 5 mg/100 gm body weight until recovery at six days following grafting (table 4). Three of seven grafts in control hosts were recovered from hosts having received an identical administration of the aqueous vehicle. Three treated and four control hosts died before the termination of the experiment; hence
the transplants were not recovered (table 22). Furthermore, one graft in a
6-HP treated and another in a control host were recovered at five days
following grafting due to an apparent toxic effect of 6-HP on the treated
host (table 22).

The incisors in all eight to 10 hour old newborn intact control mandibles
had already erupted when transplants were made. The first mandibular molars
at this time showed differentiated ameloblasts on all three cusps (figs. 1,
2). The central cusp had developed dentin and some enamel. Dentin had
begun to form on the other cusps. The second mandibular molars had developed
cusps but had not yet begun to form dentin (figs. 1, 3).

Neither molars nor incisors had survived in the grafts in the 6-HP
treated or control hosts recovered at five and six days following transpl-
plantation (table 22). Histological observations on one graft recovered at
five days from a 6-HP treated host revealed a non-viable, dentin incisor
shell with remnants of ameloblasts in its basal area and degenerated odonto-
blasts in the pulp. The pulp seemed to be avascular and the pulp cells had
undergone degeneration. The initial stages of cyst formation were in evidence
around the distal part of the incisor. The first mandibular molar revealed
four cusps, two showing dentin formation and one the formation of a thin
layer of pre-enamel. The stellate reticulum had degenerated and the tooth
was surrounded by a hemorrhagic mass. Degenerated ameloblasts and odonto-
blasts were observed. Some lymphoid cell infiltration was seen in an
avascular pulp and cyst formation seemed to have been underway in the alveolus
surrounding the tooth. The second mandibular molar in this graft revealed
only degenerated cells and the shape of the molar had been disrupted. No
dentin formation had occurred in this molar and the papilla showed some.
lymphoid cell infiltration. The remainder of the mandible was principally composed of necrotic bone except for a thin peripheral rim of viable bone. The bone of the mandible was largely avascular except for an extensive hemorrhage throughout the graft. No new bone formation was detected. The mandible proper had not become encysted although cysts had been forming in the molar alveolus and around the tip of the incisor. A slight lymphoid cell infiltration was seen consisting primarily of lymphoid cells and some polymorphonuclear cells.

The graft in a vehicle treated control host recovered at five days disclosed an incisor dentin shell surrounded by an extensive hemorrhage (table 22). The avascular pulp showed degenerated pulp cells and odontoblasts. The ameloblasts had degenerated and had largely disappeared. Lymphoid cells were found about the incisor and within the pulp. A small cyst was seen in the area of the most distal part of the tooth. Degenerated ameloblasts covered the crown of the three remaining cusps of the first molar. Dentin had formed on two of these and pre-enamel on the other. The pulp cells and the odontoblasts had undergone degeneration. Some lymphoid cell infiltration was observed in the avascular pulp. The molar was surrounded by an extensive hemorrhage and cyst formation had occurred within the molar alveolus. The second molar consisted of disrupted and degenerated odontoblasts and ameloblasts. No dentin had formed. The remainder of the mandible was largely avascular and necrotic, although some viable peripheral mandibular bone was seen on the lingual aspect of the graft. The posterior part of the mandible contained some viable cartilage, part of which had undergone some calcification and bone had formed about it. A dense connective tissue replacement of resorbed bone had occurred at the posterior and lingual
aspects of the mandible which appeared to be very vascular. The transplant revealed extensive hemorrhage within and about the graft. Noticeably more viable graft tissue was seen in the five day old transplant in the control host than in the graft in the treated host of the same age; nevertheless, more resorption of bone had also occurred in the transplant in the control host. Peripheral areas of the mandible graft in the control host also disclosed more viable osteogenic tissue. A cellular inflammatory infiltrate, consisting principally of lymphoid, some polymorphonuclear and multinucleated giant cells, seemed to be greater in the graft in the control host than in that in the treated hamster. A proliferation of squamous epithelium on the lingual surface of the graft had taken place.

Grafts in 6-MP treated hosts, recovered at six days, did not reveal survival of incisors or molars (table 22). In the four grafts in treated hosts of this series, incisors had survived as mere dentin shells. The pulps of the incisors were avascular and the odontoblasts and pulpal cells had degenerated. Some degenerating ameloblasts in the region of the basal loop were seen in a few, but these cells were usually absent or occurred as the remnants of degenerated cells in most incisors. Most of the pulps also showed some lymphoid cell infiltrations and the tips of these teeth had usually undergone encystment. The incisors in the three grafts in control hosts had also degenerated into mere dentin shells while the ameloblasts had disappeared, and the surviving avascular pulps showed only degenerated odontoblasts and pulpal cells. A lymphoid cell infiltration was also seen in the pulps of grafts in control hosts as well as encystment of the distal parts.
The first mandibular molars revealed no evidence of survival in transplants in either treated or control hosts (table 22). These molars in each of the four grafts in 6-MP treated hamsters disclosed three cusps of dentin showing necrotic and avascular pulps containing degenerated odontoblasts and pulp cells. Ameloblasts in various degrees of degeneration were seen in patches on crowns or were entirely absent from the molar. The pulps showed a mild lymphoid cell infiltration. Two of the grafts in treated hamsters did not show any cyst formation adjacent to the molars, but of the other two, one disclosed squamous epithelium tangential to the cusp surface whereas in the other, cyst formation had occurred in the molar alveolus. Hemorrhaging had occurred around all of the molars in these grafts. The three grafts in control hosts also disclosed non-viable first mandibular molars. The degree of destruction and resorption of these teeth seemed to be more advanced in the controls. Encystment had progressed to the point where it included parts of the first molars in all three controls. All of the molars were avascular and although hemorrhaging was seen about the grafts in hosts of the control series, it did not seem to be as extensive as that of the grafts in the treated hamsters. In one of the molars in a control host, ameloblasts and odontoblasts were absent while in the other two, ameloblasts were absent but odontoblasts were seen; however, they had undergone degeneration. The molars in grafts in control hosts also showed a higher degree of lymphoid cell infiltration around the teeth and within the pulp.

The second mandibular molars also did not survive in grafts in either treated or control hosts (table 22). In almost all cases these teeth consisted of only degenerated cells. The papillae were avascular and dentin formation had not occurred in either series. Two of the molars in grafts in
control hosts had been resorbed and all of the molars in grafts in both treated and control groups disclosed lymphoid cell infiltrations in the surrounding tissues and in the remnants of papillae. These molars also revealed a considerable disruption in form. None of them revealed any viable odontoblasts or ameloblasts.

The mandibular grafts from treated hosts recovered after six days were composed mostly of necrotic avascular bone in all four 6-MP treated animals. Each of these revealed a small amount of viable peripheral bone showing a very low degree of new bone formation. Some resorption and a dense connective tissue replacement of resorbed bone had occurred. The invasion of dense connective tissue was not conspicuous although a few grafts also showed an invasion by a loose connective tissue. None of the transplants in 6-MP treated hosts were very vascular, but all showed an extensive hemorrhage throughout the graft tissues. The three grafts in control hosts on the other hand revealed more new spongy bone which occurred mostly in peripheral areas on the mandible, although some was also centrally located. The bone in the mandible grafts in control hamsters appeared to be more viable although some bony necrosis was observed. More resorption of bone occurred in grafts in control hamsters and more dense connective tissue replacement of resorbed parts was also noted. Vascular ingrowths from host tissues were greater in grafts in control hosts and hemorrhage, though present, was less pronounced. Particularly noticeable was the higher degree of invasion, of necrotic bone in mandibles in control hosts, by both loose connective tissue and in some areas by osteogenic tissue. In general, the grafts in control hamsters revealed a superior vascularization. The grafts in treated hosts showed some viable cartilage in the posterior part of the mandible while those in control
hamsters showed some bone formation in regions of cartilage calcification.

Cysts were observed in most of the grafts of this series. The majority of the grafts showed encystment of the tip of the incisor but in some, parts of the first molars were also included within the cyst. Lymphoid cell infiltration seemed to be less intense in grafts in the treated than in the control hamsters. The grafts in control hamsters usually showed a much greater number of polymorphonuclear, lymphoid and giant cells.

In summary, grafts in control hosts generally showed a greater infiltration of inflammatory cells and more connective tissue surrounding transplants than were seen in most of the transplants in 6-MP treated hosts. The infiltrations consisted of some polymorphonuclear cells but mostly lymphoid and giant cells. Most of the grafts in control hamsters revealed at least some new bone formation while very little evidence of bone formation was seen in grafts in treated hosts. The resorption of graft bone seemed to be greater in grafts in control hosts. Revascularization of grafts also appeared to be greater in control hamsters than in the treated hamsters and hemorrhage throughout the transplanted tissues was less extensive in the former. Connective tissue invasion of transplants appeared to be greater in grafts in control hamsters. No significant difference in cyst formation was seen between grafts in control and treated hosts.

Gross observations on transplants at the time of recovery showed that the grafts in treated hosts were either not, or were very loosely attached to the host tissues, whereas most grafts in control hamsters had become firmly attached.

b. Experiment XB

Nine of nine half-mandible grafts of 12 to 15 hour old, neonatal
Hamsters were recovered from the subcutaneous area in the dorsal surface of the ear in inbred male hamsters having received intraperitoneal injections of 5 mg 6-MP daily/100 gm body weight beginning at time of grafting and continued for 15 days (tables 4, 23). Two of five grafts were recovered from control hosts having received identical grafts and injections of the aqueous vehicle (table 23). The other three control hosts had died before termination of the experiment; hence the grafts were not recovered. Four of four hosts, which had received only one injection of vehicle at time of grafting, but no further treatment, were recovered at 15 days (tables 4, 23). The latter group was utilized as normals since the vehicle seemed to have a toxic effect on the hosts.

The incisors in all 12 to 15 hour old neonatal intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second molars had developed cusps but had not yet begun to form dentin (figs. 1, 3).

The 5 mg/100 gm body weight/day dosage of 6-MP in this series was tolerated better than the 10 mg dosage had been in the previous series although these animals also showed a progressive weight loss throughout the experiment. It was found that the controls had died as a result of the very high pH of the aqueous vehicle. Once this pH had been adjusted to that of the 6-MP solution, the survival of control hosts showed little differences from that of the normal group.

Three of nine recovered grafts from 6-MP treated hosts revealed survival of one molar each and these were identified as second molars (tables 4, 23).
No first molars had survived in either control or normal series. No incisors had survived transplantation in this series (table 23).

One surviving molar in a graft from a 6-MP treated host revealed only a small amount of growth (table 23; animal #5). Two immature cusps had been undergoing development but no dentin or enamel formation had occurred (fig. 55). Short, immature ameloblasts covered the surfaces of the cusps and a normal appearing stratum intermedium and stellate reticulum were seen. The odontoblasts at the tips of the cusps had differentiated, but they were shorter than normal and appeared to be very immature. The papilla showed numerous small blood vessels and the pulp cells seemed to be normal. No lymphoid cell infiltration was evident in the papilla. The molar was not contained within a bony alveolus and its dental lamina appeared to be continuous with the epithelium of an adjacent cyst.

The incisor of this graft consisted of a dentin shell disclosing an encysted tip, devoid of ameloblasts, and showing bone formation on the outer dentin surface as well as ankylosis to adjacent bone. The pulp did not reveal any viable odontoblasts, but a large amount of pulpal spongy bone had formed. Invasion of the pulp by a vascular dense connective tissue had occurred. Only a small number of lymphoid cells were seen in the pulp and around the tooth. The dentin remnant had undergone resorption. The first mandibular molar consisted of three cusps; all of which had been partly resorbed. The pulps disclosed fibrous connective tissue and spongy bone formation. No ameloblasts or odontoblasts were found. Tangential to the outer surface of the cusps the squamous epithelium of an adjacent cyst was apparent. The parts of the molar cusps not covered by this epithelium were surrounded by a dense connective tissue and lymphoid cells. The alveolus of
the molar contained a small cyst. The mandible revealed a large amount of new bone mostly in the form of spongy bone and trabecular growth. The cartilage located in the posterior part of the mandible had undergone calcification. The transplant was very vascular throughout. Only a small amount of bone resorption had occurred in the mandible and dense connective tissue infiltration and replacement of resorbed tissues were not extensive. The marrow of the graft appeared to have been largely replaced with osteogenic tissue showing numerous osteoblasts. An inflammatory cell infiltration within the graft consisted primarily of lymphoid cells and was very minor. Gross observations at the time of recovery revealed a vascular transplant firmly attached to the graft bed.

A second surviving molar was also found in this 6-MP treated series. This tooth had remained in the bud stage revealing no formation of cusps (table 23; animal #13). Short immature ameloblasts were observed, but no enamel had formed (fig. 56). The odontoblasts had undergone some differentiation, but no dentin had formed. The vascular papilla disclosed no lymphoid cell infiltration. The tooth showed a normal appearing stellate reticulum and stratum intermedium. The dental lamina of the molar seemed to be continuous with the squamous epithelium of an adjacent cyst. The tooth was not encased within a bony alveolus. A dentin shell manifesting encystment of the tip and devoid of ameloblasts was all that remained of the incisor. No odontoblasts or pulpal cells were found in the pulp although considerable bone formation was apparent. Ankylosis of the resorbing remnant had occurred and inflammatory cells were notably absent from the pulp except in its most distal part.

The first mandibular molar of this transplant was found to consist of
two dentin cusps impinging on an adjacent cyst. Much of the dentin of the cusps had been resorbed and no ameloblasts were in evidence. The pulp showed bone formation, some marrow and a vascular connective tissue, but the odontoblasts had disappeared. One cusp had become ankylosed to adjacent bone. A cyst occupied most of the molar alveolus and the squamous epithelium of the cyst covered much of the surface of the molar remnant. The remaining parts of the mandible displayed a large amount of new bone formation as indicated by the increased trabecular growth, coalescence of adjacent trabeculae to form a compacta and the new spongy bone. Ossification of cartilage had occurred in the posterior parts of the mandible and bony remodeling was apparent throughout the graft. The mandible did not show a central hollowing tendency but rather a trend towards compact bone formation. A very noticeable absence of marrow was obvious throughout this transplant. The marrow appeared to have been replaced largely by osteogenic tissue. Resorption of bone seemed to be minimal and only minor degrees of resorbed bone replacement by dense connective tissue had occurred. Only a very low degree of inflammatory cell infiltration, consisting principally of lymphoid cells, was seen; however, cyst formation had occurred. Gross observations on the graft at the time of recovery revealed a fluid filled cyst containing the entire transplant.

The third surviving tooth in this series also occurred in a graft in a 6-MP treated hamster (table 23; animal #17). In contrast to other surviving molars in this series, this second mandibular molar showed a considerable amount of growth and development (fig. 57). Two cusps had developed as well as a distorted and irregularly formed root which had not undergone any bifurcation. Enamel was seen on only one side of the crown while a group of
ameloblasts, which had formed pre-enamel, were embedded in osteodentin in the area between the cusps. The enamel space on the one aspect of the crown was lined with cuboidal ameloblasts. The ameloblasts in the area between the cusps were taller, but here only a pre-enamel was seen. The remaining surface of the crown was enamel-free and revealed formation of a thin osteoid which seemed to be attached to the surrounding dense connective tissue. Hertwig's root sheath seemed to have undergone some degeneration. The stratum intermediate was absent except in areas adjacent to ameloblasts. A large amount of dentin was seen. The aspect of the crown showing surviving ameloblasts was composed of a thick layer of regularly formed tubular dentin while dentin formation had been disturbed during root development on this aspect. The second cusp consisted primarily of osteodentin and revealed cellular and vascular inclusions, however, some irregular tubular dentin formation had occurred adjacent to the pulp chamber. An irregularly formed layer of pre-dentin was observed on the inner surface of the pulp chamber. No pulpal calcification was apparent and the pulpal cells seemed to be normal. The pulp revealed capillaries within the odontoblastic layer and tall, normal appearing odontoblasts lined the pulp but were shorter than normal in areas where disturbances in the formation of dentin had occurred. No lymphoid cell infiltration was seen within the pulp. The enamel-free surfaces of the crown and outer root surface revealed an osteoid attached to adjacent connective tissue fibers. The molar was not contained within a bony alveolus.

The incisor of this transplant was a dentin shell ankylosed to adjacent bone. No odontoblasts or ameloblasts were found. The pulp consisted of degenerated cells with no evidence of bone formation in the pulp chamber. Much of the first mandibular molar had been resorbed and the two remaining
cusps were partly enclosed within the squamous epithelium of a cyst. The pulp disclosed some bone formation, degenerated cells, and connective tissue. A small amount of lymphoid cell infiltration was seen in the pulp and surrounding the tooth. The remainder of the mandible proper revealed trabecular growth and new bone formation. Bone resorption had occurred in small areas, but the rate of bone formation appeared to exceed that of resorption. The marrow of the mandibular bone had undergone replacement by loose connective and osteogenic tissue. Cyst formation had occurred on the lingual aspect of the mandible. Other cysts involving the distal portion of the incisor and the first molar were also seen. Only small foci of inflammatory cells, predominately lymphoid in nature, were found within the graft. Gross observations at the time of recovery revealed a vascular, firmly attached, graft.

In the remaining transplants in treated and control hosts of this series, the incisors had shown no evidence of survival (table 23). In one graft recovered from a 6-MP treated host, the incisor had been completely resorbed. In the other grafts in treated hosts, only dentin shells, devoid of odontoblasts and ameloblasts, were found and these revealed varying degrees of bone formation and connective tissue invasion of the pulps. The incisors in grafts in control and normal hosts were similar in appearance. Practically all of the incisors in this series disclosed encystment of at least the distal part of the tooth.

The first mandibular molars in grafts had not survived in either treated, control or normal hosts; however, in only one transplant had this tooth been completely resorbed and this had occurred in a graft from a treated host. In all first molars in the three series, two or three dentin cusps were usually
found revealing fibrous connective tissue, cellular debris and lymphoid cells within the pulps. None of the cusps manifested viable odontoblasts or ameloblasts. Three in treated and one in a normal host showed some new bone in the pulp. Almost all of the first molars were partly encysted. Vascularity of the pulp was only seen where connective tissue invasion of the pulp had occurred.

The second mandibular molars in all the grafts of this series, except three, had been resorbed. In no instance did a viable second mandibular molar in a transplant show the degree of growth seen in a 15 day old control (figs. 6, 7).

The remainder of the mandible in the grafts from 6-MP treated hosts usually revealed more trabecular growth and new bone formation, although four of the nine showed considerable resorption (figs. 58, 59). One of the latter disclosed mostly necrotic and avascular bone, whereas a second showed resorption but much growth in the bone that had remained. In the third and fourth, only small amounts of viable bone were seen. The remaining ones showed that bone formation had occurred largely as trabecular growth rather than as new spongy bone although the latter was seen in grafts from treated hosts. The grafts in treated hosts also disclosed a considerable replacement of the marrow by osteogenic tissue and less dense connective tissue. Where connective tissue invasion had occurred, it appeared to be looser in nature than seen in grafts in normal and control hamsters. The latter also revealed bone formation, but this seemed to take the form of new spongy bone. Generally, the amount of bone formed in grafts in control hamsters was less than that observed in those in treated hamsters.
Cyst formation had occurred in all but one graft, and this was from a 6-MP treated animal. In most grafts the incisors and parts of the first molars were included within these structures. Four of nine grafts in 6-MP treated hamsters revealed intense inflammatory infiltrations consisting primarily of lymphoid and some polymorphonuclear cells. The remaining five showed less infiltration whereas grafts in both control and one normal hamsters showed a limited degree of such infiltration. Nevertheless, three of the four normals on the other hand disclosed strong infiltrations. The vigorous reaction observed in grafts in the three normal hamsters was more intense than that seen in those grafts in 6-MP treated hamsters where high degrees of inflammation had occurred. These grafts in normal and control hosts also showed more dense connective tissue replacement of resorbed tissues and a greater degree of dense connective tissue invasion.

c. Experiment XC

Five of five half-mandible transplants from 12 to 14 hour old, neonatal hamsters were recovered from the subcutaneous space in the dorsal surface in the ear of adult male inbred hamsters receiving intraperitoneal injections of 2 mg 6-MP daily/100 gm body weight. Injections began at time of transplantation and were continued for 15 days at which time grafts were recovered (tables 4, 24). Three of five grafts in control hamsters were recovered from hosts having received identical transplants and injections with the aqueous vehicle (tables 4, 24). One control host had died before the end of the experiment hence the graft was not recovered (table 24). In one other control, the transplant had been resorbed before the termination of the experiment at 15 days.
The incisors in all 12 to 14 hour old neonatal intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs. 1, 3).

No evidence of surviving molars or incisors was found in any of the grafts in 6-MP treated hamsters. One surviving tooth, identified as a second mandibular molar was found in a control host (table 24; animal #8). This tooth had developed two cusps and a third cusp was undergoing development (fig. 60). Root formation had not begun. The largest cusp showed enamel and pre-enamel formation. The layer of enamel was equal in thickness to that of the dentin. Approximately half of the enamel layer was found to be pre-enamel. Enamel was found only on the largest cusp and several small areas of irregular enamel formation and retarded calcification were also seen. The other cusps were enamel-free. Tall, normal appearing ameloblasts covered the entire surface of the crown; none of which disclosed any degenerative signs. The dentin seemed to be relatively evenly calcified and no zones of disturbed formation were found. Osteodentin formation had not occurred. The innermost layer of dentin was a layer of pre-dentin approximately one third to one fourth the thickness of the dentin. No pulpal calcifications were noticed and the cells of the pulp appeared to be normal. The pulp was very vascular revealing large blood vessels and capillaries within the odontoblastic layer. Normal appearing odontoblasts lined the pulp. These cells were very tall in the largest cusp and somewhat shorter in the others. No signs of odontoblastic degeneration were detected. No lymphoid cell infil-
An incomplete bony alveolus was noted about the basal part of the molar. Cords of squamous cells adjacent to the tooth and the epithelium of a cyst seemed to be continuous with the dental lamina of the molar.

The incisor of this graft consisted largely of a dentin shell showing encystment about its tip. The distal pulp disclosed a high degree of polymorphonuclear and lymphoid cell infiltration. In addition, macrophage invasion and bone formation were also observed in the pulp. Much of the tooth had been resorbed. No surviving odontoblasts or ameloblasts were detected. The first mandibular molar revealed dentin and pre-enamel fragments of two cusps which had undergone some resorption and manifested formation of bone in the pulp. The cusp fragments were embedded in dense connective tissue containing lymphoid cells and some multinucleated giant cells. One fragment had become ankylosed to adjacent spongy bone. This molar was not encysted nor was a bony alveolus seen about the tooth. Approximately one fifth of the mandible, apparently mostly in its posterior aspect, had been resorbed. One such area disclosed an intense lymphoid cell infiltration accompanied by an extensive invasion of dense connective tissue. A vascular marrow was seen, but a considerable dense connective tissue replacement of marrow had also occurred. Nevertheless, trabecular growth as well as the formation of spongy bone was also apparent. A moderate degree of lymphoid cell infiltration was noticed throughout the transplant and cysts had formed chiefly about the distal part of the incisor and on the lingual aspect of the mandible.

No viable, intact incisors were found in the grafts in 6-MP treated hosts or controls (table 24). The incisor was completely resorbed in only one graft.
and this was found in control. In the grafts in the 6-MP treated and control hosts, the incisors were mere dentin shells which had undergone varying degrees of resorption and usually disclosed encystment of the distal quarter or tip of the incisor. None revealed survival of either odontoblasts or ameloblasts. The pulps showed different degrees of bone formation and no significant differences were detected between those in treated and control hamsters. In most cases, lymphoid cells were observed about the incisors and usually large accumulations of these cells were seen in the distal quarter of the incisor pulp.

The first mandibular molars had not survived in grafts in either the 6-MP treated or control hamsters (table 24). The only case of total resorption of this molar was seen in a graft in a control host. In the remaining grafts, two or more dentin and pre-enamel cusps were found which were devoid of both odontoblasts and ameloblasts. All of the cusps were usually only fragments and these revealed evidence that resorption had been underway. The pulps showed either a fibrous connective tissue invasion or varying degrees of spongy bone formation. Lymphoid cells were also found in relatively large numbers about these molars. There were no detectable differences between the molars in grafts in the control or 6-MP treated hosts. Partial encystment had occurred in some of the grafts of both groups. Treatment with 6-MP did not reduce the frequency of cyst formation.

The second mandibular molars also did not survive in the grafts of 6-MP treated hosts. The only surviving molar in this series was found in a transplant in a control host (table 24). The second molars had been resorbed in all but one of the remaining grafts in control and treated hosts. In one case, a fragment of dentin, found embedded in spongy bone, had been undergoing
resorption and revealed no dental cells. This fragment could not be posi-
tively identified as part of a second molar. In no instance did a viable
molar in a transplant show the degree of growth seen in a 15 day control
(figs. 6, 7).

The remainder of the mandible was recovered from all hosts except one
which was in a control host. In all but one case, the grafts from 6-MP
treated hosts revealed less resorption and more bone formation, the latter
occurring as trabecular growth rather than as new spongy bone (figs. 61, 62).
On the other hand, grafts in control hosts usually disclosed a predominance
of spongy bone formation rather than trabecular growth. The grafts in
treated hamsters also revealed a tendency toward the formation of compact
bone through the coalescence of trabeculae. The formation of compacta had
not been so extensive in grafts in the control hosts. Where necrotic bone
was observed in parts of grafts in treated hosts, osteogenic tissue was
usually seen adjacent to it and new bone formation had been underway in
these areas on the old bone. However, in grafts in control hosts, many areas
of dense connective tissue replacement were very noticeable in the areas of
necrotic trabeculae. Of special interest was the observation, that in grafts
in the treated hosts, much of the marrow had been replaced by osteogenic
tissue and bone formation appeared to have been in progress in these areas.
The extent of such osteogenic tissue replacement in the grafts in treated
hosts seemed to be more extensive than that of control grafts. However,
grafts in treated hamsters also revealed areas of normal marrow, but those
in control hosts usually showed a greater amount of marrow. It appeared
that the osteogenic activities in grafts in treated hamsters were con-
siderably greater than in those in controls.
All transplants revealed the formation of cysts which in every instance were located about the distal part of the incisors, and in some cases other cysts included portions of molar remnants. In some cases necrosis of bone was noted adjacent to the cyst. The degree of lymphoid and polymorphonuclear cell infiltration into grafts was not significantly different between the 6-MP treated and control groups and on the average would be classified as of moderate intensity. In two instances where dense accumulations of these cells were observed in grafts in treated hamsters, both showed viable bone and trabecular growth although one disclosed a more dense connective tissue infiltration into the graft. Resorption of bone in these transplants was not extensive. None of the transplants in either the treated or the control series revealed extensive necrosis accompanied by massive cell infiltration.

Gross observations at the time of recovery revealed vascular and firmly attached grafts. No significant differences in this respect were seen between the grafts from treated or control hosts.

E. Neonatal Half-Mandible Transplants in Imuran and Vehicle Treated Hamsters

1. In Ear

   a. Experiment XIA

Eight of eight transplants of half-mandibles from 12 to 14 hour old, newborn hamsters were recovered from the subcutaneous area, in the dorsal surface in the ear, in hamsters having received intraperitoneal injections of 5 mg Imuran daily/100 gm body weight beginning at time implantation and continued for 15 days (table 5, 25). Eight of eight grafts in control hamsters were recovered from hosts having received identical treatment of injections of the aqueous vehicle (tables 5, 25). All animals survived for
the duration of the experiment. Three of eight grafts from Imuran treated

hosts disclosed survival of one molar each while only one of eight controls

revealed survival of a molar. In no instance was there any evidence of

survival of either incisors or first mandibular molars.

The incisors in all 12 to 14 hour old newborn intact control mandibles

had already erupted when transplants were made. The first mandibular molars

at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had

begun to form on the other cusps. The second mandibular molars had developed

cusps but had not yet begun to form dentin (figs. 1, 3).

The one surviving molar seen in a graft in a control hamster had not

revealed much growth or differentiation. It was identified as a second

mandibular molar (table 25; animal #6). Formation of cusps had been under-

way, but no root formation had occurred. No dentin or enamel were found

(fig. 63). Tall normal appearing ameloblasts covered the entire surface of

the crown and a normal stratum intermedium was seen adjacent to these cells.

The stellate reticulum disclosed no degeneration. The odontoblasts had
differentiated only in the upper parts of the cusps while the cells in the

pulp appeared to be normal. The pulp was vascular and showed no lymphoid
cell infiltrations. The cells of the dental lamina of this molar appeared to be continuous with the squamous epithelial lining of an adjacent cyst.

A bony alveolus enclosed only a part of the molar.

The incisor remnant of this graft was merely a dentin shell, ankylosed
to bone, which had undergone some resorption. Bone formation and a dense

connective tissue invasion were seen in the pulp. In the basal pulp area

a few cords of squamous cells were found embedded in dense connective tissue.
However, no normal, viable odontoblasts or ameloblasts were seen. Only the
dentin remnants of two cusps, showing some pre-enamel, and embedded in dense
connective tissue, containing a lymphoid cell infiltrate, remained of the
first molar. Parts of the cusps had become encysted and no surviving odonto-
blasts or ameloblasts were found. Considerable resorption and dense connec-
tive tissue substitution of transplant bone had occurred. Although much of
the remaining bone appeared to be viable, some necrotic bone was also seen.
Small amounts of new spongy bone formation and trabecular growth had occurred,
but most of the marrow had been replaced by a dense connective tissue. Cysts
were found adjacent to the lingual mandibular surface and within the alveolus
of the first molar. A dense infiltration of lymphoid cells was seen through-
out the graft. These cells were more numerous than those observed in the
corresponding graft in a treated hamster which had not revealed survival of
teeth but had shown more bone and a higher degree of bone formation. Gross
observations at the time of recovery showed that the graft appeared to be
vascular and was contained within a thin connective tissue capsule firmly
attached to the host tissues.

Three transplants from Imuran treated hosts revealed one surviving molar
each (table 25). These molars showed greater growth and differentiation than
was seen in the single surviving molar in a control host. One graft in a
treated hamster disclosed a viable second molar which revealed a high degree
of growth subsequent to transplantation (table 25; animal #9). This molar
showed that four cusps had developed and a thick layer of enamel had formed
over the entire crown (fig. 64). No enamel-free areas were seen. Root
formation had been underway and tall, normal appearing ameloblasts covered
the entire surface of the crown. The layer of enamel was approximately four
times greater in thickness than the layer of dentin. Enamel calcification had been retarded, but no other serious disturbances in enamel formation were seen. A calcified layer of regular tubular dentin, approximately one fourth as thick as the enamel, covered the crown, and about one half to one third of the dentin was pre-dentin located adjacent to the pulp. A few small areas of irregular dentin formation were observed, but no osteodentin was seen. The cellular pulp was very vascular and manifested no degenerative signs. Large pulpal blood vessels and capillaries occurred within the odontoblastic layer. A lymphoid cell infiltration was evident in the pulp. The odontoblasts lining the pulp appeared as tall, normal cells revealing no degenerative signs. The molar was partly enclosed within an alveolus of viable bone.

The remnant of the incisor in the above graft was merely a dentin shell, ankylosed to bone, revealing encystment of the distal part. It had undergone some resorption. Marrow and bone were found within the pulp but no viable odontoblasts or ameloblasts were found. Only a dentin fragment of one cusp of the first molar was seen which had become incorporated into spongy bone. The bone in the remaining parts of the mandible revealed a very large amount of trabecular growth and some compacta formation through the coalescence of trabeculae. The extent of this growth was much greater than that of the graft in the corresponding control host. Marrow was found throughout the graft bone and only a low degree of connective tissue invasion was seen. This transplant also showed much more marrow than was seen in the graft in the control host. Only a low degree of resorption had occurred and the graft had become very vascular. A small amount of necrotic bone was seen and lymphoid cell infiltration was almost absent. Cysts were found about the distal part of the incisor and adjacent to the lingual surface of the
mandible. Gross observations at the time of recovery disclosed a vascular graft encapsulated by dense connective tissue and firmly attached to the host tissues.

A second graft, in an Imuran treated host, showed a viable second mandibular molar revealing less growth than the one described above (table 25; animal #11). The amount of growth was much more than had occurred in the surviving molar in the control hamster (fig. 65). This molar had developed three very distorted cusps. No root formation had occurred. Enamel was seen on one cusp while the rest of the crown was enamel-free. The layer of enamel was approximately equal in thickness to that of the underlying dentin. The calcification of the enamel was retarded. Normal appearing ameloblasts showing, no degenerative changes lined the entire outer surface of the crown. An intact Hertwig's root sheath was seen. A normal appearing stratum intermedium was found adjacent to the ameloblastic layer. A vascular, intact stellate reticulum was also noted. The other two cusps showed formation of a regular tubular dentin of which approximately half was pre-dentin. No dentin formation had occurred on the third cusp. The pre-dentin was regular in thickness throughout where dentin was seen. No osteodentin formation had occurred. Pulpal calcification had not occurred and the pulp cells seemed to be normal. The pulp was vascular and capillaries were seen within the odontoblastic layer. Tall, normal appearing odontoblasts manifesting no signs of degeneration lined the pulp; however, these cells in the immature cusp were not so tall as normals. No lymphoid cell infiltration was seen in the pulp. The dental lamina of the tooth appeared to be continuous with the squamous epithelium of an adjacent cyst. Only part of the molar was encased in a bony alveolus.
All that remained of the incisor in this graft was a dentin shell, embedded in bone revealing pulpal bone formation and some dense connective tissue invasion. A portion of the distal half of the tooth had become encysted and some resorption had occurred. No viable odontoblasts or ameloblasts were seen. The first mandibular molar had been resorbed and a cyst was seen within the molar alveolus. The remainder of the mandible had undergone a considerable amount of trabecular growth and vascular marrow was seen in half of the graft. The amount of trabecular growth seemed to be greater than that of new spongy bone. Much of the cartilage in the posterior part of the mandible had calcified. Some resorption and a dense connective tissue substitution of bone had occurred in the posterior part of the mandible, but this was not extensive. Lymphoid cell infiltration was mild and cyst formation had occurred about the distal part of the incisor, adjacent to the lingual mandibular surface, and within the first molar alveolus. Gross observations at the time of recovery revealed a vascular graft encapsulated within connective tissue and firmly attached to the host tissues.

A third surviving molar was found in a graft from an Imuran treated host and was identified as a second mandibular molar (table 25; animal #13). This graft revealed greater growth and development than was seen in the surviving molar in a control hamster. Three cusps showing some distortion had formed, but no roots had appeared (fig. 66). Enamel and pre-enamel covered most of the surface of the crown. Its absence on some areas seemed to be due to immaturity of the ameloblasts rather than to disturbances in the formative process of the ameloblasts. Tall columnar ameloblasts covered the entire surface of the crown and disclosed no detectable degenerative changes. An intact Hertwig's sheath had developed. A normal appearing stratum intermedium
was seen adjacent to the ameloblasts. The stellate reticulum was intact. The enamel layer was equal in thickness to the dentin and twice that of the dentin in some places. Some areas of the crown showed only pre-enamel. The enamel was regular in form and showed few disturbances in formation, however, calcification of the enamel had been severely retarded. Regular tubular dentin had formed and few irregularities in its formation were seen. Approximately one third to one fourth of the dentin layer which lined the entire pulp chamber was pre-dentin. No osteodentin was found and no pulpal calcification had occurred. The pulp cells seemed to be normal and no lymphoid cell infiltration was observed. The pulp disclosed numerous capillaries within the odontoblastic layer. Tall, columnar odontoblasts, showing no signs of degeneration, formed the outer limits of the pulp. The molar was encased within a bony alveolus but its dental lamina appeared to be continuous with the squamous epithelium of an adjacent cyst.

The incisor of this transplant had been partly resorbed and consisted of a dentin shell revealing no encystment. It showed marrow and bone in the pulp. No odontoblasts or ameloblasts were seen. A piece of a dentin cusp embedded in dense connective tissue was all that was found of the first mandibular molar. Odontoblasts or ameloblasts could not be found. The bony parts of the mandible revealed a large amount of new spongy bone and trabecular growth. Only a low degree of resorption and a dense connective tissue invasion had occurred. A vascular marrow was seen throughout the graft and the cartilage had undergone some calcification. A marked absence of lymphoid cell infiltration was observed, but cyst formation had occurred. Gross observations on the transplant at time of recovery disclosed a large cyst on the mandible. The graft had become encased within a connective tis-
sue capsule, was vascular, and was firmly attached to the host tissues.

The incisors did not survive intact in grafts in either Imuran treated or control hamsters (table 25). No instances of total resorption of the incisors were found; however in all cases they were seen as dentin shell remnants devoid of odontoblasts or ameloblasts. Two of these remnants from Imuran treated hosts showed a few cords of squamous cells embedded in dense connective tissue in the basal part of the remnant. These squamous cell cords were not seen in the incisors of controls. Incisors in grafts in both control and experimental hosts revealed the formation of varying degrees of bone in pulps, but there did not seem to be any significant difference between the two groups. Some teeth also showed pulpal invasions of dense connective tissue and varying degrees of lymphoid cell infiltrations. All of the transplant incisors revealed some resorption; however, this was not conspicuously greater in grafts in the treated than in the control hosts. Most of the incisors in this series revealed encystment of distal parts, and only one more graft in the treated series than in the controls, did not show encystment of this tooth.

The first mandibular molars in grafts revealed no evidence of survival in either the Imuran treated or the control hamsters. In only three cases had the molar been resorbed and these were found in grafts from treated hosts. One first molar in a graft in a control host revealed three cusps of dentin showing osteogentin formation as well as massive distortion (table 25; animal #10). One cusp of this molar had become an osteodentin mass with a small enamel space lined with short columnar to cuboidal shaped cells adjacent to some tubular dentin. Osteodentin, revealing cellular and vascular inclusions had formed near the pulp. Osteoid was seen on the outer crown surfaces
and dense connective tissue and lymphoid cells were also noted about the tooth. The middle cusp was found to be a solid mass of osteodentin and the pulp showed dense connective tissue and lymphoid cells but no normal odontoblasts. This cusp also showed cords of squamous cells on the outer surface of the cusp. Osteoid formation was seen adjacent to dense connective tissue containing lymphoid cells where these cords were absent. The epithelium of a cyst seemed to be continuous with the squamous cords on the two cusps. The third cusp also disclosed some osteodentin, but a small amount of tubular dentin was seen adjacent to some very short odontoblast-like cells on the pulpal surface. A dense lymphoid cell infiltration had developed in this part of the pulp. The remnants of this molar were contained within an incomplete alveolus which had undergone some resorption and showed a large number of foci of lymphoid cells. A dense connective tissue invasion of the pulp was seen in many regions of the molar cusps.

It appeared that more resorption of first molar remnants had occurred in grafts in treated than in control hamsters, since three of the former had been resorbed, two revealed only one cusp and two others only two cusps. None of the first molars in grafts in controls had been totally resorbed; one of these showed only one cusp, four, two cusps and three revealed three cusps each. In all cases the fragments of cusps of the first molar were devoid of ameloblasts and odontoblasts. More of these fragments in grafts in treated hamsters had become embedded in bone, than in dense connective tissue, as was the case with most of them in the control hamsters. More bone had formed in the pulps of molar remnants in grafts in treated than in control hosts. Of interest was the observation that only two molars in the treated series revealed encystment whereas four controls had become encysted.
The second mandibular molar had been resorbed in all grafts except in three from treated hosts and in one surviving control (table 25). All of the surviving molars in grafts from treated hosts showed greater growth and differentiation than was seen in the single surviving control molar but none disclosed the degree of growth seen in a normal 15 day second molar (figs. 6, 7).

Resorption of the remaining parts of the mandible was usually greater in grafts in control hosts than in those receiving Imuran treatment (figs. 67, 68). A greater degree of marrow replacement with dense connective tissue was also observed in grafts in control hosts. The mandibles in control hosts also revealed greater amounts of necrotic bone than were seen in those in treated hosts, but new bone formation had usually occurred in both groups. It appeared that new bone formation was mainly in the form of an increase in trabecular growth in grafts in treated hamsters, whereas new spongy bone was the principal osseous formative activity in those in controls, although trabecular growth was also seen in the latter. Several grafts in treated hamsters disclosed ossicles showing a vascular, densely packed marrow. The hollowing or cavitation of the mandible seen in treated hosts was not noted in grafts in controls where a more generalized resorption and replacement with dense connective tissue had occurred. A higher degree of dense connective tissue invasion of transplants was seen in grafts in control hosts and where connective tissue invasion occurred in grafts in treated hosts, the nature of the tissue appeared to be less dense.

Cyst formation had occurred in all but one transplant and this was recovered from a control host. In the remaining grafts of both treated and controls, cysts had usually formed adjacent to the lingual aspect of the
mandible. Most of grafts in the treated and control hamsters usually showed encystment of parts of the incisors while others also disclosed the involvement of cusps of the first molar. Imuran treatment did not appear to have diminished cyst formation, however, the intensity of lymphoid and other inflammatory cell infiltration had been greatly decreased in almost all grafts in treated as compared to those in control hamsters. The three grafts in treated hamsters revealing surviving molars disclosed light to minimal lymphoid cell infiltration and also showed less infiltration than was seen in most other grafts in treated hosts; however, several of the latter also showed a minimal degree of infiltrate. On the other hand, transplants in control hamsters disclosed a much greater cellular infiltration, showing greater numbers of cells and a wider distribution throughout the grafts as well as in the surrounding connective tissue. The infiltrate in most of these grafts in both groups consisted primarily of lymphoid cells.

Gross observations on transplants at the time of recovery showed that they had become encapsulated in vascular connective tissue and were firmly attached to the host tissues in both treated and control animals. The grafts were vascular in both groups and showed no significant differences.

b. Experiment XIB

Five of five transplants of half-mandibles from 13 to 14 hour old, neonatal hamsters were recovered from the subcutaneous area in the dorsal surface in the ear in hamsters having received intraperitoneal injections of 2 mg of Imuran daily /100 gm body weight beginning at time of transplantation and continuing for 15 days at which time the grafts were recovered (tables 5, 26). Five of five grafts in control hamsters were recovered from hosts having received an identical treatment except for injections of the aqueous
vehicle (tables 5, 26). All treated and control hosts survived the post-
operative period of 15 days and all grafts were recovered; none having been
completely resorbed.

The incisors in all 13 to 14 hour old neonatal intact control mandibles
had already erupted when transplants were made. The first mandibular molars
at this time showed differentiated ameloblasts on all three cusps (figs. 1,
2). The central cusp had developed dentin and some enamel. Dentin had
begun to form on the other cusps. The second mandibular molars had developed
cusps but had not yet begun to form dentin (figs. 1, 3).

No evidence of intact survival of incisors was seen in grafts in either
treated or control grafts. Only one graft showed a surviving second mandibu-
lar molar and this was found in a treated host (table 26; animal #7). Con-
siderable growth and development had occurred in this molar (figs. 69, 70).
Three large and one smaller cusp had formed, but no root development had
occurred. Almost the entire crown surface was covered with pre-enamel or
enamel; only a few small areas of the crown were enamel-free. The thickness
of the enamel was not constant on the crown as some areas showed only the
formation of pre-enamel and there appeared to have been regional disturbances
in enamel formation. Tall, columnar ameloblasts covered most of the surface
of the crown; nevertheless, some areas on the better developed cusps showed
that degeneration of these cells had occurred and these cells were shorter
than normal while in several instances only squamous cells and cellular
debris were seen (fig. 70). Parts of Hertwig's root sheath appeared to be
intact, but some areas of this sheath also revealed signs of degeneration.
A viable, normal appearing stratum intermedium was obviously adjacent to
the ameloblasts, but this was absent where the ameloblasts had undergone
degeneration. A relatively normal stellate reticulum was observed where degeneration of ameloblasts had not occurred. In the areas of ameloblastic degeneration, lymphoid invasion and replacement of normal cells by dense connective tissue was seen (fig. 70). A normal appearing tubular dentin was seen throughout the tooth; yet, many areas of irregular dentin formation were noted as indicated by variations in thickness. Some osteodentin was found in the more developed cusps. Approximately one fourth of the dentin layer was pre-dentin, but this had been replaced by osteodentin in some areas. The dentin showed a very uneven calcification. No pulpal calcification was seen and the pulp cells in general were mostly normal. The pulp was vascular and capillaries were seen within the odontoblastic layer. Odontoblasts lined the pulp cavity but were absent adjacent to osteodentin. Degenerative signs were seen where these cells were in close proximity to perivascular accumulations of lymphoid cells. Large perivascular accumulations of lymphoid cell infiltrations were noted throughout the pulp; however, these cells were not diffusely distributed. Most of the tooth was surrounded by a dense connective tissue revealing an intense lymphoid cell infiltration which in some areas had extended to the ameloblastic layer. A dense connective tissue replacement of the stellate reticulum had also occurred. The tooth was only partly encased in a bony alveolus and this had undergone some resorption.

The remnants of the incisor consisted of a dentin shell showing bone and marrow in the proximal part of the pulp and dense connective tissue and inflammatory cells distally. Encystment of the tip of the incisor had occurred and resorption of parts of the dentin were also evident. Only two dentin cusps and part of a third, embedded in dense connective tissue and
partly encysted, remained of the first molar. The pulp of the molar had been invaded by a dense connective tissue. No surviving odontoblasts or ameloblasts were found in the incisor or the first molar. The remainder of the mandible revealed a very large amount of trabecular growth and considerable new spongy bone. A dense connective tissue invasion of the graft had occurred but was not extensive. Much normal appearing, vascular marrow was found, but some areas where dense and loose connective tissue substitution had occurred were also seen. Noteworthy is the fact that less resorption than bone formation had occurred. Lymphoid cell infiltration was moderate but was more intense about the rejected first molar and incisor. Gross observations on the transplant at time of recovery revealed a vascular graft encased in a thick connective tissue capsule and firmly attached to the host tissues.

The incisors had not survived intact in grafts in either the Imuran treated or the control hosts (table 26). No instances of total resorption of the incisor had occurred. In transplants in both treated and control hamsters, a dentin shell was usually seen showing varying degrees of bone formation and dense connective tissue invasion of pulps. Some of the incisor remnants had become ankylosed to adjacent mandibular bone. In no instance were surviving ameloblasts or odontoblasts seen in grafts in either treated or control hosts. In general, there did not appear to be any difference in the appearance of incisors between those in grafts in treated and control hamsters.

In no instances were the survival of intact first mandibular molars encountered in grafts in either Imuran treated or control hamsters (table 26). One case of complete resorption of this molar was observed in a graft in a treated host. One graft in a control hamster showed only some dentin frag-
ments embedded in bone which were identified as remnants of a first molar. There appeared to be a higher degree of resorption of the fragments of cusps of the first molars in grafts in the treated group although this difference was not striking. There was very little difference in pulpal bone formation in first molars between those in treated and control hosts and no surviving odontoblasts or ameloblasts were found. Imuran treatment had not decreased encystment of the molar remnants.

Second mandibular molars had not survived grafting except in one treated graft described above (table 26). This molar did not reveal the degree of growth seen in a 15 day control (figs. 6, 7).

In this series four of five grafts from Imuran treated hosts revealed more trabecular growth and spongy bone formation than was observed in those control hamsters (figs. 71, 72). Less resorption of graft bone was also seen in treated hamsters as well as less dense connective tissue invasion and substitution of resorbed bone. Bone formation did not appear to be as intensive in this series as that observed in hosts receiving the 5 mg dosage of Imuran. In all but one case, more graft bone was seen at time of recovery in treated than in control hosts. The necrosis of graft tissues also did not appear to be as widespread as in control hosts. The central hollowing tendency of mandibles was not seen in this series. Normal marrow had developed in three of five grafts in treated hosts, whereas the remaining two showed a dense and a loose connective tissue replacement. In only two mandibles in control hamsters were large amounts of normal appearing marrow seen while in those in the remaining control hosts, most of the marrow was replaced by a very dense connective tissue.
Cyst formation was seen in all transplants and their incidence was not decreased by Imuran treatment. In general, the transplants exposed to Imuran treatment showed greater lymphoid and other inflammatory cell infiltrations in this series than was observed in identical grafts exposed to 5 mg of this drug. In the present series, utilizing a daily dosage of only 2 mg of the drug, grafts usually showed some decrease in the degree of lymphoid cell infiltrate, but this was not greatly reduced from that seen in control hosts.

Gross observations at time of recovery showed the grafts to be vascular and encased in a connective tissue capsule in both treated and control animals. Transplants were usually very firmly attached to the host tissues. No significant differences were detected in this respect between the two series.

2. In Cheek Pouch (Experiment XII)

Eight of nine transplants of half-mandibles from 12 to 14 hour old, neonatal hamsters were recovered from the cheek pouches of adult hamsters having received 5 mg of Imuran daily/100 gm body weight beginning at time of grafting and continued for 15 days at which time the grafts were recovered (table 5). Five of five control grafts were recovered from hosts having received an identical treatment except for the injections of the aqueous vehicle. The graft in one treated host was completely resorbed (tables 5, 27).

The incisors of all 12 to 14 hour old neonatal intact control mandibles had already erupted when transplants were made. The first mandibular molars at this time showed differentiated ameloblasts on all three cusps (figs. 1, 2). The central cusp had developed dentin and some enamel. Dentin had begun
to form on the other cusps. The second mandibular molars had developed cusps but had not yet begun to form dentin (figs 1, 3).

Only two molars had survived and these were found in two grafts in Imuran treated hosts (tables 5, 27). One of these, which had shown growth and differentiation, was identified as a second mandibular molar (table 27; animal #9). Three major cusps had formed, but roots had not appeared (fig. 73). Enamel was found only on the central cusp and was mostly in the form of pre-enamel. The other two cusps were enamel-free and no pre-enamel was observed. Tall columnar ameloblasts, largely normal in appearance, covered the entire surface of the crown. Nevertheless, some degenerative changes were seen in these cells on the central cusp. A viable Hertwig's root sheath was found. No hypoplastic areas were observed where pre-enamel had formed. A regularly formed tubular dentin was observed as a thick layer on the central cusp, thinner on another and had not appeared on the third. No osteodentin was found. Pre-dentin had formed as a thin layer on the pulpal aspect of the dentin. Pulpal calcification had not occurred and pulp cells were normal in appearance. The pulp revealed capillaries within the odontoblastic layer, but no pulpal accumulations of lymphoid cells were found. Tall odontoblasts formed an intact layer within the central cusp, but these cells were shorter in the other cusps. No signs of degeneration were detected in the odontoblast layer. The dental sac surrounding the tooth revealed no lymphoid cell infiltration. The molar was partly encased in an alveolus of viable bone. The cells of the dental lamina seemed to be continuous with the squamous epithelium of a cyst.

The incisor in this transplant revealed no evidence of surviving ameloblasts or odontoblasts. The distal part had become encysted and
proximally, ankylosis of the dentin shell to mandibular bone had occurred. The pulp disclosed a vascular connective tissue and bone formation, although in distal pulp, accumulations of inflammatory cells were observed. Fragments of first mandibular molar cusps, which had undergone a large degree of resorption and were embedded in spongy bone were found. No encystment of the molar had occurred. No viable odontoblasts or ameloblasts were seen. The remaining part of the mandible revealed viable bone showing a high degree of trabecular growth and new spongy bone formation. A normal appearing marrow occurred throughout the mandible, but some areas had undergone replacement with osteogenic tissue. Only a low degree of dense connective tissue invasion had occurred. Although cyst formation had occurred adjacent to the transplant, lymphoid and other inflammatory cell infiltrations were negligible except about the distal part of the incisor.

The second surviving molar was found in a graft in a treated host and this had shown much growth following grafting (table 27; animal #14). This second mandibular molar revealed development of cusps, but root formation had not occurred (fig. 74). An intact stratum intermedium was seen adjacent to tall, normal appearing ameloblasts covering the crown. An intact Hertwig's root sheath was seen. The stellate reticulum had remained viable and showed some vascular areas, but no lymphoid cell infiltrate was disclosed. Enamel had formed on the central cusp, but only pre-enamel was seen on the other two. The calcification of enamel seemed irregular and had been retarded. Dentin was observed on all cusps, but it was greatest in thickness on the central cusp. Dentin formation was regular and tubular in nature and no zones of disturbed formation or osteodentin were seen. A regular layer of pre-dentin lined the pulpal aspect of the dentin. No pulpal calcifications
were noticed and the pulp cells seemed to be normal in appearance. The pulp disclosed capillaries within the odontoblastic layer and showed tall, normal appearing odontoblasts lining the pulp chamber. These cells were somewhat shorter than normal on the two less well developed cusps. No lymphoid cell infiltration was seen in the pulp. The dental sac had not been replaced by dense connective tissue and the remainder of the tooth was surrounded by very loose connective tissue. Approximately three fourths of the molar was encased within an alveolus of viable bone.

The incisor and the first mandibular molar had been completely resorbed in this graft. Much of the mandible proper had been resorbed and those areas containing the incisor and first molar were absent. The remaining mandibular bone was mostly viable, vascular and revealed only a few small areas of necrosis and degeneration. New spongy bone had appeared and vascular marrow was observed throughout most of the bone, but in these areas osteogenic tissue had replaced the marrow. No cysts had formed in this transplant and lymphoid cell infiltration was negligible throughout the tissues of the graft. These cells were seen primarily in the form of perivascular accumulations within the graft and in the connective tissue enclosing it.

No incisors had survived in the grafts in Imuran treated or control hosts (table 27). Complete resorption of the incisors had occurred in three of eight grafts recovered from Imuran treated hamsters. Total resorption was not seen in any of the grafts in control hamsters. The remaining incisors in grafts in treated hosts were dentin shells, some of which showed bone formation while others showed dense connective tissue in the pulp. All had undergone some resorption. None of the teeth in either series revealed viable odontoblasts or ameloblasts. Most of the incisors were partly encysted.
Encystment had not been decreased as a result of treatment.

The first mandibular molars also had not survived in transplants in treated or control hamsters (table 27). Four of eight grafts in Imuran treated hamsters revealed total resorption of these molars and two of five had also been resorbed in control hosts. There appeared to be a slightly greater increase in the degree of resorption of these molars in treated animals than was seen in controls as indicated by the decrease in number of cusps and the increase resorption of dentin. However, one first molar in a graft in a treated host did show some growth after grafting, as revealed by the large amount of dentin and pre-enamel; however, the molar had become encysted and the pulp disclosed a lymphoid cell infiltrate and cellular debris. No surviving odontoblasts or ameloblasts were seen in this tooth. The remaining first molars in grafts in both treated and control hosts showed only cusps or fragments of cusps composed largely of dentin and connective tissue; inflammatory cells were absent in most of these pulps. Bone formation was not frequently seen in the pulps of this series. First molars did not reveal any evidence of survival of odontoblasts or ameloblasts in any of the transplants. Encystment of molar remnants was frequently seen.

Second mandibular molars, with the exception of the two surviving molars found in grafts in Imuran treated hosts, were totally resorbed in the remaining treated and control hosts of this series (table 27). In no instance did a viable second molar in a transplant show the degree of growth seen in a normal 15 day control (figs. 6, 7).

The remaining bone in mandibles in Imuran treated hosts generally showed less resorption, more new bone formation, less tissue necrosis and more normal, viable marrow than was found in grafts in control hamsters (figs. 75,
Nevertheless, the amount of bone formation that occurred was not so great as that seen in identical subcutaneous transplants in ears receiving identical treatment. Also the cheek pouch grafts in treated hamsters in this series revealed much less bone than the grafts in ears and resorption of bone seemed greater in the former. The control mandibles in cheek pouches showed widespread necrosis of bone and marrow and they usually showed lymphoid cell infiltrations accompanied by an extensive dense connective tissue substitution. Very little new bone formation had occurred in these control grafts. In grafts in treated hamsters, most of the new bone seemed to occur in the form of spongy bone, rather than as trabecular growth, and the formation of compacta was not usually seen. Most of the mandibular bone was necrotic and resorption had been very extensive.

Three of eight grafts in treated hosts did not reveal cysts, yet cysts were seen in all five grafts in control hosts and these usually included some graft tissues other than teeth. The encystment of bone and other graft tissues was more extensive in this series than in the other series utilizing Imuran treatment. Experiments employing other sites usually did not reveal transplant bone within the cysts. Most transplants in the cheek pouch of hosts receiving Imuran, showed a significant decrease in lymphoid cell infiltration whereas all transplants in control hosts showed dense lymphoid cell infiltrations. The reaction against cheek pouch implants in both treated and control hosts appeared to be more intense than that seen in identically treated transplants on ears.

Gross observations at the time of recovery showed encystment of many of the grafts and a low degree of vascularity in both treated and control hosts. No significant differences were detected between the two groups.
The results of this study indicate that teeth in half-mandible transplants show different degrees of viability when transplanted into different sites in the hamster and rat. The highest degree of survival of teeth in such grafts occurred in subcutaneous sites on the dorsal surface in the ear in hamsters and rats. Survival of molars tended to increase in those grafts where parts of the mandible had been excised prior to grafting to allow an earlier establishment of grafts in the host environment. The most successful growth and differentiation of teeth was seen where the first mandibular molar had been entirely removed from the mandible prior to subcutaneous transplantation in the ear.

Employing two known immunosuppressive drugs, 6-MP (6-mercaptopurine) and Imuran, (azathioprine) on subcutaneous half-mandible implants in the ear, a greater viability of molars and a decrease in the intensity of rejection was seen. A higher degree of bone formation and a decrease in resorption was seen in such transplants in drug treated hosts.

By means of studies on the influence of transplantation sites and on the effects of immunosuppressive drugs on teeth and bone in transplants in the more successful sites, an attempt has been made to study some of the factors responsible for the failure or survival of teeth in heterotopically transplanted half-mandibles in the hamster.

A. Half-Mandibles.

This study showed that half-mandible transplants in hamsters and rats did not increase in total size but were usually smaller on recovery.
than when implanted, regardless of the site of transplantation. Never­theless, the subcutaneous implants in the ear and those between the scapulae on the back showed larger amounts of bone than was found in testis or uterus with exception of those in the kidney in which consider­able bone was also observed. The largest amount of viable transplant bone and highest degree of bone formation occurred on the ear in both rats and hamsters.

Contrary to the observations derived from these studies, Felts ('61) reported an increase in mandible size in some subcutaneously transplanted 14 day fetal mouse mandibles; but most of his grafts manifested a distorted morphology and lack of growth. Truax ('58) reported that two day postnatal mouse half-mandibles subcutaneously transplanted in the backs of immature mice showed periosteal bone formation over the original surfaces of the grafts. They did not grow and develop in the same manner as did the mandibles in normal control mice, nor did they approximate the normal size and shape.

Ostergren ('58) observed that half-mandibles from 14 day fetal mice implanted subcutaneously into adults of the same inbred strain continued to grow normally. These grafts varied from the normal mandibular shape after ten days and those recovered later did not resemble normal mandibles.

Etem ('59) reported that half-mandibles from inbred 19 day fetal mice, transplanted intramuscularly and subcutaneously showed no significant difference in total size. At approximately 20 days, intramuscular grafts showed primary growth in an anterior-posterior axis. This was also the case in subcutaneous grafts, but in these it was less specifically oriented.
still, at this time evidence of resorption was detected although histological observations disclosed normal viable bone. Half-mandibles recovered from those sites showed consistent increments in size during the first three to 14 days, but later growth seemed to be less pronounced and the intramuscular grafts became smaller in size. At 30 and 50 days, the subcutaneous grafts were very flattened in shape instead of becoming thickened and attenuated like the intramuscular ones. Jones ('63) reported a generalized bone formation in half-mandible grafts in spleens of rats and mice despite some disturbances in normal patterns of growth.

Contrary to these observations, Baker ('36) reported that half-mandibles from rats three days before birth showed an increase of one-third the original length after transplantation into the leg muscles of the mother. The implants retained a pre-functional shape although some further development occurred in the body, ramus and processes. The mandibles of intact littermate controls were approximately twice as large as the grafts at time of recovery.

In the present study, resorption of half-mandibles was generalized in the grafts and did not occur primarily at the ramus; but was also seen in the anterior part of the mandible while most of the bone formation was seen at the ramus in grafts recovered at 15 days from rats and hamsters. Baker ('36) reported that resorption occurred in a specific pattern principally at the ramus where the muscles of mastication normally attached, but the body of the mandible had not undergone any appreciable resorption. Ostergren ('58), Truax ('58), Etem ('59) and Felts ('61) reported a more generalized resorption of their implants. Some of our mandibles showed a tendency to develop hollow centers while
forming a thick rim of peripheral bone. Others had undergone conversion into solid ossicles while a few had been resorbed until only a few small ossicles of viable bone remained. Where bone formation had been underway, trabeculae frequently became thickened; but noticeable increments in mandibular length never occurred.

The cartilages of the ramus in half-mandible implants frequently became calcified and many partly or completely replaced by bone. In some, the condylar cartilages persisted, but none of the mandibular growth centers functioned normally. Similarly Truax ('58) reported that the gonial and condylar cartilages were replaced by bone in subcutaneous implants half-mandibles of two-day old postnatal mice. Oster gren ('58) reported disruption of the growth cartilage in subcutaneous half-mandible implants of fetal mice, while Etem ('59) observed bony invasion into growing cartilages and bone formation on the surfaces in subcutaneous and intramuscular grafts of half-mandibles of fetal mice. That cartilage will continue to grow after grafting was seen in our autografts of hamster rib in ears of normal adults where growth as well as calcification occurred although some degeneration of chondrocytes in most central parts of the cartilage was seen. Spongy bone formation was seen adjacent to surfaces of the calcified cartilage and in most of these some endochondral ossification had been underway.

Although in most instances condylar cartilages did not persist and act as growth cartilages for the ramus of grafts in the present study, Glasstone ('68) reported bone formation in bodies of cultured jaws from 13 day fetal mice. The cartilages at the angle and condyles had
differentiated from the undifferentiated mesenchyme. Bone formation had occurred about these cartilages and remodeling as well as growth was underway. Joints had developed in cultures of condylar cartilage.

The transplants in the present experiments did not reveal further development of the condylar cartilages which had usually calcified, were resorbed or had been replaced by bone. It would seem that although some cartilage can grow in autografts and in vitro, the cartilage in homografts of half-mandibles usually do not, perhaps due to the presence of an immune rejection or to the absence of normal stimuli such as the mechanical forces acting on normal mandibles.

The site of transplantation had a considerable influence on the viability and formation of bone in half-mandible implants in both hamsters and rats. Complete resorption of transplanted half-mandibles, accompanied by a very intense lymphoid and other inflammatory cell infiltrate was seen at all implantation sites in the hamster testis. This showed that the grafts did not become established and had become subject to immunological destruction. Similarly, utilizing skin homografts in rats, Nicholas and Scothorne ('69) observed that grafts implanted deeply within the testis showed lymphocytic infiltration at 12 to 14 days and rejection at 27 days. Those transplants immediately beneath the tunica albuginia revealed lymphocyte infiltration at six to eight days and rejection by 12 days. Autografts remained viable and normal in both locations. An abundance of lymphatic vessels was found within the tunica albuginia but were absent in the interior of the testis, which the investigators felt accounted for the extended survival of skin homografts within the organ. At 20 days all that remained of the half-mandibles deeply implanted
in the hamster testis in the present experiments was a very intense inflammation and complete resorption of the grafts.

Transplants in the lumen of the uterine horn of the hamster revealed much degeneration and a low degree of bone formation. They did not become readily established and vascular. Similar observations were made by Watnick and Russo ('68) where skin of rats had been homografted into the uterine lumen. Parts of the implants which protruded through the uterine wall did not degenerate while those within the lumen showed evidence of degeneration as early as six days and had completely disappeared by nine days. Grafts of half-mandibles in the present experiments, which had become attached to the area about the uterine incision showed some vascularity and bone formation; however, in some cases a very intense inflammation had occurred and little viable bone was found.

Neonatal half-mandibles transplanted into the kidneys of rats and hamsters seemed to become established and usually showed bone formation and vascular marrow. Overall growth of the mandibles had not occurred. When the grafts had become involved in a rejection response, considerable necrosis and replacement of adjacent renal tubular tissue by dense connective tissue was seen. There was little difference between half-mandible grafts in hamsters and rats in this site except that the rejection reaction in the rat kidney was more intense.

The response of subcutaneous transplants of half-mandibles of neonatal hamsters varied greatly depending on whether they were implanted in the back or in the dorsal surface of the ear. Those in the back usually revealed only a small amount of viable bone, a minimal degree of bone formation and considerable necrosis. At time of recovery, these
grafts disclosed a much lower degree of vascularity than those in the ear and were not tightly attached to the host tissues. Transplants in backs also showed a greater lymphoid cell infiltration indicative of a more intense rejection reaction.

The half-mandibles in the ear, on the other hand, revealed good vascularity, a firm attachment to the subcutaneous tissues of the host and a lower degree of necrosis than those in the back. Bone formation was appreciably greater than in those in the back. Many showed new bone formation on older, less viable appearing bone. Many also showed a vascular marrow which usually was not seen in other sites with exception of the kidney. The presence of host ear cartilage probably had a beneficial influence on the formation of bone at this site since bone frequently formed on its surface, in the presence of a transplant. The fact that the grafts had become firmly attached and seemingly obtained a greater degree of vascularity and establishment with the host is equally important in contributing to the increase in bone formation and the greater viability of these transplants when compared with those of other sites.

The growth and formation of bone was enhanced when appropriate doses of either of two known immunosuppressive drugs, Imuran or 6-MP, were administered. Where a very large dose of 10 mg/100 gm of 6-MP was given for 10 or 12 days to hamsters having half-mandibles grafted subcutaneously in backs and recovered at 10 or 15 days respectively, the grafts disclosed a greater degree of resorption than bone formation and loose attachment to the hosts. The grafts in treated hosts disclosed less resorption than those in control hosts. It should be noted that those in treated hosts showed only a few viable ossicles. Those in control hosts revealed more
dense connective tissue invasion and in some cases more bone formation.

In another series, 10 mg/100 gm/day of 6-HP was administered and after four days reduced to 5 mg/100 gm/day to hamsters having subcutaneous implants in ears recovered at six days. The grafts in 6-HP treated hamsters were mostly avascular, but showed some peripherally viable bone and a small amount of bone formation while those in control hosts revealed more viable bone, resorption and dense connective tissue invasion in addition to a higher degree of revascularization.

In these experiments employing a dosage of 10 gm/100 gm/day of 6-HP several observations were made which probably influence the viability and growth of bone in these grafts. Grafts in backs of both treated and control hosts recovered at 10 and 15 days were loosely attached to host tissues. Where grafts in treated and control hosts were recovered from ears at six days, the implants in control hosts had become firmly attached to the host tissues while those in treated hosts were only loosely attached. These observations indicate that this dosage of 6-HP had an initial inhibitory effect on the incorporation of the graft. The grafts from treated hosts were less vascular which is indicative of a delay in revascularization. The grafts in control hamsters showed a greater invasion by dense connective tissue. The drug may have inhibited proliferation of connective tissue which would explain the delay in attachment of grafts. The delay in establishment of grafts could explain the decrease in bone formation, although it is possible that this dosage of the drug had an inhibitory effect on bone formation. A decrease in the degree of bone resorption was observed in treated animals.
Contrary to these observations, where a daily dosage of 5 mg/100 gm of 6-HP was administered in hamsters at time of grafting and continued for 15 days, grafts in treated hosts disclosed a higher degree of viability and bone formation than those in control hamsters. These grafts in treated hosts showed that much of the marrow had been replaced by osteogenic tissue, and where connective tissue invasion had occurred, it was looser in character than that of grafts in the controls. The grafts in control hosts revealed spongy bone formation rather than trabecular growth. Nevertheless, grafts in drug treated, control and normal animals all had become firmly attached at time or recovery.

Where 2 mg/100 gm/day of 6-HP was administered and grafts recovered 15 days later, those in treated hosts showed more bone formation than control hosts, but less than where 5 mg had been given. Osteogenic tissue invasion of the implants occurred in treated hosts while those in control hosts disclosed more resorption and dense connective tissue replacement. Replacement of marrow by osteogenic tissue occurred in grafts in treated hamsters, but some regions of normal vascular marrow were also seen.

None of the transplants in 6-HP treated hamsters at any dosage showed an overall increase in size although they usually disclosed a higher degree of bone formation. No normal mandibular growth occurred and calcification of growth centers and replacement by bone, similar to that of grafts in normal hamsters was seen.

Where a daily dose of 5 mg/100 gm of Imuran was administered for 15 days, half-mandible grafts in the ear showed lower degrees of resorption, replacement of marrow by dense connective tissue and necrotic
Bone than those in controls. As with 6-β-P, grafts in Imuran treated hosts showed more trabecular growth than spongy bone formation; however, some of the latter showed a tendency to form hollow, marrow containing ossicles while those in the control hamsters revealed a more generalized resorption.

Half-mandibles recovered at 15 days from the ears of hosts having received 2 mg/100 gm/day of Imuran also revealed greater trabecular growth than spongy bone formation and a decrease in resorption; however, the degree of bone formation frequently was not as high as those in hosts having received the higher dose. Grafts in treated hamsters in this series also did not manifest the hollowing tendency seen at the higher dose. In addition, grafts in treated hosts disclosed more normal marrow whereas marrow had been replaced by dense connective tissue in grafts in control hamsters.

To further test the effect of Imuran on the viability of half-mandible implants an experimental series utilizing a supposedly immunologically privileged site was undertaken. In previous experiments (Kneussl, '66) half-mandibles of fetal and neonatal hamsters were transplanted into the cheek pouch of normal hamsters. These observations revealed that the grafts had undergone rejection. A series of grafts was performed utilizing identical implants to those grafted in the very favorable ear site in Imuran treated hamsters. Where a 5 mg/100 gm/day dosage of Imuran had been administered to hamsters having half-mandible transplants in cheek pouches and recovered at 15 days, the implants contained more bone formation, less tissue necrosis and more viable bone marrow than those in control hosts. The grafts in this series did
not disclose as much bone formation, and resorption was more extensive than those recovered from the ear of hosts having received identical treatment. The predominant form of bone formation in the cheek pouch in treated hosts was spongy bone rather than trabecular growth as was the case in other experiments employing Imuran.

Imuran and 6-MP treatment had a beneficial effect on bone formation as seen by the higher degree of formation in treated hosts, although the highest dose of 6-MP was deleterious to both host and graft. The subcutaneous ear site was a better implantation site than the cheek pouch despite the drug therapy. The lymphoid cell response, indicative of the rejection reaction, tended to be less pronounced in grafts in hosts exposed to appropriate dosages of either drug.

One series of observations having some significance regarding the effect of transplantation sites on rejection and viability of grafts was the experiment where 5 mg/100 gm/day of Imuran had been administered in hamsters having grafts in the cheek pouch. These implants showed more viable teeth and bone and a decrease in lymphoid cell infiltration when compared with those in control hamsters. The drug treatment enhanced the viability of grafts. Where an immunosuppressive drug had a beneficial effect on viability of half-mandible grafts in a site, that site can not be immunologically privileged for those tissues. Earlier observations (Kneussl, '66) showed that half-mandibles of fetal and newborn hamsters implanted into the cheek pouch of hamsters undergo rejection are in accord with the rejection observed in the controls of the present series. When cortisone, an anti-inflammatory agent, was administered, the viability of the grafts was not improved. Furthermore,
such grafts showed a higher degree of resorption, more severe necrosis and generally a decrease in vascularity in all but one graft in cortisone treated hamsters.

Since Imuran treatment showed a decrease in the intensity of the immune rejection reaction in implants in ears and had a similar but lower effect on identical transplants in the cheek pouch; it is evident that the cheek pouch is not an immunologically privileged site for half-mandibles as had been reported by earlier investigators for a number of different tissues in normal hamsters. In the present experiments, rejection of transplants was more severe in cheek pouch than in the ear.

Many investigators have reported growth of a number of different tissues of homologous and heterologous origin in the cheek pouch of the Syrian hamster. Human sarcomas proliferated and grew in size in the pouch, while non-malignant tissues revealed little growth although they persisted for long periods (Lemon et al., '52). Resnick and co-workers ('60) reported survival of autologous and homologous skin grafts in cheek pouches of normal hamsters and heterografts of normal human skin in the pouches of normal and cortisone treated hamsters. Billingham and co-workers ('60) reported proliferation of hamster skin homografts in cheek pouches of nonsensitized hamsters. Identical grafts were rejected when transplanted elsewhere.

Proliferation of heterografts of adult rabbit skin was seen in cheek pouches of normal and cortisone treated hamsters and similar responses were observed in homo- and autografts of skin of hamsters in the pouches of normals (Cohen, '61). Cyst formation often occurred and a lymphocytic response was seen in surviving and rejected grafts.
Segments of oviduct from rabbits remained viable in cheek pouches of ovariectomized and normal female hamsters (McDaniel and Black, '64). Thymic tissue allografts from newborn hamsters in the cheek pouches of thymectomized and normal hamsters grew and revealed normal cells and structure until approximately six weeks, at which time the implants gradually began to decrease in size (Poole and Shepro, '66). These grafts apparently failed to elicit an immune rejection reaction.

These studies indicate that the cheek pouch of the hamster is a privileged site for certain types of implants, at least for some of the soft tissues. Many investigators have speculated concerning the mechanism involved and some have postulated that an absence of lymphatic drainage might explain the extended survival of grafts.

An observation by Billingham and co-workers ('60) has significance with respect to survival of transplants in the hamster cheek pouch. They reported that skin homografts in the cheek pouch of nonsensitized hosts were retained, but when the hosts were sensitized by another graft, either before or after the pouch graft, the pouch transplant was rejected. This observation led to the conclusion that skin homografts in the cheek pouch were incapable of sensitizing the hosts; but after the host became sensitized, grafts in the pouch were rejected demonstrating that susceptibility to rejection in the pouch was a one-way process. In the same paper these investigators reported that homografts of skin obtained from the wall of the cheek pouch retaining the loose areolar connective tissue layer survived longer than normal skin grafted to other parts of the integument. Nevertheless, these pouch skin grafts were rejected after the hosts were sensitized and their response was
similar to normal skin homografts in the pouch. Billingham and associates postulated that the loose areolar connective tissue layer in the pouch was responsible for a property of a seemingly one-way action and the privilege obtained therefrom.

In a later series, Billingham and Silvers ('62) reported that homografts of cheek pouch skin transplanted to prepared areas of the integument survived longer than normal skin, but these grafts were rejected once hosts were sensitized. When a normal skin homograft was placed into ("inlaid") the substance of a long standing pouch skin graft, the graft was retained. Similarly, when the areolar tissue layer of the pouch was grafted interposed between the normal skin and the recipient integument bed, survival of the normal skin was prolonged and this also occurred where the layer of areolar connective tissue had been devitalized before transplantation. The investigators concluded that the privileged nature of the cheek pouch was inherent in the properties of its connective tissue layer which impeded the escape of transplantation antigens so that the host does not become sensitized against grafts.

Hamsters, which had accepted cheek pouch skin homografts of long periods, were found to have lost the ability to reject grafts of neonatal skin from the inbred, pouch skin donor strain (Billingham and Silvers, '64a). The investigators concluded that antigenic material was released very slowly from the graft site resulting in tolerance rather than sensitivity through chronic exposure to very low doses of antigen. Similarly Billingham and Silvers ('64b) reported that tolerance produced by very slow release of transplantation antigens from the cheek pouch skin homografts could overcome a weak histocompatibility barrier.
That transplantation antigens are released from the cheek pouch, now seems evident; however, how they are carried to the lymph nodes of the host is not known. Many investigators have failed to demonstrate lymphatic vessels in the cheek pouch. In one study Shepro and co-workers ('63) could not show lymphatic vessels in the pouch utilizing injections of India ink, but large molecules injected into the pouch, such as chromic radiophosphate and thorotrast, were trapped and slowly released from the loose connective tissue of the pouch in only small amounts.

Others have challenged the concept of an immunologically privileged cheek pouch. Utilizing injections of India ink into the tissues of the pouch Lindenmann and Strauli ('68) observed lymphatic vessels in the oral and muscular layers. Nevertheless, they felt that their observations did not contradict the concept that the areolar tissues act as a barrier to the migration of transplantation antigens since there was no evidence for a direct lymphatic drainage from the pouch into the cheek. The investigators felt that the positioning of the graft in the wall of the pouch may be important in the survival or rejection of a transplant.

Barker and co-workers ('69) reported rejection of skin homografts inlaid into a bed of an established pouch skin graft but in direct contact with normal skin on its perimeter. Similarly established inlaid grafts of skin in cheek pouch skin homografts were rejected when one border of both was excised and normal adjacent integument opposed. Rejection was attributed to development of lymphatic connections and thereby the restoration of the afferent limb of the process of sensitization. It may be that the half-mandible transplants in the present experiments had also established such lymphoid connections, which then
resulted in their rejection in the cheek pouch.

Despite demonstrations of at least prolonged survival of homologous and heterologous tissues in the cheek pouch, and reports on the longevity of cheek pouch skin transplants on normal integument, it was consistently observed that rejection of fetal and neonatal half-mandibles implanted into cheek pouches from an intra-oral and extra-oral approach occurred (Kneussl, '66). It was also found that such grafts continued to undergo rejection in hosts treated with various regimens of cortisone. The results of the present series of experiments, on half-mandible transplants are in agreement with our previous observations. In transplants in the ear and in the cheek pouch several differences in response to grafts were seen. Cheek pouch grafts revealed a greater degree of lymphoid cell infiltration, greater resorption and less tooth survival than was seen in the ear. When Imuran was administered, grafts in cheek pouches showed a greater degree of tooth survival than those in control hosts although treatment here was not as effective as that seen in the ear. Grafts in cheek pouches of treated hamsters showed a decrease in the intensity of lymphoid cell infiltration and a greater amount of viable bone than the controls similar to the observations on grafts in the ears of treated hosts. The grafts in cheek pouches of treated hamsters showed a more intense lymphoid cell infiltration and resorption than in those identically treated in ears. The modification in the immune response in the cheek pouch following treatment indicates that the grafts had elicited the response since hosts had not been sensitized to previous transplants. It would seem that the cheek pouch was not immunologically privileged in the present experiments since the grafts elicited and underwent a
rejection response.

There are several plausible reasons why the cheek pouch, a seemingly privileged site for other tissues such as skin and oviduct, did not show similar privilege when half-mandibles were grafted. First, the mandible is a hard and relatively inflexible structure and could be mechanically forced from the loose connective tissue layer during normal movements of the pouch and thereby deprived of protection afforded by this layer. Second, the graft could pierce the loose connective tissue barrier and thus be deprived of its protection. In either case formation of lymphatic connections or a greater degree of transplantation antigen leakage could occur and result in sensitization of the host with a consequent rejection.

The presence of a viable molar was necessary for the development of a bony alveolus in transplanted half-mandibles. This finding supports that of Felts ('61) who reported that where a molar survived in a fetal mouse, half-mandible transplant, a molar bony alveolus formed, but where no molar had developed an alveolus did not appear. In some instances in the present experiments, it was found that where a molar had grown before being rejected, a partly formed bony alveolus remained. In some, molar remnants were ankylosed to adjacent bone, while in others the remnant was incorporated within spongy bone. The incisor did not remain viable and the remnants were ankylosed to adjacent mandibular bone.

When the first mandibular molars of neonatal hamsters were removed from the mandible and transplanted subcutaneously in the ear, varying amounts of alveolar bone developed. Histological examination on control molars similarly removed from the mandible showed that no bone had been
implanted with such molars. A similar formation of alveolar bone around subcutaneously transplanted, developing molars was reported by Hoffman ('60). This investigator ('66) also reported the formation of alveolar bone about developing hamster maxillary molars transplanted into the femur, and into the trapezius muscle ('67). Barton and Keenan ('67) reported the appearance of alveolar bone about second mandibular molars from two day old hamsters implanted into the cheek pouch region.

D. Incisors.

In none of the series utilizing half-mandibles of hamsters or rats homotransplanted in the ear of adults were viable incisors seen. Nor were viable incisors seen in half-mandibles of hamsters grafted in the back, into the testis, uterus or kidney of adults. Viable incisors were also not observed where half-mandibles had been grafted into the subcutaneous tissues in the back and ear of 6-HP treated or in the ear or cheek pouch of Imuran treated hamsters. These results agree with previous findings (Kneussl, '66) that incisors did not remain viable in half-mandibles of fetal or newborn hamsters transplanted into the cheek pouch of normal or cortisone treated adults.

In the present series the incisor remnants were dentin shells disclosing some resorption, degenerated odontoblasts and cellular debris. In many the odontoblasts had already disappeared by 15 days after grafting. The ameloblasts were usually absent except in some where a few squamous cell cords were seen in the basal area believed to be the remnants of ameloblasts which had transformed to a less specialized form. The pulps had also degenerated, many showing connective tissue invasions while in others varying degrees of pulpal bone formation had occurred.
Almost all incisor remnants revealed cyst formation distally. Varying amounts of lymphoid and other inflammatory cell infiltration were seen in pulps and about the incisors. The incisors in transplants of half-mandibles of rats were similar in appearance; however, they contained less pulpal bone formation and the pulps seemed to be less vascular probably indicative of a more vigorous rejection reaction.

Treatment of hamsters with Imuran or 6-IP did not enhance viability of incisors in half-mandible transplants, although, frequently a higher degree of pulpal bone formation and a less intense lymphoid cell infiltration were seen in the pulp and surrounding tissues probably indicative of a modification of the rejection reaction.

Our observations on viability of incisors agree with those of Felts ('61) and Ostergren ('58) who reported failure of incisors in subcutaneous transplants of half-mandibles of 14 day fetal and two day postnatal mice. Truax ('60) also reported the absence of viable incisors in subcutaneous grafts of half-mandibles from two day old mice, and Etem ('59) who implanted half-mandibles subcutaneously and intra-muscularly from term mice into adults reported survival of only one incisor which grew and was well formed. Willis ('35) transplanted parts of jaws into the brains of other rats and observed the growth of only one incisor.

On the other hand, Baker ('36) transplanted half-mandibles from rat fetuses, three days before birth, into the leg muscles of mothers and observed growth and development of an incisor. Jones ('63) also reported half-mandible homografts from newborn rats and mice in the spleen of adults disclosed incisor eruption. This investigator suggested
that the spleen probably was a more favorable transplantation site than subcutaneous or intramuscular sites in these animals.

Grewe and Felts ('68) reported that non-erupted mandibular incisors, from five day old mice, transplanted into the mandibular incisor sockets of seven day old mice, failed to grow and disclosed varying degrees of resorption, inflammation and cyst formation. Others were lost from the host sockets. However, reimplanted incisors did reveal evidence of growth and differentiation.

Contrary to the results of transplantation studies, rather successful growth of rodent incisors has been obtained through culture in vitro. Glasstone ('68) reported growth and differentiation of incisors in cultures of 13 day fetal mouse mandibles. She ('67) observed that after two days culture of mandibles from 11 day fetal mice, incisor tooth germs appeared in the anterior part of the mandibles which later developed into typical rodent incisors.

The failure of incisors to survive and differentiate in half-mandible transplants can be attributed to several factors. Of primary importance for the viability of an incisor is its establishment in the host before irreversible damage to its cells occurred, primarily from nutritional embarrassment. A second factor is the immune rejection reaction which will affect the establishment of the transplant or also destroy it once it has become established.

Felts ('61) postulated that incisors in subcutaneous and intramuscular transplants of fetal and neonatal mouse half-mandibles did not grow because of difficulty in obtaining revascularization. Present observations tend to verify this assumption since only the proximal parts
of the pulps in many incisors had become vascularized, while in others pulps were avascular and necrotic. All of the incisors in grafts employed in the present study showed degeneration of odontoblasts, ameloblasts and pulp cells in addition to extensive necrosis even in those areas where revascularization had occurred. It is probable that much of the vascularity seen in the incisors of our grafts at 15 days was the result of vascular ingrowths in conjunction with connective tissue invasion of the grafts and not utilization of inherent vascular structures present at time of grafting. The distal parts of the pulp did not become vascular unless the dentin wall of the incisor had become perforated; and in these, vascular connective tissue ingrowths usually occurred. These observations confirm earlier observations (Kneussl, '66) on the revascularization of incisors in fetal and newborn hamster half-mandible transplants in the cheek pouch. The incisors in half-mandibles of rats and hamsters implanted into kidneys did not disclose a higher degree of revascularization than that observed on ears. It would appear that incisors in intact half-mandible grafts have difficulty in re-establishing vascularization.

Our studies on grafts recovered from various sites revealed an intense rejection reaction about and within the incisors. It is felt that the immunological reaction normally elicited by homografts was at least partly responsible for the absence of viability and the inflammation and deficient revascularization seen in such grafts. Treatment with cortisone, an anti-inflammatory agent, did not enhance viability of incisors in fetal and neonatal half-mandible transplants in the cheek pouch (Kneussl, '66); but although treatment with the immunosuppressive
drugs, Imuran and 6-MP, did not improve the viability of the incisors, a decrease in the intensity of rejection within and about the incisors was observed. Bone formation in pulps had increased with drug treatment and many of the pulps were more vascular but no viable odontoblasts, ameloblasts or pulpal cells were found. It is concluded that the immune reaction was modified but had not been sufficiently suppressed to ensure their viability.

C. Molars.

Many of the molars in half-mandible transplants disclosed growth and differentiation. Considerable variation in viability of molars in relation to the site of transplantation was observed. Molars were completely resorbed in the testis. In the transplants in the back, only dentin remnants of molars were found which disclosed no evidence of growth and frequently the molars were completely resorbed. Transplants into the uterine lumen showed no viable molars, but one of the molars disclosed some growth and differentiation; but it had undergone degeneration some time before recovery. Transplants in hamster kidneys revealed only one viable molar with a high degree of growth and differentiation. Only one viable molar and a fragment of it or another molar was seen in the series of rat implants into kidneys.

A higher degree of success was attained by utilization of the site in the ear in both hamsters and rats. In this site a dramatic increase in viability of molars was seen. In some cases, two molars had survived in a single transplant; but generally, only one molar was found which was usually a second molar.
None of the viable molars had erupted within the 15 day post-transplantation period. This observation is not in agreement with those of Jones ('63) who reported eruption of molars in newborn rat and mouse half-mandibles homografted into the spleen of adults. In transplants made during the present study, the molars had usually changed orientation in such a manner that they could not have erupted from the mandibular bone. In any case, development in most had not progressed to the stage seen in normal teeth in intact control jaws undergoing eruption.

Studies on the survival, growth and differentiation of molars in half-mandible transplants have been reported by other investigators. Truax ('60) reported no evidence of molar development in half-mandibles from two day mice transplanted subcutaneously on backs of immature female mice. Ostergren and co-workers ('58) also reported that half-mandibles from 14 day fetal and two day postnatal mice subcutaneously implanted in backs of adults of the same strains did not show growth of molars. These observations were confirmed by our study in which half-mandibles from neonatal hamsters did not develop molars when transplanted in the backs of other hamsters. Baker ('36) observed development of molars in half-mandible transplants in the leg muscles of the female parent, while Felts ('61) reported only occasional viable molars in subcutaneously and intramuscularly transplanted mandibles from fetal and neonatal mice, which were only about half normal size. Willis ('35) reported the survival of a few molars where parts of jaws from fetal rats were transplanted subcutaneously and into brains of other rats.

The results of transplantation studies have been much less consistent than tissue culture studies. Glasstone ('68) reported that
in vitro culture of half-mandibles from 13 day fetal mice developed molars. She ('67) also reported that cultured posterior segments of mandibles from 11 day fetal mice, disclosed growth and differentiation of first and second mandibular molars showing cusp patterns similar to those of intact control mice. Dentin had formed and in some cases enamel matrix was also seen.

The molars in half-mandible grafts in our experiments showed varying degrees of growth and differentiation. In no instance in either rat or hamster did they approach the size and stage of development of those in control mandibles of the same age. All molars were much smaller and frequently the second mandibular molars only showed a very low degree of growth and differentiation. In grafts showing two viable molars, the first molars were usually more advanced in development than the second molars. Most of the molars in intact half-mandible grafts had not undergone any root formation. The viable molars in grafts in ears of rats were not as perfectly formed as those in identical grafts in hamsters. The former usually disclosed large amount of osteodentin, no enamel formation, and some viable pulp, in addition to viable odontoblasts, although most pulps showed much fibrous connective tissue. The rat molars seemed to have been involved in a more intense rejection reaction than were those in the hamster.

The present observations on transplants in the ear and in the back showed that areas of mandibles, some areas of molars, and the incisor were avascular and necrotic while peripheral areas of mandibles had become well established. To determine the occurrence of an osseous barrier interfering with the establishment and revascularization of grafts, a series
was carried out utilizing half-mandibles from which parts had been excised in order to enhance revascularization. In the first series, most of the incisor was excised leaving only its proliferating basal part, while in the second, only that part of the mandible containing the molars was utilized and in the third series only the first mandibular molar was transplanted. The results of these experiments indicated that as parts of the mandible were removed the number of viable teeth tended to increase and these were usually larger than those of intact half-mandible transplants. Many first molar transplants showed that root formation had been in progress; however, as was the case in intact half-mandible grafts, none of these molars approached the size of controls. The optimum growth and differentiation was attained where the first mandibular molar had been removed from the mandible. Although a higher degree of development had occurred, the shape of molars was greatly distorted. The degree of development of these teeth at 15 days, surpassed those in other experiments in the present study, also the number of viable molars was greater. Hence, these observations show that the molar will show a higher degree of growth and survival when the mandible had been mostly, but best where completely removed. These results indicate that the molar is capable of independent growth and development and that the bone of the mandible impedes the establishment, viability and growth of teeth in half-mandible transplants.

We observed a difference in the viability and survival of half-mandible and parts of half-mandible transplants in these experiments. Viable incisors were not found. Viable first mandibular molars were only seen on occasion and second mandibular molars more frequently. This
would seem to indicate the occurrence of a gradient of survival of molars in half-mandible transplants. Edblom and Felts ('66) reported a gradient for survival, growth and differentiation of molars in sets of first, second and third mandibular molars from 19 to 21 day fetal mice transplanted subcutaneously into adults of the same inbred strain. First molars developed most frequently, but showed the greatest growth range. Second molars were next in frequency, while third molars developed least often, but were closer to normal in size when development did occur. The present experiments showed that the second mandibular molar developed most frequently in the hamster while viable first molars were occasionally seen. Edblom and Felts ('66) reported that the least developed tooth in their experiments, the third molar, showed the greatest degree of growth. In the present experiments in the hamster, this was found to be the case in the second molar. Similarly, the second molar in the rat was observed to show the highest degree of survival, growth and differentiation.

All half-mandible transplants which did not reveal viable teeth showed an intense lymphoid cell infiltration about molar remnants and the rejection reaction was sufficiently intense to destroy the teeth. Usually, most of the rejected teeth showed no detectable growth or differentiation. To attempt to ameliorate the rejection reaction one of two immunosuppressive drugs was administered. In one series, hosts with half-mandible grafts in the back received 10 mg/100 gm of 6-HP beginning at time of grafting and continued for 12 days. At 15 days only one graft revealed a viable second mandibular molar showing some growth and differentiation. The remaining teeth were non-viable, but
the graft showed a noticeably lower degree of lymphoid cell infiltration than was seen in the graft of a non-treated control hamster. No viable molars were seen in an identical series where the grafts were recovered at 10 days instead of 15. The third series, where 10 mg/100 gm/day of the drug had been injected and then the dosage reduced to 5 mg after four days in hamsters having half-mandibles transplanted subcutaneously in ears, but recovered at six days, also did not reveal viable molars.

In another series where 5 mg/100 gm/day of 6-LP was administered at the time of grafting of half-mandibles in ears, and continued until recovery at 15 days, three of the recovered transplants revealed viable second molars, but no viable first molars were seen in control or normal hosts in this series. Two of the second molars showed only a low degree of growth and differentiation, whereas the third disclosed a higher degree of growth and development. Root formation had been underway in the latter. Lymphoid cell infiltration was greatly reduced in the transplants in treated hosts. The other cases in this series also showed a reduction in the degree of lymphoid cell infiltration although they did not reveal viable molars.

In the series where the dosage of 6-LP was decreased to a level of 2 mg/100 gm/day beginning at time of grafting, no viable molars were seen at 15 days; however, a viable molar was found in one of the controls.

The results of these experiments show that a daily dosage of 5 mg/100 gm of 6-LP tended to improve the viability of second mandibular molars while the 2 mg dose did not enhance viability of molars. It should be noted that the formation of bone was enhanced in 6-LP treated hosts at both lower dosages; however, with the 10 mg dosage the rejection
reaction did not seem to be affected and the formation of bone and viability of teeth were little different from that in control hosts. The hosts receiving the highest dosage also manifested signs indicative of drug toxicity.

These observations on grafts in 6-HP treated hamsters are in agreement with those of Morris ('63) who administered 6-HP, for a period of two weeks beginning at time of grafting, to monkeys having received autologous and homologous transplants of unerupted central incisors. The homologous transplants in 6-HP treated hosts revealed normal appearing pulp and dentin formation during the three to six weeks after grafting. However, untreated homologous controls disclosed degeneration of the pulp. At eight to 12 weeks, the homograft in the treated host showed a degenerative fibrous tissue in the pulp, but no necrosis or round cell infiltration. Normal vascularity of the graft was seen in the treated host.

In a series of experiments, Imuran at a dosage of 5 mg/100 gm/day had been administered beginning at grafting and three of the recovered grafts at 15 days showed viable second molars while only one in a control hamster showed a viable molar. The viable molars in the grafts of treated hosts showed a higher degree of growth and differentiation than was seen in the surviving control molar. The higher degree of molar growth shows that Imuran not only tended to increase the survival of molars, but also enhanced their growth.

In the second series, where 2 mg/100 gm/day of Imuran was administered to hosts for 15 days with identical grafts in ears, one of the grafts showed a viable second molar while none of the grafts in
control hamsters had any viable teeth. Contrary to the lymphocyte-free pulps of grafts in hosts having received the larger dosage, the pulp of this molar showed some lymphoid cell infiltration although considerable growth had occurred. The graft treated hosts in the latter series showed a higher degree of infiltration but it was noticeably less than that those of controls.

In a third series, daily doses of Imuran at 5 mg/100 gm were administered to hamsters with half-mandibles in cheek pouches, which were recovered 15 days later. Second molars showing growth and differentiation were seen in two of the treated hosts, but none were found in any of the control grafts. Viable first mandibular molars were not seen. Grafts in controls disclosed a very high degree of lymphoid cell infiltration whereas those in the Imuran treated hamsters usually showed significantly less infiltration. However, the rejection reaction occurring in the cheek pouch was generally more intense than that in identically treated grafts on ears.

Observations on the present experiments utilizing 6-HP and Imuran seem to indicate that these drugs had a beneficial effect on the survival of molars in half-mandible transplants in hamsters. First, there was a trend toward increased viability of molars as the dosage was increased to 5 mg. Only the second mandibular molars, however, were viable revealing growth and development. In addition where Imuran had been administered, molars showed a higher degree of growth than that of controls. Second, the drugs decreased the intensity of the immune rejection reaction. Despite the enhanced growth of molars in the grafts of Imuran treated hosts, they never approached the size of intact normal control molars.
There seem to be factors such as the immune rejection reaction which impede early establishment and revascularization of transplants. This is particularly true in the case of the molars in half-mandible grafts, since they can not become established unless the mandibles themselves form the proper relationships with hosts. We found that in normal hamsters the greatest degree of growth and differentiation occurred when only the molar had been grafted in the ear. Such teeth revealed early revascularization and attachment to host tissues so that a high degree of growth occurred. Nevertheless, many of these grafts also disclosed a pulpal lymphoid cell infiltration indicative of at least the initial stages of an immune rejection response. On the other hand, intact half-mandible transplants manifested much less survival of molars, a lower degree of growth in viable molars and widespread avascularity and necrosis in some. The survival rate of molars in such grafts tended to increase where 6-MP or Imuran had been administered, and bone formation was also enhanced, indicating that a more favorable relationship had been established between host and graft. The decrease in lymphoid cell infiltration during drug treatment, taken in account with an increase in degree of bone formation and a decrease in amount of resorption and dense connective tissue invasion, would seem to indicate that some deleterious factor between host and graft had been at least modified to the extent that a more favorable environment occurred at an earlier time. The mandibular bone itself has been seen to act as a barrier against the ingrowth of required vasculature. A combination of these vascular and immune factors may be responsible for the unsuccessful development of teeth, since they have the potential for independent growth as indicated
by their growth and differentiation when removed from the mandible.

In most grafts of first mandibular molars of hamsters, the form of a molar could be distinguished but the gross distortion in the shape of molars in the present study was greater than that reported by Hoffman ('60) who found that maxillary, first molars from newborn hamsters, subcutaneously transplanted and recovered at 28 days, showed a relatively normal morphology but little enamel formation on crowns. He also found osteodentin in the tips of some cusps. The roots were normal in length and were surrounded by alveolar bone with an intervening periodontal ligament with its fibers oriented between root and alveolar bone. The periodontal fibers were randomly arranged in contrast to the regular fiber bundle arrangement of normals. In the present experiments, first mandibular molar transplants also showed similar, but less well developed, randomly arranged connective tissue fibers intervening between the molar and alveolar bone. Barton and Keenan ('67) also reported formation of periodontal fibers attached to transplanted hamster molars.

Hoffman ('66) reported formation of crowns and roots in newborn first maxillary molars transplanted into crypts in the diaphysis of the femur in 30 day old hamsters. However, more distortion of the roots and molar shape occurred in this series than in his earlier subcutaneous grafts. Enamel formation was retarded and did not cover the entire crown surface. The present study revealed distortion in the direction of root growth. Hoffman ('66) also noted much deviation from the normal direction of root growth. First maxillary molars from newborn hamsters also showed development of crowns and roots at 28 days after implantation in the trapezius muscle but were smaller than normal (Hoffman, '67). Only one third to
one fourth of the crown surface was covered with enamel. Nevertheless, enamel formation was greater in intramuscular than in the femoral or subcutaneous implants reported by this investigator.

The molars in grafts in the present study frequently showed an abnormal dentin initially formed after transplantation which had the characteristic appearance of osteodentin, and subsequently a more tubular dentin developed. Hoffman ('67) also reported that tubular dentin was found on some enamel covered cusps, but most of the dentin formed immediately after grafting was osteodentin. An irregularly formed tubular dentin was found adjacent to the dentin and further toward the pulp the dentin progressively became more regular and normal similar to that observed in the present study. A thin layer of pre-dentin was seen lining the pulp in his grafts, but in the present series of grafts, a similar layer of pre-dentin was usually very irregular in thickness.

The dentin of roots in first mandibular molar grafts in the present series was usually a very regular tubular dentin with only small areas of osteodentin in contrast to the crown dentin. Hoffman ('67) reported that the occurrence of osteodentin in the roots of intramuscularly transplanted molars of hamsters was rare; but he also observed an irregular layer of pre-dentin similar to that seen in the roots of the present molar grafts. He attributed the abnormal changes in dentin formation to the adverse effects of transplantation on the nutritional supply of the dentin forming odontoblasts. He postulated that since no spaces were found in the dentin matrix, indicating the termination of one dentin type and the beginning of another, the altered dentin in cusps had formed from the same odontoblasts, rather than having been
the product of other cell types. Observations in the present experiments, substantiate his conclusion, since the tissue seen immediately adjacent to and toward the pulp of the dentin, which had developed prior to transplantation, was cellular in many areas and that progressively toward the pulp, the matrix became more tubular, regular and normal. The last formed dentin parts of the tooth were largely very regular, normal tubular dentin when compared with the initial dentin formation.

Zussman ('66c) reported that intact dental pulp from the incisors of adult rats transplanted subcutaneously in rats, first formed bony spicules, then bony trabeculae and finally tubular material with odontoblastic cells oriented adjacent to the tubular structures. Calcified material encased the odontoblast processes. The spongy bone described by Zussman is very similar to the osteodentin in transplants in the present experiments and that described by Hoffman ('67). It would seem that mature odontoblasts have the capacity to form both dentin and a bone-like matrix.

Similar post-operative changes in dentin formation in some of the developing molar transplants were previously reported by a number of investigators. Fleming ('52) observed that where ameloblasts had lost their normal relationship with the odontoblasts, dentin formation continued in a tubular pattern or in islands resulting in development of a tooth structure. He also observed that if the tooth was left in the anterior eye chamber for long periods, most of the dentin was replaced by a bone-like osteodentin. Fleming ('53a) also reported that revision of dentin occurred in tooth germ implants in the guinea pig anterior eye chamber. Once dentin had developed osteodentin formation followed. Where this revisional activity occurred, the odontoblasts lost their normal arrangement in the pulp and ultimately
disappeared. Fleming did not feel that the odontoblasts participated in this alteration and attributed the changes and the formation of osteodentin to cells other than odontoblasts.

In later investigations, Fleming ('55b) reported that tooth germ transplants, that had maintained intact pulps, were more normal than when the pulp was not intact and revisions of the pulps occurred more slowly. Where pulpal disruption or destruction had occurred, changes including fewer pulpal cells, fewer and smaller blood vessels, more collagen fibrils in pulps, less dentin formation and revision of the pulp into an osteoid were seen.

Hahn ('41) observed that where pulps with intact odontoblasts, from non-erupted maxillary canine teeth from female dogs, were autologously transplanted into the ovary, small areas of calcified tissue were seen seven days later resembling bone and showing small irregularly shaped cells along the border of the calcified tissue. After 15 days, normal appearing tubular dentin was seen in most of them. The character of the first dentin formed was cellular, but later tubular dentin developed which became more regular in nature as it approached the odontoblastic layer. Similarly, Huggins and co-workers ('34) observed dentin formation, in autologous transplants of isolated odontoblast containing pulp in the connective tissue of the abdominal wall, in young dogs. Circular and irregular plaques of tubular dentin showing a border of odontoblasts on one side were seen. However, some dentin was cellular in nature and a range of tissue types from normal tubular dentin through osteodentin and bone was seen.

Zussman ('66c) observed that intact dental pulp from adult rats, transplanted subcutaneously into one to four day old rats, showed formation
of bone and finally dentin, but at no time was dentin formed without prior bone formation. In another series, Zussman ('66b) transplanted subcutaneously, into three day rats, parts of enamel organs and odontoblasts from the incisors of adults. The odontoblasts again first formed bone and then dentin where ameloblasts were present. The odontoblasts remained active in the absence of ameloblasts as reported by Huggins and co-workers ('34). These investigators reported that where ameloblasts were present odontoblasts formed dentin without having previously formed bone. Sutro and Pomerantz ('39) observed that, where odontoblasts were not in contact with ameloblasts, dentin was very irregular in formation in experiments where the soft tissues of canine teeth were autografted into the tibias of kittens.

In the rabbit, Zaleski and co-workers ('67) reported the formation of osteodentin where rabbit allogeneic dental pulps were grafted subcutaneously in ears. The investigators concluded that the osteodentin had been formed by the cells in the dental pulp of grafts.

Autografts of maxillary, first molar tooth buds, transplanted subcutaneously into 10 day rats, showed recovery of the pulp following an initial post-grafting degeneration (Weinreb et al., '67a). The new dentin formation became progressively more regular with increasing postoperative intervals similar to that seen in our experiments. These investigators concluded that the process of revascularization was lengthy and when restored, normal formation of dentin ensued. The development of dentin in autografts of developing first maxillary molars in rats was shown by Weinreb and co-workers ('67b) to be dependent on the type of bony site or the type of bone in its immediate vicinity. Resorption and creeping
substitution of grafts occurred when the teeth were grafted subcutaneously with tibial bone or into the tibia. Those teeth with tibial bone formed a very irregular postoperative dentin and the pulp was gradually replaced by bone and marrow. Those in the tibia showed a similar reaction in the pulp but ankylosis of tooth to bone and greater dentin resorption occurred. Tooth bud autografts transplanted without bone, into subcutaneous tissues, produced osteodentin, then normal dentin. Toward the end of the experiment at six months, roots had formed. When the tooth bud was placed into a block of maxillary bone and subcutaneously grafted, the enamel organ was destroyed but dentin formation became more regular as the graft grew older. It would seem that alveolar bone had a beneficial effect and tibial bone a detrimental effect on the development of dentin in teeth. The present studies indicate that the bone of the alveolus seemed to have a beneficial effect on the development of molars, since the molars in half-mandible implants generally retained their normal shape and usually formed less osteodentin than when transplanted alone. Nevertheless, such molars were smaller than where transplanted alone.

Half-mandibles of neonatal rats transplanted in the ear of adults revealed viable molars with an almost total absence of enamel; but such grafts disclosed large masses of osteodentin which became tubular dentin nearest the pulp. Pre-dentin, though very irregular in nature, was observed adjacent to the pulp showing odontoblasts. These results are similar to those seen in hamster first mandibular molar grafts, but the rat first and second molars showed a much higher degree of osteodentin formation.

As reported in the present study, most of the molars in the trans-
plants of hamster and rat failed to develop enamel, or it had formed only on small areas of the crown. These observations confirm those of Barton and Keenan ('67), who reported that second mandibular molars from two day old hamsters, subcutaneously transplanted into the cheek pouch region, showed growth but severely limited enamel formation. Enamel was seen only on the tips of some cusps at 28 days. Islands of enamel epithelium were seen in the surrounding connective tissue. Transplants in the present study revealed that the enamel epithelium reverted to interconnecting squamous cell cords. Similar to these observations, when enamel had failed to form on crowns of molars, Barton and Keenan ('67) observed a cementum formation also reported by Hoffman ('60, '66, '67).

The absence of, or the very severely limited formation of enamel in molars in transplants, is a very significant finding and reflects adverse physiological conditions in the tooth. When, first mandibular molars from neonatal hamsters were extracted from mandibles and grafted in the ear, some enamel developed only on parts of the distorted crowns. Viable, first mandibular molars in half-mandible implants in hamsters also showed some enamel formation and enamel had formed in implants in kidneys. Second mandibular molars in half-mandibles showed more enamel, in relation to their stage of development, when development had progressed to the stage of matrix formation. The molars in half-mandible grafts in rats usually showed greater deficiencies in enamel formation. Frequently, where enamel had formed on crowns of molars in rats and hamsters, enamel spaces disclosed a border of short to cuboidal ameloblasts. In some molars these cells were continuous with adjacent squamous cell cords and clusters. In many grafts the cords were in surrounding connective tissue of the molar,
connecting other enamel spaces, or other groups of cell cords adjacent to parts of the crown. In others, squamous cell cords were continuous with the squamous epithelium of adjacent cysts. We have concluded that the cords and clusters of squamous cells in these grafts had their origin from ameloblasts which had reverted to a more primitive type of cell, the squamous cell.

Similar transformations of ameloblasts into squamous cells have been reported by other investigators. Huggins and co-workers ('34) reported that in autologous transplants of enamel epithelium, isolated from canine tooth germs of young dogs, implanted into the abdominal wall, the ameloblasts reverted to squamous epithelial cells. Enamel failed to form, but formation of cysts from these cells did not occur. The formation of epithelial pearls and islands of squamous cells was seen. Nevertheless, when the ameloblastic and odontoblastic layers were grafted together in a normal anatomical relationship, enamel and dentin formed; but when the odontoblasts did not persist, the ameloblasts reverted to squamous epithelium and enamel failed to develop. When these two cell layers were grafted together, without retaining their normal anatomical relationship, dentin formed; however the ameloblasts transformed into squamous cells and no enamel appeared. It was concluded that maintenance and normal function of the ameloblasts was dependent on the odontoblasts and the mesodermal components of the tooth and that the close anatomical relationship normally seen between these cell layers must be maintained for enamel formation to occur.

Similarly, Sutro and Pomerantz ('39) reported that, in transplants of the soft tissues of teeth, where islands of enamel epithelium were not
in contact with pulp, enamel was not formed although Hertwig's sheath remained viable. When the ameloblasts did not form enamel they became transformed into islands of epithelial cells.

Hahn ('41) observed, in isolated enamel epithelium from unerupted canines autografted into ovaries, that the ameloblasts reverted into a stratified squamous epithelium and occurred as solid cell strands or clusters, but no enamel had formed. Where pulp, free of odontoblasts, and enamel epithelium were transplanted together, the cells of the enamel epithelium reverted to a stratified squamous epithelium forming cords and clusters in addition to cysts and no enamel or dentin had formed. This investigator postulated that the enamel epithelium was necessary for determination of the shape of the tooth but was not necessary for further dentin formation after a layer of dentin had developed. He also believed that the presence of odontoblasts was necessary to maintain the integrity and function of the ameloblasts.

Fleming ('52) also reported that in grafts of tooth germs, the ameloblasts showed variations in fate and function. They either revealed normal function or degenerated. When the ameloblasts failed to form enamel in the anterior eye chamber, they formed clusters or cords of epithelial cells, epithelial pearls, and a keratinized material. In some instances cysts had formed. In transplants of human tooth germs in the anterior eye chamber of guinea pigs and rabbits and in the axilla of mice this investigator ('55a) reported cords and clusters of epithelial cells formed usually from the outer enamel epithelium and the stratum intermedium.

In transplants of enamel organs from incisors of adult rats into
three day old rats, Zussman ('66a) observed formation of cords and later nests of epithelial cells but no enamel. In some cases the enamel organs died shortly after implantation. After 14 days, the epithelial cells had all been rejected and disclosed lymphoid cell infiltration and necrosis.

But where enamel organs and pulps from incisors of rats were subcutaneously transplanted into one through five day old rats, epithelial cords formed from the enamel organs and later a calcified matrix appeared only where odontoblasts were present (Zussman, '66b). This matrix elicited a very intense inflammatory reaction resulting in complete destruction of the grafts. The investigator concluded that the ameloblasts reached a higher degree of maturity when transplanted with odontoblasts.

Lefkowitz ('61) reported that transplanted tooth buds, from 19 day fetal rats, into the subcutaneous tissues and beneath the mucous membrane of the oral cavity of adults, showed degeneration of the enamel organs into squamous epithelium in regions where lymphoid cell infiltration had occurred. In these cases the enamel epithelium had formed enamel before cell infiltration and degeneration.

Each of these investigators reported degeneration of ameloblasts into squamous cell epithelial cords or islands. They also concluded that the ameloblasts were incapable of carrying out their normal function in the absence of odontoblasts or dentin in close proximity. Hence, if during the process of grafting, the ameloblastic layer becomes separated from the odontoblasts, or dentin if the latter had already formed, one would expect the ameloblasts to revert to squamous cell cords. Still, other factors may also affect the viability and function of the ameloblastic layer in the developing transplanted tooth.
During a state of nutritional embarrassment prior to the establishment of the graft, the ameloblasts may revert to a less specialized form and no enamel will be formed. Furthermore, the ameloblasts may show a greater susceptibility to the presence of host lymphoid cells, the classical sign of tissue rejection (Lefkowitz, '61). This investigator observed degeneration of ameloblasts into squamous cells in the presence of invading lymphoid cells while these cells had not yet reached the interior of the pulp and interfered with dentin formation.

In the present study, many transplants in both hamsters and rats contained molars with very abnormal dentin formation while later formed parts of the tooth disclosed a more normal tubular dentin. Such molars usually were also enamel-free or showed only parts of the crown covered with enamel. The same factors that are attributed to the disturbances in dentin formation in the present investigation may have been responsible for degeneration of the ameloblasts. The immune rejection reaction is probably one of these. Zussman ('66) reported that a calcified material was formed by the ameloblasts in the presence of odontoblasts and that this tissue was rapidly attacked by lymphoid cells. In the present study it was observed that, in areas of ameloblasts where accumulations of lymphoid cells were seen, the ameloblasts had undergone degeneration although similar accumulations of lymphoid cells in the pulp did not affect odontoblasts nearly so severely. Many investigators have observed the tolerance of odontoblasts to degenerative changes with later recovery and formation of normal dentin. However, the ameloblasts may not have the potential for recovery from assaults. Furthermore, they appear to be the more susceptible of the two cell types to adverse conditions. There are
at present no reports where dedifferentiated ameloblasts re-differentiated and resumed enamel formation.

As was in the case of transplants in hamsters, the viable first molars in rat implants in ears and in kidneys showed a deficiency in enamel formation and a tendency toward osteodentin formation which later became tubular dentin adjacent to the pulp. Second mandibular molars in half-mandibles in rats also showed a greater tendency for the formation of osteodentin than was seen in similar molars in the hamster. As in the hamster, none of the molars in grafts in rats approached the size or stage of development of identical teeth in intact controls. The shape of the teeth in rats showed a higher degree of distortion and implanted half-mandibles elicited a stronger rejection reaction in rats than in hamsters as revealed by a higher degree of lymphoid cell infiltration.

That tooth grafts in rats will eventually elicit an immune reaction was shown by Lefkowitz ('61) who reported that first molar tooth buds, from 19 day old fetal rats, transplanted subcutaneously or beneath the oral mucosa of adults were rejected disclosing lymphoid cell infiltration of grafts similar to that seen in our transplants. These grafts had been revascularized but were later rejected. The lymphoid cells appeared first about the cells of the dental sac and later were seen in the papilla or pulp. In the present study, a similar sequence in lymphoid cell invasion of grafts was observed in hamsters and rats. Of particular significance was the observation by Lefkowitz ('61) that at three weeks the enamel organ in subcutaneous grafts consisted largely of degenerating squamous epithelium. However, these teeth did show some growth and formation and calcification of dentin and enamel prior to rejection. The rejected molars
in our half-mandible transplants did not usually show appreciable amounts of enamel and dentin development before rejection indicating an early rejection. Lefkowitz ('61) reported that submucous grafts revealed a much earlier lymphoid cell infiltration and degeneration than subcutaneous implants. Development in the former molars was also more retarded. When this investigator cultured molars, in a medium containing host serum before grafting in an attempt to reduce the rejection reaction, tooth buds were not rejected in either site; and furthermore, they showed normal growth and differentiation. Calcification of the teeth was retarded in older grafts. This investigator concluded that rejection was more gradual in the subcutaneous than in the submucous site.

Contrary to observations made during the present study and those of Lefkowitz ('61), Shapiro and Johnson ('58) reported that first mandibular molar tooth buds from five to ten day old rats, transplanted into third molar alveolar sockets of 24 to 28 day old rats, became established, vascularized, formed dentin and developed roots. These teeth also erupted into the oral cavity. The investigators did not discuss any rejection of their grafts.

Ivanyi and Vacek ('64) observed that tooth germs from newborn rats transplanted subcutaneously, homologously and isologously into newborn and adult rats showed different degrees of success and grew more slowly than normal teeth. Rejection was seen only in homografts of teeth in adults and in homografts between nonrelated newborn rats. As in observations of Lefkowitz ('61) and those reported here, several stages of rejection were seen. These investigators reported that during early rejection, lymphoid cell infiltration occurred in the connective tissue about the tooth and
around blood vessels immediately adjacent to the tooth. Later on these cells appeared in the pulp. Some teeth displayed a massive infiltration into the tissues of the tooth and degenerating pulps.

Oprisiu and co-workers ('68) reported that molar tooth buds from 10 day old rats subcutaneously transplanted into thymectomized 14 day old rats remained viable, grew and formed calcified tissues. Enamel and dentin formation had occurred, but no inflammatory reaction indicative of rejection was reported. Homografts of jaw fragments containing tooth germs, grafted into thymectomized rats, were all rejected attributed to infection at time of grafting.

A significant result of the present experiments was the observation that there were large differences in the degree of development between first mandibular molars in half-mandible transplants, and those that had been removed from the mandible prior to transplantation. There was also a much lower degree of molar survival in half-mandible grafts. The best developed first molars in molar grafts were much smaller than normal first molars in intact control mandibles of the same age. Hoffman ('60) observed that the size of molars in subcutaneous grafts at 28 days was comparable to that of normal controls of the same age. However, this investigator ('67) also reported that intramuscularly transplanted molars were smaller than controls. It would seem that there is a definite lag in molar development in grafts reflected in the small size of the molars. An even greater lag in development in viable first mandibular molars in half-mandible transplants was seen in the present series.

A retardation or reduction in growth was also seen in second molars in half-mandible transplants and they showed great individual differences
in the range of development after grafting. Many had not progressed beyond the stage of development seen at time of grafting while others showed considerable dentin and enamel formation; however, in no case did such a molar approach the size or stage of development seen in intact controls. On the other hand, Barton and Keenan ('67) reported that second mandibular molars, from two day old hamsters transplanted subcutaneously into the cheek pouch area for 28 days, had grown five times their original size and reached the size of controls. Such a size increase was not observed in the present experiments.

Edblom and Felts ('66 subcutaneously transplanted sets of first, second and third molars, from 19 to 21 day fetal mice, and reported a developmental lag of three to six days, with an approximate five day lag for the first molar. An even greater developmental lag was seen in the present study on mandibular grafts, regardless of the transplantation site, which was attributed to the mandibular osseous barrier which we believe is an impediment to revascularization as suggested by Felts ('61). In the present study, where only the molar part of the mandible was grafted, there was an increase in the number of viable second molars which showed more growth than those in which intact half-mandibles had been grafted. Edblom and Felts ('66) attributed the delay in development of sets of molars to the time required for revascularization; but this does not account for rejection of the molars. Evidently, the fact that the grafts were established and vascularized earlier in cases where molars had been transplanted alone than where they had been part of half-mandibles accounted for the differences in size. When Imuran, in a dose of 5 mg was administered to hosts with half-mandible transplants in the ear, the surviving second molars
showed a higher degree of growth and differentiation than in those in non-treated controls. Hence, these results of the present study implicate the immune rejection reaction as a factor affecting the process of establishment of teeth in half-mandibles and probably the intensity of this reaction affects the process of establishment and revascularization of the implants since following immunosuppressive therapy increases in viability of both the teeth and bone occurred.

That the first molars and incisors in half-mandible grafts did not survive more frequently can be explained in part by the fact that the first molar had developed some calcified dentin at time of grafting, which may have been responsible for eliciting a stronger immune rejection response than where teeth had not formed calcified tissues (Fleming, '52, '56b). If an immune reaction directed against first molars was entirely responsible for their failure in half-mandibles, such teeth would not have been capable of establishing and growing as occurred when removed from the mandible and grafted without immunosuppressive therapy. It is probable that the presence of mandibular bone elicits a strong immune reaction since immunosuppressive therapy increased the viability and formation of bone. Hence, the additive effects of the reactions against both the mandible and the calcified teeth, being strongest against the incisor, would be stronger than against the first molar only. It is probable that more severe delays in re-establishment and revascularization of the first molars occurred and that the strength of the immunosuppressive therapy employed was insufficient to ensure viability of first molars where the viability and development of non-calcified second molars had improved. However, some instances of an early and direct rejection of the teeth were
also seen. The half-mandibles in hamsters seemed to elicit a more intense rejection reaction than where the first mandibular molars were grafted alone. Immunosuppression partly subdued this rejection. The quantity and quality of antigenic stimulus presented to hosts by the various kinds of grafts may have had far-reaching effects on their ultimate fate. The mandibular bone and marrow probably produced a stronger stimulus for host sensitization than where teeth were grafted alone. The result of such a sensitization would perhaps be an earlier and more vigorous rejection of molars and may explain their inability to become established.

The role of nutritional embarrassment of the teeth in implants may be further illustrated by the fact that osteodentin was formed following grafting, but the dentin parts of the tooth which developed much later showed a normal tubular dentin. If the character of the dentin reflects the nutritive and other conditions about and within the transplant molar, then as the postoperative interval increased, the conditions within the transplant should have approached the normal. The augmented viability and growth of molars in Imuran treated hosts probably reflects an earlier attainment of more normal conditions in transplants.

Alternatively, there exists the possibility that some of the grafts were capable of adapting to the adverse conditions imposed by the host. This would seem possible in the case of the least differentiated teeth, such as the second molars, which could readily be nourished by fluid diffusion. Since the second molars had not yet formed hard tissues, fluid diffusion would readily occur to all cells in this tooth, with more difficulty in the first molar and with great difficulty in the incisor. Also there is the possibility that the cells in the least differentiated tooth,
the second molar, may not require the volume of fluid exchange necessary for a more differentiated and actively growing tooth since their metabolic requirements may be lower, and the cells may also be able to remain in a more dormant or inactive state. The cells in the least differentiated tooth may also be less labile and able to withstand greater physiological assault.

The molars in half-mandible transplants in rats showed similar dentin changes, however, the pulps of the viable teeth were more fibrous and abnormal than those in corresponding grafts in hamsters reflecting a greater abnormality in host conditions. The immune rejection was of greater intensity in the rat than in the hamster, but not sufficiently intense to destroy the teeth. The immune reaction may have occurred at a later stage since rejection reactions in transplants do not usually occur until some days after grafting in nonsensitized hosts. Immunosuppressive drugs were not employed in the rat and no attempt was made to reduce the reaction in this animal.

It is suggested that the immune reaction does play a powerful role in the ultimate survival of transplants by either interfering with their establishment or by later action against the established graft. Clearly, immunosuppression by the administration of Imuran or 6-MP showed a trend toward increased survival of molars in half-mandible transplants in hamsters. Rejected teeth in experiments on non-treated hosts revealed accumulations of lymphoid cells and similar observations were made on the controls in drug treatment experiments. In some cases surviving molars also showed some infiltration by such cells and the odontoblasts and ameloblasts adjacent to those perivascular and diffuse cell infiltrates usually
had undergone some degree of degeneration and osteodentin had formed adjacent to such accumulations. Reports in the literature on the effects of calcified material in teeth on eliciting an immune rejection are conflicting. Fleming ('52, '56b) observed that teeth containing dentin and enamel did not survive whereas tooth germs, which did not contain these, showed growth and differentiation. Haley and Costich ('68) transplanted molars from hamsters which had been immersed for two and one half hours in a solution of thimersol before being subcutaneously grafted on the thorax. A study of the axillary and brachial lymph nodes showed no activity indicative of a rejection reaction and a direct cutaneous reaction also was not elicited. Examination of the transplants revealed no lymphocyte infiltration of graft or surrounding host tissues. The investigators felt that immersion of the molars in thimersol prior to transplantation rendered the transplants non-viable; hence, only the antigenicity of the hard tissues was assessed.

Haley and Costich ('69) grafted non-viable molars homologously and subcutaneously between two inbred strains of hamsters and observed by means of lymph node preparations and histological studies that there was no evidence of an immune reaction. Viable molar grafts also did not elicit a reaction. Nevertheless, all transplants, viable and non-viable, did disclose an inflammatory reaction; but polymorphonuclear leukocytes and macrophages were the predominant cell types.

On the other hand, utilizing two strains of inbred hamsters, Coburn and Henriques ('66) allografted adult maxillary incisors in jaws. Growth after grafting was employed to evaluate success of the grafts. The allografts did not grow to occlusion whereas reimplants, autografts and
isografts did return to occlusion. The results suggested that viable allografts of teeth of hamsters underwent rejection as shown by the failure of these teeth to grow.

The results of the present study clearly showed rejection of teeth and accompanying half-mandibles as evaluated by survival, massive lymphoid cell infiltrations, and the decrease in the degree of infiltrations, and the decrease in the degree of infiltration when immunosuppressive drugs had been administered. But also revascularization was of primary importance in the survival of teeth in half-mandible implants.

Many studies have been carried out on the antigenicity of tooth transplants in laboratory animals other than the hamster. Ivanyi ('65a) reported that tooth germs from newborn rats homotransplanted onto the heads of adults were rejected while isologous transplants were not. When transplanted into rats previously immunized with spleen cells, tooth germs were rejected earlier and within four day. This investigator concluded that tooth germs generally behaved in a fashion similar to the transplants of other tissues in the rat. In a second study, almost no rejection of subcutaneously transplanted, molar tooth germs of rats into littermate newborns was seen, but when grafted between newborn litters of non-related rats, rejection occurred in most of them. (Ivanyi, '65b). The onset of the reaction in the latter series was delayed since the teeth had developed considerable hard tissue after implantation. Ivanyi ('66) reported that only one or two histocompatibility loci are responsible for survival of tooth germs as determined by the rejection of teeth after sensitization of rat hosts with spleen cells and skin grafts. Further studies carried out by Ivanyi ('68) on subcutaneously transplanted molars from newborn rats,
where the donor and host had been serologically typed for compatibility at the H-1 locus, led to the conclusion that in rats compatibility at the H-1 locus between donor and host was necessary, but not an entirely sufficient condition to ensure survival and progressive growth of grafts, since compatible grafts were also rejected. The investigator postulated that although the H-1 locus may be the only strong locus in the rat seemingly responsible for tooth rejection, the synergistic activity of a number of even weaker loci is responsible for rejection in hosts with grafts compatible at the H-1 locus.

Weinreb and co-workers ('68) utilized allografts of first maxillary molar buds from 10 day old random bred rats transplanted subcutaneously into adults of the same strain, and reported that when transplanted with a strong antigenic stimulus such as spleen, immunological rejection occurred earlier than where teeth had been transplanted alone. The investigators assumed that the tooth bud was either a tissue of low antigenicity or its antigens were too weak to elicit an immune response.

Similarly Sharav and co-workers ('69) reported that tooth buds grafted in rats showed a weak ability to elicit an immune rejection as measured by tooth graft rejection before spleen transplants. The success of grafts decreased with increasing age of the grafts. The teeth were invariably rejected when transplanted concurrently with spleen, but where the teeth had been allografted four to ten weeks prior to challenge with spleen, a higher incidence of successful grafts occurred. The investigators concluded that continuous sensitization from tooth grafts occurred whereas acceptance of the established grafts was attributed to a gradual transplant adaptation. They also concluded that the survival of a tooth germ graft was determined
by a delicate balance between the relative strength of the concurrent processes of sensitization and adaptation.

The above results indicate that the success of a tooth graft is determined by the genetic relationship between the host and donor. In the present study, inbred strains were employed and all grafts were carried out within the respective strains and never between them. In spite of this, rejection very frequently occurred and immunosuppression was partly effective in improving the viability of the grafts. The rats employed in these experiments were not inbred and consequently a stronger rejection reaction occurred. Species differences in relation to reactivity of tooth grafts do not explain the differences seen in the grafts of this study. Nevertheless, the fate of teeth in half-mandible transplants in ears and in kidneys was not greatly different in rats and hamsters, both of which showed considerably more success in the ear, emphasizing the importance of the transplantation site, in spite of other factors determining the degree of rejection and ultimate fate of grafts.

In this study, the rejected teeth in half-mandible transplants showed that molars which were not viable on recovery were mostly dentin shells, generally in the form of cusps. Usually, such teeth revealed no growth or differentiation subsequent to grafting and had undergone some resorption. In one case of a molar in a half-mandible homotransplanted into the uterine horn of a hamster, much growth had occurred; however, prior to recovery, changes had taken place such that most of the dental cells had degenerated and disappeared. This case illustrates a late rejection of a graft. From the degree of growth and dentin formation it would seem that the rejected molars had usually failed to become established initially and were rejected
early in the post-transplantation period.

Cysts were found in most half-mandible transplants and parts of mandibles in hamsters as well as in identical half-mandible grafts in rats. Some were located adjacent to the lingual surface of the mandible. Almost all incisors had become encysted about the distal quarter and sometimes these cysts communicated with each other. It is concluded that these cysts were the result of a proliferation of oral epithelium implanted with the grafts. Huggins and co-workers ('34) reported that autologous transplants of gingival epithelium to the abdominal wall formed cysts showing a squamous epithelium. Willis ('35) similarly observed stratified epithelial cysts in transplants of jaws and parts of heads of fetal rats into the brains of other rats. He concluded that these cysts represented oral or pharyngeal epithelium. As in his case, the formation of much keratin in some of the cavities of these cysts was observed in the present study.

In some half-mandible transplants, the squamous cells of the dental lamina of the second mandibular molars were continuous with the epithelium of lingually located cysts indicating their origin from the oral epithelium. Glasstone ('67) attributed the origin of keratin containing cysts in cultures of parts of mandibles of embryonic mice and in cultures of teeth to proliferation of oral epithelium.

Some cysts in half-mandible transplants in the present study were confined within the molar alveolus. The squamous cells of these were continuous with the squamous cords adjacent teeth where enamel formation had not occurred. In other cases, these cysts were continuous with the outer enamel epithelium or ameloblasts bordering enamel spaces. It is believed that these cysts originated from proliferating enamel epithelium.
and co-workers ('34) failed to observe cyst formation, when isolated enamel epithelium was autotransplanted into the abdominal wall, even though the epithelium had survived as a stratified squamous epithelium. On the other hand, Hahn ('41) observed that isolated enamel epithelium autotransplanted into the dog ovary formed squamous epithelial cysts. The absence of cyst formation in Huggins and co-workers ('34) series was attributed by Hahn to the difference in site of implants. Small cysts were also found by Hahn where odontoblast free pulp was grafted with enamel epithelium.

Zussman ('66a, '66b) did not observe formation of cysts where enamel organs, or enamel organs with pulp from adult rat incisors, were transplanted subcutaneously into three day old rats. Nevertheless, Grewe and Felts ('68) observed formation of cystic structures when non-erupted mandibular incisors from five day old mice were transplanted into mandibular incisor sockets in seven day old mice. Such cysts were also seen in cases where incisors had been reimplanted.

Fleming ('52) reported tooth germs which showed ameloblasts forming intraepidermoid keratinization and cystic degeneration of ameloblasts in anterior eye chamber implants where ameloblasts had failed to form enamel. Frequently, the ameloblasts degenerated without cyst formation.

In agreement with the findings of these investigators, it is believed that the different cysts, seen during this investigation on transplants in hamsters, originated from the oral epithelium, dental lamina, ameloblasts or the outer enamel epithelium.

With exception of the molars in mandibular transplants in rats, which all showed a high degree of distortion in shape and development after grafting, the molars in half-mandibles usually showed much less distortion.
than where molars were removed from the mandible and grafted separately. Several explanations for these distortions in different types of tooth transplants are possible.

Several investigators have shown that the form of the tooth was retained when the cell layers of the developing molar were kept intact during the process of grafting. Similarly they felt that the ameloblastic layer was primarily responsible for determining the form of the tooth, but after the shape had been established by development of a layer of dentin, the enamel epithelium was no longer considered necessary for its maintenance (Hahn, '41). It has also been shown by many investigators that the intact ameloblastic layer is necessary for the formation of the first dentin in the tooth. Hahn ('41) maintained that the development of the later formed layers of dentin was determined by the first layer. In the present experiments, many of the irregularities in tooth shape were produced primarily by excess osteodentin or a decrease in dentin formation and may have occurred due to disturbances or degeneration of the enamel organ. Similarly, Fleming ('52) reported that where the normal anatomical relationships between the odontoblasts and ameloblasts had been lost, dentin formation continued, but the resulting tooth was very amorphous in shape. Where the ameloblastic layer in the developing tooth had been destroyed, the shape of the tooth was not retained. Fleming later ('56a) reported that mature tooth structures formed from developing tooth transplants where the organ anlagen had been undamaged, and similarly, if the normal positions of the cell layers of the developing tooth had been maintained during and after grafting the morphology of the tooth remained normal.

It would seem necessary, for a tooth graft to grow and differentiate
and ultimately to produce a normally shaped tooth, that the constituent cell layers remain intact, viable, and in their normal anatomical relationships.

Fleming ('52) observed that tooth germs grafted into the anterior chamber of the eye revealed superior morphological retention than when grafted to other sites. Part of this success may be attributed to the absence of mechanical forces disrupting the normal shape of the tooth such as seen where teeth are grafted in the ear where they become tightly attached to a flexible graft bed such as the ear cartilage, or in the cheek pouch where the tooth is subject to constant variations in mechanical stress. The molars, which in their normal position, are protected by mandibular bone in half-mandible grafts are subjected to less mechanical stress than those removed from the mandible and grafted without this protective bony shell.

The integrity of the component cell layers of the developing tooth are also subjected to other factors. Most obvious is the probable mechanical disruption of the developing tooth during the process of procuring and subsequent grafting. The tooth germs removed from mandibles are subjected to considerable unavoidable surgical trauma resulting in crushing and shearing forces which will ultimately destroy or at least disrupt the necessary cell approximations for normal development. In addition, the cells of the tooth germ have shown a particular susceptibility or lability, the ameloblasts in particular being the most labile element of the developing tooth. The ameloblasts were seen to either die or revert to squamous cells under the influence of nutritional embarrassment and/or the immune rejection reaction, each of which may partially or
totally destroy the necessary relationships for normal matrix formation essential for retention of the normal tooth form. These factors may also be responsible for the distortion frequently seen in the production of osteodentin. It was found that the more immature the tooth is at time of implantation, the better its chances for retention of normal form. This may be due to the lower susceptibility of younger tooth germs to the stresses inherent in the process of grafting and subsequent readjustments.

D. Effects of Immunosuppressive Drugs.

1. 6-Mercaptopurine.

In the present study, the immunosuppressive drug 6-mercaptopurine (6-MP) was administered in several experiments, to study its effect on the viability and growth of teeth in half-mandible transplants. Doses of 6-MP at 10, 5, or 2 mg/100 gm were injected beginning at time of grafting and terminating before or at recovery of the grafts. Three series were carried out in hamsters employing 10 mg/100 gm/day.

In all three series, the hosts failed to tolerate this dosage, showing severe drug toxicity terminating in death in some cases. Large daily weight losses occurred and a severe diarrhea, a scaby and scaly appearing mouth and shabby, dull appearing fur were seen. A slow rate of respiration was noted and some hamsters became comatose. Posture was hunched and movements inhibited. Many animals died within the first five days following the first injection, while in others death was delayed. In another series, a reduction in the dosage to 5 mg after four days did not noticeably improve the condition of the hosts. In most hamsters, the toxic effects of high dosages appeared to be delayed and cumulative. Abdominal cavities opened on postmortem or after graft recovery showed extensive adhesions of
abdominal viscera.

Many similar toxic manifestations seen in mice, rats and dogs were reported by Philips and co-workers (1955). Five intraperitoneal injections of 6-HP at 100 mg/kg and 72 mg/kg in mice and rats respectively, were sufficiently high to produce an LD50. Yet, only 10 to 25 mg/kg caused an LD50 over a span of 10 intravenous injections in dogs. Rats survived from two to three days after one lethal injection whereas in mice, death did not occur prior to five days. Fibrous adhesions of the abdominal viscera, peritonitis, and ascites were seen in rats similar to those observed in hamsters in the present experiments. These effects were believed to be associated with the intraperitoneal route of administration for when given orally these effects were not seen. Depletion of bone marrow and lesions in the intestinal epithelium, in addition to hepatic necrosis were found in 6-HP treated rats and mice. Diarrhea was reported in 6-HP treated dogs and was attributed to intestinal lesions. Bone marrow damage was also seen in such animals.

Other investigators reported that 6-HP in doses of 12 mg/kg/day were toxic in the rabbit, where treatment elicited a leukopenic anemia and moderate weight loss, while the animals still retained their skin homografts (Andre and co-workers, 1962). Severe lymphoid atrophy had also occurred. Utilizing the same dosage of 6-HP, Heeker and co-workers (1959) reported a high mortality among treated rabbits. Although bone marrow suppression was detected, the deaths were not believed to be the result of marrow suppression since many died before suppression had occurred. Similarly, Heeker and co-workers (1960) observed toxic effects in the rabbit receiving this drug and in some of their experiments mortality was excessive. Many of the
rabbits died with skin grafts still intact. Leukopenia was also seen in the hosts. Harrison and Bartlett ('70) reported that a dosage of 2 mg/kg/day showed a low long term toxicity in inbred rabbits and greatly prolonged skin graft survival. However, the same dosage had no effect on skin homograft survival in non-inbred rabbits. The drug treated inbred animals showed an initial drop in the level of white blood cells but then recovery occurred, although in some a lethal toxicity developed later and about day 40 diarrhea appeared. Rabbits that died revealed denuded gastrointestinal epithelium and a wasting of muscles.

In mice, Keeker and co-workers ('60) reported that doses as high as 150 mg/kg/day, given intraperitoneally, were reasonably well tolerated over a ten day period. Single doses of 600 mg/kg were lethal. Kimbal and co-workers ('65) observed no significant weight losses in mice which received 15 mg/kg/day.

Santos and Owens ('65) reported that the highest single intraperitoneal injection revealing an LD50 in rats was 371.6 ± 26.0 mg/kg whereas a daily dose of 161.0 ± 9.7 mg/kg for five days showed an LD50. The dosage selected for single dose experiments was 175 mg/kg and 100 mg/kg for five days in others. Irrespective of whether host rats were on single or multiple dosage regimens, all rats disclosed drug toxicity as revealed by a decrease in values of peripheral blood cell levels, diarrhea, weight losses and were considered to be near the maximum doses tolerated by the rat.

It is apparent from the present experiments and those of other investigators that 6-HP is very toxic in most laboratory species. It has also been shown that there is a very wide species variation in tolerance to
the drug. The mouse appeared to be the most tolerant followed by the rat and finally the rabbit and dog. A wide range of individual variation in tolerance between members of the same inbred hamster strains was observed when a 10 mg/100 gm body weight dosage was employed in the present study. However, where daily doses of 5 and 2 mg/100 gm were injected, mortality did not usually occur and toxicity was less evident. Where the lowest dosage was given, the rate of survival of transplanted teeth was found to have decreased.

Where the 10 mg/100 gm dose had been administered for 12 consecutive days and transplants in backs recovered at 15 days, only one viable molar was found. In the remaining two series employing this dosage, no viable teeth were seen in half-mandibles either treated or control hamsters recovered at six or ten days. Several important observations were made. At 15 days, both treated and control hamsters revealed transplants on backs that were loosely attached while those in another series receiving an identical dosage, but grafts recovered at ten days also disclosed similar loose attachments. Grafts from treated hosts recovered at ten days showed a decrease in the amount of resorption, but necrosis of tissues was widespread in both treated and controls.

Where the 10 mg/100 gm dosage was administered for four days and then reduced by half, implants in ears recovered at six days from treated hosts were very loosely attached and appeared to be avascular but showed some hemorrhagic masses. Still, most grafts in control hosts had become firmly attached. Observations on grafts in treated hosts recovered at six days revealed very sparse peripheral vascularization while controls were more extensively vascularized. Those in treated animals showed only small
amounts of viable, peripherally located bone, while those in controls disclosed more viable bone. Less resorption and a decrease in the amount of connective tissue invasion was seen in grafts in treated hamsters. These observations show that treatment had retarded the establishment of the transplants recovered at six days. However, the grafts in treated hosts disclosed a decrease in inflammatory cell infiltration which was not seen in those series employing longer post-transplantation intervals and implants in backs.

Hence, 6-MP reduced the early lymphoid cell response seen at six days but did not have a similar effect on the older grafts. More important was the observation that large doses of 6-MP inhibited the establishment of transplants within the first six days. Nevertheless, resorption of bone also decreased in such grafts, but no decrease in the incidence of cyst formation had occurred in any of the series during treatment.

When a dosage of 5 mg/100 gm/day, beginning at time of grafting and continued for 15 days, was administered to hamsters with half-mandible transplants in ears, grafts showed more dramatic responses than where the higher dosage had been administered. Three half-mandible implants in the treated series showed one viable molar each; whereas none were found in either control or normal hosts. Treatment did not seem to affect adversely the growth or calcification processes in these molars. Furthermore, half-mandibles in treated hosts usually showed more bone formation and trabecular growth whereas some new spongy bone was seen in the controls. Frequently treated grafts also showed replacement of much of the marrow by osteogenic tissue not evident to the same degree in controls. Grafts in treated hosts also showed a significantly lower degree of dense
connective tissue invasion. Most of the half-mandible grafts in treated hosts in this series showed a very noticeable decrease in the degree of lymphoid cell infiltration. A firm attachment to host tissues was seen in both treated and control hamsters.

Where a daily dose of 2 mg/100 gm was administered, no viable teeth were found and only one was seen in a graft in a control host. This dosage appeared to have been too low to affect the survival of teeth in transplants. Further observations revealed other beneficial effects of treatment on other parts of the half-mandible transplants. More bone formation and less resorption of bone had occurred and bone formation was mostly in the form of trabecular growth rather than formation of spongy bone as in control hamsters. Control grafts showed more dense connective tissue invasion. As in the 5 mg series, grafts in treated hamsters showed a more extensive replacement of marrow with osteogenic tissue than control grafts which frequently had larger areas of marrow. In contrast to the 5 mg series, there was not as large a difference in degree of lymphoid cell infiltration. The 2 mg dosage was evidently not great enough to enhance the survival of teeth or to significantly reduce lymphoid cell infiltration; however, this dosage was sufficient to enhance the formation of bone.

The trend toward an increase in the degree of transplant survival, accompanied with a decrease in lymphoid cell infiltration seen in the present experiments, confirms the observations of Morris ('63) who reported that treatment of Rhesus monkeys with 6-1P for two weeks beginning at time of grafting improved the viability of homologously transplanted unerupted control incisors. The homografts in control hosts disclosed a very rapid degeneration of pulp tissues, while those in treated monkeys had a normal
appearance at three to six weeks and formed secondary dentin, but between eight and 12 weeks dentin formation ceased. The incisors of treated monkeys also showed degenerative fibrous tissue in the pulp at this time and osteogenic tissue in the apex. No round cell infiltration or necrosis were detected.

The decrease in lymphoid cell infiltration observed in grafts in treated hamsters in the present study confirms the observations of other investigators utilizing a variety of organ and tissue grafts in various laboratory animals. Schwartz and co-workers ('60) reported no difference between skin autografts on normals and homografts carried out on treated rabbits and no lymphoid cell infiltration had occurred. Where rejection occurred, homografts showed an increasing amount of lymphoid cell infiltration. These investigators reported that the rejection reactions were never partly suppressed. Andre and co-workers ('62) observed only minimal enlargement of germinal centers and lymphoid follicles in nodes in treated rabbits with skin homografts. A depletion in lymphoblasts and medium sized lymphocytes indicative of lymphoid atrophy had occurred. Also, skin homotransplants in treated hosts revealed an absence of edema and necrosis. These homografts resembled normal skin showing no lymphoid cell infiltration while grafts on untreated rabbits disclosed all the characteristic signs of rejection. Where grafts in 6-MP treated hosts were rejected, the reaction proceeded as in non-treated, but some showed hemocytoblasts in grafts not seen in transplants of non-treated hosts.

Meeker and co-workers ('59) reported that skin homografts on rabbits treated daily with 12 mg/kg of 6-MP disclosed prolonged survival when compared with identical transplants on non-treated rabbits and showed no
detectable difference from autografts. When only half this dosage was administered, homografts showed extensive small round cell infiltration in contrast to autografts in which the rejection response was absent. The absence of cell infiltration in grafts during treatment indicated a suppression of the rejection response.

Studies on the effects of 6-HP on the inflammation induced by various agents were carried out by Page and co-workers ('62). The inflammatory response, elicited by subcutaneous injections of egg white in 6-HP treated rabbits, showed a decrease, but when the drug was discontinued the response returned to normal within a few days. A retarded migration of lymphocytes into the inflammatory site was seen, but generally lymphocytes were absent. Inhibition of the inflammatory response could not be correlated with leukopenia, neutopenia or weight loss in the rabbits. In spite of the significantly reduced lymphoid cell response, the neutrophilic cell responses were normal.

Similarly, Borel and Schwartz ('64) reported that the effect of 6-HP on rabbits was immunosuppressive or mostly anti-inflammatory or a combination of these where rabbits were subjected to different means of sensitization to foreign antigens. Six-HP in doses of 10 gm/kg/day for a two week period suppressed the response to subcutaneous injections of bovine gamma globulin while a dosage of 6 mg/kg/day inhibited the reactions but not as consistently. Dermal manifestations of immunity were also diminished by injections of 6-HP. As pronounced a degree of leukopenia or lymphopenia in 6-HP treated rabbits, as reported by other investigators, was not seen and following cessation of treatment the depressed leukocyte levels returned to normal. Lesions in response to intracutaneous in-
jections of xylene were small but were further reduced following 6-HP therapy. Suppression of the Arthus reaction to injections of bovine serum albumin resulted from 6-HP treatment.

From observations made during the present study and those of others, 6-HP has an effect on the inflammatory reaction of the immune rejection response of which this lymphoid cell infiltration is an expression. It would also seem that this drug will suppress other kinds of immune and inflammatory reactions either separately or in combination as manifested in grafting experiments. In the case of skin homografts on treated hosts, Schwartz and co-workers ('60) reported that the absence of a lymphoid cell infiltrate in viable transplants during drug treatment was particularly evident since when these transplants show accumulations of lymphoid cells they are undergoing rejection. Similarly, Leibowitz and Elliott ('66) observed a reduction in the intensity of the biphasic corneal reaction when the cornea of rabbits was inoculated with bovine serum albumin and concurrently received 6-HP. Lymphocytic and plasmacytic cell infiltrations, usually seen in the limbus of the eye during this type of reaction, were greatly reduced.

Similarly in teeth, Morris ('63) observed an absence of a lymphoid cell infiltrate in tooth homografts which had been recovered from 6-HP treated monkeys. In half-mandible transplants made during the present study, bone formation did occur where a reduced degree of lymphoid cell infiltration was seen in 6-HP treated hosts. However, where a much greater number of these cells was seen, the grafts had undergone rejection as revealed by a higher degree of degeneration and necrosis similar to that of most transplants in control hosts.
During the present investigation it was observed that where 10 mg/100 gm of 6-MP had been administered in hamsters, the dosage reduced and the grafts recovered at six days, the grafts in treated hosts showed a retarded establishment. Those in control hamsters showed a greater degree of connective tissue invasion and a greater degree of resorption. Observations on the establishment of skin homografts in rabbits did not disclose any delay in the healing of such transplants on 6-MP treated animals, but they did reveal widespread hemorrhage in rejecting homografts never seen in non-treated controls (Andre et al., '62). Schwartz and co-workers ('60) reported that 6-MP therapy did not delay the healing of skin homografts in rabbits. Vascular growth and fibroblastic proliferation were identical to that of controls and to a degree, growth of successful grafts had been enhanced. At the lower doses bone formation was enhanced in our series. Contrary to observations made during the present study, on the ingrowth of connective tissue in grafts, no significant differences were seen between treated and control hosts in the healing of skin incisions.

2. Imuran.

In a second series of experiments, Imuran was injected daily intraperitoneally beginning at time of grafting and continued for 15 days at which time the half-mandible transplants were recovered. When 5 mg/100 gm body weight was administered in hamsters with half-mandible implants in ears, three grafts showed survival and a higher degree of growth of molars than was seen in the one viable control molar. With a daily dose of 2 mg/100 gm, one of the grafts in the ear revealed a viable molar, but none occurred in control hosts. When 5 mg/100 gm/day was injected in hamsters with half-mandibles in cheek pouches, two in treated hosts each
showed one viable molar while no molars had survived in control hamsters.

The hamsters showed a greater degree of tolerance to Imuran than to identical doses of 6-MP. There was no mortality in the present Imuran series and body weight losses were less severe. Other laboratory animals have been reported to be less susceptible to toxic effects of administration of Imuran than to 6-MP. Elion and co-workers ('61) reported an LD50 at single doses of Imuran at 650 mg/kg injected intraperitoneally in the mouse. Delays in death of two to three days after the injection were seen. The maximum tolerated intraperitoneal dosage injected for five consecutive days in mice was 100 mg/kg, but this increased to 200 mg/kg when administered orally. Tolerance to Imuran was less in rats showing a LD50 after a single intraperitoneal injection of 310 mg/kg. Death had been delayed for five to six days in the rats. The LD50 dosage in rats for five consecutive injections was 100 mg/kg/day. Where the drug had been administered as part of the diet the rats showed agranulocytic spleens and marrow. On the other hand, dogs showed highly depressed blood cell counts and succumbed when they were given ten doses over a 12 day period at 10 mg/kg/day. However, where 7.5 mg/kg was given in 10 daily doses, normal blood cell counts and maintenance of weight occurred.

Tinbergen ('68) reported that intraperitoneal injections of 4 and 8 mg/kg were effective in prolonging survival of kidney allografts in rats, but most of them showed a moderate degree of aplastic bone marrow and some degeneration of liver cells. Death of hosts was attributed to the rejection process rather than to drug toxicity. Shehadeh and co-workers ('70) reported that 8 to 40 mg/kg/day of Imuran did not improve kidney allograft survival in rats and they did not show an excessive depression in white
On the other hand, Nouza (1966) observed a higher mortality in mice having skin homografts where injections of 40 mg/kg of 6-MP were administered for 10 days, than where injections of 150 mg/kg of Imuran were given for the same period. Survival of grafts was also significantly increased when Imuran was administered. Where Imuran was administered at time of grafting host mortality did not occur. The drug was very effective at subtoxic levels in these experiments.

In rabbits, Leibowitz and Elliott (1966) reported that 12 mg/kg of 6-MP administered daily was highly toxic, whereas an identical 12 mg regimen of Imuran was relatively nontoxic. This dosage was not effective in delaying the rejection of corneal heterografts. A dosage of 24 mg/kg/day did effectively maintain identical transplants, but most of the hosts died of drug toxicity. When an identical daily dose of 24 mg/kg was administered for the first week, then 18 mg/kg for the second and finally 12 mg/kg thereafter, the grafts were successfully maintained. Although toxic effects were still seen, the period of tolerance had increased greatly. On the other hand, a dosage of 48 mg/kg given on alternate days disclosed the least toxicity and yet effectively suppressed the immune rejection. Polack (1966) reported that a dosage of 10 mg/kg/day was effective in preventing rejection of corneal allografts in rabbits sensitized by skin allografts.

Kiskin (1966) reported that where Imuran was given in a dose of 10 mg/kg on the day before and the day of skin allografts in thymectomized dogs and, reduced to 5 mg/kg for the next five days, followed by 2.5 mg/kg thereafter, toxicity and a depression in the white blood cell count were
seen although the grafts remained viable longer than those on control hosts.

In general, Imuran has been shown to have lower toxic effects than 6-iP in most animals. In the present experiments it was better tolerated in the hamster. A wide range of tolerance has been reported between members of a species and between different laboratory animals.

Some of our observations on teeth, in half-mandibles in ears of Imuran treated hamsters, were similar to those in ears of hosts which had received identical dosages of 6-iP. Where 5 mg/100 gm/day was given from time of grafting until recovery, implants in Imuran and 6-iP treated hosts revealed a trend toward an increase in viability of molars. Nevertheless, the growth of these molars was greater in Imuran treated than that of control hosts and was also greater than that of 6-iP treated animals. Contrary to observations where 2 mg/100 gm of 6-iP had been administered and no viable molars were found in half-mandible implants on ears, one implant in a Imuran treated hamster at this dosage revealed a viable molar but none were seen in the control hosts.

A dosage of 5 mg/100 gm/day had a beneficial effect on the viability of teeth, whereas a 2 mg/100 gm dosage had a less pronounced effect. However, more important is the observation that the larger dosage of Imuran was more efficacious than 6-iP in enhancing growth and differentiation of molars in half-mandible transplants.

In addition, half-mandible transplants in ears of hamsters having received 5 mg/100 gm/day of Imuran revealed a lower degree of resorption, less dense connective tissue replacement and a decrease in necrosis when compared with those in control hosts. A more normal appearing marrow and a higher degree of bone formation largely as trabecular growth was seen.
Spongy bone formation had occurred in control hosts. Lymphoid cell infiltration in grafts in treated hosts was usually diminished while cyst formation was unaffected. At 15 days, grafts in treated and control hosts had become firmly attached to the subcutaneous tissues in host ears.

Where a daily regimen of 2 mg/100 gm of Imuran had been followed, half-mandible transplants also showed more bone formation and a decrease in resorption; however, the degree of bone formation was lower than where the larger dosage had been administered. Although grafts in Imuran treated hamsters at the lower dosage usually revealed a decrease in degree of lymphoid cell infiltration, the decrease was not so pronounced as where the larger dose had been administered.

Several differences between half-mandibles grafted in ears and those in cheek pouches were seen in Imuran treated hamsters. A higher degree of bone formation occurred in the pouch in treated than in control hamsters, but considerably more resorption and a much lower degree of bone formation was seen in these than in ears in Imuran treated hosts. A more extensive necrosis was also seen in the pouch implants. A significant decrease in the degree of lymphoid cell infiltration was seen in cheek pouch implants after treatment, but rejection was more intense than in the ear. A more frequent encystment of grafts also occurred in the former site. Nevertheless, Imuran treatment had a beneficial effect on viability of transplants in both sites.

In 6-LP treated hamsters, grafts revealed that much of the marrow had been replaced by osteogenic tissue while in those treated with Imuran, there was more normal appearing marrow. The marrow had usually been replaced by dense connective tissue in the grafts in control hosts of all
series. Many investigators have reported that 6-HP and Imuran have profound depressive effects on bone marrow; however, Imuran treatment may not have a deleterious effect on survival of marrow in grafts but still repress the rejection reaction. Imuran therapy at a dosage of 5 mg/kg/day for eight weeks, did not suppress the proliferative activities of bone marrow in homologous and autologous transplants of ribs in the spleen of dogs (Sabet-Payman and co-workers, '64) At eight weeks, the homologous rib marrow showed proliferative activity in myeloid, erythroid and platelet elements similar to that of autografts. Identical homografts in untreated control dogs showed a disappearance of marrow while autologous grafts revealed normal marrow cell proliferation.

In the present study, a depression in degree of lymphoid cell infiltration of half-mandible grafts at the dosages and the two sites employed was observed. Tinbergen ('68) observed similar decreases in lymphoid cell infiltration in the rat where treatment with Imuran in non-toxic doses increased survival of kidney allografts. Rejection due to vascular necrosis and thrombosis had been prevented although some damage to the glomerulus was seen. The ultimate death of hosts was attributed to a chronic rejection process revealed by deleterious glomerular changes. Shahadeh and co-workers ('70) observed that small and large doses of Imuran (8 to 40 mg/kg/day) did not significantly inhibit deterioration in function of renal allografts in rats. The kidney allografts showed thrombosed glomerular capillaries, necrotic glomerular and tubular cells; but, a decrease in the number of infiltrating mononuclear cells was seen. A large number of these cells was characteristic of kidney rejection in non-treated control hosts.
In rabbits, Leibowitz and Elliott ('66) observed that sufficiently high doses of Imuran totally inhibited the rejection process in response to heterografts of calf cornea in rabbits. The inflammation characteristic of rejection was not seen in treated animals. Similarly, Imuran, if administered shortly after sensitizing skin homografts from the same donors, retarded the inflammatory rejection response in corneal homografts in rabbits (Polack, '66). Grafts in other experiments, which were rejected in spite of Imuran therapy, revealed noticeable lymphoid cell infiltration. Once rejection of corneas had begun, subconjunctival injections of Imuran did not suppress it, but the rejection reaction appeared to be milder in such cases.

Imuran therapy also reversed the rejection of skin homografts on dogs when increased above the nontoxic level (Roseley and co-workers, '66). A minimal lymphoid cell infiltration occurred in grafts where survival was prolonged, but a normal heavy cell infiltration was seen where rejection was underway despite therapy. Rejection of skin homografts occurred where the dosage had been reduced to a subtoxic level. Although renal homograft survival was extended, immunologic damage continued, but was greatly reduced by therapy.

Almgard and co-workers ('67) observed that Imuran treatment retarded the vascular damage that normally occurred in non-treated renal homografts in dogs. In some cases the kidneys revealed no signs of graft rejection while in others a mild infiltration; however, some disclosed the typical severe microscopic signs of rejection. These experiments showed that the effects of therapy on renal transplants can be highly variable, especially since the drug was more effective in some instances. Similarly, Kirchheim
and co-workers ('67) reported that most kidney homografts in dogs, which received Imuran therapy, showed a highly reduced rejection reaction which was replaced by a chronic proliferative inflammation as exemplified by interstitial fibrosis, focal cell infiltration and vascular changes. The invasive mononuclear cells, instead of infiltrating the entire transplant, as in controls, remained focal in nature.

Floersheim and Seiler ('67) observed that an immune inflammatory reaction induced by intradermal injection of homologous lymphocytes in chickens was reduced when Imuran was administered. Furthermore, the effect of the drug became more pronounced as the end of the reaction approached.

In general these observations agree with those made during the present study on the effects of Imuran in reducing the inflammatory response and concurrently increasing the viability of transplants. These observations establish the fact that Imuran had a beneficial effect on half-mandible transplants in ears and in cheek pouches in hamsters. They also establish that Imuran treatment did not completely inhibit the immune reaction, as reported by some other investigators, but merely seemed to have modified it. The nature of the rejection process changed under the influence of the immunosuppressive regimen and apparently became more chronic in nature. As a result of the short term experiments employed in the present study, where transplants were recovered at 15 days and initiation of therapy was begun at time of grafting, the ultimate fate of the grafts could not be determined. Nevertheless, these observations did indicate that the early phases of the rejection reaction had been modified, but in spite of immunosuppressive therapy, the fate of bone and teeth in heterotopic half-mandible transplants was also dependent on the site of
implantation as indicated by differences when identical grafts in ears and in cheek pouches were compared.

Both 6-LP and Imuran, when administered at a daily dose of 5 mg/100 gm were effective in increasing the number of viable molars, and while this increase was not pronounced, a higher degree of bone formation and less resorption were seen in other tissues of the grafts. Treatment of hosts with both drugs had decreased the intensity of lymphoid cell infiltration and reduced connective tissue invasion and replacement of graft tissues. However, neither drug had any detectable effect on the formation of cysts. Imuran was more effective than 6-LP in modifying the host-graft immune response in half-mandible transplants particularly evident in the enhanced growth of molars.

Several differences were seen in the effects of the immunosuppressive drugs employed. Grafts exposed to 6-LP showed considerable osteogenic tissue replacement of marrow while those in Imuran treated hosts tended to show more normal marrow. The lowest dose of 6-LP did not promote as much bone formation as the same dose of Imuran. Where a dense connective tissue invasion had occurred, the grafts in Imuran treated animals tended to show invasion of a looser type of connective tissue than was the case when 6-LP had been administered. Six-LP was more toxic in hamsters given identical doses and duration of treatment. Neither drug disclosed a beneficial effect on the viability of incisors. It was observed that these drugs, in some cases partly suppressed and in others modified the immune rejection response, yet neither drug had fully suppressed this response in our experiments.
VI. SUMMARY AND CONCLUSIONS

1. Half-mandibles from neonatal hamsters subcutaneously transplanted in the ears of adult hamsters disclosed survival of an occasional first molar and more frequently viable second molars. As more bone was removed from mandibles prior to transplantation, a trend toward an increase in molar survival occurred, and the highest degree of molar viability and growth in this site was seen where neonatal molars had been extracted from the mandible prior to transplantation. Ear grafts generally were highly vascular and firmly attached to the graft bed.

2. Viable molars were not found where half-mandibles from neonatal hamsters had been subcutaneously homotransplanted in the back of adults nor were any found in half-mandibles homografted in back from which part of the incisor had been previously excised. The half-mandible grafts in backs revealed a lower degree of revascularization and bone formation than those in the ear. On the other hand, lymphoid cell infiltration, indicative of an immune reaction, was higher than in the ear. These grafts were loosely attached to the graft bed and less well-vascularized than those in the ear.

3. Half-mandibles from neonatal hamsters transplanted into the lumen of the uterine horn of adult hamsters also revealed no viable molars; however, in one graft a molar was found which had continued to develop for a time but had undergone degeneration before recovery. A very low degree of bone formation had occurred in these grafts, most of which had failed to become established.

4. Half-mandibles from neonatal hamsters homotransplanted into the testis of adults were resorbed without exception and a very intense immune reaction was seen in all of them at the implantation site at time of recovery.
5. Only one viable molar was found where half-mandibles from neonatal hamsters had been homotransplanted into the kidney of adults. The others showed some bone formation, but they had failed to retain viable teeth.

6. Segments of rib autologously transplanted in the ears of adult hamsters revealed a continuation of cartilage growth and bone formation. No signs of rejection were seen in any of these grafts.

7. Half-mandibles from neonatal rats subcutaneously transplanted in the ears of adult rats showed an occasional viable first molar. Viable second molars were more frequently found and bone formation had occurred. The rejection reaction in the rat was more intense than that of similar homografts in the hamster. The teeth in the rats had formed very little enamel, but large amounts of osteodentin had developed in most of them.

8. Half-mandibles from neonatal rats transplanted into the kidneys disclosed only one viable first molar and possibly a second molar, or a fragment of the first which had developed independently. Bone formation had occurred in most grafts but to a lesser degree than in those on the ear.

9. The viable hamster and rat molars showed different degrees of growth, but none of them approached the size of normals. These molars had formed osteodentin initially, but more normal tubular dentin had developed later. A periodontal ligament had developed in some cases. A retarded enamel formation had occurred in most of the viable molars and in many the ameloblasts were transformed into cords or clusters of squamous cells; however, normal appearing ameloblasts were also seen in others. The highest degree of growth and viability had occurred where the molars had been removed from mandibles prior to grafting and these molars also showed the greatest amount of distortion.
10. The incisors were not found to survive in half-mandible transplants, the first molars only occasionally, and the second molars most frequently.

11. Only one viable molar was found on recovery at 15 days where 6-MP (10 mg/100 gm) had been administered daily for 12 days in hamsters with half-mandible transplants from neonatal hamsters in the back. These grafts were very loosely attached and showed no increase in viability of tissues when compared with those of non-treated animals.

12. No viable teeth were found where 6-MP (10 mg/100 gm) had been administered daily for 10 days in hamsters with implants of half-mandibles from neonatal hamsters implanted in the back. No increase in the viability of grafted tissues or decrease in the intensity of the rejection reaction had occurred.

13. No viable teeth were found in transplants of half-mandibles from neonatal hamsters in the ears of hamsters that had received daily injections of 6-MP (10 mg/100 gm) for four days beginning at time of grafting and 5 mg/100 gm thereafter. A delayed attachment, a decrease in resorption and a lower degree of dense connective tissue invasion and revascularization were seen in these grafts at six days after grafting.

14. An increase in the number of viable molars, a higher degree of bone formation, a decrease in lymphoid cell infiltration and less resorption and dense connective tissue invasion were seen in half-mandible transplants from neonatal hamsters in the ears of hamsters having received daily injections of 6-MP (5 mg/100 gm) for 15 days. Osteogenic tissue had replaced much of the mandibular marrow in these grafts.

15. Neonatal half-mandibles in the ears of hamsters having received daily injections of 6-MP (2 mg/100 gm) for 15 days showed no viable teeth, whereas
A higher degree of bone formation and a lower degree of resorption and dense connective tissue invasion than in grafts in control hosts was encountered. No significant decrease in lymphoid cell infiltration had occurred.

16. A greater viability and growth of molars, than that of controls was seen in transplants of half-mandibles from neonatal hamsters in the ears of hamsters having received daily injections of Imuran (5 mg/100 gm) for 15 days. A significant decrease in lymphoid cell infiltration and a higher degree of bone formation than that of grafts in control hosts had occurred. The degree of dense connective tissue invasion was also reduced when compared with those in control hosts.

17. Transplants of half-mandibles from neonatal hamsters in the ears of hamsters receiving daily injections of Imuran (2 mg/100 gm) for 15 days revealed one viable molar, whereas none were found in the control hosts. Those in treated hosts showed a higher degree of bone formation, a reduction in lymphoid cell infiltration and resorption and dense connective tissue invasion; however, these effects were not so pronounced as those seen where 5 mg had been administered.

18. An increase in viability and growth of molars was seen in transplants of half-mandibles from neonatal hamsters in cheek pouches of hamsters which had received daily injections (5 mg/100 gm) of Imuran. Viability and growth were not so pronounced as those seen in grafts in the ear following identical treatment. The grafts from treated animals in this group also revealed a higher degree of bone formation and less lymphoid cell infiltration than in grafts in non-treated controls. However, the degree of bone formation was considerably lower and a higher degree of resorption and rejection had
occurred than in those in the ear in identically treated hosts.

19. The most successful transplantation site was the ear in both the hamster and the rat, and the least successful in the hamster were the testis and the uterus where grafts were rejected without exception.

20. The greater viability of teeth and bone in subcutaneous transplants in the ear is believed to be due to the presence of a fibrocartilage which may provide a less foreign environment than that encountered in the other sites employed. Furthermore, it is felt that the very loose subcutaneous tissues in the back provided a less continuous host-graft contact and this is less conductive to an early incorporation of transplants.

21. The formation of osteodentin and/or dentin by the odontoblasts probably reflects the physiological condition of the environment since as the environment seemed to approach normal in these grafts, tubular dentin was formed.

22. The results of the present study indicate that the ameloblasts are the most labile cell component of the developing tooth, since they had usually disappeared from some of the teeth and in others had reverted to squamous cells. These cells must be very susceptible to the adverse effects of lymphoid cell infiltration, since they had usually degenerated whenever lymphoid cells were present.

23. The small size and retarded development of viable teeth is believed to be due to delays in the resumption of development following transplantation attributed to a delay in revascularization and establishment of grafts.

24. The increased frequency of viable molars, in cases where part of the mandible had been removed prior to grafting, may be the result of a freer access to nutrients, the character of the site, and the degree of differentiation of the tooth at the time of transplantation.
25. Revascularization in itself is not sufficient to ensure survival of molars since some vascularized molars revealed varying degrees of degeneration.

26. The immune reaction must play an important role in determining viability and that a delicate balance probably exists between the rejection reaction and the ability of the tooth to obtain revascularization and become established.

27. The cheek pouch of the hamster, contrary to the observations of some other investigators was not an immunologically privileged site in these experiments. Grafts in this site elicited a more intense reaction than those in the ear; the reasons for which are not known.

28. Imuran was more effective than 6-MP in promoting transplant viability as indicated by the greater growth of teeth and the higher degree of bone formation. It was found that the hamster tolerated Imuran better than 6-MP.

29. The rejection reaction was partly suppressed or modified by Imuran and 6-MP treatment as revealed by the reduction in lymphoid cell response and the greater viability of tissues, but in no case was this reaction fully suppressed.

30. The viability of transplanted teeth is in part determined by the intensity of the immune reaction, since growth and development of teeth and bone, particularly evident in ear and cheek pouch grafts were enhanced by appropriate immunosuppressive treatment. Nevertheless, despite the beneficial effects, complete suppression was never encountered; hence it must be assumed that successful growth of bone and teeth in heterotopic grafts is also dependent on other factors, chief of which must be those encountered in the transplantation site.
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<table>
<thead>
<tr>
<th>Exp.</th>
<th>Donor tissue Type</th>
<th>Age hr.</th>
<th>Site</th>
<th>Recovery age days</th>
<th>No. recovered</th>
<th>No. viable teeth</th>
<th>Viable teeth total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Molar</td>
<td>8-15</td>
<td>Ear</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>IB</td>
<td>Mand.*</td>
<td>2-15</td>
<td>Ear</td>
<td>15</td>
<td>12</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>IC</td>
<td>Mand.</td>
<td>12-14</td>
<td>Ear</td>
<td>15</td>
<td>10</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>ID</td>
<td>Mand.</td>
<td>14-18</td>
<td>Ear</td>
<td>10</td>
<td>14</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>IE</td>
<td>Mand. No Incisor</td>
<td>15-17</td>
<td>Ear</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>IF</td>
<td>Molar Part Mand.</td>
<td>12-14</td>
<td>Ear</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>IIA</td>
<td>Mand.</td>
<td>3-15</td>
<td>Back</td>
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<td>11</td>
<td>10</td>
<td>0</td>
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<td>IIB</td>
<td>Mand. No Incisor</td>
<td>72</td>
<td>Back</td>
<td>30</td>
<td>10</td>
<td>10</td>
<td>0</td>
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<td>III</td>
<td>Mand.</td>
<td>18-40</td>
<td>Uterine Horn</td>
<td>26</td>
<td>10</td>
<td>9</td>
<td>0</td>
</tr>
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<td>IV</td>
<td>Mand.</td>
<td>1-12</td>
<td>Testis</td>
<td>20</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>Mand.</td>
<td>8-13</td>
<td>Kidney</td>
<td>20</td>
<td>7</td>
<td>7</td>
<td>1</td>
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</table>

* Abbreviation employed for half mandible.
### TABLE 2

Experiments on Rib Autotransplants in Ear of Adult Hamsters

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Donor tissue age</th>
<th>Recovery age (days)</th>
<th>No. executed</th>
<th>No. recovered</th>
<th>No. showing formation of cartilage and/or bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI</td>
<td>Adult</td>
<td>15</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

### TABLE 3

Experiments on Neonatal Rat Half-Mandible Transplants in Normal Adults

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Donor tissue age hr.</th>
<th>Site</th>
<th>Recovery age (days)</th>
<th>No. executed</th>
<th>No. recovered</th>
<th>No. viable teeth</th>
<th>Viable teeth total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII</td>
<td>12-14</td>
<td>Ear</td>
<td>15</td>
<td>16</td>
<td>15</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>VIII</td>
<td>6-10</td>
<td>Kidney</td>
<td>15</td>
<td>12</td>
<td>12</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
### TABLE 4

**Experiments on Neonatal Hamster Half-Mandible Transplants**

**in 6-mercaptopurine Treated Adults**

<table>
<thead>
<tr>
<th>Exp. Age</th>
<th>Site</th>
<th>Daily dose/100 gm</th>
<th>Crafts</th>
<th>Viable teeth total</th>
</tr>
</thead>
<tbody>
<tr>
<td>donor</td>
<td>mg</td>
<td>days</td>
<td>Recovery age</td>
<td>No. executed</td>
</tr>
<tr>
<td>tissue</td>
<td></td>
<td></td>
<td>days</td>
<td></td>
</tr>
<tr>
<td>hr.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| IXA 12-20 Back | C<sup>1</sup>-10 | 12 | 15 | 8 | 6 | 1 | 1 |
| C<sup>2</sup>-vehicle | 12 | 15 | 8 | 6 | 0 | 0 |
| IXB 12-13 Back | C -10 | 10 | 10 | 4 | 3 | 0 | 0 |
| C -vehicle | 10 | 10 | 4 | 4 | 0 | 0 |
| T<sup>3</sup>-10 | 5 | 6 | 1 | 1 | 0 | 0 |
| C<sup>4</sup>-vehicle | 5 | 6 | 1 | 1 | 0 | 0 |
| XA 8-10 Ear | T -10 then 5 | 4 | 2 | 6 | 7 | 4 | 0 | 0 |
| C -vehicle reduced | 4 | 2 | 6 | 7 | 3 | 0 | 0 |
| T<sup>3</sup>-10 then 5 | 4 | 1 | 5 | 1 | 1 | 0 | 0 |
| C<sup>4</sup>-vehicle reduced | 4 | 1 | 5 | 1 | 1 | 0 | 0 |
| XB 12-15 Ear | C -5 | 15 | 15 | 9 | 9 | 3 | 3 |
| N<sup>5</sup>-no treatment | 15 | 15 | 5 | 2 | 0 | 0 |
| XC 12-14 Ear | C -2 | 15 | 15 | 5 | 5 | 0 | 0 |

C -vehicle | 15 | 15 | 5 | 3 | 1 | 1 |
TABLE 4 - Continued

\[ T^1 \] Experimentals.

\[ C^2 \] Controls.

\[ T^3 \] Experimentals, but recovered due to drug toxicity.

\[ C^4 \] Controls, but recovered due to drug toxicity.

\[ N^5 \] Normals, received only one injection of vehicle at time of grafting.
TABLE 5
Experiments on Neonatal Hamster Half-Mandible Transplants
in Imuran Treated Adults

<table>
<thead>
<tr>
<th>Exp. Age</th>
<th>Site</th>
<th>Daily dose/100 gm</th>
<th>Day</th>
<th>Grafts</th>
<th>Recovery age</th>
<th>Recov-</th>
<th>Viable</th>
<th>teeth</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>donor tissue hr.</td>
<td>mg</td>
<td>days</td>
<td></td>
<td>No. executed</td>
<td>recov-</td>
<td>viable</td>
<td>teeth</td>
<td></td>
</tr>
<tr>
<td>XIA</td>
<td>12-14 Ear</td>
<td>T₁-5</td>
<td>15</td>
<td>15</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>G²-vehicle</td>
<td>15</td>
<td>15</td>
<td>8</td>
<td>8</td>
<td>1</td>
<td>1</td>
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<tr>
<td>XIB</td>
<td>13-14 Ear</td>
<td>T   -2</td>
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<tr>
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<td>15</td>
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<tr>
<td>XII</td>
<td>12-14 Cheek Pouch</td>
<td>T   -5</td>
<td>15</td>
<td>15</td>
<td>9</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C   -vehicle</td>
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<td>15</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

T¹ Experimental.
C² Controls.
### TABLE 6

**EXPERIMENT IA**

**Neonatal Hamster First Mandibular Molar Transplants in Ear of Adults**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Condition of graft</th>
<th>Fate of tooth transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>++*</td>
<td>Large amount of growth and differentiation. No lymphoid cell infiltration into the pulp. Root formation</td>
</tr>
<tr>
<td>2</td>
<td>+++</td>
<td>Very large amount of growth and differentiation. No lymphoid cell infiltration into the pulp. Root formation</td>
</tr>
<tr>
<td>3</td>
<td>±</td>
<td>Large amount of growth and differentiation. Lymphoid cell infiltration into pulp. Root formation</td>
</tr>
<tr>
<td>4</td>
<td>±</td>
<td>Large amount of growth and differentiation. Lymphoid cell infiltration into pulp. Root formation</td>
</tr>
<tr>
<td>5</td>
<td>±</td>
<td>Large amount of growth and differentiation. Low degree of lymphoid cell infiltration into pulp. Root formation</td>
</tr>
<tr>
<td>6</td>
<td>±</td>
<td>Large amount of growth and differentiation. Low degree of lymphoid cell infiltration into pulp. Root formation</td>
</tr>
<tr>
<td>7</td>
<td>±</td>
<td>Large amount of growth and differentiation. High degree of lymphoid cell infiltration into pulp. Root formation</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>Fragments of cusps. Osteodentin. No viable odontoblasts or ameloblasts</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>Mostly resorbed. Only small piece of osteoid remains</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>Resorbed completely</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>Resorbed completely</td>
</tr>
</tbody>
</table>

* Symbols employed in grading the character of teeth:
<table>
<thead>
<tr>
<th>Symbols</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>Designates viable teeth showing maximum growth.</td>
</tr>
<tr>
<td>++</td>
<td>Assigned to viable teeth showing less growth than seen in category (+++).</td>
</tr>
<tr>
<td>+</td>
<td>Assigned to viable teeth with vascular pulps but showing only a small amount of growth.</td>
</tr>
<tr>
<td>±</td>
<td>Assigned to teeth which were still viable, but had undergone noticeable degeneration and rejection. These teeth usually showed vascular pulps and some viable odontoblasts and pre-dentin formation, however, the pulps showed lymphoid cell infiltration.</td>
</tr>
<tr>
<td>-</td>
<td>Employed in cases where an unmistakable rejection reaction had occurred. This category ranged from teeth in the later stages of regression to those in which only fragments remained. The symbol was also employed where complete resorption had occurred.</td>
</tr>
</tbody>
</table>
TABLE 7
EXPERIMENT IB
Neonatal Hamster Half-Mandible Transplants in Ear of Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dentin remnant</td>
<td>+ Growth and differentiation, No roots</td>
<td>- Resorbed</td>
<td>Peripheral bone formation. Minimal degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>+ No root formation</td>
<td>Bone formation and trabecular growth. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>- Dentin remnant</td>
<td>+ Much growth and differentiation, Root formation</td>
<td>+ No root formation</td>
<td>Bone formation and trabecular growth. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>- Dentin remnant</td>
<td>- Dentin fragment</td>
<td>+++ Root formation</td>
<td>Bone formation and trabecular growth. Compacta formation. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>- Dentin remnant</td>
<td>- Dentin fragments</td>
<td>++ No root formation</td>
<td>Bone formation but also resorption. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>- Dentin remnant</td>
<td>- Dentin fragments, Partial encystment</td>
<td>++ No root formation</td>
<td>Partly encysted. Much resorbed. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>7</td>
<td>Encysted dentin remnant</td>
<td>- Dentin fragments</td>
<td>+++ No root formation</td>
<td>Mostly encysted. Much necrosis. Very high degree of lymphoid cell and polymorphonuclear cell infiltration. Very small amount viable bone. Much resorbed</td>
</tr>
<tr>
<td>Animal</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>8</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Small amount of viable bone, Resorption, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>9</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Spongy bone formation and trabecular growth, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>10</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Bone formation but some necrosis, Resorption, High degree of lymphoid cell infiltration</td>
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<tr>
<td>11</td>
<td>Dentin remnant</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Very high degree of bone formation, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>12</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Much bone formation, Low degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
### TABLE 8

**EXPERIMENT IC**

Neonatal Hamster Half-Mandible Transplants in Ear of Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-* Dentin remnant</td>
<td>Dentin fragments</td>
<td>+ Growth and differentiation, No root formation</td>
<td>Peripheral bone formation, High degree of lymphoid cell infiltration, Some resorption</td>
</tr>
<tr>
<td>2</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>+++ Root formation</td>
<td>Much bone formation and peripheral trabecular growth, Active resorption, Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>Dentin remnant</td>
<td>+ Much growth and differentiation, No root formation, Much osteodentin</td>
<td>- Resorbed</td>
<td>Much bone formation and trabecular growth, Some resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Much bone formation and trabecular growth, Dense connective tissue replacement, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>Dentin remnant</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Peripheral bone formation, Some resorption, Central necrosis, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Much bone formation and trabecular growth, Moderate degree of lymphoid cell infiltration, Resorption</td>
</tr>
</tbody>
</table>
TABLE 8 - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dentin remnant</td>
<td>Dentin remnants</td>
<td>Resorbed</td>
<td>Peripheral bone formation, Compacta formation, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>8</td>
<td>Dentin remnant</td>
<td>Dentin remnants</td>
<td>Resorbed</td>
<td>Much necrosis and resorption, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>9</td>
<td>Dentin remnant</td>
<td>Dentin remnants</td>
<td>Resorbed</td>
<td>Peripheral bone formation, Spongy bone and compacta formation, Moderate degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
### TABLE 9

**EXPERIMENT ID**

Neonatal Hamster Half-Mandible Transplants in Ear of Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>+ No root formation</td>
<td>Much bone formation, Trabecular growth and compacta formation, Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>+ No root formation</td>
<td>Small amount of bone formation peripherally, Much resorption, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Much spongy bone formation and trabecular growth. Some resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Dentin fragments</td>
<td>Much spongy bone formation and trabecular growth. Some resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Much necrotic bone, Much resorption, Small amount of bone formation, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Some central resorption. Much bone formation, Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>7</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Dentin fragments encysted</td>
<td>Most of bone resorbed, Very small amount of bone formation, Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>8</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Growth and differentiation</td>
<td>Some bone formation but much resorption, Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>Animal</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>--------</td>
<td>------------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>9</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Much bone formation and trabecular growth mainly peripherally. Central resorption. Some compacta formation. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>10</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Much bone and compacta formation and trabecular growth mostly peripherally. Some resorption. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>11</td>
<td>- Resorbed</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Mostly resorbed. Small ossicles remain. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>12</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Dentin fragment</td>
<td>One small viable ossicle. Mostly resorbed and remainder necrotic. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>13</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Much resorption but some bone formation. Resorption. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>14</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>- Resorbed</td>
<td>Much bone formation. Much resorption. Moderate degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
### TABLE 10

**EXPERIMENT IE**

Neonatal Hamster Half-Mandible Transplants with Partly Excised Incisor in Ear of Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-* Dentin remnant</td>
<td>± Growth and differentiation, No roots, Much osteodentin</td>
<td>Large amount of bone formation and trabecular growth, Some resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>- Dentin remnant</td>
<td>± Growth and differentiation, No roots, Much osteodentin</td>
<td>Much bone formation mostly trabecular growth and spongy bone, Some resorption, Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>- Spherical mass of osteodentin</td>
<td>++ No roots, No osteodentin</td>
<td>Mostly viable bone but very thin and lacy trabeculae. Some resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Several large ossicles of viable bone, Remainder resorbed or necrotic, Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>Several small viable ossicles, Remainder necrotic, Much resorption, Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>- Dentin remnant</td>
<td>- Dentin remnant</td>
<td>Large amount of viable bone, Much trabecular growth and spongy bone formation, Small amount of resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>7</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>Some necrosis and resorption centrally, Much bone formation peripherally, Low degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>
TABLE 10 - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainer of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Dentin remnant</td>
<td>Dentin remnant</td>
<td>Large amount of viable bone, Bone formation and trabecular growth, Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td>Some osteodentin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Dentin remnant</td>
<td>Resorbed</td>
<td>Thin trabeculae and necrosis, Much resorption, Small amount of bone formation, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>10</td>
<td>Dentin remnant</td>
<td>Dentin remnant</td>
<td>Much bone formation and trabecular growth, Some resorption, Moderate degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
### TABLE II

**EXPERIMENT IF**

Neonatal Hamster Molar Transplants with Part of Mandible in Ear of Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>- * Dentin remnant</td>
<td>+++ Root formation underway, No osteodentin</td>
<td>Much bone formation and trabecular growth, Some compacta formation, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>- Dentin remnant</td>
<td>+++ Root formation, No osteodentin</td>
<td>Small amount of bone formation and some resorption, Thin trabeculae, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>- Dentin remnant</td>
<td>+ No root formation, No osteodentin</td>
<td>Some bone formation and trabecular growth, Peripheral compacta formation, Moderate resorption, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>- Dentin remnant</td>
<td>+ No root formation, No osteodentin</td>
<td>Much bone formation and trabecular growth, Central resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>Much resorption, Some bone formation, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>Much bone formation and trabecular growth, Moderate resorption, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>7</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>Much bone formation and trabecular growth, Small amount of resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>8</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Much bone formation and trabecular growth, Central resorption, Low degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>
TABLE II - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Dentin remnant</td>
<td>- Resorbed</td>
<td>Widespread necrosis. Small amount of viable peripheral bone. Much resorption. Very high degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>* Resorbed</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Small ossicles of viable bone, Small amount of bone formation, Much resorption, Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Resorbed</td>
</tr>
<tr>
<td>3</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Degenerated cells</td>
<td>Most bone necrotic, Much resorption and small amount of bone formation, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Degenerated cells</td>
<td>All bone necrotic, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Much spongy bone formation, Much resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Degenerated cells</td>
<td>Bone almost all necrotic, Small amount of peripheral bone viable, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>7</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Small piece of osteodentin</td>
<td>Large amount of spongy bone formation, Much resorption, Very high degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>
TABLE 12 - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Degenerated</td>
<td>Much central resorption. Remainder mostly necrotic. Small amount of peripheral bone viable. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>cells</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Resorbed</td>
<td>Dentin</td>
<td>Degenerated</td>
<td>Small peripheral ossicles of viable bone, but remainder necrotic. Much resorption. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fragments</td>
<td>cells</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Resorbed</td>
<td>Mostly necrotic. Some bone formation, but much resorption. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>remnant</td>
<td>fragments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Degenerated</td>
<td>Very small amount of viable bone. Remainder necrotic. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>remnant</td>
<td>fragments</td>
<td></td>
<td>cells</td>
<td></td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
**TABLE 13**

**EXPERIMENT IIB**

Neonatal Hamster Half-Mandible Transplants with Partly Excised Incisor in Back of Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>* Dentin remnant</td>
<td>- Dentin remnant</td>
<td>Mostly resorbed. Remainder necrotic. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>- Dentin remnant</td>
<td>- Dentin remnant</td>
<td>Two hollow ossicles. Most of graft resorbed. Small amount of bone formation. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>One small ossicle. Remainder resorbed. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>- Dentin remnant</td>
<td>- Dentin remnant</td>
<td>One small ossicle. Remainder necrotic or resorbed. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Two small viable ossicles. Remainder resorbed. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>- Dentin remnant</td>
<td>- Dentin remnant</td>
<td>Entire graft encysted and non-viable</td>
</tr>
<tr>
<td>7</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Small ossicle. Remainder resorbed. Very high degree of lymphoid cell</td>
</tr>
<tr>
<td>8</td>
<td>- Resorbed</td>
<td>- Dentin remnant</td>
<td>Two small ossicles, remainder resorbed. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>9</td>
<td>- Dentin remnant</td>
<td>- Dentin remnant</td>
<td>All bone necrotic. Much resorption. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>10</td>
<td>- Dentin remnant</td>
<td>- Dentin remnant</td>
<td>Only one small ossicle of viable bone. Very high degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
TABLE 14

EXPERIMENT III
Neonatal Hamster Half-Mandible Transplants in Uterine Horn of Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>* Dentin remnant</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Mostly necrotic non-viable bone. Much trabecular growth. Much resorption. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Necrotic non-viable bone. Thin, lacy trabeculae. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Necrotic non-viable bone. Thin, lacy trabeculae. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Some bone formation. Some resorption. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Resorbed. Only a few foci of lymphoid cells remain</td>
</tr>
<tr>
<td>6</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Encysted, necrotic, small ossicle. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>7</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Necrotic non-viable bone. High degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>
TABLE 14 - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>- Resorbed</td>
<td>- Dentin fragments</td>
<td>- Resorbed</td>
<td>Most bone necrotic and non-viable. Small areas of viable bone. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>9</td>
<td>- Resorbed</td>
<td>- Dentin fragment</td>
<td>- Resorbed</td>
<td>Small necrotic and mostly non-viable ossicles. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>10</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Resorbed completely</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
**TABLE 15**

**EXPERIMENT IV**

Neonatal Hamster Half-Mandible Transplants in Testis of Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>- *</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Resorbed</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Resorbed</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Resorbed</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Resorbed</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
# TABLE 16

## EXPERIMENT V

Neonatal Hamster Half-Mandible Transplants in Kidney of Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>* Resorbed</td>
<td>+++ Root formation</td>
<td>- Resorbed</td>
<td>Much bone formation and trabecular growth, Some resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Some bone formation and trabecular growth, Some resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>- Resorbed</td>
<td>- Dentin fragment</td>
<td>- Resorbed</td>
<td>Large hollow ossicles, Some bone formation but much resorption, Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>- Dentin remnant</td>
<td>- Dentin fragments</td>
<td>- Resorbed</td>
<td>Some bone formation and trabecular growth, Much resorption, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Large hollow ossicle, Peripheral bone formation, Some resorption, Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>- Dentin remnant</td>
<td>- Dentin fragments</td>
<td>- Dentin fragment</td>
<td>Some bone formation and trabecular growth but much resorption, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>Animal</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>-------------</td>
<td>--------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>7</td>
<td>Resorbed</td>
<td>Dentin</td>
<td>Resorbed</td>
<td>Small amount of bone formation but much resorption. Hollow ossicle. Very high degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
**TABLE 17**  
**EXPERIMENT VI**  
Rib Autografts in Ear of Adult Hamsters

<table>
<thead>
<tr>
<th>Animal</th>
<th>Condition of graft</th>
<th>Fate of autograft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+**</td>
<td>Viable and calcified cartilage. Cartilage growth and very little resorption</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>Calcified cartilage, however, pyknotic nuclei in chondrocytes and degeneration in others. Some viable compact bone. Low degree of resorption. An intensive inflammatory cell infiltration about and within graft consisting mainly of polymorphonuclear cells. Some cyst formation</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>Viable and calcified cartilage. Cartilage and bone growth. No inflammation</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>Viable and calcified cartilage. Cartilage and bone growth. No inflammation</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>Viable and calcified cartilage. Cartilage and bone growth. No inflammation</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>Viable and calcified cartilage. Cartilage and bone growth. No inflammation</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>Viable and calcified cartilage. Cartilage and bone growth. No inflammation</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>Viable and calcified cartilage. Cartilage and bone growth. No inflammation</td>
</tr>
</tbody>
</table>

* Symbols employed in grading the character of bone and cartilage in autografts:

+ designates autografts showing viable cartilage and bone revealing growth and normal bone and cartilage cells.

- assigned to autografts showing unmistakable inflammation as revealed by resorption and a high degree of infiltration of polymorphonuclear and other cell types. The characteristic lymphoid cell infiltration of the homograft was not seen in any of these autografts.
### TABLE 18

**EXPERIMENT VII**

Neonatal Rat Half-Mandible Transplants in Ear of Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>* Dentine remnant</td>
<td>+ Much growth and differentiation, Much osteodentin</td>
<td>- Dentin fragment</td>
<td>Much bone formation and trabecular growth, Moderate resorption, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>Dentine remnant</td>
<td>+ Much growth and differentiation, Root formation, Much osteodentin</td>
<td>+ Much growth and differentiation, Much osteodentin</td>
<td>Much bone formation and trabecular growth, Moderate resorption, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>Dentine remnant</td>
<td>- Resorbed</td>
<td>+ Much growth and differentiation, Root formation</td>
<td>Much bone formation and trabecular growth, Moderate resorption, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>Dentine remnant</td>
<td>- Dentin fragments</td>
<td>+ Much growth and differentiation, Root formation, Much osteodentin</td>
<td>Bone formation and trabecular growth, Much resorption, Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>Resorbed</td>
<td>+ Much growth and differentiation, No roots, Much osteodentin</td>
<td>+ Much growth and differentiation, No roots, Much osteodentin</td>
<td>Bone formation and trabecular growth, Much resorption, Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>Dentine remnant</td>
<td>- Mass of osteodentin</td>
<td>- Dentin fragments</td>
<td>Much bone formation and trabecular growth, Some resorption, High degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>
TABLE 18 - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Dentin fragments</td>
<td>Spongy bone formation and trabecular growth. Some resorption. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>8</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Much necrotic bone. Some bone formation and trabecular growth. Most resorbed. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>9</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Much trabecular growth. Some resorption. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>10</td>
<td>Dentin remnant</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Much bone formation and trabecular growth. Some resorption. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>11</td>
<td>Dentin remnant</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Much bone formation and trabecular growth. Moderate resorption. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>12</td>
<td>Dentin remnant</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Mostly necrotic and much resorption. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>13</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Mostly necrotic and much resorption. Small amount of bone formation. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>Animal</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>--------</td>
<td>---------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>14</td>
<td>Resorbed</td>
<td>Dentin fragments</td>
<td>Dentin fragments</td>
<td>Much resorption. Bone necrotic but trabecular growth had occurred. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>15</td>
<td>Resorbed</td>
<td>Mass of osteodentin</td>
<td>Resorbed</td>
<td>Much resorption, also much trabecular growth, High degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
<table>
<thead>
<tr>
<th>Animal</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-* Resorbed</td>
<td>+++ Root formation, Much osteodentin</td>
<td>++ Possible second molar or fragment of first molar</td>
<td>Large hollow ossicles. Much trabecular growth. Some resorption. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>- Dentin remnant</td>
<td>- Dentin fragment</td>
<td>- Resorbed</td>
<td>Much resorption, Some necrotic bone. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>- Dentin remnant</td>
<td>- Osteodentin mass</td>
<td>- Resorbed</td>
<td>Much bone formation and trabecular growth. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Some trabecular growth but mostly resorption. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Small ossicle of partly viable bone. Much resorption. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Much bone formation and trabecular growth. Some resorption. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>7</td>
<td>- Dentin remnant</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>Small amount of bone formation. Some resorption. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>Animal</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>8</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Very small amount of non-viable bone. Mostly resorbed. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>9</td>
<td>Dentin remnant</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Some bone formation and trabecular growth. Much resorption. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>10</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Some bone formation. Much resorption. Very high degree of lymphoid cell infiltration, Some trabecular growth</td>
</tr>
<tr>
<td>11</td>
<td>Dentin remnant</td>
<td>Dentin fragment</td>
<td>Resorbed</td>
<td>Mostly necrotic bone. Small amount of viable bone. Much resorption. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>12</td>
<td>Dentin remnant</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Very small amount of viable bone. Remainder necrotic. Much resorption. Very high degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

* For symbols employed, see footnote, table 6.
### TABLE 20

**EXPERIMENT IXA**

Neonatal Hamster Half-Mandible Transplants in Back of 6-Mercaptopurine Treated Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T¹</td>
<td>-³</td>
<td>Dentin remnant</td>
<td>- Dentin fragments</td>
<td>+ No root forma- tion, No osteo- dentin</td>
</tr>
<tr>
<td>2</td>
<td>C²</td>
<td>- Dentin remnant</td>
<td>- Dentin fragments</td>
<td>- Resorbed</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>T</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td>- Resorbed</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>Host died. Graft not recovered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>T</td>
<td>Totally resorbed before recovery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>- Dentin remnant</td>
<td>- Dentin fragments</td>
<td>- Resorbed</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>T</td>
<td>- Dentin remnant</td>
<td>- Dentin fragments</td>
<td>- Dentin fragment</td>
<td></td>
</tr>
<tr>
<td>Animal</td>
<td>Treatment</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Re-</td>
<td>Much resorption and dense connective tissue replacement. Small amount of bone formation. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>resorbed</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>T</td>
<td>Host died.</td>
<td>Graft not recovered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>Dentin</td>
<td>Re-</td>
<td>Re-</td>
<td>Much bone formation and trabecular growth. Very low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>resorbed</td>
<td>resorbed</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Re-</td>
<td>Some resorption but much bone formation. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>resorbed</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>C</td>
<td>Host died.</td>
<td>Graft not recovered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Re-</td>
<td>Viable ossicles. Much resorption. Small amount bone formation. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>resorbed</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>C</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Re-</td>
<td>Moderate resorption and a high degree of trabecular growth. Hollow centrally. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>resorbed</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Re-</td>
<td>Much spongy bone formation and trabecular growth. Moderate resorption. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>resorbed</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>C</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Re-</td>
<td>Two hollow viable ossicles. Very little bone formation. Much necrosis. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>resorbed</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 20 - Continued

1. Experimentals: 10 mg/100 gm body weight/day beginning at time of grafting and continued for 12 days. Grafts recovered at 15 days.

2. Controls: equivalent volume of vehicle/100 gm body weight/day beginning at time of grafting and continued for 12 days. Grafts recovered at 15 days.

3. For symbols employed, see footnote, table 6.
### TABLE 21

#### EXPERIMENT IXB

Neonatal Hamster Half-Mandible Transplants in Back of 6-Mercaptopurine Treated Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T_1^1 (6 da)(^2)</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Degen- erated</td>
<td>Avascular and necrotic bone, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>C_3^3 (6 da)</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Degen- erated</td>
<td>Avascular and necrotic bone, A few small areas of viable osteoid, Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>T (10 da)(^4)</td>
<td>Host died, Graft not recovered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>C (10 da)</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Degen- erated</td>
<td>Two small viable ossicles, remainder necrotic and avascular, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>T (10 da)</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Degen- erated</td>
<td>Two small viable ossicles, remainder necrotic and avascular, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>C (10 da)</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Much spongy bone forma- tion and resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>7</td>
<td>T (10 da)</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Small area of viable bone, Widespread necrosis, Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>Animal</td>
<td>Treatment</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Resorbed</td>
<td>Only small areas of viable bone. Widespread necrosis. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td>(10 da)</td>
<td>remnant</td>
<td>Dentin</td>
<td>fragments</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Degenerated</td>
<td>Small viable ossicle. Widespread necrosis. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td>(10 da)</td>
<td>remnant</td>
<td>Dentin</td>
<td>fragments</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Only small viable ossicles. Much resorbed and remainder necrotic. Most encysted. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td>(10 da)</td>
<td>remnant</td>
<td>Dentin</td>
<td>fragments</td>
<td></td>
</tr>
</tbody>
</table>

1. Experimentals: 10 mg/100 gm body weight/day beginning at time of grafting and continued until transplant was recovered.

2. (6 da) 6 days: transplant recovered at 6 days after transplantation.

3. Controls: an equivalent volume of vehicle/100 gm body weight/day beginning at time of grafting and continued until recovery of transplant.

4. (10 da) 10 days: transplant recovered at 10 days after transplantation.

5. For symbols employed, see footnote, table 6.
**TABLE 22**

**EXPERIMENT XA**

Neonatal Hamster Half-Mandible Transplants in Ear of 6-Mercaptopurine Treated Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
</table>
| 1      | T<sup>1</sup>  
(5 da)<sup>2</sup> | -<sup>5</sup> Dentin remnant | - Dentin fragments | - Degen-erated cells | Peripheral rim of viable bone, remainder necrotic. Extensive hemorrhage. Low degree of lymphoid cell infiltration |
| 2      | C<sup>3</sup>  
(5 da) | - Dentin remnant | - Dentin fragments | - Degen-erated bones | Some peripheral viable bone. Most necrotic. Some peripheral bone formation. Moderate degree of lymphoid cell infiltration |
| 3      | T<sup>4</sup>  
(6 da) | - Dentin remnant | - Dentin fragments | - Degen-erated cells | Some viable peripheral bone. Remainder necrotic. Extensive hemorrhage. Low degree of lymphoid cell infiltration |
| 4      | C         | Host died. Graft not recovered |
| 5      | T  
(6 da) | - Dentin remnant | - Dentin fragments | - Degen-erated cells | Small peripheral areas of viable bone. Remainder necrotic. Low degree of lymphoid cell infiltration. Extensive hemorrhage |
| 6      | C         | Host died. Graft not recovered |
| 7      | T  
(6 da) | - Dentin remnant | - Dentin fragments | - Degen-erated cells | Small peripheral area of viable bone. Remainder necrotic. Extensive hemorrhage. Moderate degree of lymphoid cell infiltration |
| 8      | C         | Host died. Graft not recovered |
### TABLE 22 - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>T</td>
<td>Host died</td>
<td>Graft not recovered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>Host died</td>
<td>Graft not recovered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>T</td>
<td>Host died</td>
<td>Graft not recovered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed Dentin fragments</td>
<td>Some peripheral spongy bone formation. Remainder necrotic. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td>(6 da)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>T</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Degen-erated Degenerated cells</td>
<td>Very small amount of peripheral viable bone. Low degree of lymphoid cell infiltration. Remainder graft necrotic</td>
</tr>
<tr>
<td></td>
<td>(6 da)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Degen-erated Degenerated cells</td>
<td>Some viable peripheral bone. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td>(6 da)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>T</td>
<td>Host died</td>
<td>Graft not recovered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed Dentin fragments</td>
<td>Much spongy bone formation and resorption. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td>(6 da)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Experiments: 10 mg/100 gm body weight/day for four days beginning at time of grafting then reduced to 5 mg/100 gm/day thereafter.

\(^2\) 5 days: transplant recovered at five days after transplantation.

\(^3\) Controls: an equivalent volume of vehicle/100 gm body weight/day beginning at time of grafting and continued until recovery of graft.

\(^4\) 6 days: transplant recovered at six days after transplantation.

\(^5\) For symbols employed, see footnote, table 6.
## TABLE 23

**EXPERIMENT XB**

Neonatal Hamster Half-Mandible Transplants in Ear of 6-Mercaptopurine Treated Adults

<table>
<thead>
<tr>
<th>Animal Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 T(^1)</td>
<td>4 Dentin remnant</td>
<td>Dentin</td>
<td>Re- sorbed</td>
<td>All bone necrotic except for small peripheral area, Some resorption. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2 C(^2)</td>
<td>Host died. Graft not recovered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 T</td>
<td>Dentin remnant</td>
<td>Dentin</td>
<td>Re- sorbed</td>
<td>Much resorption and dense connective tissue replacement. Peripheral bone formation. Most bone viable. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4 C</td>
<td>Host died. Graft not recovered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 T</td>
<td>Dentin</td>
<td>Dentin +No roots, No osteodentin</td>
<td></td>
<td>Large amount of bone formation and trabecular growth. Compacta formation. Small amount of resorption. Marrow replacement with osteogenic tissue, but some normal marrow. Very low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6 C</td>
<td>Host died. Graft not recovered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 T</td>
<td>Dentin remnant</td>
<td>Dentin</td>
<td>Re- sorbed</td>
<td>Much resorption, but also much trabecular growth and compacta formation. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>Animal</td>
<td>Treatment</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin fragment</td>
<td>Resorbed</td>
</tr>
<tr>
<td>9</td>
<td>T</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
</tr>
<tr>
<td>11</td>
<td>T</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Resorbed</td>
</tr>
<tr>
<td>12</td>
<td>N³</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
</tr>
<tr>
<td>13</td>
<td>T</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Very immature</td>
</tr>
<tr>
<td>Animal</td>
<td>Treatment</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td>14</td>
<td>N</td>
<td>Dentin</td>
<td>Dentin</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>resorbed</td>
</tr>
<tr>
<td>15</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>resorbed</td>
</tr>
<tr>
<td>16</td>
<td>N</td>
<td>Dentin</td>
<td>Dentin</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>resorbed</td>
</tr>
<tr>
<td>17</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>+++ Root</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>formation</td>
</tr>
<tr>
<td>18</td>
<td>N</td>
<td>Dentin</td>
<td>Dentin</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>fragments</td>
<td>resorbed</td>
</tr>
</tbody>
</table>

T<sup>1</sup> Experimental: 5 mg/100 gm body weight/day beginning at time of grafting and continued until recovery at 15 days.

C<sup>2</sup> Controls: an equivalent volume of vehicle/100 gm body weight/day beginning at time of grafting and continued until recovery at 15 days.
**TABLE 23 - Continued**

\[ \text{N}^{3} \] Normals: hosts which had received an injection of vehicle at time of grafting and no further treatment during postoperative interval of 15 days.

\[ \text{N}^{4} \] For symbols employed, see footnote, table 6.
TABLE 24

EXPERIMENT XC

Neonatal Hamster Half-Mandible Transplants in Ear of 6-Mercaptopurine Treated Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T$^1$</td>
<td>3 Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Very large amount of trabecular growth and bone formation, Some resorption, Much compacta formation, Vascular marrow and some replacement of osteogenic tissue, High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>G$^2$</td>
<td></td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Very large amount of bone formation, More spongy bone formation than trabecular growth, Moderate degree of resorption, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>T</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Very large amount of bone formation, More spongy bone formation than trabecular growth, Low degree of lymphoid cell infiltration, Much marrow replaced by osteogenic tissue</td>
</tr>
<tr>
<td>4</td>
<td>G</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Dentin fragment</td>
<td>Moderate amount of bone formation, largely in form of spongy bone, Moderate degree of lymphoid cell infiltration, Osteogenic tissue in marrow</td>
</tr>
</tbody>
</table>
TABLE 24 - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Re-</td>
<td>Very large amount of trabecular growth and spongy bone. Some resorption. Most marrow replaced with osteogenenic tissue. Low degree of lymphoid cell infiltration. Much compacta formation</td>
</tr>
<tr>
<td></td>
<td>remnant</td>
<td>fragment</td>
<td></td>
<td>sorbed</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>Host died.</td>
<td>Graft not recovered</td>
<td>Only about half of graft remains. Much trabecular growth and some spongy bone formation. Marrow mostly replaced by osteogenenic tissue. Moderate degree of lymphoid cell infiltration</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Re-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>remnant</td>
<td>fragment</td>
<td></td>
<td>sorbed</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>Dentin</td>
<td>Dentin</td>
<td>++ No roots,</td>
<td>Much resorption and dense connective tissue replacement. Moderate amount of new bone formation, primarily spongy bone. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td>remnant</td>
<td>fragment</td>
<td></td>
<td>No osteo-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dentin</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Re-</td>
<td>Small amount of resorption. More spongy bone formation than trabecular growth. Much marrow replaced by osteogenenic tissue. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td>remnant</td>
<td>fragment</td>
<td></td>
<td>sorbed</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>Graft resorbed before time of recovery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[1\] Experimentals: 2 mg/100 gm body weight/day beginning at time of grafting and continued until recovery at 15 days.

\[2\] Controls: an equivalent volume of vehicle/100 gm body weight/day beginning at time of grafting and continued until recovery at 15 days.

\[3\] For symbols employed, see footnote, table 6.
### TABLE 25

**EXPERIMENT XIA**

Neonatal Hamster Half-Mandible Transplants in Ear of Imuran Treated Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Dentin remnant</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Some resorption. Much bone formation, trabecular growth and spongy bone formation. Most marrow replaced with osteogenic tissue. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>C&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Almost all bone necrotic. Small amount of bone formation. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>T</td>
<td>Dentin remnant</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>More trabecular growth than spongy bone formation. Hollow centrally. Some compacta. Some resorption. Lymphoid cell infiltration almost absent</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin fragment</td>
<td>Resorbed</td>
<td>Very little resorption and much bone formation both as trabecular growth and spongy bone. Much marrow replaced by osteogenic tissue. Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>T</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Small amount bone formation and hollow centrally. Vascular marrow. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>Animal</td>
<td>Treatment</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin remnants</td>
<td>+ No roots.</td>
<td>Much resorption and dense connective tissue replacement. Much necrotic bone. Most marrow replaced by dense connective tissue. Very high degree of lymphoid cell infiltration.</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin remnants</td>
<td>- Resorbed</td>
<td>Moderate amount of bone resorption and some necrotic bone. Moderate degree of trabecular growth. Marrow replaced by dense connective tissue. Moderate degree of lymphoid cell infiltration.</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin remnants</td>
<td>- Resorbed</td>
<td>Much resorption and dense connective tissue replacement. Small amount of bone formation, Marrow mostly replaced by dense connective tissue. Very high degree of lymphoid cell infiltration.</td>
</tr>
<tr>
<td>Animal</td>
<td>Treatment</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>11</td>
<td>T</td>
<td>Dentin remnant</td>
<td>Re- sorbed</td>
<td>++ No roots, No osteodentin</td>
<td>Very large amount of trabecular growth, Low degree of resorption, Compacta formation, Much vascular marrow, but some replacement by osteogenic tissue, Low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>12</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Re- sorbed</td>
<td>Much resorption, necrotic bone and dense connective tissue replacement, Small amount of bone formation, High degree of lymphoid cell infiltration, Marrow replaced by dense connective tissue</td>
</tr>
<tr>
<td>13</td>
<td>T</td>
<td>Dentin remnant</td>
<td>Dentin fragment</td>
<td>++ No roots, No osteodentin</td>
<td>Very large amount of trabecular growth, compacta and spongy bone formation, Low degree of resorption, Vascular marrow, Absence of lymphoid cell infiltration</td>
</tr>
<tr>
<td>14</td>
<td>C</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Re- sorbed</td>
<td>Large amount of resorption and dense connective tissue replacement of bone and marrow, Moderate amount of spongy bone formation, Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>15</td>
<td>T</td>
<td>Dentin remnant</td>
<td>Dentin fragments</td>
<td>Re- sorbed</td>
<td>Large amount of spongy bone formation and some trabecular growth and compacta, Moderate degree of resorption and replacement of marrow with osteogenic tissue, Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>Animal</td>
<td>Treatment</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>16</td>
<td>C</td>
<td>- Dentin remnant</td>
<td>- Dentin fragments</td>
<td>- Resorbed</td>
<td>Large amount of resorption and dense connective tissue replacement of bone and marrow. Low degree of bone formation, High degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

1. Experimentals: 5 mg/100 gm body weight/day beginning at time of grafting and continued until recovery at 15 days.

2. Controls: equivalent volume of vehicle/100 gm body weight/day beginning at time of grafting and continued until recovery at 15 days.

3. For symbols employed, see footnote, table 6.
## TABLE 26

**EXPERIMENT XIB**

Neonatal Hamster Half-Mandible Transplants in Ear of Imuran Treated Adults

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-3 Dentin - Dentin fragments</td>
<td>- Re- sorbed</td>
<td>Some trabecular growth. Moderate degree of resorption. Most marrow replaced by dense connective tissue. High degree of lymphoid cell infiltration</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>C&lt;sup&gt;2&lt;/sup&gt;</td>
<td>- Dentin remnant - Dentin fragments</td>
<td>- Re- sorbed</td>
<td>Large degree of resorption and much non-viable and necrotic bone. Very small degree of peripheral bone formation. High degree of lymphoid cell infiltration</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>T</td>
<td>- Dentin remnant - Dentin fragments</td>
<td>- Re- sorbed</td>
<td>Very large degree of trabecular growth and spongy bone formation. Vascular marrow but some replacement by dense connective tissue. Small degree of resorption. Moderate degree of lymphoid cell infiltration</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>- Dentin remnant - Dentin fragments</td>
<td>- Re- sorbed</td>
<td>Very large amount of resorption and dense connective tissue replacement of bone and marrow. Small degree of bone formation. Very high degree of lymphoid cell infiltration</td>
<td></td>
</tr>
<tr>
<td>Animal</td>
<td>Treatment</td>
<td>Incisor</td>
<td>First molar</td>
<td>Second molar</td>
<td>Remainder of graft</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>5</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin - Re-</td>
<td>Re-</td>
<td>Very large degree of trabecular growth and spongy bone formation. Very low degree of resorption and lymphoid cell infiltration. Some compacta. Mostly vascular marrow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td>Dentin remnant</td>
<td>sorbed</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>Dentin</td>
<td>Re- sorbed</td>
<td>Re- sorbed</td>
<td>Most of graft resorbed. Much of the remainder necrotic. Low degree of bone formation. Marrow replaced by dense connective tissue. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin fragments</td>
<td>+ Much growth and differentiation, No roots</td>
<td>Very large degree of trabecular growth and spongy bone formation. Vascular marrow, but some replacement by osteogenic tissue. Some resorption. Compacta formation. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>Dentin</td>
<td>Dentin fragment</td>
<td>Re- sorbed</td>
<td>Much resorption but also trabecular growth and spongy bone formation. Much dense connective tissue replacement. Some vascular marrow. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin fragment</td>
<td>Re- sorbed</td>
<td>Very large degree of resorption and dense connective tissue replacement. Some trabecular growth. High degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>remnant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 26 - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>C</td>
<td>- Dentin remnant</td>
<td>- Dentin fragments</td>
<td>- Resorbed</td>
<td>Some resorption and some bone formation. Vascular marrow, but some replacement by loose connective tissue. Moderate degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>

$^1$ Experimental: 2 mg/100 gm body weight/day beginning at time of grafting and continued until recovery at 15 days.

$^2$ Controls: equivalent volume of vehicle/100 gm body weight/day beginning at time of grafting and continued until recovery at 15 days.

$^3$ For symbols employed, see footnote, table 6.
<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>-3 Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Partly resorbed. Spongy bone formation. Marrow mostly replaced with osteogenic tissue. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>2</td>
<td>C&lt;sup&gt;2&lt;/sup&gt;</td>
<td>- Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>All necrotic, non-viable bone and cellular debris. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>3</td>
<td>T</td>
<td>- Dentin remnant</td>
<td>Dentin fragment</td>
<td>Resorbed</td>
<td>Much resorption. Some spongy bone formation. Vascular marrow but some replacement by osteogenic tissue. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>- Dentin remnant</td>
<td>Dentin fragments</td>
<td>Resorbed</td>
<td>Much necrotic bone. Large degree of resorption. Only a small area of viable bone. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>5</td>
<td>T</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Mostly resorbed. Large hollow ossicle remains. Very low degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>- Dentin remnant</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Mostly necrotic bone. Much resorption. Marrow replaced by dense connective tissue. Partly encysted. Only small amount of bone viable. High degree of lymphoid cell infiltration</td>
</tr>
</tbody>
</table>
TABLE 27 - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Resorbed</td>
<td>Small amount of viable bone, Remainder of graft encysted and non-viable. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>Dentin</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Most of graft tissues necrotic. Small area of viable bone in form of hollow ossicle. Most of marrow replaced with dense connective tissue. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>9</td>
<td>T</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Resorbed</td>
<td>Large amount of trabecular growth and spongy bone formation. Low degree of osteolysis. Low degree of dentin lymphoid cell infiltration</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>Dentin</td>
<td>Dentin</td>
<td>Resorbed</td>
<td>Mostly encysted and necrotic. A few small viable ossicles. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>11</td>
<td>T</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Only one small viable ossicle. Some encysted bone. Vascular marrow. Moderate degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>12</td>
<td>T</td>
<td>Dentin</td>
<td>Resorbed</td>
<td>Resorbed</td>
<td>Mostly resorbed and only small amount of viable bone. Some necrotic bone. Very high degree of lymphoid cell infiltration</td>
</tr>
<tr>
<td>13</td>
<td>T</td>
<td>Resorbed</td>
<td>Before recovery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 27 - Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>Treatment</th>
<th>Incisor</th>
<th>First molar</th>
<th>Second molar</th>
<th>Remainder of graft</th>
</tr>
</thead>
</table>

1. Experimentals: 5 mg/100 gm body weight/day beginning at time of grafting and continued until recovery at 15 days.

2. Controls: equivalent volume of vehicle/100 gm body weight/day beginning at time of grafting and continued until recovery at 15 days.

3. For symbols employed, see footnote, table 6.
LIST OF ABBREVIATIONS

A - Ameloblasts
Ab - Alveolar bone
Bv - Blood vessel
Cy - Cyst
D - Dentin
Dp - Dental papilla
Dl - Dental lamina
E - Enamel
Es - Enamel space
Hs - Hertwig's sheath
Ie - Inner enamel epithelium
O - Odontoblasts
Od - Osteodentin
Oe - Outer enamel epithelium
P - Pulp
Pd - Pre-dentin
Pe - Pre-enamel
Pl - Periodontal ligament
Sc - Squamous cell cords
Si - Stratum intermedium
Sr - Stellate reticulum

EXPLANATION OF FIGURES

1. A sagittal section of a first and second mandibular molar in the mandible of a control neonatal (8 hr.) hamster to show the relative size and stage of development at time of transplantation. First molar is on the left (X62).

2. A sagittal section of a first mandibular molar from a control neonatal (8 hr.) hamster to show the stage of development at time of transplantation. This molar shows differentiated ameloblasts and odontoblasts and some dentin formation. The dental papilla is also shown (X101).
3 A sagittal section of a control second mandibular molar, from a normal neonatal (8 hr.) hamster, to show the stage of development at time of transplantation. The molar shows an inner and outer enamel epithelium, the latter enclosing the stellate reticulum. The dental papilla is also shown. Odontoblasts have begun to differentiate (X155).

4 A sagittal section through the crown of a control first mandibular molar in the mandible from a normal 15 day old hamster, to show degree of development. The molar shows dentin, pre-dentin, blood vessels, pulp, odontoblasts, periodontal ligament and alveolar bone. The enamel was lost during decalcification (X62).
5 A sagittal section through the roots of the intact first mandibular molar shown in Figure 4 to show stage of normal root development at 15 days. The roots show dentin, pre-dentin, odontoblasts, pulp, periodontal ligament, and alveolar bone (x62).

6 A sagittal section through the crown of a second mandibular molar from an intact mandible, from a control 15 day old hamster, to show stage of normal development at 15 days. Note ameloblasts, enamel space, dentin, pre-dentin, odontoblasts, pulp, blood vessels, periodontal ligament and alveolar bone. Note that the molar is in the process of erupting (x62).
PLATE 4
EXPLANATION OF FIGURES

7 A sagittal section through the roots of the intact, control second mandibular molar shown in Figure 6 to show stage of normal root development at 15 days. The roots show alveolar bone, periodontal ligament, dentin, odontoblasts and pulp (X62).

8 A sagittal section through the crown of a surviving, 15 day old graft of a first mandibular molar, from a neonatal hamster subcutaneously transplanted in the ear (Experiment IA; No. 1). Note degeneration of ameloblasts into squamous cell cords, osteodentin, dentin, pre-dentin, odontoblasts and blood vessels (X155).
A section through the root area of the surviving first mandibular molar in the transplant shown in Figure 8. This part of the tooth shows odontoblasts, pre-dentin, dentin, osteodentin, and pulp (X155).

A section through part of the crown and roots of a surviving first mandibular molar, from a 15 day old graft of a first mandibular molar, from a neonatal hamster, transplanted subcutaneously in the ear (Experiment IA; No. 2). Note squamous cell cords, osteodentin, dentin, pre-dentin, odontoblasts, pulp and numerous blood vessels. A cyst and some alveolar bone is also seen (X61).
PLATE 6

EXPLANATION OF FIGURES

11 A section through the crown and part of the root of the first mandibular molar transplant shown in Figure 10. Note squamous cell cords, osteodentin, dentin, pre-dentin, odontoblasts, blood vessels and pulp (X155).

12 A sagittal section through the crown of a 15 day old graft of a first mandibular molar, from a neonatal hamster, transplanted subcutaneously in the ear (Experiment IA; No. 3). The molar shows squamous cell cords, ameloblasts, osteodentin, dentin, pre-dentin, odontoblasts, pulp, blood vessels and cysts. The pulp of one cusp was still viable (X155).
PLATE 7

EXPLANATION OF FIGURES

13 A sagittal section through the crown and root of a 15 day old graft of a first mandibular molar, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IA; No. 4). Note alveolar bone, periodontal ligament, dentin, ameloblasts, enamel space, osteodentin, pre-dentin, odontoblasts, pulp, blood vessels and squamous cell cords; also the extreme deviation that had occurred in the root (X62).

14 A section through the crown of the molar shown in Figure 13, showing ameloblasts, enamel space, squamous cell cords, dentin, pre-dentin, odontoblasts, pulp, blood vessels, and cyst (X62).
PLATE 8

EXPLANATION OF FIGURES

15 A section through the root and part of the crown of a 15 day old graft of a first mandibular molar, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment LA; No. 5). Note formation of odontoblasts, osteodentin, dentin, alveolar bone and pulp (X101).

16 A section through the molar shown in Figure 15. Note dentin, predentin, odontoblasts, pulp and osteodentin. This graft shows that osteoid had formed between the tooth and the ear cartilage of the host (X101).
A section through the crown of a 15 day old graft of a first mandibular molar, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IA; No. 6). Note presence of squamous cell cords, osteodentin, dentin, pre-dentin, odontoblasts, pulp, blood vessels, and alveolar bone (X62).

A section through the crown of the molar shown in Figure 17. This part of the molar reveals formation of squamous cell cords, osteodentin, dentin, pre-dentin, cysts, odontoblasts, pulp and blood vessels (X62).
PLATE 10
EXPLANATION OF FIGURES

19 A section through the crown and one root of a 15 day old graft of a first mandibular molar, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IA; No. 7). The molar shows squamous cell cords, osteodentin, dentin, pre-dentin, pulp and blood vessels (x101).

20 A section through the crown of a 15 day old graft of a first mandibular molar, in a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IB; No. 1). Note shortened ameloblasts adjacent an enamel space, dentin, pre-dentin, alveolar bone, pulp and odontoblasts (x101).
PLATE 11
EXPLANATION OF FIGURES

21 A sagittal section through a surviving second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IB; No. 2). Note development of outer enamel epithelium, stellate reticulum, ameloblasts differentiating odontoblasts, dental papilla and alveolar bone (X201).

22 A section through the crown of a surviving first mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IB; No. 3). Note presence of ameloblasts, enamel space, osteodentin, dentin, pre-dentin, odontoblasts, pulp, blood vessels and squamous cell cords (X155).
PLATE 12

EXPLANATION OF FIGURES

23 A sagittal section through the crown of a second mandibular molar from the half-mandible transplant shown in Figure 22. Note outer enamel epithelium, stellate reticulum, stratum intermedium, ameloblasts, dentin, odontoblasts, pulp and alveolar bone (X201).

24 A section through part of the root and crown of a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IB; No. 4). Note development of alveolar bone, ameloblasts, an enamel space, pre-enamel, dentin, pre-dentin, odontoblasts, pulp, Hertwig's sheath and blood vessels (X155).
PLATE 13

EXPLANATION OF FIGURES

25 A section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment 15; No. 5). Note alveolar bone, odontoblasts, pre-dentin, dentin, enamel, pre-enamel, ameloblasts, pulp, and stellate reticulum (X101).

26 A section through the molar shown in Figure 25 showing the dental lamina to be continuous with the squamous epithelium of a cyst. Also note presence of alveolar bone, pulp, odontoblasts, and ameloblasts (X62).
PLATE 14

EXPLANATION OF FIGURES

27 A sagittal section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IB; No. 6). Note development of alveolar bone, stellate reticulum, stratum intermedium, ameloblasts, dentin, odontoblasts, and pulp (X101).

28 A sagittal section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IB; No. 7). Note development of alveolar bone, blood vessels, pulp, odontoblasts, pre-dentin, dentin, enamel, ameloblasts and stellate reticulum (X101).
PLATE 15
EXPLANATION OF FIGURES

29 A sagittal section through a second molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IC; No. 1). This molar shows some degeneration of ameloblasts, differentiating odontoblasts, pulp, stellate reticulum, outer enamel epithelium, dental lamina and alveolar bone (X155).

30 A sagittal section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment IC; No. 2). This molar shows considerable development of enamel, and some degeneration of ameloblasts. Also shown are dentin, odontoblasts, pulp, cysts, Hertwig’s sheath and alveolar bone (X155).
PLATE 16

EXPLANATION OF FIGURES

31 A section through the crown of a surviving first mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment ID; No. 3). Note squamous cell cords, ameloblasts, osteodentin, dentin, odontoblasts, blood vessels and alveolar bone (X155).

32 A section through a second mandibular molar from a 10 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment ID; No. 1). This molar shows alveolar bone, outer enamel epithelium and a dental papilla (X201).
PLATE 17

EXPLANATION OF FIGURES

33 A section through a second mandibular molar from a 10 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear (Experiment II; No. 2). Note dental lamina, outer enamel epithelium, stellate reticulum, ameloblasts, odontoblasts undergoing differentiation, the dental papilla and alveolar bone (X201).

34 A section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, from which most of the incisor had been excised before subcutaneous transplanation in the ear (Experiment II; No. 1). Note development of osteodentin, dentin, odontoblasts and alveolar bone (X155).
PLATE 18
EXPLANATION OF FIGURES

35 A section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, from which most of the incisor had been excised before subcutaneous transplantation in the ear (Experiment IE; No. 2). Note the development of osteodentin, dentin, odontoblasts, blood vessels and alveolar bone (X101).

36 A sagittal section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, from which most of the incisor had been excised before subcutaneous transplantation in the ear (Experiment IE; No. 3). Note that the dental lamina is continuous with the epithelium of an adjacent cyst. The tooth also reveals an outer enamel epithelium, stellate reticulum, odontoblasts, pulp, dentin, blood vessels and alveolar bone (X101).
PLATE 19

EXPLANATION OF FIGURES

37 A sagittal section through a second mandibular molar from a 15 day old, subcutaneous transplant of molars and adjacent mandible, from a neonatal hamster, in the ear (Experiment IF; No. 1). This molar shows an adjacent cyst, stellate reticulum, ameloblasts, enamel, dentin, odontoblasts, pulp, blood vessels, Hertwig’s sheath and alveolar bone (X101).

38 A sagittal section through a second mandibular molar from a 15 day old, subcutaneous transplant of molars and adjacent mandible, from a neonatal hamster, in the ear (Experiment IF; No. 2). Note presence of ameloblasts, enamel, dentin, odontoblasts, pulp, Hertwig’s sheath and alveolar bone (X101).
PLATE 20
EXPLANATION OF FIGURES

39 A section through a second mandibular molar from a 15 day old, subcutaneous transplant of molars and adjacent mandible, from a neonatal hamster, in the ear (Experiment IF; No. 3). The molar shows a stellate reticulum, ameloblasts, dentin, odontoblasts, pulp and alveolar bone (X101).

40 A section through a second mandibular molar from a 15 day old, subcutaneous transplant of molars and adjacent mandible, from a neonatal hamster, in the ear (Experiment IF; No. 4). The molar shows the dental lamina to be continuous with the epithelium of an adjacent cyst. A bony alveolus is also seen. The tooth reveals a stellate reticulum, ameloblasts, dentin, odontoblasts and pulp (X101).
PLATE 21

EXPLANATION OF FIGURES

41 A sagittal section through a second mandibular molar from a 26 day old transplant of a half-mandible, from a neonatal hamster, in the lumen of the uterine horn (Experiment III; No. 1). Note that this molar had undergone degeneration and shows only a few remaining ameloblasts and odontoblasts. Considerable fibrous pre-enamel has formed. Dentin has also developed and most of the cells of the pulp have degenerated. Much inflammatory cell infiltration is shown around the tooth. An alveolus of partly necrotic bone is also seen (X101).

42 A section through part of the crown of a first mandibular molar from a 20 day old transplant of a half-mandible, from a neonatal hamster, in the kidney (Experiment V; No. 1). Note that the molar shows very short ameloblasts, an enamel space, thick dentin and alveolar bone. Odontoblasts line the pulp which discloses numerous large blood vessels (X101).
Another section through the crown of the molar shown in Figure 42. This part of the tooth shows a very vascular pulp and odontoblasts lining the pulp. An irregular layer of pre-dentin and a very thick layer of dentin are also seen. Note an enamel space containing some enamel and alveolar bone adjacent to a periodontal ligament (X101).

A section through a first mandibular molar in a 15 day old graft of a half-mandible, from a neonatal rat, subcutaneously transplanted in the ear (Experiment VII; No. 1). This molar shows osteodentin, dentin, odontoblasts, and alveolar bone (X101).
45 A section through part of the crown and root of a first mandibular molar from a 15 day old graft of a half-mandible, from a neonatal rat, subcutaneously transplanted in the ear (Experiment VII; No. 2). This tooth shows osteodentin, dentin and odontoblasts. A periodontal ligament is oriented between the alveolar bone and the root (X62).

46 A section through a second mandibular molar found in the same half-mandible transplant, shown in Figure 45. This molar shows osteodentin, dentin, odontoblasts, blood vessels and pulp. Some alveolar bone is seen about the tooth (X101).
PLATE 24
EXPLANATION OF FIGURES

47 A section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal rat, subcutaneously transplanted in the ear (Experiment VII; No. 3). Note short ameloblasts, a thin layer of enamel, a thick layer of dentin and pre-dentin. Odontoblasts are seen adjacent to the pre-dentin. Some alveolar bone is seen (X101).

48 A section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal rat, subcutaneously transplanted in the ear (Experiment VII; No. 4). This molar shows osteodentin, a fibrous pulp, some odontoblasts and a small amount of alveolar bone. Inflammatory cells and fibrous connective tissue are shown about the molar and within the pulp. Some dentin has also formed (X101).
PLATE 25
EXPLANATION OF FIGURES

49 A section through a first mandibular molar from a 15 day old graft of a half-mandible, from a neonatal rat, subcutaneously transplanted in the ear (Experiment VII; No. 5). Note fibrous pulp and some odontoblasts. Some pre-dentin and dentin and much osteodentin have formed (X101).

50 A section through a second mandibular molar from the mandible graft shown in Figure 49. This molar shows some ameloblasts and a small amount of enamel. Note dentin and irregularly formed pre-dentin. Osteodentin has formed and odontoblasts line most of the pulp (X155).
PLATE 26
EXPLANATION OF FIGURES

51 A section through a first mandibular molar from a 15 day old graft of a half-mandible, from a neonatal rat, transplanted in the kidney (Experiment VIII; No. 1). A large amount of osteodentin has formed and some odontoblasts are shown in the pulp adjacent to some dentin. The molar is located adjacent to a cyst and some connective tissue, arranged in the manner of a periodontal ligament, is seen adjacent to the alveolar bone (X101).

52 A section through a very distorted root of the molar shown in Figure 51. Odontoblasts are seen in the vascular pulp and a large amount of osteodentin has formed. Some tubular dentin and pre-dentin are also seen. A bony alveolus has also formed (X101).
A possible second mandibular molar found in the transplant shown in Figure 51. This "tooth" could have been part of a root which had broken away and developed independently. Note the presence of a stratum intermedium, tall ameloblasts, enamel, dentin, pre-dentin, odontoblasts, pulp and some alveolar bone (X10).

A section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the back of a hamster having received a daily dosage of 6-MP at 10 mg/100 gm body weight (Experiment IXA; No. 1). Note a vascular stellate reticulum, ameloblasts revealing some degeneration, dentin, and a pulp showing blood vessels. Some alveolar bone is seen adjacent to the tooth (X20).
PLATE 28
EXPLANATION OF FIGURES

55 A sagittal section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received a daily dosage of 6-MP at 5 mg/100 gm body weight (Experiment XB; No. 5). Development of the molar has not progressed far beyond the stage at transplantation. The molar is located adjacent to a cyst and shows an outer enamel epithelium and ameloblasts. Odontoblasts in the papilla have undergone differentiation (X201).

56 A section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received a daily dosage of 6-MP at 5 mg/100 gm body weight (Experiment XB; No. 13). This molar reveals a very small degree of growth and development. The dental lamina is continuous with the epithelium of an adjacent cyst, Ameloblasts are seen and odontoblasts in the papilla have been undergoing differentiation (X201).
A section through the crown of a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received a daily dosage of 6-MP at 5 mg/100 g body weight (Experiment XB; No. 17). Note enamel space on one side of the crown. Osteodentin, dentin, and some predentin are also seen and odontoblasts line part of the pulp (X101).

A section through the mandibular bone of a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received a daily dosage of 6-MP at 5 mg/100 g body weight (Experiment XB). Note viable bone showing much bone formation and trabecular growth. The osteogenic tissue in the intertrabecular spaces is viable and vascular. Lymphoid cell infiltration is minimal (X88).

Figure 57

Figure 58
PLATE 30
EXPLANATION OF FIGURES

59 A section of mandibular bone from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a control hamster having received daily injections of vehicle (Experiment XB). The bone is mostly necrotic and shows degeneration. Very little osteogenic tissue remains and inflammatory cell infiltration has occurred (X88).

60 A sagittal section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a vehicle treated control hamster (Experiment XC; No. 8). Note squamous cell cords, a stellate reticulum, ameloblasts, pulp and alveolar bone partly surrounding the molar (X101).
PLATE 31
EXPLANATION OF FIGURES

61 A section of mandibular bone from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received a daily dosage of 6-MP at 2 mg/100 gm body weight (Experiment X0). The bone is viable and vascular showing considerable bone formation mostly in the form of trabecular growth and some compacta formation (X88).

62 A section of mandibular bone from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a control hamster receiving daily injections of vehicle (Experiment X0). Note that the bone is viable but shows much less bone formation than was seen in the mandibular bone in the treated hamster shown in Figure 61 (X88).
A sagittal section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a vehicle treated control hamster (Experiment XIA; No. 6). This molar shows only a low degree of growth and development following transplantation. Ameloblasts have differentiated but odontoblasts have just begun to differentiate. Note inflammatory cell infiltration in tissues encasing the molar (X201).

A sagittal section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received Imuran in daily doses of 5 mg/100 gm body weight (Experiment XIA; No. 9). This molar showed considerable growth and differentiation following implantation and shows enamel formation. Ameloblasts are mostly intact though some degeneration is seen. Dentin and pre-dentin have formed while odontoblasts line the pulp. Alveolar bone is seen around the molar (X101).
PLATE 33

EXPLANATION OF FIGURES

65 A sagittal section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received Imuran in daily doses of 5 mg/100 gm body weight (Experiment XIA; No. 11). Note ameloblasts, dentin, odontoblasts, and pulp. The molar, for the greatest part, is encased within a bony alveolus (X101).

66 A section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received Imuran in daily doses of 5 mg/100 gm body weight (Experiment XIA; No. 13). Note ameloblasts, enamel, dentin, odontoblasts and pulp (X101).
A section of mandibular bone from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received Imuran in daily doses of 5 mg/100 gm body weight (Experiment XII). The bone is viable and vascular and shows considerable bone formation mostly in the form of trabecular growth. Note viable osteogenic tissue and low degree of dense connective tissue invasion into intertrabecular spaces (X88).

A section of mandibular bone from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a control hamster having received daily injections of vehicle (Experiment XIC). Considerable resorption of bone and dense connective tissue invasion has occurred. Note low degree of bone formation when compared with transplant shown in Figure 67 (X88).
PLATE 35
EXPLANATION OF FIGURES

69 A section through a part of the crown of a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received Imuran in daily doses of 2 mg/100 gm body weight (Experiment XII; No. 7). This molar shows ameloblasts, revealing some degeneration. Note formation of enamel, dentin and pre-dentin. Odontoblasts line most of the pulp (X101).

70 Another section through the crown of the molar shown in Figure 69. Ameloblasts are shown on parts of the crown but a small cyst is also seen in this area. Dentin and pre-dentin have formed and odontoblasts are seen in the pulp. Some alveolar bone is also seen (X101).
PLATE 36
EXPLANATION OF FIGURES

71 A section of mandibular bone from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a hamster having received Imuran in daily doses of 2 mg/100 gm body weight (Experiment XIC). Note vascular and viable bone showing considerable new bone formation in the form of trabecular growth. Only a low degree of resorption has occurred (X88).

72 A section of mandibular bone from a 15 day old graft of a half-mandible, from a neonatal hamster, subcutaneously transplanted in the ear in a control hamster having received daily injections of vehicle (Experiment XIC). Much resorption of transplanted bone has occurred accompanied by dense connective tissue invasion. Note low degree of bone formation when compared with the transplant shown in Figure 71 (X88).
PLATE 37

EXPLANATION OF FIGURES

73 A section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, transplanted in the cheek pouch of a hamster having received Imuran in daily doses of 5 mg/100 gm body weight (Experiment XII; No. 9). Note ameloblasts, small amount of dentin and some odontoblasts in the pulp (X101).

74 A section through a second mandibular molar from a 15 day old graft of a half-mandible, from a neonatal hamster, transplanted in the cheek pouch of a hamster having received Imuran in daily doses of 5 mg/100 gm body weight (Experiment XII; No. 14). Note vascular stellate reticulum, tall ameloblasts, enamel, dentin, pre-dentin, odontoblasts and pulp. The tooth is encased in a bony alveolus (X101).
PLATE 38
EXPLANATION OF FIGURES

75 A section of mandibular bone from a 15 day old graft of a half-mandible, from a neonatal hamster, transplanted in the cheek pouch of a hamster having received Imuran in daily doses of 5 mg/100 gm body weight (Experiment XII). Note high degree of spongy bone formation. Note that bone is both viable and vascular (X88).

76 A section of mandibular bone from a 15 day old graft of a half-mandible, from a neonatal hamster, transplanted in the cheek pouch of a control hamster having received daily injections of vehicle (Experiment XII). Note necrotic bone showing inflammatory cells and cellular debris in the intertrabecular spaces. The bone is mostly avascular and non-viable. The absence of bone formation is noticeable, particularly when compared with the bone seen in the transplant shown in Figure 75 (X88).
X. GLOSSARY

**Allograft** - A homograft, homologous graft, homoplastic graft, allogenic transplant. The donor is of the same species as the recipient, but has a different genotype. Allografts are transplants between members of random, outbred or between members of two different inbred strains.

**Antigen** - A substance which may react in a specific manner with appropriate tissues of an animal under the proper conditions and stimulate an immune response and antibody formation.

**Arthus Reaction** - A severe local sensitivity reaction elicited at the site of subcutaneous antigen injections in an animal already having specific precipitating antibody to the antigen.

**Autograft** - An autotransplant, autoplastic graft, autologous graft. The donor and recipient are the same individual. Such grafts do not undergo a rejection reaction under normal conditions.

**First-Set or Primary Allograft or Homograft Reaction** - Usually a tissue or organ transplanted to a nonsensitized animal. The graft, in the case of skin, will usually heal, establish circulation, then at about one week, the efferent or effector limb of the rejection response begins and the graft undergoes subsequent rejection. Depending on the genetic diversity between host and donor, the rejection response will either be delayed or shortened. Also, the size of the graft will determine the intensity of the rejection reaction. Generally, a larger graft will be rejected more rapidly until a limit is reached whereby the rejection time is extended through a tendency for production of tolerance in the host.

**Graft Versus Host Reaction** - An immune response of grafted cells against the host. It is similar to immunological graft rejection, but in this instance the graft rejects the host and in many instances causes severe damage and death of the host (i.e., runt disease).

**Heterograft** - See Xenograft.

**Heterotopic Grafts** - Grafts in unnatural anatomical positions such as thymus, bone or skin transplanted beneath the skin, in the cheek pouch or in the anterior eye chamber.

**Histocompatibility Antigens** - Antigens coded for histocompatibility genes which determine the compatibility of grafted tissues and organs. The immune response to histocompatibility seems to be cumulative to a limit. The strength of the reaction correlates with the genetic and antigenic diversity between host and donor.
Histocompatibility Locus - Certain gene loci which determine the transplantation compatibility of donor and recipient tissues. These loci have been found to be primarily concerned with transplantation immunity. It is believed that they are segments of a chromosome rather than a single locus.

Histocompatible - Where host and donor tissues are immunologically similar. The immunological identity of the tissues is sufficient to permit successful homografting without rejection.

Immune Response or Reaction - A specific response which results in an immunity. The total response includes an afferent phase during which responsive cells are primed by antigen, a central response during which antibodies are formed, and an efferent or effector response, in which immunity is effected by antibodies or immune cells.

Immunocompetent Cells - Antigen sensitive cells which in grafting, are believed to be primarily lymphocytes. However, in other circumstances they can be any cell which can be stimulated by antigen to form antibodies or give rise to cells which form antibodies.

Immunological Tolerance - A situation in which the host fails to produce an antibody response, either cellular or humoral in nature, to a potential antigen following exposure. Included are the conditions of immunological unresponsiveness and immunological suppression. A genetic tolerance is an immunological tolerance which results from a genetic identity such as occurs in grafts between identical twins, highly inbred animals and tolerance in an F1 generation hybrid to parental strain tissue grafts. A self-tolerance is a tolerance to self-antigens as found in autografts.

Immunologically Incompetent - In case of transplants, the host is incapable of reacting against a graft containing certain antigens or is tolerant to that graft. Tolerance or incompetence ranges in breadth and depends on the means of induction.

Imunity - The state of being able to resist and/or overcome agents or influences. In grafting, it is an immunity against the antigens carried in the transplants.

Isograft - Syngenic, isotransplant, isogenic graft, isologous graft. The donor is of the same genotype as the recipient. Isografts are grafts between animals of the same highly inbred strain.

Isotopic Grafts - Those grafts which are in an exact, normal, anatomical topographic location.

Large Pyroninophilic Cell - A cell which stains with pyronin tain. Cells active in antibody synthesis and rich in RNA. Such cells appear in large numbers in local lymph nodes and in lymphoid tissue stimulated by antigen and can appear within two to three days after grafting. It is
believed that the pyroninophilic cells are the source of the small lymphocytes effective during transplant rejection.

**Orthotopic Grafts** - Grafts transplanted into an anatomically proper environment such as skin to a gap in skin or bone to a defect in bone but not necessarily to the exact corresponding location from which they were obtained.

**Second-Set Graft Reaction** - Accelerated rejection of a second graft in a host, usually from the same donor, due to a specific immunity developed as the result of a primary graft. A graft in an animal previously sensitized against the antigens of that graft. These are rejected more rapidly and earlier than a primary graft. The rate or intensity of the rejection reaction seems to be dependent on the strength of the immunity existing at the time of transplantation and has occurred as early as two to three days after grafting.

**Sensitive** - A state of increased capacity to respond specifically to a graft.

**Sensitize** - The process of increasing the specific reactivity of a subject or cell to an agent. The term is commonly employed to designate the process of increasing the reactivity due to specific antibodies or immune cells.

**White Graft Reaction** - A reaction to a tissue graft in which the graft neither heals nor becomes vascularized, but instead is quickly rejected. This type of rejection usually occurs when the implanted tissue is a second-set graft and is the consequence of the host having been sensitized against the antigens contained in the graft.

**Xenograft** - Heterograft, heterotransplant, heterologous transplant or xenoplastic graft. A graft transplanted to a recipient of a different species from that of the tissue donor.
APPROVAL SHEET

The dissertation submitted by Frank Maximilian Kneussl has been read and approved by five members of the Faculty of the Graduate School.

The final copies have been examined by the director of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the dissertation is now given final approval with reference to content, form and mechanical accuracy.

The dissertation is therefore accepted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

May 24, 1971

Date

Signature of Adviser