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Early Carcinomatous changes in the Cervix Uteri

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I N T R O D U C T I O N

Acknowledgements

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I am grateful to Dr. F. A. McJunkin, professor of the Dept. of Pathology for his supervision, and suggestions during the course of the study.

Purpose of the Study

The object of this work was to determine whether or not there were any histologic changes in the cervices that could be used to determine the presence of cancer in the earliest stages, and to differentiate them from chronic inflammatory changes.

Outline

LITERATURE

METHODS AND MATERIALS

RESULTS

DISCUSSION

CONCLUSION

L I T E R A T U R E

The question of early diagnosis of cancer has always been of great importance, because to obtain good therapeutic results in the treatment of carcinoma, the lesion must be recognized in its incipiency. Palmer Findley (1) stated that in the United States in 1924 approximately 13,000 women died of cancer of the uterus. James E. Davis (2) studied 1200 cervical biopsies, and found 186 malignancies: although he did not state whether or not the malignant changes were in their early stages or whether they were for advanced. Frederick E. Neef (3) emphasizes the predilic-tion which genital cancer shows for the cervical portion of the uterus, and discusses the biophysical factors concerned in the clinical course of carcinoma of the uterin cervix. G. L. Moench (4) describes various lesions which are commonly met in the study of cervical pathology. He stresses the pathology of inflammatory reaction and their stages of healing.

William P. Graves (5) in an article, "How Cancer Starts in the Cervix Uteri", shows some of the important features which in this paper are considered as signs of early carcinoma. Albert C. Broders (6) has written on a subject which is considered of importance in connection with this study. He describes lesions which he terms as carcinoma situ, in which the malignant epithelial cells have not migrated beyond the juncture of the epithelium anc connective tissue

or the so called basement membrane.

Walter Schiller (7) in a comprehensive study of cancer of the uterus brings out many features which he considers as pre-cancerous manifestations. He describes the early changes in the cells, and in the underlying connective tissue.

M E T H O D

The specimen were obtained by amputation of the cervices according to the method of Sturmdorf, or slight modification depending on the pathology present at the time of the operation.

The cervices were fixed in toto in formaldelhyde. The blocks of tissue were cut out in the axis of the cervical canal so that the microscopic sections would include the epithilial transitions at various places. The blocks were about 3 mm. thick, and most of the muscle was cut away so as to faciltate sectioning. Skip serial sections were employed in one of two ways; from some blocks fifteen sections were mounted from the first, middle and last portions; others were cut into paraffin ribbons and every twentieth section mounted. All blocks were imbedded in paraffin, and stained with hematoxylin and eosin.

In the preliminary study all the sections were examined, and classified as to whether or not the lesions were inflammatory or whether there were any evidences of malignant changes. Those that showed malignant changes, or were suspicious, were studied again and the changes were noted in detail. The emphasis being placed on

the nuclear changes of the cells, mitotic activity, size of the cells in relation to the adjacent cells, and the reaction of the underlying stroma.

R E S U L T S

It was possible to study the changes in these sections from their point of origin, character and extent of the lesion because the blocks were cut in serial section which is not possible in single sections. Seventy-five cervices were examined, fifteen showed changes which were significant and their findings were described according to the following method.

NUCLEAR CHANGES- The nuclei, as compared with those of the adjacent normal cells, take on a deeper stain, which gives the area in general a darker appearance. The nuclei are also increased in size and the relative number of mitoses is increased.

CELLULAR CHANGES-In these areas the cells are usually larger and taller than the surrounding normal cells. This increase in size of the cells causes a thickening of the epithelial layer, but there is no evidence of breaking through the basement membrande or invasion of the underlying stroma.

STROMA REACTION- In some of these sections there were definite evidences of lymphocytic infiltrations in the stroma beneath the cells which showed altered characteristics, but which could not be explained microscopically as due to an inflammatory reaction. This is explained by some workers as being due to the reaction of

the stroma to the altered cells although microscopically they show slight changes, yet their protoplastic constituents are foreign to the host, and therefore cause the reaction.

S U M M A R Y

From this study it is readily understood how it is possible to miss some of the early neoplastic changes of the cervix if only one or two sections are made from the biopsy specimen. In practically all of these sections that show early cancerous changes the areas were limited and seen only in a group of the sections. The cervix is one of the sites of the body in which this development of carcinoma is most frequent. Many reasons are given for this; such as exposure to chronic irritation, displacement of the epithelium from lacerations, and that in the cervix there is a transition of the squamous to the glandular epithelium.

Carcinoma of the cervix can be completely radicated if the cervix of every woman who has reached menapause is removed as to destroy the epithelium from the portio and as high up into the cervical canal as is possible with the cautery knife. The operation is negligible, yet the security from carcinoma is almost complete.

Fig 1. Point of transition of surface epithelium to an adjacent type with lymphocytic infiltration beneath

Fig. 2. Atypical surface epithelium with much lymphocytic infiltration beneath. At one marjin of the photograph is seen the heterotopic extension of epithelium into a laceration.

C O N C L U S I O N

1. Seventy-five cervices were sectioned serially and examined scrupulously for early neoplastic changes.
2. Early neoplastic changes were found in fifteen cervices.
3. A description of these findings are given.

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THE EFFECT OF LECITHIN ON RAT SARCOMA

by

L. A. Macaluso

I N T R O D U C T I O N

A. Acknowledgements

I am indebted to Dr. F. A. McJunkin for his initiation, criticism and advice throughout the entire experiment and wish to express my sincere appreciation and gratitude.

To Mr. L. M. Herdegen I am grateful for his preparation of the sections for the microscopic study of the tumors.

B. Purpose of the Problem

Several workers at various times have reported the inhibitory effect of lecithin of tumors and normal tissues. Recently J. W. Henry of the Department of Pathology reported that lecithin when injected into young rats caused a definite decrease in the mitotic count of the kidney tissue. The purpose of this work is to determine whether or not lecithin has any inhibitory effect on the mitosis, rate of growth and on the transplantability of rat sarcoma.

C. Outline

Literature

Methods and Materials

Part 1. History of the tumor

Part 2. Animals used.

Part 3. Preparation of the lecithin

Part 4. Methods of experiment

a. The effect of lecithin on the mitotic activity of rat sarcoma.

b. The effect of lecithin on the rate of growth of rat sarcoma.

c. The effect of lecithin on the transplantability of rat sarcoma.

Results

Conclusion

L I T E R A T U R E

The fact that there are in the body substances which accelerate and retard cellular proliferation has been demonstrated repeatedly. Robertson and Burnett (1) injected lecithin directly into tumors and found that there was some retardation in the growth of the tumors and they also noticed that the number of metastatic growths of the tumors were decreased. Henry (2) working with lecithin and normal rats found that the mitotic proliferation in the kidney of young rats was definitely decreased by the intraperitoneal injection of lecithin. Murphy and Sturm (3) demonstrated the retarding action on the growth of two transplantable carcinomas of mice by injections of extract of placenta and embryo skin; yet these extracts have no effect on sarcomas. In another article Murphy and Sturm (4) reported that extracts of dessicated homologous embryo and placenta decrease markedly the

rate of post-operative local recurrence after surgical removal of spontaneous cancer of mice. Robertson and Cutler (5) fed lecithin to female rats after they had litters and found that the growth of the suckling mice was retarded.

Methods and Materials

Part 1. History of the tumor.

The tumor used in these experiments was originally a spontaneous growth of the uterus of a rat used in the experimental laboratory, which has been transplanted into the subcutaneous tissues of rats, its growth is rapid and metastases are obtained in about 50 per cent of the rats. I found that in a series of one-hundred transplants the number of takes in rats that were thirty days or less of age was sixty per-cent. The number of takes decreases in older rats. Microscopically the tumor is a sarcoma. It shows a marked degree of anaplasia, the connective tissue is scanty.

Part 2. Animals used.

The rats used in these experiments were from our laboratory. Because of the fact that the number of takes decreased in older rats and for uniformity rats that were thirty days or slightly younger and which weighed approximately eighty grams were used.

Part 3. Preparation of the lecithin.

The lecithin used in these experiments was obtained from the Eastman Kodak Company. The lecithin was dissolved in warm water so that each cubic centimeter of the mixture contained fifty milligrams of lecithin.

Part 4. Method of procedure.

Experiment 1. In this experiment sixteen rats that had been transplanted with sarcoma in both groins and that showed definite evidence of growth of the transplants were used. At the time of the experiment the average size of the transplant was 1 X 0.5 cm. One of the transplants of each rat was removed for control. Immediately after the removal of the control tumor one-hundred and fifty milligrams of lecithin was injected into the peritoneal cavity, and the rats were placed in their cages. Twenty-four hours later the other transplant was removed. The transplants were fixed in Zenker's solution, imbedded in paraffin, sectioned and stained with haematoxylin and eosin. The number of mitotic figures in twenty high power fields were counted in each section, and compared with the controls.

Experiment 2. In order to obtain a gross idea of the experiments fifteen rats that had been successfully transplanted at the same time with the same tumor were used. When the tumors were about 1 X 0.5 cm. ten of the rats were given one-hundred-fifty mg. doses of lecithin intraperitoneally on alternate days for five doses. Five of the rats were kept for controls. The tumors of these rats were measured before the injections and after the injections and repeated on the sixth and twelvth days. The two greatest diameters of the tumor were measured through the skin at right angles.

Experiment 3. In this series of experiments the effect of lecithin on the number of takes was determined. Ten rats were used in each of the experiments.

a. Pieces of tumor from a rat which had been injected one-hundred-fifty mg. of lecithin on three alternate days were transplanted into normal rats. The last injection having been made twenty-four hours before the transplantation.

b. Similar transplants as in experiment (a) were made into ten rats that had received three intraperitoneal injections of one-hundred-fifty mg. of lecithin on alternate days, twenty-four hours after the last injection.

c. Ten rats that had received three intra-

peritoneal injections of one-hundred-fifty mg. of lecithin on alternate were transplanted with pieces of tumor twenty-four hurs after the last injection.

Experiment 4. Two rats were transplanted in both groins and after the transplants had shown definite growth one tumor from each rat was removed for control, and then both rats were given one-hundred-fifty mg. doses of lecithin intraperitoneally on alternate days for five doses and twenty-four hours after the last injection the tumors were removed. The control and tumors which were removed after the injection were sectioned and examined like the section of the tumors in experiment (1).

Results

Experiment 1. The number of mitotic figures in the control tumors in twenty high-power fields varied from a low of 4.5 to a high of 6.7. The number of mitotic figures in the twenty high power fields of the tumors of the animals that received one hundred and fifty milligrams of lecithin varied from 4.8 to 7. There were no apparent changes in the anaplastic reaction of the tissues.

Experiment 2. At the time when the injections were started the tumors of all the rats were approximately of the same size. The two greatest diameters

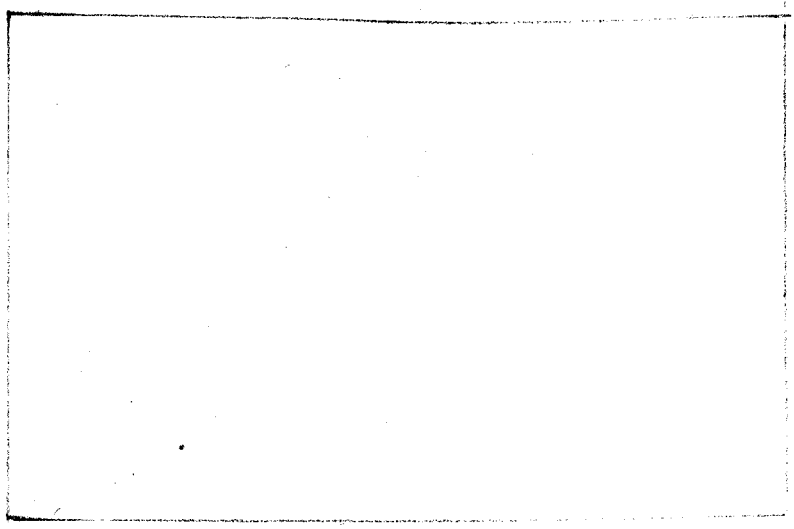

Fig. 1. Photomicrograph of high-power view of a rat sarcoma

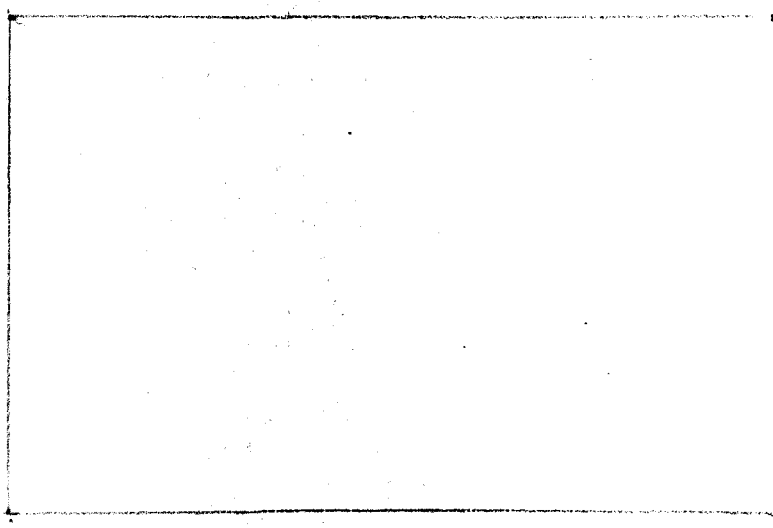

Fig. 2. Photomicrograph of rat sarcoma after the rat had received seven-hundred-fifty mg. of lecithin intraperitoneally. Notice the numerous mitotic figures and the anaplastic cells.

being one cm. and the other one-half of one cm. At the end of the injections the measurements of the tumors both the controls, and those in the injected rats had attained diameters of an average of three one one-half, and two and seventy-five cm. There was no gross evidence of retardation of growth of the tumors by the lecithin. The growth of the tumors on the sixth and twelvth days of the injected continued at the same rate.

Experiment 3.

a. In this experiment six of the transplants took. The transplant was taken from a rat that had received a total of four-hundred-fifty mg. of lecithin.

b. In this experiment in which the transplant was taken a rat that had received four-hundred-fifty mg. of lecithin and transplanted in rats that had received four-hundred-fifty mg. There were seven takes.

c. In this experiment normal tumor tissue was transplanted into rats that had received four-hundred-fifty mg. of lecithin, and the results showed that seven out of the transplants

Experiment 4. In this experiment the section of the tumors were compared microscopically before and after they had received seven-hundred and fifty mg. of lecithin. The average number of mitotic figures per high-power field in the control was 4.5 and that of the tumor after it had received the lecithin was 5.2.

Conclusion

1. Lecithin injected intraperitoneally in doses of one-hundred-fifty mg. did not decrease the mitotic activity of rat sarcoma.

2. There was no gross evidence of retardation of rat sarcoma by the intraperitoneal injection of lecithin.

3. The transplantability of rat sarcoma is not affected by injections of lecithin in the rat from which the tumor is to be transplanted from nor by injecting lecithin in the host, nor by injecting lecithin into the host, and into the animal before the tumor is removed for transplantation.

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