



1931

Studies on the Intestinal Absorption of Histamine.

Raphael William Albi
Loyola University Chicago

Follow this and additional works at: https://ecommons.luc.edu/luc_theses



Part of the [Physiology Commons](#)

Recommended Citation

Albi, Raphael William, "Studies on the Intestinal Absorption of Histamine. " (1931). *Master's Theses*. 602.
https://ecommons.luc.edu/luc_theses/602

This Thesis is brought to you for free and open access by the Theses and Dissertations at Loyola eCommons. It has been accepted for inclusion in Master's Theses by an authorized administrator of Loyola eCommons. For more information, please contact ecommons@luc.edu.



This work is licensed under a [Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 License](#).
Copyright © 1931 Raphael William Albi

LOYOLA UNIVERSITY

STUDIES ON THE INTESTINAL ABSORPTION
OF HISTAMINE . I . THE EFFECT OF REMOVAL OF THE
PARATHYROIDS . II . THE INFLUENCE OF THE RECTAL ADMINISTRATION
OF ETHER OIL MIXTURES

A THESIS

SUBMITTED IN PARTIAL FULFILMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE
IN LOYOLA UNIVERSITY

DEPARTMENT OF PHYSIOLOGY

BY

RAPHAEL WILLIAM ALBI

CHICAGO, ILLINOIS .

1931

VITA
OF THE AUTHOR

- 1903- Born Midway, British Columbia, Canada.
- 1910- Entered first grade, Webster, School,
Spokane, Washington.
- 1916- Graduated from Gonzaga Grammar School,
Spokane, Washington.
- 1920- Graduated from Gonzaga High School,
Spokane, Washington.
- 1926- Completed two years study at Gonzaga
University, College of Arts and Sciences,
Spokane, Washington.
- 1928- Completed two years study at Loyola Uni-
versity School of Medicine, Chicago, Ill-
inois. Received the degree of Bachelor
of Science in Medicine. Appointed fellow
in the department of physiology.
- 1929- Completed first quarter of required
work in department of physiology.
- 1930- Completed second quarter of required
work in department of physiology.

I

THE INFLUENCE OF PARATHYROID REMOVAL

(EXPERIMENTAL WORK DONE OCTOBER, 1928 TO
APRIL, 1929)

INTRODUCTION

It seems now to be generally conceded that parathyroid tetany results from the derangement of calcium metabolism which invariably follows removal of the parathyroid organs. Mac Callum and Voegtlin were the first to demonstrate the beneficial effects of calcium therapy in animals suffering from parathyroid tetany. With the development of improved methods for measuring the ionizable calcium of the blood, it was eventually shown that in parathyroid tetany, the blood plasma is quite deficient in calcium ions and that the onset of tetanic seizures is related to this deficiency. A respectable body of evidence still remains, however, tending to show that perhaps the calcium factor is not the only factor of importance, and that the condition of the digestive tract may bear some causal relation to the syndrome.

In 1911, Carlson and Jacobson (1) and in 1912, Carlson (2) described certain pathological changes in a high percentage of dogs which had died from the effects of parathyroid removal. Dragstedt and Peacock in 1923, (3) were able to

preserve the lives of parathyroidectomized dogs by feeding a diet of skim milk and lactose, while dogs kept on a meat diet failed to survive. The conclusion arrived at by these authors was that parathyroid tetany is caused by absorption from the intestine, of products of bacterial decomposition. The favorable influence of the milk and lactose diet was attributed to a change in the intestinal flora: the proteolytic organisms which predominate in the intestine, when the diet is rich in protein, being largely replaced by acidophilic organisms when the diet is high in carbohydrate. Such a change in the intestinal flora results in the diminished production of amines and other products of bacterial proteolysis, bringing about conditions in the digestive tract which Dragstedt and Peacock believed were effective in preventing ^{or} controlling tetany.

The work of Collip made more evident the importance of the calcium factor, and Salvesen, in 1923, (4) argued that Dragstedt and Peacock's dietary regime was effective solely because of the calcium contained in the milk. Analysis of Salvesen's results, however, reveal that his milk diet was less efficient than the milk lactose combination of Dragstedt. Of ten animals operated by the former, five died within eleven days. Of the remaining five, three received daily calcium injections, so that only two survivals can be definitely

referred to the beneficial influence of the milk alone.

Inouye in 1924 (5) confirmed the work of Dragstedt and Peacock and found moreover, that feeding galactose likewise prevented tetany. This worker ascribed to lactose and galactose a "specific" action in the control of tetany.

Luckhardt and Compere, in 1924 (6) using dogs in mild or latent tetany observed that violent attacks could be precipitated by the administration of drastic cathartics. Unoperated dogs were not so affected. Spadolini, 1924 (7), claims to have produced a syndrome similar to parathyroid tetany by treating the duodenal mucosa of otherwise normal dogs with a mixture of chloroform and paraffin oil in the proportion of 2:1. The chloroform injured the mucosa membrane, and according to Spadolini's interpretation, made it possible for toxic products of bacterial action to be absorbed.

These findings fit in with the observation that certain forms of enteritis favor the absorption of antigens through the intestine, and the consequent development of food sensitization (8). Mammoser and Boyd (9) working in this Laboratory, have found that treatment of the dog's intestinal mucosa with Spadolini's chloroform oil mixture affects markedly its permeability to histamine.

It seemed worth while to attempt to determine directly whether or not the intestine of the parathyroidectomized

dog shows a change in permeability to histamine. As a product of bacterial decomposition of proteins it is a fair representative of the class of substances held responsible for the hypothetical toxemias of intestinal origin; its powerful depressor effect gives a ready index of absorption. It does not pass through the intestinal mucosa of the normal dog in sufficient amounts to affect the blood pressure (10), but may do so when the mucosa has been exposed to such relatively mild agents as 0.4% HCL or 20% alcohol (9). If there is ulceration or inflammation in the intestine following loss of the parathyroids, the mucosa might very conceivably suffer changes in permeability similar to those produced by HCL or alcohol.

PROCEDURE

Aseptic thyro-parathyroidectomy was performed upon healthy dogs and after the animals had recovered from the effects of the operation and tetany had developed, they were kept for a period of six or seven days longer, no measures being taken to prevent or treat the tetany unless there was immediate danger to the animal's life. In other words, if an animal was so exhausted by previous attacks of tetany that it did not seem likely that it could with-

stand an incipient attack, a small dose of calcium lactate was given, usually intravenously, to help allay distressing symptoms. If, on the other hand, the animal appeared strong and capable of weathering succeeding attacks, no calcium was given.

The animal's post operative diet consisted of milk and water, until the day before experiment, when only water was given.

As anesthetic, a solution of sodium barbital, was used, given by stomach tube. The dose varied between .3 and .35 grams per kilo body weight of animal.

After the animal was under complete anesthesia, the abdomen was opened and a rubber catheter passed into the duodenum through an incision in the stomach wall just above the pylorus. The catheter had been cut off about four inches from the tip, and the two parts reunited by a short piece of glass tubing. The catheter was so arranged that this piece of glass tubing lay exactly in the pylorus, being fixed there by a ligature which included no important vessels nor nerves. The free end of the tube led to the outside, the abdominal wound being closed around it. Blood pressure was recorded from a carotid cannula in the usual manner.

After an animal had been prepared as described above, and the blood pressure tracing was at a stable level,

injections into the duodenum were made by means of the catheter. First, as a control, 20 c. c. of warm physiological NaCl solution was introduced, followed in a like manner in one-half to one hours, by a solution of histamine acid phosphate, (Burroughs, Wellcome Co.) in 20 c.c. of warm normal saline.

Upon all animals subjected to these experiments, autopsy was performed, immediately after death. In each case, death was brought about by clamping off the trachea after a suitable period had elapsed following the histamine injection.

Blood calcium determinations were made upon some of the animals. The method employed was that described by Tweedy and Koch (11).

RESULTS

The records include tracings on eight dogs, with post-mortem examinations on all of them. In addition there were two animals which were prepared for experiment but which died under anesthesia before histamine was administered. These also were subjected to post-mortem examination.

In seven tracings, the blood pressure level remained entirely unchanged for at least twenty minutes, in most cases

much longer. In one case there was a very gradual fall beginning ten minutes after the histamine was injected, and equivalent to eight mm. of mercury. It was quite different from the prompt abrupt fall found by Meakins and Harrington (12), and by Mammoser and Boyd (9).

In none of the animals was there observed any gross pathological change in the stomach or duodenum. The digestive tube of a parathyroidectomized dog differs in no way from that of a normal dog, apparently, if other conditions remain equal. A protocol of a typical experiment follows:

NUMBER 21 ♀

1-11-29.

Sex - ♀

Weight - 6.36 kg.

Blood Cd. - 12.40 mg. per 100 c.c. Plasma

Remarks:

Thyro-parathyroidectomy performed.

Ether anesthesia (preceded by atropine morphine injection).

1-12-29.

Apparently in good condition. Milk and water given.

Animal drank of each.

1-14-29.

Tetany observed. Milk and water not touched.

1-15-29.

Violent tetany. 3/4 pint of milk and 4 gm calcium.

lactate given after the attack. Stomach tube used.

1-16-29.

Mild tetany. Blood calcium 6.89 mg (average of three determinations)

Weight found to be 6.1 kg.

1-17-29.

8:30 A.M. - Animal in incipient tetany.

1.8 gm sodium barbital given by stomach tube.

11 A.M. - Anesthesia - preparation for experiment.

1.47 P.M. - 20 c.c. normal saline sol. into duodenum.

2.22 P.M. - 60 mg histamine acid phosphate in 20 c.c. warm normal saline into duodenum.

3.15 P.M. - No effect on blood pressure as yet.

Animal killed. Alimentary tract examined immediately.

Blood drawn while animal being prepared for experiment.

Blood calcium 6.22 mg 100 c.c. (average of two)

Autopsy Findings:-

No apparent abnormality in gastro-intestinal tract.

DISCUSSION

Apparently, there is no absorption of histamine from the intestine of the dog after removal of the parathyroid glands. As stated above none of the tracings, save one, showed any change in the blood pressure level within twenty minutes after introduction of the histamine into the in-

testinal tract. In the case cited as showing a fall in arterial pressure, the diminution was slight, and not typically that following histamine injection. It was most probably an effect of the prolonged anesthesia.

Regarding the reported findings of Carlson and others of gross pathological changes in the gastro-intestinal tract following parathyroidectomy, I might suggest that their observations were made incidentally upon dogs which were being used for other studies, and the tetany was allowed to run its full course. Presumably there was a considerable interval between the death and autopsy of at least some of their animals. I also have found erosion of the mucosa in the stomach and duodenum of operated animals, which had died in their cages and were autopsied from two to twelve hours later. The post-mortem action of gastric juice in this region, however, is well known and may produce similar changes in animal's dying from causes other than the loss of the parathyroids.

SUMMARY

Removal of the parathyroids, in dogs, does not apparently change the intestine's normal impermeability ^{to} histamine, nor are there evident, any gross pathological changes in the gastro-intestinal tract following this operation.

It is suggested that reported gastro-intestinal lesions,

found at autopsy in dogs which have been affected with parathyroid tetany, might be a result of post-mortem changes.

II

THE INFLUENCE OF THE RECTAL ADMINISTRATION OF ETHER-OIL MIXTURES

(EXPERIMENTAL WORK DONE JUNE TO AUGUST, 1930)

INTRODUCTION

In 1924 Koessler and Hanke, having found that histamine is normally present in the contents of the lower bowel, carried out extensive studies on its absorption. They found that 100 mg. may be put into any part of the alimentary tract of a normal dog without causing any apparent systemic effects, although .5 mg. of this substance injected intravenously causes an abrupt fall in arterial blood pressure. A reference to their work is made in part I, (10). Recently, Best and McHenry, (13), found an enzyme, particularly abundant in the intestine and kidney of the dog, which is capable of destroying the physiological activity of histamine. It seems likely, therefore, that inactivation of histamine by the intestinal mucosa may be a normal physiological process. If so, it is reasonable to suppose that damage to the epithelium might permit the absorption of unchanged histamine in sufficient quantities to cause systemic effects. That this supposition is very likely correct, has been shown by the studies of Mammoser and Boyd (9). As stated above, these workers

found that following exposure of the intestine to chloroform paraffin oil mixtures, 15% to 30% alcohol, carbon tetrachloride and .4% HCl, the permeability of the intestine to histamine, is markedly increased, as evidenced by the resulting fall of arterial blood pressure.

Ether might be expected to act on the intestine in somewhat the same manner as chloroform or alcohol. With regard to the rectal administration of ether and oil for anesthesia, considerable attention has been given to the local effects, limited chiefly to observations on motility and to the anatomical evidences of irritation or injury. A review of the literature if given by Hatcher (14). It appeared not improbable that a study of absorption of histamine, following the rectal administration of ether and oil, might give some information as to the effect of the latter on epithelial function.

PROCEDURE

Dogs of small or medium size and in good condition were used. No food was given for at least eighteen hours before the experiment. A preliminary dose of morphine sulphate, 10 mg. per kilo was given subcutaneously. This was followed by an enema of tap water at body temperature. Half an hour later the animal was anesthetized and a carotid artery cannulated for a blood pressure record. The rectal injections were made through a number 26 French catheter inserted for four to six inches and connected on the outside to a funnel. The catheter was held in place by

a strip of adhesive around the base of the tail.

The ratio by volume of ether to oil used for each animal is given in the table below. The amount of the mixture given was in all instances, one ounce per 20 lbs. body weight. This dose was never repeated except in the case of dog 1 (see table). This animal received four doses of a 75/25 ether-oil mixture in a vain attempt to maintain anesthesia by the rectally administered ether alone. Additional ether was finally given as required by inhalation.

In all later experiments ether inhalation was employed from the first. After the blood pressure record had been started, the standard dose of ether-oil was admitted through the catheter and allowed to remain for a measured period, five to twenty minutes. The bowel was then flushed with physiological saline solution, the inhaled ether being so regulated meanwhile, as to maintain uniform anesthesia. Finally, histamine in saline solution was run into the intestine. The dose used was 5 mg. of the dichloride (Eastman) or 10 mg. of the acid phosphate (Pfanstiehl)

For control experiments the same procedure was followed except that no ether was given per rectum. The histamine injection in these experiments was preceded by an enema of warm saline solution. Results are summarized in the accompanying tables.

RESULTS

T A B L E - I

NUMBER	DATE	WEIGHT	ETHER-OIL VOL..CONC.	EXPOSURE	HISTAMINE	BLOOD PRESSURE	
						I	II
1 ♀	6-21-30	10 lbs. 4.5kg.	15cc. 75%	2hr.45min	45mg. PO ₄ *	100	60
2 ♀	6-23-30	13 lbs. 6kg.	19½cc. 75%	5min	60mg. PO ₄ *	112	70
3 ♂	6-25-30	15 lbs. 6.82kg.	22½cc. 50%	6min	65mg. PO ₄ *	114	86
13 ♀	8- 6-30	15 lbs. 6.82kg.	22½cc. 65%	20min	35mg. HCl	96	66
14 ♀	8- 8-30	23 lbs. 10.5kg.	34½cc. 65%	15min	50mg. HCl	130	98
15 ♀	8-11-30	21 lbs. 9.5kg.	31½cc. 50%	15min	50mg. HCl	100	64
16 ♀	8-13-30	21 lbs. 9.5kg.	31½cc. 50%	10min	50mg. HCl	124	90
18 ♀	8-18-30	20.25lbs. 9.2kg.	31cc. 35%	20min	50mg. HCl	118	106
19 ♀	8-19-30 8-20-30	19 lbs. 8.5kg.	28½cc. 65%	1hr. (8-19-30)	45mg. HCl	140	132
20 ♀	8-21-30 8-22-30	24.5 lbs 11kg.	37cc. 65%	1hr. (8-21-30)	55mg. HCl	134	132

T A B L E II

C O N T R O L S

NUMBER	DATE	W E I G H T	CONTROL	EXPOSURE	H I S T A M I N E	B L O O D P R E S S U R E	
4 ♂	6-27-30	11 lbs. 5kg.	Olive oil 16.5cc	19min	50mg. PO ₄ *	114	112
5 ♂	7- 1-30	18 lbs. 8.2.kg.	Olive oil 27cc.	10min	80mg. PO ₄ *	104	104
7 ♂	7-22-30	24 lbs. 10.9kg.	Olive oil 36cc	15min	55mg. HCl	98	98
8 ♂	7-18-30	33 lbs. 15 kg.	Olive oil 49.5cc	5min	150mg. PO ₄ *	128	124
9 ♀	7-26-30	17 lbs. 7.7kg.	0.9% NaCl 25.5cc	18min	39mg. HCl	92	84
12 ♂	8-4-30	11.5lbs 5.2kg	0.9%NaCl 20cc	Not Drained	52mg. PO ₄ *	108	108

PO₄* indicates Histamine Acid Phosphate.

HCl indicates Histamine Di Chloride.

All the ether-oil mixtures employed, from the 75% down to the 35% by volume of ether, apparently render the intestinal mucosa permeable in some degree to histamine. The drop in blood pressure was in all cases clear cut, beginning within one minute after the histamine solution had entered the intestine, reaching a minimum within ten minutes at most, and followed by a more gradual rise toward the original level. The duration and magnitude of the depressor effect correspond roughly to the concentration of ether to which the intestine had been exposed. With the control animals the administration of histamine had no effect on the blood pressure (see table II). The values in the second blood pressure column of the table represent the minimum level observed at any time within 10 minutes after the administration of the histamine and are within the normal range of fluctuation under the experimental conditions.

After exposure to ether the mucosa seems to regain with fair rapidity its normal impermeability to histamine. Two dogs received the routine preparation. A 65/35 ether-oil mixture was then given by rectal catheter and allowed to remain in the colon for one hour. The residue was then washed out with warm saline solution and the animals allowed to recover. Twenty-four hours later they were anesthetized by ether inhalation, prepared for bloodpressure record, and the usual dose of histamine was administered by catheter. One animal (No. 19) showed a slight drop in blood pressure (140 to 132) but the normal

level was regained in six minutes. The second dog (No. 20) showed no change at all (See table I, Nos. 19 and 20).

DISCUSSION

The rectal administration of ether-oil mixtures evidently modifies temporarily the normal detoxifying function of the mucosa of the large intestine. This is not necessarily a serious objection to the procedure, the advantages of which have been dwelt on by Gwathmey (15) and others. The amounts of histamine used in these experiments were probably larger than is normally found in the bowel and the routine preparation of patients hardly favors the accumulation of bacterial products in the colon. Nevertheless, the results obtained were marked and presumably much smaller amounts would have produced effects of physiological importance. Moreover, other substances in the colon may be present which are rendered non toxic by the intestinal mucosa in the process of absorption and it must be remembered that in all experiments tabulated except in the first, the epithelium was exposed to ether for a comparatively brief period.

SUMMARY

The result of this work may be briefly summarized.

Exposure of the mucosa of the dog's colon to ether-oil mixtures, for periods of five to twenty minutes, renders it permeable to histamine temporarily. This effect is most

pronounced with high concentrations of ether, but can be demonstrated readily for concentrations of ether as low as 35% by volume.

I take sincere pleasure in acknowledging my great indebtedness to Professor Boyd for help and direction in my experiments.

BIBLIOGRAPHY

1. Carlson, A. J. and Jacobson, Clara, 1911,
Further Studies on the Nature of
Parathyroid Tetany.
Am. Jour. Phys.
28, No. 3:133.
2. Carlson, A. J. 1912, The Condition of the Digestive
Tract in Parathyroid Tetany in Cats and Dogs.
Am. Jour. Phys.
30, No. 4:338.
3. Dragstedt, L. K. and Peacock, S. G. 1923, Studies on
the Pathogenesis of Tetany, I, The Control
and Cure of Parathyroid Tetany by Diet.
Am. Jour. Phys.
64, No. 5:424.
4. Salvesen, H. A. 1923, The Function of the Parathyroids,
Jour. Biol. Chem.
56, No. 2:443
5. Inouye, T. 1924, Experimental Tetany and Diet.
Am. Jour. Phys. 70, No. 3:524.
6. Luckhardt, A. B. and Compere, Edward L. 1924. Increased
Gastro-intestinal Permeability as a Possible Factor in
Parathyroid Tetany. Proc. Soc. Exper.
Biol. and Med. 21, 523.
7. Spadolini, I. 1924, Ricerche Sulla Pathogenesi Della

**Tetaniche in Animali Che Hanno Subito Ampie
Distruzioni Della Mucosa Intestinale.**

Arch. Di Fisiol. 22, Fasc. V:435.

8. Schloss, O. M. in Harvey Lectures
Philadelphia, J. B. Lippincott Co.
1924-25 Pp-156-187.
9. Mammoser, Lambert F. and Boyd, T. E. 1929, The
Influence of Various Chemical Agents on the
Absorption of Histamine from the
Intestine.
Proc. Soc. Exp. Biol. and Med.
26:765 (June)
10. Koessler, K. K. and Hauke, M. T. 1924, Studies on
Proteinogenous Amines XXI. The Intestinal
Absorption and Detoxication of Histamine.
Jour. Biol. Chem. 59, No. 3:889.
11. Tweedy, W. R. and Koch, F. G. 1929,
A Suggested Modification of the Kramer-
Tisdall Method for the Microchemical
Estimation of Ionizable Calcium in
Blood Plasma.
Jour. Lab. and Clin. Med.
14, No. 8:747.
12. Meakins, J. and Harrington, C. R. 1922. The Relation
of Histamine to Intestinal Intoxication II.

The Absorption of Histamine from the Intestine.

Jour. Pharm. and Exp. Therap.

20, No. 1:45

13. Best, C. H. and McHenry, E. 1930,

The Inactivation of Histamine.

Amer. Jour. Phys. 93, No. 2:633.

14. Hatcher, R. A. 1927, The Rectal Administration
of Ether and Oil.

J. A. M. A. 89, No 25:2114.

15. Gwathmey, J. T. 1929, Oil-Ether

Colonic Anesthesia.

J. A. M. A.

93, No. 6:447.