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ACUTE CHANGES IN THE THYROID GLAND

PRODUCED BY FECAL TOXINS.

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Department of Physiology.

Master's, thesis, Oregon.

by

Lester Tallmon Jones

Oregon Medical School

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ACUTE CHANGES IN THE THYROID PRODUCED BY  
FECAL TOXINS.

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There has been a controversy among both clinicians and physiologists for a long time concerning the effects of various toxins on the thyroid gland. On one side we have the evidence from exhaustive work done by McCarrison (1) in 1911 to show that the feeding of fecal extracts and fecal residues to rats produced thyroid changes, loosely classed as "goitre", in 100% of the animals. So closely do the symptoms of acute tuberculosis and acute toxic goitre resemble each other in the first stages that it has been definitely established by Goetsch, in 1919, and Otis, in 1920, (2) that the thyroid hypersecretion is involved in both.

Farrant (3), in 1914, reported seven hundred cases of various diseases in which he has proved that the thyroid has undergone structural changes indicating hyperactivity. McCarrison (4) in 1914-15 found that rheumatism, rheumatic arthritis and malaria are repeatedly accompanied by thyroid changes. Barget (5), in 1917, produced goitre in rats kept under unhygienic conditions. Marine and Lenhart (6), in 1914, produced goitre in fish kept in impure and stagnant water. Many observers have noted the greater predominance of thyroid imbalance in the poorer classes who live under unsanitary conditions. Hart and Steinbach (7), in 1918, fed normal sows a diet containing no roughage, thereby producing poorer elimination and increasing intestinal putrefaction; and in 100% of the offspring congenital goitre

appeared.

On the other hand, Whipple (8), in 1921, and Dragstedt (9), in 1920, both showed that very little, if any, fecal toxin is absorbed from the normal digestive tract. Barget (5), in 1917, fed fecal emulsions to cats with negative results. Bassinger (10), in 1917, injected diphtheria toxins directly into the thyroid and found no structural or functional changes. Kalkus (11), in 1920, showed that when there is no iodine deficiency goitre never develops in animals.

To gain a further knowledge of the effect of toxins on the thyroid the following experiments were carried out, rabbits being used in all cases. One lobe of the thyroid of each was first removed to establish the normal for each animal. After allowing from one week to ten days for recovery, intraperitoneal injections of a fecal extract were given over various periods of time. The injections were made intraperitoneally to rule out the possibility of non-absorption by the digestive tract. This paper will be limited to giving the immediate or acute changes produced by the toxins.

#### Technique.

Fecal extracts were prepared by macerating 100 grams of fresh rabbit feces, which had been run through a meat grinder to facilitate the quick solution of toxins, in 400 c.c. of normal salt solution for 24 hours. This was then filtered through gauze, sand, filter paper and, lastly, through a Berkefeld filter into a sterile flask. This

eliminated the element of bacterial infection, as was proven by incubating portions of the filtrate for 48 hours with negative results. Fresh solutions were made each day. Absolute sterility was not maintained throughout, as we found that by using fresh solutions and thoroughly washing the final container each day, no infections resulted.

The belly of each rabbit was shaved and the injections made six days a week. Three control rabbits were kept under the same conditions of diet, light, temperature and cleanliness of cages. All animals used were females, for, as McCarrison (1) and many others have shown, this sex, at least in the human, is from seven to ten times as susceptible to thyroid imbalances as the male. Each rabbit was weighed twice a week, and the temperature was taken per rectum before each injection.

The first injection was 10 c.c. of toxin. This was increased by 10 c.c. on each succeeding day until the dose reached 40 c.c., which dose was maintained until death. This amount was established as the approximate maximal sub-lethal dose by a previous experiment. The only variation from the above routine was in the case of rabbit No. 45 and No. 46, which were given doses of one half the above amounts for three weeks before they were increased to 40 c.c.

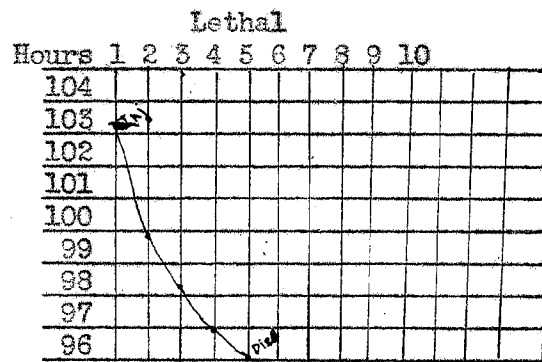
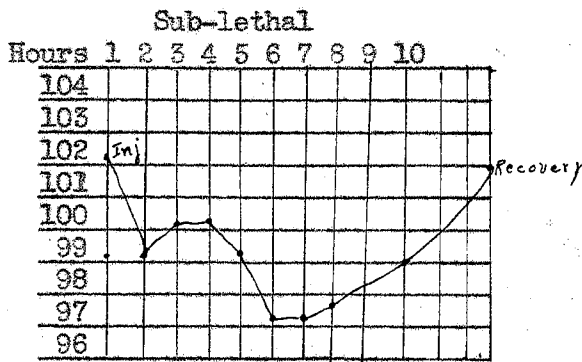
A complete autopsy was performed on all animals as soon as possible after death. The remaining lobe and

isthmus of the thyroid were removed, weighed and placed in the fixing fluid. All tissues were fixed in Orth's fluid (9 parts Muller's to 1 part 40% formalin), imbedded in paraffin, sectioned in thicknesses of 5 microns each, and stained with hematoxylin and erythresin.

#### Clinical Observations.

Following each injection the rabbits always showed marked signs of abdominal distress, crawling about so that their bellies would rub against the bottom of the cage. Respirations invariably became greatly increased in rate at first. Within 15 to 30 minutes the animals would begin to show signs of depression, appearing to be in a state of shock. Muscular weakness developed, the rabbits being unable to sustain their weight on their legs. The respiratory rate slowed and became subnormal. The animals almost always would defecate or urinate within 30 minutes after the injections. The temperature became subnormal shortly after each injection, and all animals died with an extremely low temperature, except one (No. 65), which had a terminal peritonitis and temperature of 105.4 degrees, due to an intestinal perforation from the hypodermic needle. The following is a typical temperature curve; the normal temperature for rabbits being approximately 102.5 degrees.





Three control rabbits (Nos. 81, 83, and 84), which were given the same amounts of normal saline intraperitoneally, showed none of the above symptoms. All animals except the controls lost weight, those living the longest becoming extremely emaciated.

The following chart gives all the important data concerning the progress of the experiment.

Rabbit No.	Duration of Injec.	Weight loss gain	Wt. of Thyroid 1st Lobe	2nd.	Appearance of Thyroid Gross	Microscopic.	
2	Control	—	3/4 lb.—	—	Normal	Normal	
34	"	—	1/2 lb.	60mg.	75mg.	"	"
69	"	none	none	50mg.	55mg.	"	" (active*)
61	2 days 1 injec.	1/4 lb.—	95mg.	100mg.	Hyperemic	Hyperplastic	
71	3 days 2 injec.	3/4 lb.—	145mg.	170mg.	"	"	
66	4 days 3 injec.	1 lb —	340mg.	275mg.	Normal	"	
68	8 days 6 injec.	3/4 lb.—	175mg.	270mg.	Hyperemic	"	
60	8 days 6 injec.	1/4 lb.—	?	?	Enlarged	"	
65	16 days 14 injec.	1 1/2 lb —	105mg.	150mg.	Hyperemic	" (extreme)	
67	30 days 26 injec.	2 1/2 lb —	150mg.	140mg.	"	" (extreme)	
45	50 days 38 injec.	?	not removed	?	"	" (marked)	

Histological Examination.

Histological examination of all thyroid tissues removed revealed the following:

Rabbit No.

2. 1st lobe. Normal.

2nd lobe. Normal.

34. 1st lobe. Normal.

2nd lobe. Normal

There is mild vacuolization of colloid in a few of the acini. The epithelium is high cuboidal.

69. 1st lobe. Normal.

2nd lobe. Normal.

There is evidence of moderate absorption of colloid, but the acini are uniform, and the colloid stains normally.

61. 1st lobe. Normal.

There is moderate vacuolization in some of the acini. The epithelium is high cuboidal. The gland is in active stage.

2nd lobe. Hyperplastic.

There is marked absorption of colloid, part of which stains poorly, is intensely vacuolated, and somewhat granular in appearance. The acini are unequal in size, some being completely empty. The epithelium is high cuboidal to columnar. The intervesicular tissue is not increased. The blood vessels are dilated. Two types of epithelial cells

are seen; those with large, clear, granular nuclei, and clear cytoplasm, and those with smaller, dark nuclei and granular cytoplasm, staining as normal cells.

71. 1st lobe. Normal.

A large amount of colloid is present. The acini are uniform in size. There is very little vacuolization. The gland is in resting stage.

2nd lobe. Marked hyperplasia.

There is great absorption of colloid, with extreme vacuolization of all acini. Most of the colloid stains lightly, and much is granular in appearance. Processes from the cells seem to extend into the colloid so that the cell boundaries are indistinguishable in places. A few acini show definite desquamation of epithelium into the lumen. The epithelium is high cuboidal to columnar, both types of nuclei are abundant. The blood vessels are dilated. There is slightly more intervesicular tissue to be seen.

66. 1st lobe. Normal.

A typical gland in active stage.

2nd lobe. Marked hyperplasia.

The picture is the same as in No. 71, 2nd lobe, as regards blood vessels, nuclei, and epithelium. Less comparative absorption of colloid is present, but the acini are more unequal in size. Vacuolization is moderate and the colloid has a paler, more granular

staining appearance.

68. 1st lobe. Normal.

2nd lobe. Marked hyperplasia.

This is almost the same in appearance as the 2nd lobes of rabbits No. 71 and 66. There is slightly more intervesicular tissue and slightly more "budding" or new formation of acini.

60. 1st lobe. Normal.

2nd lobe. Marked hyperplasia.

About the same degree of hyperplasia as described above except that there is slightly greater vascularity and vacuolization.

65. 1st lobe. Normal.

There is a slight amount of vacuolization.

2nd. lobe. Extreme hyperplasia.

The colloid is almost completely absorbed throughout, only a reticular "debris" remaining. Cytolysis is apparent in many of the epithelial cells and regressive changes in the whole gland. The picture is comparable to that of acute cloudy swelling of other parenchymatous tissue. Mononuclear phagocytes are seen in the intervesicular spaces. The epithelium is columnar and its cytoplasm poorly defined. Both types of nuclei are in abundance, the large ones are irregular in outline, structureless and contain a few small dark granules.

67. 1st lobe. Normal.

2nd lobe. Extreme hyperplasia.

This gland does not show the degenerative changes that are seen in the 2nd lobe of No. 65. but there is a greater degree of intervesicular cell growth and formation of new acini. Epithelial projections into the larger alveoli are abundant. The epithelium is columnar with a more granular, red appearance to the cytoplasm. Both types of nuclei are in abundance, many of the darker-staining nuclei having the appearance of early and late stages of mitosis. An occasional typical mitotic figure was seen. Polychromatic granules are present in the cytoplasm of many of the lining cells of the acini at the pole of the cell nearest the lumen and there seems to be a continuity between the cell and the adjacent colloid. Other signs of hyperplasia described above were present.

45. 1st lobe. (Not removed)

Entire gland at autopsy. Extreme hyperplasia.

The picture is the same as that seen in the 2nd lobe of No. 67 except that there is no formation of polychromatic granules and that there is some vacuolization to be seen even in the intervesicular tissue.

#### Discussion.

These experiments show that acute changes were produced

in the thyroid gland by the administration of fecal toxins. Concerning permanent dysfunction or imbalance, they have nothing to offer. The factor of shock being due to any fluid introduced into the peritoneal cavity of an animal was ruled out by the injection of normal saline into three control rabbits, with negative results. Infection as the cause of the symptoms and acute changes in the thyroid, was ruled out by the negative cultures and the post-mortem findings.

In controls No. 2, 34, and 69, the glands removed at autopsy showed slightly greater activity than the first portions removed. This is accounted for by the fact that the remaining thyroid tissue must undergo some degree of hyperplasia to compensate for that which was removed. That it cannot explain the marked changes produced in the animals given injections of toxins is shown, not only by the histological appearance of the glands but also by the fact that in No. 45, no preliminary removal of thyroid tissue was made and yet the gland at autopsy showed the same degree of hyperactivity as that of No. 67.

The extreme picture shown by rabbit No. 65 must be discounted to some extent because of the terminal peritonitis accidentally caused by perforating the intestine with the hypodermic needle. However it is scarcely possible that an infection of only one or two days' duration could produce the changes which were also found in the other thyroids examined.

Summary.

To summarize the changes produced in the thyroids of rabbits given fecal toxins intraperitoneally:

1. Colloid. Unequal absorption of colloid from the acini in each. A more granular appearance and loss of the deep red staining property with erythrosin. Vacuolization in every case. Some desquamation of epithelium in those of the animals receiving the most toxin. Great reduction in the amount of colloid as compared with the normal gland tissue of each. In those of the rabbits that received toxins for periods of more than one week, there is complete absorption of colloid in many of the acini while in others it has a honey-combed appearance or only traces of a reticular "debris" is left. In many acini the ends of the epithelial cells nearest the lumen seem to be prolonged into processes which are continuous with the colloid or incorporated in it.
2. Acini. Instead of being relatively uniform in size, they vary from large, irregular ones to those completely collapsed, and from old ones, lined with twenty or more epithelial cells, to newly formed ones with only five or six lining cells. Projections of epithelial processes into the lumen of the alveoli are frequent, especially in the glands of the rabbits which received the most toxin.
3. Epithelium. This is of two distinct types:
  - (a) Cells with clear cytoplasm and very large, clear, structureless nuclei that contain a few dark granules.

(b) Cells with a normal sized nucleus and cytoplasm which appear almost the same as normal epithelium. Several mitotic figures were seen in this type.

4. Stroma. No changes in the stroma were noted, fibrous changes being dependent on more chronic conditions.
5. Intervesicular Cells. There is a very slight increase of intervesicular tissue in the glands of those which received only one, two or three doses of toxin. But those receiving larger amounts of toxin, show a marked increase in the intervesicular cells. Most of these are of the small nuclear type and appear, in some instances, to be undergoing rapid mitosis.
6. Vascularity. Without exception the blood vessels are dilated to some degree above normal. Often this is so marked that a column of erythrocytes may be traced in the capillaries completely around the acini. No sclerosis of the vessel walls is demonstrable.

#### Conclusions

1. There is marked uniformity in all the thyroid tissue removed preliminary to experimentation.
2. Removal of one lobe does not materially affect the remaining thyroid tissue.
3. Large doses of toxins administered through the peritoneal cavity will produce changes in the thyroid within one or two days following the injection. The first signs being increased vascularity, absorption of colloid and increase in the height and granular appearance of the cells.



4. Toxins administered over periods of from two to four weeks produce more marked changes in the thyroid, the most evident of which are, (a) hyperplasia shown both by new formation of "budding" of acini and increased intervesicular tissue, (b) complete absorption of colloid in many of the acini and (c) columnar epithelium lining the acini.
5. From these experiments one concludes that the thyroid gland is in some way involved in the neutralization of certain toxins.

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-14-  
No. 71  
Normal Thyroid

See Oregon Collection  
copy for figure

No. 71  
Thyroid at Autopsy

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-15-  
No. 65  
Normal Thyroid

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No. 65  
Thyroid at Autopsy

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copy for figure.