THE EFFECT OF FECAL EXTRACT UPON THE THYROID GLAND. CHRONIC EFFECT.

by

Homer P. Rush.

Master's thesis, University of Oregon

-TABLE OF CONTENTS-

-Bibliography-

1. - Remedi: Sperimentale, 1902, 56, p.500, (quoted by Basinger).
2. - Basinger: Jr. of Inf. Dis., 1917, Vol.20,p.131.
3. - Farrant: Lancet, Dec. 27, 1913, Vol.2.p.1820.
4. - " Br.Med.Jr., Feb.28, 1914, Vol.1, p.470.
5. - Roger & Garnier: Compt. rend. Soc. de Biol. 1898, Vol.50,p.873. (Basinger).
6. - McGarrison: Annals of Tropical Med. 1911, Vol.5, p.87
7. - " The Thyroid Gland
8. - " Annals of Tropical Med., 1912, Vol.5, p.1.
9. - Marine & Lenhart: Bull. Johns Hopkins Hosp. 1910, Vol. 21, p.95.
10. - Bircher: Deutsche Ztschi of Chir. 1911, CXII, p. 368. (quoted by Burget).
11. - Burget: Am. Jr. of Phy., Nov. 1917, Vol. XLIV, p. 492.
12. - Dragstedt: J. A. M. A., Nov. 4, 1922, Vol. 79, p. 1593.
13. - Luckhart & Goldberg: J.A.M.A., Vol. 80, p. 79.
14. - " & Rosenbloom: Proc. Soc. Exp.Biol. & Med., 1921, Vol.19, p.129.
15. - " " " Science, July 1922, Vol. 56.
16. - " " Blumenstock: Science, Sept. 1922, Vol. 56.
17. - McGarrison: Indian Jr.of Med. Research, 1914-15, Vol.2, p.214.
18. - " " " " " " " p.183.
19. - " " " " " 1913-14, Vol. 1, p. 505.
20. - Mills: Am. Jr. Phys., 1918, Vol. 45, p. 557.
21. - Aschoff: Munchen Med. Wchnschr, 1922, Vol. 69, p.874. (Ab. Encrin, Nov. 1922).
22. - Watson: Jr. Phys., XXIV, p. 3.
23. - Williams: Obstetrics
24. - Bensly: Am. Jr. Anatomy, 1916 - Vol. XIX, p. 57.
25. - Kendall: Harvey Lecture, 1920-21.

The Effect of Fecal Extract upon the Thyroid Gland.
Chronic Effect.

The early work of Remedi (1) using separately diptheria toxin and tetanus toxin injections directly into the thyroid gland indicated changes occuring in that gland. Basinger (2) repeating this work found no evidence from which to infer that the thyroid had under gone any change. Farrant (3), who attacked the problem from a different angle, injected various toxins intraperitoneally including both tetanus and diptheria toxins, and he draws a midway conclusion. He found that after administrating thyroid and diptheria toxin simultaneously that no appreciable antagonistic effect was demonstrated. He also reports that in those instances where diptheria toxin was administered alone, a hyperplasia of the thyroid always resulted. On the other hand in the cases where the two substances were given simultaneously a different picture was obtained, the hyperplasia being less marked and the colloid content greater. Thus it is seen that the effect of such toxin injections on the thyroid gland has not been satisfactorily proven.

It would seem however in the light of a later publication by Farrant (4) that toxins must cause some change in this gland. After an examination of some seven hundred glands histologically, part of them from human material and the remainder from experimental animals, he has classified a great number of toxins by the effect they show upon the thyroid. The details must be omitted here but in brief his classes may be stated. Group I includes the toxins accompaning such diseases as typhoid fever, pneumonia, malignancies in other parts of the body, diabetis, etc., which diseases cause no change in the appearance of this gland. Group II includes the coliform bacillus infection, syphillis tertiary, chronic nephritis, etc., which conditions produce a moderate degree of thyroid hyperplasia. Group III

includes dysentery, syphillis secondary, malaria, chronic nephritis, measles, the toxins of diptheria and tetanus, etc., which cause almost a complete or "acute hyperplasia" of the gland. As a result of experimental work he also concludes that it is the toxins from the micro-organisms and not the micro-organisms themselves which produce this change. Roger and Garnier (5) obtained changes in the gland following infections. McGarrison (6),(7),(8), reports that he found a strong tendency for enlargement of the thyroid in animals which drank highly of water contaminated by feces. His work was carried out on rats and goats for the most part although he did some work on humans by administering the sediment of goitre water (Water that contained the excretia and waste material from goitre districts). In these experiments he reports a thyroid enlargement. This disappeared if the water was boiled. Intestinal antiseptics also proved of value in treating goitre in these districts according to this author. Marine and Lenhart (9) found goitre present in fish which were in unhygenic pools. The conditions automatically disappeared after proper sanitary procedures. Bircher (10) fed feces with cooked rice to rats and obtained positive thyroid changes. Burget (11), using cats and giving the emulsion of feces from both goitre and non-goitrous individuals by stomach tube, found no change in the thyroid.

The recent experiments by Dragstedt (12), Luckhardt, and Co-Workers (13), (14),(15),(16), on the parathyroids open again the question of detoxication by the glands of internal secretion. Dragstedt (12) has shown that the function of the parathyroid glands is to prevent intoxication by poisons arising from the intestinal tract. If measures were taken to prevent this intoxication, the animals live indefinitely and the inference is drawn that the parathyroids furnish no harmon necessary to life. In Dragstedt's experiments the thyroids were removed during the parathyroidectomy. No note is given concerning a myxoedemitous condition developing in these dogs, although no thyroid tissue was left. The

question arises as to whether the treatment used prevented an intoxication from the intestinal track which otherwise might have caused myxoedemitous symptoms.

We started a series of experiments to determine if fecal extracts, which are known to contain more or less toxic material, might have any effect upon the thyroid gland when injected intraperitoneally. This paper will be confined entirely to those effects which seem to develop over a relatively long period of time, otherwise known as chronic.

In this work rabbits were used as the experimental animals, not because of their particular fitness to the problem, but because they were the most accessible laboratory animal. We wished to cause an absorption of the fecal extract by as normal a route as possible. The absorption of fecal toxins that may take place in the human body must be from the intestines either through the blood stream or from the lacteals which drain this region. Since Burget (11) reports no effect noted in cats when feces were administered by the stomach tube we decided to administer the toxin by intraperitoneal injection. This should give absorption through the abdominal lacteals and also rule out the factor of failure of absorption through the normal intestinal wall. The animals were all kept in large, clean cages, since Burget (11), McGarrison (17), and others, have shown unhygenic conditions to cause a hyperplasia of the gland. All other factors were governed according to ordinary laboratory methods. Thus the same temperature was kept for the injected rabbits and the controls, as Mills (20) has shown that this may effect the thyroid. The amount of light was also roughly controlled. (Aschoff (21)). All animals had practically the same diet. (Watson (22), Burget (11), Bensley (23)). Lastly, we were very careful to keep all iodine fumes from the room in which the animals were kept.

The extract used was prepared fresh daily. Fresh feces were used in order to keep the concentration of our extract as constant as possible. A known amount was taken and ground up in a small meat grinder. Four times this quantity of normal saline was added and the mixture allowed to stand 24 hours. It was then run through a series of filters: gauze, filter paper and lastly through the Berkfeld filter under pressure. This last measure insured a more bacteria free preparation. A number of bacterialogical tests of this extract showed no growth at the end of 48 hours. We did not always sterilize our filter and suction flask before using, although they were always well cleaned. Sterilization was resorted to, however, every few days.

The animals were usually injected in the early part of the afternoon immediately after observations had been recorded. Daily observations were made during the first few weeks of the experiment, but later these were recorded every two or three days as the charts of typical examples will signify.

In the first and third series of animals a partial thyroidectomy was performed before any injections were made. Sufficient time was always allowed in these cases for recovery before any experimental conditions were imposed. This procedure was followed in order to have a better histological check upon the conditions of the thyroid. In the second series this was not repeated but a section of the gland was removed before the end of the injection time in order to make a later comparison and to give some idea as to the progression of any changes which might occur.

At the conclusion of the experiment the animals were killed and an autopsy performed. The histological tissues were fixed in Orth's fluid and dehydrated through graduated alcohols. The tissues were cleared in cedar oil and embeded in parafin. The sections were stained in haemotoxin and eosin.

The concurrent opinion of four later observers agreed with out judgment relative to the activity of the various glands. The precaution to examine a complete series at one sitting in order to keep in mind the comparative changes in the sections was also taken.

The following tables give the date of results:-

Series I.

Rabbit	Sex	Days	Amt.of Toxin	Doses	Avg. Dose	Gland before Injections	Gland after Injections	Weight-start	Weight-end
1	F	77	308.3	46	6.7	-1	1	2.8	2.7
2	F	77	Control			1	1-2	3.5	2.7
3	F	75	333.2	46	7.2	-1	1-2	3.3	3
4	M	72	420.2	46	9.13	-1	2	2.5	2.5

Series II.

Rabbit	Sex	Days	Amt.of Toxin	Doses	Avg. Dose	Gland during Injections	Gland after Injections	Weight-start	Weight-end
44	F	57	842	35	24	D	D	2.1	1.3
45	F	71	769	45	17	5	5	2.3	2.6
46	F	71	593	39	15.2	5	3-4	1.7	2.0
55	F	71	523.6	45	11.6	4	3	1.6	2.4

Series III.

Rabbit	Sex	Days	Amt.of Toxin	Doses	Avg. Dose	Gland before Injections	Gland after Injections	Weight-start	Weight-end
69	F	28	Control			2	2	3	3
64	F	27	860	23	37.4	2	3	2.7	1.3
67	F	27	860	23	37.4	3	D	3.3	1.9

To show the relative activity of the thyroid in comparison to the amount of toxin given. (Average dose)

Ordinate - different rabbits.

Abscissas - outside figures represent relative activity of thyroid.
inside figures represent cc. of fecal extract.

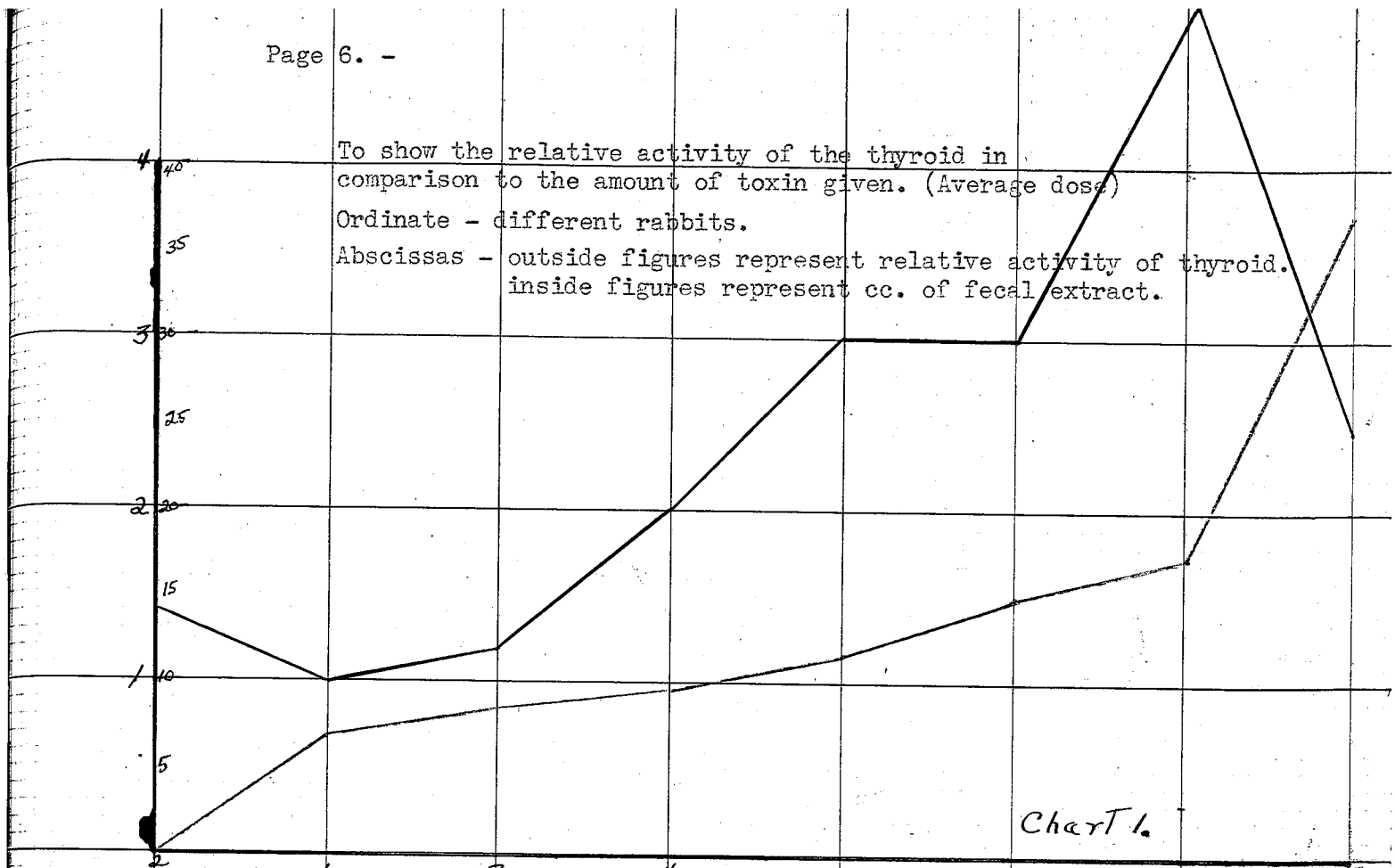


Chart 1.

To show the relative decrease in activity of the thyroid as the condition became more chronic and the dosage was cut down.

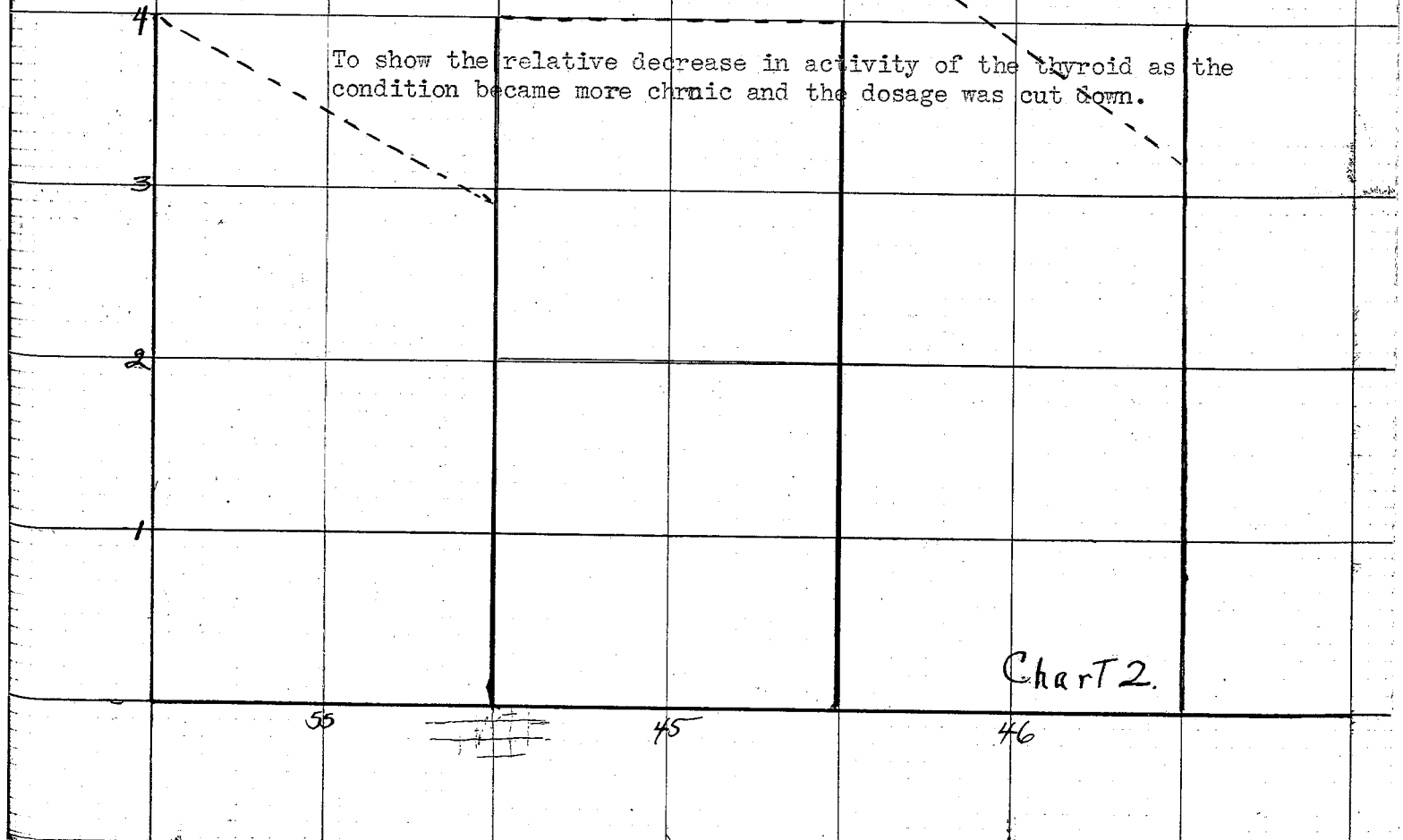


Chart 2.

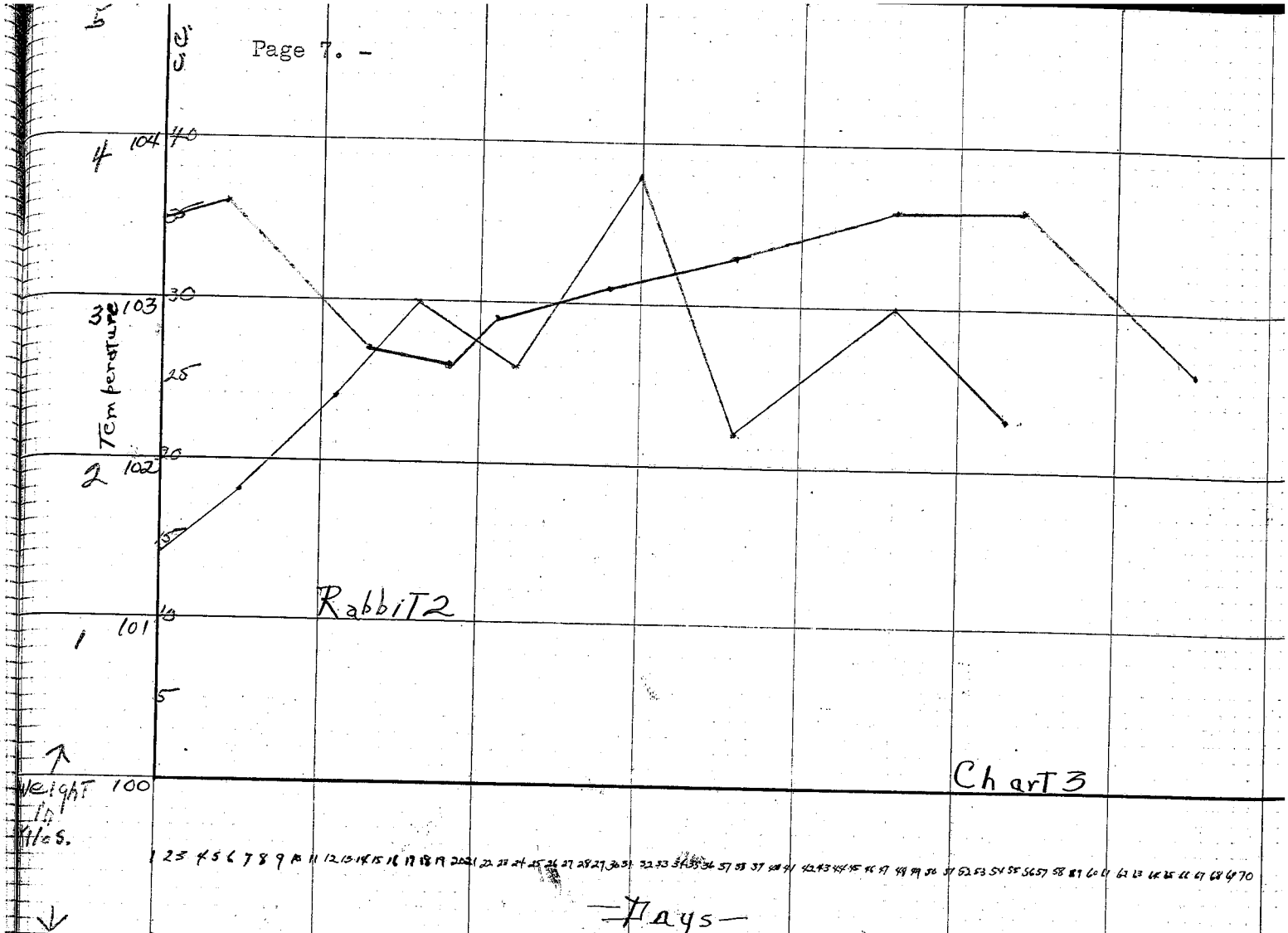


Chart 3

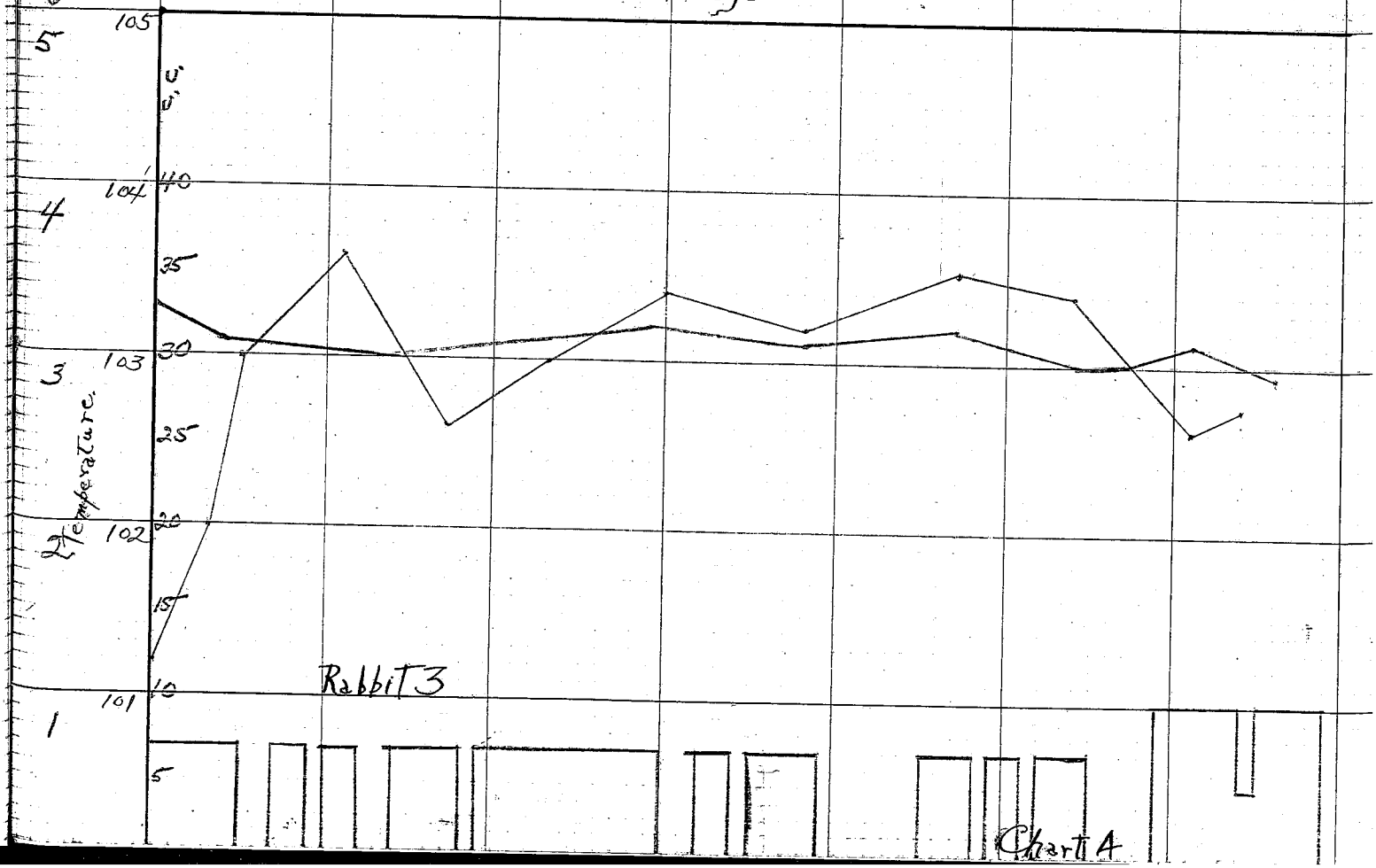


Chart 4

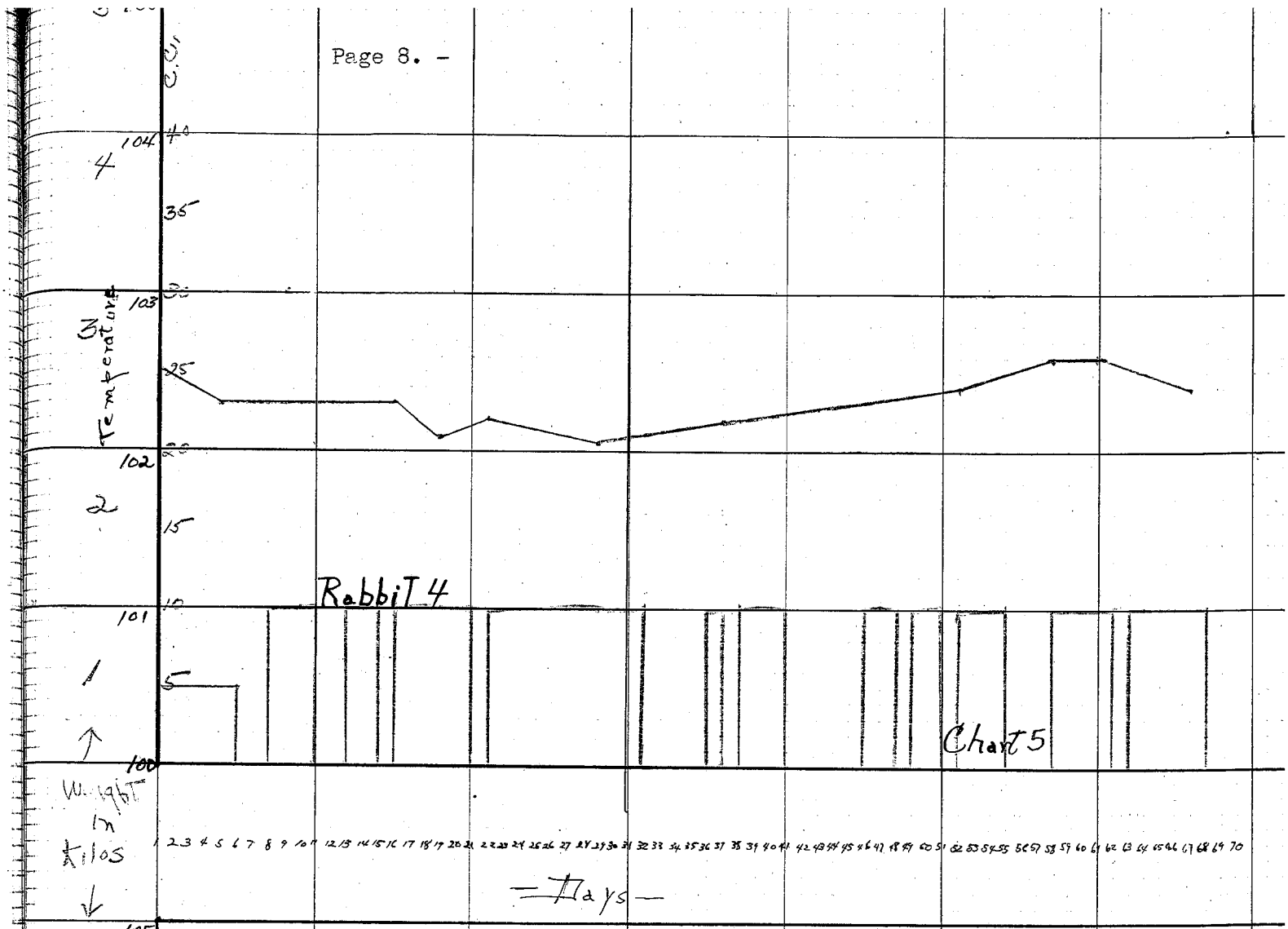


Chart 5

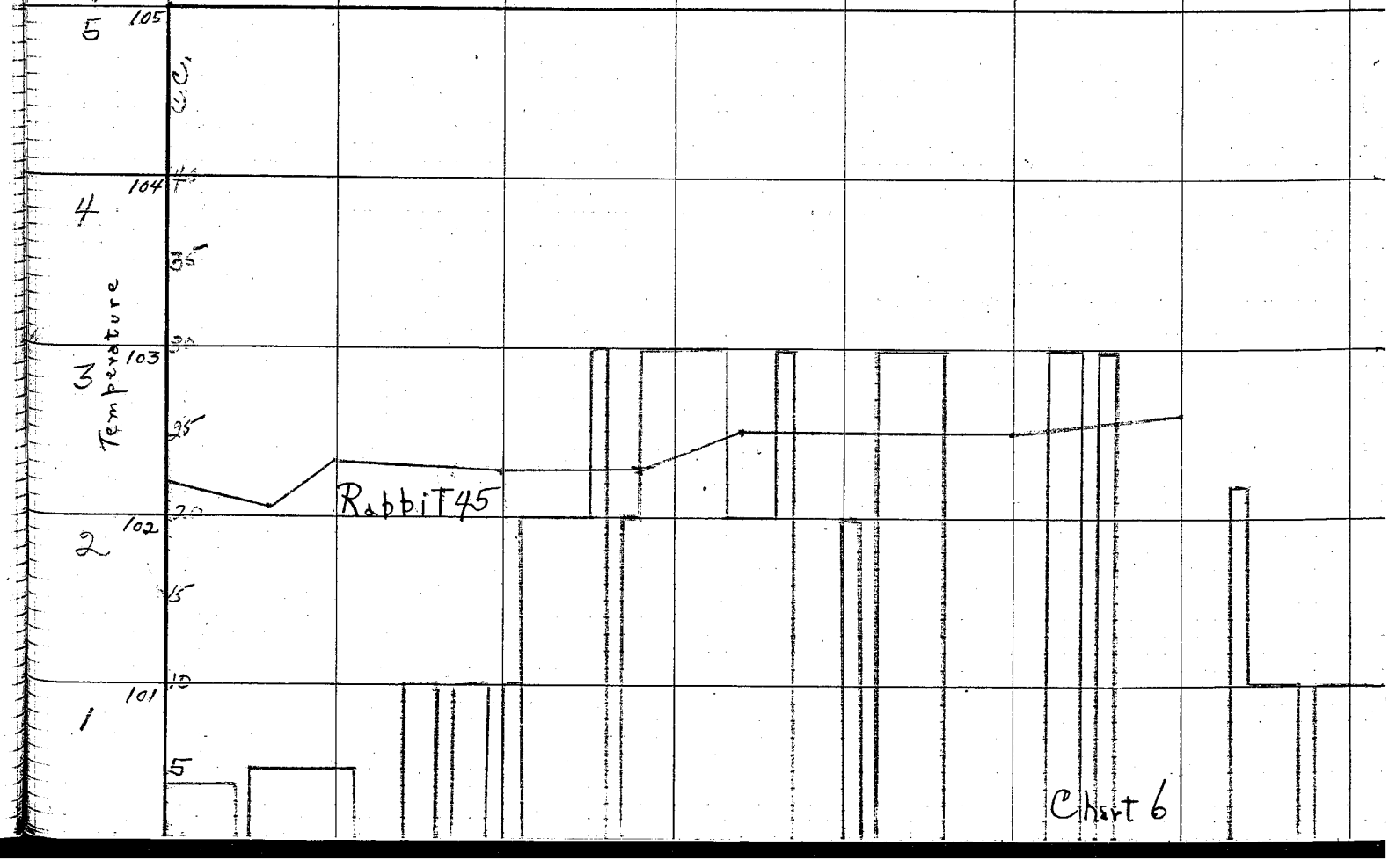
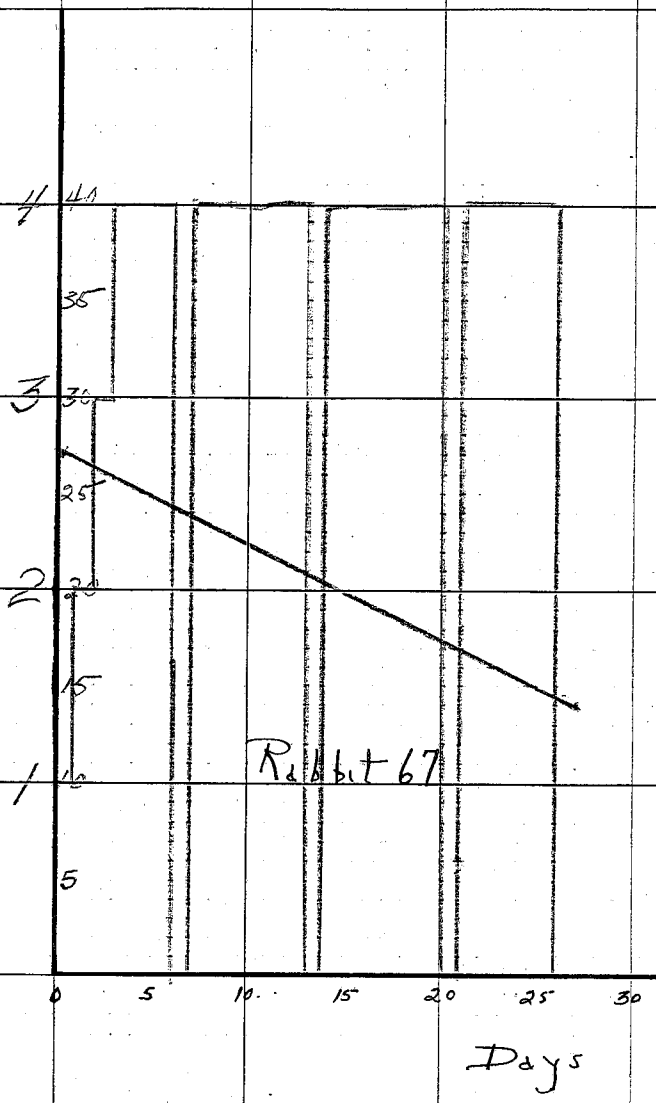


Chart 6



Explanation of Charts 3-4-5-6-7.

Ordinate - number of days.

Abscissas - inside red figures represent cc of toxin (fecal extract)
outside red figures represent weight in kilos.
~~outside black figures represent temperature.~~

It will be seen by making a comparative study of the above charts covering results that in almost every case a change was noted in the gland. This change, as the histological evidence will later show, is one of an increased activity. Exceptions to this general result are noted in animals 44 of series 2, and 67 of series 3. In the thyroids of these animals we found a degeneration of the parenchyma appearing. This was quite marked, as photographs (7 & 8) will show. Both of these animals were receiving large doses over a comparatively long period of time and it would seem as though the thyroid tissue had broken under the strain. Our control animals, 69-2-36, give what we think is the normal variation in the thyroids of rabbits. Control 2 was a female rabbit that was pregnant twice during the experiment. A slight degree of hyperplasia is noted in her thyroid. Control 69 shows a more marked degree of hyperplasia, this too being a female rabbit which undoubtedly had been a mother. It is a common accepted clincal observation that pregnancies produce more or less change in the gland. Ref. Williams (24). Control 36, a younger growing rabbit, shows but a mild degree of hyperplasia. On comparison with the experimentally injected rabbits it will be noticed that they show a more marked degree of activity. The figures 1-2-3-4-5-6 are used to give a rough comparison concerning the activity of the gland, figure 1 representing a resting or mild hyperplasia, and figure 6, a marked or complete hyperplasia. The other figures give the various grades of activity between these two extremes. We were governed in this comparison by the relative amount of hyperplasia, hypertophy, colloidal content, vacuolization which show colloid absorption, increase in interfollicular cells, new follicles appearing, and general condition of the cell and nuclei.

Another point noted in the tables is the relative activity of the glands in series 2. These animals were given small doses at the start, chart VII, which were increased during the experiment until a maximum of

20 cc. to 40 cc. was reached. The first section of gland was removed at this time and examined histologically. A comparison between these sections and the sections removed at the end of the experiment were made. Chart II shows graphically these results which demonstrate a degree of activity roughly comparable to the amount of toxin injected. The dosage used in the last part of the experiment was less than maximum but sufficient to keep up a moderate intoxication.

Grossly, the autopsies of these animals showed supprisingly little. All animals were practically free from any signs of general peritonitis although in Rabbit 55 of series 2 a localized hyperemia of the peritoneum was observed. This irritation was in the region of the injections. Rabbit 44 of the same series showed a more marked peritoneal hyperaemia but it was not generalized. It seemed to be most severe in the region near the liver and some fibrin deposit was noted. The left side of the peritoneal cavity appeared quite normal. The thyroids showed slight enlargements in some cases but in others no gross change could be observed.

Typical minute descriptions of glands which have been subjected to toxins in varying amounts and the normal or control picture will be given.

The normal rabbit gland is quite uniformly constant. The cells vary from a flat to a low cuboidal. The nuclei are slightly angular or round, very distinct and stain moderately deep. The colloid content is moderate in amount and takes a pinkish, occasionally very slight bluish tint. The staining is for the most part uniform. The follicles vary in size from small to medium, the shape being round or ovoid and the edges quite constantly regular. Projections into the follicles by the epithelial cells are not observed. The interfollicular cells are not of great qualtity. Masses of solid epithelial cells are uncommon but not lacking. The stroma

is scant. Vacuolization of the colloid is sometimes observed but not in any large degree.

The thyroid which has been subjected to a small dose over a long period of time shows some variation from this normal picture. Here the cells have taken on a more cuboidal appearance, although some flat cells may be seen. The colloid seems to be in less amount and the follicles show a slight irregularity in places. They vary in size from small to medium large and in some cases quite a large size is reached. Vacuolization of the colloid is not common. Hyperplasia of the parenchyma is moderate. The interfollicular cells are more prominent and in places masses of epithelium can be seen. Slight hypertrophy of the cells is noted. The stroma is scant. All changes are very moderate in degree.

The thyroid taken from animals having a relatively large dose over a medium period of time show more pronounced colloid absorption than the picture just described. They have more the appearance of the acute stage of the gland.

Thyroids examined from certain animals which received very large doses over a comparatively long period of time give us an entirely different picture. Here we see pronounced signs of degeneration. The nuclei have undergone pycnosis. The cells appear swollen and indistinct. The cell outline in many cases is lost. The colloid shows a marked decrease and in one, (44), it seemed to be entirely absent. Two types of nuclei are noted in some of these sections: one a small, slightly angular type; the other, a larger, round, vesicular type which takes a much lighter stain than the first. Colloid vacuolization seemed abundant. In the earlier stages these glands showed many characteristics of the acute toxemia rabbits. Inflammatory changes were also noted in these sections.

The following tables and photographs indicate the histological changes.

-Histological Table-

	Rabbit No.1			Rabbit No. 2			Rabbit No.3			Rabbit No.4		
	S	D	E	S	D	E	S	D	E	S	D	E
Colloid												
Staining	U		U	U		U	U		U	U		U
Abundance	2-3		2-3	3-4		3-4	3-4		2-3	3-4		3-4
Vacuolization	-		+	-		-	- +		+	+		-
Follicles	U			U			U					
Size	M-L		S-L	M		S-L	M-L		S-L	S-L		VS-M
Shape	R-O		R-O	R-O		R-O	R-O		R-O	R-O		R-O
Projection of wall	-		+	-		+	-		- +	-		+
Cells	Cub.		Cub.	Flat L.Cub.		Cub.	Flat L.Cub.		H.Cub.	Flat L.Cub.		H.Cub.
Hypertrophy	-		+	-		-	-		- +	-		+ +
Hyperplasia	+		+	-		+	-		+ +	-		+
Areas of Masses of Cells	+		+	-		-	-		+ +	-		+
Interfollicular Tissue	+ +		+ +	+ +		+ +	+ +		++++	+ +		+++
Nuclei	1		1	1		1	1		1	1		1
Stroma	S		S	S		S	S		S	S		S
Mitosis	-		-	-		-	-		-	-		-
Inflamation	-		-	-		-	-		-	-		-
Degeneration	-		-	-		-	-		-	-		-
Activity	+		+	-		+	+		+ +	-		+ +

- Histological Table 2. -

	Rabbit No.55			Rabbit No.46			Rabbit No.45			Rabbit No.44.		
	S	D	E	S	D	E	S	D	E	S	D	E
Colloid												
Staining		U	U		U	U		U	U			
Abundance		2–3	3–4		1–2	2–3		1–2	2–3		2–3	1
Vacuolization		+++	–	1	+++ +++	+ +		+++ + +	+		–	–
Follicles		U	U									
Size		S–M	S–M		S	S		S–L	S–L		S–L irreg.	irreg.
Shape		S irreg	R–O		S–irreg	reg.		irreg.	R–O			
Projection of Wall		– +	– +		+	+		+	–		+	–
Cells		H–Cub.	Cub.		Cub. L–Sql	H–Cub.		Col. Cub.	H–Cub.		H–Cub.	Cyto–lysis H–Cub.
Hypertrophy		+ +	– +		–	–		+ +	+			
Hyperplasia		+ +	+		+++	+		+++	+			
Areas of Masses of cells		+ +	+		+++	+		+				
Interfollicular Tissues		+++	++		+++ + +	+++		++++	++		+++	+++
Nuclei		2	1		1	1		1	1		1	1
Stroma		S	S		S	S		S	S		M	M
Mitosis		–	–		+	–		–	–		–	–
Inflammation		–	–		–	–		–	–		+	+ +
Degeneration		–	–		–	–		–	–		+ +	++++
Activity		++++	+++		+++ +	+++		++++	+++ +			

- Histological Tabe No. 3-

	Rabbit No.64			Rabbit No.67			Rabbit No.69		
	S	D	E	S	D	E	S	D	E
Colloid	64								
Staining	U		U	U		U	U		U
Abundance	2-3		2-3	3-4		2	2-3		2-3
Vacuolization	3+		2+	1+		3+	1+		2+
Follicles	S-L		S-L	S-M		S-L	M		S-M
Size									
Shape	R-O		irreg.	R-O		R-O	R-O		R-O
Projection of wall	-		+	-		+	- +		+
Cells	L-Cub		L-H Cub.	Cub		Swollen Cub	Cub		L-H Cub
Hyperthrophy	-		-	-		+	-		+
Hyperplasia	++++		+++++	+++		++++	+++		+++++
Areas of Mass of Cells	+		+++	-		++	+		++
Interfollicular Tissues	++		+++	++		+++	++		+++
Nuclei	1		1	1		2	1		1
Stroma	S		S	S		S	S		S
Mitosis	-		-	-		-	-		-
Inflamation	-		-	-		+	-		-
Degeneration	-		-	-		+	-		-
Activity	+++		++++	++		?	+++		+++

Key to Table:

U-Uniform
6-Abundance
5-Moderate Abundance
4-Moderate
3-Scanty
2-Very Scant
1-Absent
M-Medium
S-Small
L-Large
R-Round
O-Ovid
S-Start of Experiment
D-During Experiment
E-End of Experiment

See Oregon Collection copy for figure

See Oregon Collection copy for figure

No.9 - Rabbit 46. Relative decrease in Colloid and moderate Hyperplasia.

No.10 - Rabbit 1. Normal gland. Uniform distrubiton of colloid.

No.11 - Rabbit 46. Earlier section than No.9. Colloid absorpiton marked.

See Oregon Collection copy for figure.

See Oregon Collection copy for figure

No.1 - Rabbit 4.

Normal gland.
Note size of cells, nuclei and follicles.

See Oregon Collection copy for figure

No.2 - Rabbit 4.
After injections.
Note moderate increase in number of cells.

No.3 - Rabbit 1.

See Oregon Collection copy for figure

Small long time injections. Moderate increase.

No.4 - Rabbit 2.

See Oregon Collection copy for figure

Moderate hyperplasia from pregnancy. Control rabbit.

See Oregon Collection copy for figure

No.5 - Rabbit 45
Note colloid absorption and moderate hypertrophy of cells. Some hyperplasia.

See Oregon Collection copy for figure

No. 6.- Rabbit 45.

Gland taken after no.5. Note m rked hypertrpphy and lack of colloid.

See Oregon Collection copy
for figure

No.7 - Rabbit 67.
Gland shows early
degenerative changes

See Oregon Collection copy
for figure

No. 8 - Rabbit 44
Pronounced degeneration.
Note absence of colloid.
Note lack of cell
structure.

Discussion:

The results of these injections of fecal extract would indicate that the thyroid does react in quite a specific manner to toxins. The first point of doubt might be one concerning the toxicity of the extract. In a separate set of experiments, not reported here, we determined that a dose of this toxic material, between 10 cc. and 12 cc. per pound of body weight, was usually fatal when injected intraperitoneally. In a good sized rabbit, six to eight pounds, this means a considerable quantity, and the shock must be considered. We controlled this point by injecting normal saline in the same manner. In no case did death follow and furthermore, the symptoms produced by the fecal injections were not seen in the control experiment.

The first reaction of a systemic intoxication on the thyroid must be to call forth an increased output of some substance. We are not in a position at the present time to know whether this substance is thyroxin, the active extract discovered by Kendall (25), or some other product of the gland (26). This activity is made manifest in the more acute condition as will be indicated in another paper (short time injections) by a pronounced colloid absorption with a beginning hyperplasia and in some cases, at least, a mild hypertrophy. The process progresses if the intoxication continues or becomes more severe. This is evidenced by the small amount of absorption of colloid and more pronounced hyperplasia in the rabbits whose injections covered a long period of time. The gland then shows an activity at a higher level than previously which is indicated by the increased amount of secreting cells noticed in the rabbits injected as compared to the normals.

Perhaps the process which involves the thyroid during these intoxications can best be explained by comparing the gland to a factory and its warehouse. The secreting cells would represent the machinery, the

follicles, the warehouse. When a sudden demand is made for the product the needs must be supplied from the warehouse, and areas of vacancy will be seen, just as the colloid shows areas of vacuolization along the cell edges. If this increased demand is maintained, the factory will be equipped with more machinery for the increased output, so the thyroid cells undergo hyperplasia and hypertrophy to meet the increased needs.

The greater the amount of fecal extract given, the greater are the changes observed in the thyroid, providing quantities closely approaching the lethal dose are not given. The length of time over which the injections are administered also have a bearing upon the change in activity, but once the gland has passed through the first stages of compensation, the degree of activity seems roughly proportional to the dosage. This is best shown by referring to Chart I, where it will be seen that the rabbits receiving the smaller doses show the lease amount of change and those receiving the larger doses, a more pronounced change.

All rabbits used in these experiments did not show the typical increased activity described but some (67 and 44) gave a picture of degeneration. While these two animals are not sufficient from which to draw conclusions, it would seem that the heavy dosage used could not be tolerated by the rabbits and the thyroid activity was not able to meet the demand. During the attempt of the secretory cells to meet this increased demand, the over-activity required or the succumbing to the intoxication produced, caused degenerative changes to appear in the gland. These are seen in photographs seven and eight, the latter showing the greatest degree of degeneration. It will be noted in this section that the colloid has entirely disappeared. Cytolysis, parenchymitous degeneration, destruction of nuclei, and evidence of inflamatory reaction, signifies the complete exhaustion of the gland.

It is evident from these results that a factor in thyroid hyperplasia is undoubtedly found when certain intoxications occur. It would seem as though a great demand were made upon the gland. Whether this increased activity shows a direct detoxicating action by the thyroid or an increased body need for the secretory product or products, can not be decided with the evidence at hand. The glands for the most part indicate no or but little enlargement. Increased activity of the gland is found during pregnancies. While this activity was not as marked as the activity resulting from toxin injections, in one supposedly normal, mature, female rabbit, quite a marked degree of hyperplasia was noticed. It would seem, in the light of the evidence at hand, that the changes observed in the thyroids studied may consistently be classed as high normal activity. The degeneration previously mentioned, of course, falls in a different category and more work must be done to determine its significance.

The negative results obtained by previous investigators deserve note. Few of these workers used a similar toxic product and it may be that only certain classes of toxins cause the changes we observed. Burget's negative findings may be due to a lack of absorption through the intestinal wall, and, again, it must be remembered that a different laboratory animal was used in this previous investigation. The cat, used by Burget, seems to be more thyroid stable than many other animals used in thyroid work. Our finding agree in many respects with McGarrison's work and yet he reports enlargement of the thyroid as being produced by certain micro-organisms found in the intestines. He has not, however, ruled out all of the possibilities of toxic products arising from these organisms as producing the change.

Conclusions:-

1. - Fecal extract when injected intraperitoneally into rabbits causes an increased activity of the thyroid gland as evidence by colloid absorption, hyperplasia and in some cases hypertrophy.

2. - If the toxin absorption is present over a long period of time (chronic) the gland maintaines its normal activity at a higher level than previously.

3. - The increase in the activity of the gland seems to be in a rough way comparable to the amount of toxin given, dosage and time.

4. - It would seem as though the thyroid breaks under the strain of large doses of toxins in certain animals and undergoes degenerative changes as evidenced by picnosis of the nuclei, parenchymitous degeneration, and cytolysis of the cells with a varying degree of inflammatory changes.

5. - This response so far has shown itself to be merely a physiological increase in the gland and while it may be a factor in disorders of this gland we have gained no evidence to show its importance.