

## **Thyroid Action and Reaction, with Special Reference to the Formation of Thyroid Tumours.**

By RUPERT FARRANT.

FOUR main ductless glands are developed from the primitive pharynx: the tonsil, the anterior lobe of the pituitary, the thymus, and the thyroid. Of these, the thymus and tonsil are lymphoid in character, and one of their functions is the formation of lymphocytes, and though the exact functions of lymphocytes is at present unknown, I think we may for the purpose of analogy look on them as being concerned in the first line of defence against certain micro-organisms. The anterior lobe of the pituitary and the thyroid are secretory glands. Can either one or both of these act as the second line of defence for the destruction of some poisons that some micro-organisms produce?

The thyroid, as opposed to the thymus, continues to grow and obtains a very free blood supply. The gland secretion reaches the circulation by means of the veins. It was thought at one time that the secretion was absorbed by means of the lymphatics; this has been shown to be erroneous. Carlson and Woelfel [1] collected the lymph coming from the thyroid in dogs and found it to be inactive and to contain no iodine. The substance taken for colloid entering the lymphatics has since been shown to be indistinguishable from coagulated lymph [3].

### THE ANATOMY OF THE THYROID VEINS.

There are six thyroid veins; of these four open on the left side and two on the right, owing to the inferior thyroid veins opening either singly or together into the left innominate vein. The inferior thyroid veins are the largest, thus more than two-thirds of the thyroid secretion reaches the left side by means of the thyroid veins. Is there any reason for this? The left innominate vein receives the thoracic duct, the right innominate vein the right lymphatic trunk. The thoracic duct drains more than two-thirds of the total lymph area, and the right lymphatic trunk less than one-third. Thus the thyroid veins and the lymphatic trunks correspond in size. The thyroid veins may be said to guard the openings of the terminal lymphatic trunks. The right upper and middle thyroid veins open into the right internal jugular above the

opening of the lymphatic trunk, the left upper and middle thyroid veins open into the left internal jugular above the thoracic duct, and the two inferior thyroid veins into the left innominate below it.

Variations occur in both the thyroid veins and in the thoracic duct, but I have been unable to discover whether in their various anomalies these anatomical relations and proportions are true. The thoracic duct normally carries lymph and chyle, but we know that certain toxins are absorbed by the lymphatics and reach the circulation via the thoracic duct and right lymphatic trunk. The chyle and certain toxins thus enter the circulation at a place where there is a maximum quantity of thyroid secretion in the blood, and before reaching the central nervous system and tissues generally they will be exposed to the action of iodine in organic combination and oxygenation in the lungs.

We know that the thyroid has a marked influence on the metabolism of fat. Has it also any influence in the destruction of toxins? If so, one would expect a reaction and evidence of increased secretion in certain toxæmias. To-night I only propose to show the reaction that the thyroid undergoes in some of the simplest toxæmias, where, as far as possible, any previous change can be eliminated.

#### OBSERVATIONS ON THE THYROID IN CLINICAL TOXÆMIAS.

The following are the changes that occur: Firstly, the colloid becomes finely granular; secondly, it becomes vacuolated and partially absorbed; thirdly, an alternation occurs in the cells, they become more numerous, elongated, approaching the columnar type and arranged in masses; fourthly, the colloid becomes entirely absorbed and the walls of the vesicles become crenated and infolded; fifthly, the infolding and cell increase go on to transform the vesicles into solid masses of cells. These changes go on side by side so that several of them may be seen in the same section, but the section is placed according to the change that is most marked.

*The First Series is one of Infantile Diarrhœa.*—Simpson [10] noted colloid absorption and cell infiltration in marasmus and acute diseases. Section 1 (see p. 34) shows slight granulation and absorption of the colloid, otherwise it is normal. Section 2 shows a further absorption of colloid, and the cells are beginning to alter in shape. Section 3 shows an increased cell reaction and how the colloid is being eaten away at its edges. Section 4 shows the colloid entirely absorbed, and

the vesicles are transformed into solid masses of cells by the infolding of their walls. Section 5 shows half of the first and last of this series under the low power, the left side showing the colloidal thyroid, and the right the hyperplastic thyroid: they were both taken from uncomplicated cases of infantile diarrhoea, the only difference being the duration of the disease; but, as in infantile diarrhoea, one has to depend on the history, the exact duration cannot be obtained, but the series is roughly arranged in the order of the disease from early to late stages.

*Second Series: From Cases of Diphtheria.*—Section 6 (see p. 36) shows the granulation and absorption of the colloid; this was a case of hæmorrhagic diphtheria of four days' duration. Section 7 shows the granulation of the colloid very well and early cell reaction. This patient died on the seventh day of the disease. Section 8 shows total colloid absorption, the elongated type of cell and crenation and infolding of the lining wall for the formation of cell masses. This patient died on the seventh day and was of a very severe type. Section 9 shows marked cell reaction; the cells are columnar in type, the infolding of the walls of the vesicles having produced solidification. This patient died on the twelfth day. Section 10 shows half of the first and last of this series to compare the extent to which this reaction has gone on during eight days; on the left is the thyroid hyperplasia of late diphtheria, on the right the almost normal thyroid of early diphtheria. The patient with the latter died on the fourth day, that with the former died on the twelfth day.

*Third Series: From Cases of Measles and Broncho-pneumonia.*—Section 11 (see p. 39) shows that the colloid is entirely absorbed and the walls of the vesicle are commencing to fold inwards. This patient died on the tenth day. Section 12 shows total colloid absorption, with infolding of the vesicles. This patient died on the fourteenth day. Section 13 shows complete thyroid hyperplasia, with solidification of the vesicles. This patient died on the eleventh day. Section 14 shows the comparison under the low power of two of these sections—a difference of even one day can be detected by the thyroid change. The right side is taken from a patient who died on the ninth day, the left from one who died on the tenth day. However, as it is, of course, impossible to say when the pneumonia started, the dates of this series cannot be entirely accurate.

*Fourth Series: From Cases of Whooping-cough and Broncho-pneumonia.*—Section 15 (see p. 41), under the low power, shows the

granulation and absorption of the colloid. This patient died on the fourth day. Section 16, under the high power, shows a much further stage—total colloid absorption with the walls of the vesicles infolded; the cells are apparently being directly changed into colloid. This patient died on the fifteenth day. Section 17, under the low power, shows very well the infolding of the walls of the vesicles by which they become solidified. This patient died on the thirty-seventh day. These plates are somewhat small, so the slides themselves are also shown in series under the microscope. These changes occur so regularly and exactly that in any given group it is quite an easy matter to arrange them in the order of the duration of the disease. What is the significance of this reaction? Is it simply a reaction for increased metabolism or is it a reaction for the production of antitoxin? One can dismiss at once the idea of its being simply a reaction for increased metabolism, as the thyroid only reacts in the way I have described to certain diseases; other diseases, such as infections with streptococcus, staphylococcus, or *Bacillus coli communis*, even if accompanied by high fever, do not produce this reaction. I am afraid that time does not allow me to arrange these toxæmias into groups according to the organisms that produce them.

I propose now to try and prove that this reaction is antitoxic in function.

#### EXPERIMENTAL TOXÆMIA.

If thyroid reaction is produced by the effect of the toxins, the same changes should occur in guinea-pigs when injected with diphtheria toxin. A number of guinea-pigs were daily given diphtheria toxin in doses from the minimal lethal to one-eighth part of it.

*First Series.*—Section 18 (*see* p. 42) shows the thyroid of a normal guinea-pig; (five sections were shown of the thyroids of guinea-pigs dead on the second, third, fourth, fifth, and sixth days respectively of diphtheria toxin; the changes were similar to those shown previously from early diphtheria in children, colloid absorption, and cell reaction). Section 19 shows this typical cell reaction and colloid absorption; this guinea-pig died on the fifth day after injection. Thus diphtheria toxin can produce the reaction. Half of these guinea-pigs were at the same time given thyroid powder by the mouth in doses from 0.05 gm. to 0.01 gm. The doses of the toxin and the thyroid powder were continued daily until they died. The animals to which thyroid was given

were exactly similar in appearance and weight to those to which the toxin was given alone.

*Second Series.*—This showed the same changes, but less marked. The five guinea-pigs died on the second, third, fourth, fifth, and sixth days respectively, and were given thyroid by the mouth as well as daily injections of toxin. Section 20 shows the terminal thyroid hyperplasia of a guinea-pig dead on the seventh day after injection. The reaction in the series was distinctly less in those guinea-pigs that were given thyroid as well as toxin.

#### HAS THYROID FEEDING ANY ANTITOXIC ACTION TO DIPHTHERIA TOXIN ?

A further series of fourteen guinea-pigs was arranged in seven pairs and were injected with different doses of toxin. Half were otherwise untreated, while the other half were given thyroid powder every day; the dose of thyroid varied with the dose of toxin.

TABLE I.

Weight	Toxin, daily dose	Thyroid daily	Days of toxin	Days of thyroid	Died, days	Weight loss
220	0·6	—	4	—	5	50
215	0·6	0·04	4	4	6	70
200	0·5	—	4	—	5	45
205	0·5	0·03	4	4	5	50
165	0·4	—	4	—	5	45
160	0·4	0·03	4	4	7	45
270	0·5	—	2	—	2	—
260	0·5	0·05	2	3	2	—
190	0·2	—	3	—	3	30
190	0·2	0·04	3	4	3	45
180	0·15	—	2	—	2	—
180	0·15	0·03	3	5	4	30
180	0·05	—	2	—	2	—
190	0·05	0·01	3	5	4	55

The minimal lethal dose of the toxin used was 1 c.c. when given in one injection.

It can be seen from the table that, of the seven pairs, four of those given thyroid outlived those not given thyroid; the other three pairs

died on the same day. These guinea-pigs were injected every day, as I wanted their thyroids to confirm the changes shown in the last series of slides; these changes were confirmed. To a certain extent the giving of thyroid resisted the action of the diphtheria toxin, but the daily pricking with the needle discounts almost entirely any antitoxic effect, as guinea-pigs die if repeatedly pricked with a needle.

A further series of twelve guinea-pigs were given a single injection of one and a half times the minimal lethal dose of diphtheria toxin. Half of them were given 0.3 grm. of thyroid in three doses of 0.1 grm. during the forty-eight hours previous to injection. All the guinea-pigs previously given thyroid powder outlived the other guinea-pigs (*vide* table).

TABLE II.

Weight			Died in days			Thyroid, grammes of
270	...	...	5	...	...	—
270	...	...	7	...	...	0.3
320	...	...	2	...	...	—
325	...	...	3	...	...	0.3
210	...	...	1	...	...	—
220	...	...	2	...	...	0.3
265	...	...	4	...	...	—
265	...	...	5	...	...	0.3
275	...	...	3	...	...	—
255	...	...	5	...	...	0.3
290	...	...	5	...	...	—
315	...	...	6	...	...	0.3

One can say from this series that those guinea-pigs previously fed on thyroid resisted the effect of one and a half times the minimal dose of toxin longer than those not so fed.

#### IS THE SERUM OF A THYROID-FED ANIMAL ANTITOXIC?

Two rabbits were fed with 0.5 grm. of thyroid daily by the mouth until one died, on the seventh day, of hyperthyroidism. The other was bled and its serum collected. Ten guinea-pigs were arranged in pairs; this serum was used on five of them in doses from 0.9 c.c. to 0.25 c.c. to protect them from one and a half times the minimal lethal dose of toxin.

TABLE III.

Weight	Toxin, cubic centimetres of		Serum	Died, days	Lived
280	...	1.5	—	6	—
270	...	1.5	0.9	—	Yes
270	...	1.5	—	2	—
250	...	1.5	0.6	—	Yes
290	...	1.5	—	4	—
280	...	1.5	0.5	4	—
				(Died of an abscess in neck)	
235	...	1.5	—	3	—
240	...	1.5	0.3	—	Yes
270	...	1.5	—	4	—
270	...	1.5	0.25	—	Yes

So all those guinea-pigs given the serum of a thyroid-fed rabbit lived except one, which died from an abscess which developed in its neck. This shows that the serum of thyroid-fed animals is antitoxic to diphtheria toxin.

#### DOES DIPHTHERIA ANTITOXIN CONTAIN MORE THYROID SECRETION THAN NORMAL SERUM ?

A rabbit was fed on not less than 4,000 units of diphtheria antitoxin a day, about 10 c.c. in amount. The antitoxin was mixed with its food. This rabbit developed exactly the same symptoms as those produced by thyroid feeding—loss of weight, tachycardia, fur changes, &c. It died at the end of sixteen days, having lost 31 per cent. of its weight; it dropped from 1,690 gm. to 1,160 gm. The post-mortem changes were similar to those of a rabbit dead from thyroid feeding—absence of fat, wasting of the muscles, dilatation of the heart, &c. Another rabbit weighing 1,170 gm. was fed on 10 c.c. normal horse serum a day. This rabbit exhibited no signs of thyroid excess, and instead of losing weight it put on 85 gm. in sixteen days.

If diphtheria antitoxin contains an excess of thyroid secretion it should have no ill-effect on thyroidectomized animals. A young rabbit weighing 905 gm. was thyroidectomized. At the end of ten days its wound was healed and it had regained to within 15 gm. of its former weight. It was given not less than 2,000 units of diphtheria antitoxin a day, that is, the units given per body-weight were roughly proportional to those of the former experiment. At the end of fourteen days it had

put on 250 gm. in weight and showed no ill-effects from the feeding. At the end of seven weeks it weighed 1,220 gm. So diphtheria antitoxin is harmless when fed to thyroidectomized rabbits, but normal rabbits when fed with it develop symptoms of thyroid excess and die.

#### OBSERVATIONS ON ANTITOXIN.

We should be able to gain some confirmation of thyroid reaction and its relation to diphtheria antitoxin by the examination of the thyroids of horses that have been used in the preparation of antitoxin. These horses are injected with increasing doses for about a year, with periods of bleeding and periods of rest. A week to ten days from the last injection of toxin the horses are finally bled out, as after several bleedings the antitoxic value of the serum falls so that it is of no practical use.

*Horse Series.*—Section 21 (*see p. 44*) shows an active hyperplasia with small vesicles containing some colloid, the feature of the section being the masses of cells in the centre of which colloid is being formed. Section 22 shows an active hyperplasia with colloid in larger vesicles; the active formation of the colloid is well seen by the rows of cells gradually shading off into colloid material. This method of the production of the secretion is similar to that occurring in sebaceous glands [2]. Section 23 shows a further formation of colloid, the cells being squeezed together between the enlarging vesicles. Section 24 shows a more advanced stage of colloid formation, though the hyperplasia can still be seen by the number and active type of the cells. Section 25 shows the comparison under the low power of the first and last of this series, the one on the left the hyperplasia, the one on the right the colloid formation.

This series of horse thyroids is arranged in order of hyperplasia, the first being most marked, the last least. The antitoxic value runs in the reverse order; the serum of the first horse was only valued at 200, whilst the last was 300.

Is there any relation between thyroid hyperplasia, its iodine value, and the antitoxic value of the serum? Marine and Williams [7] estimated the amount of iodine contained in various conditions of thyroids and found that it was less in hyperplasia than in normal or in colloid glands. Marine and Lenhart [4] showed by numerous experiments that the hyperplasias always in time revert to colloid glands, and that this change was hastened by the administration of substances containing iodine. In these observations on the horse hyperplasia of the thyroid



was accompanied by a low antitoxic value of the serum, but I have had no opportunity of estimating the amount of iodine contained in these glands. But if hyperplasia varies inversely with the iodine content, as Marine and Williams [7] state, the glands of the horses associated with low antitoxic value would show a low iodine value.

I have had, and still am having, the iodine content estimated in the various sera. This work has been carefully done for me by Mr. Bosworth at the Westminster Hospital Medical School Laboratories, according to Oswald's [9] modification of Baumann's method.

The following are the results for anti-diphtheritic serum :—

One gramme of dried serum contained	0.036	mgrm. of iodine in organic combination.
“ “ “	0.081	“ “ “
“ “ “	0.0259	“ “ “

The last of these was of too low an antitoxic value to be used for injections.

The estimation for normal horse serum was that it contained less than 1.6 parts per million of serum. So we find the amount of iodine present in the serum is much larger in the toxin-treated horse than in the normal animal. Marine and Williams [7] also showed that the physiological value of the thyroid varies with its percentage of iodine ; and as far as my estimations go they show that the value of the diphtheria antitoxic serum also varies with its iodine content ; though I shall before long be able to present you with a larger and more convincing series.

Taking these results together : Certain toxins stimulate the thyroid into a condition of hyperplasia ; during this change it seems probable that the iodine-containing substances are poured out into the circulation, for the serum of the immunized horse contains an excess of iodine, while the thyroid is hyperplastic. I assume from the experiments of Marine and Williams that the thyroid itself becomes deficient in iodine at the same time. During the reversion back to the colloid the iodine is once more taken up by the thyroid, and it changes back to the colloid gland ; the rate of change is directly proportional to the amount of iodine present.

## SUMMARY.

(1) The thyroid undergoes hyperplasia in certain diseases. This hyperplasia resembles that following partial thyroidectomy. A similar hyperplasia is induced in guinea-pigs by the injection of diphtheria toxin, and is mitigated if thyroid administration be combined with the diphtheria toxin. These guinea-pigs also survive longer than the controls.

(2) The blood serum of a thyroid-fed rabbit is antitoxic to diphtheria toxin.

(3) Antitoxin fed to normal rabbits produces symptoms similar to those arising from feeding thyroid, while in thyroidectomized rabbits antitoxin is borne without symptoms.

(4) Diphtheria antitoxin contains iodine in organic combination; normal horse serum contains but the slightest trace. This indicates some close relationship between the thyroid function and the development of certain antitoxins. It may be suggested that the hyperplasia observed in these toxæmias arises from the attempt to form antitoxin.

## THE FORMATION OF THYROID TUMOURS.

(a) *From the Normal to Hyperplasia.*—The toxins that produce thyroid hyperplasia may be divided into two main groups: the exogenous, where they are supplied from without; and the endogenous, where they are produced within the body. The production of thyroid hyperplasia by exogenous toxins has been shown by Wilms, who produced it in rats by giving them water from an infected well. Marine and Lenhart [5] examined the cause of the hyperplasia in the pike and bass of Lake Erie, the brook trout of the Pennsylvania Fisheries [6], and found the latter due to the polluted water. McCarrison found that water containing coliform organisms produced it in man. It was not all the rats or all the patients, and only 6 per cent. of the fish so exposed, that developed an enlargement of the thyroid. From the slides I have shown one saw that certain endogenous toxæmias produce hyperplasia of the thyroid; most of these involute back again and no thyroid enlargement is produced, though some may go on to definite enlargement. So in both endogenous and exogenous, if the toxins be withdrawn early, the hyperplasia will disappear. McCarrison [8] showed in the exogenous that

even when the hyperplasia has gone to a general enlargement, if the toxæmia be removed, the gland will regain its normal size. As regards this, for the endogenous toxins I can show it better clinically. Section 26 (*see* p. 46) shows on the left the hyperplasia from a case of exophthalmic goitre, on the right the hyperplasia produced by a case of measles and broncho-pneumonia of eleven days' duration. The two halves are very similar; microscopically the vesicles are a little more broken in the exophthalmic portion, and macroscopically it formed an enlargement of the thyroid, whilst the measles did not. The earliest stage of hyperplasia would not produce an enlargement of the thyroid, but rather a diminution of size from absorption of the colloid material.

(b) *Hyperplasia to Colloid*.—Marine and Williams [7] found that all thyroid hyperplasias in dogs have an increased capacity for iodine and for colloid formation, and from their experiments proved that a thyroid circle takes place from the normal gland to hyperplasia and from hyperplasia to the colloid gland. The reversion from the early hyperplasia due to endogenous toxins to the colloidal type of gland is well seen in section 27. The left portion shows a hyperplasia, due to whooping-cough and broncho-pneumonia, dead on the thirty-seventh day. The right portion is from a similar case, the patient dying three to four months after the recovery from the broncho-pneumonia; the cause of death was a toxæmia that has no effect on the thyroid. Section 28 shows on the left a thyroid from an exophthalmic gland, and on the right a colloidal gland from a later stage of a similar case. Section 29 shows the comparison between the involution of an early hyperplasia on the left and that of a late hyperplasia on the right. During this process of excessive colloid formation the thyroid would increase in size, and the portion that had been in the highest degree of hyperplasia would have a greater deposit of colloid; this would lead to the formation of the so-called adenoma. Adenomata may develop at any stage of the hyperplasia, and so the adenomata may be combined with the early, moderate, or marked hyperplasia. This process of colloid formation is the form which involution takes in the thyroid and the masses of colloid are inactive, as shown by Stoland [11]. During this involution degeneration changes are liable to take place as in any other gland, the breast for example. The degeneration will show itself in the formation of single or multiple cysts. The rest of the gland may be in any of its stages, so leading to the occurrence of cysts in a hyperplastic gland, or the cyst-adenoma. The involution may go on to fibrosis.

To sum up these changes: Hyperplasia without thyroid enlargement; hyperplasia with various degrees of enlargement; adenomata of involution; cysts and cyst-adenomata of degeneration.

#### THE FORMATION OF THYROID TUMOURS IN CRETINS.

The facts known about cretins may briefly be stated to be that their parents have goitres, and usually live in endemic goitre districts, but that if they remove from the district they no longer bear cretins. So the cause of the thyroid changes in the infant is not the thyroid change in the mother, but the cause that produces these thyroid changes. Seventy-five per cent. of cretins have enlarged thyroids at one period or another. Cretinism usually develops between the first and second years. On examination of the literature one finds exactly the same cycle of changes that occurs in adult thyroids, only the active hyperplasia is rarely seen, and though cases of exophthalmic goitre have been recorded in the newly born, the rate of involution and degeneration is complete in two to three years. There are two facts to account for this: (1) The toxin circulating in the blood of the foetus will be relatively large in amount as it will correspond to the toxicity of the mother's blood; (2) from section 30 it will be seen that the thyroid of the normal foetus is already in a condition corresponding to hyperplasia, and, considering the delicate condition of foetal organs, one would expect the involution and degeneration changes to follow rapidly. It is of interest to note that cretins usually die of those diseases that produce a thyroid reaction in normal beings.

Time prevents me from producing to-night the results of my work on the normal stimulus and the production of the symptoms of thyroid excess. The whole of the experimental work was done at the University College Laboratories, and I cannot say how much I am indebted to Professor Cushny for his care and advice.

I am much indebted to Dr. Braxton Hicks, Dr. McConkey, Dr. Rolleston, and Dr. Thompson, for supplying me with the material that I have used to-night; also to Dr. Cartwright Wood for giving me antitoxin to enable me to repeat some of these experiments.

## REFERENCES,

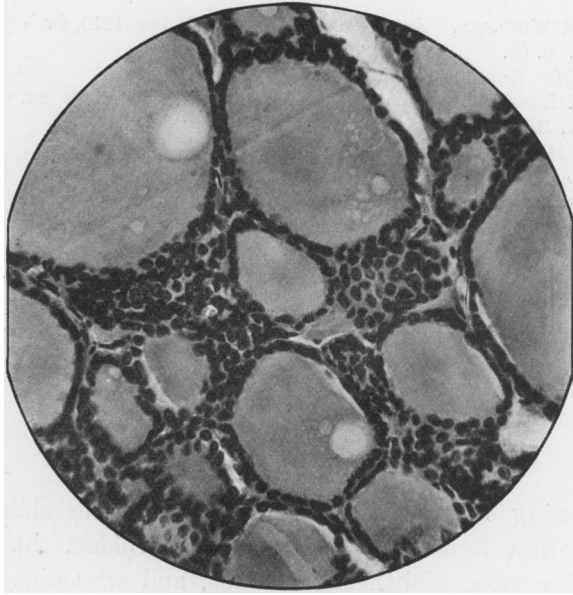
- [1] CARLSON and WOELFEL. *Amer. Journ. of Phys.*, Boston, 1910, xxvi, p. 40.
- [2] *Idem. Ibid.*, p. 63.
- [3] CHAMBERS, H. *Lancet*, 1912, i, p. 680.
- [4] MARINE and LENHART. *Johns Hopkins Hosp. Bull.*, Balt., 1909, xx, pp. 131-39.
- [5] *Idem. Ibid.*, 1910, xxi, p. 95.
- [6] *Idem. Depart. Pennsylv. Fisheries Bull.*, vii.
- [7] MARINE and WILLIAMS. *Arch. Internat. Med.*, Chicago, 1908, i, pp. 349-84.
- [8] McCARRISON. *Med. Chir. Trans.*, 1906, lxxxix, pp. 437-70; *Quart. Journ. Med.*, Oxf., 1908-09, ii, p. 279-88.
- [9] OSWALD. *Zeitschr. f. Physiol. Chem.*, Strasb., 1897, xxiii, p. 265-310.
- [10] SIMPSON. *Scottish Med. and Surg. Journ.*, Edinb. and Lond., 1906, xix, p. 504-19; *Brit. Med. Journ.*, 1910, i, p. 1049.
- [11] STOLAND. *Amer. Journ. Phys.*, 1912, xxx, p. 37.

## ILLUSTRATIONS (pp. 34-48).

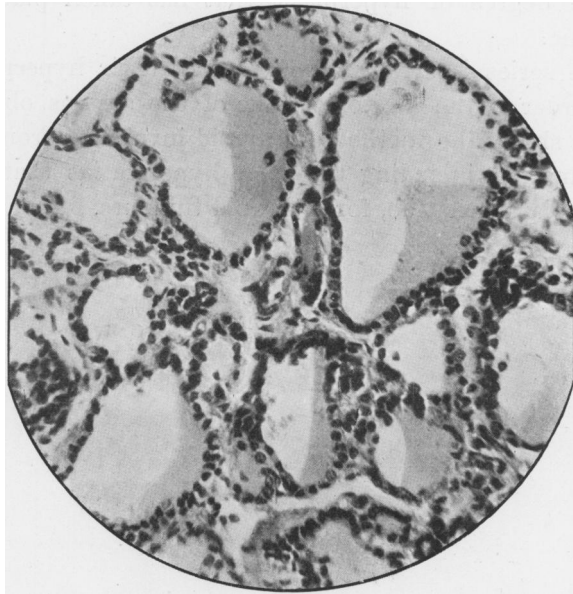
The following illustrations are of some of the slides that were shown. The first four series show the hyperplasia that is produced by infantile diarrhoea, diphtheria, measles, and whooping-cough. The hyperplasia shown in an illustration corresponds to the duration of the disease of its series. The double illustration at the end of each series compares the degree of hyperplasia that has taken place in various periods of time.

The horse series is arranged in order of their hyperplasia, but in the reverse order of the antitoxic value of the serums obtained. The tumour series shows the method of thyroid involution from hyperplasia to colloid formation, including the early hyperplasias that do not, and the late hyperplasias that do, form thyroid tumours.

## SERIES I.—INFANTILE DIARRHŒA.

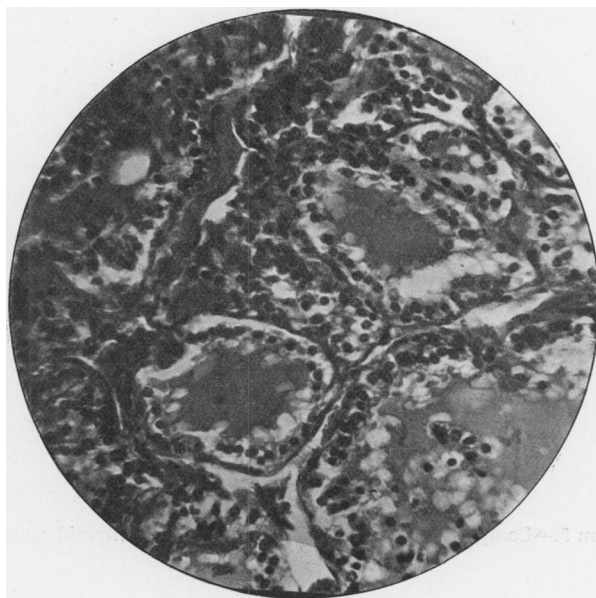


Section 1.—The first stage of colloid absorption ; granulations at the margins.

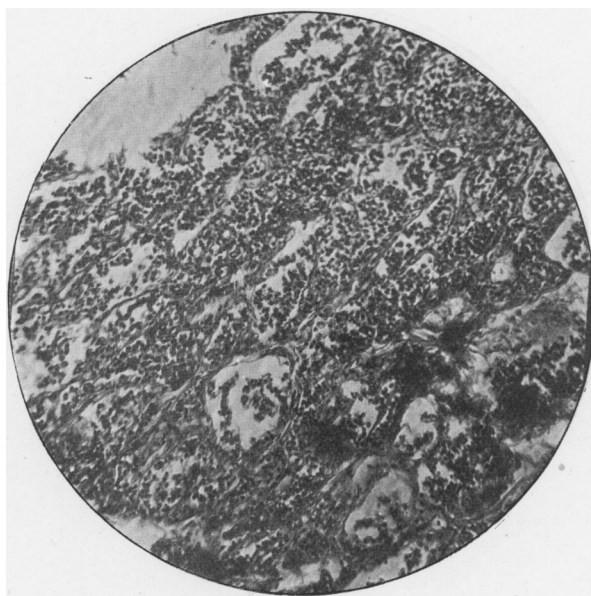


Section 2.—Latest stage of colloid absorption.

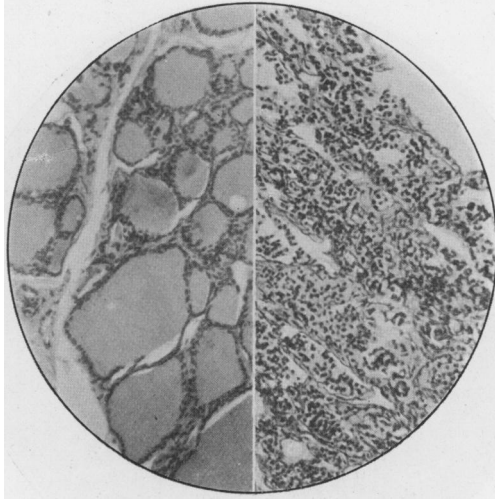
SERIES I.—INFANTILE DIARRHŒA (*continued*).



Section 3.—Colloid eaten away at the edges ; cell reaction.

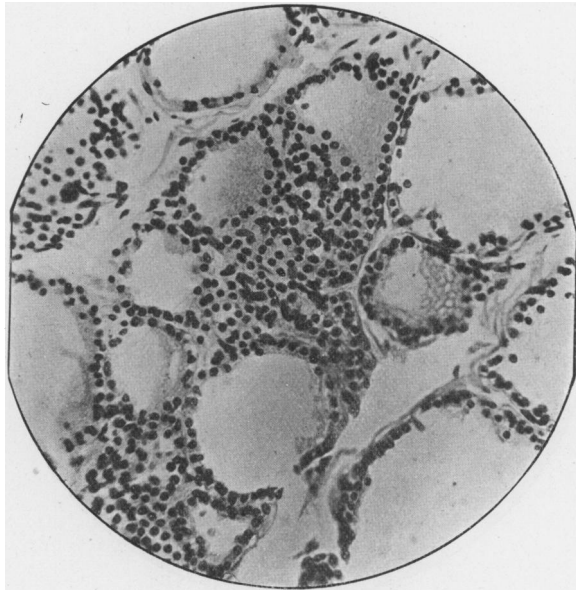


Section 4.—Complete hyperplasia ; cellular mass.

SERIES I.—INFANTILE DIARRHŒA (*continued*).

Section 5.—Comparison of early (left) and late (right) thyroid reaction.

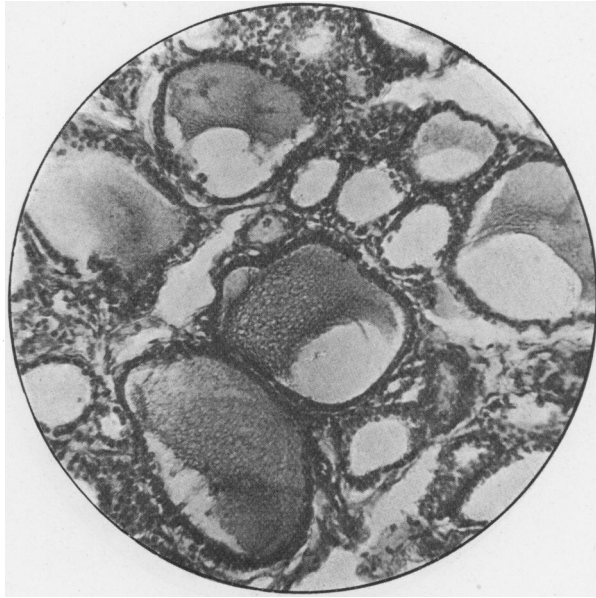
## SERIES II.—DIPHTHERIA.



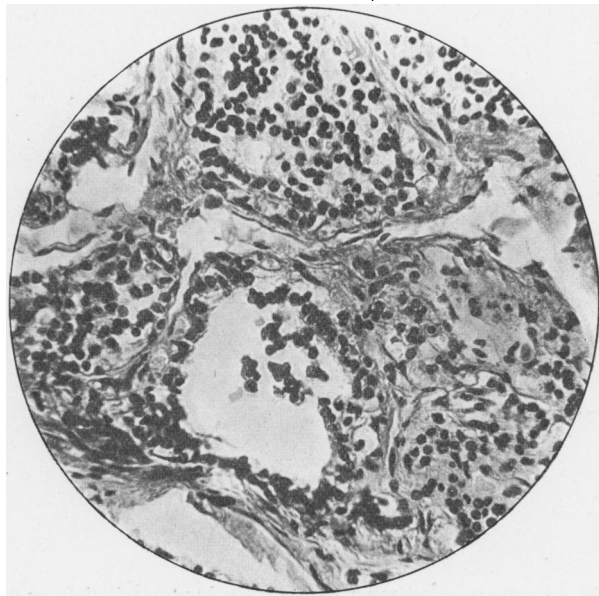
Section 6.—Early thyroid reaction.



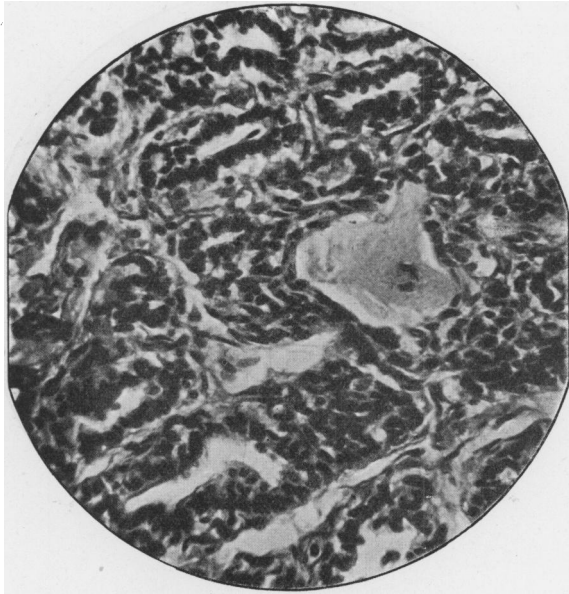
SERIES II.—DIPHThERIA (*continued*).



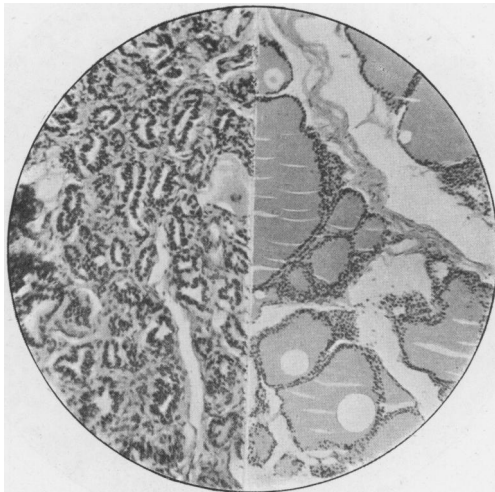
Section 7.—Granulation and colloid absorption.



Section 8.—Medium cell reaction.

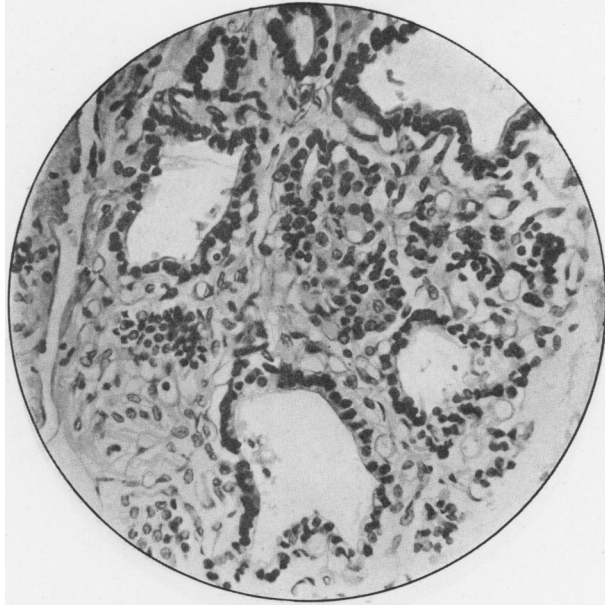
SERIES II.—DIPHTHERIA (*continued*).

Section 9.—Columnar cells; vesicles infolded and crenated. Complete hyperplasia, twelve days.

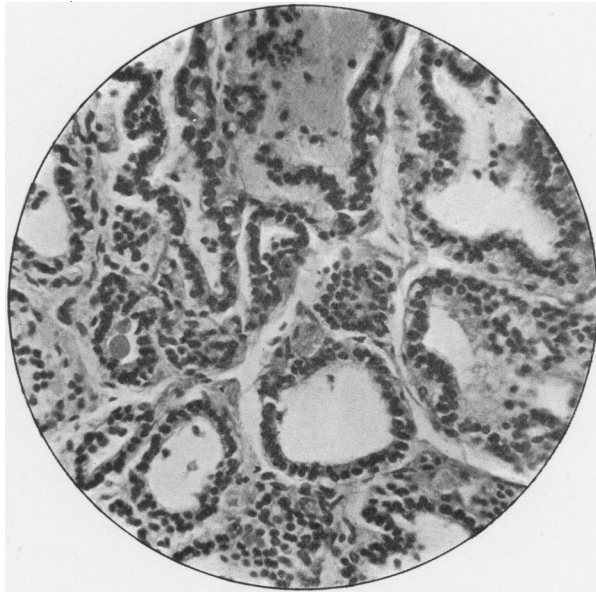


Section 10.—Comparison between twelve days' hyperplasia (left) and four days' hyperplasia (right).

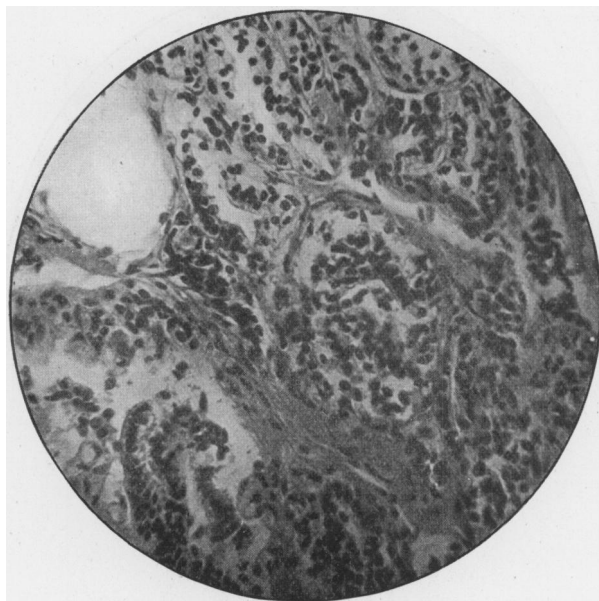
**SERIES III.—MEASLES AND BRONCHO-PNEUMONIA.**



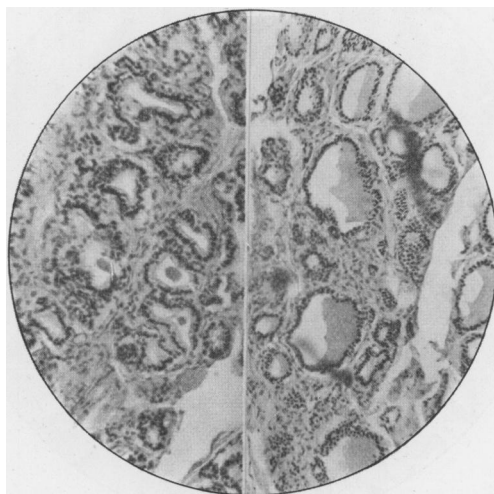
**Section 11.—Colloid absorbed ; commencing crenation.**



**Section 12.—Colloid absorbed ; vesicles crenated ; cell reaction.**

SERIES III.—MEASLES AND BRONCHO-PNEUMONIA (*continued*).

Section 13.—Complete hyperplasia, eleven days.

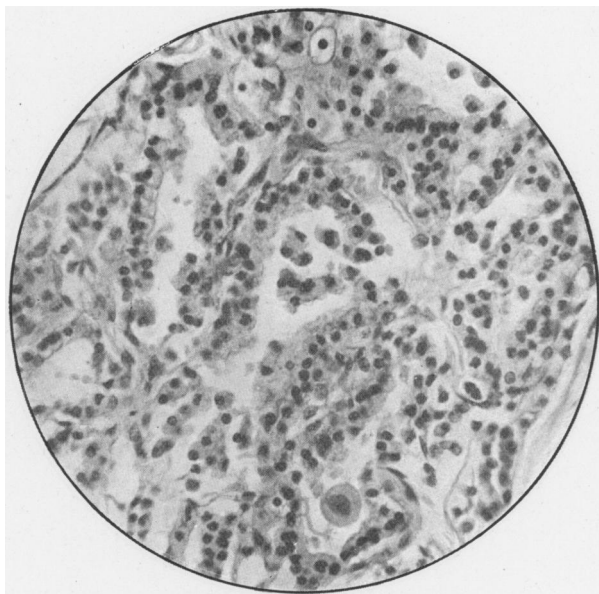


Section 14.—Left side, ten days' hyperplasia ; right side, nine days' hyperplasia.

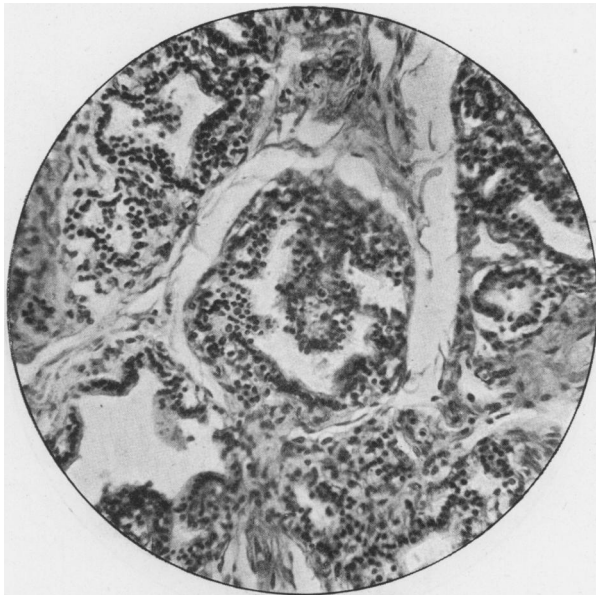
SERIES IV.—WHOOPING-COUGH AND BRONCHO-PNEUMONIA.



Section 15.—Granulation and absorption of colloid, four days. Low power.

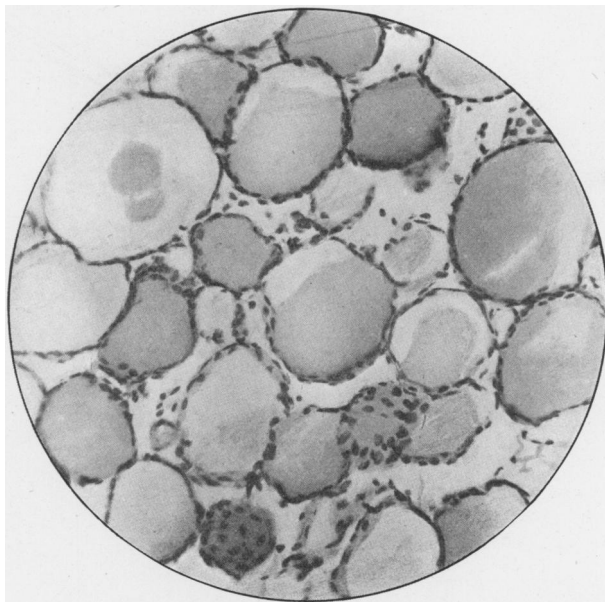


Section 16.—Vesicles infolded, colloid absorbed, fifteen days. High power.

SERIES IV.—WHOOPING-COUGH AND BRONCHO-PNEUMONIA (*continued*).

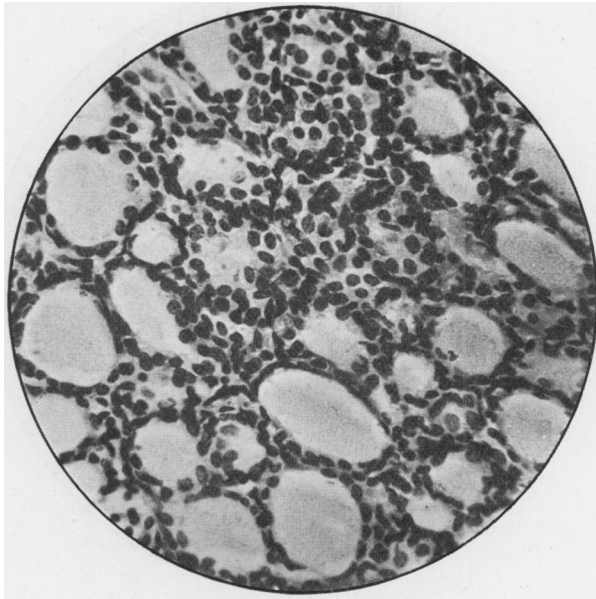
Section 17.—Method of solidification of the vesicles by infolding of their walls.

## EXPERIMENTAL TOXÆMIA.

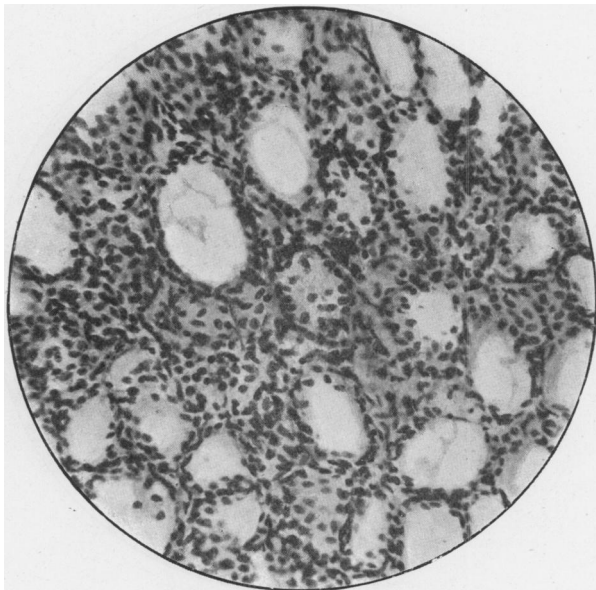


Section 18.—Thyroid from normal guinea-pig.

EXPERIMENTAL TOXÆMIA (*continued*).

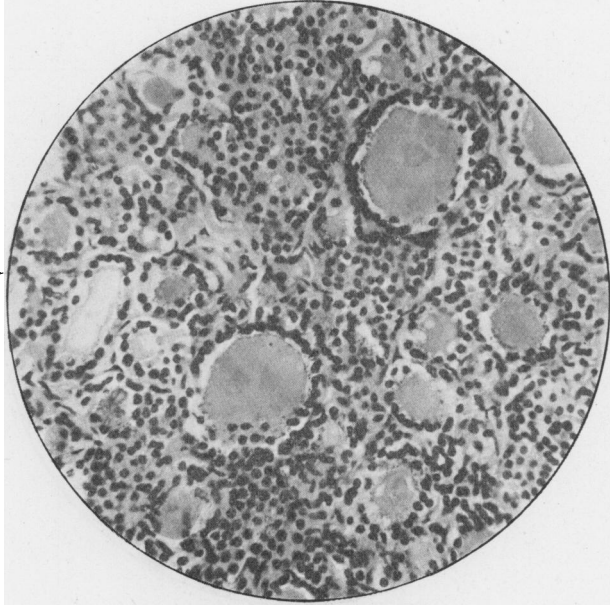


Section 19.—Cell reaction five days after injection with diphtheria toxin.

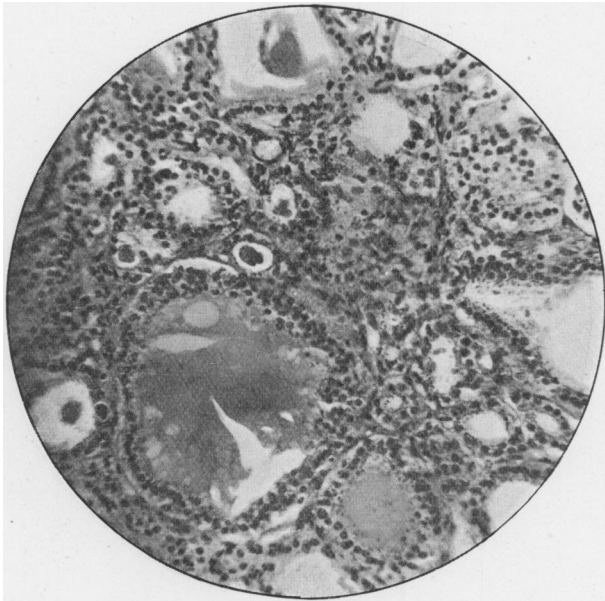


Section 20.—Hyperplasia seven days after injection with diphtheria toxin, even with thyroid administration.

## HORSE SERIES.



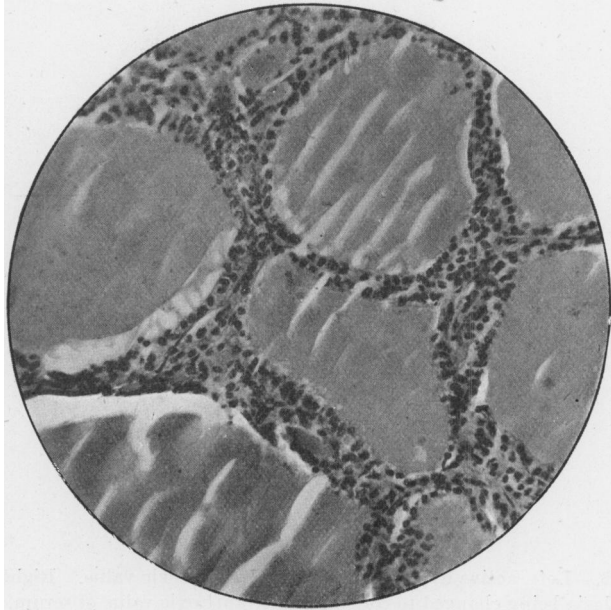
Section 21.—Active hyperplasia.



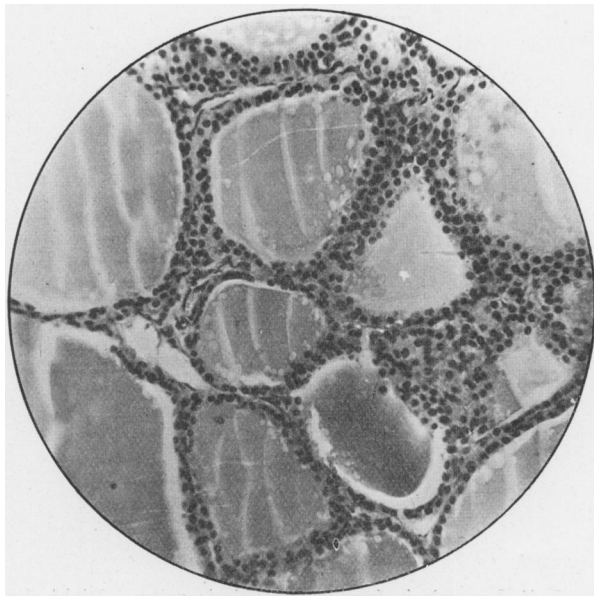
Section 22.—Hyperplasi changing to colloid gland by direct transformation of cells into colloid.



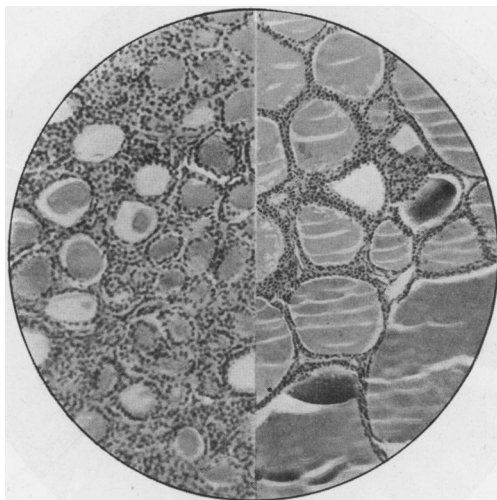
HORSE SERIES (*continued*).



Section 23.—Cells being squeezed into rows by the increasing colloid.

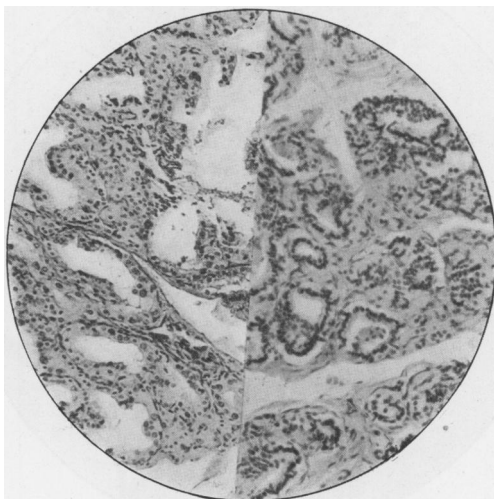


Section 24.—Similar to 23, also showing cells being transformed into colloid.

HORSE SERIES (*continued*).

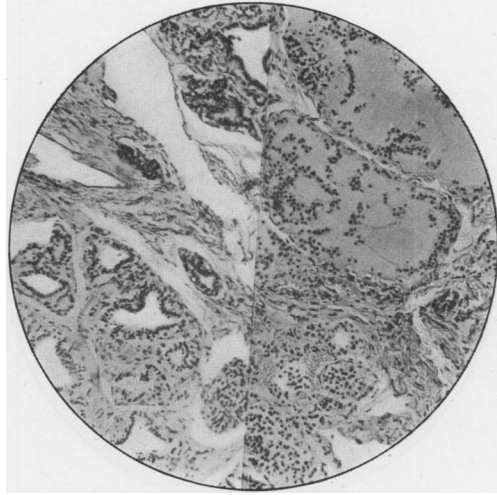
Section 25.—Left, active hyperplasia serum, low antitoxic value. Right, hyperplasia being changed to colloid, higher antitoxic value of serum.

## TUMOUR SERIES.

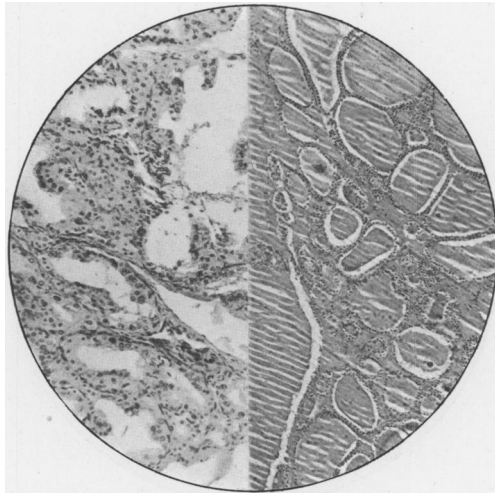


Section 26.—Left, hyperplasia from exophthalmic goitre. Right, hyperplasia from eleven days' measles.

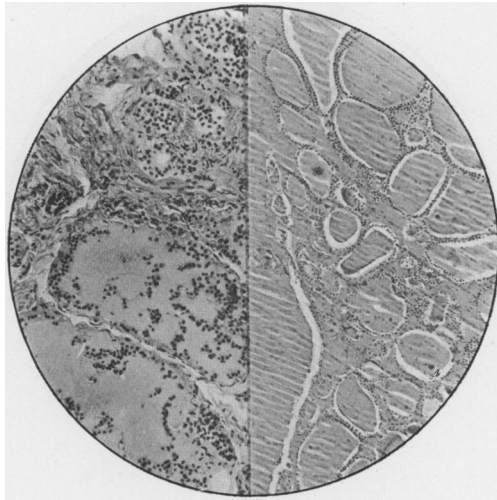
**TUMOUR SERIES** (*continued*).



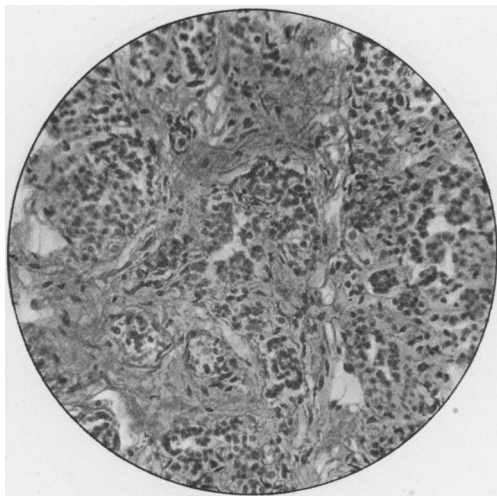
**Section 27.**—Left, hyperplasia from thirty-seven days' whooping-cough. Right, involution to colloid gland three months later.



**Section 28.**—Left, hyperplasia from active Graves's disease. Right, its involution to colloid gland.

TUMOUR SERIES (*continued*).

Section 29.—Left, involution to colloid after whooping-cough. Right, involution to colloid after exophthalmic goitre.



Section 30.—Fœtal thyroid. Condition corresponding to hyperplasia.