because when neurasthenia is definitely set up in these cases the treatment which would deal satisfactorily with his condition is not at the man's disposal. In these cases only Weir Mitchell treatment is of any avail, yet how seldom can a miner working in mining districts, remote from great hospital centres, have the advantage of what is the only treatment which will result in an efficient cure!

I have seen so many of these neurasthenic cases in North Staffordshire that I feel convinced that malingering plays practically no part in this class of case, and it should not be forgotten that one attack of neurasthenia, even if the condition improves to such an extent that the man is able to resume some form of employment, may predispose to another attack, even after a slight injury, and on one occasion I saw a coal-miner with typical symptoms who had met with no injury at all; he had been working with another man as his companion in a new cutting when the roof fell in and injured his fellow-worker, and the uninjured man was so upset at this occurrence that he became very nervous, and within a few days he presented characteristic symptoms of neurasthenia.

THE PATHOLOGICAL CHANGES OF THE THYROID IN DISEASE.*

BY

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In a paper on hyperthyroidism¹ (published in this JOURNAL last November) it was shown that the pathological changes of exophthalmic goitre could only to a certain extent be reproduced by thyroid feeding in cats, rabbits, guinea-pigs, and dormice, and, as was to be expected, hyperplasia of the thyroid was one of the changes that could not be reproduced. In another paper² it was demonstrated that a hyperplasia of the thyroid microscopically similar to that of exophthalmic goitre was to be found in diseases such as infantile diarrhoea, measles, diphtheria, and whooping-cough, and that it could be artificially induced in guinea-pigs by the injection of diphtheria toxin. Hale White³ first pointed out that if a large series of thyroids were examined they would be found to vary greatly. This was confirmed by Simpson,⁴ who described thyroid changes in certain acute diseases, and by Marine and Lenhart, who examined a series of 73 from various conditions. No attempt has yet been made to separate the diseases according to their action on the thyroid.

The object of this paper is to point out those diseases and toxæmias that do and those that do not produce an alteration in the thyroid, to describe the pathological changes in the gland, to demonstrate them by a series of illustrations, to compare them with those seen in goitre, and to note when these changes are associated with signs of thyroid excess.

The work is based on some 700 thyroids collected from *post-mortem* examinations during the last five years, but, as I have been unable to procure them from man in certain of the rarer diseases, recourse has been had to guinea-pigs and inoculation, though it is hoped that in time these may be confirmed by specimens obtained from man. There is no wish to be dogmatic from the appearance of single sections; doubtful cases have been as far as possible eliminated.

It is proposed to take the micro-organisms in alphabetical order.

BACILLI.

Bacillus aerogenes capsulatus.

The thyroids were taken from 2 cases of spreading traumatic gangrene, the one thirty-six hours, and the other four days, after infection. Pure cultures of the bacillus were grown in the first case; the thyroid showed no change. In the second case other micro-organisms were present, and the thyroid presented a complete hyperplasia with total colloid absorption.

Bacillus anthracis.

Five guinea-pigs were inoculated with anthrax and the thyroids obtained after death. Sections showed total

colloid absorption, cell hyperplasia, and some intervesicular haemorrhage. The change took place within two days.

Bacillus coli communis.

Three guinea-pigs received intraperitoneal injections of *Bacillus coli communis*. An illustration represented the thyroid of one of them that died after two inoculations, one on the sixteenth day and the other twenty-four hours before death; it showed total colloid absorption, marked cell hyperplasia and intervesicular haemorrhage.

Coliform Bacillus.

Cultures of this organism were grown from the faeces of a patient affected with endemic goitre. It is the organism that has been described by Major McCarrison⁵ as the one that produces endemic goitre in the Gilgit Valley; its characteristics are that it merely decolorizes sucrose-litmus and produces no indol. Emulsions from a culture were injected into the peritoneal cavity of three guinea-pigs; they each received two injections to give them a coliform septicaemia. The effect on the thyroid was to produce total colloid absorption and cell hyperplasia.

Bacillus diphtheriae.

The thyroids have been collected from 8 cases of diphtheria; they show an active hyperplasia, and will be described in full later.

Bacillus of Dysentery.

Three guinea-pigs were inoculated with emulsions of Flexner's bacillus and three with Shiga's bacillus. They both showed total colloid absorption with intervesicular haemorrhage; cell hyperplasia was rather more marked from the injection of Shiga's bacillus. Fig. 1 represents the thyroid from one that received two injections of Shiga's bacillus on the eleventh day and twenty-four hours before death.

Asylum Dysentery.

The glands were taken from 9 cases of asylum dysentery, and no change was observed in 3 cases before the fifth day; on the fifth day and on the sixth colloid absorption with commencing hyperplasia was present; at the end of a month complete hyperplasia had taken place, but at the end of several months the glands were found to have reverted to the colloid state.

Gaertner's Bacillus.

The thyroids were taken from 12 cases of infantile diarrhoea; an active hyperplasia was found, the degree of which varied with the duration of the disease.

Bacillus mallei.

Three guinea-pigs were inoculated with glanders. Fig. 2 represents the thyroids of one that died in twenty-four hours. It shows total colloid absorption, extreme cell hyperplasia and intervesicular haemorrhage. The change produced in this short space of time is quite remarkable.

Bacillus of Tetanus.

Three guinea-pigs were inoculated with an emulsion of the tetanus bacillus. A coloured photomicrograph of the thyroid of one that died five days after the inoculation served as a good example of the acute haemorrhagic change, though the degree of cell hyperplasia was not so marked as in some other toxæmias. This appearance is borne out by the appearance of a child's thyroid taken twelve days after an injury and four days after the commencement of tetanic convulsions.

Tubercle Bacillus.

The changes of the thyroid in tuberculosis have been gauged from 48 cases. They vary according to the type of infection. The acute miliary form produces a complete thyroid hyperplasia, the chronic a colloid hyperplasia. These reactions will be fully described later.

Bacillus typhosus.

The thyroids have been obtained from 2 cases of typhoid fever, four weeks and nine weeks respectively after infection; practically no change was found. In the specimen of four weeks' duration there was a slight chronic hyperplasia, with some excess of colloid, all but negligible.

COCCI.

Gonococcus.

No thyroid has been obtained from any case of gonococcal septicaemia, but two have been taken, one from a case of gonorrhoea that died as the result of an injury, the other from a case that died from lobar

* Read before the Pathological Section of the Royal Society of Medicine.

pneumonia; they both appeared quite normal, and showed no sign of any reaction. These two cases are, of course, insufficient from which to state that the thyroid does not react to the gonococcus.

Meningococcus.

The thyroids taken from 2 cases of cerebro-spinal meningitis in which the meningococcus had been isolated from the cerebro-spinal fluid showed but a slight change of colloid hyperplasia. The date of death after the onset of the disease was in one instance the twelfth and in the other the forty-second day.

Micrococcus catarrhalis.

Three guinea-pigs were injected with an emulsion containing the *Micrococcus catarrhalis* and were killed on the eleventh day; an acute hyperplasia was found.

Micrococcus melitensis.

Twelve Maltese goats whose serum reaction showed that they were infected with Malta fever were killed and their thyroids examined. Hyperplasia was found, which varied from a slight chronic change with excess of colloid to an extreme hyperplasia with total colloid absorption.

Pneumococcus.

Clinically, two main varieties of pneumonia are described in man, lobar pneumonia and bronchopneumonia.

Fig. 1.—Guinea-pig's thyroid after two inoculations with Shiga's bacillus on the eleventh day and twenty-four hours before death. Total colloid absorption, cell hyperplasia, and intervesicular haemorrhagic hyperplasia.

The bacteriology of the two is thought to be different. Lobar pneumonia is said to be produced by the pneumococcus, whilst bronchopneumonia is said to be capable of production by many micro-organisms. The thyroids have been taken from 39 cases, 27 being bronchopneumonia and 12 lobar. The microscopic appearances were found to vary according to the variety of infection. Fig. 3 represents two thyroids to show the comparison in the effect produced by lobar pneumonia and bronchopneumonia; the right-hand one was taken from a case of lobar pneumonia of five days' duration; it shows no trace of any reaction. The left-hand one was taken from a case of bronchopneumonia of eight days' duration; it shows a complete hyperplasia. Thus, whereas the infecting micro-organisms of bronchopneumonia may produce a thyroid hyperplasia, the pneumococcus of lobar pneumonia is incapable of doing so.

Staphylococcus.

The thyroids taken from 8 cases of septicaemia due to the *Staphylococcus pyogenes aureus* and *albus* showed no evidence of any thyroid reaction.

Streptococcus.

The thyroids have been taken from 41 cases of streptococcal septicaemia and other infections commonly thought to be due to some variety of streptococcus: *Streptococcus anginosus* of scarlet fever, *Streptococcus equinus* from bone infections in the horse, *Streptococcus erysipelas* from erysipelas, *Streptococcus faecalis* from streptococcal septicaemia, *Streptococcus puerperalis* from puerperal fever, and *Streptococcus rheumaticus* from malignant endo-

carditis. The effect of these diseases was found to vary. No opinion could be given of the effect of erysipelas, as complications capable of producing a thyroid change were present. Cases infected with *Streptococcus equinus*, *faecalis*, or *pneumoniae* presented normal thyroids. The thyroids from cases of scarlet fever showed a colloid hyperplasia. These changes have been described by K. E. Gregor.⁷ No thyroid changes other than the hyperplasia of pregnancy were found in 6 cases of puerperal fever.

Eleven thyroids were examined from cases of malignant endocarditis and rheumatic fever; the age of the patients varied from 8 to 55, and the duration of the disease, in the acute cases, from seven days to seven months, and in the chronic had existed over a period of years. The acute cases may be classified into three groups, though the bacteriology has not been completely worked out. First, cases of malignant endocarditis in which a streptococcus was found in the blood; secondly, those in which it was not found; and thirdly, those described as acute rheumatic fever in which again no micro-organism was found. Of the 2 cases of malignant endocarditis in which a streptococcus was found in the blood, the thyroid of one was quite normal, but the other presented a slight colloid hyperplasia. The cases of malignant endocarditis in which the streptococcus was not found showed some colloid hyperplasia, whilst the 3 cases of rheumatic fever showed a well-marked colloid hyperplasia. Uncomplicated cases of old endocarditis showed an intervesicular

Fig. 2.—Complete hyperplasia produced in guinea-pig's thyroid twenty-four hours after inoculation with *B. mallei*.

fibrosis, but cases with renal and other complications from cardiac incompetence showed as well absorption of the colloid and stages towards a complete hyperplasia. From these results one concludes that the streptococcus has no effect on the thyroid except in scarlet and rheumatic fever, but the changes in these diseases may be due to the presence of other micro-organisms.

Acute Surgical Infections.

The acute surgical infections, such as appendix abscess, intestinal obstruction, acute general peritonitis, produce no change in the thyroid. This led me to suppose, and to state in a preliminary paper, that the *Bacillus coli communis* had no effect on the thyroid, but it has just been demonstrated that when it is injected into guinea-pigs an acute hyperplasia is produced. This apparent difference may be ascribed to the rapidity with which the *Bacillus coli* dies out in the presence of excess of streptococci, so that these infections must be regarded as streptococcal.

PROTOZOA.

Coccidiosis.

The thyroids taken from rabbits affected with coccidiosis showed no evidence of any change.

Spirochaeta pallida.

Up to the present I have been unable to collect any thyroids from cases of primary or secondary syphilis, but a hyperplasia has been described in cases of malignant secondary syphilis. The thyroids from two cases of congenital syphilis showed extreme hyperplasia, but nothing

can be deduced from this, as there was coexisting syphilitic cirrhosis of the liver with ascites. The thyroids taken from 19 cases of general paralysis of the insane and from other late syphilitic affections, such as multiple gummata and arteritis, show some excessive intervesicular fibrosis.

Malaria (Blackwater Fever).

The thyroid taken from a case of blackwater fever of five days' duration showed granulation and partial absorption of the colloid, with commencing acute hyperplasia. There was a two years' history of malaria with three definite attacks. The last attack was the only one accompanied by haemoglobinuria.

STREPTOTHRIX.

Actinomycosis.

The thyroids were taken from 2 cases of actinomycosis, one of eight and a half and one of four months' duration. An illustration showed mild chronic hyperplasia with excessive colloid formation; the small newly formed vesicles were squeezed up between the large. In the second specimen they appeared as encapsuled adenomata.

DISEASES DUE TO UNKNOWN ORGANISMS.

Measles.

The thyroids from 8 cases of measles all showed an extreme hyperplasia, the degree of which varied with the duration of the disease.

Fig. 3.—Two human thyroids taken from cases of pneumonia; the left-hand one shows complete hyperplasia after eight days' bronchopneumonia; the right-hand one shows a normal thyroid after five days' lobar pneumonia.

Acute Anterior Poliomyelitis.

The thyroid from a case of acute anterior poliomyelitis showed a mild chronic hyperplasia with cell increase and excess of colloid.

Polyserositis.

A case of polyserositis due to some unknown cause produced no change in the thyroid.

Small-pox.

I have been unable to obtain the thyroids from any cases dead of small-pox; changes have been described by other observers.

Whooping-cough.

Extreme thyroid hyperplasia was found in 3 cases of whooping-cough.

MALIGNANT DISEASE.

The thyroids taken from 31 cases of sarcoma and carcinoma showed no evidence of any reaction. The cells were small, flattened, and appeared inactive, except in those cases in which death occurred from some intercurrent infection capable of producing a thyroid change.

GLAND DISEASES.

Addison's Disease.

The thyroids taken from cases of Addison's disease were found to vary according to the infection that produced the disease. An illustration represented two thyroids from

cases of tuberculosis of the suprarenals; the right half showed an extreme degree of hyperplasia, the left half a slight colloid hyperplasia. This difference is to be accounted for by the presence of tuberculosis elsewhere; in the left half it was practically limited to the suprarenal, whilst in the right pulmonary and other tuberculosis was present. Absence of the suprarenal secretion appears to produce no thyroid change.

Cirrhosis of the Liver.

The thyroids taken from 6 cases of cirrhosis of the liver all showed considerable fibrosis, but between the strands of fibrous tissue complete hyperplasia with total colloid absorption was found. The degree of this hyperplasia varied somewhat. It was most marked in the late stages of cirrhosis combined with ascites.

Diabetes.

The thyroids were taken from 3 cases of diabetes caused by fibrosis of the pancreas; they showed no hyperplasia. Two of the cases had died of coma and the other of exhaustion. One concludes that diabetes and its accompanying acidosis have no effect on the thyroid.

Jaundice.

Jaundice produces no thyroid change, for no hyperplasia was found in cases dead from carcinoma of the liver or gall bladder, even though accompanied by severe jaundice.

Fig. 4.—Four human thyroids taken from cases of diphtheria dead on the fourth, seventh, seventh, and twelfth days. (A) On the fourth day the colloid is granular and partially absorbed; (B) on the seventh day it is totally absorbed; (C) on the seventh day there is cell proliferation and infolding of the walls of the vesicles; (D) on the twelfth day the vesicles cannot be distinguished, and the cells are columnar in shape.

Diseases of the Kidney.

Some acute inflammatory conditions of the kidney cause a thyroid reaction, whilst others seem to have no such effect. In chronic interstitial nephritis the thyroids sometimes appear quite normal, even though the cases died of uraemia; in others there is an excessive formation of fibrous tissue, which is, perhaps, a late effect of the original toxæmia that caused the nephritis; while, again, others show an extreme hyperplasia, the most marked case of which was associated with gout. In other words, renal disorders, either acute or chronic, are not necessarily accompanied by thyroid changes, though these may occur.

BLOOD DISEASES.

Lymphadenoma.

The thyroids taken from a case of Hodgkin's disease of one year's duration showed no thyroid reaction.

Lymphatic Leukaemia.

The thyroid taken from a case of lymphatic leukaemia showed no change.

Pernicious Anaemia.

The thyroid taken from a case of pernicious anaemia showed a well-marked colloid hyperplasia.

ARTIFICIAL TOXAEMIAS.

In a former article it was proved from the injection of 15 horses and some 50 guinea-pigs that thyroid hyperplasia could be produced by the injection of diphtheria toxin. From the injection of 6 guinea-pigs it was found that similar effects could be produced by substances such as abrin and ricin. An illustration represented a guinea-pig's thyroid fourteen days after an injection of 0.0000025 gram of ricin; extreme cell hyperplasia and colloid absorption was shown. Ten times this dose was used in the injections of abrin. From these examples the conclusion is drawn that thyroid hyperplasia is caused by certain toxins; that is, that it is not caused by micro-organisms, but by the toxins that certain micro-organisms produce.

DESCRIPTION OF THE THYROID CHANGES.

It will have been noticed from the preceding illustrations that the degree of hyperplasia has varied from a total absence of colloid and cell increase with intervesicular haemorrhage—acute haemorrhagic hyperplasia—to a slight cell increase, accompanied by abundant masses of colloid—colloid hyperplasia. From observations on thyroid, obtained from man and animals, one finds that the thyroid change is dependent on the amount, virulence, and duration of the toxæmia with a slight variation in the individual. In making these observations it is necessary to take into account the age of the patient, as the vesicles are smaller and the gland more cellular in early than in later life.

The diseases and toxæmias may be divided into three groups according to the effect that they have on the thyroid. In the first are those that produce no thyroid change; in the second those that slightly stimulate it and induce a colloid hyperplasia; in the third those that have a marked effect and cause a complete or acute thyroid hyperplasia:

GROUP I.—Diseases which produce no Effect.

Bacilli: Typhoid.

Cocci:

Gonococcus (?)	Staph. albus	Strep. puerperalis
Pneumococcus	Strep. equinus	Strep. rheumaticus
Staph. aureus	Strep. faecalis	Acute surgical

Protozoa: Coccidiosis.

Diseases due to Unknown Micro-organisms: Polyserositis; carcinoma; sarcoma.

Gland Diseases: Addison's disease; diabetes; jaundice.

Blood Diseases: Lymphadenoma; lymphatic leukaemia.

GROUP II.—Diseases which induce a Colloid or Chronic Hyperplasia.

Bacilli: Coliform (chronic in man); tuberculosis (chronic).

Cocci: Micrococcus melitensis; meningococcus (slight).

Protozoa: Syphilis (tertiary).

Streptothrix: Actinomycosis.

Diseases due to Unknown Micro-organisms: Acute anterior poliomyelitis; rheumatic fever; scarlet fever.

Gland Diseases: Chronic nephritis.

Blood Diseases: Pernicious anaemia.

GROUP III.—Diseases which cause a Complete or Acute Hyperplasia.

Bacilli:

Aërogenes capsulatus (?)	Dysentery (Flexner)
Anthrax	Dysentery (Shiga)
Coliform—acute (guinea-pigs)	Gaertner
Diphtheria (man)	Mallei
Diphtheria toxin (horses, guinea-pigs)	Tetanus
Dysentery (asylum)	Tuberculosis (acute)

Cocci: Micrococcus catarrhalis.

Protozoa: Syphilis (secondary); malaria.

Diseases due to Unknown Micro-organisms: Measles; broncho-pneumonia; small-pox (?); whooping-cough.

Gland Diseases: Chronic nephritis; cirrhosis of liver.

Artificial Toxaemias: Abrin; ricin; diphtheria toxin.

Judging from the effect of tuberculosis, one concludes that when the toxæmias of Group III are small in amount and chronic in duration they may produce a colloid hyperplasia instead of a complete hyperplasia, but no increase in the intensity or duration of the toxæmias of Group I will enable them to have the effect of either Group II or Group III.

ACUTE AND COMPLETE HYPERPLASIA.

The first change that the thyroid undergoes as the result of an acute toxæmia is an alteration in the colloid material. It loses its staining capacity, becomes

granular, vacuolated, and finally disappears. During this change the gland is congested with perhaps inter-vesicular haemorrhage. The walls of the empty vesicles become plicated, the short or flat epithelial cells lining the vesicles become high cubical, and finally columnar and greatly increased in number. The plication of the walls and the cell increase go on until the vesicles, as such, are indistinguishable; during the transition the appearance is given of villous processes growing from the walls of the vesicles. When the hyperplasia is complete, the gland is hypertrophied, but its store of secretion is exhausted. The distinction between the acute and the complete hyperplasia is that in the acute the intervesicular haemorrhage is the most marked feature, the cell and vesicular changes have not progressed as far as that seen in the complete. The length of time that it takes to undergo a complete hyperplasia varies with the toxæmia and its intensity; the whole change may take place in twenty-four hours, as was shown in Fig. 2, which represented the thyroid of a guinea-pig twenty-four hours after an inoculation with glanders.

Diphtheria may be taken as a fair example of the acute toxæmias that act on the thyroid. Fig. 4 represents four thyroids taken from cases dead of diphtheria on the fourth, seventh, seventh, and twelfth days respectively. The stages in the production of complete thyroid hyperplasia are shown. In (A), on the fourth day, the colloid is granular and partially absorbed; in (B), on the seventh day, it has been totally absorbed, and the cells have commenced to increase in number and to elongate; in (C), also on the seventh day, a further change is shown; the walls of the vesicles are infolded, so that the outline of the vesicles can only just be distinguished; the cells are proliferated; in (D), on the twelfth day, the vesicles cannot be distinguished, and the cells are columnar in shape.

So certain is this hyperplasia that the thyroids taken from any one of these acute infections can be arranged in the order of the duration of the disease as it corresponds to the degree of hyperplasia, allowance being made for the very acute infections which can be noted by the extreme degree of intervesicular extravasation. From a series it is possible to estimate the duration of a toxæmia by making a comparison of the hyperplasia with a series the duration of which is known. It has also served to differentiate one disease from another. A thyroid was sent to me as being from a case of tuberculous meningitis, but, as it showed no hyperplasia, inquiry was made, and it was found that the diagnosis *intra vitam* was tuberculous meningitis; but *post-mortem* examination showed it to be a case of pneumococcic meningitis. The pneumococcus, as previously shown, produces no thyroid hyperplasia, whilst tuberculosis does.

THE INVOLUTION OF ACUTE HYPERPLASIA.

The question now arises as to the manner in which acute or complete hyperplasia involutes back to normal. Guinea-pigs were inoculated with sublethal doses of micro-organisms and the animals killed at various dates after recovery and the thyroid changes noted. It was found that the vesicles were reformed by the direct transformation of the cells into colloid material. This process is well seen in the horse that has been injected with diphtheria toxin; collections of cells are found arranged more or less concentrically; the outer two or three layers stain normally, but as the rows are traced towards the centre the staining capacity diminishes and they become brown in colour, partially broken up, and are, towards the centre, indistinguishable from the colloid material. The vesicles are at first small in size and full of colloid; they enlarge as fresh colloid is formed, and the lining cells become flattened. The blood that had been extravasated into the intervesicular spaces is invaded by a round-celled infiltration and transformed into young fibrous tissue. To sum up, the involution of an acute hyperplasia is associated with three distinct changes: The reformation of the vesicles by the direct change of the cells into colloid, the enlargement of the vesicles with the squeezing up of the cells between them, and the inter-vesicular fibrosis. At the end of the process there is some destruction of thyroid tissue with fibrosis. During the involution different portions of the gland may present different stages, so that colloid material may be absent in one part and in excess in another.

The difference between the involution of the acute and the complete hyperplasia is that fibrosis is the most marked feature of the acute and excessive colloid formation in the complete. The production of thyroid fibrosis will be further considered in a later paper.

An illustration represented the thyroid of a guinea-pig killed twenty days after inoculation with glanders; it showed the formation of young fibrous tissue and new vesicles. Another illustration represented the thyroid from a guinea-pig thirty days after a sublethal injection of abrin; the gland had undergone involution and the vesicles were small in size, sparse in number, full of colloid, and separated by strands of fibrous tissue.

An acute toxæmia thus causes a cycle of thyroid changes. First, there is an acute hyperplasia in which the gland becomes hypertrophied and exhausted; when the toxin is overcome the gland involutes back to normal, but the effect of the toxæmia is evident by the diminution of thyroid tissue and the intervesicular fibrosis. In the less acute toxæmias the cell hyperplasia is more marked and the subsequent formation of excess of colloid during involution.

Fig. 5.—Six human thyroids from cases of tuberculosis. A, After three weeks' miliary tuberculosis, an active hyperplasia, with colloid absorption. B, After seven weeks' miliary tuberculosis, a more marked hyperplasia, with some intervesicular fibrosis. C, After three months' miliary tuberculosis, a complete hyperplasia. D, Chronic tuberculosis; early colloid hyperplasia; small vesicles amidst surrounding cell proliferation. E, Further stage of chronic tuberculosis, an increased colloid hyperplasia; the vesicles are larger, but unequal in size and packed with colloid; the cell proliferation is squeezed up between them. F, The final stage of fibrosis.

PRODUCTION AND INVOLUTION OF CHRONIC OR COLLOID HYPERPLASIA.

The effect of the toxæmias in Group II and the chronic forms of Group III is at first to cause some granulation and vacuolation of the colloid. The granulation is coarser than that found in the acute hyperplasias; it is indicative of some colloid absorption. The lining cells become high cubical and are proliferated; between the vesicles there may be several rows. The vesicles are at first of equal and of normal size, the gland is congested. The degree of this change varies with the toxæmia—the greater the intensity the greater the absorption of colloid and cell proliferation. The further change is brought about because the new formation of colloid from the proliferated cells is greater than the colloid absorption. The result is that large vesicles are formed and are distended with densely packed colloid which cracks on the microtome. In the colloid may be seen sprig-like projections of cells called by Marine reversions; between the large vesicles fresh ones are formed from the cell proliferation, so that at this stage the vesicles are of unequal size; some are larger and some smaller than normal. The chronic congestion of the gland leads to intervesicular fibrosis. The

cell proliferation and colloid formation may proceed for some years, but eventually the gland becomes cirrhotic with destruction of thyroid tissue; the small portion of active gland left then undergoes an active hyperplasia. Thus there are three characteristic stages in chronic hyperplasia: First, when the vesicles are of equal size, the colloid is partially absorbed and coarsely granular and the cells are proliferated; secondly, when the vesicles are of unequal size and packed with colloid with cell hyperplasia between them; and, thirdly, when the gland is cirrhotic with deficiency of thyroid tissue.

Tuberculosis may be taken as a typical example of the chronic toxæmias, but the miliary variety must be regarded as an acute or subacute toxæmia. The two may be taken together and arranged in one complete thyroid circle and be followed over a period of years, and the comparison seen between the complete and the colloid hyperplasia. Fig. 5 represents six thyroids taken from cases of tuberculosis. They are arranged in a circle passing up to the complete hyperplasia and involuting down towards normal. A, B, and C are from cases of miliary tubercle; D, E, and F are from cases of chronic tuberculosis. A represents a thyroid from a case of miliary

Fig. 6.—Thyroid from a case of cirrhosis of the liver; cirrhotic thyroid, intervesicular fibrosis, with complete hyperplasia.

tubercle of three weeks' duration; it shows an active hyperplasia with colloid absorption. B represents a thyroid after seven weeks' miliary tubercle; it shows a further hyperplasia with some intervesicular fibrosis. C shows a complete hyperplasia after three months' miliary tubercle; the thyroid hyperplasia has here reached its height. D, taken from a case of chronic tuberculosis, shows a colloid hyperplasia in its first stage. E shows a colloid hyperplasia in its second stage; the vesicles are of unequal size and packed with colloid; between them is the cell hyperplasia. In F the thyroid is represented by a mass of fibrous tissue. This fibrosis is independent of the local tubercles seen in the illustration. The series of changes seen in Fig. 5 could not occur in such typical form in any one case, since the disease in such severity as is illustrated in A, B, C would have proved fatal at too early a stage to permit of the changes shown in D, E, F.

The extent of these changes varies according to the amount, intensity, and duration of the toxæmia. These thyroid cycles must be altered accordingly, and the final condition of the gland after involution will also vary in the extent of the destruction that has been produced. In Fig. 5 the thyroid is represented as being finally left in a state of almost complete fibrosis, but the final condition may be anywhere between this fibrosis and the normal according to the degree and duration of hyperplasia.

It is to be specially noted that colloid hyperplasia can be produced by three different conditions: First, during the involution following an acute toxæmia; secondly, during the production, and thirdly, during the involution following a chronic toxæmia.

COMPARISON OF THE EFFECTS OF THE SINGLE TOXAEMIAS WITH THE PATHOLOGICAL CHANGES FOUND IN GOITRE.

The microscopical appearances of the thyroid during these cycles correspond to those described in goitre by Marine and Lenhart; exophthalmic goitre represents the complete hyperplasia, and in the course of time involutes through a stage of colloid hyperplasia to a condition of fibrosis. An illustration of this was given in a previous paper. Endemic goitre, as described by Marine and Lenhart, corresponds to a colloid hyperplasia due to the effect of a chronic toxæmia, the final result of which is the destruction of thyroid tissue with fibrosis.

The size of the glands would appear to be not so greatly affected by the toxæmias as might be expected. The absorption of the colloid and the crenation of the vesicles, which would reduce the size in the first stage of acute hyperplasia, appears to be largely counteracted by the intervesicular extravasation. During the stage of involution the gland tends to increase in size, as is suggested by the squeezing up of the cells between the enlarging vesicles. In the very acute toxæmias, however, the gland is swollen from extravasation, while in the later stages it is smaller than normal, as is suggested by the diminution of the number of vesicles. In the chronic toxæmias the gland is increased in size in both stages. Comparing the variations in size from the toxæmias with the alteration in goitre, one finds that the gland may or may not be enlarged in exophthalmic goitre, but that the thyroid in endemic goitre shows considerable enlargement; thus the thyroids in the acute toxæmias and in exophthalmic goitre may be of the same size, but there is a great disparity between the chronic toxæmias and endemic goitre.

No signs of thyroid excess are found in the hyperplasia of either the acute or the chronic toxæmias nor in the colloid hyperplasia of endemic goitre, though they are found in the hyperplasia of exophthalmic goitre. So it may be said that there are two main differences between the hyperplasias of the toxæmias and the hyperplasias of the goitres, one the hyperthyroidism of exophthalmic goitre when compared to the complete hyperplasia of the toxæmias, and the other the increase in size seen in endemic goitre compared to that of the chronic toxæmias.

REPEATED AND DOUBLE TOXAEMIAS.

Repeated toxæmias, or at any rate repeated injections of diphtheria toxin, lead not only to the production of thyroid hyperplasia, but also to the formation of antitoxin. It was found from observations on 15 horses that the hyperplasia decreased as the antitoxic value of the serum increased. (For a full account see *Lancet*,⁶ December 27th, 1913.) The antitoxin in the serum protected the thyroid from the action of the toxin. Unfortunately, practically nothing is known of the production of antitoxin, or even whether antitoxins are formed in the toxæmias other than that of diphtheria. So this can only be applied to the extent of saying that it is probable that the toxæmias that are counteracted by the formation of antitoxin only produce a thyroid hyperplasia when antitoxin is absent or deficient.

To give the effect of a second toxæmia acting on the thyroid before recovery is complete from the first, guinea-pigs were injected twice with emulsions of *Bacillus coli communis*, *B. mallei*, and of dysentery and other micro-organisms; it was found that an increased hæmorrhagic hyperplasia was produced.

The result of an acute toxæmia supervening on a chronic can be seen in man when miliary develops on chronic tuberculosis, but the toxæmia only differs in intensity. An illustration showed the thyroid of a man who developed miliary on tuberculosis of two years' duration; extreme hyperplasia was shown amongst excess of fibrous tissue. The gland was not increased in size, but after the onset of miliary tuberculosis exophthalmos developed, and *post mortem* there was no reason to account for this beyond the hyperplasia of the thyroid. Signs of hyperthyroidism developed in this way one would expect to be rare, as the toxin of miliary tuberculosis would have to act during the stage of active colloid hyperplasia, not during the stage of involution or fibrosis; also the acuteness of the toxæmia would mask the symptoms except exophthalmos, even if it did not cause death before its production.

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Of the toxæmias that have been described, cirrhosis of the liver is an example in which a subacute toxæmia develops on a chronic; at the onset of ascites a subacute toxæmia arises which acts together with the existing toxæmia caused by the deficiency of the liver. Observations have been made on the occurrence of exophthalmos in cases of cirrhosis of the liver, and it has been found in 10 out of 12; it may be either unilateral or bilateral. It occurred in both hypertrophic and atrophic cirrhosis with or without ascites, but it was most marked in the late cases of cirrhosis with ascites. The photograph shows double exophthalmos in a late case of cirrhosis with ascites, and Fig. 6 shows the cirrhotic thyroid that has undergone complete hyperplasia. It was previously noted that chronic interstitial nephritis is sometimes associated with complete thyroid hyperplasia. This disease may be taken as an example of a steadily increasing toxæmia with exacerbations in the later stages. There is no enlargement of the thyroid, yet exophthalmos would appear from the literature to be not uncommon. Professor Barker⁹ found it in 16 out of 33 of his cases at the Johns Hopkins Hospital, and he stated that it was not due to chronic arterial hypertension and that it varied with the exacerbations of the disease. From personal observations on a small number of cases it was noted, but in a smaller percentage. Levison¹⁰ also described it in chronic nephritis, and stated that it occurred in other chronic toxæmias.

Fig. 7.—Photograph. Cirrhosis of the liver, with ascites, and exophthalmos.

These examples are of importance in that they serve to bridge over the gap between the thyroid changes and hyperthyroidism of the toxæmias and those of goitre. These considerations enable one to trace the effect of diseases on the thyroid from birth upwards, and they lead to the production, prevention and cure of certain thyroid conditions.

The experimental portion of this work was done in Professor A. R. Cushny's laboratory at University College, and I am much indebted to him for his care and advice. The infective injections were made at the Lister Institute, for which I am indebted to Dr. J. C. G. Ledingham and Dr. Schutz. The morbid material was largely obtained from the Westminster Hospital; for this and for his advice I am very grateful to Dr. R. G. Hebb, also to Dr. Braxton Hicks, Dr. Lazarus-Barlow, Colonel Blenkinsop, D.S.O., Dr. A. Davies, Dr. R. R. Elworthy, Dr. A. C. Inman, Major Kennedy, Dr. F. W. Mott, Dr. O. P. N. Pearn, Dr. J. D. Rolleston, Dr. G. L. Thompson, Dr. F. M. Turner, and Dr. Them Zammitt. The photomicrographs were taken at the Bethlem Royal Hospital, for which I am indebted to Dr. W. H. B. Stoddart and Mr. Crow.

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THE fifth congress of French-speaking practitioners of medicine is to be held in Paris on April 14th and two following days. There will be an exposition of apparatus, drawings, etc., in connexion with the congress.

A MEETING of members of the Italian Chamber of Deputies was recently held for the purpose of appointing a medico-parliamentary committee to watch the course of legislation in regard to questions of public hygiene. Professor Santoliquido was in the chair. Drs. Maffi, Bussi, and Morisani were chosen as secretaries. There is no president and no council.