THE CAUSATION, PREVENTION, AND CURE OF GOITRE, ENDEMIC AND EXOPHTHALMIC.

By RUPERT FARRANT, F.R.C.S.,

SURGICAL REGISTRAR TO THE WESTMINSTER HOSPITAL.

[WITH SPECIAL PLATE.]

In an article published in the *Proceedings of the Royal Society of Medicine*, February, 1914,¹³ it was shown that the toxæmias could be divided into three groups according to their action on the thyroid. In the first group were those that had no effect on the gland, in the second those that caused a colloid hyperplasia, and in the third those that caused a complete or acute hyperplasia. It was found that the microscopical appearances of the colloid hyperplasia were indistinguishable from those seen in endemic goitre, whilst the microscopical appearances of complete hyperplasia were indistinguishable from those seen in exophthalmic goitre. No definite signs of hyperthyroidism were observed in cases affected with a single toxæmia. Neither were they seen in guinea-pigs after inoculation with two acute toxæmias—the second being injected before recovery was complete from the first. But hyperthyroidism, as judged by the occurrence of exophthalmos, was found in a man in whom an acute toxæmia had supervened on a chronic. The case was one in which miliary tuberculosis had developed on chronic. It was also found when a subacute toxæmia had supervened on a chronic. Ten out of 12 cases of cirrhosis of the liver presented exophthalmos. It had also been described in chronic interstitial nephritis, which may be regarded as a chronic toxæmia liable to exacerbations. As death occurred in these cases soon after the occurrence of hyperthyroidism, a complete picture was obtained of the toxæmias causing extreme thyroid hyperplasia and the thyroid hyperplasia causing signs of hyperthyroidism.

These examples serve to bridge over the gap between the thyroid changes found *post mortem* and the thyroid changes and hyperthyroidism found clinically in either endemic or exophthalmic goitre.

The object of this paper is to record observations made on 85 cases of goitre (exclusive of simple hyperthyroidism) between 1909 and 1914 as to the relationship between toxæmias and diseases of the thyroid; to prove that cases in which the thyroid is diseased the causatory micro-organism or toxæmia can be determined; to show that in this way not only can diseases of the thyroid be cured, but also prevented.

CAUSATION.

It is proposed, for the sake of convenience, to subdivide the micro-organisms and toxæmias into four groups, according to their situation; they are usually in the mouth, nose, lung, or intestine.

The Mouth.

Pyorrhoea and dental caries are associated with micro-organisms of all kinds; some, such as the streptococcus, staphylococcus, and pneumococcus, can at once be eliminated, as they have no effect upon the thyroid. Any change must, then, necessarily be determined by some other infection. Observations were made at Mr. Landon Whitehouse's dental clinic in 1909 on cases that attended for teeth extraction. Signs of hyperthyroidism were found in about 7 per cent. of cases. Bacteriological examination of the teeth was made in too small a number for the causatory organisms to be determined. The cases were mostly females between the ages of 17 and 30. The history given was that of nervousness, with falling out of the hair and moistness of the palms of the hands, slight loss of weight. Examination revealed a fine moist skin, fine glistening hair, tremor, tachycardia of about 110, perhaps slight prominence of one or both eyes, with or without general fullness or enlargement of the thyroid. No one of these signs was sufficiently prominent for any gross thyroid lesion to be suspected, but taken together they showed a typical picture of hyperthyroidism. Cases of dental

caries frequently do not attend until they are suffering from one of the secondary results, as chlorosis, dyspepsia, or osteo-arthritis. Observations were therefore extended to such cases. An exactly similar condition was found in a few of the early cases of dyspepsia, in a large proportion of the early cases of osteo-arthritis, and in some cases of chlorosis.

This association of hyperthyroidism and chlorosis was first described by Chvostek; he thought it was a forme fruste of exophthalmic goitre. The symptoms of hyperthyroidism in these cases thus pass unnoticed, as they are masked by the other more prominent effects of the toxæmia. There is one exception, that is, when the case comes to the ophthalmic surgeon with unilateral exophthalmos. Any one of the symptoms of hyperthyroidism may become more prominent than the others. It may affect the hair, skin, vasomotor or central nervous system; the cases being diagnosed and treated for this one symptom, thus alopecia, hyperidrosis, urticaria scripta, tachycardia, and hysteria. Examination has shown that in some of the cases so affected the other signs of hyperthyroidism are to be found.

CASE I.—M. L., female, 33. A case with carious teeth, pyorrhoea, dyspepsia, and commencing pains in her joints associated with hyperthyroidism, the most prominent symptom of which was unilateral exophthalmos (Fig. 1). There was some slight fullness of the thyroid.

Fig. 2 shows the diminution of the exophthalmos after ten weeks; no treatment or drug of any kind was given, and she continued her work (Mr. Brooksbank James's case).

The relation between the pyorrhoea and hyperthyroidism is not merely a coincidence, but is that of cause and effect, as the following shows. After teeth extraction, for the first week there is some increase of symptoms; they then rapidly clear up for two or three months, but it is usually six months before they disappear entirely.

CASE II.—M. W., female, 32. A similar case, but with slight bilateral exophthalmos; refused to have her teeth removed. She was treated for one year with the following drugs: Iron, arsenic, nuxvomica, belladonna, and aloin, without improvement. Her teeth were then put in order; the hyperthyroidism disappeared in six weeks.

An attempt was made to follow these cases over a period of five years—letters were written to 10 cases, no answers were received from 9 whose teeth had been removed; the tenth, who had refused to have her teeth removed, came up for examination; the signs of hyperthyroidism had increased, she had unilateral exophthalmos, marked tremor, and a pulse of 120.

The occurrence of some nervous shock causes an exacerbation of the symptoms, especially those connected with the nervous system.

CASE III.—M. M., female, 23. Carious teeth, dyspepsia (for which gastro-jejunostomy had been performed), associated with hyperthyroidism. Her teeth were removed, but her father died a few days later, and she developed typical exophthalmic goitre. This subsided in a few months. She then nursed her brother, who died, and she again developed exophthalmic goitre, which again subsided after some months.

A second toxæmia acting on a gland that is already in a condition of complete hyperplasia from infection of the teeth causes an enlargement of the gland, with an exacerbation of the symptoms, the degree of which varies with the intensity and duration of the toxæmia. The symptoms may continue for one to two months after the infection has to all appearances ceased.

CASE IV (Dr. Purves Stewart's case) (Fig. 3).—A. L., male, 30. He had had bad teeth since a child, a persistent cough three years, with slight hæmoptysis two years ago. Eighteen months ago he had had a bad attack of influenza. He stated that he had always been nervous; he first noticed palpitation two to three years ago. Following the influenza his eyes became prominent, he lost weight, and became weak and tremulous. Examination revealed acute exophthalmic goitre accompanied by sleeplessness, delirium and mania, persistent vomiting, and diarrhoea. Amyotonia was so marked that it was first thought to be a case of myasthenia gravis. His mouth was foul from pyorrhoea; the nasal septum was deviated, but there was no evidence of tuberculosis.

In this case the effect of toxæmias on the thyroid appeared to be, from the history, that the pyorrhoea organism caused a condition of hyperthyroidism. The deviated septum rendered him liable to recurring nasal infection; the intermittent toxæmia from this (? *B. catarrhalis*) caused a further thyroid change; the last acute attack of this toxæmia led to the development of exophthalmic goitre. The later history of this patient will be noted under the heading "Cure" (p. 111).

The Nose and Nasal Sinuses.

The nose is one of the sites for acute, subacute and chronic infections. Amongst the micro-organisms that cause them are: *B. catarrhalis*, Friedländer's bacillus, *B. influenzae*, pneumococcus, staphylococcus, streptococcus. Of these, the last three can be eliminated. Of the others *B. catarrhalis* was found from inoculation of guinea-pigs to cause a complete hyperplasia. The rest were not so injected, but as they nearly always occur in symbiotic combination with *B. catarrhalis* these infections may be regarded as having such an action—if not from their own power, from the fact that *catarrhalis* is present.

In a normal nose in a normal individual an infection with a common or "influenzal" cold would cause a transient thyroid hyperplasia. The gland would involute to normal soon after the subsidence of the toxæmia. But if the patient were already in a condition of hyperthyroidism from any other cause the fresh stimulus from the *B. catarrhalis* would lead to an exacerbation of the hyperthyroidism. The nose may be abnormal, there may be some deformity leading to chronic infection and thickening or atrophy of the mucous membrane, polypi may be present, or chronic sinusitis—conditions likely to cause a chronic or constantly recurring toxæmia. In these, if *B. catarrhalis* was present, thyroid hyperplasia with hyperthyroidism would occur, as has just been described in cases of pyorrhoea. It, however, should be remembered that the nose is generally sterile, and that an original infecting micro-organism frequently dies out in the presence of an excessive number of pyogenic organisms.

The association of exophthalmic goitre with nasal infections has been described by Hack,¹ Semon,² and Scanes Spicer.³

The following examples serve to illustrate the occurrence of hyperthyroidism and exophthalmic goitre from these causes:

CASE V (Fig. 4).—F. H., male, 24. Thirteen months ago was quite well, and weighed over 12 st.; four months later he noticed an enlargement of his neck and other symptoms of exophthalmic goitre; these steadily increased despite all drugs and antithyroid treatment. (Fig. 4 shows his condition on admission to hospital; he weighed 7 st. 4 lb.)

For some years he had drunk water from a goitre-producing well without noticing any thyroid enlargement. Thirteen months ago he began to work with lime, the dust from which caused a chronic nasal irritation. Examination showed that he had ulceration of the middle turbinates with opacity of his antra. There was only a slight nasal discharge, a swab from which showed no growth on culture. An extension of his infection occurred with pharyngitis, laryngitis, and some crepitations at his right apex. He lost 9 lb. in eight days and died. A *post-mortem* examination was refused. Thyroid hyperplasia was caused by the well water, and the exophthalmic goitre from the fresh toxæmia acting upon this.

CASE VI (Fig. 5).—M. J., female, 36. Three years ago the symptoms of hyperthyroidism had developed with exophthalmos. Her neck enlarged six months ago, and she lost 14 lb. in weight. She stated that she had had bad teeth for some years, and a chronic nasal discharge. Examination showed a mild type of exophthalmic goitre associated with pyorrhoea and chronic rhinitis, with perforation of the septal cartilage. Hyperthyroidism was caused by the teeth infection and exophthalmic goitre by the sequence of a chronic nasal infection.

CASE VII.—M. B., female, 31. For eighteen months she had noticed the gradual onset of the symptoms of exophthalmic goitre. She had had bad teeth for some years, and constantly recurring colds. Examination showed pyorrhoea, a deflected nasal septum, with chronic hypertrophic rhinitis.

CASE VIII.—M. C., female, 39. A case of similar nature, but exophthalmic goitre developed after chronic sinusitis.

Lung.

The common infection found in the lung is that due to *B. tuberculosis*. In my last paper it was shown that its action on the thyroid varies with the degree of the infection; miliary tuberculosis causes a complete hyperplasia, whilst the chronic causes a colloid hyperplasia. The thyroid changes occurring in a case of tuberculosis can be arranged in a circle which passes through the stages of both complete and colloid hyperplasia to a final condition of fibrosis. The vertical diameter of this circle is dependent on the extent of the infection. At one stage tuberculosis is associated with complete hyperplasia, during which stage signs of hyperthyroidism may become evident.

The onset of exophthalmos has been described following the onset of miliary or chronic tuberculosis, and the

condition of the thyroid ratified *post mortem*. Dufour⁴ has described two cases of exophthalmic goitre in association with tuberculosis. Holles made observations on 33 cases of exophthalmic goitre, and concluded that the majority were tuberculous in origin. Similar cases have been also described by Poncet and Lincke.

The following examples serve to illustrate these points clinically:

CASE IX.—C. F., male, 39. Had early chronic phthisis; exophthalmos was noted temporarily following the development of fresh foci.

CASE X.—F. S., female, 22. Developed whooping-cough two years previously, which was followed by phthisis which was said to have been cured. Latterly she had noticed a fullness of her neck, which she thought was getting bigger. Examination showed that there was tenderness and slight enlargement of the thyroid. Pyorrhoea was present, and signs of tuberculosis at the right apex, with tubercle bacilli present in the sputum.

CASE XI.—B. S., female, 43. Presented a mild type of exophthalmic goitre, associated with pyorrhoea and chronic phthisis. From her history she appeared to have developed symptoms of hyperthyroidism from pyorrhoea, the super-venition of phthisis caused an exacerbation which gradually developed into exophthalmic goitre.

Intestine.

The intestine may be the site of all kinds of micro-organisms and be the medium through which various poisons are absorbed. The toxic products may be divided into two main groups—(a) material derived from the decomposition of the intestinal contents from the action of the putrefactive anaerobes; (b) toxins directly derived from the micro-organisms infecting the tract.

(a) Decomposition of the intestinal contents occurs especially when any obstruction is present in the tract. A toxæmia becomes evident in cases of either acute or chronic intestinal obstruction and in the more subtle cases of intestinal stasis. Observations made on the thyroids obtained *post mortem* from cases of acute and chronic intestinal obstruction have revealed no signs of hyperplasia. Neither has hyperthyroidism been observed in cases of intestinal stasis nor have cases of hyperthyroidism shown signs of intestinal stasis, in fact the reverse—frequent action of the bowels or diarrhoea—is a common symptom. Many thyroids have been obtained from cases in which intestinal stasis was present, but it is considered advisable to defer their consideration until a later paper on another subject. It is concluded that there is no evidence to show that products of the intestinal putrefaction have any action on the thyroid.

(b) The micro-organisms infecting the intestinal tract. McCarrison⁵ in his last paper has shown that some organism living in the alimentary canal of an infected individual gives rise to thyroid enlargement. He produced goitre in goats by giving them water contaminated with the faeces of goitrous people and by feeding them with cultures of the organisms grown on agar. He obtained the same results by using the faeces of non-goitrous people.

The Micro-organisms Present in Faeces.

The micro-organisms may be divided into two groups, the aerobic and the anaerobic. The true anaerobic have not been examined beyond the *B. aerogenes capsulatus*, which appears to have no action on the thyroid.

Of the aerobic, the pneumococcus, streptococcus, and staphylococcus can be eliminated as having no action on the gland. There is left the *typho-coli* series which may be subdivided into the *B. typhosus*, *B. enteritidis*, and the *B. coli* groups. It is proposed to trace these from the *B. typhosus* towards the *B. coli*. Infection with *B. typhosus* does not cause a thyroid hyperplasia. The result of infection with *B. alcaligenes* has not been examined. *B. dysenteriae* causes a complete or acute hyperplasia, judged from the effect of inoculation of Flexner's and Shiga's bacilli into guinea-pigs and from asylum dysentery in man. Of the *enteritidis* group, Gaertner's bacillus as found in infantile diarrhoea causes a complete hyperplasia. These two groups can be dismissed as being causatory agents in the production of endemic goitre, as they are not present in the faeces of goitrous individuals. It is possible to conceive, however, that when they are present in combination with other micro-organisms they might be concerned in causing thyroid changes and hyperthyroidism. The *B. coli* group is still left. Typical *B. coli* can be

eliminated as it is a normal inhabitant of the intestinal tract of normal individuals.*

The Effect of Water on the Coli Group.

A good deal of discussion has arisen as to what is a normal *B. coli*. In this work the normal *B. coli* is regarded as being one that is a Gram-negative, feebly motile, non spore-bearing bacillus, that coagulates and acidifies milk and produces indol; that forms acid and gas from glucose, lactose, dulcitol, maltose, and mannite, but not from sucrose.

Whipple⁷ in 1903 found that the type of *B. coli* changes if it be kept under abnormal conditions. Horrocks⁸ found that *B. coli* kept in unsterilized well and tap waters develops a delayed action on milk and neutral red, and but feebly produces indol. Penfold showed that bacteria of the colon-typhoid group can produce a mutant. Houston⁹ found that in filtered water typical *B. coli* are outnumbered by the atypical. This he ascribed to the mutation of *B. coli*. Clemesha,¹⁰ however, thought this finding was due rather to the extinction of some forms, and rapid growth of others. This is as it may be. Yet these data are sufficiently striking to suggest that a bacteriological examination be made of the water supply in goitrous districts, and that a like examination be made of the faeces of goitrous persons coming from these districts. The presence of the mutants of *B. coli* in either would suggest that *B. coli* had somewhere been placed under abnormal conditions.

Bacteriological Examination of the Water.

Opportunity for examination of a large series has been, for obvious reasons, limited. Samples have been obtained from surface wells in Wiltshire, Bucks, and Herts. The following organisms were grown:

1. *Wiltshire*.—Water obtained from a surface well in a chalk district. From a sample normal *B. coli* and two mutants were isolated. Of the mutants, one had a negative action on dulcitol, the other a diminished action on all the sugars with the exception of dulcitol, which was increased.
2. *Bucks*.—Two varieties of colonies appeared, the one wavy the other circular. The former constituted 92 per cent., and had no action on dulcitol and sucrose; the latter constituted 8 per cent., and caused no changes in dulcitol, but altered sucrose with acid and gas formation.
3. *Herts*.—Two types of colonies grew; one produced acid and gas with all the sugars, the other no gas with lactose.

Etiology of Endemic Goitre.

It is proposed now to consider the etiology of endemic goitre from the point of view of infection with the *B. coli* group.

The number of cases among people who have always lived in London is small. It appears that goitre rapidly diminished in London after the closure of the wells and the establishment of a pure water supply. Still London has an advantage that the cases seen come from all over the world. Those examined have come from places as far apart as Cashmere, Central India, Australia, South and West Africa, and various parts of England. The character of the water supplied to these individuals has varied from 48 per cent. of hardness to snow or rain water. The strata over which it has flowed has varied from chalk, granite, clay, and limestone. One can eliminate both the chemical constituents and the soil as being direct causatory agents of endemic goitre.

Contamination of Water and its Consideration as a Culture Medium.

Goitre is common in the valleys of mountainous districts. Inquiry shows that the water supply in these districts is of surface origin, and so liable to surface pollution. Usually it neither passes through filtering beds nor stands in volume. The two great safeguards in the removal of surface contamination and its consequent micro-organisms are absent. The same applies to surface wells and springs. Rain-water, though in the first instance pure, soon reeks

with micro-organisms from the methods adopted in its collection, and the barrels and tanks in which it is kept. Water derived from snow is also open to surface contamination, and, as shown by Houston, micro-organisms survive longer in water at lower than higher temperatures. Thus in all these instances inquiry shows that there are factors present which render the water liable to contamination, and that they may also tend to the development of, or the prolongation of the life of, micro-organisms derived from such contamination.

Examination of Faeces.

(a) *Normal Faeces*.—Clemesha in India examined 46 samples of normal human faeces and 25 samples of cow dung, including about 3,500 different colonies isolated by various methods. McConkey made similar examinations in England. They divided the organisms into four groups, and the following table shows the percentages obtained:—

	McConkey.	Clemesha.
Sucrose - Dulcitol - ...	34	53.2
Sucrose - Dulcitol + ...	38	17.4
Sucrose + Dulcitol + ...	15	6.8
Sucrose + Dulcitol - ...	12	22.2

Under 5 per cent. were Glucose + Lactose -.

(b) *Faeces of Goitrous Patients*.—Bacteriological examination of the faeces of cases of endemic goitre have been made; in one case McConkey's B.S.A. plates were used, in the others Conradi-Drigalski's agar plates. One case had left the goitrous district nine years.

B. coli and the following varieties were found:—

1. Negative to sucrose and dulcitol.
2. Were negative to sucrose but positive to dulcitol (*B. coli*).
3. Were positive to sucrose and dulcitol.
4. Were positive to sucrose and negative to dulcitol.

The percentages in which 1, 3, and 4 were present was excessive. They occurred up to 100 per cent. and the total exclusion of normal *B. coli*.

5. Merely decolorized sucrose, and produced no indol (*B. coliformis*).
6. Produced acid and gas with sucrose, the acid being ++.
7. Had a negative action to litmus milk, lactose, sucrose, and dulcitol, but were positive to glucose, maltose, and mannite (*B. paracoli*).
8. Caused acid but no gas in sucrose, lactose, maltose and mannite, and had no action on sucrose or dulcitol.
9. Had a diminished action on all the sugars, with the exception of dulcitol, which was increased.
10. Had no action on sucrose or lactose.

The percentages of these atypical forms varied up to 86 per cent. It may be said that water containing members of the *B. coli* group has been supplied to individuals; these individuals became goitrous, and mutants of *B. coli* have been isolated from their faeces. The mutants found in the faeces were not necessarily the same as those found in the water.

If there is any causatory relation between infection with atypical members of the *B. coli* group and goitre formation, it should be possible to experimentally make an exact reproduction of the series of events. Evidence might also be forthcoming that the organism is specific to the individual in whose faeces it occurred.

Fixation of the Complement.

Blood has been examined for fixation of the complement in three cases of endemic goitre, in which the following organisms were isolated from the faeces: (1) Normal *B. coli*, (2) those positive to sucrose, (3) those negative to dulcitol, (4) those negative to dulcitol, and produced no gas with glucose, lactose, maltose, and mannite. It was found that there was no fixation of the complement.

This was only to be expected, as the condition is an apyrexial toxæmia. No confirmation can be derived from the complement fixation test.

Experimental Production of Goitre.—These and other experiments will be published in detail later.

Transmutation of B. coli.

A typical healthy strain of *B. coli* with normal sugar reactions was inoculated into distilled and tap water containing various amounts of broth and into water containing various salt solutions. The sugar reactions are being taken at the end of every week for the occurrence of mutation.

* I am sorry that Major McCarrison was misquoted in my last paper. He wishes me to correct this. Instead of coliform bacillus causes endemic goitre in the Gilgit Valley, the passage should read, vaccines of coliform bacillus, staphylococcus, etc., have been used with success in the treatment of goitre.

Pathogenicity and Action on the Thyroid of Typical and Atypical B. coli.

Guinea-pigs were used in these experiments, as Eyre¹¹ found that *B. coli* was a normal inhabitant of the guinea-pig intestine.

Septicaemia.

Three guinea-pigs received intraperitoneal inoculation with typical *B. coli* and three with *B. coliformis* to cause a septicaemia. The thyroids showed an acute haemorrhagic hyperplasia.

Toxaemia Subacute.

Eighteen guinea-pigs were divided into three groups and fed respectively with bread and milk contaminated with fresh cultures of typical *B. coli*, *B. paracoli*, and *B. coliformis*. The guinea-pigs died. The order of the pathogenicity of the cultures appeared to be—*B. paracoli*, *B. coliformis*, *B. coli*. Those fed with *B. paracoli* survived on an average 10.8 days. Those fed with *B. coliformis* survived on an average 12.6 days. Those fed with *B. coli* survived on an average 16 days. The thyroids showed a varying degree of hyperplasia from a complete to a colloid hyperplasia. Those that survived the longest showed the colloid hyperplasia indistinguishable from that seen in endemic goitre. The glands appeared enlarged, but as they are small in guinea-pigs no reliable observations on this point can be made.

Chronic Toxaemia.

A similar number of guinea-pigs were fed in an exactly similar manner except that they received smaller doses of the cultures given every alternate day. Three died from each group at the end of ten days, and others were killed at periods varying from the nineteenth to the thirty-second day. The thyroids appeared to be enlarged, and were microscopically indistinguishable from endemic goitre. The amount of colloid formed varied with the organisms: with *B. coli* it was slight; with *B. paracoli* it was more apparent; whilst with *B. coliformis* it filled all the interstitial spaces. The vesicles were packed and surrounded with colloid. In one, cysts filled with colloid were present.

It is concluded that these micro-organisms are pathogenic to guinea-pigs in the following order: *Paracoli*, *coliformis*, and *coli*. An acute toxaemia, either from intraperitoneal inoculation or by feeding with large doses of broth cultures, causes the thyroid to undergo a complete hyperplasia. A chronic toxaemia causes a change similar, both microscopically and macroscopically, to endemic goitre, which is most marked with *B. coliformis*. The proportion of cell hyperplasia to excessive colloid formation is found to vary in each individual guinea-pig and with the degree of the toxaemia. Endemic goitre can be artificially induced in guinea-pigs. The complete cycle, commencing with water contamination and the presence of the mutants of *B. coli* to goitre formation, can be performed in the laboratory.

It is concluded that endemic goitre, whether it occurs in isolated habitations or in goitrous districts, is caused in man by the chronic ingestion of organisms of the *B. coli* group.

B. coli are washed away from surface droppings and contaminate surface waters, and unless means are taken to get rid of them they become ingested by man. The *coli*, being placed under abnormal conditions either in the water or in the upper part of the intestinal tract, undergo mutation. The mutants are present in the faeces of individuals affected with endemic goitre, and when once lodged there may remain for many years. The pathogenicity of the mutants appears to vary; some members cause a colloid hyperplasia of the thyroid with enlargement and no signs of hyperthyroidism. It is possible to conceive that some of the varieties may produce a toxin capable of further stimulating the thyroid to a condition of complete hyperplasia accompanied by signs of hyperthyroidism. At present no further attempt has been made to separate them, as there are some hundred varieties. The amount of thyroid change varies with the degree of infection.

The following may be taken as an example of the induction of endemic goitre:

CASE XII.—G. F., female, 13. At the age of 10 she went to reside in a goitre district and drank well water for seven

months. She then returned to London; eighteen months later she noticed an enlargement of her neck. She was seen a year later and found to have a general enlargement of the thyroid with an adenoma of the right lobe. The mutants isolated from the faeces had negative reactions to litmus milk, lactose, sucrose, and dulcitol.

The Effect of other Toxaemias acting on a Thyroid already in a Condition of Endemic Goitre.

Pyorrhoea.—The thyroids in cases in which pyorrhoea coexisted with endemic goitre were softer and more vascular than that seen in endemic goitre alone. Signs of hyperthyroidism were present up to a forme fruste of exophthalmic goitre. Cases of this type were described by F. V. Muller¹²:

CASE XIII. *B. catarrhalis*.—M. W., female, 12. Had drunk water from a well and developed goitre, as had her grandmother and sister. *B. coliformis* was isolated from her faeces. She had a deviated septum and was constantly catching colds. The thyroid was soft and evenly enlarged, and there were some signs of hyperthyroidism. Whilst under observation she caught several colds. After each of these there was an exacerbation of the symptoms of thyroid excess, which subsided about a month after each attack.

CASE XIV. *An Acute and a Chronic Toxaemia supervening on Endemic Goitre.*—C. G., female, 39. Resided in a goitre district in the Himalayas from the age of 18 to 31. Her teeth were removed for caries when she was 32. She developed whooping-cough when 36½. Her neck enlarged about the age of 30, accompanied with slight symptoms of hyperthyroidism. After whooping-cough the hyperthyroidism increased and she developed exophthalmic goitre. Seen a year later, the thyroid presented an adenoma of the right lobe and isthmus, the symptoms of exophthalmic goitre had largely subsided, pulse 96. In this case endemic goitre caused an enlargement of the thyroid; the pyorrhoea, slight hyperthyroidism; the temporary acute toxaemia of whooping-cough caused exophthalmic goitre, which gradually subsided after its termination.

In a similar way other toxaemias or combination of toxaemias can be considered, the chronic toxaemias causing a colloid hyperplasia and the subacute a complete hyperplasia with signs of excessive secretion. Thus small encapsulated adenomata were found in a case of actinomycosis seven months after infection. An adenoma occurred in one case a year after the combination of rheumatic fever and mumps.

Formation of Adenomata.

In my last paper it was noticed that colloid hyperplasia is found in two other conditions besides chronic toxaemias—namely, during the involution of either the acute or chronic toxaemias. They are not generally found during the involution following a single acute toxaemia. They are typically found in the late stages of exophthalmic goitre, that is, following a combination of subacute toxaemias. Masses of colloid are formed from the hypertrophied tissue which become encapsulated to form adenomata. Adenomata after the involution of the chronic toxaemias is typically seen in the late stages of endemic goitre.

PREVENTION.

It is proposed to separate the diseases of the thyroid into two groups: (a) Those in which the most prominent feature is hyperthyroidism (exophthalmic goitre type); (b) those in which the most prominent feature is thyroid enlargement (endemic goitre type). The methods adopted in preventing these will be considered separately.

The prevention of exophthalmic goitre depends entirely on the recognition of the first stage—the early condition of hyperthyroidism. The presence of this is usually marked by the occurrence of nervousness, followed by falling out of the hair, sweating, and slight loss of weight; examination reveals all the signs of exophthalmic goitre in a minor degree; its detection necessitates examination of the skin, hair, and sweat glands, of the muscular tone, the sympathetic nervous, and the cardio-vascular system. The cases are to be found amongst those diagnosed as pyorrhoea, dyspepsia, early osteo-arthritis, chronic rhinitis, tuberculosis, cirrhosis of the liver, and chronic interstitial nephritis, the last two being of interest rather than of importance. In these cases the infection and its results are more prominent than the signs of thyroid excess. The cases are also to be found amongst the following, in which one symptom of thyroid excess is more prominent than the other: Hyperidrosis, alopecia, urticaria scripta, tachycardia, myocarditis, hysteria, any exophthalmia. These cases come under notice, not only

in general practice, but also in the special departments. When a diagnosis is made, the case becomes a bacteriological study; both the nature and the focus of the infecting micro-organisms are to be found. A methodical examination should be undertaken, the history of any past illnesses elicited, and the date of onset of each noted.

Reference to a previous paper will determine whether any of these have an effect on the thyroid. The date of the onset of the symptom of thyroid excess should be compared with the date of the occurrence of the toxæmias. In this way a connexion between the causatory toxæmia and the hyperthyroidism can often be elicited. An examination of the mouth, nose, lungs, etc., must be carried out for the site of the infection, and swabs and cultures to find the causatory micro-organisms. In those cases in which the micro-organisms have been constantly swallowed a bacteriological examination of the faeces should be made to find if the organisms have become indigenous in the intestine. When the causatory micro-organism and its site has been determined, means should be undertaken for its removal. Some minor surgical operation, such as teeth extraction, submucous resection of the nasal septum, removal of the nasal polypi, suffice to cure the condition, accompanied in appropriate cases with intestinal antiseptics such as thymol. In the cases that have been so treated the symptoms entirely disappeared in about six months; no intestinal antiseptics were used, as it was necessary to determine the exact connexion between the toxæmia and the hyperthyroidism without the intervention of drugs. It may be as well to state that because carious teeth or a deviated septum happen to be present it is not sufficient to at once ascribe the cause to them. Only about 7 per cent. of cases of dental caries exhibit such symptoms. With a deflected septum there must be a very definite history of constantly recurring infection. It is also as well to remember that owing to the general vaso-dilatation all the mucous surfaces are flushed. Enlarged tonsils are but an effect, a part of the disease.

The following example shows the benefit of prevention:

CASE XV.—N. B., female, aged 33, was seen with signs of early exophthalmic goitre, including double exophthalmos in association with pyorrhoea and carious teeth and frequent nasal infection. Six months after the removal of her teeth no signs of hyperthyroidism were present. Her sister, aged 38, gave a history of an exactly similar condition, but after an acute attack of influenza she developed exophthalmic goitre which after eight years terminated in myxoedema. When seen, her primary infecting foci were still present. (Fig. 6.)

Though there are several combinations of chronic toxæmias that can cause thyroid enlargement, endemic goitre is the only one that can be prevented. After the experiments already outlined dealing with the etiology of this condition have been completed, it is proposed to put forward a definite plan for the collection, storage, and purification of water in endemic goitre districts and on the notification of goitrous wells, the object of which will be the removal of *B. coli*, typical and atypical, from these water supplies, either by filters, prolonged storage, or the use of antiseptics. As these micro-organisms belong to the *typho-coli* series, precautions should be taken similar to those adopted in the prevention of typhoid fever or any other water-borne disease.

CURE.

The cases will again be divided into two groups: (a) Those associated with signs of excessive secretion; (b) those only associated simply with enlargement of the gland.

In group (a) are those cases that have advanced beyond the stage of hyperthyroidism to that of the formes frustes and of typical exophthalmic goitre. The question arises, Can the gland retrace its steps after the removal of the causatory toxæmias and involute to normal, and can those organs that have been affected by the excessive secretion do the same? When a comparison is made between the microscopical appearances of a normal gland and those of exophthalmic goitre one is struck by the enormous cell increase that has taken place. In the solidification of the vesicles there are nearly ten times as many cells per vesicle; the vesicles themselves are also increased in number, so that when the gland is doubled in size the secreting area is increased some forty times. Involution to normal thus necessitates a reduction in the secreting cells to $\frac{1}{40}$. It may be deduced from the length of time taken for the symptoms of thyroid excess to disappear in

the cases of simple hyperthyroidism that complete involution of the gland and the disappearance of the symptoms in exophthalmic goitre would take over six months. Any incidental toxæmia acting as a fresh stimulus would lead to a recurrence, the extent and duration of which would depend on the intensity and duration of the toxæmia. Observations have been made on cases following the removal of the infecting agent.

As far as possible, the patients while in hospital did not rest in bed—they got up early in the morning and did ward work, no medicinal or other treatment was given, so that any improvement could only be accounted for by the removal of the toxæmia. The cases were first examined along the following lines:

(a) Gland changes: Alteration in the pituitary fossa (x ray), hyperplasia of the tonsil, post-sterno-mastoid glands, thymus, and spleen were noted with any alteration in the blood. The neck was measured, and the consistency of the thyroid observed especially for the presence of adenomata, cysts, and other signs of commencing degeneration.

(b) The presence and degree of the signs of thyroid excess.

(c) The site, and if possible the nature, of the infecting micro-organisms.

From (a) an estimate was made of the reaction of the ductless glands to the toxæmia, and whether the thyroid had commenced to involute by a process of degeneration.

From (b) an estimate of the degree of hypersecretion.

From (c) the causatory agent was determined.

The treatment adopted and the results obtained necessarily varied with the nature and the situation of the infecting micro-organisms. The most striking results were obtained in the very acute cases in which the infecting process could be completely removed. The following examples demonstrate the results obtained from removal of the infection in the four common situations.

Teeth.

The toxæmia derived from the source has but a preliminary action. It serves as a basis for the action of another to cause exophthalmic goitre. Only one example will be given, as it was discussed under prevention.

CASE IV (Fig. 7).—A. L., male, 30. Hyperthyroidism was present for three years, associated with pyorrhoea. Following an acute infection in his nose, to which he was rendered liable by a badly deviated septum, exophthalmic goitre developed, accompanied with acute mania; pulse 130, respirations 36, and extreme myasthenia. He was treated with all the usual medicinal remedies without avail, and given up as moriturus. His mouth was put in order, and twenty-one teeth removed under gas and oxygen. Five days later he became quiet, and slept, and his three attendants were no longer needed. After fourteen days he had put on 23 lb. in weight, and at the end of three months he had put on 34½ lb.; pulse 108; exophthalmos had disappeared and the thyroid had diminished 1½ in. It was realized that the onset of any fresh toxæmia before involution was completed would cause a recurrence and probable death; but owing to myocardial degeneration it was thought inadvisable to attempt to prevent such by an operation on his nose or to diminish the effect that such could have by removal of a portion of his thyroid. It was hoped that complete involution would take place before the onset of a toxæmia. Four months later he developed another acute nasal infection, his symptoms rapidly recurred, and he died in another hospital despite all medicinal measures.

Nasal Cases.

Canterization of the nose became the standard treatment for exophthalmic goitre after Hack, Frankel, Semon, and Spicer recorded cases cured by the removal of nasal polypi and other nasal affections. This soon dropped into disrepute, as the majority of cases are not nasal in origin.

CASE XVI.—E. L., female, 27. Gave a history of the symptoms of hyperthyroidism for some years associated with carious teeth, and constantly recurring colds. Three months ago she had developed a very bad cold which lasted for a month, when exophthalmic goitre occurred. Examination showed a soft enlargement of thyroid, an adenoma in the left lobe, with an average degree of symptoms; pulse 120. The teeth were carious, and right nasal septum and inferior turbinates were adherent. The adhesions were divided and the teeth removed; the symptoms cleared up with the exception of the adenoma in the left lobe, which was subsequently removed by operation. It had undergone cystic degeneration.

CASE XVII (Figs. 8 and 9).—L. C., female, 26. Gave a four years' history of exophthalmic goitre. She had drunk water from a goitrous well, and had carious teeth and a chronic cold. The thyroid was but little enlarged, pulse (?) 160, marked exophthalmos, weight 86 lb. She was kept in bed until her condition had subsided from the last nasal infection, her teeth were then removed and a submucous resection performed. In nine weeks she weighed 105 lb., the tachycardia and exophthalmos were only present during excitement.

CASE VI (Fig. 10).—M. J., female, 35. Three years' history of hyperthyroidism in association with carious teeth. Her thyroid had enlarged six months previously. Examination: A firm, hard enlargement of the thyroid with well-marked exophthalmic goitre, pulse 150, double exophthalmos, weight 87 lb. Her nose presented a black slough surrounding a perforation of the septal cartilage and chronic rhinitis. Her teeth were removed and the nose treated with nasal antiseptics. In four weeks her neck had diminished $1\frac{1}{2}$ in. At the end of fourteen weeks she weighed 124 lb., and the exophthalmos was not noticeable. During the involution an adenoma developed in the left lobe of her thyroid. Her heart was left in a condition of some myocardial degeneration with dilatation, and a pulse of 110.

In the nasal cases for the most part the toxæmia is not always present, but constantly recurs. Removal of the basal toxæmia causes the symptoms of exophthalmic goitre to subside. After-operations can with safety be performed on the nose to prevent the recurrence of the nasal infection and consequent exophthalmic goitre.

Lung.

The association of tuberculosis with hyperthyroidism and exophthalmic goitre has led some observers (Hollos) to believe that the great majority are tuberculous in origin. He reported 28 cases that he had treated with I.K. with recovery in 10.

From the microscopic appearances of the thyroids obtained from cases dead of tuberculosis it is concluded that only for a period of a few years is the gland in a hyperactive condition. It is only during this time that exophthalmic goitre is liable to develop.

In the early cases hyperthyroidism may be a transient phase which disappears perhaps to return after an exacerbation of the tuberculosis or the onset of another toxæmia. Observations have been made on five cases of typical exophthalmic goitre associated with chronic tuberculosis of the lungs. They were of a mild type with the exception of one case, which is quoted below. The basal toxæmia in four was pyorrhoea. The cases were observed for over a year, during which time the symptoms partially subsided, and the gland underwent degeneration with the formation of adenomata.

CASE XVIII.—M. R. F., female, 22. Gave a history of constant colds and hæmoptysis at 17, followed by exophthalmic goitre. Examination showed a pulsating thyroid, pulse 156, double exophthalmos, weight 115 lb., steadily decreasing. The nasal septum was deviated, and the mucous membrane in a condition of chronic rhinitis. Tuberculosis was present in the right apex. Partial thyroidectomy was performed under Crile's anæsthesia. At the end of a month there was a great reduction in symptoms, but she had lost a further 9 lb. in weight. She was sent to the seaside, and her symptoms cleared up *pari passu* with the tuberculosis.

The indications for treatment of exophthalmic goitre associated with phthisis appear to depend on the extent of the infection, the degree of hyperthyroidism, and the condition of the gland. In the first stage, when the condition is transient, the treatment should be directed to the tuberculous focus. The same line also may be adopted in chronic phthisis; the symptoms subside with the cure of the infection or upon fibrosis of the gland. In the more acute variety the treatment will depend on the coexisting toxæmia. In all cases this should be removed or prevented. Sometimes it is not feasible, as in the above case, when prevention involves a serious operation on the nose. Here it seemed preferable to remove half the thyroid first, and then to complete the cure by sanatorium treatment.

Before recommending treatment with tuberculin, it is advisable to note the effects of vaccines on a normal gland. Mention of this will be made in a paper on the normal stimulus.

Intestinal.

Hyperthyroidism and exophthalmic goitre, caused by the association of a toxæmia with that derived from the presence of coliform organisms in the intestine, are cured by removal of the source of the toxæmias.

The simplest of these is when endemic goitre is associated with carious teeth. Removal of the teeth and the administration of an intestinal antiseptic cause a rapid disappearance of the thyroid enlargement and the symptom of hyperthyroidism.

CASE XIX.—Female, 24 (Figs. 11 and 12). Drank well water from a goitre-producing well until $2\frac{1}{2}$ years ago. She had had carious teeth for some years. Examination showed a soft even enlargement of the thyroid, medium type of exophthalmic goitre. Double exophthalmos, pulse 92. A mutant of *B. coli* was isolated from the faeces which decolorized litmus, sucrose, and produced no indol. Many carious teeth were present. After teeth extraction and the administration of thymol the neck diminished 1 in., the pulse became 78, and exophthalmos was not noticeable, and she increased 8 lb. in weight in a fortnight. The mutant of *B. coli* was not found after seventeen days' treatment, three days from the last dose of thymol.

CASE XX.—A. F., female, 25, was in a condition of hyperthyroidism from endemic goitre and carious teeth; exophthalmic goitre developed after an attack of influenza and pleurisy. She was treated for two years with drugs and x rays without effect. Examination showed a soft even enlargement of the thyroid, pulse 120, and marked unilateral exophthalmos. The carious teeth and inferior turbinates were removed and thymol administered. In six months she increased 25 lb. in weight; the exophthalmos was only present on excitement and her pulse rate was 84. An adenoma developed in the right lobe during involution.

Enlargement of the Thyroid without Signs of Excessive Secretion.

This group may be subdivided into three. (a) Those caused from the ingestion of the atypical forms of *B. coli* (endemic goitre). (b) Those caused by the combined effect of two toxæmias other than atypical *B. coli* that are capable of inducing a colloid hyperplasia. (c) During the involution following either the acute or chronic toxæmias.

(a) *Endemic Goitre*.—The history of the case is of great help in making a diagnosis. Every toxæmia from birth upwards and their date of onset should be noted. The character of the water supply should be ascertained both in the district in which the patient was born and in the districts where they have afterwards resided, with the dates and the time of onset of the thyroid enlargement. In this way the cases may be placed into groups according to their cause. A routine examination should then be made. A sample of the water should if possible be subjected to a bacteriological examination and the different members of the *B. coli* group isolated. The faeces are similarly examined and the causatory organism determined. Before treatment is commenced a careful examination of the gland should be made for the presence of adenomata and cysts. A preliminary purge is given (castor oil should not be used), thymol gr. x in cachets is administered two to three times a day for fourteen days; after a three days' interval it is repeated for another fourteen days. A week later the faeces are again examined. If the organism is still present another course of thymol is necessary. (Fats and oils must not be given within two to three hours of taking thymol.) Under this treatment the organisms are killed, the gland rapidly diminishes in size. The following may be taken as an example of the sixteen cases treated.

CASE XXI.—G. F., female. The paracolon and the *B. lactis aerogenes* were isolated from the faeces. Twelve days after treatment with thymol her neck had diminished 1 in.; at the end of eight weeks it was of normal size, having diminished 2 in. She had previously been treated for six months with syr. ferri iodidi with only a $\frac{1}{2}$ in. diminution.

The action of vaccines and their use in the treatment of endemic goitre will be discussed in a later paper on the normal stimulus.

Group (b). After the nature of the toxæmias has been determined they should be removed, though for the most part they have ceased to act before the cases are seen.

Group (c) consists of adenomata and cysts that have developed in the course of involution. If the cause be still present it should be removed; often it has ceased to act long before the cases are seen, though from the history the causatory agent may be determined even twenty or thirty years after its onset.

The question arises—Up to what point can thyroid affections be cured by removal of the cause?

Enlargements of the thyroid, whether of the exophthalmic or endemic type, entirely subside after removal of

the cause, providing this is done before the development of adenomata or cysts. Glands containing these will subside as a whole, but the adenomata or cysts are left. The administration of iodine may cause a slight diminution in their size, but they have not disappeared even after eighteen months' treatment. Cysts and adenomata should be treated along the usual surgical lines.

The symptoms of excessive secretion at first rapidly diminish after removal of the cause, and then more slowly *pari passu* with the diminution in the size of the gland. Any excitement will for the moment bring these symptoms again into evidence. If the disease has progressed so far that the various organs have become degenerated, only partial recovery can be made. The patient may be left with a dilated heart, permanent albuminuria or glycosuria, or with some weakness of the nervous system, either central, peripheral, or sympathetic, leading to feeble mentality, paralysis of a nerve, or some vasomotor disturbance. These require appropriate treatment.

Acute Exophthalmic Goitre.

These cases arise from the effect of a toxæmia acting on a gland that is already hypertrophied and has led to hyperthyroidism or typical exophthalmic goitre. The added stimulus gives rise to an acute exacerbation which may rapidly lead to death. Treatment is a matter of difficulty, as the five cases quoted show. Medicinal measures may prove unavailing, removal of the toxæmia may be impracticable, and any attempt to remove a portion of the gland may prove fatal.

CASE IV.—A. L., male, 30, developed an acute *catarrhalis* infection before involution was complete from exophthalmic goitre and died in a few weeks despite all medical remedies.

CASE V.—F. H., male, 30. An extension of a *catarrhalis* infection on exophthalmic goitre caused death in five days despite medical remedies.

CASE XXII.—S. L., female, 28. Developed an acute *catarrhalis* infection on medium type exophthalmic goitre and went rapidly down hill. An attempt to remove half the thyroid under Crile's anaesthesia proved fatal.

CASE XXIII.—V. D., female, 25. Developed acute exophthalmic goitre on endemic goitre and teeth infection. She lost 26 lb. in weight, but recovered under medicinal treatment after appearing moribund for some weeks. She now exhibits the combination of myxoedema and degeneration of various organs from exophthalmic goitre.

CASE XXIV.—M. R., female, 51. An acute exophthalmic goitre developed from the effect of acute *catarrhalis* on exophthalmic goitre from chronic *catarrhalis* and teeth infection. Recovery after partial thyroidectomy under Crile's anaesthesia.

Such cases can only be treated on their own merits.

CONCLUSIONS AND SUMMARY.

Endemic goitre is caused by the toxins from the atypical forms of *B. coli*. The mutants are usually conveyed by water. They become indigenous in the intestine, and different mutants of *B. coli* are to be found in the faeces of cases of endemic goitre. The mutants are but rarely present in the faeces of normal individuals or in the faeces of individuals goitrous from other causes. It is possible to conceive circumstances which place the *B. coli* under abnormal conditions in the intestine itself, and lead to mutation and the temporary appearance of mutants in the faeces of normal individuals.

The mutants set up an apyrexial toxæmia, which stimulates the thyroid, so leading to a colloid hyperplasia and eventually to enlargement of the gland.

The whole process can be imitated in the laboratory, and endemic goitre induced in guinea-pigs by feeding with small doses of the mutants.

The supervention of a fresh toxæmia whilst the gland is in a hyperactive state causes a complete hyperplasia, with absorption of colloid and signs of hyperthyroidism up to a condition of exophthalmic goitre. This is dependent on the intensity and duration of the fresh toxæmia.

Endemic goitre is preventable by the avoidance of water contamination and by the sterilization of contaminated water.

It can be cured by the administration of intestinal antiseptics, the gland returns to normal, providing no degeneration has taken place. The gland as a whole involutes to normal, but the adenomata or cysts are left.

A condition similar to endemic goitre can be caused by other toxæmias capable of inducing a colloid hyperplasia.

Exophthalmic Goitre.

Exophthalmic goitre is due to a combination of toxæmias of an intensity sufficient to cause a hyperplasia with absorption of the colloid material. One acts during a period sufficient to give rise to a complete hyperplasia associated perhaps with slightly marked signs of hyperthyroidism without necessarily any glandular enlargement. The supervention of another infection stimulates the gland, which usually enlarges, and the signs of hyperthyroidism become very evident; the case develops into one of typical exophthalmic goitre. A nervous shock may lead to the diagnosis by suddenly bringing into evidence the symptoms of hyperthyroidism, especially those connected with the nervous system.

The severity and duration of exophthalmic goitre is dependent on the intensity and duration of the toxæmias. If they be of short duration the disease will disappear in a few months.

Exophthalmic goitre can be prevented by the detection of the early cases of hyperthyroidism and the consequent removal of the basal toxæmia.

Exophthalmic goitre can be cured if the causatory agents be removed before degeneration has occurred either in the gland or in those organs that are affected by the hypersecretion.

When degeneration has taken place in the thyroid, removal of the toxæmias causes involution to take place only in the hypertrophied portion; the adenomata and cysts are left. These require appropriate surgical treatment, as they to a certain extent keep up the symptoms of thyroid excess. Surgical treatment without removal of the cause is followed by recurrence unless so much of the gland substance has been removed that hypersecretion is impossible. Degeneration in the other organs partially recovers after involution of the thyroid; appropriate treatment is necessary for those that remain. Acute cases of exophthalmic goitre may present themselves in which surgical treatment is the only means of saving them, though the risk of death under the anaesthetic perhaps precludes operation.

As our knowledge of toxæmia is limited, so necessarily must be that of exophthalmic goitre.

The bacteriological work was done in the Westminster Hospital Laboratory, and I am much indebted to Dr. Braxton Hicks and Mr. Chopping for the care which they have taken over the work. I am also much indebted to Mr. Spencer for giving me the opportunity of making observations on clinical material.

REFERENCES.

- ¹ Hack, *Deut. med. Woch.*, 1889, p. 434. ² Semon, *Clin. Soc. Journ.*, vol. xxii, p. 234. ³ Scanes Spicer, *ibid.*, vol. xxviii, p. 265. ⁴ Dufour, *Lyon med.*, cxx, No. 14. ⁵ McCarrison, *Ind. Journ. Med. Research*, vol. iii. ⁶ Houston, Annual Report Local Government Board, 1904-5. ⁷ Whipple, *Technology Quart.*, xvi, 18. ⁸ Horrocks, *Journ. Hygiene*, xii, 195. ⁹ Clemesha, *Bacteriology of Surface Waters in the Tropics*, 1912. ¹⁰ Eyre, *Lancet*, 1904, vol. i, p. 648. ¹¹ Müller, *Archiv f. Anatomie und Physiol.*, Suppl., 1906, p. 411. ¹² Farrant, *Proc. Roy. Soc. Med.*, 1914, vol. vii.

ANOCI-ASSOCIATION IN THE PREVENTION OF SHOCK AND POST-OPERATIVE DISCOMFORTS:

AN EXPERIENCE OF 143 CASES.

BY

H. B. BUTLER, F.R.C.S.E.,

AND E. W. SHEAF, M.C.CANTAB.,

ASSISTANT SURGEONS, ROYAL SURREY COUNTY HOSPITAL, GUILDFORD.

CRILE'S theory of shock is that it is due to the exhaustion of the vasomotor centres in the medulla and cord, the most important factors in the production of surgical shock being fear, pain, and anaesthetic poisoning. In operations done by ordinary methods these three factors are not sufficiently eliminated, and the operation is followed by a fall in blood pressure and definite changes in the cells of the central nervous system.

Ether and chloroform prevent feeling and movement, but they do not prevent the reception of stimuli and the discharge of nervous energy. Theoretically, nitrous oxide

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 4.

FIG. 6.

FIG. 5.

FIG. 10.

FIG. 11.

FIG. 12.