

latrine," a selected and probably sequestered spot to which an individual will constantly return; (3) what may be designated a "casual privy," any spot whose use the call of the moment necessitates. Accepting these experiments it is impossible to admit that hookworm infection is a general infection of the soil, one which tends to evenness of diffusion; nor can one admit that it is of such a nature that the agriculturist must necessarily meet wandering larvae in the course of his work. Were this so, however, we could agree with those who clearly look upon the soil as one uniform whole more or less uniformly infected, and maintain that the amount of soil infection generally, and the consequent risk to those who work on it, must be proportionate to the number of ova which fall upon it—that is, to the number of ankylostomes harboured by the inhabitants. On such grounds, too, one would have to agree with Darling³ that, could one reduce the number of ankylostomes to a certain level, one would reduce the larvae they breed to a point where human infection would be slight, and, if one be willing to concede this without proof, negligible; and that no increase in the infection rate of a community could occur without importation of a heavier infection from outside.

But, on the contrary, the evidence of Augustine's experiments is that infection must be constantly, presumably preponderatingly, a "privy" infection, and that in the case of man-made latrines and "natural latrines" it is what I have termed a dejectional infection¹⁰—obtained, that is, at the time of defaecation. Only in case of his skin coming into contact with ground which has been used as a casual privy will an individual acquire what I have termed a casual infection¹⁰; and that will generally be but seldom.

If, then, one conclude—and it is difficult to escape doing so—that recent evidence points to hookworm infection as being under ordinary conditions practically always a privy infection, and preponderatingly a dejectional infection, one is confronted with this question: Does the man-made latrine, as recommended by the sanitarian, prevent infection; or does it actively disseminate it? There will scarcely be opposition to the statement that ankylostome infestation cannot occur from a clean sewered water-closet, whence the infected stool is at once removed. But in those widely used, because widely recommended, latrines where the stools are dealt with *in situ* with a view to larval destruction, the position is unsatisfactory and disquieting. McVail¹¹ has found that ova and larvae, identified as those of hookworms, are constantly present in the effluent of those fine septic tanks which stand on the banks of the Hugli; Minett¹² and Khalil¹³ have found them similarly in the West Indies; Khalil¹⁴ quotes experiments to show that these larvae can swim; Payne¹⁵ has shown that even if larvae do not migrate laterally on the surface of the ground, they can mount vertically through at least 36 inches of soil. Accordingly any latrine which permits of direct or indirect pollution of the soil or subsoil is, under present conditions, unsafe.

Since, apart from sewered latrines, there are such grave reasons for suspecting all man-made latrines as disseminators of hookworm infection, it is pertinent to inquire the extent to which a man, conscientiously using his privy and harbouring but a single pair of ankylostomes, will infect that privy. The answer lies in the work of Baermann and of Darling, to which reference has been made above. Assuming for the sake of even numbers that this particular pair of worms produced 2,740 fertile eggs daily, the number deposited in the latrine will be a million a year. We are assured that nine ankylostomes, or four to five million eggs a year, are hygienically negligible. It is not unreasonable to ask of those who are maintaining that this prodigious figure is hygienically negligible that they should either prove it or cease to urge it as a working hypothesis. There is an unfortunate disposition to take sides on this matter, and as one who is credited with leading the opinion that all infection matters² I would suggest that it is immaterial what anyone's opinion is, except in so far as it acts as a spur to the collection of facts. What is required is fact, and pending the collection of further facts there seems ample justification for the refusal to accept as personally or hygienically negligible any infection however slight.

The Needs of Hookworm Campaigns.

Seeing, then, that, by the evidence, accurate microscopic diagnosis is a reality; that treatment does not produce effective disinfection; and that ankylostomiasis must, on our present evidence, be looked upon as, in the main, a privy

disease, and not a general soil disease; the case which has been stated, and as I believe fairly stated, above collapses.

The problem is really a somewhat pathetic one. In the face of an urgent situation hookworm campaigns have been pushed forward. Certainly something had to be done; but the results are in certain respects deplorable. Promises have been rashly made which have not been, and could not be, substantiated, because the premises on which the argument for their validity rested were unsound.

The present position would seem to be fairly stated thus: Diagnosis, thanks largely to the recognition of the principle of the limit of effective concentration, has now been placed in such a position that it will cheaply, certainly, and rapidly detect hookworm infection, provided normal oviposition proceeded. Treatment and prevention lag far behind. We need a drug which will disinfest certainly, preferably in one treatment. Why should we rest content to say, as is said, that certain and complete disinfection is impossible of attainment? The acceptance of defeat in the situation is unthinkable. We need a latrine, simple, cheap, profitable, foolproof, suitable for the poor hut dweller. We have no approach to it, nor are we likely to have so long as there is no active dissatisfaction with, no strenuous striving to better, what we have. We need properly financed research to solve these and like urgent and vital problems in ankylostomiasis. We need research in order to avoid the heavy waste of money which has occurred so strikingly in the past in hookworm campaigns; for most of the work which has been done will have to be done again. Money spent in adequate research will come back multiplied many fold, not only in the capacity for work and earning, but in that measure of health, happiness, and length of life which our national commitments make it incumbent that we should at least offer to those backward races for whom we have made ourselves responsible.

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THE INFLUENCE OF INTESTINAL BACTERIA UPON THE THYROID GLAND.

BY

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SEVERAL years ago Sir Arbuthnot Lane suggested that exophthalmic goitre was produced by the toxins absorbed from the alimentary canal in intestinal stasis, and advocated colectomy as one of the methods of treatment. As a result of several years of study of the diseases of the thyroid gland I have arrived at the conclusion that his suggestion regarding the etiology of the disease was nearer the truth than most people thought at the time. His suggested method of treating the disease has not been widely adopted.

To appreciate the conclusions I have arrived at it is necessary to consider some factors arising out of the metabolism of certain proteins; these factors bear an intimate relation to the causation of diseases of the thyroid gland.

The Normal Digestion of Proteins in the Alimentary Canal.

All proteins are broken down into amino-acids, and, with the exception of gelatin and some protamines, produce aromatic as well as other amino-acids. In this article I am concerned only with the amino-acid tryptophane. Normally a certain percentage of this substance is absorbed into the blood and utilized in the metabolism of the body; the remainder is decomposed in the alimentary canal, with the production of indole and skatole. These bodies are absorbed and then converted into indoxyl and skatoxyl potassium sulphates and excreted as such by the kidneys into the urine, where they can be identified and estimated.

The Importance of Tryptophane in Diseases of the Thyroid Gland.

It has recently been shown by Professor Kendall that thyroxin, the active principle of the thyroid gland, is a tri-iodo tri-hydro derivative of tryptophane; the exact chemical formula is a matter of very little importance, as far as this article is concerned. For the time being I am taking for granted the generally accepted idea that exophthalmic goitre is due to the excessive production of thyroxin; that diffuse parenchymatous goitre is an attempt at producing a sufficient amount of thyroxin for the needs of the body by compensatory hypertrophy of the gland; and that in myxoedema there is a failure of the gland to produce the necessary amount of thyroxin. Acting on the assumption that these ideas were somewhere near the truth, I investigated the factors controlling the supply of tryptophane to the thyroid gland, and the variations in the supply in the diseases mentioned above. Theoretically we should find that in exophthalmic goitre the gland is well supplied with tryptophane, that in parenchymatous goitre the supply is inadequate, and that in myxoedema either the supply is very inadequate or else the gland is unable to utilize the supply available. Before proceeding farther it is necessary to have a rough idea of the normal flora of the intestine.

The Normal Flora of the Intestine.

The flora can be divided into two main groups: the fermentative or acid producers, and the putrefactive or indole producers. Normally both groups are represented in the human intestine, but in disease, and experimentally in health, one group assumes undue, and sometimes absolute, predominance over the other. It has been proved that in the lower animals it is possible to change the predominant group in two to three days by making certain alterations in the food taken. In the human being, unfortunately, this is not easily done. Some time ago Dr. Distaso and I carried out a number of experiments on guinea-pigs, and found that the predominance of the indole producers runs parallel with the amount of indoxyl sulphate in the urine. We also found that by the addition of lactose to the diet we could destroy all the putrefactive indole producers in two to three days, and that the disappearance of the indoxyl sulphate from the urine occurred on the same day as the disappearance of the indole producers from the faeces. Within two days of discontinuing the lactose putrefactive organisms reappeared in the faeces and indoxyl sulphate in the urine.

The Application of these Observations to Diseases of the Thyroid Gland.

During the last two years I have been fortunate in having a number of thyroid cases under my care at the City Lodge and King Edward VII Hospitals. The general practitioners of the district have also allowed me to examine several of their private cases.

Normally, in the human subject, the urine contains roughly 0.2 to 0.3 gram of organic sulphates and about 2 grams of inorganic sulphates per litre. The indoxyl sulphate was estimated by converting it into indigo and comparing the depth of the colour with a series of solutions of known strength. The total sulphates and inorganic sulphates were estimated separately by the benzidine method. I examined the urine of all the cases that I saw during the last two years, and I found that, as a rule, the total amount of organic sulphates runs parallel with the amount of indican in the urine. I also found that in all cases of well established exophthalmic goitre there was no indican in the urine. I now consider that the examination of the urine for indican provides a sound guide to the prognosis, as its early disappearance means that the case is certain to get worse. In

some very early cases I have been able to give such a prognosis.

If, in spite of medical treatment for two or three months, a particular case is not showing signs of improvement, and the symptoms are sufficiently pronounced to interfere seriously with the patient's health, I remove about half the gland—but only if there is no indican in the urine. The operation has no effect on the intestinal flora, or on the amount of indican in the urine, but the symptoms will be reduced for a few months, and during that period there may be a change in the flora. If there is no reappearance of the indole producers, then the symptoms recur, their severity depending on the activity and the amount of thyroxin left. From these observations I concluded that the putrefactive indole producers had been exterminated in all cases of exophthalmic goitre, and that all the tryptophane was absorbed as such, and was therefore available for the production of thyroxin. The change in the flora takes place before the onset of definite exophthalmic symptoms and is responsible for the diminution, and later the disappearance, of the indican from the urine.

In cases of parenchymatous goitre there was no diminution in the amount of indican—in fact, most cases showed a slight increase with 0.4 to 0.5 gram of total organic sulphates per litre, indicating a predominance of the putrefactive indole producers. In these cases a fall in the amount of indican to below the normal is a sign of grave significance; it means that exophthalmic symptoms are likely to supervene—in other words, the indole producers are being replaced by the fermenters.

In one case of myxoedema investigated there was no indican in the urine—a condition suitable for the development of exophthalmic goitre—and the absence of symptoms can be explained by the atrophic condition of the gland found in all cases of myxoedema.

The Intestinal Flora in Exophthalmic and Parenchymatous Goitre.

Dr. W. Parry Morgan has kindly examined the faeces of some of my cases, and his results have been exactly what I expected from my analysis of the urine and the results obtained experimentally in lower animals by Dr. Distaso and myself. In other words, the indole producers are absent in exophthalmic and present in parenchymatous goitre.

It is well known that women often develop parenchymatous goitre in the hill stations of India, and McCarrison has shown that this is due to the contamination of the drinking water by a coliform type of bacillus, an indole producer, which is what one would expect. It is possible that the altitude has something to do with the rapidity with which the indole producers obtain predominance, as it has a definite influence on the rate of growth of various bacteria.

Methods of Altering the Character of the Intestinal Flora.

Distaso showed that, in rats and guinea-pigs, the addition of lactose to the diet for two or three days suppresses the growth of the putrefactive group. Torrey showed that dogs behaved in much the same way, and that dextrin acts more powerfully than lactose; also that unboiled milk and animal proteins stimulate the growth of putrefactive organisms, while boiled milk and vegetable proteins tend to suppress them. Distaso found that, in the healthy human being, lactose, given by the mouth, produces very little effect on the indole producers, and this explains the absence of any change in the amount of indican found in the urine.

TREATMENT OF EXOPHTHALMIC AND PARENCHYMATOUS GOITRE.

It is unnecessary to discuss the treatment of myxoedema as this is now familiar. The fact that the administration of thyroid extract has to be continued as long as the patient lives shows that the thyroid gland never recovers once myxoedema is established, and the absence of indole producers from the intestine shows that the disease is not caused by an undue destruction of tryptophane, but by the inability of the thyroid to utilize the material at its disposal.

In parenchymatous goitre it is necessary to encourage the growth of the fermentative group by cutting down animal proteins and giving fats, vegetable proteins, boiled milk, rice, bread, and dextrin or lactose. The amount of lactose required to produce any appreciable effect is considerable—1/4 to 1/2 lb. a day—and therefore not within the realms of practical treatment.

In exophthalmic goitre unboiled milk, eggs, and fish should be given freely. The supply of meat protein should be controlled by the symptoms and the examination of the urine. In the complete absence of indican, and therefore of putrefactive organisms, the administration of meat aggravates the symptoms, but in the presence of indican meat will encourage the growth of the putrefactive bacteria already present. I have found that in the complete absence of indican the patient is more comfortable if all animal protein is withheld, and jelly given instead. The reason is obvious, as jelly contains no aromatic radical. In serious cases, with pulse rates of 150 or over, I have found this fact of great value. It is rare for the pulse rate not to fall below 120 if animal protein is withheld for a fortnight; in addition, the patient feels better, and the dangers of an anaesthetic will be reduced if the goitre has to be treated surgically.

Operative Treatment of Goitre.

Obviously, a case of parenchymatous goitre with no exophthalmic symptoms superadded is not benefited by removing a part of the gland unless the trachea is pressed on and the breathing interfered with. Ladies, however, are prepared to sacrifice a lot in the interests of their personal appearance. Needless to say, I am not referring to adenomatous or cystic goitres, which are obviously surgical conditions.

In exophthalmic goitre I am guided by the intensity of the symptoms, by the result of dietetic and medical treatment, and especially by the absence or presence of indican in the urine. The complete disappearance of indican, as I have already insisted, means that the chances of early improvement are remote, and if the symptoms are at all severe I advise operation. Partial thyroidectomy improves the patient for several months, as it diminishes the amount of thyroxin manufactured. The operation does not attack the cause of the disease, but the improvement in the symptoms may be enough to justify the operative risk. Both parenchymatous and exophthalmic goitre are diseases which run a definite course; the patients get progressively worse up to a certain point, and then, for no apparent reason, they improve, and ultimately get perfectly well—provided, of course, that the symptoms have not proved fatal before improvement sets in. The patients commence to improve when the intestinal flora becomes normal, and, in all probability, an acquired immunity to the suppressed organisms explains the difficulty found in re-establishing the normal flora in these cases. When the subject has been more fully investigated it may be possible, if such is really the case, to diminish or destroy this immunity. Possibly equally good results might be obtained by increasing the immunity of the body to the predominant group, as this would encourage the growth of the opposite group. It is possible that the improvement following removal of a part of the gland in exophthalmic goitre has a definite effect on the degree of immunity to the putrefactive group.

Unfortunately, bacteriology is still in a very primitive stage of development; comparatively unimportant matters have been fully investigated, such as the exact type of growth obtained on rare and complicated media, but very little interest seems to be taken in the exact chemical composition of the bodies formed by pathogenic bacteria when growing in animal tissues. When this subject is worked out, then we can hope to make a decided advance in our methods of treating the diseases caused by them.

The treatment of goitre by means of x rays is a non-operative method of destroying a part of the gland tissue, and its use should be regulated by the same considerations that govern operative treatment.

Medicinal Treatment of Goitre.

In parenchymatous goitre I doubt if any preparation does as much good as the local application of dilute mercuric iodide ointment; its beneficial results may be due to the excretion of some of the mercury into the alimentary canal. In exophthalmic goitre treatment is mainly symptomatic, and is useful in that it improves the patient's general condition and comfort; it does not cure the disease, and no one pretends that it does.

GENERAL CONCLUSIONS.

1. Exophthalmic goitre is due to the excessive absorption of tryptophane from the intestine; this in turn is traceable to the absence of the indole producers from the intestine.
2. The absence of indican from the urine indicates the absence of indole producers from the intestine.

3. In exophthalmic goitre the early disappearance of indican from the urine is of serious prognostic importance.

4. Operative surgery has a definite place in the treatment of exophthalmic goitre. Medically, much can be done by suitable dietetic measures.

5. Diffuse parenchymatous goitre is characterized by an excess of indican in the urine, suggesting an excessive destruction of tryptophane. If this excess gives place to a diminution or complete disappearance of indican, that suggests that the case is assuming the exophthalmic form.

6. Myxoedema is due to atrophic changes in the thyroid gland, which loses its capacity for dealing with the circulating tryptophane, whether that substance be excessive, deficient, or normal in amount. The disease is thus compatible with the presence or absence of urinary indican.

THE TREATMENT OF INCIPIENT PHTHISIS.

BY

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MORE than a quarter of a century has now elapsed since the open-air treatment of phthisis was brought home again to this country by Dr. Burton-Fanning of Norwich and Dr. Jane Walker, and the time is ripe for a general stocktaking of sanatorium experience.

ENGLISH SANATORiums.

There is a general impression that this experience is on the whole disappointing, and recently Dr. Ernest Ward has shown that in his district working-class cases of phthisis have done better in their own homes than those sent to a sanatorium.

No one who remembers working-class consumption thirty years ago will regard open-air treatment as anything but a great advance; and since it was in sanatoriums that open-air methods were developed, no one can hold that sanatorium treatment in a general sense has failed. If there is failure in England, it must be due either to our climate or to defects in individual sanatoriums. That England is less capable than other countries of furnishing the best results is unproved, though the point needs investigation. But that individual sanatoriums are unsatisfactory is suggested by the variations which are becoming evident in the results of treatment in different localities.

THEIR HISTORY.

Bodington.—The open-air treatment of phthisis was an English discovery, first announced, in 1840, by Dr. George Bodington of Sutton Coldfield, but the English medical profession turned it down.

Görbersdorf.—Happily for the tuberculous, the German realized its value. In 1859 Brehmer opened the first open-air phthisis sanatorium at Görbersdorf in Silesia, and I would draw attention to two points about this sanatorium which have been curiously overlooked. In the first place Brehmer chose a locality almost free from indigenous phthisis. In the second place he chose a site which was exceptionally wind-sheltered.

Davos.—In 1862 Spengler of Davos pointed out that indigenous phthisis was rare amongst the inhabitants of his valley, and that such of them as had contracted it elsewhere frequently recovered on returning to their homes. In 1865 patients from Germany began to be sent to Davos and the results were eminently satisfactory. In Davos also there is remarkable wind-shelter, and this "wind-stille" has been insisted on by all competent writers as an important factor in the curative influence of the place.

Nordrach and Falkenstein.—The success of Görbersdorf led to the establishment of daughter sanatoriums in different parts of Germany. Two of these have been specially noteworthy—namely, Dettweiler's at Falkenstein and Walther's at Nordrach. Nothing could be more striking than the contrast between their sites and their fortunes. For the first time in the history of sanatoriums we come upon a disappointment. Nordrach was a success; Falkenstein has been demolished.* Falkenstein, the failure, stood high on the southern slopes of the Taunus, "well protected from north

* The reason of the closure of Falkenstein has of course to be inferred. Most really successful phthisis sanatoriums do not close down. It is noteworthy that no new sanatorium has arisen at Falkenstein and that the sanatorium for the poor, opened at Falkenstein by Dettweiler on a small scale in 1892, was afterwards moved to a very different site, in marked shelter from westerly winds, at Ruppertsheim, where it remains.