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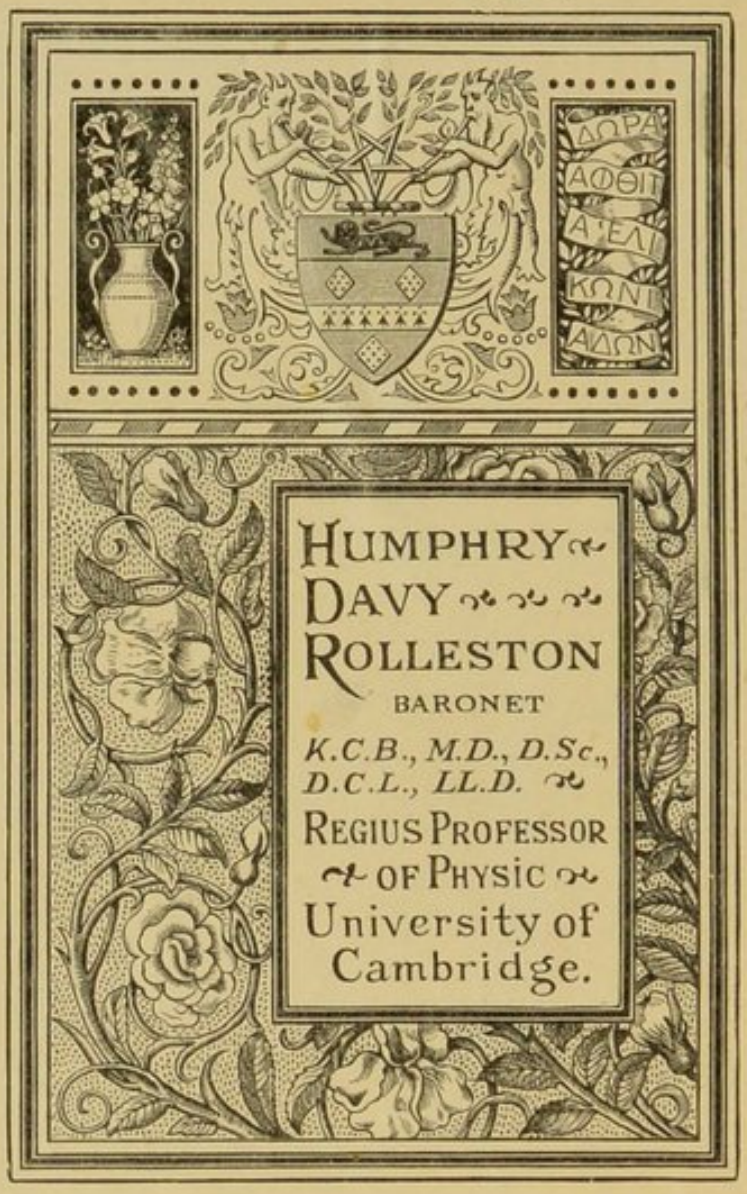
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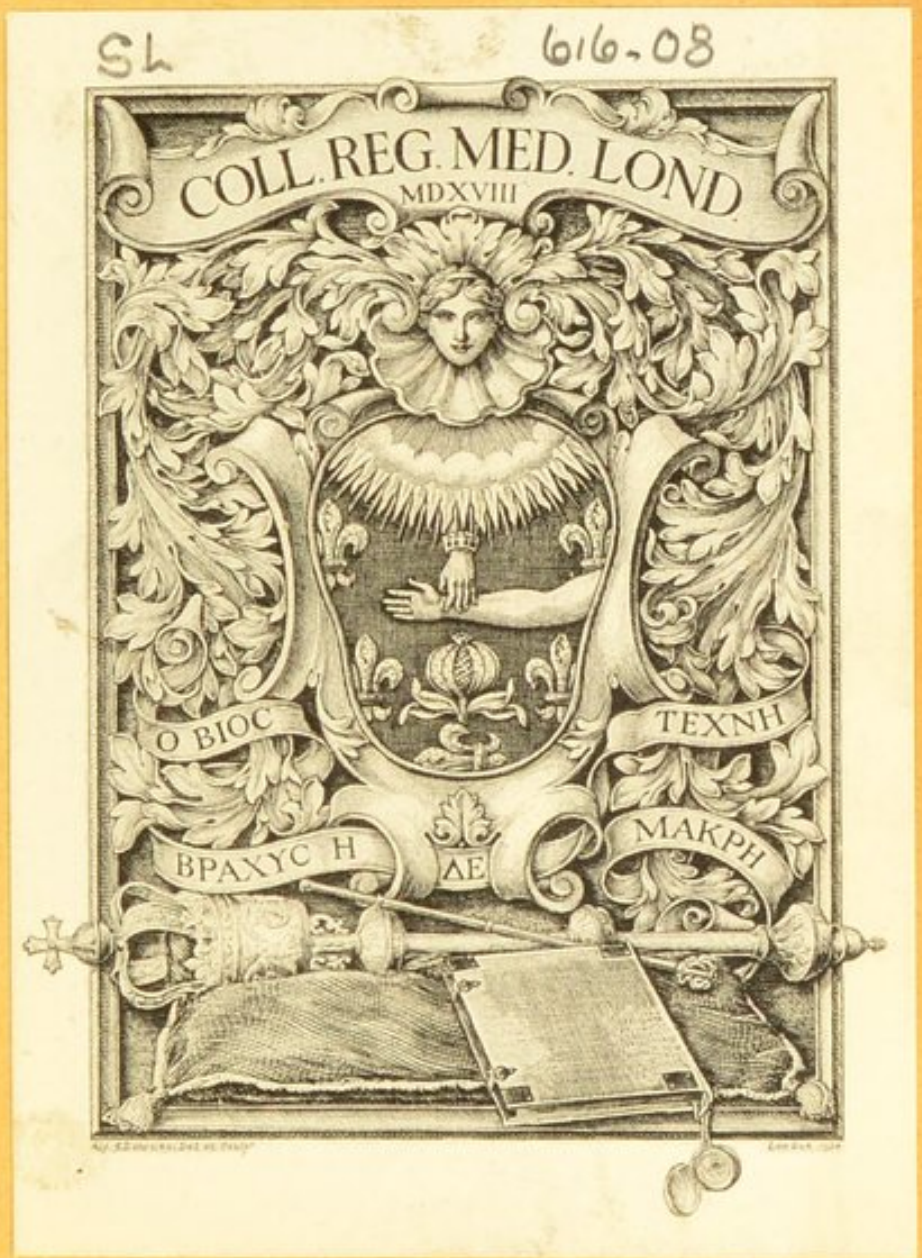

CLINICAL LECTURES AND ESSAYS

CLINICAL LECTURES AND ESSAYS

ON ABDOMINAL AND OTHER SUBJECTS

BY

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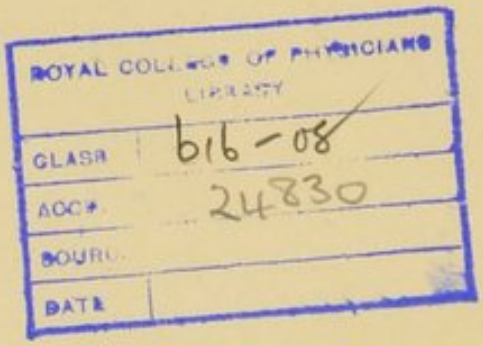

PREFACE

The clinical lectures and papers which are reprinted here, with such additions and alterations as have seemed desirable in the light of any subsequent knowledge, have all appeared elsewhere, and I am indebted to the editors and proprietors of *The Lancet* *British Medical Journal*, *Clinical Journal*, *Treatment*, and *The Medical Magazine* for their courtesy in allowing me to reproduce them.

I am further indebted to the proprietors of *The Lancet* for their extreme courtesy in lending me the blocks of the figures in the text.

H. D. ROLLESTON.

London, *April 4th*, 1904.

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CLINICAL LECTURES

I

VOMITING IN DIPHTHERIA [1]

To-day I propose to consider the subject of vomiting in diphtheria. A comparison of diphtheria with scarlet fever—diseases in many ways alike—shows that there is a very great difference with regard to the occurrence of vomiting in these two diseases. Vomiting is perhaps one of the most characteristic features about the onset of scarlet fever, whereas in diphtheria—a disease where the throat is commonly affected—vomiting does not usher in the disease, and though it may be a complication, it is in no way a usual symptom of the disease. When vomiting is persistent and often repeated in diphtheria, the prognosis is very bad indeed. This is a point that I am especially anxious to impress upon your minds. This bad prognosis does not depend entirely on the effects of vomiting—starvation, exhaustion, and so on—but to a great extent on the fact that the further complication of cardiac failure is especially likely to supervene. There is here an association between the stomach and the heart which is anatomically represented by the pneumogastric nerve.

[1] A clinical lecture at St. George's Hospital, reprinted from *The Clinical Journal* of January 28th, 1900.

Now with regard to the kinds of vomiting met with in diphtheria, we may at once divide them into two.

1. ACCIDENTAL OR OCCASIONAL VOMITING

That which may be spoken of as occasional or accidental vomiting is not infrequent at the time that the antitoxin rash comes out. About a week or ten days after antitoxin has been injected the child becomes restless; not uncommonly the temperature rises, and a rash appears on the skin. Sometimes this antitoxin reaction is accompanied by pain in the joints, more rarely by the effusion of fluid into their synovial cavities. These events depend, not on the antitoxin which is contained in the serum, but on the presence of something in the blood serum of the horse, and are independent of the antitoxic curative properties of the serum. There is considerable variation in the after effects manifested by curative sera derived from different sources. With the brand employed here, eruptions, without any joint symptoms, are commonly seen. At the time that the eruption comes out and the temperature goes up, the patient may vomit. This vomiting is entirely accidental in character. It does not depend on the diphtheria at all; it really depends on the remedy, and not on the essential part of the remedy—the antitoxin—but on the serum in which the antitoxin is, so to speak, suspended.

Another example of the accidental vomiting that may occur in the course of diphtheria is seen in the early stage of diphtheritic paralysis—a little of the food works its way into the larynx and sets up choking and vomiting. In the same way, some of the membrane in the throat may become detached, and, acting much in the same way as a feather applied to the back of the throat, produce vomiting. These cases of accidental vomiting, in which the child vomits once or twice, are

of little or no importance. Indeed, vomiting is sometimes of use, inasmuch as it dislodges some of the membrane.

2. GRAVE, PERSISTENT VOMITING

It is not of the occasional vomiting I wish to speak mainly, but about the grave and persistent vomiting which is so often followed by cardiac failure and death, so that one may really speak of it as a sort of malignant vomiting.

In speaking of the vomiting of diphtheria, a sharp distinction must be drawn between (*a*) the real vomiting (emesis), in which the contents of the stomach are forcibly ejected through the mouth, and sometimes also through the nose; and (*b*) the regurgitation of the food through the nose, which so commonly occurs in diphtheritic paralysis. When paralysis attacks the palate—as it generally does earlier than other parts of the body, because the diphtheritic toxin, or poison, is manufactured in the tonsils, and, therefore, readily exerts a local action on the muscles of the palate—the liquid food regurgitates through the nose.

As to the onset of the grave, persistent vomiting in diphtheria, it may occur at any period of the disease. It may take place when the membrane is on the tonsils, or it may not begin until after the appearance of diphtheritic paralysis. In one of the cases which I have had in the hospital this year, vomiting did not come on until rather more than three months after the initial attack of diphtheria. It may come on before or after diphtheritic paralysis, or may accompany the diphtheria itself.

Now with regard to the different means by which the vomiting is set up. A good many different causes have been suggested, and as is generally the case when more than one cause is put forward to account for the

same effect, there is at first rather a tendency to refer the effect to one cause, and to one cause alone. Thus vomiting in diphtheria is by some explained as being due to irritation of the pneumogastric nerve; by others it is said to be due to a local condition of the stomach; and on yet another theory it is supposed to be uræmic vomiting. I shall discuss these in a moment; but the point I want to lay stress on first is that vomiting is a symptom, and that this symptom may be produced in diphtheria in several ways, and that it is by no means necessary that one cause, and one cause only, is concerned in its production. In different cases different causes may be at work.

The different causes which have been given for vomiting in diphtheria are as follows: (1) The older view was that it was uræmic; Dr. Gee,[1] in a paper with the title "Repeated Vomiting in Diphtheria as a Bad Prognostic," related nine cases, eight of which proved fatal. He said that in most of the cases he had seen, there was evidence of kidney disease; and that in some of the patients the urine was suppressed. The uræmic theory of the vomiting which occurs in diphtheria might perhaps be most successfully invoked to account for those cases in which death is preceded by convulsions. But at the present time, with the advantages of the antitoxin treatment, the course of diphtheria is so modified that we never see any cases of severe kidney disease with suppression of urine. I have inquired about this point from the Sister in the Diphtheria Ward of this hospital, and she tells me she has not seen a case of it. But in past days, when diphtheria was very much more virulent, because it was not in any way antagonised by antitoxin, secondary infection may have taken place from the tonsils, and so, acute septic nephritis having resulted, may account for the convulsions

[1] *St. Bartholomew's Hospital Reports*, vol. xxv. p. 69; see also Allbutt's *System of Medicine*, vol. i. p. 739.

and for uræmic vomiting. But at the present time one cannot explain the vomiting which occurs in diphtheria as being uræmic in origin.

The second view is the nervous view. Put shortly, it is this: that in diphtheria, when the degenerative change is about to begin in the vagi, before any definite change has occurred, there is a stage of heightened irritability, which would be shown by vomiting and by slowing of the heart's action. Now you may remember that in the very early stage of neuritis there is an exaggeration of the knee-jerk. This exaggeration of the knee-jerk probably depends upon the nerve fibres, that form the reflex arc, being irritated before they become further affected by the poison. It has been thought that in the early stage of neuritis of the vagus, there may be a condition of transient irritability, and that this shows itself as regards the stomach by vomiting. Some of the cases may be satisfactorily explained on this view. In one of the two cases I have had under my care this year, the boy had not only vomiting, but he also had a kind of laryngeal crisis. This leads me to draw your attention to the resemblance which exists between the gastric crises of locomotor ataxy and the vomiting in diphtheria. In tabes the crises depend upon degenerative changes taking place in the visceral nerves; possibly there is from time to time an exacerbation in the morbid change in the visceral fibres, which sets up the various crises of which the gastric form is the most familiar example.

Sometimes in cases of diphtheria there are other symptoms which may be correlated with gastric crises. For instance, the patients have a good deal of pain in the abdomen. I mentioned to you that in one of my cases the boy appeared to have something like a laryngeal crisis; he was seized suddenly one night with extreme shortness of breath, which, however, passed off. After vomiting ceases, if life is prolonged, there may be

an extremely quiescent condition of the intestines, which, theoretically, might be referred to nerve degeneration and paralysis. Both the boys who were under my care for persistent vomiting associated with diphtheritic paralysis suffered while recovering from marked constipation. So in the early stage there are signs of irritation and vomiting, and in the later stage constipation. The nervous theory, pure and simple, therefore explains most satisfactorily the occurrence of vomiting about the time that diphtheritic paralysis is manifested. It is impossible to disprove the theory which explains vomiting in diphtheria as depending on incipient neuritis of the vagus, for neuritis of the vagi has been shown to exist histologically. The only difficulties are in explaining all the cases of vomiting as due to incipient neuritis of the vagus.

Now the difficulty in making the nervous theory fit all the cases is that in the early stages of neuritis of the vagus there ought to be, as a result of that irritation, slowing of the heart at the same time as vomiting takes place, an event which is far from being constant. Later, when the vagus becomes paralysed, the heart should be much quickened, but this is not by any means constant. In answer to this objection it might be said that in some instances the gastric fibres of the vagus alone are affected by changes taking place near their termination in the stomach wall—in other words, that there is a peripheral neuritis of the gastric part of the pneumogastric.

Another argument against explaining all the cases of vomiting in diphtheria as due to nervous influence is that the vomiting so often occurs very much earlier—weeks, or perhaps even months before diphtheritic paralysis. A large number of cases of diphtheria with persistent vomiting die within the first week of the illness.

In these cases a third suggestion must be considered,

viz. that in cases of diphtheria the diphtheritic process also involves the stomach. Sometimes it does so by extension of the membrane along the œsophagus; but this is so rare that such cases are almost curiosities. It has indeed been said by Kalmus (quoted by Soltau Fenwick, *Trans. Path. Soc.* vol. xlv. p. 60) that 6½ per cent. of the cases of fatal diphtheria show some diphtheritic membrane inside the stomach. At any rate, observations in this country show that that figure is in excess of what we see in England. But there are undoubtedly cases in which, although there may not be any extension of membrane directly from the throat to the stomach, the stomach is affected. Momentary consideration will show that it is only natural to suppose that a child who is continually swallowing must thereby convey infection to the stomach. Dr. Villy (*Medical Chronicle*, September 1899, p. 405) examined the stomach microscopically in fifteen fatal cases of diphtheria, and in all these cases he found marked changes, viz. fatty degeneration in the gastric glands, and very definite inflammatory reaction in the stomach, as shown by the presence of a number of leucocytes in both the mucous and submucous coats. As a result he came to the conclusion that the vomiting is, like that of gastritis, due to direct irritation. He further examined the heart; and here I may remind you that there is a marked tendency in fevers generally and particularly in diphtheria to get dilatation of the heart, as the heart muscle is acted on by the toxins which are circulating in the blood. Not only the kidneys and heart, but also the stomach, suffer from the effect of the diphtheritic poison. It is only reasonable to think that the poison is to a considerable extent conveyed from the throat to the stomach by swallowing; hence the stomach is particularly liable to suffer. The vomiting, especially when it sets in early—while membrane is still present in the throat—may be due

to inflammation of the stomach. In some cases the character of the vomit supports this view, for it contains blood. In about half his cases Dr. Villy found hæmorrhage into the submucous coat of the stomach. This explanation perhaps accounts better for the early cases of vomiting—those in which the vomiting takes place in the first week; whereas in the cases where the vomiting supervenes just before or just after diphtheritic paralysis, it may be accounted for by the view that it is really due to incipient neuritis, a certain amount of irritation taking place before the degenerative change becomes complete.

A fourth explanation is a combination of the two last, and is to the effect that the primary lesion is diphtheritic gastritis, which spreads to the gastric terminations of the left vagus and sets up irritation and an ascending inflammatory neuritis, and so reflex vomiting. In such cases cardiac dilatation would be due to degeneration of the myocardium, induced by toxins reaching the heart muscle by the blood stream, and would be independent of vagus influence.

So much for the causes of vomiting in diphtheria.

Now for a few words about the prognosis. The outlook when persistent vomiting occurs is extremely bad. This is well shown by the following statistics, collected by Dr. Hector Mackenzie.[1]

Of 36 cases where vomiting occurred in the first week of the disease, 34 died.

Of 35 cases where vomiting occurred in the second week of the disease, 31 died.

Of 12 cases where vomiting occurred in the third week of the disease, 7 died.

Of 12 cases where vomiting occurred in the fourth week of the disease, 2 died.

Of 16 cases where vomiting occurred later in the course of the disease, 6 died.

[1] *St. Thomas's Hospital Reports*, vol. xxi. p. 87.

The prognosis is thus worse when vomiting coincides with active disease in the throat, or comes on directly after the acute disease, and is less grave when the vomiting comes on later, when the patient has to some extent recovered from the effects of the acute disease.

I have had two cases of diphtheritic paralysis in the hospital this year, with persistent vomiting, that were both very bad, but recovered. Probably their recovery depended largely on the fact that they had more or less recovered from the acute stage of the disease. In one case it was three months after the original attack of diphtheria. When persistent vomiting occurs in the first week the prognosis is extremely grave, and very likely to be followed by cardiac failure. I cannot impress too strongly upon you the association between vomiting and cardiac failure. In many cases the two processes are due to the same cause—either irritation of the vagus followed by paralysis, or to the poison manufactured in the throat in diphtheria attacking various parts of the body at the same time—the heart, giving rise to fatty degeneration, dilatation, and cardiac failure; the stomach, giving rise to inflammation, and so to vomiting; the nerves, giving rise first to irritation, etc., then to degenerative neuritis; while at the same time toxic changes in the renal epithelium produce albuminuria.

There is, I repeat, a very close association between vomiting and the subsequent advent of cardiac failure. The heart dilates while vomiting is taking place, partly because the same cause affects both viscera, and partly because vomiting leads to starvation and mal-nutrition of the heart muscle. In the case recently under observation, as the vomiting persisted the heart could be seen to be undergoing progressive dilatation. If the heart is in a feeble condition, the mere exertion of vomiting must exaggerate this, and may sometimes act as a last straw and give rise to fatal dilatation of the

heart. With regard to the prognosis, therefore, whereas the accidental vomiting, especially when it appears at the same time as the antitoxin rash, is of little or no importance, persistent vomiting is extremely grave.

TREATMENT

The treatment of the vomiting depends largely on the nursing of the patient, and in nursing I include careful and judicious feeding. I really think the case which I had recently under my care owed its recovery probably almost entirely to the careful nursing.

Of course a very important part of the treatment is to avoid giving rise to vomiting, and as this may be brought on if food is given by the mouth, the patients are usually fed by the rectum. There are, however, objections to rectal feeding. One of them is that after about a fortnight, or before, the rectum begins to get irritable, and the enemata may be ejected before there has been time to allow sufficient absorption to take place; so the child begins to starve. This, added to the constant vomiting, makes the condition of the patient very grave. Rectal feeding, therefore, should not be persisted in too long, and a little food should be given by the mouth as soon as possible. In the case of one of the boys who recovered this was done; his likes and dislikes as regards his food were humoured, and he kept his food down. He was an hysterical, nervous boy, and it was not easy to get him to retain his food. But perhaps this was helped by a morphia draught, and by the injection of morphia under the skin. At any rate the boy began to improve directly he was able to keep food on the stomach. Before that he had wasted very much, and looked as if he were going to die of starvation. He was so ill, indeed, that I asked Mr. Turner to see him, with a view to the adoption of an heroic and desperate form of treatment.

It has been shown by experiment that if a dog has tracheotomy done, or if one of the laryngeal tubes introduced by O'Dwyer be passed through the upper opening of the larynx, so that the rima glottidis can not be closed, the dog is unable to vomit. This has been shown satisfactorily in a dog that had been intubated, and then injected with apomorphia. The dog made tremendous exertions to be sick, but was not able to do so; immediately the tube was removed, however, violent vomiting followed. It was thought that this would be the case in a human subject, and the performance of tracheotomy in desperate cases of vomiting was recommended by Dr. Green,[1] of Minnesota, U.S.A. It struck me as being reasonable to try this in this boy, rather than that he should be left to die. Mr. Turner thought the boy's condition so critical that he would therefore rather not attempt any operation, and none was done. I inquired from the Sister in the Diphtheria Ward some months ago as to whether tracheotomised patients ever vomited. At the time she thought that they did not, but after I spoke to her about it she specially watched the cases with regard to this point, and in a little while she was able to give me the notes of three tracheotomy patients who had vomited, and in whom there was no suspicion of any blocking of the tube; in one of the cases death was due to a considerable extent to the vomiting. So that the principle on which this desperate form of treatment is based, though it is all right for dogs, does not seem to hold for men, inasmuch as tracheotomy or intubation does not seem to prevent vomiting in the human being. This is a point which it is well to bear in mind. When one sees everything else failing, one is inclined to give a patient the benefit of the last straw; but it is important to know whether the last straw will bear something. It is possible that if tracheotomy had been performed the

[1] *Brit. Med. Journ.* 1897, vol. ii. p. 1058.

boy might still have gone on being sick, and that he might have suffered from the tracheotomy, for as a result of it he would have been exposed to the danger of getting broncho-pneumonia or bronchitis.

Another point is the question of giving alcoholic stimulants to these patients. It is one which is rather difficult to decide. In cases where cardiac failure is imminent, one is, of course, impelled to give alcohol, in order to tide over the immediate danger. But the nerves are probably in a condition of incipient degeneration, and alcohol being a nerve poison, its administration might hasten or cause further degeneration. I should be inclined to content myself by stimulating such cases by hypodermic injections of strychnia, and to withhold alcohol, or give it in very small quantities.

With regard to drugs, for the vomiting itself the hypodermic injection of one-fortieth to one-twentieth of a grain of morphia is a most valuable remedy. If there is an inflammatory condition of the stomach, it is only reasonable to believe that it may be given by the mouth, and by its local action lead to a good result. Perhaps it produces rather more effect if given by the mouth than if it is given underneath the skin. But you must remember that even when morphia is injected underneath the skin, a certain quantity of it circulates round, and is excreted in the stomach. It is important to bear in mind that in cases of poisoning by hypodermic injection of large quantities of morphia, permanganate of potash should be given by the mouth, even though the poison was administered under the skin, because the stomach excretes into its cavity a certain amount of the morphia which is circulating through the body.

Another drug which is beneficial when given hypodermically is strychnine. It is given, not for the vomiting, but to keep the heart in good working condition. Two minims, or even three minims of liquor strychninæ,

injected under the skin twice a day, may be given with this end in view, for patients do not die from the vomiting so much as from the heart collapse; and if the heart is kept in good condition, and cardiac failure prevented, recovery may result.

A third drug, useful in those cases where respiration begins to fail, and where the diaphragm is paralysed, is atropine. It is administered hypodermically. The object of giving belladonna in cases of diphtheritic paralysis is to stimulate the respiratory system.

II

THE TREATMENT OF GASTRIC ULCER[1]

On the present occasion we are concerned with the medical treatment of gastric ulcer, and though it will be well to consider the indications for surgical treatment in cases which obstinately resist medical measures, it is unnecessary to deal with the treatment of perforation, as this is, or should be, a purely surgical question. Further, the scope of the discussion renders impossible any reference to the attractive subject of diagnosis.

GENERAL TREATMENT

In the acute stage of an ordinary clinical case of gastric ulcer, in a young woman, with localised tenderness, vomiting, pain, etc., the principle of absolute physiological rest, though universally accepted, is not so consistently carried out. While most medical men cut off all food by the mouth, some allow sips of water, hot or cold, or ice by the mouth to relieve thirst. Probably this depends in part on the erroneous belief that water is quietly absorbed by the mucous membrane of the stomach. As a matter of fact, water taken into the stomach is only absorbed in the intestine, and has first to be expelled from the stomach by peristaltic

[1] Introduction to a discussion in the Section of Medicine, Annual Meeting of the British Medical Association, Swansea, July 1903. Reprinted by permission from *The British Medical Journal*, October 24th, 1903.

action. In this way not only is healing delayed, but a gastric ulcer may be so disturbed that severe hæmorrhage is induced. I have seen hæmatemesis set up when water was first allowed by the mouth five days after a previous hæmatemesis, and when deep tenderness had disappeared. My own practice is to forbid any water by the mouth, and to rely on rectal injections of from 10 oz. to 20 oz. of water, given slowly four or more times a day. Thirst is not, as a rule, relieved so well by rectal injections of water as by fluid given by the mouth. The thirst, restlessness, and attendant discomfort may at the outset of treatment be temporarily relieved by a hypodermic injection of morphine, but it is not advisable to repeat this often, as the habit may thus be started. The mouth should be kept as clean as possible by a mouth wash, such as listerine. Even though patients are not given fluid of any kind by the mouth, they still swallow their saliva, and when, as not uncommonly happens, there is pyorrhœa alveolaris, infection and irritation of the stomach are kept up, and may, as will be seen later, account for vomiting. The question might, indeed, be raised whether it is more harmful to swallow these buccal secretions as such, or when diluted with a considerable amount of water. The risk of infection of the stomach from the mouth is probably diminished by the use of a mouth wash. A few words may be said about the disadvantages of withholding all liquid—even water in small quantities—by the mouth. Thirst is often very trying, and patients suffer from dryness of the mouth and tongue, though this may be relieved by washing out the mouth with water. Occasionally—sometimes it would appear almost in small epidemics—patients with gastric ulcer develop parotitis on rectal feeding. I have seen this parotitis attack a patient with gastric ulcer, and a day or two later develop in the patient in the next bed, and it has occurred to me as possible that patients

with dry mouths are specially susceptible to the infection of ordinary parotitis. Dr. B. N. Tebbs has found from an analysis of the cases at St. George's Hospital that parotitis is more frequently a sequel of gastric ulcer than of other abdominal diseases such as appendicitis, that the patients affected were all on nutrient enemata, and that the routine use of antiseptic mouth washes does not influence or protect against the incidence of parotitis. The latter point is of interest, as it militates against the view that there is an ascending infection of Stenson's ducts from the mouth.

The proteids of nutrient enemata should, of course, always be peptonised, and the enemata should contain eggs and a sufficiency of salt, in addition to the ordinary constituents, such as milk, beef-tea, and sugar, and may be given every four or six hours. The irritability of the rectum should be guarded against by washing out the bowel daily with boracic solution, or with a dilute solution of perchloride of mercury, 1 in 10,000, or, in addition, by the occasional introduction of morphine suppositories into the rectum.

VALUE OF RECTAL FEEDING

It is a question of considerable interest whether nutrient enemata are necessary during the period—usually one to two weeks—in which no food is given by the mouth. My own impression is that, provided plenty of water is given by the bowel, it is unnecessary to give nutrient enemata, though I usually do give them, or allow the patient to have them if desired, when a week has passed without food of any kind having been introduced into the body. The pulse and heart should, of course, be most carefully watched. It is somewhat surprising how well patients bear complete starvation when plenty of water is given by the bowel; and it has been said epigrammatically that nutrient

enemata satisfy the minds rather than the bodies of the patients (Wynter).[1] At any rate, this may be applied, with little fear of exaggeration, to the use of nutrient suppositories. As a result of careful chemical analysis of the enemata, urine, and fæces in cases of gastric ulcer on exclusive rectal feeding, and from a critical review of the data obtained by other observers, Edsall and Miller conclude that in exceptional cases rectal feeding provides sufficient food to prevent tissue loss, but even then only maintains the patient in a condition of decided subnutrition; usually nutrient enemata are very imperfectly absorbed, and only supply a very small part of the food necessary to maintain a nutritive equilibrium.[2]

It is interesting to note that diacetic acid is extremely common in the urine of patients who are starving or are on rectal feeding, and that it disappears from the urine when feeding by the mouth is resumed.

More efficient nutrient enemata can be given in a semi-solid form as advised by Leube; and O. F. F. Grünbaum[3] has advocated ox serum in rectal alimentation, in combination with starch and glucose, as a satisfactory method of supplying the necessary amount of caloric energy to the body and of minimising loss of weight. It would be of value to hear the experience of members on improved methods of rectal feeding and on the hypodermic injection of sterilised olive oil or other forms of food. My senior colleague, Dr. Ewart, has employed a method of giving continuous nutrient enemata much on the same lines as continuous irrigation of the colon.

I do not propose to discuss the return to feeding by the mouth and the gradual improvement in the diet.

[1] W. E. Wynter, *British Medical Journal*, 1902, vol. ii. p. 1710.

[2] Edsall and Miller, *Trans. Coll. Physicians*, Philadelphia, vol. xxiv. p 225, 1902.

[3] O. F. F. Grünbaum, *British Medical Journal*, 1901, vol. i. p. 823.

Drug treatment of gastric ulcer may be divided into two headings:

(i) The symptomatic treatment of pain by opium, bismuth, nitrate of silver, counter-irritation, of hæmorrhage, and of vomiting.

(ii) Attempts to bring about a cure and to prevent a relapse may be directed (*a*) to improving the general health and resistance, and removing any underlying cause such as chlorosis, syphilis, or oral sepsis; or (*b*) to the purely local treatment of the ulcer.

(*a*) In the cases commonly recognised as gastric ulcer in young women, which, however, Hale White[1] regards as a different disease, there is no doubt that as soon as gastric irritation has subsided, iron is a most valuable remedy, and should be given to prevent a relapse in the same manner as in chlorosis. In the more chronic gastric ulcers usually seen in men after thirty years of age, potassium iodide should be tried, as a certain percentage of these ulcers are syphilitic in origin. If iodides disagree, they should be discontinued; but if well borne, which they are not in ordinary gastric ulcers, there is a fair probability that the process is syphilitic and that a cure will result. It is, perhaps, hardly necessary to dignify the application of mouth washes, listerine, hydrogen peroxide, etc., to the teeth and gums as "drug treatment," but its importance can hardly be over-estimated.

(*b*) Cautiously washing out the stomach with water or mild antiseptic solutions, or running in a large amount of bismuth, so as to get the local soothing effect of bismuth on the surface of the ulcer, are curative measures sometimes employed. (Fleiner's and Fenwick's modification of Fleiner's method.)

"Erosion" of the gastric mucous membrane has been

[1] Hale White, *Lancet*, 1901, vol. i. p. 1819. "Are not some patients said to be afflicted with gastric ulcer really suffering from a different disease?"

treated by an intragastric spray of nitrate of silver: 1 to 2 per cent. (Max Einhorn).[1]

INDICATIONS FOR SURGICAL TREATMENT

Apart from perforation, the only acute complication requiring operative interference is repeated hæmorrhage which does not yield to medical treatment and is manifestly endangering life. Repeated hæmorrhage may be due (1) to an ordinary gastric ulcer with an exposed and ulcerated artery in its floor, or (2) to "exulceratio simplex" (Dieulafoy) or "pore-like erosions of the gastric arteries" (J. L. Steven). In the latter condition the bleeding spots may be so small as to escape observation when the gastric mucous membrane is examined during an operation, and yet may be found after death. This has occurred in at least two published cases, and in one case under my own care.

Parotitis, which is an acute complication occasionally seen in patients with gastric ulcer on rectal feeding, hardly ever requires surgical treatment, and although its appearances may be highly suggestive of suppuration, it is extremely rare to find pus.

VOMITING

Vomiting in patients with gastric ulcer is an indication that absolute physiological rest should be given to the stomach, and that nothing, except drugs like opium, bismuth, hydrocyanic acid, etc., should be given by the mouth. Quite recently Dr. Jex-Blake and I[2] found that a certain percentage (27·1) of patients with gastric ulcer vomited material other than blood, in spite of the fact that they were having absolutely nothing by the mouth.

[1] Max Einhorn, *Journ. of the Amer. Med. Assoc.* May 20th, 1889.

[2] Rolleston and Jex-Blake, *British Medical Journal*, 1903, vol. ii. p. 68.

In order to treat this troublesome and rather perplexing symptom it is desirable to know what factors are responsible for the vomiting. In some instances it appeared that the vomiting was reflex, and due to the irritation of rectal injections, since, on cautiously giving liquid food by the mouth, and omitting rectal feeding, vomiting ceased. In a few cases of persistent vomiting the cause was probably oral sepsis, and the swallowing of pus and micro-organisms, as shown by the fact that removal of bad teeth cured this symptom in two instances, and improvement followed special attention to the condition of the teeth in others. The part played by oral sepsis in this form of vomiting is of considerable importance, since the effects of bismuth, morphine, etc., by the mouth are very disappointing; while I have not seen striking benefit from counter-irritation, in the form of blisters, to the epigastrium.

It was suggested that in some cases vomiting depended on the administration of common salt, which was given with eggs to increase absorption of the nutrient enemata. Nothnagel showed experimentally that sodium chloride set up reversed peristalsis, but Cannon's[1] observations with X-rays show that there is normally reversed peristalsis in the colon. Further, patients on nutrient enemata containing common salt do not necessarily vomit. Patients prone to vomit should, of course, be kept scrupulously still, and any movement of the bed must be avoided as far as possible.

HÆMATEMESIS

It is impossible, and indeed unnecessary, to enter fully into the treatment of hæmatemesis. Absolute rest, which is assisted by morphine hypodermically to quiet anxiety, is, of course, essential. Patients should not be allowed to suck ice. Unless hæmatemesis is repeated it

[1] W. B. Cannon, *Amer. Jour. Phys.*, vol. vi. p. 253.

is probably better not to give any drugs by the mouth. When hæmatemesis recurs, or there are signs of continued though concealed hæmorrhage, Ruspini's styptic or adrenalin by the mouth for their purely local action on the bleeding spot, and a rectal injection of a drachm of chloride of calcium, in order to increase the coagulability of the blood, may be given with advantage. The hypodermic injection of ergot seems irrational, as it will constrict the blood vessels, raise the general blood pressure, and so favour hæmorrhage from any weak spot. There is no reason to suppose it will concentrate its energy on the bleeding vessel, and I have seen hæmorrhage occur after, though I am not, perhaps, justified in saying because of, its use. The analogy between hærmorrhage from a hollow muscle like the uterus and hæmorrhage from blood vessels in mucous membranes is very fallacious. The injection of digitalin and the use of lead comes under the same condemnation. It would be interesting to hear more of the influence of an icebag on the epigastrium in hæmatemesis. It has appeared to me to be harmless, but it might increase collapse by abstracting heat. As a minor point, attention may be drawn to the advisability of testing the coagulation time of the blood some time after hæmatemesis, and, if it be abnormally short, of giving citric acid as directed by A. E. Wright, so as to diminish the tendency to venous thrombosis.

In chronic gastric ulcer operative interference is justified in the following circumstances:—(1) When there is constant pain which is not relieved by medical measures and leads to a condition of chronic invalidism; this may be due to adhesions (adhesion dyspepsia), or may depend on the presence of a large gastric ulcer. (2) When there is intermittent or permanent pyloric obstruction; the first may be due to spasm set up by a chronic ulcer near the pylorus, and is met by gastro-enterotomy; the second is due to cicatricial

contraction. (3) When hæmatemesis recurs in spite of medical treatment.

In conclusion, the following are some of the points in the treatment of gastric ulcers to which discussion may be directed:—

1. The question of fluid by the mouth in the acute stage.
2. The value of ordinary rectal alimentation and of special modifications of nutrient enemata.
3. The treatment of vomiting in patients fed exclusively per rectum.
4. The drug treatment of gastric hæmorrhage.
5. The indications for surgical treatment (excluding perforation).

III

CARCINOMATOUS STRICTURE OF THE DUODENUM [1]

A PLUMBER, aged fifty years, was admitted to the hospital on November 29th, 1900, with weakness, anæmia, vomiting, and abdominal pain. His past history showed that he had been healthy until two years ago, when he began to suffer from pain in the epigastrium immediately after food; this pain had continued on and off since. In July and August, 1900, he was laid up with vomiting, and again on November 8th. During the last year he had lost weight and had grown paler, and had suffered from constipation. He had had no previous illnesses, there was no reason to think that he had had syphilis, and he had taken beer moderately. The patient was big-boned, spare, and anæmic, and presented practically no objective signs of disease in the chest or abdomen. The tongue was moist and slightly furred, the teeth were bad, but there was no blue line on the gums. The lungs were normal, the heart was not enlarged, and the sounds, though distant and rather weak, were otherwise normal; the second sound was not accentuated either over the pulmonary or aortic areas. Nothing abnormal could be felt in the abdomen, but the skin was

[1] A clinical lecture delivered at St. George's Hospital on March 11th, 1901. Reprinted by permission from *The Lancet* of April 20th, 1901.

dry and inelastic. There was no abnormal resistance in the abdomen and no distension; at times, indeed, in the course of the case the abdomen became retracted, while before bouts of vomiting it became rather fuller. No enlarged glands could be felt in any part of the body. The blood showed a secondary anæmia, the red corpuscles numbered 3,340,000, the hæmoglobin amounted to 70 per cent., and there was a slight leucocytosis. The urine varied in specific gravity, with the occurrence of vomiting, from 1,010 to 1,030, and sometimes contained a trace of albumin. Further changes in the urine will be referred to later. The pulse was normal in rate, rhythm, and tension. The vomited matters did not contain any free hydrochloric acid. On admission a tentative diagnosis of carcinoma of the pylorus was made, although no tumour could be felt. After a few days the stomach increased in size and seemed to support this diagnosis. On the other hand, the man's work, that of a plumber, and the history that he often took his meals without being able to wash his hands, suggested that the anæmia, debility, and gastro-intestinal disturbance might be due to lead poisoning. However, there was no lead line on the gums such as there would have been, since his teeth were bad, if lead had recently been introduced into the system. There was no wrist-drop or paralysis, and the pain was not that of lead colic. It is well to remember that it is easy to overlook the presence of grave abdominal disease in cases of suspected plumbism; thus I remember performing a post-mortem examination on a worker in lead who had a blue line on his gums and had had vomiting, constipation, and abdominal pain; he had a twist in the small intestine near the ileo-cæcal valve, at a point where the ileum was bound down for the last five inches to the posterior abdominal wall by a congenital deficiency of the mesentery. Incidentally it may be mentioned what an anxious problem

the diagnosis of acute intestinal obstruction is in a patient with tabes; gastric crises may closely intimate mechanical obstruction, and yet, of course, tabes in no way protects against acute intestinal obstruction. One is conscious of the importance of making a correct diagnosis so as to avoid an unnecessary operation on the one hand, and the calamity of allowing a patient to die from unrelieved obstruction on the other. Some years ago a patient under my care with tabes had an unusually severe and prolonged gastric crisis, and these questions were solved by waiting for developments.

A third possibility as to the condition at work in our patient was that it was a case of oral sepsis, and that he was suffering from septic gastritis due to micro-organisms and pus swallowed as the result of pyorrhœa alveolaris. He was, indeed, given Giesshübler water to wash his mouth and teeth with, and was provided with a tooth-brush; this simple mineral water was recommended to me by Mr. H. L. Albert for its purifying and cleansing effect on the teeth. The fact that the patient's general aspect suggested malignant disease did not necessarily render it unlikely that the whole condition was one of gastritis due to pyorrhœa alveolaris, for cases in which an initial diagnosis of carcinoma of the stomach had been arrived at have been cured by removing the cause—pyorrhœa alveolaris (W. Hunter[1] and R. J. Godlee[2]).

Turning now to the progress of the case, the patient vomited occasionally after admission, and on December 6th brought up $11\frac{1}{4}$ pints in fifteen hours; the vomit contained bile but no free acid. Some of the vomit was dark in colour and extremely offensive; the presence of bile made it clear that the obstruction, if any existed, was below the level of the biliary papilla

[1] W. Hunter: *Transactions of the Odontological Society of Great Britain*, February, 1899.

[2] R. J. Godlee: *Medico-Chirurg. Trans.*, vol. lxxxiii. p. 342, 1900.

in the duodenum, and it put the tentative diagnosis of carcinoma of the stomach out of court. After this copious vomiting the excretion of urine was suppressed. This is sometimes seen in cases of dilated stomach with copious vomiting, and is analogous to the anuria that occurs in cholera. The stomach was washed out, and the patient was put on rectal feeding. As the vomiting stopped, he was, three days later, put back on to some food by the mouth, water being given by the bowel. On December 10th the stomach was washed out. Two days later he vomited 78 oz., having only had 30 oz. by the mouth since the stomach was washed out. After this rectal feeding was again resorted to for a time. On December 17th the urine (specific gravity 1012) was found to turn a dark port wine to brown colour when heated with nitric or any other mineral acid. The darkening was extremely marked and attracted instant attention. This colouration is produced by two different substances in the urine, the commonest being a colourless chromogen, which represents indol in the alimentary canal and indican in the urine. The other body is melanin, the pigment found in melanotic sarcoma. Melanin is passed in the urine in cases of large secondary melanotic growths in the liver, such as are generally secondary to a primary melanotic sarcoma of the uveal tract in the eye. Melanin is nearly always passed in a colourless or chromogen form (melanogen), and only appears after standing and oxidation, or when nitric acid or some other agent, such as bichromate of potassium or a solution of perchloride of iron, is added to it. The colouration then occurs at once. The patient's urine did not darken with perchloride of iron, so the body was not melanin. It was therefore plain that there was some body allied to indican in the urine which was due to putrefaction taking place in the intestinal tract and the absorption of bodies allied to indol. Auto-

intoxication of intestinal origin frequently shows itself in this way in the urine. The appearance of the urine was exactly the same as that figured by Mr. A. Pearce Gould[1] in a case in which death occurred from toxæmia following acute intestinal obstruction. Dr. G. A. Buckmaster, who devoted much time to examining the urine, prepared considerable quantities of indican from the urine, and found that there was 1·6 per cent. of creatinin in the urine, making the approximate weight passed in the twenty-four hours' urine 2·4 grammes as against the normal 0·9 gramme. What this increase in creatinin was due to or what it signifies is doubtful. It occurred to me that possibly it was due to creatin taken in from the suppositories on which the patient was subsisting, but Dr. Buckmaster's analysis of a suppository showed that it contained practically no creatin. Creatinin in the urine is either due to creatin taken by the mouth or is derived from the metabolism of the muscles. As it was apparently not due to food, it must be assumed that it was derived from the muscles of the body. The amount of urinary creatinin is said to be increased in wasting diseases, and as the patient was certainly losing flesh this seems the most likely explanation. For a few days the patient rallied and he took food by the mouth, but on December 21st he vomited four times, bringing up 58 oz. of bilious fluid, and rectal feeding was again employed. The next day hiccough began, and in spite of all kinds of varied remedies continued for a week, only stopping after intravenous transfusion (80 oz.) was performed by Dr. S. V. Pearson. After this the patient again improved for a time. On January 7th, 1901, a rash appeared on the abdomen, and on the following day the amount of chromogen (indican) in the urine, which had for some time been small, was much increased, the urine, when warmed, turning a brown sherry colour

[1] *Transactions of the Clinical Society of London*, vol. xxxi. p. 47.

with HNO_3. The interest of this rash is that in Mr. A. Pearce Gould's case of toxæmia after acute intestinal obstruction there was an urticarial eruption associated with this change in the urine. The patient began to wander, tried to get out of bed, passed his urine and fæces in bed, and was presumably suffering from auto-intoxication. On January 10th he was again transfused, and he showed some slight improvement. His temperature now began to go up and the left knee became swollen. Mr. Sheild opened the knee-joint and let out some thin pus, which was found by Dr. C. Slater to contain streptococci. A few abscesses appeared in other parts of the body, and it was clear that he had developed pyæmia. The probable source of infection was the transfusion wound, which had been slow to heal. The treatment was directed against the streptococcal pyæmia by giving subcutaneous injections of anti-streptococcic serum. Sera from different sources were employed so as to hit off, if possible, a strain of streptococci the same as, or similar to, that causing the hæmic infection. The patient gradually got weaker, passed into a condition of semi-coma, and, as before, had attacks of vomiting from time to time; the severity of the pyæmia passed away, and as far as that was concerned the treatment was successful, but the patient died from exhaustion on February 6th.

The urine, which throughout the course of the disease was diminished in amount, was constantly noted by Mr. A. J. Jex-Blake. Its specific gravity was usually between 1010 and 1018; it was acid, sometimes it showed a trace of albumin, but never, even when suppuration was taking place, contained albumose. The amount of urea varied between 1·6 per cent. and 2·3 per cent., the normal being about 2 per cent. The indican reaction varied from time to time, sometimes being marked, at other times almost disappearing. The urine was free from urobilin; sometimes the chlorides

were practically absent, while at other times they returned. The fæces contained bile, and were often extremely offensive.

The case presented the features of recurrent attacks of vomiting, probably due to a dilated stomach, but as the vomit contained bile the obstruction was evidently lower down. The abdomen was never distended and was often much retracted, so it was assumed that there was obstruction in the small intestine, but as no tumour could be felt at any time the diagnosis was not thought to be sufficiently assured to justify an exploratory operation. It is noticeable that the bouts of vomiting followed the return to feeding by the mouth. That the obstruction was not absolute was shown by the passage of fæces containing bile.

At the necropsy, performed by Dr. W. J. Fenton, there was no ascites nor peritonitis. There was a tight stricture of the third part of the duodenum just where the mesentery crosses over it. From the outside it looked as if a string had been tightly tied round the duodenum; no growth could be seen externally. At first sight it looked like an example of stricture of the duodenum caused by pressure exerted by the superior mesenteric vessels and nerve. This condition has been described by Byrom Robinson,[1] who performed laparotomy unsuccessfully on a case with enormous dilatation of the stomach and duodenum from this cause; he has also noted twenty cases in which dilatation of the duodenum began at this point, and considers that it is especially apt to develop in patients with visceroptosis when lying on their backs. This is perhaps rather a novel view, but it deserves testing, and is at any rate on the same lines as the production of hydronephrosis by the pressure of abnormal renal arteries on the ureter.[2]

[1] *The American Practitioner and News*, August 15th, 1900, p. 125.

[2] G. N. Pitt: *Transactions of the Pathological Society of London*, vol. xlv. p. 107.

Above the stricture the duodenum and stomach were slightly dilated, and their muscular walls were a little hypertrophied. The small intestines and colon were collapsed. On opening the duodenum there was seen to be a white flat growth replacing the mucous membrane of the duodenum in the immediate neighbourhood of the stricture; there was more growth above the stricture than on the side towards the jejunum. The growth looked like a thick filter paper, perforated at the apex, fitted into a funnel. The stricture just admitted a cedar pencil. Above the stricture the growth tracked up towards the biliary papilla, which it touched, and was just beginning to obstruct the outflow of bile, since the common bile duct was dilated.

Microscopically the growth was a carcinoma with columnar cells. There were no secondary growths in any part of the body. The pancreas was large and fibrotic, probably from extension of infective catarrh from the duodenum into its ducts; Wirsung's duct was not dilated; there was no trace of growth in the pancreas. The mucosa of the stomach appeared healthy to the naked eye. Microscopically the cells of the glands were much altered and degenerated, but possibly this was a postmortem change. The liver, which weighed four pounds, was in a condition of cloudy swelling; the gall-bladder was full of bile, and the ducts were dilated. There was no jaundice, and there never had been any during the patient's stay in the hospital. The other organs were healthy, except for obsolete tubercle at the apices of the lungs.

There was, therefore, a carcinomatous stricture of the third part of the duodenum, which, though not entirely occluding the lumen of the bowel, had given rise to recurring attacks of obstruction. Liquid food in small quantities could have passed into the jejunum, but it is probable that from time to time food collected in the commencement of the third part of the duodenum just

above the stricture, and by bulging it downwards led to traction and so to complete closure of the fixed and already strictured part of the bowel.

As to treatment, rectal feeding was successful in temporarily alleviating the symptoms, but could not be permanently persisted in, as the condition of the patient was far from being good. Gastro-enterotomy would no doubt have relieved him for a time—*i.e.* until he died from malignant disease—but the diagnosis was never sufficiently dogmatic to justify a speculative laparotomy in a man so gravely ill. It is true that stricture or growth in the small intestine was suspected on the grounds of the bilious vomiting, but in the absence of anything palpable on the abdomen this hardly justified an appeal to surgery.

GENERAL REMARKS

Malignant disease rarely attacks the small intestine, and when it does the growth is usually either in the duodenum or close to the ileo-cæcal valve. Malignant disease is less infrequent in the duodenum than in the lower part of the ileum, but is decidedly rare even there, as shown by the following statistics given by Schlesinger.[1] In twenty-five years there were in Vienna only seven cases of primary malignant disease of the duodenum among 42,000 postmortem examinations, of which 3,583 were cases of malignant disease, and of these 443 involved the intestines. In 18,000 necropsies at Guy's Hospital there were ten cases of primary malignant disease of the duodenum, four of which were carcinoma (Perry and Shaw).

Malignant disease of the duodenum may be either carcinoma or more rarely sarcoma. Libman[2] has collected fifteen cases of primary sarcoma of the duodenum.

[1] *Wiener Klinische Wochenschrift*, 1898, No. 10, S. 245.
[2] *American Journal of the Medical Sciences*, vol. cxx. p. 309.

Some of the cases described as lympho-sarcoma, however, may have been only lymphadenoma. A comparatively extensive tract of the duodenum may be involved by sarcoma. Its wall is usually softened by the sarcomatous growth and is often dilated, so that there are no symptoms of stenosis.

Primary carcinoma of the duodenum is much more localised, and tends in most instances to produce an annular stricture. The cases in which it does not produce this effect are those where a small growth arising from the duodenal surface of the biliary papilla proves fatal by inducing jaundice and cholæmia, or suppurative inflammation of the biliary tract before it has had time to grow to any size. There was an excellent example of this in a man, aged fifty-two years, under the care of Sir Isambard Owen, with jaundice and rigors, who had a small columnar-celled carcinoma involving the duodenal surface of the biliary papilla and setting up suppuration throughout the bile-ducts and in the gall-bladder. With this general exception duodenal carcinoma gives rise to stricture of the intestine, at least in the great majority of cases, for Schlesinger, Letulle,[1] and others have, however, recorded examples of exceptions to this general rule.

Like carcinoma of other parts of the body, carcinoma of the duodenum is a disease of late middle or advanced life. In 41 cases which I have collected from various sources the average age was 52 years, being 53·4 years in 10 females and 51·7 years in 31 males. In 10 out of 33 cases collected by Nattan-Larrier[2] the patients were over 70 years of age. In the 41 cases which I have tabulated, probably including many of Nattan-Larrier's, seven patients were 70 years of age or upwards, the extremes being 80 years and 27 years. In 42 collected cases (not including the present case)

[1] *Gazette des Hôpitaux*, December 9th, 1897.
[2] *Gazette des Hôpitaux*, December 9th, 1897.

32 of the patients were males and 10 were females. The marked predominances of the male sex corresponds with the greater number of male victims in carcinoma of the tongue, œsophagus, stomach, and rectum. Malignant disease resembles ulcer of the duodenum in its preference for the male sex; in 127 cases of duodenal ulcer tabulated by Cullen[1] 108 were males and 19 were females.

Carcinoma of the duodenum is a columnar-celled carcinoma which may show a transition to a spheroidal-celled type or can undergo colloid change. The growth almost always leads to stricture of the duodenum and to dilatation and hypertrophy of the proximal part of the duodenum and stomach. In a few instances the growth has perforated into the general peritoneal cavity and given rise to peritonitis; a localised abscess has also been observed from perforation. A definite tumour is palpable in the position of the duodenum in a small number of cases.

Carcinoma of the duodenum is difficult to recognise during life, and presents a different clinical picture according as the growth is situated in the first, the second, or the third portion. It will therefore be most convenient to describe the three different forms.

1. *Carcinoma of the first part of the duodenum* is rare; in forty collected cases the first part alone was affected in eight, and together with the second part in five more. It is indeed remarkable that carcinoma of the pylorus does not extend into the duodenum more often than it does. It is, of course, in some cases where there is a growth in the position of the pylorus, difficult or impossible to be certain exactly how much or how little of the commencement of the duodenum has been involved, but most observers believe that carcinoma of the pylorus stops short at the pylorus. It is important to have some evidence for or against this

[1] *The Scottish Medical and Surgical Journal*, 1897, vol. i. p. 639.

belief, since if carcinoma of the pylorus does not tend to infiltrate the duodenum, excision of the pylorus for growth may, as far as this point is concerned, be recommended with a fair prospect of success. This question has recently been investigated by Cuneo and Lucène;[1] out of ten specimens removed during life for pyloric carcinoma, in only one did the growth manifestly extend into the duodenum, and in three others there were microscopic foci of infection cells in the lymphatic vessels, but not extending more than two centimetres from the pylorus; in the other six cases the duodenum was microscopically healthy. Therefore, in cases where the duodenum appears to be healthy to the naked eye, a surgeon should, in excising the pylorus for carcinoma, be fairly safe if he removes the first three centimetres of the duodenum at the same time. Carcinoma of the first part of the duodenum has practically the same clinical picture as carcinoma of the pyloric end of the stomach, and as it is a rare disease the commoner form will probably always be diagnosed in its place. It is, therefore, conveniently called "juxta-pyloric carcinoma of the duodenum"; another name for it, since it is above the level of the biliary papilla, is "supra-ampullary carcinoma." It is interesting to note that, just as in the case of the stomach, so in the first part of the duodenum, carcinoma may develop on a former ulcer. Perry and Shaw[2] give five cases in which a simple ulcer was thought to have become malignant. Nattan-Larrier refers to five additional cases of ulcer carcinomatosus of the duodenum, including one published by Letulle of colloid cancer in a man who had some years before been under his care with definite symptoms of duodenal ulcer. Ulcer can hardly be an important factor in the causation of duodenal carcinoma, since duodenal ulcer is practically limited to the first part of the duodenum, and

[1] *Bulletin de la Société Anatomique*, Paris, 1900, p. 732.

[2] *Guy's Hospital Reports*, 1893, vol. iv. p. 274.

carcinoma in that situation is rare. Thus 123 out of 149 duodenal ulcers collected by Dreschfeld[1] were in the first part of the duodenum. Again, from the frequency with which duodenal ulcer is latent during life, clinical evidence in favour of the previous existence of a simple ulcer is seldom forthcoming. It is, therefore, on post-mortem observation that we have to depend, and it may be rather difficult to be sure whether there is wide ulceration and sloughing of a growth or the development of carcinoma in a pre-existing ulcer.

2. *Carcinoma of the second part of the duodenum.*—This is the most frequent form of primary carcinoma of the duodenum. In forty collected cases the growth was limited to the second part in twenty-four, while in five others the first part was invaded as well. If it occurs in the upper part of the second portion of the duodenum—that is, above the level of the biliary papilla—it will give rise to much the same symptoms as carcinoma of the pylorus; if, on the other hand, it involves the biliary papilla, the flow of bile will be interfered with and jaundice or other complications will occur; while if it is well below the biliary papilla it will, by narrowing the lumen, give rise to obstruction with bilious vomiting. Carcinoma has a special tendency to arise in the duodenal mucous membrane covering the biliary papilla. This must be differentiated from carcinoma arising inside the biliary papilla or in the ampulla of Vater, the channel common to the terminations of the common bile-duct, and Wirsung's duct of the pancreas. The term "carcinoma of the ampulla of Vater" is sometimes erroneously applied to a carcinoma of the duodenum involving the biliary papilla. When carcinoma arises in the duodenal surface of the biliary papilla the flow of bile is interfered with, though it is not, as a rule, completely blocked. A change that very frequently follows on this and may rapidly kill the

[1] *Allbutt's System of Medicine*, vol. iii. p. 549.

patient is suppurative inflammation of the bile ducts. The partial stagnation favours infection, and the growth, while not completely occluding the lumen of the papilla, favours duodenal catarrh and its extension into the common bile and pancreatic ducts. The duct of Wirsung may also become dilated. The biliary papilla is a favourite site for the development of carcinoma; possibly this is due to some fœtal displacement or irregular inclusion of epithelial cells during the development of the hepatic diverticula from the primitive duodenum. It is interesting to note that the disturbance, incident on the outgrowth of the hepatic diverticula from the duodenum, may lead to a congenital narrowing or to atresia of the bowel at this point, analogous to congenital atresia of the œsophagus. An innocent papilloma is sometimes seen to arise from the duodenal surface of the biliary papilla, and it is, I think, probable that carcinoma may subsequently develop in such a growth. The question has been raised whether impacted gall-stones inside the ampulla of Vater have any bearing on the development of new growth on the duodenal surface of the papilla. On the face of it this seems improbable, and though D. K. Dickinson[1] has recorded the association of these two conditions, this experience is almost unique.

From its situation, primary carcinoma of the intestinal mucous membrane of the biliary papilla is spoken of as juxta- or peri-ampullary carcinoma. As a rule, peri-ampullary duodenal carcinoma imitates carcinoma of the head of the pancreas and gives rise to jaundice associated with an enlarged gall-bladder. Jaundice was present in twenty-three out of twenty-five cases quoted by Mathieu.[2] In rare instances, however,[3]

[1] *New York Medical Journal*, 1879, vol. xxx. p. 149.

[2] *Traité des Maladies de l'Estomac et l'Intestine*, p. 921.

[3] Descos et Bériel: *Revue de Médicine*, 1899, p. 633. Lannois et Courmont: *Ibid.*, 1894, p. 291.

the growth, although involving the papilla or invading the bile duct, does not give rise to jaundice. The jaundice may vary, be intermittent, or, as in the case under the care of Sir Isambard Owen, disappear for a time; it thus differs from the permanent and progressive jaundice seen in carcinoma involving the common bile duct, the cavity of the ampulla Vateri, or the head of the pancreas. The intermittence or disappearance of jaundice in duodenal carcinoma involving the biliary papilla must depend on the growth ulcerating and thus no longer obstructing the flow of bile; if the tumour goes on growing it may again lead to obstructive jaundice. Though the biliary papilla is a favourite starting point for carcinoma, the growth may begin elsewhere in the second part of the duodenum and involve it by extension.

3. *Carcinoma of the third part of the duodenum* is the least frequent of all the three varieties. In forty collected cases (not including the present example) it was only found in three. It is sometimes spoken of as infra-ampullary or juxta-jejunal carcinoma of the duodenum. The symptoms are those of intermittent obstruction, as in the case brought forward to-day, with bile in the vomit. It thus resembles pyloric obstruction except for the presence of bile and pancreatic juice in the vomit. The occurrence of bile should at once suggest carcinoma of the duodenum below the biliary papilla or a gastro-biliary fistula. In such a case the vomit should be tested for trypsin by seeing whether fibrin is digested in an alkaline solution. In this way the diagnosis between the two conditions might be made.

IV

PRIMARY CARCINOMA OF THE AMPULLA OF VATER, WITH REPORT OF A CASE PRESENTING SOME SPECIAL FEATURES OF INTEREST[1]

Normally, before opening into the duodenum, the common bile duct and Wirsung's duct of the pancreas open into a common channel inside the biliary papilla. This short duct is called the ampulla or diverticulum Vateri. Normally its mucous membrane is rougher and more villous than that of the common bile duct, but the so-called ampulla of Vater is little, if at all, larger than the common bile duct, except when pathologically dilated by an impacted gall-stone. Carcinoma may start in the mucous membrane lining this ampulla of Vater, or may spread into the ampulla from the lower end of the bile duct, and possibly from the termination of Wirsung's duct. In a paper on primary carcinoma of the larger bile ducts published in 1896 I came to the conclusion that most cases of so-called carcinoma of the ampulla of Vater originated in the termination of the common bile duct;[2] later in the year R. Durand-Fardel[3] showed a specimen supporting this and adopted the same view. The clinical aspects of the two are

[1] Reprinted, with some additions, by permission from *The Lancet* of February 16th, 1901.

[2] *Medical Chronicle*, January, 1896.

[3] *Presse Médicale*, June 17th, 1896.

identical, and the histological structure of the growths in the two situations is the same—viz. a columnar-celled carcinoma. Their pathological effects, however, may differ; thus carcinoma of the ampulla of Vater may obstruct Wirsung's duct and so lead to cystic dilatation with fibrosis of the pancreas, while carcinoma of the termination of the common bile duct is not so likely to do this. Pic[1] regarded carcinoma of the ampulla of Vater as an aberrant form of pancreatic carcinoma, corresponding apparently to the excretory type (columnar-celled) of pancreatic carcinoma described by Bard and Pic.[2] This is practically saying that carcinoma of the ampulla of Vater is carcinoma of the termination of the pancreatic duct. While admitting that carcinoma might spread to the ampulla of Vater from the termination of the common bile duct or from Wirsung's duct, Hanot[3] insisted on the occurrence of primary carcinoma starting in the lining membrane of the ampulla, and described two cases. He spoke of it as "cancer du pylore pancréatico-biliare," and instanced it as an "orificial cancer."

Primary carcinoma of the ampulla Vateri, or, as it might more conveniently be called, the choledocho-pancreatic duct, must be also distinguished from primary carcinoma attacking the mucous membrane covering the duodenal surface of the biliary papilla. Specimens of this form of duodenal carcinoma are to be found in the museums of St. Bartholomew's, Guy's, and St. Thomas's Hospitals. This lesion seems to be especially prone to lead to infective cholangitis and intra-hepatic suppuration. Carcinoma of the ampulla of Vater must thus be distinguished from carcinoma (1) of the termination of the common bile duct; (2) of the termination of

[1] *Revue de Médecine*, 1895, p. 7.

[2] *Ibid.* 1898, p. 394.

[3] *Archives Générales de Médecine*, vol. clxxviii. p. 547, November, 1896.

Wirsung's duct; and (3) of the duodenal surface of the biliary papilla. The accompanying diagram illustrates these distinctions. Confusion may also occur between carcinoma of the head of the pancreas and primary carcinoma of the ampulla Vateri. Histologically they differ; carcinoma of the pancreas is spheroidal-celled, while carcinoma of the diverticulum Vateri is columnar-celled.

It may be difficult to decide where the growth started when the tumour has had time to spread and invade

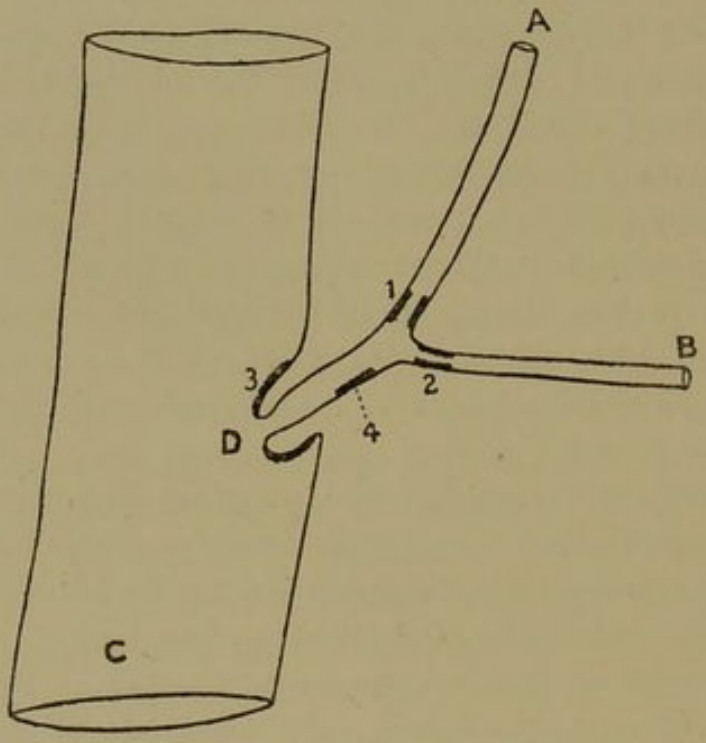


Diagram of the ampulla Vateri, showing the various situations where carcinoma may arise in relation with it and in its neighbourhood. A, Common bile duct. B, Wirsung's duct. C, Duodenum. D, Biliary papilla. 1. Carcinoma of the termination of the common bile duct. 2. Carcinoma of the termination of Wirsung's duct. 3. Carcinoma of the duodenal surface of the biliary papilla. 4. Carcinoma of the ampulla Vateri itself.[1]

adjacent parts. Thus in some instances doubt will arise whether the tumour arose in the lower end of

[1] Reproduced by permission of the proprietors of *The Lancet*.

the bile duct, in the ampulla of Vater, or in the head of the pancreas. In forming a decision from a naked-eye examination in such cases it may be pointed out that carcinoma of the ampulla of Vater may, when of considerable size, project as a tumour through the gaping lips of the biliary papilla and be visible in the duodenum; this is not met with in carcinoma of the pancreas or of the termination of the common bile duct.

The clinical characters of primary carcinoma of the ampulla of Vater are the same as those of primary carcinoma of the common bile duct—viz. progressive jaundice and wasting, the patient finally passing into a condition of cholæmia or biliary toxæmia. It thus very closely resembles cases of carcinoma of the head of the pancreas. The only difference is that jaundice is exceptionally absent in malignant disease of the head of the pancreas. The treatment has so far been palliative except in one case where Halsted [1] successfully removed a columnar-celled carcinoma of the ampulla of Vater, but the growth recurred in the head of the pancreas and in the duodenum, and proved fatal within a year of the operation. Busson,[2] in 1890, collected eleven cases of carcinoma of the ampulla, and in 1896 Vincent-Georges,[3] a pupil of Hanot, added nine more; later in the same year Hanot [4] described another case. Of these twenty-one reported cases about seven are above suspicion; most of the remainder are either carcinoma of the termination of the common bile duct or of the duodenal surface of the biliary papilla. It is, therefore, a rare condition. The following case is recorded as an example of primary carcinoma of the ampulla Vateri with some special points of interest.

[1] *Johns Hopkins Hospital Bull.*, No. 106, January, 1900.
[2] *Thèse de Paris*, 1890.
[3] *Thèse de Paris*, No. 404, 1896.
[4] *Loc. cit.*

Carcinoma of the ampulla Vateri; dilated common bile and Wirsung's ducts; death from hæmorrhage into the dilated duct of Wirsung.—A man, aged sixty-six years, was admitted into St. George's Hospital under my care on July 22nd, 1900, with jaundice, pruritus, weakness, and wasting. Ten weeks previously he had considered himself quite well; jaundice then appeared quite painlessly, and a month later he got weaker and felt drowsy; six weeks after the onset of jaundice the skin began to itch. There was no history of gall-stones. When examined on admission he was deeply jaundiced and the skin showed the effects of scratching; the liver was enlarged, reaching to the fourth rib above and extending two and a half finger-breadths below the costal arch in the right nipple line, the surface was smooth, and the gall-bladder could be indistinctly felt. No splenic enlargement could be made out. There was some abdominal distension but no ascites. There was tenderness at a spot over the eleventh and twelfth ribs in the right hypochondrium. Per rectum nothing but an hypertrophied prostate could be felt. The urine contained albumin and bile but no sugar. The patient had been sent up to the hospital as a case of cancer of the liver; it appeared probable, however, that the growth was in the head of the pancreas. On July 25th there was some diarrhœa; on July 26th he vomited, had a rigor, and the temperature fell to 96° F., the pulse was small, and he was collapsed. The abdomen moved well, and it appeared unlikely that perforation of the gall-bladder from over-distension, as in a case recorded by Coats and Finlayson,[1] had occurred. Suppuration around the gall-bladder was thought of, but his condition precluded any surgical treatment, and he was given morphia. Death occurred eighteen hours after the onset of acute symptoms.

At the *necropsy*, performed by Dr. W. J. Fenton, the

[1] *Glasgow Medical Journal*, vol. xxxiv., August, 1890.

peritoneal cavity showed no recent peritonitis, but contained two parts of bile-stained fluid. A flat growth was found, limited to the ampulla of Vater and occluding the orifices of both the common bile duct and the duct of Wirsung. This growth was not visible from the duodenum, and was only seen when the papilla was opened up. Microscopically the growth was a columnar-celled carcinoma, and was found to be invading the smooth muscular tissue around the ampulla Vateri. The common bile duct was greatly dilated with dark bile, and was as thick as one's thumb. When the finger was introduced into the duct and directed downwards towards the biliary papilla the common duct was felt to end blindly like a test tube. The hepatic and cystic ducts and the gall-bladder were greatly dilated; no gall-stones were found. The liver weighed 4 lb.; it was enlarged, smooth on the surface, and deeply bile-stained. Microscopically there was no cirrhosis, though the atrophied and degenerated condition of the liver cells allowed the existing fibrous tissue of the portal spaces to appear more prominent than in health. Wirsung's duct was tortuous and dilated throughout the whole of the pancreas; in the head of the gland there was a large cystic dilatation of the duct which contained recent blood-clot; the rest of the dilated duct contained dark brown fluid. No calculi were seen. The tail of the pancreas was adherent to the stomach by old adhesions, evidently the result of past inflammation. To the naked eye the pancreas was extremely fibrotic. Microscopically the glandular tissue of the organ was widely replaced by fibrous tissue, and, where it could be made out, was much disorganised. Numerous dilated ducts were seen, some of which contained microscopic calculi. There was some recent small cell infiltration. The islands of Langerhans were quite intact and not diminished in number. The stomach and intestines showed signs of recent catarrhal inflammation. The kidneys presented

senile changes and a few cysts. The heart weighed 11 oz., and was normal for the time of life. The lungs were emphysematous. No secondary growths were found in any part of the body.

The additional points of interest are :—1. The sudden onset of acute symptoms, followed by death in eighteen hours. The preliminary diarrhœa, taken in conjunction with the signs of catarrhal inflammation found after death, make it probable that an infective gastro-enteritis set up inflammation in the chronically inflamed pancreas, and that acute pancreatitis, with the resulting hæmorrhage into the dilated duct, accounted for the severe collapse and death. The fact that the growth obstructed the orifice of Wirsung's duct renders it improbable that the acute hæmorrhagic pancreatitis was due to retrojection of bile into the pancreatic duct. In cases where the ampulla of Vater is blocked below the opening of Wirsung's duct, bile may pass into the pancreatic duct and Opie[1] has shown that hæmorrhagic pancreatitis may be thus produced. 2. The extremely fibrotic condition of the pancreas appeared to be too advanced to be accounted for by obstruction of eleven weeks' duration. It is probable that, if the chronic pancreatitis was due to obstruction of Wirsung's duct, the growth must have interferred with the duct of Wirsung for a considerable period before it set up biliary obstruction. 3. It is noticeable that with such extreme fibrosis of the pancreas there was no glycosuria or diabetes. The absence of glycosuria was probably due to the preservation of the islands of Langerhans which provide the internal secretion of the pancreas and thus prevent glycosuria.

[1] Opie, *Johns Hopkins Hosp. Bull.* vol. xii. pp. 121-3, June, 1901.

V

PRIMARY CARCINOMA OF THE VERMIFORM APPENDIX[1]

A WOMAN, aged twenty-six years, was admitted into St. George's Hospital on March 26th, 1900, under the care of Dr. F. G. Penrose, with a fourth attack of appendicitis, the first attack having occurred in January 1899. On March 27th, 1900, the day after admission, the appendix was removed by Mr. A. Marmaduke Sheild. There was a small peritoneal adhesion connecting the apex of the appendix with the posterior surface of the uterus. No enlarged glands or anything in any way suggesting secondary growths were seen at the time of the operation. When the appendix was cut open a globular mass, a little larger than a marble, was found near the apex arising in the mucous membrane. It was somewhat caseous in appearance and suggested the possibility of tuberculous disease. The patient recovered from the operation, but during the middle of April she had an erratic temperature with some pain on the left side of the abdomen. This, however, subsided, and she went to the convalescent home in May. I have since heard from Dr. H. M. Ramsay that the patient was in perfect health in 1902. The appendix was sent to me, for microscopical examination and report, by Mr. Sheild, to whom I am indebted for permission to publish this interesting case.

[1] Reprinted, with some alterations, from *The Lancet* July 7th, 1900, by permission.

Microscopical examination of the vermiform appendix showed, most unexpectedly, that it was the site of primary spheroidal-celled carcinoma. In its earliest stage the growth was seen to be limited to the mucous membrane (*vide* Fig. 1), but its histological structure in this situation was exactly the same as in the other sections of adjacent parts of the appendix, where it was seen to be widely infiltrating the muscular coats and extending nearly up to the peritoneal covering (*vide* Fig. 2).

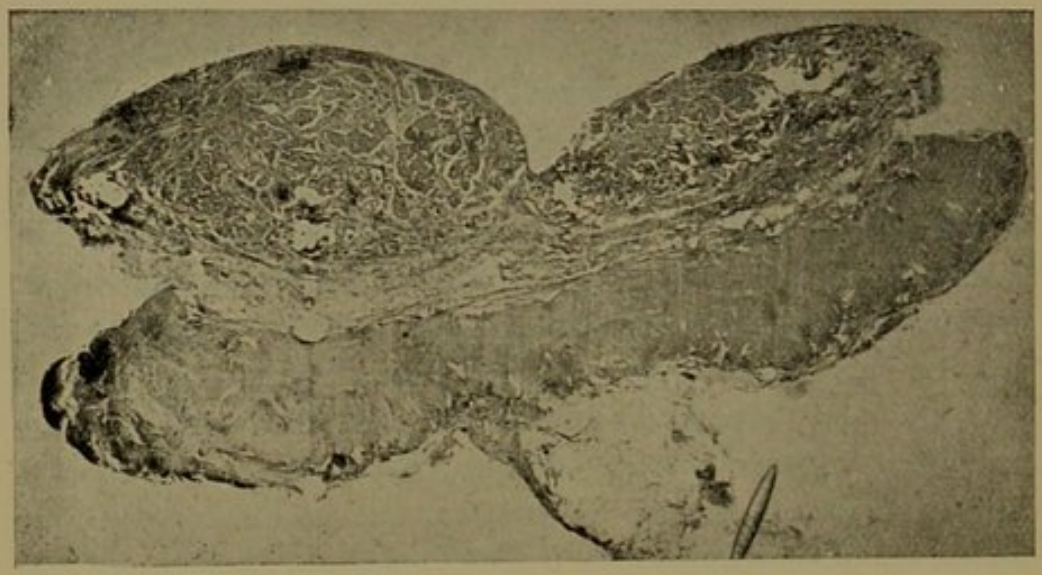


FIG. 1.

Photo-micrograph No. 1. Section of vermiform appendix, showing carcinoma beginning in mucous coat. × 6.[1]

The facts that (1) the growth was most extensive in the mucous coat, (2) that it could be traced outwards into the muscular coats, and (3) that there was no growth on the outside of the peritoneum, showed that the growth originated in the mucous membrane of the appendix, and that it was not a secondary growth either implanted on the peritoneum or arising as a result of embolism within its substance. I have several times seen secondary growths, in generalised malignant

[1] For this block I am indebted to the proprietors of *The Lancet*.

disease of the peritoneum, invading the appendix from without. If such an appendix were removed during life it might, if only superficially inspected, give rise to an erroneous diagnosis of primary malignant disease of the vermiform appendix. In the case of secondary malignant disease of the bowel due to emboli of infective tumour-cells the growth arises, and is most prominent,

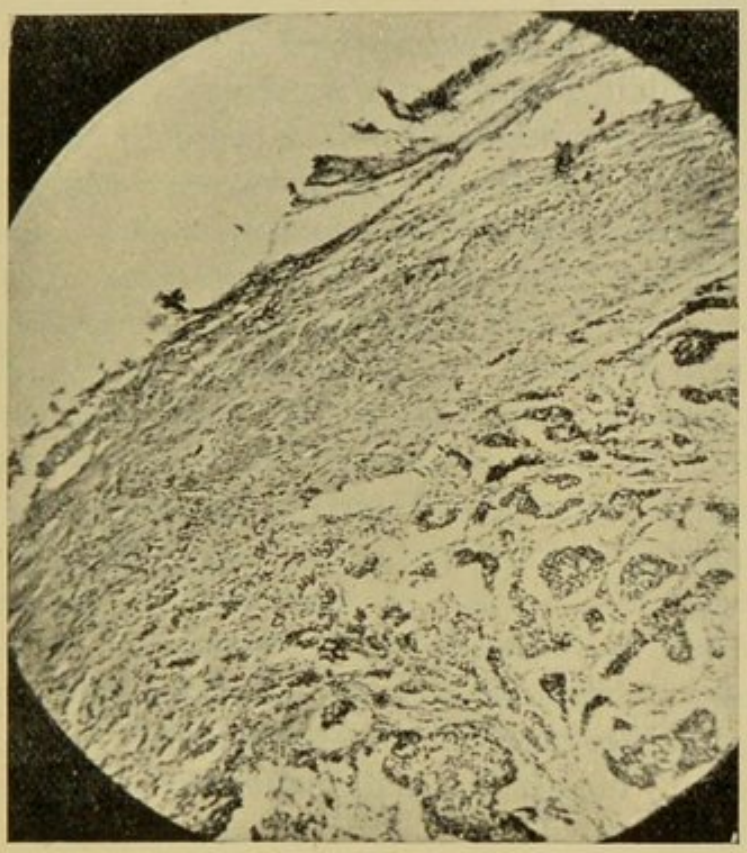


FIG. 2.

Photo-micrograph No. 2. Section of vermiform appendix, showing carcinoma invading muscular coats. × 126.[1]

in the sub-mucous or muscular coats, and only secondarily involves the mucous membrane. For the excellent photo-micrographs I am greatly indebted to the kindness of Mr. E. J. Spitta of Clapham, and Dr. Harold R. D. Spitta of St. George's Hospital.

[1] For this block I am indebted to the proprietors of *The Lancet*.

THE RARITY OF THE DISEASE

Primary malignant disease of the vermiform appendix is not mentioned in Hawkins's work on *Diseases of the Vermiform Appendix* (1895) or in Allbutt's *System of Medicine.* Kelynack in his monograph on *The Pathology of the Vermiform Appendix* (1893) could not bring forward any undoubted case, but he refers to three cases in a tabular statement drawn up by Leichtenstern, and to a case of colloid carcinoma described by Draper, which he, Kelynack, thought probably arose in the ileocæcal valve. In the last ten years, however, a comparatively large number of cases have been reported—thus Elting[1] has collected forty-three published cases, though he only accepts as genuine twenty-three. Among the earliest cases were those of Letulle and Weinberg,[2] who in a careful investigation into the histology of twelve cases of obliterative appendicitis discovered quite unexpectedly that two of their cases showed microscopical evidence of developing carcinoma at the level of the cicatricial obliteration of the tube. In most of the recorded cases the growth is a spheroidal-celled carcinoma, and thus differs from carcinoma of the rest of the colon, which is practically always a spheroidal-celled growth.

The rarity of primary malignant disease of the appendix is rather striking when it is considered how comparatively frequently carcinoma develops in another annexe of the alimentary canal, the gall-bladder, which resembles it in its liability to infection and in the occurrence of a calculous or lithogenic catarrh.[3] It is often said that fœtal relics and atrophying organs are especially prone to malignant disease, but whatever the

[1] Elting, *Annals of Surgerg*, part cxxiv. p. 549, April, 1903.

[2] Letulle and Weinberg, *Bull. Soc. Anat.* Paris, 1897, p. 47.

[3] "Fæcal concretions" are, like gall-stones, products of inflammation of the surface surrounding them, and not concentrated residues of its normal contents.

value of this general statement, and I believe it to be rather exaggerated, it is not true of the vermiform appendix.

Primary malignant disease of the appendix is perhaps not so rare as would appear from literature, for two reasons. 1. Because in the early stage of carcinoma the appendix may be removed for symptoms of appendicitis, and in the absence of a routine histological examination of removed appendices some cases may thus escape recognition. The present case is an instance in point, the condition naturally being unsuspected until a microscopical examination was made. 2. Because if the disease runs its course without interference, a large mass of growth would probably result which might become adherent to the cæcum, the bladder, or the bowel, and then be thought to have been originated there, rather than in such an unusual site as the appendix.

Age incidence.—It is remarkable that carcinoma occurs at a much earlier age in the vermiform appendix than in the colon. Thus in 17 cases tabulated by Elting, no less than 53 per cent. were under 30 years of age and 24 per cent. under 20 years; while in 30 cases of carcinoma of the cæcum which I collected some years ago, the average age was 47·76 years, and in 100 examples of carcinoma of various parts of the colon the average age was 49·3 years.

CLINICAL FEATURES

While no symptoms have been present, or at any rate recorded, in some instances, the clinical picture has in about half the cases been that of appendicitis, and in some instances, as in the case described here, of the relapsing form. It is quite possible, on the analogy of tumour myelitis in the spinal cord, that the growth sets up appendicitis; thus in two cases recorded by

Harte and Willson,[1] there was histological evidence of both carcinoma and inflammation; while, as suggested by Wright's case, a small perforation in connexion with the growth may set up peritonitis.[2]

On the other hand Letulle, and Weinberg's discovery of carcinoma developing in cases of obliterative appendicitis suggests that the growth is related to appendicitis much in the same way as carcinoma of the gall-bladder is related to cholelithiasis, which is of course the outcome of cholecystitis. It is, however, quite possible that the growth alone, without the addition of any ordinary inflammation, may account for the symptoms in some instances.

It may be worth while putting forward the suggestion that, when apparently multiple primary (nodular) malignant disease of the liver occurs, the vermiform appendix should always be carefully examined at the necropsy. It is hardly likely that multiple secondary growths would develop in the liver while the primary growth in the appendix is so small as to require microscopical examination. But it is quite conceivable that in a case of multiple carcinoma, apparently primary in the liver, the real primary growth might have been in an appendix previously removed for supposed appendicitis.

[1] *Medical News*, New York, August 2nd, 1902.
[2] *Boston Med. and Surg. Jour.*, February 24th, 1898.

VI

SOME POINTS IN THE TREATMENT OF TYPHOID FEVER[1]

The indefinite title of these remarks fortunately does not oblige me to attempt the formidable task of covering the whole ground of the treatment of this common disease. There are a number of points to which I shall not refer, not because they are unimportant, but because, time being somewhat limited, I have chosen those parts of the subjects in which I am more especially interested.

DIET

Probably every one is agreed as to the great importance of diet in typhoid fever. This is a most essential part of the treatment, and should be ever before the medical attendant's mind, and not left, as it sometimes is to a very considerable extent, in the hands of the nurses. When this course is adopted, the medical man probably believes, or at any rate by his action justifies the assumption, that his supervision and care of the case is subordinate in importance to that of the trained nurse in attendance. This is perhaps in some degree a personal question, but there can be little doubt that

[1] An address delivered to the North London Medico-Chirurgical Society, October 9th, 1902. Originally published in *Treatment*, October, 1902, and now reprinted with some alterations by permission of the publishers and proprietors, Messrs. Rebman, Ltd., 129, Shaftesbury Avenue, W.C.

the diet should be as carefully considered and regulated as the giving of drugs, and that in typhoid fever it is, generally speaking, of more importance. In no disease is it more true that it is the patient, and not the disease, that should be treated. Treatment directed solely to the disease leads to routine, and there can be little doubt that routine has usurped an undesirable prominence in the dietary of this disease. Thus, during the course of the fever, the average nurse feeds the patient willy-nilly every two hours throughout the twenty-four. The disease is a continued fever, considerable wasting occurs, and it is no doubt important to maintain the patient's strength. On the other hand, the intestinal tract is in an unfavourable state for digestion and absorption, and if food is not absorbed it undergoes fermentation and putrefaction in the intestine, and thereby increases the toxæmic state of the patient.

In the early stages of the disease the large quantity of liquid food sometimes gives rise to vomiting, probably from overdistension of the stomach. I have several times noticed sickness in patients directly after admission to hospital and the establishment of routine feeding, which has passed off after curtailing the amount of food.

In the third week of the fever, in cases where the patient is in a "typhoid state," feeding may increase abdominal distension, toxæmia, and diarrhœa. This is due to stagnation of milk in the bowels, favouring putrefaction from microbic activity.

There has, however, recently been some return to the practice of "starving the fever." Thus, F. J. Smith,[1] in an original address on the treatment of typhoid fever, vigorously rebelled against routine feeding, and stated that he had long made it a cardinal rule to allow "the patient's appetite to be, within very wide limits indeed, the sole arbiter of his diet, provided that vomiting,

[1] *Transactions Medical Society*, 1901, vol. xxiv. p. 87.

hæmorrhage, or distension of the abdomen are all absent." He had had very good results with patients given nothing but water for four or five days, and had never regretted keeping this treatment on for too long, though once or twice he had had reason to wish that he had persisted in it longer. Inglis [1] about the same time expressed his conviction that "the ideal food for typhoid fever is pure water in abundance." He did not give any stimulant except good coffee, and spoke highly of the nutritive value of sugar, which has not been much employed as a food in typhoid fever. Dr. William Williams [2] has also carried out the starvation method of treatment with good results.

When I was in South Africa in 1901, I was very much interested to find that the "starvation" treatment had been employed both at Bloemfontein and elsewhere. Surgeon-Captain E. C. Anderson, R.A.M.C., my informer, used it, not as a routine form of treatment, but in a number of cases selected because the abdominal symptoms were well marked, and the tongue dry and cracked. The results were extremely good, one death only occurring, and that from septicæmia from a large pectoral abscess fourteen days after a solid diet had been started. The treatment was very simple; the patients were allowed to drink as much water as they liked, and were given 6 oz. of brandy daily. In nearly all the cases after the third day of this treatment the temperature began to remit, tympanites to subside, and the tongue to become moist. Hunger was never complained of after the first forty-eight hours. When feeding was restarted it was begun by degrees, and in small quantities. Patients often went without food at all for a week. I have also heard that during a famous protracted siege, where provisions were very

[1] *Philadelphia Medical Journal*, February 9th, 1901, vol. i. p. 308.

[2] *Reports of Royal Southern Hospital, Liverpool*, vol. ii. p. 59, 1903.

scanty, many typhoid patients had very little food indeed, and that as a result they did extremely well during the severe febrile stages, but that later, during early convalescence, they did very badly for want of more food. These reports show that, during the severe stages of typhoid fever, starvation can be well borne, and, indeed, leads to improvement. There can be no doubt that rest to the inflamed mucous membrane and Peyer's patches in the intestine must have a powerful influence for good, and that this principle is just as applicable to inflamed intestines as to arthritis or acute gastritis.

The importance of maintaining the patient's strength is always before our minds, and rightly so, but we must remember that it is absorption and assimilation of food that are essential, and that if, as seems probable, these processes are much delayed, or even temporarily suspended, during some periods in severe cases of typhoid fever, continued feeding may do harm rather than good.

Personally, I have never carried out the plan of starvation in its entirety, but I have adopted the principle, and employed it in a very modified form, with, I think, good results. In cases where diarrhœa or tympanites comes on, giving the patient nothing but water for one or two days has been followed by general improvement, diminution of abdominal distension, of diarrhœa, and tremor. In other less severe cases this omission of feeds often makes the patient more comfortable, and relieves distension or diarrhœa. No routine or rule is desirable in the dietary of typhoid fever, but I believe that feeding every four or six hours during the fever is, generally speaking, a better basis to go upon than the more frequent feeds at two hourly intervals. Smith's dictum, that the patient's appetite should direct the feeding, is, to my mind, correct, and should enter into the question whether a patient should be gently roused when a feed becomes due during sleep.

During the fever peptonised milk diluted with soda-water, barley-water, or ordinary water, is preferable, except in mild cases, to ordinary milk, as, when thus modified, it is more readily digested and absorbed. It is hardly necessary to insist on the importance of a careful examination of the stools in order to gauge the processes of intestinal digestion. The presence of milk-curds in the dejecta should dictate peptonised milk or smaller quantities more freely diluted.

Whey and albumin-water often agree when milk is not well borne, probably for the same reasons that water is sometimes better than milk.

Of the employment of beef-tea and chicken-broth as adjuvants to milk, there is not much to say. When a patient is digesting milk well they are not necessary, and need only be given as a change in the proportion of 1 pint to 3 of milk. Peptonised milk gruel, recommended by Sir W. Roberts, is a valuable addition to the dietary in the fourth week of the fever when the temperature is falling, but not yet normal. It is practically bread and milk in a peptonised form. Cold water or soda-water should be freely given, but I have no experience of the very large quantities—5 to 6 quarts of water—which have been recommended.

A gradual improvement of the diet as soon as the temperature reaches normal is a good rule; eggs beaten up, or custard, may be given at once. Practice among different men and schools differs as to the time when solid food should be given. No rigid rule can be formulated. Most patients are the better for solid food a week after the temperature is normal, and it is very seldom that it is necessary to wait until ten or fourteen days have gone by.

My own impression is that a relapse, though often synchronous with an improvement in the diet, is very rarely a result of it.

There is no doubt that in some cases where the

temperature remains raised for no very obvious reason the administration of solid food is followed by a normal temperature. Probably improved diet increases the patient's strength and resistance. Keeping these patients out of doors in a balcony, and so out of the air of the wards or sick-room, may have the same effect, but I have had little opportunity of putting this to the proof in England.

INTESTINAL ANTISEPTICS

The use of intestinal antiseptics, such as β-naphthol, betol, salol, derivatives or compounds of salicylic acid, is, I think, less to the fore than it was ten or fifteen years ago. Experiments show that the administration of such antiseptic drugs by the mouth does not diminish the number of micro-organisms in the fæces. Herter,[1] in a discussion on this point, sums up by saying that we do not know of any safe antiseptic which can be relied on to exert a distinct effect in reducing intestinal putrefaction, much less to check it.

In spite of this very definite statement, I must confess that I have, ever since I read Sir William Broadbent's masterly Cavendish Lecture on the treatment of typhoid fever,[2] been accustomed to give, with good results, liquor hydrargyri perchloridi in half-drachm doses three or four times during the twenty-four hours. My strong impression is that it reduces distension and checks diarrhœa. Incidentally, it may be mentioned that diarrhœa, which was formerly regarded as a more or less constant feature of the disease, is now coming to be regarded in the light of a complication indicating excessive intestinal fermentation, or calling for some modification in the quality or quantity of the food.

[1] *Chemical Pathology*, p. 232.
[2] *Lancet*, 1894, vol. ii. p. 423.

The number of drugs which have been employed to prevent excessive intestinal fermentation in typhoid fever is very considerable. Fractional doses of calomel are said to have the same effect as perchloride of mercury, and I have seen grey powder given throughout the course of the fever.

Salol, β-naphthol, betol, urotropin, and other synthetic bodies, have had a very considerable trial. Salol I have used and seen employed more frequently than the others, but it seems decidedly inferior to perchloride of mercury.

Salol should be given powdered up, otherwise it may pass through the alimentary canal in a compact tabloid form, and do little good, even if it does not do any mechanical harm, to the ulcerated intestines. In this connection it is interesting to recall a case of Dr. J. K. Fowler's, where diarrhœa, thought to be of septic origin, was much improved after, and it was thought as a result of, the administration of salol tabloids, until the tabloids were found unaltered in the dejecta.

The powdered salol is conveniently given in small cachets, so as to avoid the slightly unpleasant sensation —like powdered glass—of the particles of salol in the mouth. Salol is decomposed in the duodenum and intestine by the pancreatic juice into carbolic acid and salicylic acid. When salol is given in considerable doses, carboluria may be produced. I have several times seen this in typhoid fever.

Further, salol may form calculi in the intestines, and set up colic and vomiting. This should be borne in mind as a possible and readily overlooked cause of pain in typhoid fever. According to Marshall,[1] who has discussed the formation of these salol calculi, the drug should be given rubbed up with some innocuous powder, or, as Sahli suggests, in an emulsion. By these

[1] *British Medical Journal*, 1897, vol. ii. p. 78.

means calculus formation is prevented, and its action on micro-organisms is in no way interfered with.

Urotropin, which has been widely used to prevent typhoidal cystitis and bacilluria, is probably of considerable use in the bowel. With regard to this drug, the fact that ordinary doses—viz. 10 grains twice a day—may set up hæmaturia in some cases should be borne in mind.[1]

Turpentine is an antiseptic, but I have only employed it by the mouth in small doses for hæmorrhage, and in enemata for tympanitic distension. Its administration by the mouth in repeated doses, unless in rather minute quantities, is not without danger. The urine should be carefully watched, as inflammation of the kidneys may be set up.

From the success attending the treatment of South African dysentery with powdered sulphur, it was tentatively suggested by Richmond[2] that it might be useful in typhoid fever by restraining the growth of micro-organisms other than the *B. typhi* in the bowel. I have no experience of its use myself, but Dr. W. F. Tyndale has kindly placed at my disposal the notes of two cases of typhoid fever which he treated with 20 grains of sulphur twice a day. The cases, soldiers at Pretoria, were ordinary straightforward examples of the disease, and were, indeed, chosen for this reason. In both instances sulphur appeared to have a distinctly bad effect by producing abdominal distension, in one on the second, in the other on the third day of its administration. In one case the distension lasted for four days after the sulphur was cut off. It is curious that sulphur should give rise to distension, since, from its antiseptic action, it would be expected to have the opposite effect. Presumably the distension was due to the formation in excessive quantities of H_2S. At any rate, this

[1] Langdon Brown, *British Medical Journal*, 1901, vol. ii. p. 1472.

[2] *Lancet*, 1901, vol. ii. p. 1408.

experience would render us unwilling to investigate its effect on typhoid fever any further.[1]

CONSTIPATION

In this respect, as well as in many others, treatment has undergone a very considerable change. Years ago I remember the practice, at any rate of some thoughtful physicians, was to leave the bowels alone, and sometimes constipation was allowed to go on for weeks. Besides the discomfort to the patient, fæcal impaction may give rise to severe symptoms, initiating the onset of a relapse, or even, as in Herringham's case, perforation. In the latter case Bowlby performed laparotomy, and only found the whole of the colon occupied by scybala.[2]

The prevention of constipation minimises intestinal fermentation, and probably tends to remove conditions favourable to the occurrence of relapses.

The administration of a common enema every other day if the bowels are not open regularly works well. Later in the course of the disease mild laxative waters may be allowed, but it is probably safer not to give castor-oil or regular purgatives until the temperature has been down for a week.

TREATMENT OF CARDIAC FAILURE

This, though sometimes underestimated, is one of the most important points in the treatment of the disease, for more patients die with gradually increasing asthenia, in which the heart-muscle plays a very prominent rôle, than from the more striking and special complications—perforation and hæmorrhage.

[1] Voroschilsky (Vratch, No. 24, 1902, quoted in *Rev. de Thérapeut.*, September 1st, 1902), however, has obtained good results with sulphur in typhoid fever.

[2] *Medico-Chirurgical Transactions*, vol. lxxx. p. 127.

Of the cardiac stimulants, the most commonly used, and the one which probably retains the most widespread confidence, is alcohol in some form or another, such as brandy, whisky, champagne.

At one time I regarded alcohol as *the* remedy for failing heart in typhoid fever, and considered that it should be given with no niggardly hand in bad cases; but gradually, partly from observation of cases and partly from the experience of others, especially from consideration of the facts insisted upon by Dr. Graham Steell—that cardiac dilatation is frequently in the otherwise healthy due to alcoholic excess—I have come to distrust the value of alcohol in large quantities in typhoid fever. In that disease the myocardium is already suffering from the toxic action of one poison, and would therefore be more likely to suffer from the effects of alcohol. Alcohol does temporary good by stimulating the neuro-muscular mechanism of the heart, but there is danger that it may do more lasting harm to the myocardium. If alcohol were only required to get over one critical period, it would not be so likely to be harmful, but since the failing condition of the heart often requires rather prolonged help, there is some risk of doing harm instead of good.

Ether and ammonia are probably much less prone to damage the cardiac muscle, but are not very welcome drinks to a patient with fever.

In alcoholic patients it might naturally be assumed that alcohol would necessarily be required during the course of typhoid fever. No such rule can be maintained. I have been surprised sometimes to see how well an alcoholic patient may do in typhoid fever without any of his accustomed stimulant.

There is a theoretical, and possibly somewhat remote, consideration which makes one loath to give alcohol during typhoid, or, indeed, in any other infectious fever, unless it is absolutely necessary. It is the possible

danger of setting up cirrhosis of the liver. During typhoid fever changes which are temporary in nature, and consist of focal necrosis of the liver-cells, are not uncommon. It is quite conceivable that alcohol, if taken in excess, might interfere with recovery of the liver, and lead to permanent changes in that organ of the nature of cirrhosis. While bearing this in mind, and also the possibility that post-typhoidal neuritis may in some instances be partly due to alcohol taken during the fever, few would abstain from giving alcohol if it was thought to be demanded by the gravity of the patient's condition.

Without, I hope, taking up an extreme position, I am inclined to minimise the amount of alcohol given to counteract cardiac debility, and rely on other means, and chiefly on the hypodermic injection of strychnine. It is not uninteresting to recall the origin of this method of stimulating a failing heart. It is now in very general use; so much so, that I have heard of a nurse surreptitiously supplementing what she regarded as the doctor's inadequate treatment, and producing convulsions. It was, I believe, first brought before the profession by Dr. S. H. Habershon,[1] in 1886, as the result of observations made when house physician at St. Bartholomew's Hospital. He advocated it for cases where the heart is prone to fail in the course of some acute illness. He did not in this paper quote any cases of typhoid fever, the seven cases referred to being two of double pneumonia, and five of valvular disease of the heart.

It is curious how soon and how often we forget the originator or discoverer of valuable methods of treatment or of new diseases, unless some dutiful friend or former pupil renders this impossible by labelling the

[1] *St. Bartholomew's Hospital Reports*, vol. xxii. p. 115. Dr. Habershon tells me that this use of strychnine was suggested to him by Dr. Gilbart Smith, who, together with Sir Stephen Mackenzie, had employed it at the London Hospital.

articles "Tufnell's treatment" or "Hodgkin's disease." To take as an example a drug most of us have at the tips of our tongues every working day, iodide of potassium, how many of us can even recall the benefactor's name?[1]

It is important that the strychnine should be given hypodermically, and not by the mouth, and this for two reasons. First, its action is much more rapid when given under the skin (in cases of typhoid fever with cardiac weakness absorption may be very considerably delayed); and secondly, because the liver has a detoxicating influence on, or interferes with the action of, poisons that reach it. When injected under the skin, strychnine acts both more rapidly and more effectually than when given in the ordinary way by the mouth.

Strychnine may be given in the form of the ordinary liquor of the British Pharmacopœia in doses of 2 to 5 minims twice, or more often if required, during the twenty-four hours, or it may be given in a special solution of 1 grain in 50 minims.

The heart should, of course, always be carefully watched during the course of the fever, so that, as soon as dilatation commences, as shown by an accentuated pulmonary second sound in association with alteration of the first sound and displacement outwards of the apex-beat, the hypodermic injection of strychnine should be started. To be successful it should be employed

[1] Wallace of Dublin is usually credited with having been, in 1832, the first to use iodide of potassium, though iodine—a comparatively recently discovered metal—had been given in syphilis some years previously (*vide* Lancereaux, "Syphilis," *Transactions New Sydenham Society*, vol. ii. p. 300). According to Sir James Paget, however, Dr. R. Williams, physician to St. Thomas's Hospital, employed iodide of potassium in 1831 ("Address to the Abernethian Society, St. Bartholomew's Hospital," 1885, p. 19. Quoted by Mr. H. Marsh in obituary notice of Sir James Paget, *St. Bartholomew's Hospital Reports*, vol. xxxvi. p. 6).

early, and not called in only where cardiac dilatation is well marked.

Strychnine thus given is far superior to digitalis and strophanthus by the mouth. I have no real experience of digitalin hypodermically. When I have employed this preparation, it has been in combination with strychnine.

VII

A CLINICAL LECTURE ON ASCITES[1]

As there are a number of cases of ascites in the hospital under my care, I propose to make that condition the subject of to-day's clinical lecture.

First of all with regard to the word "ascites." It is derived from the Greek word *ἀσκός*, meaning a wine-skin; ascites, or in its full form, *ἡ ἀσκίτης νόσος*, is literally the wine-skin disease, *i.e.* that in which the abdomen resembles a skin distended with wine. The adjective "ites" [*ιτης*], also seen in tympanites, is much the same as the termination -itis (*ιτις*)—*e.g.* in iritis and peritonitis —and is a feminine adjectival termination agreeing with the word *νόσος* (disease) understood. It is interesting to note that the termination -itis, which now always implies "inflammation of," has only acquired this meaning secondarily because the disease *par excellence* of various organs is inflammatory.

The different forms of ascites may be considered under two heads: (1) according to the different kinds of fluid; or (2) in connection with the causes of ascites. The latter is perhaps the most practical and convenient way, since of course ascites is only a symptom of some underlying condition which must be correctly diagnosed before it can be satisfactorily treated.

[1] Delivered at St. George's Hospital, July 2nd, 1900. Reprinted, with a few additions, from *The Clinical Journal*, August 29th, 1900.

THE DIFFERENT KINDS OF ASCITIC FLUIDS

(1) *Serous ascitic fluid.*—The commonest form is that in which the fluid is clear, of a slight citron colour, but quite transparent, with a specific gravity of 1010—1016. Thus we are dealing with a fluid which is more like a transudation than an inflammatory exudation. This condition is sometimes spoken of under the name hydroperitoneum; this form is commonly seen in cirrhosis of the liver and in chronic peritonitis.

(2) *Turbid ascitic fluid.*—When inflammation attacks the peritoneum the fluid contains leucocytes and more fibrin-forming factors. This turbid appearance may be seen in cases where previous tappings have brought away clear fluid.

(3) *Chylous ascites.*—In rare instances the effusion into the peritoneum is exactly like milk. The milky aspect is very well shown in this specimen of pleural effusion drawn off from a little girl aged six years, under Sir I. Owen's care; this remarkably realistic milky appearance may be due to the presence of chyle in the pleural effusion. A similar appearance in the peritoneal fluid may result from rupture of a thoracic duct or some of its branches, and is spoken of as a true chylous ascites.

(4) *Chyliform ascites.*—In some instances the turbidity of the effusion gives rise to an appearance like that of milk, and may be spoken of as chyliform ascites. In other words, the ascitic effusion is like that seen in cases where real chyle is mixed with the effusion.

In chyliform or adipose ascites microscopic examination shows large globules of fat often in the suspended cells, the explanation probably being that the leucocytes have undergone fatty degeneration. Chyliform ascites is sometimes seen in cases of new growth inside the peritoneum; it has been supposed that the presence of new growth inside the peritoneum produces a poison, and that this poison acts on the

cells in the ascitic exudation so as to induce fatty degeneration in them.

(5) *Milky non-fatty ascites.*—Another variety of milky effusion is met with occasionally in which no fat can be found in the fluid. Such cases are sometimes spoken of as milky or lactescent non-fatty effusion. The cause of the lactescent appearance has been much discussed, and has been variously described as due (*a*) to some proteid body formed as the outcome of degenerative processes in the cells suspended in the fluid, analogous to, but on different lines from, the fatty degeneration met with in chyliform or adipose ascites; (*β*) to a limpid condition of the blood-serum seen in some patients, and said to be associated with parenchymatous nephritis; and (*γ*) to the presence of lecithin in the fluid.

There are thus three forms of milky effusions: the true chylous, due to the escape of chyle; the chyliform; and the milky non-fatty. The distinction between the first two is very difficult.

(6) *Hæmorrhagic ascites.*—Another condition, which is rare but very striking, is that in which there is blood in the ascitic fluid. When it is met with it is often due to new growth inside the peritoneum, and usually sarcoma, as might be expected from the hæmorrhagic nature of that growth. It is not often seen in connection with carcinoma. The rarity of disseminated sarcoma in the peritoneal cavity may be correlated with the fact that hæmorrhagic ascites is decidedly infrequent.

Hæmorrhagic ascites is sometimes met with in cirrhosis of the liver, and may be due to traumatism taking place at the time that the effusion is tapped. Perhaps the needle damages the capsule of the liver, or pierces one of the dilated veins underneath the peritoneum. In other cases some of the vascular adhesions, commonly found in connection with a cirrhotic liver, break down, and thus lead to rupture of the contained blood-vessels so that the blood gradually oozes into the

peritoneum. The admixture of blood with ascitic fluid does not appear to be due to tuberculous infection of the peritoneum, as is sometimes the case with hæmorrhagic pleural effusions. In these very rare cases where the fluid is almost entirely blood, the term hæmoperitoneum may be applied. As a pathological curiosity, reference may be made to cases where the peritoneum fills up time after time with fluid which is practically entirely blood, without any satisfactory cause such as new growth or traumatism. Such a condition, however, does not come under the same heading as hæmorrhagic ascites.

CAUSES OF ASCITES

We will now consider the different causes of ascites. Those that are commoner, and therefore more important than the others, will be considered first.

Ascites due to—

1. Cirrhosis.
2. Chronic peritonitis of various kinds.
3. Cardiac and pericardiac disease.
4. Peritonitis, subacute or acute.

1. *Cirrhosis.*—There are two-well-marked and fairly distinct kinds of cirrhosis of the liver, in one of these, hypertrophic biliary cirrhosis, which is a somewhat rare disease, characterised by jaundice, a large, smooth liver and an enlarged spleen, ascites either does not occur or is only seen very late in its course, and then, as a rule, only to a slight degree. It may be mentioned, however, that sometimes, after a patient has for years manifested the symptoms and signs of hypertrophic biliary cirrhosis, the clinical picture alters and becomes that of ordinary cirrhosis. This I believe to be due to the secondary development of multilobular cirrhosis on the top of the biliary (or monolobular) cirrhosis, the condition becoming one of mixed cirrhosis.

In portal or common cirrhosis, which is so notoriously

associated with alcoholic excess, ascites very commonly supervenes towards the end of the disease. In the cases which die directly from cirrhosis, ascites is met with in about 80 per cent.

Now as to the mechanism by which cirrhosis gives rise to ascites. It is very often ascribed to the great obstruction to the passage of blood through the portal vein exerted by the cirrhotic state of the liver. But there are difficulties in the way of acceptance of this simple explanation. These difficulties are:—(1) That the blood-pressure inside the portal vein is probably highest earlier in the disease, at the time that melæna and hæmatemesis take place, whereas ascites occurs late in the disease, and may come on rather suddenly or rapidly. Sometimes the fluid is poured out at the rate of a pint a day, and that in a patient who has very little fluid to spare in the body. (2) Another objection is that in many cases of cirrhosis of the liver the legs may become œdematous before the ascites appears. When the converse occurs it is quite easy to explain it mechanically by saying the ascites compresses the veins inside the abdomen. But when the legs become œdematous first, another explanation of the production of ascites must be invoked, namely, that it is due to the presence of a poison in the blood which has a kind of lymphagogue action, and which excites exudation from the blood-vessels of the peritoneum. (3) Another reason against the view that ascites is simply due to the increased blood-pressure is that ligature of the portal vein in animals is not necessarily followed by ascites; there are, indeed, some cases of slow obliteration of the portal vein in man in which ascites does not occur.

On the other hand, in considering the causation of ascites it is only right to mention that when the portal vein suddenly becomes thrombosed ascites rapidly results. Thrombosis of the portal vein usually occurs

in association with cirrhosis of the liver. There are also cases of extensive secondary malignant infiltration of the liver—for example, in melanotic sarcoma, where the liver is so infiltrated with growth, the capillaries being widely blocked with emboli of new growth, that the passage of blood through the liver is greatly interfered with and ascites occurs. There are, therefore, reasons to think that in certain cases pressure of tumours on the portal vein or blocking of the portal vein or its intra-hepatic radicles may play a causal part in the production of ascites. These facts are rather in favour of the ascites of cirrhosis being due, at any rate in part, to increased blood-pressure in the portal vein.

The following explanation is probably the most satisfactory—viz. that the occurrence of ascites is not due solely to the increased blood-pressure inside the portal vein, but that it very largely depends on the presence of a poison which so alters the vessel walls in the peritoneum that fluid is poured out, and that increased blood-pressure favours the rapid exudation of the ascitic fluid.

With regard to the clinical characters of ascites occurring in cirrhosis of the liver, I pointed out to you that it is a phenomenon which is terminal, or which occurs very late indeed in the life history of the disease. It is very rare for a patient with cirrhosis of the liver pure and simple to require tapping more than twice. This forms a great contrast to what we see in chronic peritonitis, where the patient may require and survive frequent tappings, in extreme instances even a hundred times. In some patients with cirrhosis ascites may be due to concomitant chronic peritonitis and not to the cirrhosis; these cases may require repeated tappings. Hale White and Campbell Thomson have insisted on the difference between ascites directly due to cirrhosis and ascites merely associated with it.

2. *Chronic Peritonitis* is a very frequent cause of

ascites; it will be convenient to consider in order the different kinds of chronic peritonitis:

A. Simple chronic peritonitis.
   (*a*) Associated with adherent pericardium.
   (*b*) Associated with arterio-sclerosis.
B. Tuberculous peritonitis.
C. Malignant peritonitis.
D. Chronic peritonitis associated with the presence of innocent new growth.

(A) In *simple chronic peritonitis* the peritoneum is uniformly thickened and opaque; since it contains a good deal of scar-tissue, it tends to contract and to compress the viscera it surrounds. Sometimes it is especially marked over the surface of the liver and the condition then is often spoken of as perihepatitis.[1] I may say that, clinically, this chronic perihepatitis is nearly always a part of chronic peritonitis, and that in the rare cases where perihepatitis or thickening of the capsule of the liver occurs, without any affection of the peritoneum elsewhere, ascites is rarely seen. Simple chronic peritonitis, sometimes called perivisceritis, seems to be due to, or at any rate to be associated with, one of two conditions. The first associated condition is adherent pericardium. There are cases in which the adherent layers of the pericardium are very thick, and in which the inflammation seems to spread through the diaphragm to the peritoneum, and by a process of extension or continuity, general thickening of the peritoneum results.

In the other class of cases of simple chronic peritonitis, the associated condition is arterio-sclerosis, or widespread atheroma of the vascular system. This very often shows itself largely by its results in the kidney—viz. by producing the familiar granular or arterio-sclerotic kidney. Taking a large number of cases of

[1] The term "iced" liver (zuckergussleber) is applied to this condition from the resemblance to the "icing" of cakes.

chronic peritonitis it will be found that the great majority of those which are not associated with adherent pericardium are correlated with the presence of arterio-sclerosis and granular kidney. In cases of chronic peritonitis associated with arterio-sclerosis the effusion occurs again and again. The patient should be tapped whenever this distension of the abdomen gives rise to discomfort, but the tapping is a palliative and can in no way be regarded as a curative measure. The necessity for multiple tappings is very characteristic and forms a marked contrast to hepatic cirrhoses in which after one or two tappings the ascites does not, as a rule, recur. The cirrhotic patient, however, is no better off on this account, and generally becomes drowsy and passes on to a toxæmic state which is followed at no long interval by death.

(B) *Tuberculous peritonitis.*—There are other kinds of chronic peritonitis, and one of them—a very familiar form—is tuberculous peritonitis. Tuberculous affection of the peritoneum probably nearly always is secondary to the passage of tubercle bacilli through the walls of the intestine into the mesenteric and lymphatic vessels and glands; the peritoneum then becoming involved. It occurs most commonly in children. When met with in adults it is rather commoner in women, and then may have spread from the Fallopian tubes; this form of tuberculous peritonitis tends to be rather localised, and may limit itself to the lower half of the abdomen—encysted peritonitis. Thus the whole of the peritoneal cavity is not necessarily involved, perhaps only the lower third or lower half, and in some cases the encystment of the ascites has been so marked that its real nature has been overlooked and it has been regarded as a cyst, and sometimes described as a cyst derived from the remains of the allantois.

When tuberculous peritonitis occurs in men, a rare event, it is generally associated with cirrhosis of the

liver. You cannot impress upon your minds too firmly that alcoholic excess disposes not only to the production of cirrhosis of the liver but also to the development of tubercle. There is no doubt, to take a common example, that pulmonary tuberculosis is much commoner in publicans than in persons otherwise similarly situated who have not indulged in alcoholic excess. Chronic venous congestion of the peritoneum, which is associated with cirrhosis of the liver, appears really rather to predispose to tuberculous infection than to protect against it.

There are several types of tuberculous peritonitis. In some of them the onset is almost acute, and may possibly be due to the acute and wide-spread infection involved when a tuberculous lymphatic gland bursts into the peritoneal cavity. In other acute cases the explanation may be that the peritoneum is the site of a mixed infection, other micro-organisms besides the bacillus tuberculosis being present in the peritoneal cavity. There are some cases of tuberculous peritonitis in which the chief clinical manifestation is not ascites but tympanites.

In the commoner and more typical forms of tuberculous peritonitis there may be a very considerable quantity of fluid, which may very closely simulate ascites due to cirrhosis of the liver, while in other cases the most salient features are bands, adhesions, or enlarged tuberculous lymphatic glands, palpable through the abdominal wall.

(C) *Malignant peritonitis.*—An important variety of chronic peritonitis is that associated with the presence of multiple nodules of malignant disease in the abdominal cavity. When malignant disease is generalised over the surface of the peritoneal cavity, as is often the case in malignant disease of the female genital organs, or of the stomach, a chronic irritative process is set up which results in ascites. This ascites, like the other forms of ascites due to chronic peritonitis, though in a less marked degree, tends to recur time after time.

In some cases, where the growth is sarcomatous, the fluid which is drawn off may contain blood; while in cases of carcinomatous infection the fluid may be milky or chyliform. Sometimes when carcinoma, the commoner form of intra-abdominal malignant disease, has undergone colloid degeneration, the fluid which is drawn off may be sufficiently thick and tenacious to block up the cannula. There is a woman in the hospital at the present time who has been tapped twice or three times, and has definite evidence of malignant disease, viz. nodules, probably secondary, in the wall of the rectum, while a large tumour can also be felt below the umbilicus. The fluid drawn off from her abdomen is very tenacious, suggesting the possibility that not only is there colloid carcinoma of the peritoneum, but that it has set up a certain amount of ascites, and that some of the colloid material has become mixed with the ascitic fluid.

The fluid drawn off from an ascitic abdomen frequently contains leucocytes and cells which are swollen up from imbibition. It is sometimes thought that malignant peritonitis may be diagnosed by examination of the cells in the fluid. Personally I do not think that this can be done with any degree of success; but it is only fair to say that some recent observers believe that in the ascitic fluid of malignant peritonitis more cells show mitoses than in simple or tuberculous peritoneal effusions, that the mitoses in the former are atypical, and that by careful observation of these data a satisfactory diagnosis can often be made.

There is a rather rare form of malignant disease, namely, primary sarcoma of the mesenteric glands. When it occurs it sometimes gives rise to a very rapid development of ascites indeed. There was a boy, aged eleven years, under my care in the hospital in 1896, who, clinically, looked exactly like a case of tuberculous peritonitis; he had the wasted face and typical

complexion associated with tubercle. It was said that his abdomen only began to swell a week before admission, and that it did so very rapidly; he was tapped ten days after admission, and six pints of turbid fluid removed. He died two days after being tapped, and it was found that he had not tuberculous peritonitis as I thought, but sarcoma of the mesenteric glands. The fluid drawn off did not show any tubercle bacilli; but a similar failure to find bacilli may be experienced in tuberculous peritonitis, since the bacilli tend to stick to the serous surface, and only to appear in the fluid in such small numbers as to escape microscopic examination. The tuberculous nature of such cases may, however, be demonstrated by inoculation experiments.

(D) *Chronic peritonitis associated with the presence of innocent new growths in the peritoneal cavity.*—In rare instances ovarian cysts or uterine fibromyomata are associated with ascites, which is probably due to chronic irritation of the peritoneum set up by the growths.

A rare but very remarkable condition is that in which papillomatous disease of the ovaries sets up recurrent ascites; fragments from the original growth may become widely implanted on the surface of the peritoneum, and grow independently of the main tumour. They are implantation growths, and not infiltrating or malignant formations. Such cases imitate chronic peritonitis; their detection depends on the ovarian growths being felt in the pelvis by vaginal or rectal examination, or on fragments of the growth coming away through the trocar when the abdomen is tapped. Dr. Pye-Smith has recorded (*Trans. Path. Soc.*, vol. xliv. p. iii.) a remarkable example of this disease in a woman who was under his care for nearly nine years, and was tapped 299 times "without once complaining of her lot."

3. *Ascites due to cardiac disease.*—In cases of backward pressure due to mitral disease it is a general rule that the œdema begins first of all in the feet. But there

are, however, some instances in which the œdema begins first inside the abdomen, and considerable ascites develops while there is comparatively little œdema of the feet. These cases may be spoken of as examples of cardiac ascites. It has been thought by a French observer that the occurrence of ascites in cases of cardiac disease without much œdema of the lower extremities, depends upon a congenital condition of the hepatic veins, enabling the blood which regurgitates from the right side of the heart to enter into the hepatic veins more readily than into the other branches of the inferior vena cava, so that the stress of backward pressure falls chiefly on the liver. The truth of this explanation is doubtful; it is more probable that the dilated condition of the hepatic veins seen after death in such cases is secondary, and dependent on the backward pressure, than that it is congenital.

Backward pressure due to heart disease most commonly shows itself by œdema of the legs, but by no means always. There are three main tributaries of the inferior vena cava—viz. the iliac, hepatic, and renal veins, and though the iliac veins generally suffer the most, the other two are sometimes more prominently affected. I have seen cases of mitral disease where albuminuria was so constant as to suggest that there was primary renal disease, but in which microscopic examination of the kidneys after death only showed the effects of chronic venous engorgement. In other instances the brunt of backward pressure falls on the hepatic veins and the liver, phenomena such as enlargement, etc., being the prominent features. Such a condition has been called hepatic asystole, and may be mistaken for cirrhosis of the liver.

Ascites due to hepatic pseudo-cirrhosis of pericardial origin.—In some cases of ascites the associated condition is, not mitral regurgitation and tricuspid regurgitation, but adherent pericardium. These cases

have sometimes been spoken of as hepatic pseudo-cirrhosis, and have especially been described by a German authority, Pick. As the result of pericarditis in these cases, the inflammatory process probably spreads to the hepatic veins during the acute stage, and weakens the walls of the hepatic veins so that they become permanently dilated. This enables the blood to regurgitate more readily into the hepatic veins than into the other branches of the inferior vena cava.

There is no universal chronic peritonitis or perihepatitis, and these cases are distinct from the condition described above of chronic peritonitis associated with adherent or calcified pericardium. I have, however, in cases of pseudo-cirrhosis seen an opacity of the surface of the liver which at first was described as perihepatitis, but was shown microscopically to be subcapsular cirrhosis, the capsule itself not being thickened.

As the result of long-continued and extreme chronic venous congestion, the liver is necessarily badly nourished, and the hepatic cells undergo atrophy, so that the supporting fibrous tissue of the organ becomes more evident. This explains the term pseudo-cirrhosis. There is a certain apparent increase in the amount of fibrous tissue visible (replacement fibrosis of Adami), but this appearance is largely due to the shrinking of the more noble and highly functional part of the liver—viz. its cells—and not to the active hyperplasia of fibrous tissue seen in ordinary cirrhosis.

4. *Acute and subacute peritonitis.*—Lastly, we ought to mention as causes of ascites, though it does not practically appeal to us in that way, cases of acute or subacute inflammation of the peritoneum. In all cases where there is acute inflammation of the peritoneum, there is so much shock and the symptoms are so acute that we naturally and rightly pay practically little or no attention to the presence of ascites. Still, from an academic point of view, acute or subacute inflammation of

the peritoneum is a cause of exudation of fluid into the peritoneum; the fluid contains a large amount of fibrin.

RESULTS OF ASCITES

Having reviewed the different kinds and causes of ascites, a few words may now be said about the results of the condition. The results are chiefly due to pressure. The pressure of fluid inside the peritoneal cavity gives rise to a certain amount of pain, as you can imagine from the tension and stretching of the abdominal walls; but the patients do not often complain of it. The muscles of the abdominal wall, after having been repeatedly stretched, lose their tone and become very flaccid. The skin suffers, and you get a rupture of the deeper layers of the skin, giving rise to lineæ albicantes, familiar appearances in women who have been pregnant as lineæ gravidarum. It is interesting to note, in passing, that lineæ albicantes are not invariably due to mechanical distension; they may be trophic, and occur after severe illnesses. I have seen them on the shoulders in pulmonary tuberculosis. Osler mentions their appearance after fevers, such as scarlet fever, and states they may be idiopathic, and that then they occur in men as frequently as in women.

The distension of the abdomen by ascites presses the diaphragm up and leads to collapse of the bases of the lungs. A very good indication as to the necessity for paracentesis may be obtained from seeing whether the patient is short of breath or not. When ascites has pressed the diaphragm up considerably, collapse of the bases of the lungs, especially of the right, may take place. Sometimes the resulting congestion of the collapsed lung tissue is so extreme that hæmoptysis occurs; the occurrence of hæmoptysis is therefore an immediate indication for relieving the tension caused by the fluid. The fluid also pushes the heart up and presses on the intestines and the stomach, and to a

certain extent impairs their function. When the pressure of fluid inside the abdomen is considerable, the renal veins, which are much thinner than the renal arteries, may be compressed. This interferes with the return of blood from the kidneys and so gives rise to chronic venous congestion of the kidneys. This again impedes the passage of arterial blood into the kidney, and if the kidney is not properly nourished with arterial blood degeneration of the delicate epithelium which covers over the glomeruli tuft follows, and, as a direct result of that, albuminuria. Probably, in a certain number of these cases, albuminuria is produced in this mechanical way. In some other cases, the same poison which gives rise to the ascites may act on the kidney and cause toxic albuminuria. This accounts for some of the cases of albuminuria occurring in cirrhosis of the liver. While again in chronic peritonitis associated with arterio-sclerosis, albuminuria may depend on granular kidneys.

The *treatment* of ascites is conveniently divided into two. (A) The radical treatment, or removing the cause of the ascites, which is sometimes possible. Now, in some cases, generally diagnosed as cirrhosis of the liver, the ascites disappears after treatment with iodide of potassium, and does not recur. It is certainly possible that some of these cases are due to cirrhosis, but probably, in the majority, this diagnosis is wrong though the treatment is right, and the condition is in reality syphilitic disease of the liver. It may not be possible to diagnose during life between cirrhosis and syphilitic disease of the liver, and therefore in all cases of ascites which may be due to cirrhosis it is well to give iodide of potassium on the chance that one's diagnosis is wrong and that the iodide of potassium may cure the patient by removing the cause, viz. such as the pressure of a gumma on the portal vein. Another radical mode of treatment is that often followed by success in cases of chronic tuberculous peritonitis, viz. simple laparotomy.

When tubercle is scattered over the peritoneum its vitality seems to be so comparatively feeble that, if the abdomen is opened and air admitted, the life of these tubercles comes to an end. In the first case in which this was done it was the result of a fortunate error in diagnosis. A lady was diagnosed as having an ovarian cyst, and the abdomen was accordingly opened for its removal. The operator found to his horror that she had tuberculous peritonitis and the abdomen was therefore quickly closed. But from that time the patient improved and lived for a long time afterwards. It has been thought recently that oxygen is the best thing to let in, and that it may do good, not only in tuberculous, but in other kinds of chronic peritonitis. At any rate, in whatever way it acts, operative treatment is followed by very successful results in a certain number of cases of tuberculous peritonitis. *Per contra*, one must always remember that there are some cases of tuberculous peritonitis which gradually get well while they are lying in bed, being well fed, taking cod-liver oil, and having mercurial ointment rubbed into the abdominal wall. In other words, some cases of tubercle of the peritoneum get better if they are fed well and kept at rest, just as in pulmonary tuberculosis.

Now let us consider the treatment of ascites due to cirrhosis. Operative treatment has been employed for that, and since it was thought that the ascites was due to obstruction of the passage of blood through the liver, the treatment employed was directed to produce further vascular adhesions between the surfaces of the peritoneum, so that the number of anastomoses between the portal vein and the general systemic system was multiplied, and in that way the blood-pressure inside the portal vein diminished. This procedure often spoken of as the Talma-Morison operation, has been performed very frequently, and Greenough[1] has

[1] *Amer. Jour. Med. Scien.*, vol. cxxiv. p. 979.

collected 105 reported cases, 44 of which were improved, nine of them being alive and in better health two years after the operation. In a man operated upon by Mr. Turner on July 31st, 1899, paracentesis was not required till January 1902, but he died in May 1902. It is an interesting question as to how uniting the two opposed surfaces of the peritoneum and the production of vascular adhesions bring about any improvement. It is somewhat unlikely that it is due entirely to simply producing a fresh collateral circulation between the portal vein and the general systemic veins and thus relieving the blood-pressure and stagnation in the portal vein. It is perhaps more probable that the way it does good is by removing some of the extra stress of blood from the liver, and so enabling the liver to deal more satisfactorily with the blood which does come through it. The production of fresh vascular adhesions may supply the surface of the liver with an increased blood supply and so give rise to a better condition and vitality of the cells, so that they may proliferate and compensate for those cells which have been destroyed.

Now as to the palliative treatment. Formerly, paracentesis of the abdomen was put off as long as possible, because the peritoneum sometimes became secondarily infected as the result of paracentesis; acute peritonitis was set up, and thus the patient died somewhat before his time. Bad results invariably follow deferring paracentesis as long as possible. At the present time, with antiseptic precautions, paracentesis should be performed as soon as there is inconvenience. The tapping should be done with a Southey's trocar, so that the fluid takes several hours to come away.[1]

[1] I have recently obtained good results by injecting a dram of adrenalin chloride (1 in 1000) into the peritoneum after tapping a case of recurrent ascites of cardiac origin. This method was suggested by Dr. Barr (*Brit. Med. Journ.*, 1904, vol. i. p. 649).

After the paracentesis a binder should be applied or the abdomen should be bandaged; this gives support to the flaccid abdominal walls, and to some extent prevents the troublesome tympanites and possibly the reaccumulation of fluid.

By the administration of diuretics and purgatives an attempt is usually made to remove the fluid from the peritoneal cavity. Suitable diuretics may be given, but care must be taken not to purge the patient excessively and thus weaken him. By these means fair results may be obtained, but by no means constantly. When any discomfort from ascites arises paracentesis should be performed.

DIAGNOSIS OF ASCITES FROM OTHER CONDITIONS

I will now mention very briefly some of the conditions which may give rise to difficulty in the diagnosis of ascites.

One of these conditions is the presence of a very large cyst inside the peritoneal cavity. The commonest of those is a very large ovarian cyst. It rises up from the pelvis, so that it may be first noticed as a tumour there. It distends the abdomen, first of all below the umbilicus, so that the measurement between the umbilicus and the pubes is bigger in the cases of an ovarian cyst than under other conditions. It may also displace the umbilicus laterally. An ovarian cyst grows up towards the anterior abdominal wall, which is dull while the flanks are resonant.

A very rare condition, which has been known to simulate ascites, is a very large hepatic abscess; this could only occur where an hepatic abscess is so large as nearly to fill the abdomen. Another condition is a very large hydatid cyst. A very large and distended urinary bladder has been known to give much the same impression. It is reported that John Hunter once tapped

a urinary bladder as a case of ascites. Then, again, extreme obesity of the abdominal wall may sometimes simulate ascites; indeed, in fat people it is often very difficult to be certain whether there is fluid inside the peritoneal cavity or not. Extreme œdema of the abdominal wall may give rise to the same difficulty.

Another very rare but interesting condition is a very large fatty tumour or lipoma inside the abdomen. These are cases in which a fatty tumour grows, either from the fat around the kidney or from behind the peritoneum; it forms a slow-growing tumour which eventually may weigh as much as 40 lb.; the fat being more or less fluid at the temperature of the body, gives rise to fluctuation. These cases have frequently been tapped under the idea that they were ascites. As no fluid is removed, the case is sometimes looked on as malignant disease, especially as the rest of the patient is emaciated. The consequence is that nothing is done, and then, after death, an enormous fatty tumour, which might perhaps have been successfully removed, is found. In forty-two cases collected by Adami, the fatty tumour was removed wholly or partially in twenty-six; of these patients twelve recovered. The fatty tumour, from its retro-peritoneal position, carries the intestine in front of it. Removal of the tumour may, therefore, deprive a considerable extent of the intestine of its blood-supply.

A large hydro- or pyo-nephrosis is so unilateral that it should not be in danger of being mistaken for ascites.

In rare instances doubt has arisen when the real condition was a dilated stomach, a greatly dilated gall-bladder, and a pregnant uterus with hydramnios.

VIII

SECONDARY MELANOTIC SARCOMA OF THE LIVER[1]

A MAN, aged fifty-nine years, was admitted to St. George's Hospital on January 5th, 1899, complaining of abdominal swelling, of œdema of the legs and scrotum, and of great weakness. Two years before the vision of the right eye had begun to fail and on February 13th, 1897, the globe was removed for melanotic sarcoma. Mr. C. D. Marshall, the curator of the Royal Ophthalmic Hospital, Moorfields, kindly sent up a beautiful microscopic section of the globe of the eye, showing the retina detached and pushed forwards by a mixed-celled sarcomatous growth. This growth was cut up by spaces, which may have contained blood, so as to appear somewhat alveolar; the cells of the growth were spindle-shaped and often contained pigment, and round or slightly oval cells which were generally free from pigment. After looking many times at the section I am inclined to think it is a mixed-celled sarcoma, although I am fully alive to the fallacy of regarding the cross section of a spindle cell as a round cell.

On admission the patient's abdomen was found to be enlarged and distended, and the cutaneous veins running over it were dilated and prominent. No ascites could

[1] A clinical lecture delivered at St. George's Hospital on February 6th, 1899, and reprinted, by permission, from *The Lancet* of May 13th, 1899.

be made out and the enlargement was found to be due to an enormous liver, the surface of which was knobby and irregular. The liver reached in an upward direction to the fifth rib in the nipple line and extended downwards below the anterior superior spines of the ilium. It was tender on palpation. The urine (the specific gravity of which was 1030) was clear and of a natural colour when passed, but on standing, or on the addition of nitric acid or a solution of perchloride of iron, a dark-brown colour developed, due to melanin. There was a cloud of albumin in the urine. The legs were œdematous, and the scrotum and penis were much swollen. Bronchitic sounds were heard over both lungs. The heart was normal. The skin had a slightly dirty appearance, but there was not sufficient change to say that it was definitely pigmented. No other secondary growths were found. There was a little colourless discharge from the right orbit. The patient became progressively weaker and suffered considerably from orthopnœa, which appeared to be due to the abdominal distension encroaching on the thorax; and, although there were no manifest signs of ascites, the question of tapping the abdomen to relieve the pulmonary embarrassment was considered, but it was decided against. The liver enlarged in its dimensions while under observation and œdema of the left side of the chest developed. The man died after being in the hospital for eighteen days, during which time his temperature had been almost entirely subnormal. Treatment was confined to relieving pain by hypodermic injections of morphia.

At the necropsy, which was performed by Dr. W. S. Lazarus-Barlow, there was no local recurrence in the right orbit. There was a little clear, yellow, ascitic fluid, which, however, became dark on the addition of solution of perchloride of iron, showing that melanogen was present. The liver weighed 15 lb. 12 oz. and showed

discrete growths both in the capsule and on section, and areas of diffuse infiltration with growth. The nodules of growth were of various sizes and colours—some white, some variegated, others black. The areas of infiltration were, as a rule, more pigmented than the nodules. In one part the liver tissue was replaced by black, infiltrating growth somewhat softened and oozing a black juice. There were some small secondary nodules on the under surface of the right leaflet of the diaphragm, but no inflammation past or present of the capsule of the liver or of the diaphragm. There were no growths in connection with the gall-bladder or bile-ducts and no calculi in the gall-bladder. There was an enlarged gland resting on the portal vein but not compressing or invading it; the portal vein was normal. The inferior vena cava was dilated and distended with post-mortem blood-clot; this was due to the liver pressing on, and obstructing the flow through, the vein just before the latter passed through the diaphragm. There was a minute growth in one adrenal body and two small, almost unpigmented, growths on the mucous membrane of the small intestine. There were no growths in the kidneys, spleen, or peritoneum. The lungs were free from growth, but there was collapse of both the lower lobes with very marked engorgement. There were a few adhesions at the left base, but no signs of pleurisy or adhesions on the right side, and no effusion or growths in the thoracic cavity. The veins at the lower end of the œsophagus were dilated and prominent, showing that the collateral circulation, between the gastric vein opening into the portal system, and the œsophageal veins opening into the azygos vein and so into the superior vena cava, had been well developed, as if to compensate for portal obstruction. Microscopically, the growth was alveolar and composed of spindle and oval cells, some of which were deeply pigmented while others were quite free from melanin.

Some of the alveolation was undoubtedly due to the cells of the growth being inside and distending the capillaries of the liver; as in the primary growth, so here, the distribution of pigment was most irregular and capricious.

In this case the diagnosis was perfectly easy, as the history of removal of a melanotic sarcoma from the right eye left very little doubt that the enlargement and nodular condition of the liver was due to recurrence in that organ. As a proof that this diagnosis was correct the presence of melanin in the urine was all that was necessary; but another proof, which would, if present, have further clinched the diagnosis was, the presence of secondary melanotic nodules in the skin.

The occurrence of secondary melanotic sarcoma in the liver is well known, and is such a striking morbid lesion that once seen—and all museums have specimens illustrating it—it is never forgotten. Since this is a condition every one is familiar with and is a matter, so to speak, of common knowledge, it might be thought that it is frequently met with in ordinary hospital work. This is hardly the case, for since I have been in touch with the post-mortem room at St. George's Hospital (a period of nine years) there has only been one other example, though two years previously (in 1888) there was a case of melanotic sarcoma of the liver thought to be primary in that organ.

With regard to the pathological anatomy, melanotic sarcoma is usually primary on the uveal tract; in a much smaller number of cases it arises in the skin, especially in pigmented moles; in a few exceptional instances—of which I have examined one—it occurs in the rectum; and lastly it appears to arise primarily in the liver. Of the latter class I have only been able to collect ten examples, and most of these are not absolutely above suspicion. Histologically, melanotic sarcoma is composed of large spindle-, oval-, or oat-shaped cells

and so justifies its title to the name "sarcoma." In many cases a similar pigmented growth which generalises in the same manner is composed of round cells and has an alveolar arrangement, so resembling carcinoma. There has been a tendency to consider every melanotic tumour as *ipso facto* sarcomatous. Structurally, however, many of them are exactly like carcinoma with the addition of pigment in the cells. There are other ways in which many of the cases usually called "melanotic sarcoma" approach the carcinomatous type. Thus both in the uveal tract and in the skin the primary tumour arises, if not absolutely from pigmented epithelium, at any rate, in the closest contact with that epiblastic tissue. Like carcinoma it may spread by the lymphatics, though it must be remembered that it generalises chiefly by the blood-stream. There is, however, a reaction against the view that malignant melanotic tumours are always sarcomatous and a number of melanotic carcinomata both of the skin (Bowlby,[1] Solly,[2] and Hutchinson[3]) and also of the liver (W. Legg[4] and Hale White[5]) have been described. Lancereaux, indeed, in his recent *Traité des Maladies du Foie et du Pancreas*, goes so far as to consider that the great majority of pigmented hepatic tumours are carcinomatous. On the other hand, it must be remembered that undoubted sarcoma has a great tendency, probably because it so often grows inside the capillaries, to assume an alveolar form in the liver. From the unsettled state of opinion at the present time some authors prefer to speak of the pigmented tumours in the liver, whether primary or secondary, as "melanomas" or simply as "pigmented tumours," without labelling them as "sarcoma" or

[1] *Transactions of the Pathological Society*, vol. xli. p. 314.
[2] *Ibid.*, p. 315. [3] *Ibid.*, vol. xliv. p. 148.
[4] *St. Bartholomew's Hospital Reports*, 1887, vol. xiii. p. 160.
[5] *Guy's Hospital Reports*, 1890, p. 73.

"carcinoma." In the meanwhile we should judge each case on its microscopic merits and not assume that a pigmented tumour is necessarily sarcomatous. It is not, as far as can be seen at present, a matter of any great clinical importance what the exact structure of a malignant melanoma is, though more careful classification in the future might be expected to show that there was some difference in the rapidity of generalisation. The truly sarcomatous would *a priori* be expected to be the more malignant. In the remarks which follow, the term "melanotic sarcoma" will be used, as it generally is, as synonymous with malignant pigmented tumours.

In its age incidence malignant melanotic growths resemble carcinoma, and rarely occur in early life as the other forms of sarcoma do. In 103 cases of sarcoma of the uveal tract, all of which except one, where no note was made, being more or less melanotic, collected by Lawford and Collins,[1] the average age was 48·4 years, the extremes of age being 15 years and 84 years. In 35 cases of secondary melanotic growths in the liver which I have collected the average age almost exactly corresponds to this, being 48·7 years, or 46·7 years for the males and 53·3 for the females, the extremes being 27 years and 75 years. As to sex, of Lawford's and Collins's 103 cases 59 were males and 44 were females; in my 35 collected cases, where the sex was stated, 25 were males and 10 were females; this shows a much more marked preference for males than in the series of primary growths of the uveal tract. The right eye was affected 41 times and the left 60 times in Lawford's and Collins's cases, while in the cases I have collected of hepatic growths the right eye was rather more frequently the primary seat of growth, but the numbers are small.

Secondary melanotic tumours of the liver are more

[1] *Royal London Ophthalmic Hospital Reports*, vol. xiii. p. 104.

often secondary to a primary growth in the uveal tract than in the skin. Thus, in 36 cases of a melanotic sarcoma in the liver, the primary growth was 24 times on the eye and 12 times in the skin. This is partly due to melanotic sarcoma being commoner in the uveal tract than in the skin. Examination of the recorded cases shows that the growths in the liver following cutaneous melanosis are not so big or so striking as those following melanotic sarcoma of the uveal tract. In most of the cases I have collected where the liver contained secondary growths following cutaneous melanosis the organ was little above the ordinary size, though in two cases it weighed over 7 lb., while, on the other hand, some of the largest livers recorded have been due to melanotic sarcoma originating in the eye. Thus Litten[1] has described a case where the liver weighed 27 lb., Sayre[2] one of 23 lb., and Hamburger[3] one of 22 lb. The average weight of the liver in 22 cases of melanotic growth, secondary to a growth in the uveal tract, was 13 lb. 3 oz. In cases of primary melanotic growths of the skin there is a marked tendency to wide and general dissemination of the secondary growths, more so perhaps on the whole than in the primary growths of the uveal tract.

The liver is a very favourite site for secondary infiltration in melanotic sarcoma of the uveal tract. In a few cases it is found to co-exist with an intra-ocular growth, but it usually occurs within three years after removal of the eye and generally without there being any local recurrence in the optic nerve or orbit. It would thus appear that the infective cells of the growth must remain latent in the liver for some time. The liver may indeed be the only organ in the body affected,

[1] *Deutsche Medicinische Wochenschrift*, 15, S. 41, 1889.

[2] *Transactions of the New York Pathological Society*, 1879, vol. iii. p. 42.

[3] *Johns Hopkins Hospital Bulletin*, March, 1898.

while in other instances almost every viscus and tissue shows metastases. Melanotic sarcoma is the only form of sarcoma which is often seen in the liver; the lungs, on the other hand, are the seat of election for ordinary secondary sarcoma, the infecting cells of which travelling by the blood are caught in the lungs, which thus, to a certain extent, protect the rest of the body against sarcomatosis. It is plain that in carcinoma of the alimentary canal the liver plays the same rôle. It is remarkable that the cells of melanotic sarcoma being, as they usually are, larger than the cells of the other sarcomata, which are stopped by the lungs, manage to pass through the pulmonary capillaries and to infect the liver. The liver may show a number of discrete nodules, may be diffusely infiltrated with growths so that it resembles granite, or in extreme instances it may look as if it had been steeped in pitch; or a combination of these two conditions may exist, parts of the same liver being differently affected. Some of the growths may be free from pigment, others show a little, and then have a greenish or variegated aspect. The diffusely infiltrated areas may be softened and exude an inky juice. Pigmentation of the liver may occur in conditions other than melanotic tumours. It is hardly necessary to refer to the post-mortem blackening of the parts of the liver in contact with the stomach and intestine. This common appearance is due to sulphuretted hydrogen formed in the alimentary canal passing into the adjacent substance of the liver, and there meeting with iron, and producing sulphide of iron. This discoloration of the liver is almost entirely superficial. Pathological pigmentation of the liver does also occur in the melanæmia of malaria and in hæmo-chromatosis, where cirrhosis may subsequently be complicated by diabetes (bronzed diabetes). The pigment—hæmosiderin—is due to blood destruction, and is directly derived from hæmoglobin; it is therefore

quite distinct from melanin. It is more striking when seen under the microscope than to the unaided eye. The pigment granules occupy the liver cells and the fibrous tissue. The specimens of pigmented cirrhosis which I have seen, have appeared of a reddish-brown colour to the naked eye, and did not resemble the diffuse infiltration seen in melanotic sarcoma. As a curiosity anthracosis of the liver or the presence of coal particles in its substance may be mentioned. Professor Welch [1] found this associated with cirrhosis.

To consider now in detail some of the symptoms of melanotic sarcoma. A complaint of great weakness is not infrequently made by patients. This may be explained by the following hypotheses. It might be the result of such extensive destruction of the liver substance, that the organ fails to do its work of stopping poisons, which, in the ordinary course of events, are absorbed from the alimentary canal and then destroyed or rendered innocuous. This condition of hepatic inadequacy leads to the body becoming flooded with poisons, which produce great feebleness and loss of appetite. The latter symptom was present in this case, and of course tends to increase the patient's weakness. Hepatic inadequacy would also interfere with the absorption and proper assimilation of food. In some cases such hepatic inadequacy may further lead to a toxæmic condition resembling uræmia and to numerous hæmorrhages. There is another possible explanation, that the new growth produces a poison which leads to the cachexia seen in malignant disease. This is perhaps less probable in sarcoma than in carcinoma, but it is a theory which appeals to one's mind at the present time when the importance of internal secretions is becoming recognised, and cannot be lightly put aside. Heaviness or pain in the hepatic region is due to the distension of the liver by the rapidly increasing growths inside it;

[1] *Ibid.*, 1891.

this tension also accounts for tenderness on pressure. When implicating the capsule the nodules of growth may give rise to local inflammation of the peritoneum and so to sharp pain, aggravated by respiration. On one occasion the patient did complain of stabbing pain in the right side, but no remains of past perihepatitic inflammation or pleurisy were forthcoming at the necropsy to explain it. Shortness of breath may occur from the enlarged liver pushing up the diaphragm and compressing the lungs, and this was marked in the present case. Compression and displacement of the thoracic organs may also be due to concomitant ascites, and these may be temporarily relieved by removing the fluid. It has been stated that ascites is rare, or even that it does not occur in melanotic sarcoma of the liver, but this is not borne out by the cases I have collected, for it was stated to be present in ten out of the collected cases of secondary melanotic disease of the liver; and in at least three of the primary melanotic growths of the liver there was ascites; in the case examined by Dr. Penrose in this hospital in 1888 there was as much as three gallons of fluid.

In a few cases the ascitic fluid has been pigmented; in our case it was clear, but treating it with ferric chloride showed the presence of melanogen, the colourless form in which the melanin is often passed in the urine. I ought, however, to mention that Dr. Garrod told me that in two similar cases tested by him the ascitic fluid did not give any such reaction. As to the way in which ascites is produced in these cases it may be due to the great obstruction to the passage of blood through the hepatic capillaries: Hektoen and Herrick[1] have recently called attention to the wide-spread intra-capillary masses of growth in melanotic sarcoma of the liver. The resulting condition of obstructed circulation

[1] *American Journal of Medical Sciences*, September, 1898, vol. cxvi. p. 255.

through the liver thus to some extent resembles that in cirrhosis of the liver, and it is interesting to note that in our case the collateral circulation between the portal vein and the general systemic veins was well developed at the lower end of the œsophagus. This compensation may have accounted for the comparatively small amount of ascites. In a case of melanotic sarcoma of the liver, possibly primary, recorded by Frerichs, the collateral circulation was well developed, and there was no ascites. There are other ways in which melanotic sarcoma of the liver might give rise to peritoneal effusion, such as the production of portal thrombosis by extension of the growth into the portal vein or its branches, the pressure of growths on the trunk of the vein, and, lastly, by other secondary growths in the peritoneum, causing an inflammatory effusion as opposed to the passive transudation in the foregoing.

Jaundice was not present in this patient, and is generally absent. Its presence may easily be brought about by a growth exerting pressure on the ducts; but it so happens that this is a rare accident. It was stated to be present in six cases of those collected. The œdema of the feet was in this case due to pressure on the inferior vena cava, and is a frequent symptom in these cases; but in some instances it may be due to other factors such as cardiac debility. The œdema of the scrotum and chest-wall are similarly explained by pressure on venous tracts, but are less frequently seen.

The urine in this patient was, as is usually the case, clear when passed, but subsequently darkened on standing and exposure to the air. A black ring or coloration could also be obtained by the addition of solution of perchloride of iron or nitric acid. It is well to employ both these reagents, so as to avoid mistakes, for the urine of patients taking salicylic acid turns of a dark purple colour with ferric chloride, and a blackening may occur under other conditions with ferric chloride,

and yet no change occurs on adding nitric acid. Again, in urines containing much indican, the addition of nitric acid gives a dark ring, but ferric chloride has no such effect. Sometimes in melanotic sarcoma of the liver the urine is brown or dark-coloured when evacuated, and it then contains melanin. Usually, as has already been said, it is clear at first, and only shows the presence of melanin after exposure to the air or when acted upon by bichromate of potash or nitric acid. The pigment has then been passed in a colourless form or chromogen (melanogen). It is supposed that the melanin manufactured by the cells of the growth passes into the circulation, and is changed by the tissues into melanogen before it passes into the urine, where it may, unless specially tested for, entirely escape notice. The presence of melanin in the urine or melanuria does not in any way depend on there being secondary growths in the kidney, for in this, as in other cases, it may occur without any metastatic nodules being present in these organs. It appears that melanuria only occurs in cases with extensive visceral growths, especially when in the liver. Dr. Garrod has kindly told me that he has failed to find it in cases of local growth confined to the eye.

Melanin is normally found in the eye and in the skin; it is manufactured by the activity of cells, and is a proteid containing sulphur, but not iron. It is not derived directly from hæmoglobin. It has been described as being found in corpuscles in the blood, in cases of melanotic sarcoma. A few cases have been recorded where the skin generally has become pigmented in the course of extensive melanotic sarcoma, not from the presence of cutaneous growths, but presumably from deposit of melanin on the skin, conveyed there by the circulation from the neoplasm. A remarkable case is described, with a coloured plate, by Dr. W. Legg,[1] in

[1] *Transactions of the Pathological Society*, vol. xxxv. p. 367.

which the pigmentation strongly suggested argyria. The patient was a man, aged fifty-nine years, who had never taken silver as a drug, but had melanuria, and had had an eye removed for a growth two years before. His liver weighed 12½ lb., and was infiltrated with melanotic sarcoma.

As to treatment, there is unfortunately little to be said. When the liver is involved any surgical interference or injection with Coley's fluid is useless. Morphia to relieve pain, tapping the abdomen, and the relief of symptoms as they arise, are all that can be done.

To recapitulate. 1. Malignant melanotic tumours, though usually spoken of as sarcomatous, are not so necessarily; probably a fair proportion are carcinomatous. 2. Secondary melanotic growths in the liver are more often found to follow primary growths of the uveal tract, and reach a larger size than when secondary to cutaneous growths. 3. The hepatic growths are more frequent in men than in women, in the proportion of two and a half to one. 4. The average age of patients dying with secondary melanotic hepatic growths is 48·7 years. 5. Ascites occurs in more than one-fourth of the cases, and jaundice in about one-sixth of the collected cases. 6. The urine contains melanin, though when freshly passed it may be of a colourless form (melanogen). Its detection may be of use in diagnosing a doubtful case of hepatic enlargement.

IX

ON HYPOSTATIC ALBUMINURIA OF SPLENIC ORIGIN[1]

This short communication deals with a small point which has very probably often been observed before, but being an isolated observation has not been thought worthy of much notice. The point to which I wish to draw attention is that, in some patients with considerable splenic enlargement, rest in bed or in the recumbent position may be accompanied by albuminuria, and that the albumin may disappear from the urine when the patient assumes the erect position. This fact was first brought to my notice in a case of advanced leukæmia which I often saw with Dr. C. J. Heaton of Westgate-on-Sea, who drew attention to the intermittent albuminuria and explained it on Falkenheim's[2] suggestion that in the recumbent position the spleen pressed on the left renal vein, interfered with the return of venous blood from the kidney, and thus gave rise to albuminuria. This seems to be a very reasonable explanation of the occurrence. I have recently had under my care two other patients, with hepatic cirrhosis

[1] A paper read at the meeting of the Medical Society of London on February 24th, 1902. Reprinted, with permission, from *The Lancet*, February 28th, 1902.

[2] Falkenheim (*Deutsches Archiv. für Klinische Medicin*, band xxxv. S. 446, 1884) described exactly this condition in a man, aged fifty years, with hepatic cirrhosis and a large spleen. He observed that lying on the right side and on the abdomen did not induce albuminuria.

and splenic anæmia respectively, with considerable splenic enlargement, presenting a rather large quantity of albumin in the urine while lying in bed, which disappeared after they had been up for several hours. The albuminous urine was often high coloured, and, like the urine of backward pressure in cardiac disease, lithatic. In all my three cases the night urine was sometimes found to become free from albumin.

It is, of course, necessary that the bladder should be emptied of urine when the patient gets up, otherwise an admixture of the albuminous urine, excreted while in the recumbent position, with the normal urine of the erect position will occur, and the patient may be thought to have continuous albuminuria. The existence of this hypostatic albuminuria, if the term may be used, should be borne in mind when dealing with cases where, as in hospitals, the sample of urine provided for examination is taken from the whole amount passed in the twenty-four hours, or is that passed early in the morning while the patient is in bed.

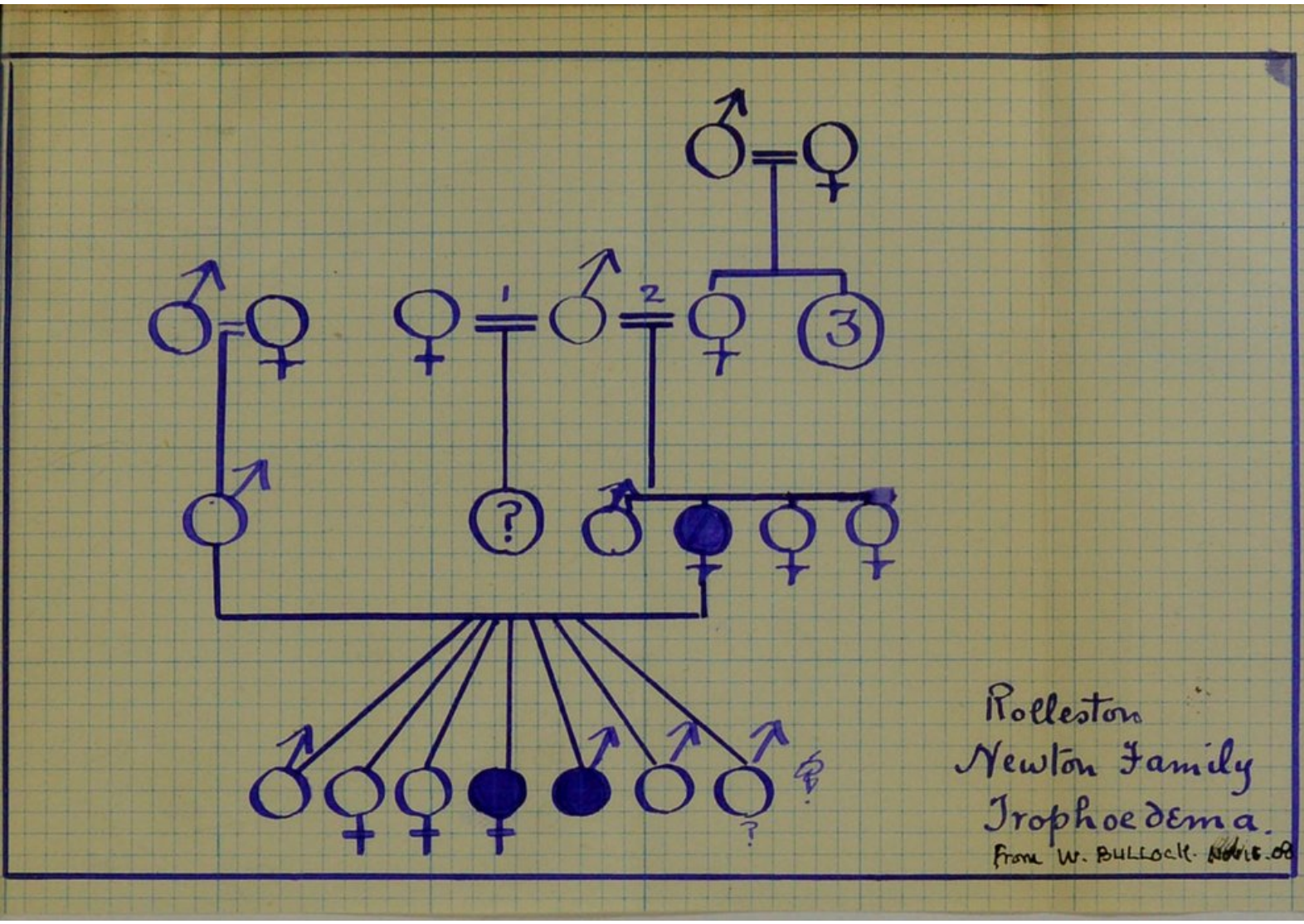
While the albuminuria is probably due to the mechanical pressure of the spleen on the left renal vein in the recumbent posture, the occurrence of this intermittent or hypostatic albuminuria is very far from constant in cases of splenic enlargement. In this it resembles albuminuria from chronic venous engorgement induced in other ways, as, for example, in the backward pressure of mitral disease. It does not depend on the size of the spleen, for hypostatic albuminuria may be, and, indeed, usually is, absent when the spleen is very large, and may be present, as in two of my three cases, where the spleen is relatively smaller. It is possible that its occurrence or absence may depend on some differences, such as elongation, in the condition of the suspensory peritoneal ligaments of the spleen, which thus determine or prevent direct pressure on the left renal vein. On this point there is as yet no anatomical evidence. It is

also conceivable that the appearance of albuminuria is dependent on an underlying want of vitality or nutrition in the kidney which, though not sufficiently marked to induce albuminuria under ordinary conditions, does so when chronic venous engorgement is superadded. This is to some extent supported by the observation that in one of the more recent cases albuminuria disappeared from the night urine after the patient had been some time in the hospital, and had somewhat improved under treatment; subsequently, after a slight attack of influenza, the night urine again contained albumin.

The appearance of albuminuria in the recumbent position and its disappearance in the erect position is not absolutely constant, even in those individuals with enlarged spleen in whom its presence has been noticed; but its temporary occurrence in three cases justifies the suggestion that it may not be so very infrequent.

This hypostatic albuminuria is the reverse of what usually occurs in cyclical albuminuria, but it is possible that there may be some cases of cyclical albuminuria in which albumin appears when the patient is lying down and disappears when he is up. I have not yet met with a case, but the possibility of such an event is suggested by Edel's[1] recent observations that a weak pulse and the appearance of albumin in the urine in cyclical albuminuria are related, and that if, by regular muscular exertion, such as marching or hill-climbing, always stopping short of fatigue, the heart's action is strengthened, the urine becomes free from albumin, lighter in colour, and more copious.

[1] *Münchener Medicinische Wochenschrift*, 1901, Nos. 46, 47 (Abstract, *Brit. Med. Jour.*, 1902, vol. i. epitome No. 63).



Rolleston
Newton Family
Trophoedema.
From W. BULLOCK. NOV 15 08

X

PERSISTENT HEREDITARY ŒDEMA OF THE LOWER LIMBS[1]

I HAVE recently had under my care in St. George's Hospital a brother and a sister (patients of Dr. H. Hollis, of Wellingborough), who were both the subjects of a peculiar form of œdema of the legs. The œdema was permanent as long as they led an ordinary life and got more marked after exercise or a warm bath, but disappeared after rest in bed for some days. It was only troublesome from the weight and size of the swollen legs and did not give rise to pain or to any other bad results. The mother, aged forty-five years, who had suffered for thirty-five years from the same condition, had long ceased to think of her own legs and was only concerned for her children. There were five other children, both older and younger, but they were not subject to swollen legs or to chilblains. None of the mother's brothers or sisters survived infancy, and this condition, which had apparently been transmitted from the mother to her two children, could not be traced any further. There was no history or trace of syphilitic infection in any of the patients. Some years ago a fatty tumour had been removed from one thigh of the mother by Mr. A. A. Bowlby. There was no evidence of hæmophilia. The œdema was limited

[1] Reprinted, with permission, from *The Lancet*, September 20th, 1902.

to the lower extremities, and chiefly to the legs and feet. It varied, as already pointed out, gradually increasing when the patients were up, and slowly receding when they remained for some days in bed, but there was no sudden appearance of the swelling as in angioneurotic œdema. When the limbs were kept warm the skin was natural in colour, but the circulation was very feeble, pressure on the skin leaving an anæmic area for a much longer time than in normal persons. The œdematous skin pitted fairly readily and was distinctly cold to the touch. In appearance the skin was quite free from any structural change; there was no thickening such as is seen in elephantiasis. The absence of any such change in the mother in whom œdema had existed for thirty-five years was remarkable. There was no tenderness on pressure over the swollen parts. There was no puffiness of the face, hands, or any part of the body except the lower extremities. No recognised cause for œdema was forthcoming in any of the three patients. Examination of the heart showed nothing abnormal and there was no anæmia; in fact, in both the brother and sister the number of red blood corpuscles was 5,800,000 per cubic millimetre. The urine was healthy; there had been no hæmoglobinuria, and no signs of pressure on the inferior vena cava, or of lymphatic obstruction, venous thrombosis, or peripheral neuritis could be found. They had not been out of England and had never had erysipelas, and they were not subject to urticaria or to any gastro-intestinal disturbance such as is common in angio-neurotic œdema. There was, however, evidence of what was popularly called "a feeble circulation." At birth they were both "blue children," and were very subject to chilblains, both the feet and hands readily getting livid by cold. When the skin was in this condition it resembled the stage of local asphyxia in Raynaud's disease. The phenomena of local syncope,

gangrene of the extremities, or hæmoglobinuria, had not, so far as history and observation went, occurred in these two patients. The lividity and blueness of the hands were exaggerated, as in erythromelalgia, when they were allowed to hang down, and diminished when they were elevated. But there was no pain or tenderness associated with the lividity, thus differing from erythromelalgia. Pressure on the congested skin left an anæmic area for a considerable time. The patients were healthy-looking, intelligent, thin, and perhaps a little small for their ages. A few further details may be recorded about their condition.

The girl was aged sixteen years. Swelling of the legs began three years ago and had been constant except when she was confined to bed for a few days. When the legs were bandaged the œdema mounted to the thighs. On July 8th the following measurements were taken:—The left calf, maximum measurement, 13½ in. circumference; the right calf, maximum measurement, 16½ in. circumference. A fortnight later, after being in bed most of the time, the right calf measured 12 in. and the left 11½ in. in its maximum circumference. The urine was healthy. The blood showed 5,830,000 red and 16,000 white corpuscles per cubic millimetre; a differential count showed a slight diminution of the polymorphonuclears and a corresponding increase in the lymphocytes. Blood-pressure at the wrist taken with Barnard's sphygmometer was 125 millimetres of mercury, or just about the normal.

The boy was aged thirteen years. His legs began to swell three years ago. The œdema occupied both legs and ascended about half-way up the left thigh. On admission, on May 28th, the following measurements were taken:—Left calf, maximum, 12¾ in. circumference; right calf, maximum, 13 in. circumference. On June 13th, after rest in bed with the end of the bed raised by blocks and treatment with ergot

and digitalis in small doses, and galvanism, as practised

Shows persistent hereditary œdema of the feet, legs, and left thigh, and cyanotic condition of the hands. The creasing of the skin above the ankles was temporary and was due to the pressure of boots. The patient had been up for some hours before the photograph was taken in order to increase the amount of œdema.

by Sir T. Barlow[1] in Raynaud's disease, the maximum circumference of the right calf was 11 in. and that of

[1] *Allbutt's System of Medicine*, vol. vi. p. 605.

the left was 11¾ in. The skin of the legs showed no structural change and no resemblance to elephantiasis. The creasing of the skin above the ankles shown in the photograph, kindly taken by Mr. J. W. Mercer, was due to the pressure exerted by boots. The knee-jerks and sensation were normal. On exposure to cold the extremities became cyanotic; this was exaggerated when the hands were allowed to hang down. The specific gravity of the blood was 1056 and the blood-pressure taken when the hands were warm by Mr. Golla with Barnard's sphygmometer, was 95 millimetres of mercury, or below the normal. The red blood corpuscles were 5,800,000 and the white 16,000 per cubic millimetre, with a diminution in the polymorphonuclear and an increase in the mononuclear forms. The urine was natural. On July 22nd he unfortunately developed scarlet fever and was transferred to a fever hospital.

Treatment consisted in rest in bed with elevation of the bed, and though drugs and the application of the constant current to the œdematous legs on the lines indicated by Sir T. Barlow in Raynaud's disease were employed, position appeared to be the only thing which really had any definite effect on the œdema. Small doses of digitalis and ergot were given with the intention of improving the vascular tone.

REMARKS

The occurrence of hereditary angioneurotic œdema is well known. Osler[1] has given a description of a family in which that disease was present in five generations, and quite recently Wardrop Griffith[2] has recorded a case of hereditary angioneurotic œdema which suddenly proved fatal from acute laryngeal œdema. The cases

[1] *American Journal of the Medical Sciences*, vol. xcv. p. 362, 1888.
[2] *British Medical Journal*, 1902, vol. i. p. 1170.

under my care differed entirely from angioneurotic œdema and superficially present more resemblance to the œdema of cardiac disease or of chlorosis. But there is no evidence that the œdema can be referred to either of these causes. The cases appear to resemble the remarkable family described by Milroy,[1] of Omaha, in which out of ninety-seven individuals in six generations twenty-two persons (twelve males, seven females, and three unknown) had solid œdema of one or both legs without any special inconvenience or progressive increase in the disease. The condition was congenital, except in one case, in which it developed at the age of twelve years. In one case only did the œdema disappear even temporarily. Crozier, Griffith, and Newcombe,[2] in their paper on "Types of Œdema in Infancy and Childhood," report a case which they regard as allied in some respects to Milroy's cases. In a child, aged four years, œdema of the face and left leg developed at three months of age after measles. Milroy, after very tentatively suggesting that the condition might depend on a congenital absence of valves in the veins, came to the conclusion that it was more closely allied to angioneurotic œdema than to any other known disease. My cases, however, differ from Milroy's in developing at or after ten years of age. They are therefore hereditary but not congenital in addition, as were all but one of Milroy's. The disease in some respects resembles both Raynaud's disease and erythromelalgia but differs from them, as has already been pointed out, in many essential particulars.

The pathogeny of this curious condition offers a wide and tempting field for speculation. It might be suggested that the persistent tendency to œdema

[1] "An Undescribed Variety of Hereditary Œdema," *New York Medical Journal*, November 5th, 1892.

[2] *Transactions of the Association of American Physicians*, vol. xii. p. 411.

from gravitation depends on some inherent defect or peculiarity of the small blood-vessels, which allows excessive transudation to occur on very slight provocation. Isolated examples of œdema for which no satisfactory cause can be found come under observation from time to time. I had a case of this apparently idiopathic œdema in a healthy young woman, aged twenty-four years, under my care in St. George's Hospital last year, and I have heard of a few other cases in women. Œdema of obscure origin is less rare in the newly born and in very young children and may be due to a number of different causes, but some of the cases where no satisfactory cause is forthcoming may be sporadic examples of the condition described by Milroy.

The object of this paper has been to attract attention to a definite group of cases characterised by persistent œdema of the lower extremities which is hereditary and may be congenital but does not depend on any of the factors ordinarily recognised as responsible for œdema.

XI

A CASE SHOWING SOME OF THE FEATURES OF ERYTHROMELALGIA AND OF RAYNAUD'S DISEASE[1]

The following case is allied both to Raynaud's disease and to the rarer, or at least less generally recognised, condition of erythromelalgia. Erythromelalgia was the name suggested as long ago as 1878 by Weir Mitchell[2] for a red and painful condition, or, as he afterwards called it, red neuralgia of the extremities, of which he collected sixteen examples, chiefly in the feet. The condition may be thought to be a peripheral neuritis affecting the vasomotor nerves, and so to be closely allied to other angioneuroses, such as angio-neurotic œdema and Raynaud's disease.

A male, aged twenty-nine years, formerly a miner and at one time a seafaring man, came to my out-patient room, and was subsequently admitted under my care at St. George's Hospital on December 20th, 1897. He complained of loss of energy, which had troubled him for twelve months; but, in addition to this, his hands and feet were so painful that he was unable to do his work, that of an excavator, and had given it up since July 1897. He had become much more susceptible to cold for the past year, and had noticed that

[1] Originally published in *The Lancet* of March 19th, 1898, and now reprinted, with some few additions, by permission.

[2] *American Journal of the Medical Sciences*, 1878, vol. lxxvi.

during this time his hands and feet had swollen when exposed to cold, especially when in a dependent position. Holding his hands up afforded him distinct relief. On exposure his hands became cold, both subjectively and objectively, and persons shaking hands with him had, he said, complained of this. His hands went dead, and at the same time swelled and throbbed. They were worse in cold weather, but were not free from pain and swelling in the summer. In addition to the deadness and pain he had considerable tenderness, so that he was unable to bear the pressure entailed in walking. This was felt especially in the little toes. During cold weather or exposure the symptoms were continuous and constant, but they became slighter and tended to disappear if he was kept warm. No history of hæmaglobinuria or hæmaturia could be obtained, and during his stay in the hospital his urine was quite natural. Four years ago his right ear became frost-bitten. There was no history of ague, and no history of any symptoms like angina pectoris. He had had syphilis seven years ago. No details of his family history could be provided by the patient. On admission he was found to be a burly man with a pimply face and a good deal of eczema from exposure to wind, rain, etc. His aspect suggested alcoholism, but he professed teetotalism. His nose was somewhat tender and sometimes painful, and there was a general resemblance between the red areas of the skin on the various exposed parts of the body. There was a small chilblain on the right ear. There was no facial resemblance either to acromegaly or to myxœdema, and no enlargement of the cranium. The hands were red and puffy, but were not definitely œdematous. The skin was hypersensitive, and this condition was aggravated if his hands were held in a dependent position. The skin was permanently red, but this was less marked when they were kept warm. There was also marked tenderness of the muscles of the hands, and compara-

tively slight pressure appeared to give rise to considerable pain. The hands were enlarged, and were not unlike those seen in acromegaly; but, as already mentioned, there was no evidence of this in the head. There was no manifest bony enlargement. A peculiar feature was the bulbous condition of the terminal phalanges with some over-curving of the nails. The nails themselves were otherwise normal. There was no sign of scleroderma.[1] There was no muscular tenderness in the forearms or arms, but he complained of some pain in the elbows and shoulders. The temperature of the hands, taken at the same time as that in the axilla, was always a degree or a degree and a half lower than the axillary reading. The feet were broad and of large size, the toes being thick and clubbed, and the skin hyperæsthetic and red. The muscles of the feet were tender on pressure. This rendered walking or standing painful. There was, however, no tenderness of the muscles of the calves. There was an old scar on the dorsum of the right foot due to a burn. The knee-jerks were exaggerated, but there was no ankle clonus. The knees and legs were slightly tender. The tongue was not specially large; his teeth were few in number, which was, he explained, due to their having been knocked out in fights; what there were, were bad. Digestion was good. There was a good deal of constipation. The lungs and heart were normal. There was no evidence of enlargement of the thyroid or thymus glands. The abdomen was natural, and no enlarged glands could be felt in any part of the body. Vision was fairly good, though muscæ volitantes not infrequently troubled him. There was no hemianopsia. The fundi appeared to be normal. The specific gravity of the urine was 1,024; no sugar and no albumin. The

[1] Compare Hutchinson's *Archives of Clinical Surgery*, vol. ii. p. 30 *et seq.*, where cases of scleroderma showing alliance to Raynaud's disease are recorded.

pulse was 60, of normal tension. There was no arterial thickening. The patient was kept in bed protected from the cold, and given tabellæ trinitrini three times daily. Some rheumatic pains were treated with salicylate of soda, and as a result of warmth the subjective condition of his hands and feet very greatly improved. He left the hospital and went to a convalescent home.

REMARKS

This case has affinities with, and at the same time differs from, both Raynaud's disease and erythromelalgia. It resembles Raynaud's disease in being aggravated by cold, whereas erythromelalgia is made worse by heat and relieved by cold. It resembles erythromelalgia in the hypersensitiveness and redness of the skin of the extremities, while in Raynaud's disease the parts become pale and anæsthetic and analgesic, although they may be painful. The frost-bite four years before and the chilblain on the ear connect the case with Raynaud's disease. Prentiss,[1] in an elaborate discussion of two cases of erythromelalgia, says that of twenty-seven cases of that disease twenty-five were males, whereas four-fifths of the cases of Raynaud's disease were in females. The bulbous condition of the fingers and toes is worthy of note, and is not explained by any cardiac or pulmonary lesion. It may, perhaps, be regarded as the result of impaired nutrition due to peripheral circulatory disturbance of neurotic origin. There is certainly no reason to think it is due to the absorption of poisons from any other part of the body, as has been suggested, and is probably the case in Marie's hypertrophic pulmonary osteoarthropathy. The condition of clubbing of the fingers is not recognised either in Raynaud's disease or erythromelalgia; but it

[1] *Transactions of the Association of American Physicians*, vol. xii. p. 310, with bibliographical references.

is interesting to note that Dr. Wardrop Griffith,[1] in a paper on three cases illustrating some of the affinities of Raynaud's disease, noticed that in his first case the thumbs were slightly bulbous at the extremities. It seems reasonable to suppose that the muscular fatigue of which the patient complained was due to the narrowing of the muscular arterioles, and therefore somewhat analogous to intermittent claudication in horses. In this condition muscular inability and spasm result on exertion, and are found to depend on vascular occlusion. In the present case there was no mention of any muscular spasm, but from a consideration of Allan Burns's[2] original remarks and general physiological knowledge it does not appear necessary that muscular anæmia should cause anything beyond paresis.

It is possible that there was endarteritis obliterans of syphilitic origin in this case, and that this lesion was responsible for the manifestation. Batty Shaw[3] has found marked narrowing of the arteries in three cases of typical erythromelalgia, and concludes that when the disease occurs independently of the central nervous system, it is associated with but one morbid picture—viz. local vascular change.

[1] *Medical Chronicle*, vol. xx., 1891-92, p. 89.
[2] Quoted by Osler: *Angina Pectoris and Allied States*, p. 116, 1897.
[3] *Trans. Path. Soc.*, vol. liv. p. 175.

XII

A CASE OF RECKLINGHAUSEN'S DISEASE COMPLICATED WITH A SARCOMATOUS GROWTH INVOLVING THE BRACHIAL PLEXUS [1]

In Recklinghausen's disease there is a combination of multiple lesions affecting the integument and the nervous system. Though the association is sufficiently coherent to justify its being classed as a special disease, there is a considerable variation in the prominence of the individual symptoms and many cases have therefore to be regarded as incomplete.

The cardinal signs of this morbid entity which was first isolated by von Recklinghausen [2] are: 1. Tumours of the skin of the nature of molluscum fibrosum. 2. Subcutaneous tumours situated on the nerves, either plexiform or fibroneuromata; these are multiple and usually of small size, but one of them may reach a large size and require removal. They may occur on the peripheral nerves, on the larger nerve trunks, or close to the nerve roots, and on the cranial and sympathetic nerves. 3. Pigmentation of the skin; this occurs in two forms—as patches of considerable size and in small specks somewhat resembling freckles. When one of these three essential lesions is absent the disease has

[1] Reprinted, with permission, from *The Lancet*, July 29th, 1899.

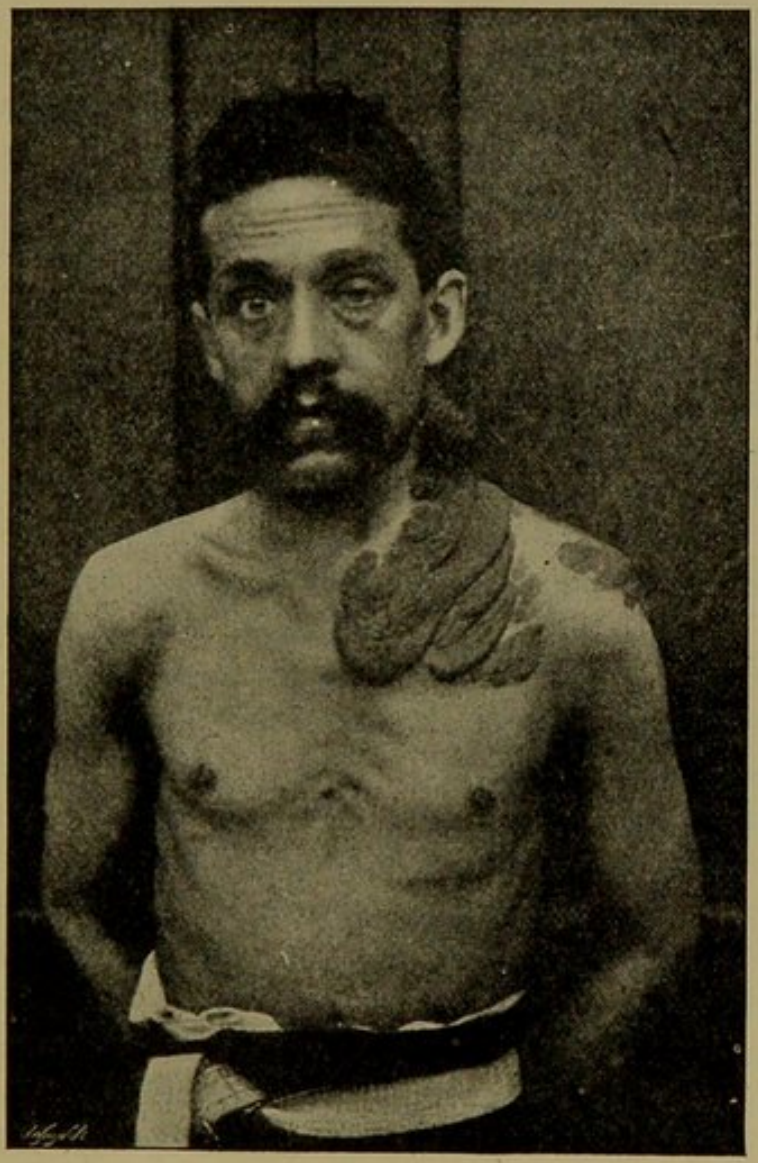
[2] *Die multiple Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen*, Festschrift, Berlin, 1882.

been spoken of as incomplete. In addition there are phenomena of secondary importance, such as pain, arthralgia, alteration of sensation, and impaired mental activity. After this brief *résumé* of the nature of Recklinghausen's disease or, as it has sometimes been called, generalised neurofibromatosis,[1] an account of a case recently under observation in St. George's Hospital which presented some interesting features will be given.

A man, aged 32 years, had had all his life a mass of molluscum fibrosum covering the back of the left side of the head and neck and upper part of the left front of the chest and left shoulder. This growth had not increased in size except in so far as it had developed equally with the rest of the patient's body. The skin of the body was generally brownish, but scattered all over the trunk, limbs, head, and neck there were areas where the pigmentation was concentrated, either into patches of considerable size, as large as a shilling or in a few instances larger, or in small discrete patches resembling freckles. Neither the hands nor the feet were pigmented. This peculiar pigmentation was not more marked on one side of the body than on the other except that the two largest areas were over the inferior spine of the right scapula and to the right of the base of the sacrum; the latter area measured two inches by two inches. In this respect it contrasted with the localisation of the cutaneous tumours which, as will be seen, chiefly affected the left side. There was more pigmentation on the back than on the front of the body and it seemed to me that the pigmentation had increased since he had been under observation. The patient himself was not aware of the pigmentation, so it is impossible to say how long it had existed or whether it was congenital. One of his children, a boy of about

[1] For an excellent clinical account of the disease see P. Marie's *Leçons de Clinique Médicale, Hôtel Dieu*, 1894-5, p. 242.

three years of age, whom I examined, had similar areas of pigmentation, but no tumours. Under the skin of the back on the left side of the body there were a number of smooth, firm subcutaneous tumours readily



Reproduction of photograph of patient with Recklinghausen's disease, showing the molluscum fibrosum and pseudo-ptosis on the left side.

movable under the skin. They were not tender, and ordinary pressure did not give rise to any pain in the course of the nerves of the back. They appeared to be multiple fibroneuromata on the intercostal nerves.

Some of them were somewhat elongated. There were a few similar subcutaneous tumours under the skin on the right side of the abdomen in front, and a larger single tumour of the size of a florin on the inner side of the right groin. There was no correspondence between the distribution of these tumours and the pigmentation of the skin. The patient was perfectly intelligent and showed no sign of any mental deficiency. There had been no diarrhœa, a symptom which had been present in some of the recorded cases. So far the case presented the association of the three pathological conditions which go to make up the morbid entity of Recklinghausen's disease, but the molluscum fibrosum and the pigmentation were much better marked than the multiple subcutaneous fibroneuromata.

To pass now to the unusual features presented by this case. The patient had had an exostosis on the front of the sternum towards the left border at the junction of the second rib cartilage all his life. In September 1898 he noticed drooping of the left upper eyelid and about the same time his voice altered and became hoarse, and he was under treatment at a special hospital. In December numbness and swelling of the left hand with loss of power developed. When he came under my care in April 1899 he was found to have a hard tumour, growing apparently from the left side of the vertebral column at about the base of the first dorsal or last cervical vertebra. This tumour lay underneath the molluscous growth in the left supraclavicular fossa. Skiagrams which were kindly taken by Mr. Addyman did not throw any light on the nature of the deeply seated growth in the neck, probably because any shadow due to the growth was obscured by that of the spinal column. It appeared to be the cause of the following pressure symptoms:—1. Complete ulnar nerve paralysis. 2. Pain in the course of the ulnar nerve. 3. Transient swelling of the left hand, together with

a red mottled aspect of the skin. 4. Slight diminution in the size of the pulse in the left radial. 5. Paralysis of part of the left sympathetic chain giving rise: (*a*) To loss of power of dilating the pupil. The left pupil was small, contracted slightly on exposure to light, and though it could be dilated by atropine did not dilate when darkened. The patient was perfectly well able to accommodate with that eye for reading. (*b*) To pseudo-ptosis; the left upper eyelid could be raised by the levator palpebræ, but as seen in the accompanying illustration which is reproduced from a photograph (for which I am greatly indebted to Mr. H. G. Drake Brockman) it is relaxed and suggests ordinary ptosis. This relaxation of the upper eyelid can be explained as the result of paralysis of the involuntary muscular fibres in the upper eyelid. This physical sign is therefore the exact opposite of Stellwag's sign, or retraction of the upper eyelid as seen in Graves's disease. There was no dilatation of the vessels on the left side of the face, alteration of perspiration or increased growth of hair. The local vasomotor mechanism had therefore compensated for the paralysing effects of pressure on the main trunk. 6. The rapid pulse rate, which was constantly 128. It has been suggested that the frequent febrile pulse rate of 120 is due to the inhibitory action of the vagus being removed. It seemed reasonable to believe that the cardiac branches of the left vagus were so compressed by the tumour as to bring about a similar result. At the post-mortem examination there were numerous neuromata on the right vagus, so it was unnecessary to suppose that all the cardio-inhibitory fibres ran in the left vagus. 7. Alteration of voice and brassy aneurysmal cough. My colleague, Mr. Sheild, reported that there was paresis, not paralysis, of the left vocal cord, but added that he regarded this as being more probably due to pressure on the trachea or bronchi than to involvement of the

recurrent laryngeal nerve. 8. Pressure on the left bronchus as shown by stridor over the left lung.

The patient's right ear presented a scarred appearance resembling that seen after Raynaud's disease, which was due to a chilblain some few winters back. The second and third ribs on the left side of the chest in front were unduly movable and displaceable, as if some absorption of their substance had taken place near their junction with the sternum.

PROGRESS AND TERMINATION OF THE CASE

The growth in the neck steadily increased in size and threatened to obstruct the inlet to the thorax on the left side. The patient got thinner and progressively shorter of breath. The tumour was at first thought to be a cervical rib or exostosis, but the possibility of its being a neuroma of the brachial plexus or a sarcoma was raised, and became more probable as the growth developed. The question of surgical interference and removal of the growth was considered by my colleague, Mr. G. R. Turner, but it was thought that the great difficulties of removing a growth in that situation and the special difficulty of operating on the part, inasmuch as it was covered by molluscous growth, which would not only render asepsis difficult, but probably give rise to very free hæmorrhage, rendered any attempt at removal inadvisable.

On July 2nd and 3rd the patient had several severe attacks of dyspnœa which threatened his life. Mr. G. R. Turner was asked to see the patient in consultation and kindly consented to perform an exploratory operation with a view of, if possible, relieving the pressure symptoms. At the operation a growth was found displacing the trachea towards the right, and having such widespread connections that any attempt at complete removal was out of the question. A little of

the growth was removed, and was found to have the structure of a spindle-celled sarcoma. Tracheotomy was performed, and a stiff rubber tube was introduced. The man was somewhat relieved, but on July 6th his temperature went up to 102° F., his pulse became very rapid (180), and he died on July 7th, at 2 a.m., from collapse.

A necropsy was very carefully performed by Dr. W. S. Lazarus-Barlow. The body was found to be thin and showed little subcutaneous fat. Small subcutaneous tumours were removed from the left side of the back and from the right side of the abdomen anteriorly. Some, but not all of them, were seen to be on small nerve filaments. They were firm, and of a greyish translucent colour, somewhat resembling boiled sago grains. Microscopically, they were found to be fibro-neuromata, with a certain amount of myxomatous tissue. The tumour in the right groin was found to be merely fat. The tumour in the neck was systematically dissected. It was a diffuse white growth varying in consistency, in places firm, especially near the brachial plexus, while the more outlying parts of the growth were soft. It involved the inner and, to a lesser extent, the other cords of the brachial plexus. The growth spread down into the thorax, occupying the superior mediastinum on the left side. Microscopically, the growth was a spindle-celled sarcoma, with a fair amount of fibrous tissue. It obliterated the left internal jugular vein at its opening into the innominate vein, displacing and compressing the trachea, surrounding the left bronchus, invading the left lung, and destroying the left vagus and its recurrent and cardiac branches. The thoracic duct was involved at its termination and its trunk was dilated, but there were no chylous effusions anywhere. There was recent antemortem thrombosis in both innominate veins. The left phrenic nerve was involved. The posterior wall of the trachea was

adherent to the growth, and there was recent ulceration on the lateral walls of the trachea some three inches below the tracheotomy wound. This may have been due to the pressure of the tube which was in the trachea for three and a half days. The anterior wall of the œsophagus in its middle third was raised up into a prominence by a separate outlying mass of soft growth; this, it would have seemed, must have caused dysphagia, but the patient had been able to take his food without any difficulty until tracheotomy was performed. There were a number of enlarged glands in the immediate neighbourhood of the main tumour. The growth extended down in front of, and behind, the arch of the aorta on the left side, surrounded the left common carotid artery, and was closely adherent to the bodies of the fifth, sixth, and seventh cervical vertebræ which were eroded. The cervical sympathetic was extensively destroyed in this situation.

The roots of the brachial plexus were enlarged, more especially the eighth cervical and first dorsal. These two roots were united into a firm mass of growth, which was examined microscopically, and found to be composed of nerve bundles embedded in, and separated from each other by, fibrous tissue; in parts there was spindle-celled growth. These appearances suggested that a fibroneuroma had undergone sarcomatous change. Sections of the thickened trunks of the plexus at a little distance from this mass of growth showed that they were infiltrated with a spindle-celled sarcomatous growth. The affected nerve roots inside the theca vertebralis were also enlarged, but in other parts of the cord the nerve roots were normal. No neuromata were found on the cauda equina or on any of the cranial nerves inside the skull. The spinal cord and the brain were normal. The right vagus was not involved in the growth, but showed a number of neuromata in its course, and presented a moniliform

outline. The left vagus also showed neuromatous enlargement, and ran into the thoracic extension of the growth over the arch of the aorta.

Where the growth started it is not easy to say with absolute certainty; it involved the brachial plexus, and very probably started in connection with a fibro-neuroma on the roots of the eighth cervical and first dorsal nerves, close to their exit from the spinal column. From the microscopic appearances in this case, and from the occurrence in other examples of Recklinghausen's disease of large neuromata on the brachial plexus, which may become sarcomatous, I am inclined to believe that the sarcomatous growth in this case was a malignant neuroma. Though careful dissection of the parts after removal from the body did not positively establish this view no other manifest origin was found. So although the growth might have begun in the surrounding connective tissues, and spread to the brachial plexus, it seems more reasonable to believe that the growth originated in connection with the brachial plexus and then spread to the neighbouring parts.

The exostosis felt during life at the junction of the second left costal cartilage with the sternum was found not to be a true exostosis, but to be due to a forward projection of that chondro-sternal articulation. The second and third costal cartilages on the left side were intact though rather slender. The sternum was pushed forward by the intra-thoracic growth. The left lung was adherent to the intra-thoracic prolongation of the growth which surrounded its root, and was invaded at one place by an outlying process of growth. The left bronchus was much narrowed. Both the lungs showed bronchitis. The heart (nine ounces) was normal. The abdominal organs were normal with the exception of some pigmentation of Peyer's patches in the ileum, and of the solitary follicles in the colon. The adrenal bodies were quite healthy. On the abdominal sym-

pathetic around the aorta there were a number of neuromata, but none was seen on the intestines or on the stomach. Dr. Lazarus-Barlow examined microscopic sections of these neuromata on the sympathetic, and found that, like those on the spinal nerves, they were pseudo-neuromata.

REMARKS

It has been suggested by Feindel[1] that Recklinghausen's disease is the outcome of a congenital malformation of the ectoderm. This hypothesis has quite recently been supported by Feindel and Oppenheim.[2] The more probable theory seems to me to be that put forward 12 years ago by Dr. Payne[3]—viz. that the disease is due to a developmental vice on the part of the mesoblast in the corium and in the nerves. This accounts for the fibroneuromata and the molluscous growths, while the pigmentation of the skin is allied to the common pigmented moles that occasionally develop into malignant melanotic growths. Recklinghausen's disease, therefore, may be regarded as depending on a congenital hyperplasia and tumour formation arising in the mesoblast at its junction with the epiblast—viz. in the skin and nerves. In this case it appears probable that as a result of progressive changes taking place the growth in the neck, at first an innocent neuroma, eventually became a sarcoma. This late development of sarcoma on congenital defects is, of course, well known to occur in pigmented moles of the skin. It also occurs in another defect of the mesoblast—viz. in multiple exostoses. An interesting example of this occurred in 1890 under the care of Mr. Warrington

[1] *Thèse, Paris*, No. 104, 1896.

[2] *Archives Générales de Médecine*, July, 1898, p. 77 ; *Sur les Formes Incomplètes de la Neuro-fibromatose.*

[3] *Transactions of the Pathological Society of London*, vol. xxxviii. p. 69.

Haward, who kindly allows me to refer to his case. A man, aged 33 years, had had exostoses all his life; one of them had pressed on the sciatic nerve, and had given rise to pain for five years; the exostosis was therefore removed, but a spindle-celled sarcoma developed on its site, and eventually proved fatal. The patient and his son, aged seven years, also with exostoses, were shown at the Clinical Society of London by the late Mr. C. E. Cotes, on October 24th, 1890.[1]

Sarcomatous change in neuromata also occurs. Goldmann,[2] in his monograph, gives a careful description of a malignant neuroma in a woman, aged 54 years, the subject of multiple neuromata, and Bowlby[3] quotes examples of multiple neuromata associated with sarcomatous change. It is probable that many cases described as multiple neuromata show in addition some degree of molluscous growth and pigmentation, but that the more important clinical feature being connected with the neuromata the other changes attract little or no attention. In the present case the molluscous growth was a very striking feature, and at first sight threw into the shade the small subcutaneous tumours and the pigmentation of the skin.

Other points of interest in the case are: 1. That the brunt of the tumour growth fell on the left side of the body, as shown by the molluscum fibrosum, the fibroneuromata, and the tumour in the neck, while the pigmentation was bilateral. 2. The curious condition of pseudo-ptosis due to paralysis not of the levator palpebræ, but of the unstriated muscular fibres in the upper eyelid, a condition which is the exact converse of Stellwag's symptom in exophthalmic goitre.

[1] *Transactions of the Clinical Society of London*, vol. xxiv. p. 228.

[2] *Beitrage zur klinischen Chirurgie*, Band x. Heft i., redegiert von P. Bruns, 1892.

[3] *Injuries and Diseases of Nerves*, 1889, p. 496.

XIII

PROGRESSIVE MYOSITIS OSSIFICANS, WITH REMARKS ON OTHER DEVELOPMENTAL DISEASES OF THE MESOBLAST [1]

Generally in a clinical lecture a case of ordinary occurrence—one which is of practical every-day use—is taken as the text. Though to-day our subject is a rarity, I shall attempt to show that, not only is it of interest, but that its consideration is of use, as bearing upon and enlarging our conception of some other diseases which attack the mesoblast. The last phrase I shall fully explain later. The case of progressive myositis ossificans probably many of you have already seen in the wards. The patient, a boy aged eight, was kindly sent to me by Dr. J. W. Carr, of the Royal Free Hospital, who showed him before the Clinical Society (*The British Medical Journal*, November 3rd, 1900). This boy is one of eight children. There is no history of any similar abnormality in his family. His father recently died of carcinoma—a point of possible interest as bearing on the development of this condition of myositis ossificans. There is no history of rheumatism in the family; also a point of importance, because, as I shall tell you later, myositis ossificans has been thought to be connected with rheumatism.

[1] A Clinical Lecture delivered at St. George's Hospital, November 26th, 1900. Reprinted, by permission, from *The Clinical Journal*, January 23rd, 1901.

The first thing noticeable about the patient is his peculiar attitude—flexion of the neck and upper part of the trunk, with fixation of the neck depending on ossification of the cervical muscles, a condition which is also very well shown in one of these pictures of another case under the care of Dr. Crawfurd (*Trans. Clin. Soc.*, vol. xxxii. p. 261). The body is bent forwards like that of an old man, while the shoulders and elbows are fixed, so that the body looks as if he were carrying some invisible, though not inconsiderable, weight. The chest hardly moves at all with respiration, which is, therefore, diaphragmatic. There are ossifications in the two sterno-mastoid, complexi, and posterior scalene muscles, and in the scapular attachments of the rhomboid muscles. There are bony plates in the lower parts of the latissimus dorsi muscles close to their spinal attachment, while the same muscles in the posterior folds of both the axillæ are so hard as to feel like a knife-edge. Over the lumbar spine, in the region of the erectores spinæ, there are hard masses. The trapezii muscles are also affected. A marked feature is the comparative fixation of the upper extremities. The pectoral and latissimus dorsi muscles in the anterior and posterior folds of both axillæ are markedly ossified; they feel almost like the blade of a knife under the skin in the folds of the axillæ. In both arms the biceps and brachialis anticus muscles are extensively ossified; this, no doubt, adds to the fixation of the shoulders and elbow-joints. The pulse is small, probably from pressure on the brachial artery. The triceps and the muscles of the forearms are unaffected. The recti abdominis muscles are both affected, but none of the muscles in the lower extremities are involved. The change, therefore, chiefly affects the upper part of the trunk and the neck. There is a peculiar alteration in the thumbs and great toes; they are much shorter than they should be. The great toes

do not reach up to the level of the second toes. This condition of microdactylie is very characteristic of the disease, and occurs in 75 per cent. of the cases. It, however, varies considerably in detail, and is not the same in the thumbs and in the great toes. In this case there is no ankylosis of the phalanges of the thumbs, such as has been described in some other cases, and the phalanges are fairly normal; the shortening seems to depend largely on dwarfing of the metacarpal bone. The left great toe is smaller than the right; there is commencing ankylosis between the two phalanges; slight movement is possible, and conveys a sensation of crepitus. The skiagram, kindly taken by Mr. F. T. Addyman, shows that there is no bony continuity between the two phalanges. The right great toe shows ankylosis of the interphalangeal joint. Both the great toes are directed outwards, so that there is partial dislocation of the metatarso-phalangeal articulation. The terminal phalanges of the little toes feel as if they were tending to ankylosis, though the skiagrams do not support this. It may be mentioned that ankylosis in this situation is not very infrequently seen in otherwise normal persons. The dwarfing of the thumbs and great toes would appear to be a congenital deficiency, and is of interest as indicating that some inherent vice of development underlies progressive myositis ossificans. Ankylosis is probably a secondary and progressive change, like the ossification in the muscles and the eruption of exostoses. Before the days of the X rays the condition resulting from ankylosis of the phalanges of the great toes was described as absence of one phalanx.

A very curious point about our patient is this exostosis on the head of the first phalanx of the right middle finger. It is a remarkable fact that in Dr. Herringham's case (*Clinical Society's Trans.*, vol. xxxii. p. 1) there was exactly the same peculiarity. On both

tibiæ, close to the attachments of the sartorius muscles, there are exostoses; the one on the left side is the more prominent; they are both enlarging. There is a considerable thickening of the bridge of the nose, involving the nasal bones, which has struck me as being a little like the condition figured and described by Professor Macalister in his paper ("Royal Irish Academy," December 11th, 1882), which I pass round, on the horned men in West Africa. In Sir P. Manson's book on tropical diseases, where you will see an illustration of this same condition under the name of Goundou or Anakre, it is stated that it has been thought to be due to a parasite setting up an inflammation of the bones; while by others it has been regarded as the result of periostitis due to yaws, or—and of this there is no proof—as atavism, or reversion to a lower type.

The head is elongated or dolichocephalic. The eyelids are somewhat pigmented. The thyroid gland cannot be felt. There are exostoses asymetrically placed on the frontal bones, and marked bony ridges and projections, apparently exaggerations of those normally seen, on the occipital bone.

So much for the boy himself. We will now consider the general outlines of the disease myositis ossificans. It is divided into two forms:—(1) Local, which is not progressive, and is dependent on inflammation, such as may be started by phlebitis and thrombosis, or by inflammation of a gland, spreading into the adjacent muscles. The inflammatory exudation undergoes calcification, as it often does in other parts of the body, for example, in the capsule of an old hydatid cyst, in tuberculous glands, or, to take an example in the muscles, the calcification which takes place in connection with trichina spiralis. The local form of myositis ossificans is of little or no clinical interest. (2) Myositis ossificans progressiva, which concerns us to-day. This extremely striking disease has been known for a long

time. The first case seems to have been recorded in 1740 by Freke, in the "Philosophical Transactions of the Royal Society." For a full account of this disease I may refer you to a recent exhaustive paper by an American physician, Dr. Lydia M. De Witt,[1] based on seventy-eight cases. Such a remarkable condition has naturally attracted a good deal of attention, and sometimes the same case has been described by two different observers. It is a disease which is not hereditary; I believe there is only one recorded case in which parent and child have suffered from the same disease. It generally, however, comes on early in life, and progressively gets worse. It attacks the male sex by preference in the proportion of five males to one female. It is spoken of as being a congenital disease, meaning that it depends on some congenital aberration of growth; but children are not born with it, although the disease depends on some congenital deficiency. It may start after some definite exciting cause, such as an injury. An accident which would not be sufficient in ordinary people to give rise to the bony formation sets up this condition in these children. It has been supposed to be sometimes started by rickets; this seems reasonable, as the affected bones and the attached muscles are so close to each other.

Now a few words about the course of the disease. I have already said that it gets progressively worse. From time to time painful areas of induration appear in the muscles, due not to ossification or to calcification, but to inflammation. These thickenings of the muscles are very much like those described in rheumatic myositis. At the same time the local temperature may be found to be raised, and the skin may be reddened and possibly œdematous, so that there is definite evidence of inflammation. After an attack the area becomes calcified, and

[1] *The American Journal of the Medical Sciences*, September, 1900, vol. cxx. p. 294.

eventually changes into bone. As time goes on more and more muscles become affected, and in greater degree, and of course become useless. It is often associated with exostoses, as in this boy.

With regard to the morbid anatomy of the disease three stages are described. In the first stage there is a definite inflammation taking place in the muscle, between the muscular fibres. It seems to be a fairly acute interstitial myositis. In the second stage organisation has taken place, and there is very considerable fibrosis—an increase in the amount of fibrous tissue—with atrophy and degenerative changes in the muscular fibres. In the third stage this fibrous tissue has become changed into bone. The muscular fibres are only affected secondarily. They are healthy, except where they are invaded and compressed by the interstitial tissue, so that primarily it is an interstitial inflammatory process. As the disease progresses more and more muscles become affected, and the corresponding joints fixed. You will have noticed that the breathing in this boy is almost entirely diaphragmatic; his thorax hardly moves at all. You will readily understand, therefore, that one of the dangers in a case of this kind is that the patient is very likely to die if he gets bronchitis or pneumonia. In other cases, probably as a result of traumatism, these hard masses in the muscles undergo suppuration, and as the result of continued suppuration the patient becomes worn out and dies of weakness. In other cases bed sores may come on. This boy, in fact, shows healed bedsores on the great trochanters of the femora.

DIAGNOSIS

The disease is so marked that perhaps it is hardly necessary to say very much about the differential diagnosis of it from other diseases. Still, there are some conditions for which it may possibly be mistaken.

One of these is multiple exostoses. This developmental aberration, which may be hereditary, may also extend into the muscles. Here is a specimen showing a very marked rider's bone, from a man under Mr. Haward about ten years ago, who had multiple exostoses; one of the exostoses underwent sarcomatous change, and led to his death. He had a son seven years of age, who was also covered with multiple exostoses. When multiple exostoses spread into the muscles by their periosteal attachments, the condition approaches that seen in myositis ossificans.

Another condition is osteitis deformans. Here is a skull exhibiting this change. Probably most of you have seen the entire skeleton of osteitis deformans recently put up in the museum. This change comes on later in life, and only attacks the bones, not the muscles.

There is also tabetic arthropathy, or Charcot's disease of the joints in locomotor ataxia. This acute degenerative change in the joints often leads to very extensive ossification taking place in the neighbouring muscles. Here is a rectus femoris muscle, eight inches long, which forms a rigid spike, and looks exactly like bone. Of course there should be no difficulty in distinguishing the two; in myositis ossificans the joints are not themselves absolutely affected, whereas the morbid change in Charcot's disease begins and has all its chief clinical manifestations there.

There is a rare condition, rhizomelic spondylosis (Marie), in which the vertebræ are ankylosed, and the extremities become ankylosed to the trunk at the shoulder and hip. In fixation of the spine and shoulder-joints myositis ossificans may resemble this rare form of disease, which probably belongs to the overgrown group of diseases classed under the term of rheumatoid arthritis. But there is no myositis ossificans in rhizomelic spondylosis.

TREATMENT

With regard to the treatment of myositis ossificans, iodide of potassium, arsenic, and various other drugs have been tried, but nothing has been found to have any real effect on the course of the disease. Thyroid extract is being tried on this boy, and for the reason that the thyroid gland seems to have a special association with connective tissue, or with the mesoblast. In cases of myxœdema there is an overgrowth of the connective tissue. In very rare cases of atrophy and calcification of the thyroid gland, multiple painful fatty tumours appear over the body; this form of myxœdema is spoken of as adiposis dolorosa, or Dercum's disease; here is a picture of a woman with this rare affection exhibited by Sir H. Beevor (Clinical Society's *Transactions*, vol. xxxiii. p. 251). Its treatment is that of myxœdema—viz. thyroid extract. Thyroid medication also produces improvement in congenital myxœdema or cretinism, where fatty lumps are present in the supra-clavicular fossæ. Though, perhaps a forlorn hope, it seems reasonable to give thyroid extract, and watch the effect in lesions due to some inherent aberration of the mesoblast. As I pointed out, this boy's thyroid is extremely small. [This treatment did not appear to lead to any improvement, or check the progressive character of the disease, December 23rd, 1900.] The occurrence of attacks of myositis should, as far as possible, be guarded against by protecting the patient against cold and traumatism. Possibly salicylates might prove of use in warding off rheumatic myositis.

PATHOGENY

Perhaps the chief interest in a rare disease like this is connected with the explanation which can be given of the condition. It is generally admitted that its

pathology is unknown, or, at any rate, not satisfactorily explained. Several theories have naturally been put forward to account for it. It has been thought that this ossification in the muscles is purely a new growth, very much the same kind of change as multiple exostoses, taking place in the muscles instead of in the skeleton. Now against this view is the fact that the microscopical appearances seem to show that the process is primarily and essentially an inflammation. Virchow considered that it was on the borderland between an inflammation and a new growth. It has been thought to be a developmental abnormality. Another view is that this change in the muscles is analogous to the change which takes place in some of the primary diseases of muscles, or the myopathies, and that it is analogous to pseudo-hypertrophic paralysis, in which there is an increase in the amount of fibrous tissue and fat in the muscles, but that the process goes further than that, and that there is an ossification on the top of the fibrosis. Another view, put forward by Stonham, is that it is a rheumatic condition, allied to muscular rheumatism and rheumatoid arthritis, bony formations occurring in the muscles instead of around the joints. It may possibly be allied to that condition, but it evidently is not rheumatoid arthritis, since the joints are either not affected at all, or not in the same way as in osteoarthritis.

A rather vague suggestion has been put forward that it is a reversion to a lower type, and due to atavistic influences. There do not appear to be any convincing arguments in favour of this hypothesis.

A reasonable view as to the nature of myositis ossificans is as follows:—The microscopic appearance would tend to show that it is primarily an inflammation. Myositis, such as is seen in connection with rheumatism or other infections, does not go on to calcification and ossification; but in Charcot's disease, where presumably

the nutrition of the muscles near the joint is altered, extensive ossification may occur; while in myositis due to the trichina spiralis calcification of the capsules of the parasites may be met with. In myositis ossificans progressiva there appears to be a marked tendency both to myositis and to subsequent calcification. The muscles, as in the myopathies, seem to be endowed with specially feeble powers of resistance. There would appear to be a disposing factor of congenital origin; further evidence in favour of this is seen in the presence of microdactylie and of exostoses. As bearing on this, I may quote a case recorded by Mr. Willmott Evans (*Transactions Clinical Society*, vol. xxxii. p. 280), of a man, aged fifty-four, with malformed fingers and congenital constriction of the right thigh, who developed a hard calcareous mass in the left tendo Achillis some years after injuries. In short, *myositis ossificans depends on* (a) *a congenital weakness or want of resistance, and* (b) *a tendency to aberrant growth on the part of the mesoblast; as the result of diminished resistance the muscles are more susceptible to inflammation, while the tendency to aberrant growth subsequently shows itself in the calcification and ossification of the inflammatory products.*

DEVELOPMENTAL DISEASES OF THE MESOBLAST

I will now say a few words about the developmental diseases of the mesoblast. It is a noticeable fact that the mesoblast is very much more prone to irregularities of growth than either the superficial skin layer (epiblast) or the lining of the alimentary canal (hypoblast). Like other innocent tumours, those of the mesoblast tend to be multiple. There are a number of diseases which seem to depend on some congenital aberration of development and growth in the mesoblast. In this connection it will be convenient to divide the mesoblast into the following layers:—

1. Tegmentary layer—
   (*a*) Superficial. Junction of epiblast and mesoblast. Affected by molluscum fibrosum, and by generalised neuro-fibromatosis.
   (*b*) Deep. Affected by multiple fatty tumours.
2. Skeletal layer—
   (*a*) Muscular layer. Affected by myositis ossificans and by myopathies.
   (*b*) Bony layer. Affected in multiple exostoses and enchondromata.

1. The tegmentary layer of the mesoblast, meaning by that the true skin or dermis, and the subcutaneous tissues, may be divided into—

(*a*) The more superficial part. Where the mesoblast joins the epiblast there seems to be a considerable tendency to irregularity of growth; for example, multiple molluscum fibrosum, and tumours situated on, and derived from, the fibrous sheaths of the nerves. In connection with these fibroneuromata or pseudo-neuromata, you will remember that the nerves come partly (sheath) from the mesoblast and partly (nerve-fibres) from the epiblast. In generalised neurofibromatosis, or v. Recklinghausen's disease, there are a collection of mesoblastic lesions—viz. multiple tumours of the nerves—formed of fibrous tissue, and due to some irregularity of growth taking place where the mesoblast joins the epiblast, pigmentation of the skin, and the development of multiple tumours (molluscum fibrosum) arising from the superficial part of the dermis.

(*b*) The deeper part of the tegmentary layer of the mesoblast may give rise to multiple fatty tumours.

2. The deeper and skeletal layer of the mesoblast may again be divided into two—(*a*) the muscular layer and (*b*) the bony layer.

(*a*) Aberration in development and growth of the muscular layer may be thought to give rise to pseudo-

hypertrophic paralysis, where the really atrophied muscles are increased in size from the addition of fibrous tissue and fat, and also to be responsible for the evolution of other myopathies and myositis ossificans.

(*b*) Diseases of the bony layer, such as multiple exostoses and enchondromata, I have mentioned already.

In these examples the aberrations of growth are limited respectively to different parts of the mesoblast, but the aberrations may be much more extensive and widespread, and produce great deformity. Fortunately this is rare. Here is a picture of "the elephant man" who was in the London Hospital under Mr. Treves (*Trans. Path. Soc.*, vol. xxxvi. p. 494, plate xx.). He had masses of pendulous skin, evidently containing much of the subcutaneous connective tissues, and extensive bony growths. He therefore had overgrowth of the greater part of the mesoblast. Myositis ossificans, when combined with multiple exostoses, is an example of developmental aberration attacking the whole of the skeleton layer of the mesoblast.

XIV

A CASE OF ACUTE MULTIPLE NON-RHEUMATIC SYNOVITIS[1]

A MAN, æt. 30 years, who had been ill since December 17th with a sore throat, got very wet a few days after Christmas, and was seized with acute pains in the limbs on December 31st. He was then treated with salicylates for the joint pain, and with morphia for sleeplessness, but without any benefit. On January 6th his nose bled, and he lost, according to his own estimation, as much as four pints.

On admission to the hospital on January 6th, he was anæmic, with dry, hot skin, slightly yellow, suggesting sepsis, but with no icteric tinge of the conjunctiva. His knees and wrists were hot, painful, and swollen, the outline of the synovial membranes being well shown, but there was no redness of the skin over the affected joints. His heart was normal in every way, and it may be said at once that it remained so during the whole of his illness.

His dry skin did not suggest acute rheumatism, and his general appearance was rather that of a septic process. The most probable cause of a septic arthritis, as being perhaps the commonest, seemed to be gonorrhœa; but he had no urethral discharge, and was quite clear that he never had had. With the exception of

[1] A Clinical Lecture delivered at St. George's Hospital, London, on February 13th, 1899, and reprinted with additions, by permission, from *The Clinical Journal* of March 1st, 1899.

tonsilitis, to which he had always been subject, he had been remarkably free from illnesses of any kind. He had never had rheumatism, pneumonia, or syphilis.

On admission it was thought well, in spite of the fact that his illness did not closely resemble acute rheumatism, to try him with a combined treatment of salicylate of soda ten grains every four hours, and salicin ten grains three times a day. I was inclined to do this because quite a short time before an anæmic girl was admitted under my care with a dry hot skin, dry tongue, and joint pains; although from her aspect and dry skin I suspected septic and not rheumatic disease, no definite evidence of the former condition was forthcoming, and she was accordingly given the chance of reacting to salicylates, and did so in a very satisfactory manner. It therefore seems well to adopt this course in a case where, though suspected, septic infection cannot be definitely established. In this man, however, salicylate treatment gave no relief, and did not affect the temperature in the least. From January 7th to January 14th his temperature was between 102° and 100°, for the following week 100° to 101°, and came down by degrees to normal about January 26th.

On January 13th the salicylate was cut off, and quinine substituted; after twelve days of this, just as his temperature was becoming normal, he was put on iodide of potassium and liquor hydrargyri perchloridi. But it cannot be said that any treatment by the mouth relieved him, or made any appreciable difference to his condition.

When salicylates completely failed to modify his condition, it seemed probable that he might be affected by some septic process; though that it must be of a comparatively mild nature was manifest, since no suppuration had occurred. Accordingly Dr. Slater kindly examined the blood, but reported that the cultures only showed a staphylococcus almost certainly derived from

the skin. There was therefore no proof of any bacterial blood infection.

After he had been nine days in the hospital his hips became affected, and there was visible and very considerable distension of the synovial membrane in the groins. Some small lymphatic glands were felt in the groins and in the axillæ, but they were not definitely enlarged, and it may here be mentioned that the spleen was never felt to be enlarged. At this time he had pain on breathing on the right side of his chest, but no friction rub could be heard; this pleurodynia readily yielded to poulticing. The constant application of an ice bag to his hip-joints, and afterwards to his hands and wrists, gave him marked relief. The pain and swelling migrated after this to his elbows, but only for a few days. A recurrence of right pleurodynia later on was relieved entirely by dry-cupping. After his temperature had been normal for some days, he was got up a little, as I was anxious to get him into the fresh air as soon as possible; but this was apparently premature, for a return of pain in the left ankle followed. This again was removed by rest in bed and the local application of lead lotion. After this he went on well, eating and drinking well, and could move his joints perfectly well and without any stiffness or limitation. He was naturally very weak and pulled down by his illness, which had lasted over four weeks; his weight before was 11 st., and afterwards 8 st. 2 lb.

To summarise, the most remarkable points about the case were—

(1) The occurrence of multiple painful swellings of the joints, accompanied by fever, but with little perspiration, no cardiac lesions, and not reacting to salicylates.

(2) The absence of any evidence of adhesions in the affected joints—a sign that the inflammation had after all not been very severe.

(3) The ease with which local applications, such as the ice-bag, acted upon the affected joints and gave relief.

As to the nature of the joint affection in this case there was an inflammatory reaction in the joints, which might be called an arthritis. As shown by the readiness with which the articular inflammation and pain yielded to local treatment, and by the fact that no adhesions were left behind, the inflammatory changes in the joints did not progress further than leading to a considerable effusion; the ligaments, cartilages, and bones showed no evidence of having suffered, and the only tissue that with certainty can be said to have been inflamed is the synovial membrane. There was, therefore, an acute multiple synovitis. It is better to reserve the terms arthritis and osteo-arthritis for more severe inflammatory affections of joints that spread to the ligaments, cartilages, and bones.

The cause of this wide-spread and acute synovitis is an interesting subject for discussion, but it must be admitted that it is easier to say what it was not than to say definitely what it actually was.

It was not the synovitis of acute rheumatism, as has been already seen, inasmuch as salicylic treatment had no effect. The late Dr. James Andrew, Physician to St. Bartholomew's Hospital, used to describe as acute osteo-arthritis, cases resembling acute rheumatism generally, but differing from it, just as this man did, in not reacting to salicylates, in not having any cardiac complications, and in not perspiring so freely.

It was not pyæmic in the ordinary sense of the word, since there was no suppuration, and the cultures from the blood did not prove that there was any septicæmia.

There is a large class of infective affections of joints; their number is increasing year by year with our knowledge, and to it are being added cases which were formerly considered as belonging to the vague class of rheumatic affections, whether acute, subacute, or

chronic. We may divide infective joint affections, at any rate theoretically, into two groups: (1) that in which a micro-organism settles down in the joint, multiplies there, and by producing a poison sets up inflammatory changes—to cases of this kind the term septic is applicable; and (2) that in which micro-organisms elsewhere in the body manufacture a toxin. This poison is carried by the circulation to the joints, which, presumably being especially susceptible, become acutely inflamed; to cases of this kind the term toxic may be applied.

As examples of *septic arthritis* secondary to a primary infection elsewhere in the body, there is the familiar urethral or gonorrhœal arthritis, in which gonococci or other microbes are carried by the blood from the original site of infection to the joints, and there multiply. It is somewhat doubtful how many or what proportion of joint affections secondary to urethritis should be regarded as gonorrhœa of the joints, for the gonococcus is not always found in the joints, and often there appears to be a mixed infection, other micro-organisms having gained an entrance through the inflamed mucous membrane of the urethra into the circulation. But at any rate it is a good example of microbic arthritis; there are different degrees of intensity in urethral arthritis in different cases, and possibly it may be found that these are correlated with differences in the species of the micro-organisms found in the joints.

Gonorrhœal inflammation elsewhere than in the urethra is comparatively infrequent, but primary gonorrhœal conjunctivitis is known, especially in children, to be occasionally followed by joint manifestations exactly like those just mentioned. Mr. R. C. Lucas has collected twenty-three cases of arthritis in infants secondary to gonorrhœal ophthalmia.[1]

[1] Lucas, *Lancet*, 1899, vol. i. p. 230.

In cerebro-spinal meningitis the characteristic micro-organism, the diplococcus intra-cellularis, may give rise to arthritis, and be found in the joints (Osler).[1] Transference of the typhoid and pneumonia micro-organisms to the joints is also well established, though rarely seen in ordinary hospital practice.

Now with regard to the second group of infective joint affections which were spoken of as *toxic*; here there is microbic activity in some other part of the body, and it may reasonably be supposed that a poison produced by these micro-organisms passes into the blood, and is carried to the joints, while the micro-organisms themselves remain *in loco*, and do not pass into the blood. Before going into the sequence of events any further, it may be well to remember that besides gouty arthritis—where there is undoubtedly a poison, uric acid, responsible for the change—an excellent example of a purely toxic synovitis is to be found in the swollen and painful joints sometimes seen after the injection of diphtheria antitoxic serum. In this hospital an antitoxin rash is commonly seen seven days after injection, but pain or swelling in the joints do not occur. Elsewhere, however, with different serums articular pain or effusion are occasionally seen. It is probable that they depend on the blood serum, and have nothing to do with its antidiphtheritic properties.

The existence of toxic joint disturbances secondary to septic absorption elsewhere, is perhaps difficult to prove absolutely, but cases occur in which suppuration around the teeth, vaginal discharge, etc., are associated with pain and swelling of joints. Wallis[2] has drawn attention to the occurrence of acute attacks of synovitis in patients with septic ulceration of the rectum; as the joint manifestations disappeared when the rectal disease was

[1] Osler, *Boston Med. and Surg. Journ.*, vol. cxxxix. p. 641.

[2] Wallis, F. C., *Brit. Med. Journ.*, 1900, vol. ii. p. 1002, and 1903, vol. i. p. 7.

cured, it is quite possible that the former were toxic in character. It is not improbable that the arthralgia and synovitis sometimes seen after dysentery is of the same nature. In hypertrophic pulmonary osteo-arthropathy it is very probable, as Marie suggests, that the cause of the bony lesions is a poison absorbed from the lungs and carried to the articular ends of the bones.

In pyæmia, apart from purulent arthritis, the joints may become painful and swollen without anything further taking place; this synovitis, for such it appeared to be in a few joints I have examined after death, may pass away. Possibly the synovitis may be due to micro-organisms that have reached the joint in such small quantities as not to succeed in setting up suppuration, and this is perhaps the most probable view; it is conceivable, however, that some of these slight cases are toxic and due to poisons, rather than septic or microbic.

Recently a form of acute inflammation of the joints imitating rheumatic fever has been described in France as occurring in patients with tuberculosis, which is quite a different condition from ordinary tuberculous arthritis. It moves from joint to joint, may disappear, relapse, or persist for weeks with remissions and exacerbations (Poncet,[1] Maillard[2]). I have seen a case of generalised tuberculosis with imitated rheumatism.[3]

To sum up, it may be said that toxic arthritis certainly occurs (*e.g.* antitoxin synovitis), that it is slight in degree, and thus forms a contrast to septic or microbic arthritis, where the process is more severe and where suppuration is likely (though this is not by any means universally the case, *e.g.* in urethral arthritis) to supervene.

In the case of this man there was no very satisfactory

[1] Poncet, *Soc. de Chirurg.*, Paris, April, 1903.
[2] Maillard, *Rev. de. Méd.*, September, 1903, p. 785.
[3] *Trans. Clin. Soc.*, vol. xxxvi. p. 133.

inlet, so to speak, for the poison or micro-organisms; before he came into the hospital he had had a sore throat, and at first I was inclined to think that the arthritic effusions were secondary to a microbic blood infection that had gained an entry through the tonsils, but, as has been already said, cultures taken from his blood did not prove that there was any hæmic infection. It is of course possible that the joints were occupied by micro-organisms of a comparatively low degree of virulence; but as it did not seem desirable to aspirate his joints, this point cannot be absolutely settled. The ease with which the synovitis yielded to simple local measures, and the absence of any manifest damage to the joints, point to the inflammation being comparatively slight, and this point is, as far as it goes, against a microbic invasion and in favour of a toxic synovitis.

While in the hospital no active inflammatory process was manifest in his throat, or indeed in any part of the body except the joints, and if the synovitis was due to toxins formed elsewhere, it is difficult to imagine where they were formed. The alimentary canal is a possible source; thus in connection with dysentery arthritis has been described, but there was no reason to think that any abnormal processes were taking place in his stomach or intestines; and if there had been, the salicylates should by their antiseptic action have produced some amelioration, which they certainly did not.

Thus, while the synovitis should with perhaps greater probability be regarded as toxic rather than septic, it cannot be said with certainty that this was so.

Finally, one point with regard to treatment came out forcibly in this case—salicylates and quinine produced practically no effect on the condition of his joints, while the application of dry cold by means of an ice-bag covered with flannel had a very beneficial effect. No

doubt the treatment of the manifestations of a disease, or symptomatic treatment, is to be deprecated if there is any danger of our looking no further, and neglecting the primary disease; but it is important not to forget the relief that the patient may get from simple, even household, local applications and counter-irritants, "old-fashioned" though they may be.

XV

SOME REMARKS ON THE USES AND ABUSES OF ARSENIC[1]

The title of the paper is "The Uses and Abuses of Arsenic"; but, as a matter of fact, I find I have more to say about the bad effects than the good effects. I often find that students, at any rate, are not sufficiently careful to see that their patients are not being harmed by the drugs they are taking. With drugs that are powerful for good it is essential to be on the alert to detect any evidence that points to the toxic effects of the remedy. This is important in the case of digitalis, belladonna, iodides, and in none more than in arsenic.

Arsenic is one of the remedies that probably most of us would retain, if the Pharmacopœia was reduced to a dozen drugs. It often acts with unexpected brilliancy, and in a way that is not always easy to explain on scientific grounds. I hope that the discussion will bring out some uses of arsenic not generally known that have, perhaps, been found out accidentally in the course of practice. I will now run over some of the uses of arsenic, but I shall not attempt to exhaust its therapeutic applications.

[1] Read at a meeting of the Windsor and District Medical Society, March 13th, 1901. Originally published in *Treatment*, April 1901, and now reprinted, with some alterations, by permission of the proprietors and publishers, Messrs. Rebman, Ltd., 129, Shaftesbury Avenue, W.C.

GOOD EFFECTS OF ARSENIC

For the curious condition, *geographical tongue*, arsenic may save us further trouble in wondering what to do.

As an *appetiser* or pick-me-up, a dose before meals of a minim of Fowler's solution, with 10 grains of bicarbonate of soda and infusion of gentian, is a useful and popular prescription.

It is also recommended in small doses in some forms of *dyspepsia*, and especially in irritative dyspepsia and alcoholic vomiting. Curious as it may seem, it produces a good effect if given before meals (Ringer and Sainsbury, p. 291 ed. xii.).

In the annoying form of *morning diarrhœa*, where a large evacuation is passed with but little warning half an hour or so after breakfast, often when the victim is in a railway-carriage on his way to the City, a minim of Fowler's solution before breakfast frequently acts like a charm.

In *blood diseases*, such as pernicious anæmia, splenic anæmia, and leukæmia, arsenic is in common use, and probably does more good than anything else. It is an interesting problem as to how it effects this. Is it by stimulating the red marrow of bone, and so increasing the output of red blood corpuscles? Stockman and Greig's[1] experimental results might be interpreted in this sense; but if so, as they point out, arsenic does not necessarily touch the real cause of the disease, and must therefore be regarded as a purely symptomatic treatment. Or, on the other hand, does arsenic act as an antidote or disinfectant, antagonising or destroying the cause of the disease? It might be suggested that the local action of arsenic on the stomach in pernicious anæmia might inhibit those morbid processes that lead to hæmolysis. In this connection it is interesting to

[1] *Journal of Physiology*, vol. xxiii. p. 376, 1898.

note that Wiener (*Soc. de Biologie*, December 16th, 1900) has found that, by treating animals with increasing doses of arsenic, their blood serum becomes able to protect other animals against infection with the colon and typhoid bacilli.

Lymphadenoma.—Arsenic is sometimes of great use in this disease, which is presumably of infective origin. How it acts it is difficult to say—whether it inhibits the growth of a micro-organism not yet discovered, antagonises a poison, or merely increases the resistance of the body. As in other diseases where a considerable quantity of the drug has to be taken, it is better to give it hypodermically than by the mouth. It may be injected directly into the growth, and with strict antiseptic precautions no suppuration should follow.

Malignant Disease.—The local application of arsenical paste as an escharotic has long been known. It has recently been revived by orthodox practitioners for inoperative cases of carcinoma. A solution of arsenic (1 part) in alcohol and water mixed (50 to 60 parts) is painted on the surface of the growth.[1] A case of sarcoma completely cured by hypodermic injections of cacodylate of soda has recently been recorded by Petrini, who also refers to another case where cutaneous sarcomata disappeared under this treatment, but a fatal result was due to internal growths.

Exophthalmic Goitre.—It has been observed that toxic symptoms due to medicinal administration of thyroid gland may be held in check by small doses of arsenic. On the theory that exophthalmic goitre is due to excessive and probably abnormal secretion on the part of the thyroid, it seems reasonable to treat that disease with small doses of arsenic. I have tried this, and for a time one patient seemed wonderfully improved, but relapsed while still taking arsenic.

[1] Trunecek, *Journ. de Practiciens*, May 5th, 1900; *Klinisch-Therapeutische Wochenschrift*, No. 32, 1900.

Chorea.—How does arsenic benefit cases of chorea? Does arsenic cure chorea because it makes the patient ill in another way, and unable to manifest the original disease? This seems unlikely in ordinary practice, where the toxic effects of the drug are hardly likely to be pushed too far. On the other hand, it might be urged that arsenic is less successful in ordinary practice than in the hands of the successful quack in Newcastle, who on his death-bed told Dr. W. Murray (*Rough Notes on Remedies*, p. 17, third edition, 1899) that the secret of success in his bottle of medicine, which was warranted to cure chorea, was the large amount of arsenic in it—15 to 20 minims in each dose. Possibly in some cases arsenic may help in this way; usually it does good, not as a specific, but as a general tonic.

As a *nervine tonic*, arsenic is widely used in neuralgia and other affections, such as rheumatoid arthritis. It has been much recommended for pain left behind after herpes in old people, but is now somewhat superseded by phenacetin.

Malaria.—Arsenic is said to be the best remedy after quinine, and to be particularly useful in long-standing cases. Personally I have no experience of it.

Diabetes.—Arsenic has been recommended on clinical grounds by Dr. W. Murray for diabetes when the disease has been first modified by dieting and codeia. He gives 10 minims of the liquor arsenici hydrochloricus three times a day, combining it in the morning with hydrochloric acid and strychnine. He finds that the most lasting cures have been obtained in this way. Possibly it has a beneficial effect by inhibiting the glycogenic function of the liver, since it is said that in arsenical poisoning this function of the liver ceases.

In *Chronic Skin Diseases*, such as psoriasis, eczema, and so forth, the administration of arsenic is too familiar to allow of any illustration. It is, however, worth while inquiring how it acts. It is usually assumed it does so

by increasing proliferation of the cells of the skin, but some writers believe that it improves the skin condition by making the patient ill in other ways, and that its apparently beneficial effect is analogous to the disappearance of a chronic skin eruption during an acute fever, an event which sometimes occurs. A further point of interest is to be found in the observation that chronic skin affections are acted upon in a somewhat similar manner by arsenic and by thyroid extract. Does this depend on the fact that the arsenic in the body is chiefly contained in the thyroid gland, and that it is eliminated in the epidermic scales and in the hair? This might suggest a comparison of the therapeutics of arsenic and of thyroid gland substance, both of them general tonics that are employed very widely and somewhat empirically, though none the less successfully. Loss of hair and pigmentation of the skin in pregnant women are thought by Gautier (*Bull. Acad. de Méd.*, Paris, August 7th, 1900) to be due to loss of arsenic, since a combination of arsenic with nucleo-proteid is transferred from the mother to the fœtus. In such cases, with which we are commonly met, it might be worth while giving arsenic.

Sclerodermia is an obstinate affection that has been much improved after hypodermic injection of arsenic; but further observations are necessary to determine whether the improvement was necessarily the direct result of this treatment.

In *Bullous Eruptions*, such as pemphigus, and some forms of dermatitis herpetiformis, the use of arsenic is too well known to require insisting on. The tendency that some persons have to develop labial herpes on slight provocation can be kept in check, it is said, by small doses of arsenic. Probably most of us give a minute dose of arsenic in combination with bromides in order to prevent the bromide eruption.

Asthma.—Arsenic is particularly useful in spasmodic

asthma. Dr. W. Murray[1] emphasises its good effect in the asthma of young children and in that of old emphysematous persons, and adds that it is not of much use where there is bronchitis or a gouty basis. Repeated and paroxysmal sneezing, allied to spasmodic asthma, may yield to small doses of arsenic. In advanced emphysema of the small-lung type arsenic is also a valuable remedy.

As a Means of Preventing Frequent Cold-catching.—Mr. Hutchinson[2] mentions a case of a woman who had arsenic prescribed for filmy patches on the tongue, and lost the tendency to catch cold on the slightest exposure, a susceptibility she had suffered from for thirty years. This is an example of the accidental discovery of one of the uses of arsenic.

In *Phthisis* arsenic has long been thought to have a useful action in removing inflammatory products, and by a general tonic action. Lately, the cacodylate of soda has been much vaunted, especially abroad, as a remedy for tuberculosis. It has been shown that, in tuberculosis, arsenic, which normally is chiefly found in the thyroid, is almost entirely absent from that gland.

As to the *Administration* of arsenic, except for special purposes, such as a pick-me-up, or to prevent morning diarrhœa, it is hardly necessary to say it should be given after food. When arsenic given in the ordinary way by the mouth disagrees—and it sometimes does so in quite small doses—it can be given hypodermically, and may be more conveniently injected into the substance of muscles than into the subcutaneous tissues. Large doses can thus be often borne without any bad effects. In a case that I saw several times with Dr. Heaton small doses (two or three minims twice a day) given by the mouth produced gastro-intestinal trouble. Hypodermic injections of arseniate of soda in one in five

[1] Murray, *Rough Notes on Remedies*, 1897, p. 25.
[2] Hutchinson's *Archives*, vol. v. p. 268.

hundred eucaine β were therefore employed, and acted so satisfactority that 105 grains of arseniate of soda were given practically without toxic effects in 271 days. Dr. Heaton (*vide Lancet*, January 26th, 1901) of course employed strict antiseptic precautions in these injections, and found that if the solution was injected at blood-heat no local irritation resulted. This is important, for I have seen hard lumps, at first suggesting suppuration, but passing away, arise at the site of injection of the cold solutions. I have tried the new preparation of arsenic known as cacodylate of soda, or arsycodile, both by the mouth and hypodermically. It is certainly much less toxic than arsenic; personally I have never seen any bad effects from its use, but toxic symptoms have already been described after its administration.[1] When given by the mouth, it usually justifies the name cacodylate in producing a garlicky odour of the breath. This is said not to occur when hypodermic injections are employed. On the whole, I regard cacodylate of soda as less powerful, both for good and for evil, than ordinary arsenic.

BAD EFFECTS OF ARSENIC

It is interesting to note that, generally speaking, excessive doses of arsenic produce conditions like those which are cured by its administration in small quantities. Thus, it clears and improves the complexion, but if persisted in may produce pigmentation and keratosis. In minute doses it cures gastro-intestinal irritability, while in larger quantities it acts, as is well known, as an irritant. It will now be convenient to consider briefly some of the bad effects of arsenic seriatim.

In the *Mouth* the tongue may show a silvery appearance from proliferation of the epithelium, a process

[1] Murrell, *British Medical Journal*, 1900, vol. ii., p. 1823.

analogous to that of keratosis. Ptyalism and gingivitis are said to occur.[1] Stomatitis may occur, and was met with in the epidemic of arsenical neuritis at Manchester.[2] When cacodylate of soda is given as a less toxic form of arsenic, the breath may be distinctly alliaceous, or tainted with the odour of garlic.

Pharyngitis, like coryza and bronchitis, may also be due to the medicinal use of arsenic.

From the excessive stimulation of the *Gastric Mucous Membrane* loss of appetite, gastric pain, nausea, and vomiting commonly follow; while diarrhœa is the result of gastro-enteritis.

On the *Respiratory Tract* arsenic has comparatively few bad effects. Coryza, it is true, is frequent, but more marked changes are seldom noticed. Tracheitis and bronchitis are also due to arsenic. The question has been raised whether pulmonary tuberculosis may be favoured by the excessive use of the drug;[3] this is a point of considerable interest, since, as has been mentioned, it has been thought to have the reverse effect—viz. a curative action. In the recent epidemic of arsenical neuritis, hæmoptysis without any evidence of phthisis is mentioned by Reynolds, and also the fact that patients with phthisis did badly;[4] but here again it must be borne in mind that this may have been a concomitant effect of alcohol. Spontaneous hæmorrhages may, it should be mentioned, be set up by arsenic.

Heart.—Arsenic may give rise to cardiac failure. Reynolds compares[5] this effect, observed in the recent epidemic of arsenical neuritis, to the same event in alcoholic neuritis and in beri-beri. As in the epidemic

[1] Tessier, *Rev. Méd.-chirurg.*, Paris, August, 1848.

[2] Reynolds, *British Medical Journal*, 1900, vol. ii. p. 1493.

[3] Imbert-Gourbeyre, *Gaz. Méd.*, 1862. Quoted by Dupoux, *Gaz. des Hôp.*, October 25th, 1900, p. 1324.

[4] Reynolds, *British Medical Journal*, 1900, vol. ii. p. 1770; *Lancet*, 1901, vol. i. p. 98.

[5] Reynolds, *British Medical Journal*, 1900, vol. ii. p. 1770.

alcohol was the medium by which arsenic got into the system, the effects may have been due to two poisons; but there seems no doubt that arsenic alone may be the cause of cardiac failure. It has long been known that arsenic induces fatty degeneration in internal organs, and probably it is in this way that cardiac failure is brought about.

Peripheral Neuritis.—Degeneration of the peripheral nerves is a well-known result from the medicinal use of arsenic. It is, however, remarkable what variations in its incidence are met with. Arsenic may be given freely and for long periods in skin diseases and leukæmia without producing this effect, while in chorea by no means large doses may produce severe paraplegia. Railton noticed[1] that in children who had not had more than four grains during the illness, severe paralysis might follow, the first signs perhaps not developing until two weeks after the medicine had been stopped This interval is of interest in connection with Reynolds' statement[2] that the urine may contain arsenic a fortnight after its ingestion has ceased. The variability of the toxic manifestations of arsenic may depend on several factors; thus, idiosyncrasy, no doubt, is important. If the patient is simultaneously exposed to the influence of some other toxic agent, such as alcohol or the poisons produced by diseases, the effects will probably be more marked. Thus, in the recent epidemic due to arsenical beer, the peripheral neuritis may have been due to the combined toxic effects of these two poisons, or even to the additional action of a third poison, selenious acid (Tunnicliffe). Examples of arsenical neuritis apparently precipitated by tonsilitis and by influenza have been recently recorded.[3] The ease with which peripheral neuritis sometimes follows

[1] Railton, *Medical Chronicle*, February, 1900.
[2] Reynolds, *Lancet*, 1901, vol. i. p. 98.
[3] Henderson, *British Medical Journal*, 1901, vol. i. p. 145.

arsenical treatment of chorea may be due to the nervous system being already affected by the toxin of acute rheumatism. It is noteworthy, as further showing the influence of diminished resistance in determining the toxic manifestations of arsenic, that, in cases of long-standing psoriasis, pigmentation of the skin seems to be more frequent than neuritis. The widespread epidemic of peripheral neuritis in beer and porter drinkers in Manchester and the surrounding districts has naturally aroused a great deal of interest. The patients were at first thought to be suffering from alcoholic neuritis, but the occurrence of herpes, pigmentation of the skin, keratosis of the skin, and other features, suggested arsenical neuritis, a conjecture which chemical analysis of the beer proved to be correct (Reynolds).[1] The arsenic was found to have got into the beer in the glucose, which was manufactured with sulphuric acid made from iron pyrites and containing arsenic.

My former house-physician, Dr. Fraser, has drawn my attention to an old and interesting observation of Sir Astley Cooper's on arsenical paralysis.[2] A drawing-master had bow legs, which he considered "stood between him and preferment." To remove this blemish he put himself into the hands of a doctor. The skin was incised, and the patient and his father in turn assisted the doctor to rasp away the front of the tibiæ with an instrument called a rougee until the bones became so thin that the doctor stopped this proceeding. The wounds healed kindly, but the granulations *would* form bone, so the doctor applied arsenic over the whole surface. As a result the patient became paralytic in all four limbs, and was seen by Sir A. Cooper. Osler (*Principles and Practice of Medicine*, third edition, p. 1079) speaks of tremor as a rare event in arsenical

[1] Reynolds, *British Medical Journal*, 1900, vol. ii. p. 1492.

[2] *Lectures on the Principles and Practice of Surgery*, by Sir A. Cooper, eighth edition, 1835, p. 71.

poisoning. Neuralgic pains are frequent, and a special form of red neuralgia or erythromelalgia (painful red extremities) may develop.

Considerable doses of arsenic may produce *Herpes Zoster*. This is interesting from several points of view. It is now known that herpes zoster is due to inflammation of the posterior root ganglion; arsenic, being a nervine tonic, may therefore, when given in excess, set up over-stimulation, and lead to a condition resembling inflammation. It is further of interest, since arsenic has a curative action on bullous eruptions, such as pemphigus and the recurrent form of bullous eruption on the lips, known as herpes labialis; while arsenic is an excellent remedy for a severe pain left after herpes zoster in old people. Arsenic appears to be the only drug that can produce herpes, and this fact raised a suspicion as to the causation of the recent epidemic of peripheral neuritis in and around Manchester.

Delirium.—Cerebral manifestations of arsenic are extremely rare. Joffroy recently recorded a man who had various delusions, and imagined he was Antichrist; this passed away when he ceased to take arsenic. Mental symptoms allied to confusional insanity were met with in the recent epidemic of arsenical beer poisoning.

Cutaneous Lesions.—Erythemata may be brought out by the use of arsenic, even of very short duration. In the widespread epidemic of arsenical neuritis observed in and around Manchester in the latter half of 1900, various erythematous eruptions were noticed, scarlatiniform, morbilliform, or with considerable itching. The erythemata may be followed by pigmentation.

Pigmentation.—Arsenic in certain persons leads to pigmentation of the skin; this may occur after acute poisoning, but is naturally more often seen after long-continued treatment. It begins as brown spots; these enlarge and coalesce, the parts of the body that

normally show pigment are, as in Addison's disease, those that are chiefly affected, with the important diagnostic difference that the exposed parts of the body are not much affected. Kelynack and Kirby, in their recent book on arsenical poisoning as seen in the Manchester district, describe the "Addisonian" type with pigmentation. Nielsen[1] says that cases of pigmentation have been erroneously regarded as Addison's disease. This is very natural, since gastro-intestinal disturbance and debility may readily follow abuse of arsenic. Possibly some of the cases of Addison's disease, in which the adrenal bodies have been found to be normal were examples of chronic arsenical poisoning. The differential diagnosis is very difficult, since in arsenical pigmentation the visible mucous membranes may, though rarely, be affected;[2] while pigmentation of the tongue and buccal mucous membrane is often absent in Addison's disease, and when it is present seems to be due to a complication (carious teeth), and not to be an integral part of the disease.

The occurrence of pigmentation is somewhat variable: it does not appear in all patients; probably it depends on the amount of pigment in the skin. Reynolds[3] states that, in the epidemic of peripheral neuritis, pigmentation did not occur in fair-complexioned persons, or only to a very slight degree. As an outlying speculation it is interesting to inquire how much of the pigmentation which is seen in some cases of exophthalmic goitre is due to arsenic. It has sometimes been thought that it is the result of arsenic given medicinally in the disease, but this will certainly not account for many cases. Another explanation which suggests itself is that, exophthalmic goitre being a disease due to an excessive

[1] Nielsen, *Selected Essays and Monographs*, 1900, p. 303 (New Sydenham Society).

[2] Joffroy, *Journ. de Méd. et de Chir. Pract.*, January 10th, 1901.

[3] *British Medical Journal*, 1900, vol. ii. p. 1770.

and probably abnormal secretion of the thyroid gland, there is an excess of arsenic supplied to the body by that gland. Normally, according to Gautier,[1] arsenic, like iodine, is chiefly found in the thyroid, and is secreted together with iodine in the form of a nucleo-proteid. Of course, the amount of arsenic in the thyroid must depend on the supply, but it is reasonable to believe that with excessive thyroid activity the arsenic is furnished to the skin both more rapidly, and in the most suitable form for inducing metabolic processes, of which pigmentation is one. As to the prognosis of pigmentation after arsenical medication, it usually disappears a few weeks or months after the treatment has been suspended, but it has been known to last for years. In the treatment of this condition efforts should be made to eliminate the drug by giving iodide of potassium and diuretics. The mechanism by which the pigmentation is produced is no doubt stimulation and active proliferation of the cells of the skin.

Keratosis.—Long-continued courses of arsenic may lead to thickening of the skin, especially over the hands and feet. It may present itself as a diffuse thickening or as localised corns, and may appear as scattered horny growths. It has been thought that the thickening is due to arsenic being excreted by the glands of the skin, and then acting locally and directly on the epidermis; this view fits in with the observation that it may be associated with excessive secretion of sweat. Another and plausible explanation is that it is a trophoneurosis. With regard to prognosis, usually the keratosis subsides and disappears when the administration of arsenic is suspended; but it may require local treatment, such as salicylic plaster, resorcin, and bathing. In a few striking cases the keratosis may pass into squamous-celled epithelioma.

[1] Gautier, *Bull. Acad. de Méd.*, Paris, August 7th, 1900.

Warts.—Multiple and discrete warts are in rare cases brought out by giving arsenic medicinally. Some years ago I had a patient with leukæmia who always got feathery warts over his hands when he took arsenic. It, however, improved his condition so much that he bore the warts quite contentedly.

Arsenic Cancer.—The long-continued use of arsenic for psoriasis may not only result in a thickening of the skin (keratosis) and warts, but in a further proliferative change of the skin, squamous-celled epithelioma. This was first described by Mr. Jonathan Hutchinson, but other cases have been recorded. Hamburger[1] has brought together nine such examples and one of doubtful nature, and Hartzell[2] has added another. Fagge[3] quotes Hesse's observation that lymphosarcoma at the root of the lung among the miners of Schneeburg is so common that 75 per cent. of the miners die of it. The minerals worked in these mines contain bismuth, cobalt, nickel, and some arsenic and sulphur. It is possible that the proliferative effect of arsenic may have had some influence in the production of the new growth. Workers in arsenic mines of Cornwall and smelters exposed to fumes of arsenic (Butlin[4]) do not appear to suffer from cancer; but Geyer[5] finds that the arsenic miners of Reichenstein, in Prussia, frequently get carcinoma developing on arsenic warts on the fingers.

Ascites.—Mr. Hutchinson[6] and Dr. Hamburger[7] have reported cases where ascites developed in patients after long-continued medicinal use of arsenic. In both instances suspension of the arsenic was followed by recovery, but in Hutchinson's case the abdomen had to

[1] Hamburger, *Johns Hopkins Hospital Bulletin*, April, 1900, p. 87.
[2] Hartzell, *American Journal of Medical Sciences*, September, 1899.
[3] Hilton Fagge, *Medicine*, vol. ii. p. 82, ed. 1886.
[4] Butlin, *British Medical Journal*, 1892.
[5] Geyer, *Archiv. f. Derm. u. Syphil.*, Bd. xliii.
[6] Hutchinson, *Archives of Surgery*, 1895, vol. vi. p. 389.
[7] Hamburger, *Johns Hopkins Hospital Bulletin*, April, 1900.

be tapped on three occasions. Possibly the ascites is due to early cirrhosis of the liver. In connection with this suggestion, it may be noted that silver has been found in the liver in early cirrhosis (Frommann [1]); while experimentally a similar result has been obtained by feeding animals with lead (Lafitte [2]). It is significant that cirrhosis with ascites has been observed with increased frequency during the recent epidemic due to arsenicated beer around Manchester (Reynolds,[3] Sturrock).[4]

COMPARISON OF THE ACTION OF ARSENIC AND THE IODIDES AND SALICYLATES

Arsenic acts almost entirely on the epithelial parts of the body, both in doing good and in producing bad results, and thus forms a contrast to iodides and salicylates, which have more effect on the connective tissues. While arsenic may produce carcinoma, iodides have been known to produce a growth like sarcoma—iodide sarcoma (Hutchinson). I have, indeed, seen a granulomatous growth, which to the naked eye in some degree resembled sarcoma, produced by the local action of salicylic acid on a sore.

[1] Frommann, *Archiv. f. Path. Anat. u. Physiol.*, Berlin, Bd. xvii. 1860.

[2] Lafitte, *Thèse de Paris*, 1892.

[3] Reynolds, *Transactions of the Royal Medical and Chirurgical Society*, 1901.

[4] Sturrock, *British Medical Journal*, 1900, vol. ii. p. 1815.

XVI

ON THE TREATMENT OF ACROMEGALY BY THE EXTRACTS OF THYROID AND PITUITARY GLANDS SIMULTANEOUSLY[1]

In *The Lancet* of April 25th, 1896, p. 1137, I recorded the unsuccessful treatment of a case of acromegaly by pituitary gland substance. In some remarks which followed on the relation between the changes observed in the pituitary body (generally simple enlargement, cystic change, or more rarely sarcoma) and this disease it was pointed out that the internal secretion of the gland might theoretically be modified in three ways—viz. (*a*) by suppression, (*b*) by hypersecretion, or (*c*) by perversion of its composition. Suppression of secretion alone was not likely to account for the disease inasmuch as on that hypothesis the administration of pituitary extract should relieve the symptoms, whereas this therapeutic effect had not been definitely established. Hypersecretion again was improbable, since the administration of the pituitary extract had not been shown to accentuate the symptoms. With regard to the possibility that the nature of the secretion was altered, and that this perversion of its composition accounted for the changes characteristic of acromegaly, the following suggestion was put forward: "That, owing to alteration in the secretion of the pituitary, the equilibrium between it and the other internal secretions

[1] Reprinted, by permission, from *The Lancet* December 4th, 1897.

is disturbed. Possibly some toxic body . . . might be thus produced. The thyroid and pituitary glands have been thought to be compensatory (to each other); recently, however, their extracts have been shown to be physiologically antagonistic.[1] Superficially there are some resemblances between acromegaly and myxœdema, and it might be thought that acromegaly is the result of a disturbance of the chemico-physiological equilibrium maintained in health by the normal activity of these two glands.[2] Such a consideration suggests that acromegaly might be benefited by giving pituitary and thyroid extracts at the same time."

I have since the publication of this case in *The Lancet* been able to test this theoretical consideration as to

[1] Schäfer and Oliver (*Journal of Physiology*, vol. xviii. p. 277) found that the effect of pituitary extract on blood-pressure was to raise it while the effect of thyroid extract was the reverse. Their "observations would appear to indicate that the opinion which has been freely expressed that the pituitary and thyroid are vicarious in function and which has been based upon the apparent enlargement of the pituitary after thyroidectomy is probably incorrect, seeing that the extracts of the two glands produce entirely contrary physiological effects." On the other hand, it does not follow that because the effects on blood-pressure of these extracts are antagonistic their other physiological actions necessarily follow suit. Dr. Abrahams has kindly called my attention to an interesting paper by Dr. A. Schiff in the *Wiener Klinische Wochenschrift* of March 25th, 1897, on the influence of thyroid and pituitary glands on metabolism. After referring to the clinical relations and resemblances existing between acromegaly and myxœdema he goes fully into the effects of thyroid and pituitary extracts on metabolism and shows that they resemble each other in increasing the excretion of phosphoric acid.

[2] In connection with this speculation reference may be made to a valuable paper on "Acromegaly with Goitre and Exophthalmic Goitre," by Dr. G. R. Murray, in *The Edinburgh Medical Journal*, February, 1897. He quotes five cases in which exophthalmic goitre and acromegaly have existed together. While inclining to the view that acromegaly is in some way dependent on alteration in the function of the pituitary gland, he says that the coexistence of acromegaly and exophthalmic goitre suggests that there may be some common cause, which brings about similar changes in both thyroid and pituitary glands, each in turn producing its attendant symptoms.

treatment in two cases of acromegaly. In both cases the pressing symptom of which the patient complained—headache—was relieved by taking twice a day five-grain tabloids of thyroid and of pituitary extract, ten grains of each being taken daily. It is to be added that the skeletal changes remained unaffected and that the amenorrhœa, from which both patients had suffered since the onset, remained.

Case 1

This patient was the woman described in *The Lancet* in the communication already referred to. She was thirty-five years of age and had been ailing since 1891, but definite symptoms of acromegaly only dated from 1894, when her hands and feet began to enlarge and her sight began to fail. This was a well-marked case of the disease and the patient had optic atrophy and transient glycosuria. After being treated in the hospital with pituitary extract in February 1896, she went home and was under the care of Dr. Hollis, of Wellingborough; towards the end of last year (1896) headache became so intense that she was anxious to undergo any operation that would relieve it. Accordingly she came under my care again at St. George's Hospital. After consultation with my colleague, Mr. Shield, who had seen her when previously in the hospital, it was decided that no attempt to remove the pituitary body, which from the primary atrophy of the optic nerves was probably much enlarged, was justifiable, but that if the pain continued the skull might be trephined and the subdural space opened with the object of relieving intracranial pressure. She was given the combined thyroid and pituitary extracts and she gradually lost the headache and was able to get up. Her improvement being sustained she went back to her home in March 1897, with directions to continue the treatment. This advice, however, probably from the extra expense entailed, she did not

follow. In June she began to get epileptiform fits with loss of consciousness, and gradually getting weaker she died early on August 16th, on which day Dr. Hollis and I examined her body—fourteen hours after death. The results of this examination were communicated to the Pathological Society of London at the meeting on November 2nd, 1897, but it may be stated here that the pituitary body was greatly enlarged by a soft white growth, which invaded the right optic thalamus and microscopically had the structure of a medium sized round-celled sarcoma. The thymus was persistent and microscopically showed marked enlargement of the concentric corpuscles of Hassall. The thyroid body was healthy, both to the naked eye and microscopically.

This case belongs to the class of acute acromegaly, of which Maximilian Sternberg[1] has collected six examples, all accompanied by sarcoma of the pituitary body and running their clinical course rapidly in from three to four years.

Case 2.

A woman, aged twenty-six years, with symptoms of acromegaly for two and a half years was shown at a meeting of the Medical Society of London on April 12th, 1897. This was a less advanced case than the previous one, presenting no changes in the optic nerves. When she came under observation, in October 1896, she had had severe headache for six weeks. She was taken into the hospital and treated with the combined extracts of thyroid and pituitary glands. She soon lost the headache and subsequently attended as an out-patient until July 1897, the same treatment being continued. As there was no return of the headache when she was an out-patient, its disappearance can hardly be explained as being merely due to rest and improved physical conditions.

[1] Sternberg, "Die Akromegalie," p. 67, 1897.

In these two cases amelioration of one symptom and that an urgent one—headache—followed the combined administration of thyroid and pituitary gland extracts, but the structural changes remained unaltered. The results are too scanty to establish any reliable conclusion as to the value of the treatment, but they justify a more extended trial, and it is with the object, if possible, of inducing others, who have cases of acromegaly under their care, to try this form of treatment that this note is published. One point that specially requires investigation is whether any good effect that may result from the administration of the combined extracts, is solely due to the contained thyroid extract or whether the two combined extracts have more effect than the administration of thyroid alone. Pituitary extract has been generally unsuccessful in the treatment of acromegaly, while the treatment with thyroid extract has given variable results. Benson,[1] Bruns, and Bramwell,[2] record improvement, Bramwell and Ransom[3] report no effect, and Murray[4] mentions temporary improvement which disappeared while the treatment was continued. Under these circumstances it has been thought that any beneficial effects it may have are of a general nature, and not due to any specific action on the morbid processes at work in acromegaly. But since thyroid extract has been found to relieve the headache of acromegaly,[5] it is possible that the apparent success of the administration of the combined extracts was in reality due to the thyroid extract and not to the combination. In this connection it would be interesting to ascertain what is the effect of thyroid extract on

[1] *Brit. Med. Jour.*, 1895, vol. ii. p. 949.
[2] Quoted by Murray.
[3] *Brit. Med. Jour.*, vol. i. p. 1259.
[4] *Ibid.*, p. 293.
[5] Bruns : *Neurologisches Centralblatt*, December, 1895 (quoted in epitome, *Brit. Med. Jour.*, 1896, vol. i. No. 51).

headache other than that of acromegaly; from the fact that it lowers arterial pressure it might be expected to relieve some forms of headache. In the Report of the Clinical Society of London on Myxœdema[1] occipital headache was present in one-fifth of the cases. On the other hand, excessive doses of the extract give rise among other symptoms to headache.[2]

At the present time the relation of changes in the pituitary gland to acromegaly cannot be considered as entirely understood or definitely settled; it is true that the change in the gland is generally regarded as primary. But it may be that they are both the manifestations of some primary change elsewhere,[3] or, as the occasional association of acromegaly with some, or in very rare cases with all the, symptoms of exophthalmic goitre on the one hand and the superficial resemblance to myxœdema on the other suggests, the symptoms of the disease may be due to some disturbance of a theoretical equilibrium which in health is maintained between the internal secretions of the thyroid and pituitary glands. In this state of the question the results of more extended therapeutical trial of thyroid extract, both alone and in combination with pituitary extract, might be of considerable value.

[1] *Transactions of the Clinical Society*, supplement to vol. xxi. p. 29.

[2] Osler: Principles and Practice of Medicine, 1895, p. 751.

[3] Compare remarks by Professor Panas of Paris reported in *Brit. Med. Jour.*, 1885, vol. ii. p. 950.

XVII

ON THE ANTAGONISM OF SOME DISEASES AND THE CURATIVE EFFECT OF ONE DISEASE ON ANOTHER, REAL AND REPUTED[1]

We are all of us fully aware of the way in which one disease, by lowering the resistance of the body disposes the patient to the incidence of another and different disease. Thus measles reduces the resistance of the respiratory tract, and renders its victims liable to secondary infections such as diphtheritic laryngitis, broncho-pneumonia, and pulmonary tuberculosis, while in chronic renal and cardiac disease the bactericidal power of the blood is, as Flexner[2] has shown, reduced, and accordingly secondary infections, which may be terminal or fatal, are common.

While fully recognising this tendency of one disease to prepare the way for another, and acting upon it in every-day practice, it may be worth while to turn aside for a few moments and to consider the more speculative problems of how far one disease or morbid condition may interfere with, counteract, or neutralise another.

Diseases are largely toxic or due to poisons, and it is a familiar fact that the actions of different poisons

[1] A paper read before the South-West London Medical Society, January 10th, 1900, and now reprinted, with some few additions, by kind permission from *The Medical Magazine* of February, 1900.

[2] *The Journal of Experimental Medicine*, vol. i. No. 3, 1896.

may be so opposed as to neutralise each other or act as mutual antidotes. It is therefore *a priori* logical to believe that one disease may cure another, for example the toxin of erysipelas destroys the active effects of the cause, whatever it may be, of some sarcomata, as shown by the injection of Coley's fluid. To put the thesis in other words, some drugs are mutually incompatible, the line of distinction between useful drugs and poisons is one of degree or of quantity, diseases are due to poisons, therefore some diseases will be found to be incompatible.

In considering systematically the subject of the antagonism of different diseases it will be convenient in the first place to refer to those examples where the diseases are not really antagonistic but only appear or have been thought, erroneously, to be so.

Under this heading come (1) the phenomena of metastasis of disease ; for example it might conceivably be suggested that orchitis cured mumps, whereas of course every one knows that it is merely a change of the situation of the same disease. (2) Those diseases that are largely due to, or are disposed to by opposite conditions, such as gluttony and starvation, laziness and overwork, heat and cold, and so forth.

There are (3) as well some examples of diseases at one time thought to be incompatible but now known not to be so. This question is only of historical interest, but a few minutes will be devoted to its consideration.

After this the real antagonism of disease will be discussed under the heads (*a*) of one disease mechanically protecting against or curing another.

(*b*) The direct cure of a disease, usually a chronic one, by an acute illness. In some cases this may be due to the production of a toxin analogous to a drug, which exerts its influence on a chronic morbid condition. In other cases an acute illness may interfere with the evolution of a pre-existing malady and either cure it

or render it latent for a time; in this way an acute disease may break the habit of a chronic affection.

(*c*) The possibility of a chronic disease protecting chemically against other diseases.

1. ANTAGONISM OF DISEASE ONLY APPARENT, NOT REAL

Metastasis of disease from one part of the body accounts for some phenomena which might conceivably be regarded as the cure of one disease by another. Thus when eczema is cured by frank gout in the big toe, it is only a change of site in the activity of the poison. Depression and mental disturbances may fly away when gout manifests itself locally, but this is not an example of gout curing headache, melancholia, and so forth, but merely of metastasis. Thus a local disease or discharge may provide an outlet for poisons which would otherwise affect more important or vital parts of the body. This is a fact that has long been recognised, and descriptions have been given of "diseases that it is dangerous to cure." To take a very commonplace instance, checking or curing diarrhœa in granular kidney may kill the patient by precipitating uræmia.

2. DISEASES NOT ANTAGONISTIC, BUT FAVOURED BY OPPOSITE CONDITIONS

Arterio-sclerosis, granular kidney, and gout are not really antagonistic to, and curative of, tuberculosis. These at first sight antagonistic conditions are favoured respectively by the opposite conditions of overfeeding and insufficient food.

Thus, in cases of granular kidney, tubercle commonly runs a slow course, and may become fibroid and obsolete.

A small boy, aged seven, was admitted under my care in St. George's Hospital at the end of 1898, with

pericarditis and nephritis. After a time he recovered from the acute disease, but showed signs of widespread tuberculous disease of the skeleton, affecting the bones of the face and skull, all four limbs and the spine (the last lesion, though extensive, only being recognised at the autopsy). As the tuberculous disease advanced the symptoms of renal disease diminished, the pulse became much less tense, and the patient was no longer constantly drowsy or sick. It is interesting to note that his urine contained albumose, derived from the areas of suppuration in his bones; this may have reduced his arterial tension, which was decidedly high on admission.

As a subdivision of this heading we might consider diseases the treatment of which prevents the development of another, or cures a second disease when already present.

Although temporary glycosuria may occur in biliary colic, gallstones seem to be rarely found in patients dying of diabetes mellitus. Thus, in 220 cases of diabetes mellitus collected by Windle, there was only one of cholelithiasis, or ·45 per cent., instead of an incidence of from 5 to 12 per cent. of all cases. Brockbank,[1] who quotes Windle's figures, is inclined to explain this by the largely nitrogenous diet in diabetes mellitus, providing plenty of bile acids which keep the cholesterine in solution. If so, this is an example of the treatment of one disease preventing the development of another.

3. DISEASES ERRONEOUSLY THOUGHT TO BE ANTAGONISTIC

Malaria and Pulmonary Tuberculosis. — It was formerly believed that malaria and pulmonary tuberculosis were antagonistic, and that phthisis was not

[1] Brockbank, "Cholelithiasis."

only much rarer but more curable in aguish districts than elsewhere; indeed, early in the last century, phthisical patients used to be sent to the fens to be cured. In 1802, Dr. Harrison of Horncastle drew attention to the infrequency of phthisis in the fens; the antagonism between phthisis and malaria was more elaborately dealt with by Wells (1811), and Boudin (1841), and subsequently considerable discussion arose, in which Drs. Greenhow and Peacock[1] joined, and tended by their contributions to undermine any basis of statistical support for this then popular belief.

It was also once thought that malaria and typhoid fever were antagonistic, but without any real basis of fact.

Cancer and Tuberculosis.—Probably there is no real antagonism between the two, but they occur at different ages, and under different circumstances. Mr. Haviland (*Allbutt's System*, vol. i. p. 53) has shown that the geographical distribution of cancer and tubercle present a contrast; where the death rate from one is high, that from the other is low, and *vice versâ*.

Cancer often seems to attack those immune from other diseases; thus it is a common observation that cancer attacks persons who have previously been particularly strong and well—"without a day's illness," as the victims sometimes put it.

I have several times seen the two conditions associated with the same body; tubercle and cancer have been seen simultaneously in the same organs—for example, in the œsophagus or mamma[2]—and tuberculous lesions have even been seen engrafted on to carcinoma of the stomach in a phthisical patient who, as they so often do, swallowed his own sputum.[3] In

[1] Peacock, *British and Foreign Medico-Chirurgical Review*, vol. xxiii. p. 202, January-April, 1859.

[2] Warthim, *American Journ. Med. Sciences*, July, 1899.

[3] H. Claude, *Soc. Biolog., Paris*, January 28th, 1899.

fact, carcinoma of the stomach, by leading to an absence of free hydrochloric acid in the gastric juices, actually favours tuberculous infection of the stomach.

Leukæmia and Tuberculosis.—The administration of nuclein has been recommended for several diseases, of which tuberculosis is the commonest. Now leukæmia is a disease in which there is an excessive formation and destruction of leucocytes with a corresponding increase, as shown by the large amount of uric acid in the urine, of nuclein. It would therefore be reasonable to expect that leukæmia would protect against tuberculosis. This appears to be supported by the extreme rarity of the combination of these two diseases; thus Susmann,[3] who has specially investigated this point, could only find twenty-five recorded cases. When it does occur it is two and a half times commoner in lymphatic leukæmia.

Other diseases which have without sufficient reason been thought to be mutually antagonistic are typhoid fever and tuberculosis, and acute rheumatism and tuberculosis.

REAL ANTAGONISM OF DISEASE

(1) One Disease Mechanically Protecting Against or Curing Another

Mitral Stenosis and Pulmonary Tuberculosis.—These are two common diseases, but they are very rarely seen in the same person. I have only seen a few examples of this coincidence, and those that I remember have chiefly been "show cases" in hospitals. Tuberculosis elsewhere in the body may be associated with mitral stenosis; there is no antagonism between them.

I cannot help quoting a remarkable case, illustrating this and something more, that I examined post mortem seven years ago. A girl, aged twenty-two years, had

[1] *Practitioner*, vol. lxxii. p. 536, October, 1903.

tuberculous disease of the left hip, tuberculous ulcers in the intestines, colloid carcinoma of the sigmoid flexure, secondary colloid carcinoma of the peritoneum and ovaries, one of which weighed 14 oz., lardaceous disease of the spleen, and calculi in both kidneys. There was mitral stenosis, the heart weighing 8 oz., and showing no hypertrophy of the right side; a pulmonary apoplexy in the lower lobe of the right lung, but no tubercle in either lung. There was, however, a calcified bronchial gland.

This case seems to bear out the view that mitral stenosis protects the lungs from tuberculosis, while incidentally it is an illustration of the association of carcinoma of the colon, at a very early age, with tuberculosis.

Although I believe that mitral stenosis does to a certain extent protect against pulmonary tuberculosis, the two lesions may be found in the same body, because the tuberculous process began before the mitral disease, and in such cases it may be that a partial cure was favoured by the altered vascular conditions brought about in the lungs by the subsequent development of mitral disease. As to the coincidence of these two diseases, Sansom has collected thirty-one cases in which the two lesions were found together after death.[1]

Potain has gone so far as to consider that there is a direct connection between mitral stenosis and pulmonary tuberculosis, while Teissier regards the mitral stenosis as due to the lung lesion. In 130 cases of tuberculosis examined by Walsham[2] post-mortem, there was only one of mitral stenosis, and there the pulmonary lesion was quiescent; while in twelve cases of mitral stenosis the lungs were in every case free from tuberculosis. He also quotes cases of mitral stenosis in which there were clinical signs, at first sight suggesting pulmonary

[1] Sansom, *Allbutt's System*, vol. v. 1012.

[2] Walsham, *British Medical Journal*, 1899, vol. ii.

tubercle, but which either cleared up rapidly, failed to show bacilli in the sputum, or showed at the autopsy an absence of tubercle and the presence of a pulmonary apoplexy. He does not commit himself to saying mitral stenosis and pulmonary tuberculosis are antagonistic to each other, but cautiously contents himself with thinking that pulmonary tuberculosis cannot be regarded as causing mitral stenosis. The antagonism between heart disease and pulmonary tuberculosis was insisted on by Rokitansky, who explained this immunity as due to cyanosis. At the present time the general statement that morbus cordis protects against pulmonary tuberculosis must be given up; indeed, as already shown, there is doubt in the minds of some as to whether mitral stenosis, the condition for which most can be said on this score, is antagonistic to pulmonary tuberculosis. Further, there is no evidence that aortic disease prevents the development of tubercle. Cyanosis of itself does not prevent the growth of tubercles in the lung, for in congenital pulmonary stenosis, where cyanosis is such a marked feature, pulmonary tuberculosis is very frequent.

Is the protection against pulmonary tuberculosis exerted by mitral disease, and especially stenosis, due—

(i) To chronic venous engorgement, keeping the lungs moist and so allowing of the removal of bacilli before they can take root and flourish; or

(ii) To the increased quantity of blood in the lung leading to better nutrition and increased resistance?

These same questions apply to the explanation that is to be given as to the comparative rarity of pulmonary tubercle arising in the subjects of asthma, chronic bronchitis, or advanced emphysema. Does the moisture of the lungs prevent their infection, or is the hypertrophied right ventricle the factor of importance in virtue of the good supply of blood that it drives, necessarily at high pressure, through the diminished

area of the pulmonary artery? It is interesting to note in this connection that Sir S. Wilks[1] mentions that at one time Dr. Ramadge, an Oxford graduate, invented a cure for phthisis which was based on the assumption that emphysema and pulmonary tuberculosis were incompatible; in a patient who had the latter the indication, therefore, was to produce emphysema.

We will now pass on to some examples where one morbid condition has compensated for the bad effects of another.

A curious example came under my observation some years ago, in which extensive lardaceous disease of the intestines, by keeping the fæces liquid, prevented any symptoms of obstruction that would otherwise have been produced by three tuberculous structures of the colon.[2]

It is possible that an adherent pericardium may to some extent neutralise mitral stenosis, by tending to dilate the narrowing mitral orifice. Where symptoms are due to an unduly movable organ such as wandering spleen, or liver, an attack of peritonitis may bring the organ to anchor and alleviate the symptoms due to its locomotory habits. In a woman with a wandering spleen, who was under the late Dr. James Andrew's care ten years ago in St. Bartholomew's Hospital, an attack of peritonitis led to the organ becoming fixed, and thus relieved her symptoms.[3] On the other hand, the spleen has been known to become fixed in the inlet to the pelvis, and thus to be in such a situation as to interfere with parturition.

The production of adhesions around a cirrhotic liver as a result of an independent attack of peritonitis has been thought to have some effect in preventing the

[1] *Practitioner*, June, 1898, p. 571.

[2] *Trans. Path. Soc.*, vol. xli. p. 131.

[3] Andrewes, F. W., *St. Bartholomew's Hospital Reports*, vol. xxvi. p. 131, 1890.

development of symptoms,[1] and the operative treatment of the ascites of cirrhosis, by setting up vascular adhesions around the liver, started by Morison of Newcastle, has had some success.

The natural cure of too freely movable viscera by accidental attacks of peritonitis has been imitated by the artificial production of inflammation around the erring organ.

Dr. Campbell, in his valuable paper on the beneficial results of one disease as regards another, quotes a case where the symptoms of a loose cartilage in the knee-joint disappeared after an attack of traumatic arthritis, which led to fixation of the loose body.[2]

Traumatism may break down troublesome adhesions in a joint, and at the same time take the bread out of the bone-setter's mouth.

(2) Acute Disease May Cure Pre-existing Disease

Here the toxins of the second disease may act like a drug and destroy the pre-existing morbid process.

This is well illustrated by the curative effect of erysipelas inoculated on malignant growths; Coley has utilised this observation in the composition of his fluid, viz.: the combined toxins of the streptococcus erysipelatosus and the bacillus prodigiosus, which when injected into sarcomatous growths exerts a destructive action on them. Very possibly other bacterial poisons may have a destructive influence on the tumour formation. Dr. Campbell quotes a case[3] in which influenza, supervening in the course of malignant disease of the liver, was followed by rapid diminution in the size of the liver. The patient, indeed, seemed to get well, but in one and a half year's time the

[1] See case by F. P. Weber, *St. Bartholomew's Hospital Reports*, vol. xxxiv. p. 321.

[2] H. Campbell, *Brit. Med. Journ.*, vol. i. 1124.

[3] *Ibid.*, 1126.

growth returned and killed the patient. It is possible that in this instance a secondary streptococcal infection on the influenza attack may have manufactured a toxin that acted on the hepatic growth.

Other and familiar examples are afforded by the cure of a chronic affection such as granular lids by an acute inflammation set up by abrin, the vegetable albumose of Jequirity seeds, and by the cure of slowly healing ulcers by stimulation with lunar caustic.

Chronic skin affections are readily watched, and hence a number of examples where they have disappeared after acute illness are forthcoming:—

Chronic eczema of thirty years' standing, lupus, syphilitic eruptions, and chronic ulcers, have passed away under the fiery influence of erysipelas.

Psoriasis is a chronic disease, somewhat capricious in its course, which may be cured by acute disease such as acute gastritis. Most of us believe psoriasis to be so markedly influenced by arsenic that the drug is often regarded as a specific for it. In this connection it is interesting to quote the following remarks made by Dr. P. S. Abraham (*Clinical Journal*, February 15th, 1899): "My view about arsenic is that if you give enough of it to make the person very ill it influences the nutrition of the skin as of other parts, and the psoriasis may for a time disappear. It is the same with thyroid gland. If you use thyroid gland in some cases you will cure psoriasis, but the question is whether it is not at the expense of other organs." This same writer quotes cases showing the temporary cure of psoriasis by syphilis, influenza, and other fevers.

Dr. John Archer discovered that in the early stages of whooping cough vaccination will so modify the disease that its course is rendered comparatively harmless, even in winter.[1] This observation, which I must

[1] *Biographical Sketch of John Archer, M.B.*, by one of his descendants, *Johns Hopkins Bull.*, August—September, 1899.

admit is quite new to me, was made about the year 1800. If this is true, it is reasonable to suppose that the poison of vaccine may exert an inhibitory action on the development of whooping cough.

Dr. H. Campbell refers to the supposed beneficial effect of vaccination on influenza, pulmonary tuberculosis, and chronic skin affections.

Typhoid Fever as a Vermifuge.—One old name for enteric fever, and there are many, is worm fever. Louis noticed that round worms were often passed by typhoid patients, and Murchison had repeatedly seen round or tape worms voided by typhoid patients.[1] I have seen round worms vomited as well as passed by the bowel during typhoid fever; usually the worms are alive, and presumably have been driven from their usual habitat by the febrile lesions. As far as I know, the prognosis of enteric cases from which worms are voided does not in any way resemble that of a vessel deserted by rats. The few cases that I have seen have recovered.

In epilepsy, where morbid habit becomes an important factor, anything that breaks this habit will, temporarily at any rate, have a good effect. Thus epilepsy is usually successfully treated by a fresh doctor—for a time; change is the thing. Hence the transient success of operations or accidents in epilepsy, trephining, cutting off a meat diet, superseding a bromide course by borax, or *vice versâ*.

Chorea is a chronic disease, in which acute fevers like pneumonia or typhoid[2] have been thought to exert a curative influence. It is an old saying, Hippocratic in fact, that at the onset of fever the movements of chorea pass away. Sometimes the commencement of acute illness may make the chorea worse, and as the disease passes away the choreic movements also wane.

[1] Murchison, *Continued Fevers*, p. 616, ed. iii.

[2] West, *St. Bartholomew's Hospital Reports*, vol. xxii. p. 224.

Does the poison of an acute disease act on the cells of the cerebral cortex and render them incapable of continuing their riotous behaviour? Does it act as in former days a counter-irritant was thought to act—viz. neutralising the pre-existing lesion by setting up an additional morbid process?

Of these hypotheses to explain the cure of chorea by acute disease the former is the more probable, while both are more likely to be true than that the poison of the second disease directly neutralises that of the first.

These considerations are of interest in connection with the rationale of the treatment of chorea by arsenic. Does arsenic cure chorea because it makes the patient ill in another way, and unable to manifest the original disease? This seems unlikely in ordinary practice, where the toxic effects of the drug are hardly likely to be pushed too far. On the other hand it might be urged that arsenic is less successful in ordinary practice than in the hands of the successful quack in Newcastle, who gained a great reputation by giving heroic doses of arsenic. [*Vide* p. 146.]

In some instances it is said that an acute disease like pneumonia or typhoid fever may so interfere with the evolution of the secondary stage of syphilis that the latter is postponed for several months; possibly in some cases the primary infection is completely cured by the intervention of some acute disease, and the disease does not appear at all; if so, the occurrence of this happy cure is withheld from our knowledge.

If scarlet fever or measles supervene in the course of whooping cough, the whoop is often entirely dropped during the febrile access, to return when the temperature becomes normal.[1]

I have heard of influenza removing the pain of

[1] Caiger, "Co-existence of Infectious Diseases," *Allbutt's System of Medicine*, vol. ii. p. 291.

obstinate sciatica, and Dr. M. Mackintosh has mentioned to me two cases where during influenza pre-existing neuralgia disappeared.

Occasionally one hears that after a severe illness like typhoid fever a person is better than ever before in his life. Sometimes this may be due to rest and careful feeding—a kind of enforced rest cure. In other cases it may be due to the good effects of the low diet of the febrile period, and to the impossibility of gluttony and drunkenness. A possible explanation may be that the feeling of well-being after long illness is merely deceptive from contrast with the recent aches and *malaise*. As an example of the rest cure influence of typhoid fever, Sir H. Beevor has mentioned to me a case under the care of his colleague, Dr. Curnow, where a large aneurysm underwent consolidation while the patient was passing through an attack of typhoid fever.

(3) The Possibility of a Chronic Disease Protecting Chemically against Secondary Infection

This is highly hypothetical, but still, for that reason, of considerable interest. As a rule, chronic disease lowers the resistance of the body and disposes to infection; it is only exceptionally that it can be considered to serve a useful end in protecting against secondary infections. It is possible that this is the case in the relationship between Graves' disease and tuberculosis.

The subjects of Graves' disease seem immune from tuberculosis, while patients suffering from the opposite condition, myxœdema, are susceptible to it. This may be correlated with the infrequency of tubercle in the thyroid body, the good effect of thyroid extract in lupus, and with the condition of the thyroid body in Graves' disease and in myxœdema. It might be sug-

gested that Graves' disease, by supplying an increased quantity, though probably altered quality of the internal secretion of the thyroid body, protects the organism against the inroads of tuberculosis, just as it protects against obesity.

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31,
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PARK LANE, W.

Nov. 30. 1904

Dear Rolleston

Very many thanks for your book of Lectures & Essays. I see nothing juvenile in it: on the contrary it seems to me to bear marks of a ripe & extensive experience. For surely experience consists not so much in seeing many patients, as in turning those we see to good account.

Believe me yours truly,

Samuel Wilks

Mensque pacti
Experiens, animusque pelix.

as was said of Sydenham.