THE GOULSTONIAN LECTURES

ON

THE TYPHOID BACILLUS AND TYPHOID FEVER.

Delivered before the Royal College of Physicians of London,

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[ABSTRACTS.]

[THE introductory portion of the first lecture consisted of a historical account of the differentiation effected by Sir William Jenner between typhoid fever and typhus fever, and the recognition of the typhoid bacilli by Eberth. The lecturer then proceeded to discuss the methods which should be employed in identifying the typhoid bacillus. He laid especial stress on the serum test when performed in dilutions of at least 1 in 1,000, but pointed out that positive results obtained with lower dilutions could not be relied upon. He then proceeded to ask:]

Are we justified in saying that a bacillus which is only slightly sensitive to a strong typhoid serum is therefore not the typhoid bacillus, even though in all other respects it may resemble the latter? In other words, are all typhoid bacilli agglutinated by a given serum to an exactly equal extent? In the opinion of most observers this is the case, but Van de Velde,¹ from observations on twenty different typhoid stocks, found very considerable variations in the clumping power. The following observations also show that using 18-hour broth cultures, as is now the usual practice, marked variations in the clumping power manifested by different typhoid bacilli do exist. In these experiments typhoid serums of different typhoid clumping power were tested against the laboratory standard typhoid bacillus, and also against typhoid bacilli isolated from stools, urine, mesenteric glands, and spleen—bacilli which, be it remembered, were found to resemble the typhoid bacillus in all respects both morphologically and culturally. As a result it was found that their clumping powers differed most materially, some refusing to clump at all, others agglutinating with ease.

If broth cultures be used, typhoid bacilli often differ markedly among themselves in the ease with which they are affected by the typhoid agglutinins. With cultures on solid media, however, the case is different. Thus it is not uncommon to find that while a broth culture of a given typhoid bacillus cannot be agglutinated at all, the agar culture of the same bacillus may be easily and rapidly clumped by the very serum which failed with the broth culture. This extraordinary difference I have noticed in the case of six typhoid bacilli, isolated from different patients (and in a seventh case a similar result was obtained on using a gelatine culture), so that it cannot really be rare. It is possible, too, that it should be associated with a fact observed by Kraus,² who showed that if broth cultures of the typhoid bacillus be incubated for some days, and be then filtered, the filtrate gave rise, on the addition of typhoid serum, to a precipitate closely resembling in appearance that produced by agglutinated micro-organisms. The reaction was specific, and only occurred when typhoid serum was added. It may be that the constituent of the bacillary body, on which the agglutinins act, and which thus seems normally to pass into the surrounding liquid, may in some cases diffuse much more easily, and even after twenty-four hours be no longer present in the bacilli themselves. We should thus have an easy explanation of the absence of the reaction in the broth-grown bacilli, and its presence in those obtained from solid media. Be this as it may, the obvious moral to be drawn from the fact is that in testing the agglutinable qualities of a suspected bacillus, cultures on solid media should always be used, and especially therefore agar cultures.

So far, too, though my experiments are not numerous enough for me to speak with certainty, I have not noticed more than slight differences in agglutinable capacity between different typhoid bacilli, provided agar cultures be compared.

Pfeiffer's Test.—Should, however, a bacillus be discovered which culturally or morphologically resembles the typhoid bacillus in all respects, and which yet agglutinates but feebly

or not at all, then one further test must be applied to it—namely, Pfeiffer's test. This consists in injecting into the peritoneum of a guinea-pig a 10-times fatal dose of the bacillus in question, together with a very small quantity (0.001 c.cm. may be quite sufficient) of typhoid serum from a highly-immunised animal. If the bacillus in question be the typhoid bacillus, then while a control animal injected only with the bacillus will die this animal will recover, the bacilli being converted first into granular masses (Pfeiffer's phenomenon) and then gradually disappearing under the influence of the lysogenic properties of the serum. Such a serum, however, is specific, and can therefore only protect, in minute doses, against the corresponding micro-organism. If, therefore, the bacillus in question be not the typhoid bacillus, but some variety of bacillus coli, the animal will infallibly die like the control animal. This test is of the highest importance, for if properly performed a positive result is infallible. The test should always be applied in any case in which there can be doubt as to the nature of the micro-organism. If for example, a bacillus which should fail to agglutinate nevertheless should react like the typhoid bacillus to this test, then we must accept it as the latter.

[In regard to the typhoid bacillus as a saprophyte, the lecturer remarked that we must allow that so far there was no proof that the typhoid bacilli could multiply outside the human body. Two points respecting the toxins of the typhoid bacillus were emphasised, one that the toxins of that bacillus are for the most part contained within the bacillus itself, and are chiefly set free when the latter is destroyed; and the other that the toxin is a very feeble one as compared with those of certain other micro-organisms, and that to explain the symptoms of typhoid fever the number of bacilli present in the body should be very large, so that sufficient toxin may be formed. The lecturer recounted the evidence which went to prove that typhoid fever could be communicated to animals by means of the typhoid bacillus. The situations of the body in which the bacillus may be found were shown to be the mesenteric glands and spleen, the Peyer's patches, the liver, including the bile, the bone marrow, the kidney, the lung, and certain other glands, and in the blood. He continued:]

The reason why the bacilli are not found in greater numbers in the blood during life probably depends on the fact that in ordinary cases the blood is an extremely bad medium for their growth. Indeed, owing to its bactericidal power, it is likely that such bacilli as do not succeed in finding shelter in some viscus are rapidly destroyed. This would not occur to the same extent in fatal cases (perforation and similar cases being excluded), for often it is owing to such patients failing to acquire this power that a fatal termination ensues, and on this fact doubtless in part depends the greater ease with which the bacilli can be demonstrated in the blood after death. We may believe, therefore, as indeed we should expect from the distribution of the bacillus in the body, that the micro-organisms pass into the blood in all cases of typhoid fever. They are, however, rapidly eliminated from it into the various organs or destroyed. In rarer cases, on the contrary, probably always fatal, when the blood fails to acquire bactericidal properties, the typhoid bacilli may develop therein, and be found after death in considerable numbers.

THE TYPHOID ERUPTION.

It is obvious from the facts brought forward that typhoid fever is far from being merely an intestinal disease. Bearing this in mind, it will be interesting to consider the relation of the bacilli to the "spots"—the roseolous eruption characteristic of the illness.

The early observers for the most part were unable to demonstrate the presence of the bacilli in this lesion. Thus Wiltshur,³ Beitz,⁴ Curschmann,⁵ Merkel and Goldschmidt,⁶ and others in their numerous experiments all obtained negative results, while Rutimeyer⁷ obtained one positive result in six observations. In the light of these results the statement of Neuhäus,⁸ made as long ago as 1886, that he had obtained nine positive results in 15 cases, was generally received with incredulity. It may be said, therefore, that until quite recently the received opinion was that the spots in typhoid fever were not due to a local growth of the typhoid bacilli, but were more probably due to the absorption of the typhoid toxins into the general circulation.

Observers, however, were not entirely satisfied and continued working at the subject. In 1895 Thiemich⁹ reported that he had found the bacilli in the spots in three cases out of seven, while early in 1899 appeared the important paper by Neufeld,¹⁰ which apparently explained the discrepancies between the results of various observers. Neufeld argued that if the bacilli really were the cause it was evident they were only able to obtain their foothold in the skin and subcutaneous tissue for a very short time, otherwise the spots themselves would not be so fleeting; hence

to find them spots should be examined quite early in their development. Secondly, to eliminate as far as possible the bactericidal power of the blood itself, which would come in contact with the bacilli as soon as the spot was opened, he advocated the use of liquid culture media (broth) in order to dilute the blood and so diminish this source of error. The value of these suggestions was shown by his results. He examined the spots in 14 cases, and in 13 he obtained a positive result. His methods of testing the bacilli obtained were, it may be stated, admirable. These results were confirmed in November of last year by Curschmann¹¹ of Leipzig. Following Neufeld's methods he examined the spots in 20 cases, and in 14 he was able to demonstrate the typhoid bacilli, certain of his negative results also being evidently due to his having in some cases chosen spots already beginning to fade. Lastly, within the last few weeks, Richardson¹² of Boston, an extremely careful observer, reports similar successful results, the bacilli being isolated from the spots on an average six days before the Widal reaction was obtained. It should be added, however, that the number of typhoid bacilli in each individual spot must be very small, for though many observers have endeavoured to demonstrate them microscopically therein, they have never yet succeeded (Erast¹³ and Neufeld¹⁴).

There would seem, then, to be hardly any doubt whatever that the rose spots are truly specific in nature and are the result of the direct presence of the typhoid bacillus.

THE EXCRETIONS.

There are four excretions which have been described as infectious with more or less frequency—the sweat, the expectoration, the faeces, and the urine. At present there is no evidence to show that the bacilli do occur in the sweat, but we should always look upon the expectoration in the case of typhoid fever, if there be any, as a possible means of spreading the disease, and should take measures accordingly.

There can be now no reasonable doubt that in the first and second weeks of typhoid fever the stools are highly infectious. At later periods of the disease, however, and also during convalescence, if care be taken to obtain faeces uncontaminated with urine, it is extremely difficult to isolate the micro-organism. Thus Jemma,¹⁵ Richardson,¹⁶ and Lazarus¹⁷ all found great difficulty at this stage, and my own observations bear out their results. Thus out of 20 observations made during the later periods of the disease, sloughs being actually present in the stools in some instances, in one only was a positive result obtained, and in this case a relapse very shortly followed, though in the three cases in which the examinations were made before the seventeenth day in each the typhoid bacilli were demonstrated at the second attempt.

The specific micro-organism then can be demonstrated in the stools if care be taken during the first and second and early part of the third week of the disease, and possibly during the early part of the relapse. Later it cannot be demonstrated by our present methods. It follows, therefore, that the faeces are highly infectious at the commencement of the disease, and that later they become much less dangerous. How soon they become absolutely innocuous cannot be stated, but we must be prepared for the possibility of their remaining in some cases a source of danger for long periods after the patient is apparently well—as long, that is to say, as the bile continues to harbour the parasite.

The urine is the other great secretion by means of which typhoid fever is spread, or, as I believe myself, the chief means. Unlike the faeces, the urine only becomes dangerous in 1 out of every 4 cases of the disease, also as a rule it is towards the end of the disease or during convalescence that this condition occurs. While it is always difficult to find the typhoid bacilli in the stools, in the urine it is always easy, for when they occur they are nearly always in pure culture, and not uncommonly they are present in such extraordinary numbers that 1 c.cm. may contain as many as 500,000,000 micro-organisms.

[In conclusion, the lecturer considered how the facts adduced bore upon our conception of typhoid fever, and proceeded:]

Any conception of this disease which regards it merely as affecting the alimentary canal only can no longer be maintained. On the contrary, so far from considering it as an intestinal disease pure and simple, we should rather look upon it as a modified form of septicæmia. It is septicæmia in that always and in all cases the bacilli pass into the blood and then into the various organs, and in that the symptoms, excepting as far as they are intestinal, are referable to the poisons there produced. It is a modified form, however, in that in nearly all cases there is a definite local and primary disease whence the secondary dissemination of the micro-organism takes place.

Looked at in this way we have a ready explanation of the

fact that the severity of the disease bears no relation to the number and character of the intestinal lesions. For just as a fatal septicæmia may originate in a scratch, so one or two small typhoidal ulcers may be quite sufficient to allow the entry of the micro-organism and the development of the disease.

[The second lecture commenced with a discussion of the relation of relapses of the disease to the typhoid bacilli on the one hand, and to autointoxication by the toxins of non-specific organisms on the other. Reference was then made to the occurrence of typhoid fever without intestinal lesions, and the lecturer proceeded as follows:]

In this connection an important fact strikes one on reading the records of the *post-mortem* examinations. It is that, though in all cases the intestine is described as being quite natural, yet in nearly all we find that the mesenteric glands were affected, being for the most part enlarged, swollen, and reddened, very much indeed as we find them in ordinary cases of typhoid fever. This would seem to suggest strongly that in these cases also the bacilli commonly enter the body through the intestine, passing, however, directly through the intestinal wall into the lymphatic glands, where they germinate and whence they become generalised as usual. The passage of micro-organisms through an apparently intact mucous membrane would seem to be by no means an uncommon event, the common presence of tubercle bacilli in the bronchial glands being a well-known example in point.

There would seem, then, to be the strongest evidence in favour of the view that sometimes, though rarely, the typhoid bacillus may pass into the blood and become generalised in the organs, just as occurs in ordinary typhoid fever, but without first causing any intestinal disease, even though, as is probable, the bacilli enter through the intestinal tract.

TYPHOID FEVER IN THE FŒTUS.

It is interesting to notice that a very similar form of the disease is by no means uncommon in the foetus. Indeed, fetal typhoid fever of the primary septicæmic type is a frequent, though by no means the only, cause of the abortion which so commonly occurs during the disease. Experimentally it was shown many years ago by Chantemesse and Widal¹⁸ that the placenta formed no bar to the typhoid bacillus, and at the present time a considerable number of cases are on record in which the micro-organism has been found in the human foetus. One of the most interesting of these is the following, observed by Dr. Andrewes, in the case of a foetus from a woman suffering from typhoid fever, who aborted in the fourth month during the epidemic at King's Lynn. The typhoid bacillus in this instance was found in pure culture in the heart's blood and also in the spleen. Morphologically (including flagella) and culturally in all respects it resembled the typhoid bacillus, while its agglutinable qualities were so marked that for a time it was used as the laboratory standard culture.

It should be noted, too, that in these cases, though the bacillus may be found in the blood and in many of the internal organs, the intestine is always natural (Etienne,¹⁹ Freund and Lévy,²⁰ and Janiszewski²¹), and this indeed is what we might expect, seeing that the bacilli having broken through the placental barrier pass directly into the circulating blood without coming first in contact with the alimentary canal. Typhoid fever, then, in the foetus is an example of a primary typhoid septicæmia.

[Evidence was then adduced to show that as in the lower animals, so in man, a local disease such as cystitis might be set up by the typhoid bacilli without producing a general infection. The question of the complications of typhoid fever was then discussed, and an analysis of the results of 300 cases which had occurred at St. Bartholomew's Hospital during the past thirty years was brought forward and commented upon. It was shown that while meningitis and neuritis were probably due to the typhoid bacilli, and that arteritis was possibly so, lobar pneumonia, laryngeal ulceration, and phlebitis occurring in typhoid fever were probably not specific; that, although the presence of nephritis in typhoid fever was no certain indication of the presence of typhoid bacilli in the kidney, yet, as evidence was advanced to show, the nephritis was sometimes directly due to the specific bacilli. The lecturer then passed on to the subject of]

TYPHOID BACILLURIA AND CYSTITIS.

In drawing attention to the presence of the bacilli in the urine some little time ago²² I was only able to prove without doubt the existence of the condition, and could not venture at that time to state how frequent its occurrence might be. Lately, however, I have had the opportunity of examining a large series of cases, and the results of my observations I now bring forward. In all, 45 cases of typhoid fever were examined; in 28 of these the urine was never found to contain typhoid bacilli, while in 17 these bacilli were found. This would give apparently a percentage of nearly 38 for the positive results. It is, however, undoubtedly too high, for out of the 17 positive results 6 were cases in which the abnormal condition of the urine had attracted attention, and in which a bacteriological examination was therefore requested. Eliminating these, then, we find that 39 typhoid fever cases have been taken at random in the wards, and the urine examined on several occasions. Of these cases 28 never contained typhoid bacilli, while 11 contained them in large quantities, constituting a percentage of 28. In London, then, at all events it will probably be correct to say that at least 25 per cent. of all cases present this serious and dangerous condition. This conclusion is also supported by the fact that it agrees approximately with the results obtained by Richardson,²³ This observer, working in Boston, examined the urine in 102 cases of typhoid fever, and in 23 he was able to isolate the bacillus, obtaining, therefore, a percentage of 22.5. At the present time, then, the evidence would show that the condition is one frequently met with, and that it probably occurs in one out of every four typhoid fever patients. An important point also in connection with the condition is the fact that very commonly the bacilli are present in enormous numbers, so that the urine is rendered turbid. I was at first inclined to regard these cases as rare, but really they are the rule rather than the exception. Thus out of 14 recent cases in which this point was especially looked for, in 12 I found that the urine was turbid with bacilli, while in 2 only was it noted as "clear," and the microbes were accordingly first discovered on culture. The enormous numbers in which the micro-organisms may be present has been already referred to; but this very fact, though it increases the danger of the complication, brings with it the advantage that the condition can be recognised, or rather suspected, more easily. Indeed, this can often be effected by the naked eye. All that is necessary is to pour the turbid urine into a test tube and then hold it up to the light and gently shake it. If the turbidity be due to the presence of micro-organisms, we notice at once a curious shimmer in the liquid exactly comparable to that seen in shaking any turbid broth culture, a phenomenon which is not seen when the urine is cloudy from other causes, such as phosphates, urates, etc., probably because the amorphous particles of which these deposits consist are unable to catch and reflect the light in the same way as the regularly shaped bodies of the bacteria. If, then, in a turbid typhoid urine this curious shimmer is seen it may at once be predicted that the urine is full of micro-organisms, and the typhoid bacillus should be at once suspected, for experience shows that when this condition is noticed in typhoid fever, if the patient be a male, it is most commonly due to the presence of the true typhoid bacillus. This, however, can only be proved by cultivation, and even in the male the same naked-eye appearance may sometimes, though much less commonly, be produced by other microbes, such as the bacillus coli communis, the streptococcus pyogenes, and the staphylococcus aureus. In the female, however, much less reliance can be placed on a mere inspection of a naturally passed urine, the sources of contamination being so gross.

Conditions Governing the Appearance of the Bacilli.—The bacilli may make their first appearance in the urine at any period of the disease. The earliest date on which I have myself isolated them was the thirteenth day, and in this case they had undoubtedly been present from a much earlier period. The latest date on which I have known them first to occur was the fourteenth day of convalescence. Speaking generally, however, we may say that the condition is rare before the third week of the disease. After this it may occur at any time during the fever, but not uncommonly its occurrence is delayed until the early days of convalescence. It

is, therefore, much more closely associated with the later stages of the disease. The duration of the bacilluria also varies. The shortest duration recorded is eight days, but in four other cases it had not disappeared until after the lapse of twenty-one days, twenty-five days, thirty days, and seventy days. Occasionally it may persist, not for months, but for years, as in a remarkable case recorded by Gwyn.²⁴ In this case the patient had been in the hospital five years before with an attack of typhoid fever. Ever since his discharge he had had trouble with his bladder, and on readmission he was found to be suffering from cystitis and the typhoid bacillus was obtained in pure culture from his urine. The condition of the urine, too, offers no constant qualities. Not uncommonly, even when millions of bacilli are present, albumen is totally absent, and when present, it usually does not amount to more than a trace or a cloud. In rare cases it may be present in larger quantities—one-sixth or one-seventh in two of my cases. In one case hæmaturia occurred.

Frequency of Associated Pyuria.—Although, however, albuminuria is not conspicuous in these cases it is not at all uncommon to find pus, sometimes even in considerable quantities. Thus of my 17 cases, 9, or over 50 per cent., showed pyuria. The urine in nearly all cases was acid. It was never ammoniacal. Lastly, it has sometimes been said that the cases in which typhoid bacilluria occurs are more severe than those not showing this condition. Taken as a whole this is true, but it is equally true that patients may have typhoid fever of extreme severity without the urine ever becoming infected. In no case, then, we can say from the condition of the patient or from the presence or absence of albuminuria that bacilluria has occurred. We should however, suspect it if either the urine becomes suddenly turbid and manifests the "shimmer phenomenon" or if pyuria occurs.

THE PATHOLOGY OF THE CONDITION.

How is the bacilluria produced and on what does it depend? The simplest explanation which suggests itself—namely, that we have to do with a mere filtration of the bacilli from the blood—may be at once dismissed. The extreme difficulty in finding the bacilli in the blood during life would point to its improbability. Moreover, I have on four occasions examined the blood bacteriologically, at a time when the urine was swarming with bacilli, and on all occasions I failed to find the typhoid bacilli therein. A second suggestion is that the condition arises from suppuration set up in the kidney by the typhoid bacillus, accompanied by the secondary passage of the bacilli and pus into the urine. Such cases do undoubtedly occur, one being recently recorded by Flexner,²⁵ but they are extremely rare. Thus out of 289 *post-mortem* examinations on patients who had died from typhoid fever at St. Bartholomew's Hospital during the last thirty years, in one case only were abscesses found in the kidneys. This rare condition, therefore, could hardly explain the very frequent presence of the bacilluria.

We are driven, then, to our third possibility to offer an adequate explanation of the condition. According to this view, which I believe to be correct, the whole would depend on a rapid growth in the urine itself within the bladder of the bacillus, a stray micro-organism having found its way there from the blood, doubtless after its passage through the kidney. This explanation would seem to meet the facts of the case, for it would explain the chief peculiarities of the condition—namely, the sudden onset of the affection, the enormous numbers of the micro-organisms, and not uncommonly the total absence of albuminuria. It would also readily explain the frequency of pyuria in these cases, which would be due to the onset of cystitis. It has, however, by some observers been doubted whether the typhoid bacillus can grow and multiply in urine. As a matter of fact there is no doubt that it is able to do so.

Thus I found that out of six samples of urine taken and inoculated with the typhoid bacillus and then incubated at 37° C. four showed general turbidity, though varying in degree, from growth of the micro-organism at the end of eighteen hours, while two did not. These latter, however, showed good growth at the end of forty-eight hours.

The typhoid bacillus evidently, then, can grow in most urines, though the rapidity of growth varies with the specimen of the urine used. On the latter fact, also, doubtless in part depends the absence of the bacilli in the urine in so many

cases of typhoid fever. We must believe that in every case, since the bacilli always pass into the blood, every now and then a stray bacillus is carried into the kidney and so passes into the urine. If, however, the urine be in this case not very suitable to the growth of the micro-organism, and if, too the bladder be evacuated frequently and completely, then the micro-organism will be excreted in the urine before it has time to multiply. If, however, as is often the case in typhoid fever, the patient only passes his urine at long intervals, perhaps not emptying the bladder completely, then, if the urine be a favourable medium, the bacillus will have ample opportunities to grow and multiply and marked infection of the urine will result.

In addition, however, to the above considerations we have positive evidence that the *fons et origo* of the condition lies in the bladder itself. In the first place, the condition can be cured by the injection of antiseptics into the bladder. This was shown very clearly by Richardson,²⁶ who in a given case, having failed with boric acid, was at once successful when perchloride of mercury (1 in 7,000) was substituted. Gwyn²⁷ also has had a similar experience. Secondly, a short time ago I had the opportunity of examining one of these cases *post mortem*.

The patient was a man, aged 31 years, who died on the nineteenth day of the disease from heart failure. The urine was examined a few hours before death, and was found to contain one-seventh of albumen and to be strongly turbid with typhoid bacilli in pure culture. Death occurred a few hours later. At the *post-mortem* examination the usual intestinal lesions of typhoid fever were found. The Peyer's patches and solitary follicles were swollen and beginning to ulcerate. The spleen was enlarged and soft. The kidneys to the naked eye showed only engorgement, and microscopically nothing beyond cloudy swelling could be demonstrated. The bladder, however, showed a few scattered hemorrhages and its mucous membrane was slightly injected. Bacteriologically the typhoid bacilli were demonstrated by culture in the spleen, the liver, and the gall bladder, as well as the bladder urine, but the cultures from the heart's blood, the lungs, and both kidneys were sterile. I should say that, in all, four separate bacteriological examinations were made from the kidneys, two from each organ, but all four yielded absolutely negative results.

In this perfectly typical case, then, there can be no doubt as to the source of the bacilli. They were not found in the blood or in the kidneys, but they were present in the urine in enormous numbers. There would seem to be no reasonable doubt that a stray bacillus had passed into the urine and had multiplied there, and so given rise to this condition.

We are, then, evidently dealing with what foreign writers would call a specific "bacteriuria," meaning by this term that the urine is swarming with micro-organisms, though no definite symptoms are produced by this condition. This affection has been known for years. Indeed, it was the late Sir William Roberts²⁸ who first drew attention to it. His observations, however, did not attract general attention, and it was not until 1894 that Krogus²⁹ published 8 cases all due to the presence of bacillus coli communis, and since this other writers have confirmed his observations. No hard and fast line, however, can be drawn between bacteriuria and cystitis. While a typical case of bacteriuria will give rise to no symptoms, and will at most show under the microscope a few scattered pus cells in addition to the bacilli, there are others in which the patient may complain of slight pain in passing the urine and slight frequency of micturition, the number of leucocytes also increasing, but still not forming a deposit visible to the naked eye. Finally, these cases merge again into cases of frank cystitis. Now, this is exactly what is also noticed in the bacilluria of typhoid fever. According to my experience about half the cases are examples of simple bacteriuria. The patients complain of absolutely no symptoms whatever; there is no frequency of micturition, and no pain accompanies the act. The urine itself swarms with bacilli, and beyond this nothing can be seen abnormal in it. Under the microscope, however, an occasional pus cell can generally be found. These cases are nearly always undetected because of the absence of symptoms. There are, however, others in which, in addition to the bacilli, there is an evident deposit of pus visible to the naked eye, showing that the bladder mucous membrane has become slightly inflamed. The inflammation, however, must be very slight, for usually in these also no symptoms are manifested. Lastly, we have cases in which, while the urine contains bacilli and pus, but remaining of course acid, since the typhoid bacillus has no power to decompose urea—we have clinical symptoms—namely, pain and frequency of micturition and possibly tenderness over the

region of the bladder. These cases of obvious typhoid cystitis are rare. The mere presence of bacteria in the bladder is not sufficient of itself to cause cystitis. Some predisposing cause is also necessary, as, for example, some injury to the bladder walls. Now in typhoid fever so many tissues suffer from the effects of the fever that it is not very hazardous to assume that in some cases the mucous membrane of the bladder may be damaged with the rest. If, then, in a case of typhoid fever the mucous membrane is in a natural condition, and if the urine be passed at the usual intervals, then if bacilluria occurs it will remain a simple bacilluria. But should there be marked retention, or should the bladder walls have been damaged in any way during the course of the disease, then we have the condition in which a frank cystitis may be set up. This view receives valuable support from experiment, which shows that according as the circumstances vary the typhoid bacillus is capable of causing now a simple bacilluria, now a pure cystitis.

CHOLECYSTITIS.

[The lecturer then pointed out that a very close parallel might be drawn between the relation of the bacillus to the urinary bladder and that which it bears to the gall-bladder. He continued as follows:]

In the latter, just as in the former, it is not uncommon for the micro-organisms to be present in large numbers, but to give rise to no symptoms. Should, however, retention be produced or the walls irritated by the presence of gall stones, then cholecystitis follows, just as cystitis does in the case of the urinary bladder. In reading the record of the true typhoid cases of cholecystitis it is noteworthy how almost constantly gall stones were found at the time of operation. If inflammation of the gall bladder occur after a case of typhoid fever, and the specific bacilli be found in pure culture, the sequence of events in all probability has been, first the formation of gall stones, and only secondly cholecystitis. In a few cases—and this is especially seen in those rare ones occurring in the fever itself—the gall bladder may become inflamed primarily through the action of the typhoid bacillus, without gall stones being present. But in these cases, just as with typhoid cystitis, the walls have in all probability been damaged through the stress of the disease and the predisposing cause is therefore already present.

SUPPURATION IN TYPHOID FEVER.

We may now turn our attention to suppuration in typhoid fever. In the earlier days of bacteriology all suppurations occurring in typhoid fever were regarded as due to a secondary infection by the pyogenic micro-organisms, and the experiments of Dmochowski and Janowski³⁰ and others, showing that experimentally the typhoid bacillus is quite capable of producing suppuration, came therefore somewhat as a surprise. Their correctness, however, was soon demonstrated, for it was shown that not uncommonly in man, especially in the abscesses connected with bone, the typhoid bacillus could be obtained from the pus in pure culture.

[Reference was made to 12 cases of typhoid suppuration occurring at St. Bartholomew's Hospital, which had been examined bacteriologically; in two of these, both of which were connected with bone, typhoid bacilli were found in the pus, but in the other 10 they were not found although in 2 of them the suppuration was associated with periostitis.]

THE PERSISTENCE OF THE TYPHOID BACILLUS IN THE BODY.

There is one other point which it may be of interest now to consider, and that is, What is the length of time during which the bacillus may remain in the body? It was naturally supposed at first that as the fever passed away and as health returned the bacillus, the cause of the disease, would disappear from the tissues also. This apparently was demonstrated by the earlier observations. Thus it was shown long ago that if the spleen or mesenteric glands—the classical breeding grounds of the microbe—be examined late in the disease, no typhoid bacilli would be found, the organs being either sterile or possibly containing bacillus coli communis. This has been noticed by Flexner³¹ as early as the sixth week. Dr. Klein³² recorded it in the ninth week, and recently a case dying at St. Bartholomew's Hospital in the thirteenth week showed the same disappearance of the specific organisms. The experiments of Blackstein and Welch,³³ however, showed that, some-

times at least, the typhoid bacillus might remain for much longer times in the body. Thus after intravenous injections of the bacillus into rabbits, they found that the bile still contained the micro-organisms when the animals died or were killed at such long intervals as 84 days, 109 days, and even 128 days after the date of inoculation. The other organs were, however, found sterile.

These experimental results in animals naturally suggested that the same thing might occur in man after typhoid fever, and this has been amply proved, for we now know that it is nothing uncommon for the bacilli to remain dormant in the bile or the bone marrow for long periods, the patient, just like the experimentally inoculated animal, being meanwhile often in perfect health, and then, possibly after several years, under the influence of some passing stimulus, to resume their activity and to give rise now to periostitis, now to osteomyelitis, or it may be to cholecystitis.

CONCLUSIONS.

We can no longer regard typhoid fever as purely a disease of the intestines. In ordinary cases indeed the intestinal lesions form the starting point of the disease, but rapidly the bacilli become generalised, and a septicæmic condition ensues, the micro-organisms being found in the most varied portions of the body and not uncommonly in the blood itself. Secondly, this septicæmic condition may occur without any obvious lesion of the intestinal tract. In some cases, too, both of the ordinary intestinal variety and of those without intestinal lesions, the stress of the disease may fall with special severity on one of the internal organs—for example, the meninges or the kidneys—so that the terms “meningo-typhoid” and “nephro-typhoid” may actually represent a pathological fact. It is probable that the typhoid bacillus is capable under certain circumstances of producing a local lesion only—such as a cholecystitis or a cystitis—without giving rise to a general disease.

[The third lecture commenced with a historical account of the discovery of the agglutinating power of the blood in typhoid fever. The technique which should be employed in performing the reaction was next discussed.]

TECHNIQUE.

The Dilution to be Used.—As originally proposed by Widal for the “extemporaneous” or microscopical method, a dilution of the serum 1 in 10 was adopted. This was somewhat too low, a considerable number of cases being recorded in which a positive reaction was obtained although the patients were not suffering from, and had never had, typhoid fever. The dilution has therefore been generally raised, and the only question at issue is the exact dilution which should be decided upon. If we raise the dilution considerably to 1 in 100, for example—we diminish the value of the test, for some 20 per cent. of cases never show a clumping power as marked as this, while others again only reach this height late in the disease, when the reaction is as a rule no longer needed. If, on the contrary, we choose too low a dilution, we run the risk of error of diagnosing as typhoid fever cases which are not really so. Without pursuing the subject further at this moment, I may say that on the whole a 1 in 20 dilution would seem from a practical point of view to attain the results in the most satisfactory manner.

The Time Limit.—It would seem that a short time limit should be employed, one hour perhaps being the most suitable. It is, of course, possible that slight delayed reactions may be due to the presence of small amounts of the typhoid agglutinin, but it is equally true that they may also result from the agglutinins of other micro-organisms, such as Gärtner's bacillus enteritidis, which in small amounts would only produce an effect after some considerable time.

The Typhoid Culture.—If broth cultures are used most marked differences in clumping power between various typhoid bacilli can be demonstrated. The difference seems to be in some way connected with the culture media, and does not mark as a rule any inherent difference in clumping power between various typhoid stocks, for often an agar culture from the same bacillus would clump admirably in high dilutions with the very serum which produced no effect on the broth culture. Since, however, the latter from their convenience are always now used in performing the reaction, it behoves us to select a culture the clumping power of which in this medium is not diminished.

The Use of Dead Bacilli.—It was early shown by Bordet that the reaction was not concerned with the life of the bacillus. This was confirmed by Widal and Sicard³⁴ as regards the typhoid bacillus, and they showed that perhaps formalin was the best reagent for killing the bacillus, while yet leaving its sensibility towards the agglutinating serum absolutely intact. From a practical point of view, however, it may be said that while dead cultures act admirably if the agglutinating power of the serum be marked, they are less satisfactory in doubtful cases, which would be returned merely as “suspicious,” for owing to the bacilli being dead we no longer see those characteristic movements made by the bacilli in their efforts, as it were, to free themselves, which so often attract attention and lead us to examine the blood again a day or two later. The routine use, therefore, of dead cultures would thus seem to be hardly advisable, though for emergency use they are of great value.

We may now ask, What reliance may be placed upon the

test if it be performed in the manner suggested, that is to say, using a very sensitive eighteen-hour broth culture, a dilution of 1 in 20, and a time limit of one hour, a “positive reaction” only being returned when the clumping is marked and general, and when the few bacilli not clumped are rendered motionless? In the first place, it may be said that, tested by experience at St. Bartholomew's Hospital, even though here as a rule a time limit of two hours has been allowed, this low dilution does not seem to have failed. During the last three years, 1897 to 1899, the reaction has been tested and the result noted on 546 occasions. Of the cases so examined over 200 proved themselves later by their clinical course, verified not uncommonly by *post-mortem* examination, to be not typhoid fever, and in only one of them was the reaction positive.

The one exception was a case of great interest. It was that of a woman who while in the hospital had symptoms resembling those of typhoid fever. The Widal reaction was returned as “just positive.” At her death, however, a few days later, the case proved to be one of septicæmia. No typhoid lesions were found at all, nor was the typhoid bacillus found in her spleen. This organ, however, contained the staphylococcus pyogenes aureus in enormous quantities. It seemed at first sight as though the reaction was here at fault. Inquiries, however, were made by Dr. Drysdale, and it was ascertained that four months before her death the patient had been treated at home for typhoid fever. An easy explanation was thus afforded for the presence of the agglutinating reaction during her stay in the hospital.

Mr. H. E. Durham has shown that the serum of a patient suffering from typhoid fever may react strongly to the bacillus enteritidis (Gärtner), and there can be no doubt that the agglutinins of Gärtner's bacillus as well as the typhoid agglutinins are present in the blood in many cases of typhoid fever. But is this any reason against using a 1 in 20 dilution in performing the test, as has been urged? It would seem not, for it was found that the serum of an animal artificially immunised against Gärtner's bacillus does not clump the typhoid bacillus in a 1 in 20 dilution (microscopical method, time limit one hour) until the serum is capable of agglutinating Gärtner's bacillus itself, at least in a dilution of 1 in 1,000. Now such a condition of affairs rarely if ever occurs in human typhoid fever or in cases resembling it clinically. If, then, the serum of a case which suggests typhoid fever produces complete clumping of the typhoid bacillus within one hour in a dilution of 1 in 20, then only in the rarest cases can this be due to the presence of Gärtner rather than the true typhoid agglutinins.

Rare Cases in which the Reaction is at Fault.—It should be noticed, however, that a positive reaction obtained with a 1 in 20, or even a 1 in 40 or 1 in 50 dilution and a one-hour time limit is not an absolute proof that the patient is suffering from typhoid fever. Such reactions have been obtained in a few cases which afterwards proved themselves to be not typhoid fever; not a few of them were possibly due to anterior attacks of typhoid fever, or occurred in the earlier days as the result of faulty technique, too long a time limit, for example, being allowed.

Conclusion.—For all practical purposes a 1 in 20 dilution with a short time limit (one hour) gives admirable results. A positive reaction so obtained has a diagnostic value about equal to that of the eruption, that is to say, that in extremely rare cases both may be observed in cases which are not typhoid. If, however, in any given case we require from the test absolute infallibility, then we must use in addition greater dilutions, such as 1 in 100, or even higher, employing of course the same time limit (one hour). But to use such dilutions as a matter of routine would be an error, since we should thereby wilfully diminish the value of the test by excluding many cases of typhoid fever (nearly 20 per cent.) which never reach even the 1 in 100 limit during any part of their course. It is probable that in 97 per cent. of all typhoid fever cases the reaction can be obtained in a dilution of 1 in 20 at some period of the disease. If, however, a 1 in 100 dilution be used as a routine, then the percentage falls very greatly. Widal's cases show that under these circumstances out of every 100 cases 17 would never show the reaction, while Lorrain Smith's cases would place the percentage of negative results even higher.

VALUE AND DURATION OF THE REACTION.

Date of Appearance of Reaction.—Dr. Churchill was able to analyse 40 of the positive cases at St. Bartholomew's Hospital in which the commencement of the illness could be fixed, and

he found that the average date of the first appearance was not later than the thirteenth day, though 9 of the 40 cases gave a positive reaction between the fifth and eighth days. We may say, then, that while the reaction may occur before the end of the first week this is unusual. It is more common for it to make its first appearance during the second week, but not rarely it may be delayed until the third or fourth week or even beyond this period.

Complete Absence of the Reaction throughout the Disease.—It has been stated that the reaction is not to be obtained in roughly 3 per cent. of all cases of typhoid fever. Possibly even this number may be too high, for conceivably some of the cases may not have been really typhoid fever. There is no doubt, however, that cases proved bacteriologically to be typhoid do exist, in which throughout the whole course of the disease no reaction can be obtained. Three cases of this kind have been recorded, and a fourth was recently observed in St. Bartholomew's Hospital (under the care of Dr. Church).

Duration of Reaction.—The only way of ascertaining how long the reaction persists after recovery is to follow a series of cases month by month until the final disappearance of the clumping power be noticed. Fourteen cases were examined in this way. In 2 it was never obtained after defervescence, in 5 it disappeared within six months, in 4 within one year, while in 2 it was still present at periods of one year and six months and two years respectively after the attack. In other words, we may say that in half the cases the reaction was no longer observed after six months, while in the great majority (12 out of 14) it had disappeared by the end of a year.

Prognosis.—It has been suggested by some observers that it is possible to use the reaction as a means of prognosis as well as of diagnosis. So far as my own observations extend, I have seen nothing which lends support to the view. A very weak serum reaction, even in a severe case, is no bar to a complete recovery without relapse and complication, and should not therefore indicate a bad prognosis.

THE ORIGIN AND NATURE OF THE AGGLUTINATING SUBSTANCE.

[The lecturer at this point discussed the nature of the agglutinating substance, advancing evidence to show that it was of the nature of an enzyme.]

Concerning the mode of origin of the agglutinins, the view which originally suggested itself was that the agglutinins are secreted by the body cells, much in the same way as are the antitoxins. It should be noted, however, that recently a totally different theory has been put forward, according to which the agglutinins are a direct secretion of the bacilli themselves.

[The lecturer examined the evidence on this point, and arrived at the conclusion expressed in the following sentence:]

The evidence at present in our possession points strongly to the view that the agglutinins are ferments not directly secreted by the bacilli themselves, but produced by the cells of the body, and especially those of the spleen, the lymph glands, and the bone marrow (Deutsch)³⁵ under the influence of the stimulus produced by the invading micro-organism.

[The mechanism of agglutination and the relation of agglutinins to lysins and the connection of the former with immunity were then discussed. In regard to the latter point the lecturer summarised his views as follows:]

Agglutination is a reaction of infection. But at present we have no direct evidence proving that it takes a share in the production of immunity probable though this is. It may be that agglutinated bacilli are more sensitive than others to the action of the alexins or bactericidal bodies, and that the object of agglutination is therefore really to prepare the way for the action of the latter. This, however, is not yet proved, and meanwhile we must remember that a patient or an animal may be rendered absolutely immune to typhoid fever or cholera without the blood ever acquiring agglutinative properties at all, so that agglutination in the ordinary sense cannot be necessary for the production of immunity. It is possible, however, that even in these cases traces of the agglutinins may by slightly affecting the bacilli further the action of the lysins and thus assist in bringing the immunity about.

ANTITOXIC POWER.

Does the blood acquire antitoxic as well as agglutinative and bacteriolytic properties? At present we have no evidence

whatever that such formation takes place. Sanarelli,³⁶ Pfeiffer and Kolle,³⁷ and Funck³⁸ are all agreed on this point, and the result of their observations, both on typhoid patients as well as on immunised animals, shows that, just as in cholera, so also in typhoid fever, antitoxins, if developed, are formed only in such small quantities that their presence cannot be demonstrated.

THE VALUE OF UROTROPIN IN TYPHOID FEVER.

I desire, in conclusion, to bring before you the marvellous effects which are produced by the administration of urotropin in cases of typhoid bacilluria and cystitis. Urotropin is formed by the action of formalin on ammonia, and was recently introduced into medical practice by Dr. Arthur Nicolaier³⁹ as a urinary antiseptic. It was soon found to have considerable value in checking the decomposition of the urine in cases of ammoniacal cystitis, the effect being due, as Dr. Nicolaier has shown, to the liberation of free formalin from the drug after its passage into the urine. It is true that in the acid cystitis produced by bacillus coli its effect is almost nil, so that it cannot be regarded, as some too hastily have thought, as a specific for all forms of urinary infection. So far, however, as one variety is concerned it does deserve the name. I allude to its effect on the true typhoidal affections of the urinary tract. Attention was called to the matter last year by Richardson,⁴⁰ who in nine cases found that the typhoid bacilli rapidly disappeared from the urine after its use, and I may say at once that my own observations most strongly support his results.

The following photographs represent more clearly than any figures could do the valuable action of the drug:

Fig. 1.—(a) A cultivation made from 2 drops of the urine before taking urotropin; many typhoid colonies seen (the slightly opaque appearance of the colonies is due to their having sunk a little from the surface into the gelatine owing to the very hot weather). (b) From 2 drops after taking 30 grs.; nothing grown.

Fig. 2 shows two tubes of gelatine. Tube a was inoculated on the twenty-fourth day of the illness with two drops of the patient's urine. A pure cultivation of what proved to be the typhoid bacilli developed (the slightly opaque appearance of the colonies being due to their having sunk a little from the surface into the gelatine owing to the very hot weather). The patient was then put on urotropin, 30 grains three times a day; and on the twenty-sixth day of his illness, after 30 grains of the drug had been taken, cultures were again made. Tube b shows such a one made with two drops of urine: Nothing, however, grew. The typhoid bacilli had all been destroyed and eliminated, and though the drug was stopped after 60 grains had been given, cultures made on four subsequent occasions never showed any return of the typhoid bacilli.

Fig. 3 shows a somewhat similar result. Tube c represents a gelatine tube inoculated with a trace of urine of September 16th (the fifty-first day).

A pure culture of typical typhoid colonies is seen. The patient was then put on urotropin, 10 grains three times a day, and in tube *d* we see a gelatine tube over the surface of which three drops of urine were spread, the urine having been obtained after 30 grains of the drug had been taken. Again the cultivation proved sterile. The typhoid bacillus had been

Fig. 2.—(*c*) A cultivation made from a trace of the urine before taking urotropin; many typhoid colonies seen. (*d*) From 3 drops after taking 30 grs.; nothing grown.

eliminated and destroyed. The drug was, however, continued until 120 grains had been given (four days in all), but the typhoid bacilli did not return, as proved by subsequent cultivation of the urine.

Fig. 3.—Showing the change from the turbid bacilluric urine (*e*) to a normal clear urine (*f*) after 30 grs. of urotropin; cultures proved the absence of the bacilli.

Fig. 4 represents the same result, but in a somewhat different way. In this case a drop of the urine itself was stained before and after the administration of 30 grains of the drug. In the one case enormous numbers of

typhoid bacilli are seen, in the other none were visible. Cultures also showed their absence. The drug was continued until 120 grains had been given and it was then stopped; the bacilli, however, did not return.

Fig. 4.—A drop of the urine dried and stained, showing innumerable typhoid bacilli. A drop prepared in the same way after taking 30 grs. of urotropin showing no typhoid bacilli; their absence was confirmed also by cultivation.

Fig. 3 shows the marvellous naked-eye change which is produced in the urine by the administration of the drug; *e* represents the urine itself, on the eighteenth day, turbid as it was with bacilli; *f* shows the test tube full of urine passed on the following day, after 20 grains only of the drug had been taken. It was now quite clear to the naked eye. Cultures also made with three drops of the urine showed no growth. Further examination, however, proved that in this case a few bacilli were really present, even after 60 grains had been taken, and that, therefore, to be quite certain of curing the condition, it would always be wise to continue the use of the drug for about a week.

The photographs happen to deal with cases of bacilluria, but in cases of typhoid cystitis, as the detailed record of the cases shows, the effect of the drug is almost as instantaneous, the pus as well as the bacilli disappearing within one, or at most two, days.

If, then, we sum up the effect of the drug on cases of typhoid bacilluria and cystitis we may say that the immediate effect of the drug is extraordinary. If the urine has been turbid before with bacilli, at the end of twenty-four hours—that is to say after 30 grains have been given—the urine will be found quite clear. Possibly cultures may reveal a few bacilli, but this is not always the case. So marked and immediate, indeed, is the effect of the drug that, if the urine is not clear at the end of twenty-four hours, we may at once suspect most strongly that the bacillus present is not the typhoid bacillus, but one of the varieties of bacillus coli. If the drug be continued a permanent cure will be effected (unless possibly in the event of reinfection from the blood). Such a permanent cure may sometimes be effected by 60 grains of urotropin, but to make certain it would be well always to continue the drug for at least one week.

Under what circumstances, then, should the drug be given in cases of typhoid fever? Evidently whenever a urinary complication due to the typhoid bacillus has occurred. But seeing that at the present time the bacilluria and even the cystitis most often passes unnoticed from the patient complaining of no symptoms, and seeing that they are always a source of danger, the question arises whether the drug should not be given (30 grains daily) in all cases of typhoid fever, throughout its whole course and during the first three weeks of convalescence, as was first suggested by Richardson, with the intention of preventing these complications. It should be added that, taken in such doses, and during such a prolonged period, the drug produces no ill-effect beyond occasionally some urethral pain if the urine is allowed to become concentrated. It may be combined, too, with any ordinary medicine, and therefore interferes in no way with the usual routine treatment of the disease. There can be little doubt, therefore, that the drug should be so given, for no nursing, however good, no care taken with the urine, can

possibly prevent some soiling of the linen and the possible spread of infection if the case be one of typhoid bacilluria. In hospital practice, however, with good nursing, the matter is of less importance. In private practice among the poor the case is very different. Since in all probability in such cases, as I have elsewhere pointed out, the urine rather than the faeces is chiefly at fault, it is permissible to hope that by eliminating the former source of danger altogether a very sensible diminution in the spread of the disease may in time be brought about.

[In an appendix to his lecture Dr. Horton-Smith gave the exact details concerning four cases of typhoid bacilluria and cystitis treated with urotropin. These demonstrated clearly that if the drug be given for a week (10 grains three times a day), an almost certain cure of the condition can be brought about. Often, indeed, much smaller amounts were in reality sufficient.]

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THE ACTION OF VARIOUS DRUGS AND DIETS ON THE EXCRETION OF NITROGEN IN GOUT.*

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THE study of the elimination of nitrogen in gouty cases is of special importance on account of the relationship which uric acid holds to gout, and the consequent view that gout is essentially a disease of disordered metabolism. The object of this series of observations was to determine, if possible, the variations in nitrogenous elimination occurring in a case of gout under ordinary conditions, and to note the effect of different diets and certain drugs. For this purpose urea, uric acid, alloxur base, and ammonia were all separately determined—the urea to serve as a measure of the total nitrogenous changes—the uric acid and alloxur base as a possible sign of modified production of these bodies, and the ammonia as an indication of the general amount of inorganic acid dealt with during the day's metabolism. There are two alleged sources of uric acid:

1. It may be a derivative of the alloxur base combined within the molecule of the nucleo-proteid of cells, or similar substances in the food.

2. It may be produced by synthetic processes in the liver or elsewhere from simpler nitrogenous compounds such as ammonia.

If the former view be the correct one, variations in the amount of uric acid excreted must simultaneously produce variations in the final waste products resulting from the disintegration of nucleo-proteid, one of which—phosphorus—we can follow. For this reason the phosphorus pentoxide excretion was also determined, but it must be remembered that the main amount of phosphates excreted in the urine has been derived from the phosphates taken as such in the food. The amount of ammonia excreted has been shown to depend

largely, if not entirely, on the excess of mineral acid over fixed bases available, and consequently fluctuations in its amount follow variations in the diet.

I am indebted to Dr. Barrs for the opportunity of investigating the following case of chronic gout:

G. D., aged 65, a well-built man, 6 feet in height and weighing 12 st. 4 lbs., who followed the curious vocation of tailor and dancing master, was readmitted into the Leeds General Infirmary on November 2nd, 1899. His family history revealed little of positive importance. An uncle had suffered from gout; but while his father, dying at the age of 67, was believed to have shortened his life by over-indulgence in alcohol, he had never been affected by gout. There was, however, a history of rheumatism in his case. The patient's mother, aged 77, at the time of her death, was always free both from gout and rheumatism. The patient's past record was excellent. Apart from the affection for which he was admitted, and an attack of erysipelas twenty-three years previously, his health had been very good. The history of gout covered five years. At the beginning the patient attributed the swelling of the joints to the fact that his feet ceased to perspire profusely. The recurring attacks were ushered in by shooting pains, the joints becoming red, swollen, and very hot. These symptoms gradually subsided after two or three days, with exception of the swelling, which persisted. At the time of readmission his general health was good, and no disease of internal organs could be discovered. Gouty changes were marked both in the hands and feet, the enlargement due to deposits being indeed extreme. In the hands the metacarpo-phalangeal and first interphalangeal joints were mainly affected. The dorsum of the left wrist was occupied by a considerable swelling. The elbow of the same arm was affected at two points, there being a very hard swelling in connection with the ulna, and a softer one forming a cushion-like expansion of the apex of the joint. At the back of the internal condyle of the other elbow-joint was a nodulated enlargement equaling a filbert in size. The fifth metatarsal joint of the left foot showed a large hard swelling, and a similar enlargement existed on the outer side of the fifth toe, with a smaller one on the dorsum of the fourth. The lower part of the tendo Achillis was irregularly swollen. The small toe of the right foot was enlarged dorsally, a smaller swelling affecting same surface of the first and fifth tarso-metatarsal joints. The tendo Achillis was in a condition similar to that described in the case of the left foot. The patient stated that the joints gave rise to no pain, except when at long and irregular intervals an inflammatory condition supervened.

The case was interesting from the fact that although the first manifestations of gout presented themselves only five years before, the deposits described were so large as to render it almost unique. A feature of interest, from an etiological point of view, was the abstemiousness of the patient combined with his active habits. Except for a slight hereditary taint no possible clue in relation to its causation was obtainable. The urine, repeatedly examined, was free from albumen, albumose, and peptone; and throughout the investigation was acid in reaction.

Methods of Analysis.—The urea was estimated by the hypobromite method and uric acid both by Hopkins's and Salkowski's processes. Schlösing's method was adopted for ammonia and titration by uranium nitrate for the P_2O_5 . The alloxur bases were estimated by Salkowski's recent method described in a former paper on gout.

While under observation the patient was placed on the subjoined diets:

Fixed Diet.—Cocoa 1 pint, tea 2 pints, milk 1 pint, tea cake 2 oz., bread 11 oz., butter 1 oz.; dinner, 1 lb. 6 oz., including 4 oz. of meat and 1 apple.

Vegetable Diet.—This consisted to a large extent of peas and beans. Milk 1 pint, oatmeal porridge $\frac{1}{2}$ pint, pea soup $\frac{1}{2}$ pint, peas porridge $\frac{1}{2}$ pint, bread 11 oz., butter 1 oz., peas, beans, and other vegetables 1 lb. 8 oz.

Animal Diet.—Milk $\frac{1}{2}$ pint, lemonade 1 pint, meat 10 oz., bread 10 oz., butter 1 oz., potatoes 4 oz., and 1 apple.

In addition to being dieted, the patient took the same amount of exercise each day.

The results obtained are tabulated on p. 835.

Referring first to the estimations made before the administration of drugs and the adoption of experimental diets—that is to say, under ordinary conditions—it will be observed that the fluctuations were well within physiological limits with the exception of urea, which was somewhat low, a common feature in connection with hospital patients, resulting, of course, from the small quantity of nitrogenous food taken; but in this case the alternative possibility of a nitrogen retention must be borne in mind. Taking into consideration the patient's age, the uric acid excretion must be regarded as normal. The bases also bore the usual relationship to uric acid. The estimation of the bases gains much interest from the important researches of Minkowski, who administered adenin to four dogs in doses varying from 0.25 to 0.5 gram several times a day. Three of the animals were killed about the fourth day, and the other died on the second day. After 2 grams vomiting ensued, and the other symptoms noted were violent action of the heart, a heaving pulse, and an increase in blood pressure. The urine contained albumen, leucocytes, casts, and epithelial cells. *Post mortem* crystals of biurate were found deposited in the convoluted and Henle's tubules, but not in the glomeruli. There was also cellular infiltration of the connective tissue.

It is certainly striking that this train of symptoms, with

* Read before the Medical Society of London.