say most of these patients die within one year of the diagnosis of albuminuric retinitis, but as vision is often for some time so little affected, patients do not probably seek advice at first, and therefore this rule cannot be made hard and fast.

Remarks

ON

THE TREATMENT OF SYPHILIS,

WITH SPECIAL REFERENCE TO INTRAMUSCULAR INJECTIONS.

By GEORGE PERNET,

ASSISTANT TO THE SKIN DEPARTMENT, UNIVERSITY COLLEGE HOSPITAL; LATE PATHOLOGIST TO THE HOSPITAL FOR DISEASES OF THE SKIN, BLACKFRIARS, LONDON.

THE subject of the treatment of syphilis, though an old one, is perennially youthful and full of life and vigour. The clashing of opinions, the struggles of partisans, the alarms and excursions which have circled round it as a storm centre have been fast and furious, and I may add, as some points of my present paper will show, discussions as to the proper mode of treatment are still going on with unabated energy.

If there is a disease about the treatment of which there is a fascinating divergence of opinion—it is syphilis. Ideas and methods regarding it vary not only from medical man to medical man, so much so that one might be tempted to exclaim: *Tot homines, tot sententiae*, but also from country to country. About one thing every one appears to be quite sure, however, namely, that he knows how to treat syphilis better than anybody else. As far as I am concerned, I consider it is very necessary to be eclectic in the choice of method and that the golden rule of treating every case on its merits should be our guiding principle. It will be my endeavour to show that there are a variety of methods of treating syphilis, or as I prefer to put it, of treating syphilitics—for there is really no such thing as syphilis in itself, convenient an abstraction though it be. What we, as professional men, have to deal with is a human organism suffering from the invasion of another organism, the *Spirochaeta pallida*, for there appears to be little doubt now as to specificity.

Having diagnosed the kind of infection, the next step before prescribing treatment is to consider the kind of patient infected—sex, age, nationality, occupation, history, habits, weight, general condition, giving special attention to the state of the mouth and teeth, the stomach and intestines. The urine should be tested, and an approximate idea at least of the amount passed in the twenty-four hours obtained, for the state of the eliminatory processes in each individual case, including the condition of the heart and circulation, is of primary importance, especially in the early days of the infection.

I would again strongly insist on examining the teeth and mouth carefully in a routine way. The success or otherwise of mercurial treatment may depend on the good or bad state of the buccal cavity. In many cases it will be of the first necessity to send the patient to a reliable dental surgeon, and thus avoid the vexation of having to interrupt the treatment on account of stomatitis, gingivitis, and so forth.

The mode of life is a factor not to be neglected, for it has been shown over and over again that syphilitics leading outdoor lives, with every comfort secure about them and without incentive to cerebral exertion, do better than individuals in the hurly-burly of competition or following unhealthy occupations.

I need hardly call attention at this time of day to the bad effects of alcohol on the syphilitic processes. Not only does alcohol interfere with the play of the phagocytes,¹ but it also impairs the nervous system generally.

Smoking, again, especially if excessive, is bad from the mouth point of view.

There are syphilitics, again, with what we call in our ignorance—idiosyncrasies. Mercury upsets them, but it should be borne in mind that mercury which may not suit them in one form may in another. Therefore attempts should be made to deal with the case by the trial of various preparations, preference being given in my opinion to a mixture of liq. hydrarg. perchlor. and pot.

iod., the mercury of which is much more rapidly eliminated than when mercury is given alone, as demonstrated by the experiments of Tschiriew.² Iodide of potassium appears to act as a diuretic. But it may happen that mercury cannot be tolerated at all. Then I would recommend a salicin mixture, commencing with gr. xv ad 3j; increasing rapidly to gr. xx and upwards, ter in die, p. c. I have little in the way of proof to support this view, but what little I have, and judging by analogy, I consider that salicin as an adjuvant or alternative in the treatment of syphilis may be of service. The knowledge that mercury is the treatment for syphilis renders it a difficult matter to withhold it for the purpose of experimenting with another drug. Such idiosyncrasies, again, make an overhauling of the patient imperative, more particularly as regards the renal, hepatic, and circulatory conditions, especially in elderly patients.

I will first deal with drugs and methods, and later with the syphilitic manifestations themselves and their treatment.

It is frequently stated that syphilis and its mercurial treatment were well known to the Chinese ages ago. This view rests mainly on the work of a French writer, Captain Dabry, who, by the way, was not a medical man. The hoary antiquity of the disease in China has, however, been rudely shaken by Okamura,³ a Japanese physician, who has recently searched the Chinese records, with the result that he found nothing relating to syphilis earlier than the sixteenth century.

In more recent times the employment of mercury met with much opposition, many maintaining that syphilis could be cured without mercury. A good English account of the battles of the mercurialists and non-mercurialists will be found in Cooper's *Dictionary of Surgery*.⁴ But it must not be forgotten that the proper analysis of the so-called venereal diseases has been accomplished, comparatively speaking, quite recently, although the earlier writers in the sixteenth century had apparently distinguished syphilitic manifestations as a separate thing. For many years gonorrhoea, soft sores, and syphilis proper were all jumbled up together. Owing to the influence of John Hunter, to whom every one bowed down, the clock was kept back, for his fallacious experiment on himself had satisfied him, and therefore the medical profession at that time, that gonorrhoea and syphilis were one and the same infection.

Later, when gonorrhoea had been separated out, Ricord, another great authority, remained a unicist as regards soft sores and syphilis. Bassereau, however, in the face of much opposition naturally, showed that the soft sore and syphilis were two different affections. This was followed by Rollet, who demonstrated the fact that both the infection of the soft sore and of the syphilitic chancre might occur at one and the same time; *chancre mixte*.

Ricord's influence also retarded the recognition of the infectious nature of the early secondary, so-called, manifestations of syphilis—authority gone wrong again leading to most unfortunate results as can well be imagined.⁵

It is not to be wondered at, therefore, that rational treatment made but slow advance in the circumstances.

At the present day the value of mercury in the treatment of syphilis is generally admitted. It is still contended, however, that mercury is not absolutely essential to the cure of the disease. G. H. Fox⁶ of New York, although he employs mercury, is of this latter opinion for instance, and he adds "that cases will get well by virtue of the *vis medicatrix*, even when no mercury is administered." I would here remark that, as far as the syphilitic infection is concerned, this beneficent *vis*, whatever is meant by that term, has done very little apparently to stay the evil effects of syphilis in Turkish Asia Minor, for instance, as investigated by von Düring.⁷

This leads me to point out that, however benign an attack of syphilis may appear to be, the treacherous nature of the infection and its protean effects must ever be present to the mind. Many a serious late manifestation has a past which was full of hopefulness, nay, in some cases, especially in women, the early morbid phenomena may have been so evanescent as to have escaped attention altogether. It is recognized generally that severe late syphilis occurs more frequently in those who have been insufficiently treated in the early stages. There are exceptions to this, as to all rules, and I have observed such myself.

In the present connexion I would call your attention to the experiments of Neisser,⁸ and of Finger and Landsteiner,⁹ who have obtained positive results in apes by the inoculation of gummatous products derived from man. The importance of these positive results are obvious, but as I am dealing here with treatment only I will take this opportunity of insisting on a practical point which is frequently overlooked, namely, the absolute necessity of employing mercury in all stages of syphilis. If this rule were always observed much better results would be obtained, and unpleasant consequences avoided. Over and over again I have seen late or so-called tertiary lesions treated by means of iodide of potassium only. Now, we all agree that this drug is most valuable in clearing up gummatous material in many instances; but this can be achieved much more rapidly in obstinate cases by combining mercury in the form of inunction, for example, with the iodide treatment. Moreover, where nerve structures are involved, this rule of exhibiting mercury becomes imperative.

With regard to pills, I need not detain you long on that score. The usual pill employed in this country is hyd. c. cretâ, in varying doses. Reduced iron is also apparently useful, especially where there is marked anaemia, either due to the syphilitic infection, an anaemia accompanied by leucocytosis, or to this *plus* an already existing anaemia due to other causes (chloro-anaemia, etc.). I say that reduced iron is apparently useful, for Bunge found by experiment on animals that inorganic iron did not increase the haemoglobin, but an increase occurred only when organic iron was added in the form of haemoglobin or haematin to the food.¹⁰

Here it is convenient to refer to the action of mercury itself on the blood. According to Justus,¹¹ when a fairly large dose of mercury is introduced into a syphilitic patient, either by inunction or intramuscular injection, a rapid and characteristic sinking of the haemoglobin takes place. This reaction he considered a test, as it was said not to occur in healthy subjects, but only in syphilitics. Subsequent observers have not, however, confirmed this view. After the mercury has been administered for a time the haemoglobin content rises again and reaches a higher level than before treatment (Justus).

With the other preparations of mercury employed in the form of pill, tablet, cachet, or mass I need not detain you. In this country it is usual to give hyd. c. cretâ either in small doses—say, gr. j, ter in die—continuously for six to twelve months, or to exhibit it in larger doses—gr. ij, gr. iij, ter in die—intermittently, alternately with a course of iodide of potassium. There are other combinations, which I do not think it is necessary for me to enumerate. Others, again, think highly of a mixture of perchloride of mercury, whereas some swear by the combination of this salt with iodide of potassium. On *a priori* grounds the latter mixture would not appear to recommend itself as a method of treatment, for the reasons I have alluded to, namely, the rapid elimination of the mercury.

Inunction is a much more energetic and useful method of introducing mercury into the organism. The ordinary ung. hydrarg. or capsules of mercury-vasogen 33½ per cent. can be employed, but even in the latter form, although the penetrating power is apparently superior to the ordinary ung. hydrarg. from the point of view of cleanliness, the preparation still leaves much to be desired. The capsules are put up in boxes, and look like sweetmeats, so should be kept locked up, especially where there are children.

Unless one has a patient under direct control the drawbacks where private patients are concerned are obvious. Moreover, to be effectual the mercury must be thoroughly rubbed in; of course, better results are obtained when the rubbing is carried out by another person, wearing a rubber glove. In Copenhagen I noticed that in the wards of the late Professor Haslund at the Communal Hospital the syphilitics rubbed one another, both getting in that way mercurial treatment. The inunctions are best carried out at night, that time being more convenient in various ways. Moreover, the *Spirochaeta pallida* appears to swarm at night (in the tissues of indurated chancres, at any rate). If such turned out to be a general fact, it would perhaps explain the well-known nocturnal exacerbations of syphilitic headache and boneache.¹²

In fat subjects, a severe dermatitis may be induced if

the inunctions be too vigorously carried out. Mayer records a recent case of this kind which was fatal.¹³

In patients who are cachectic, broken down through alcoholic excess, or in whom there exists renal inadequacy, a stomatitis may be readily produced. In such an occurrence, I would point out the importance of seeing that the soiled undervest worn during the inunctions should be removed, as I have seen the stomatitis go on from bad to worse by overlooking this precaution, the patient continuing to absorb mercury, although the inunctions had been stopped.¹⁴

When a good deal of the body surface is affected by ulcerating lesions so as to make inunction difficult, Welander spreads 6 grams of ung. hydrarg. at a time with a spatula on a part that is free—a limb for instance—and bandages the part. The same writer also employs cotton-wool or linen smeared with the ointment to be worn in the form of a sachet on the chest, scapularly fashion. The so-called mercolint is used in this way; and Blaschko has recommended a kind of chest protector, worn day and night in the same way. But this mode of exhibiting mercury is no new thing, for Daniel Turner, a dermatologist of the early eighteenth century, mentions that mercury spread on a flannel girdle was recommended in his time.¹⁵

Calomel fumigations were at one time in current use. I need only call your attention here to their excellent effects in some obstinate cases which have resisted other methods of treatment.

In the efforts to open up new ways for the introduction of mercury into the organism, the rectum had apparently been overlooked. This has now been rectified, for Audry has treated cases of syphilis by employing suppositories made up of 40 per cent. grey oil (oleum cinereum) in various strengths.* According to him, the method is efficacious, simple and safe.¹⁶

I now come to the hypodermic, or rather the intramuscular method. Scarenzio in 1864¹⁷ was the first to practise it. He used calomel and injected it hypodermically. Later it was found preferable, in order to avoid abscesses, to introduce the mercury into the muscles, and that is the method generally employed now. Lang, of Vienna, employed grey oil (metallic mercury with lanoline and olive oil) in this manner. As to the soluble preparations, Lewin was the first to use perchloride of mercury.

The syringe should be either of m xx capacity or 1 c.cm. divided into 20, or one of the special small calibre syringes (Barthélemy-Edmond Fournier-Duhot); for some of the soluble preparations a syringe of 2 c.cm. capacity is required. The syringes should be of the all-glass type so as to allow of thorough sterilization by boiling in water or, as Lambkin advises, in liquid paraffin.

Platino-iridium needles should be employed. They can be boiled or passed through the alcohol flame; but they require sharpening from time to time, for it is very important the point should be very sharp to avoid pain when plunging it through the skin into the muscles. As to the length, this varies from 2½ to 5 cm. and over. Much depends, of course, on the buttocks to be operated on and the seat of the injections. Various positions in this situation have been recommended, such as the post-trochanteric fossa (Smirnoff); the intersection of a horizontal line passing two fingerbreadths above the great trochanter and of another, vertical, separating the inner third of the buttock from the outer two-thirds (Galliot); the middle of a line uniting the anterior superior iliac spine and the base of the coccyx (Barthélemy). These are the usual points, but Duhot, Lévy-Bing, and Pedersen recommend other positions. The injections should be made alternately in right and left buttock, and a note kept of their position, with the dose injected each time.

The *modus operandi* is as follows: The part selected having been thoroughly disinfected with soap and water, and a brush if need be, perchloride of mercury solution, ether, alcohol, or other method preferred, the sharp needle attached to the barrel of the syringe (all previously sterilized by boiling, is plunged quite perpendicularly and rapidly through the skin into the subjacent muscle, the patient standing at ease or lying face downwards on a couch. Some prefer the patient standing at attention. The syringe is then detached from the needle, the proximal

* This method of treatment is not new, for it is mentioned in *Bryant's Surgery*, 4th ed., p. 142, vol. i. I am indebted to Dr. Humphreys, of Hampstead, for this reference.

end of which is watched to see if any blood issue forth. Or the syringe can be left attached to the needle and the piston withdrawn a little to see if any blood comes up into the barrel. The syringe is then charged with the sterilized mercurial preparation, all air being driven out, reattached to the needle, and the contents slowly and firmly injected. Duhot recommends that when this has been done the syringe should again be detached and a little air or sterilized salt solution drawn into the barrel, which is then reattached and the piston pushed down, to clear out any preparation remaining in the needle, and thus avoid leaving any of it behind in the track of the needle when this is withdrawn. A little collodion and wool or zinc oxide adhesive plaster may be applied over the puncture or not. It is not necessary to massage the part; indeed, massage is best avoided.

Another method is to fill the syringe, fix on the needle, and drive out excess over amount of mercurial preparation required, taking care to wipe the end of the needle clean with a sterilized piece of linen or closely-woven gauze, but not with wool. With the latter there is risk of introducing some of the material into the tissues. The injection is then made direct into the muscle. This I have found answer, too, but I have aspirated first to see if any blood came up into the barrel before pushing the dose home.

As to the insoluble preparations, calomel, specially prepared, suspended in vaseline or in olive oil, is employed in doses of 5 cg. This is injected weekly, or at somewhat longer intervals, to test the patient and avoid cumulative effects. Calomel injections are in some subjects extremely painful, but by associating guaiacol and camphor with the olive oil, Emery has had good results *quæ* pain.¹⁸ The preparation put on the market by Zambelletti of Turin is practically painless, but it is not known how it is made. In all cases the preparation should be well shaken before injecting.

Neisser's method is not to employ calomel straight off, but to begin with hydrarg. salicylas, followed by hydrarg. thymolacetat, finally injecting calomel.¹⁹

Although calomel thus used has given brilliant results in some cases that had resisted all other treatment it has disadvantages—pain, toxic symptoms, and so forth—which have relegated its employment to special cases only. But even in some of those cases where it acted like a charm relapses of the local syphilitic trouble have occurred.

The insoluble preparation which is now generally used is metallic mercury suspended in various media, such as lamoline, paraffin oil, and vaseline.²⁰ In this country Lambkin²¹ has demonstrated the value of this preparation, and the Advisory Board for Army Medical Services has recognized its importance in the treatment of syphilis.²² The advantages of intramuscular injections of grey oil or mercurial cream are great, not only for the services but also for Civil private practice, if patients will submit to them. Of course the patients must be properly selected. By giving one injection a week in series of 6, 8, or more, as the case may be, one is sure of introducing a sufficient quantity of mercury.

In well fed, sound as regards the urine, and fairly muscular subjects of good weight, I have found 12 successive weekly injections of 5 to 8 cg. (0.065 gram = 1 grain) in the very early stage well borne, even in patients who were liable to attacks of diarrhoea before the infection. As to this symptom 5 gr. cachets of salicylate of Bismuth (one or two before meals) always acted readily. After a rest I have given a fresh series of 12, and so on. Of course, the number of injections must depend on the kind of patient and the kind of syphilis, 6 being the most usual; but where the injections agree well they should be pushed, with care of course.

Duhot insists on the importance of what he calls the abortive treatment of syphilis.²³ There is much to be said in favour of pushing the injections, and starting them as early as possible in the disease.

With regard to insoluble preparations, it is very important to remember to shake them thoroughly after warming, and stirring in case of creams before injecting. Of course, unpleasant consequences may occur when this is overlooked, as much too large amounts of mercury may be given owing to the settlement of the metal at the bottom of the vessel containing the preparation.

It has been stated that these injections are very dangerous. This is too alarmist a view to maintain and

promulgate. That there have been serious complications is quite certain, but if care be taken such mishaps can be reduced to a minimum. Considering the enormous number of injections of insoluble salts that have been given all over the world the bad cases have been few.

Recently, Claude and Dobrovici have published some cases in which death followed injections of grey oil.²⁴ But I would point out that these patients were, I should say after reading the notes, not quite suitable cases for such a treatment.

I must again insist that we must be eclectic in our treatment of syphilis, and not go off our heads in favour of any one method to the exclusion of all the others. Injections of grey oil are often contraindicated absolutely. It is not a routine treatment, and is not applicable in the case of old people, the broken-down, those with renal inadequacy or with albumen in the urine, patients suffering from tuberculosis, lead poisoning, or decidedly active gout, and alcoholics.

When cases are carefully selected I have never seen mercurial intoxication or other complication, nor have I ever seen embolism occur.

I will now pass on to the soluble preparations, such as perchloride, benzoate, succinimide, peptonate, cyanide, biniodide, énésol (salicylarsinate of mercury), and sozoiodolate of mercury, which have all their partisans. They are all useful, are more easy to handle than the insoluble preparations, but are also more evanescent in their action. They are more or less painful, but this symptom varies very much from patient to patient, and with the preparation used. Among the best soluble preparations are the sozoiodolate, succinimide, and benzoate, but it is useful to follow up their action by injections of an insoluble salt, in suitable cases.

As to the sozoiodolate, gr. 4 is injected once a week, but when the urgency of the case called for it the injection could be given more frequently, carefully observing the patient the while. It is less painful, on the whole, than the perchloride.

The benzoate of mercury is employed in daily doses of 2 cg., that is, 2 c.cm. of the hypertonic benzoate of mercury as used in France, with good results. As compared with grey oil or mercurial cream this daily injection is a drawback in ordinary private cases, but it is of great service to combat severe symptoms, especially with the patient in bed at home or in hospital; or, again, when a patient is undergoing a cure at a health resort, especially where there are sulphur springs.

Instead of employing small doses of perchloride of mercury daily, or every other day, some observers have recommended large weekly ones, that is, 5 cg. on average, and speak well of this procedure.²⁵

Chéron advocated, and employed, large doses of perchloride in salt solution, but *a priori* this appears to be an imprudent proceeding with such a preparation of mercury, seeing how rapidly absorbed the latter constituent is. Jullien tried it once, and then with only 2½ cg. instead of 5, the result proving very nearly fatal.²⁶

Biniodide of mercury in watery solution, though painful, is considered by Emery and Druelle as a very useful method in cases where the mercury has to be pushed, owing to its good effects.²⁷ This is no doubt quite true as regards clearing up symptoms, but I would certainly not rely on it as a sufficient and fundamental treatment of syphilis in the early stages. It should certainly be followed up by an insoluble preparation, preferably grey oil, or inunction, or other mercurial method, as the case may be.

With regard to organic mercurial salts, the fact that the mercurial molecule is split off with difficulty in the organism may account for the want of success in some cases, the original salt having been found again as such in the urine.²⁸

It now remains for me to say a few words about the intravenous method. This was introduced by Baccelli in 1893, who employed perchloride of mercury. The salt now used is cyanide of mercury in a 1 per cent. solution, the usual dose being mxx, which may be given daily. The arm is prepared as for bleeding by placing a ligature round it to make the vein prominent, usually the median basilic. The parts are thoroughly cleansed in the usual way; the needle is introduced into the lumen of the vein, in the direction of the blood stream. The ligature being removed, the contents of the syringe are injected,

and the needle rapidly withdrawn, a finger being placed on the puncture, and wool and collodion applied. The operation is very simple and without danger, provided all the rules of asepsis be observed, and any air in the syringe got rid of before injecting. Opinions are divided as usual, but it is maintained by some who have tried it that the effects are not comparable with those obtained by intramuscular injections of insoluble salts, for instance, a larger number of intravenous injections being required to achieve the same end.²⁹

It is, however, a method which should not be overlooked, as it may in some cases give good results, especially in syphilitic conditions of the eye,³⁰ and where other means have failed. In some patients the veins are so poorly developed as to make the application difficult or impossible. Other observers have seen various complications, such as phlebitis, thrombosis, etc.

In the early manifestations iodide of potassium should be given in doses of gr. v t. d., p.c., diluted, in the intervals of mercurial treatment. But a point to remember is when there is stomatitis as a result of mercury the iodide should not be prescribed, as it will bring more mercury into the circulation, and make matters worse. In such cases it is good treatment to rely on mag. sulph., and, of course, suitable mouth washes. Where it is inconvenient for a mixture to be taken three times a day, the iodide of potassium can be prescribed in doses of gr. xv ad 3j, and taken first thing in the morning or at bedtime, with 3, 4, or 5 drops of tinct. iodi, the effects being watched.

In small doses iodide of potassium is generally well borne, but larger doses upset the stomach in some cases, especially in gouty subjects. Where there is renal inadequacy, circulatory troubles, etc., the drug may lead to other complications, and it may be necessary at times to employ the other iodides (sodium, ammonium) instead of the potassium salt.

As is well known, iodide of potassium often gives rise to coryza in the susceptible, and may also lead to conjunctivitis and to iodide rashes, which may be tumour-like, bullous, or purpuric. One word of warning: iodide of potassium should never be ordered in bullous eruptions, which will be considerably aggravated thereby.

Iodipin (Merck) and lipiodol (Lafay³¹) are iodized oils. They can be given by the mouth (capsules, etc.), or are preferably injected hypodermically, where the tissues are lax (back, loins in posterior axillary line; the abdomen is recommended by some and not by others; the antero-external part of thigh, etc.), so as to allow of the injection of 5 or 6 c.cm. at a time. The daily dose in injection varies from 5 to 15 c.cm., according to the kind of case. Large doses have been employed in this way for many days (15, 20, 30) together without inconvenience of any sort. The parts to be injected should be left and right alternately. The Germans recommend an ordinary large asbestos piston syringe with a long needle, but as a matter of fact a platino-iridium needle of 4 cm. with a good lumen suffices, so long as the oil is slightly warmed. The French, too, employ a syringe with a screw (somewhat on the principle of Guyon's instillation syringe), and this answers better (Chatin's, also Barthélemy and Lévy-Bing's pattern). Of course, I need hardly say the syringe and needle and the skin must be, respectively, thoroughly and carefully sterilized and cleaned up.

The preparation is slowly absorbed into the organism and slowly eliminated, a very different state of affairs to that which obtains in the case of ordinary iodide of potassium mixtures, in which elimination is rapid. These iodized oils have proved valuable in the treatment of severe cases, especially in syphilitic conditions of the eye.

In passing, I must briefly allude to the Zittmann treatment, the good effects of which appear to be mainly due to the large amount of fluid taken. It is a treatment to bear in mind in obstinate cases, when other remedies have failed. Competent writers speak very highly of it.

As to immunization, it has been shown by experiments on monkeys and man that the immunity to syphilis is not readily or quickly established. The attempts at prophylactic vaccination carried out by Metchnikoff and Roux on monkeys have failed, as have also similar attempts with gummatous products.³²

Further attempts have been made to prepare anti-syphilitic serums, but up to the present without success, or rather with little success, for Metchnikoff and Roux have obtained interesting but inconstant results by the

use of serum obtained from the lower monkeys inoculated with syphilis. These results, such as they are, have encouraged them to persevere, and they are engaged in experiments with a view to obtaining a more powerful serum.³³

As to the general hygiene, good feeding and clothing, and so forth, I need hardly insist on such important matters. There is no doubt that in the upper ranks of life syphilitics do uncommonly well, a fact that has been noted by many of us, and more particularly by life assurance medical officers.³⁴ Of course, it must not be overlooked that patients of that class are much more likely to be adequately treated, besides being able to travel and sojourn in favourable climates.

This brings me to refer to the use of sulphur in the shape of waters and baths. It must be quite understood that sulphur waters are valuable auxiliaries; but the fundamental treatment must, of course, be mercury.

As a result of various researches on the subject, the following appears to be in brief the fate of mercury introduced into the organism. In the first place, it combines with the chloride of sodium contained in the body fluids to form a double chloride of sodium and mercury, which with the albumen of the tissues leads to the formation of an albuminate. Under the influence of sulphur waters taken by the mouth a sulphate of mercury is formed, which is rapidly eliminated,³⁵ coming into contact with the syphilitic lesions. This "mobilization" of mercury explains why very large quantities of mercury, either inunctions or injections, can be administered to patients concurrently with the sulphur water, also why obstinate syphilitic lesions can be cleared up in these circumstances. This has been shown to be the case even in Paris hospitals with bottled waters.³⁶ When the treatment is carried out at a watering place, the change of air and scene, and so forth, naturally play an important and beneficial part.

In connexion with the foregoing I may be allowed to call attention to the demineralization which occurs as a result of the syphilitic infection. A number of observers have dealt with this point, the upshot being that there is an excessive elimination of chlorides, sodium, potassium, lime salts, especially sulphur.³⁷ That we should endeavour to remedy this malnutrition is obvious, and for this purpose injections of salt solution might prove useful in some cases, where the onslaught of the syphilis has been severe, as in poor, badly-fed women chiefly, as far as my observation goes. Phosphoric acid, the hypophosphites, etc., are also very useful in dealing with such cases.

I will now touch on the various stages of syphilis and on some of its baneful effects, which call for special remark.

Let us begin with the hard chancre. Excision was long ago recommended and carried out, by John Hunter for instance,³⁸ and the method has been more recently tried by many, but the results have not been encouraging. Numerous experiments on monkeys, by Neisser in Java for instance, have demonstrated its uselessness, for excision even as early as eight hours after inoculation did not prevent the formation of a primary chancre.³⁹ In the case of a primary chancre of the prepuce, especially with phimosis, circumcision is good treatment.

This is an opportune place for mentioning the prophylactic treatment at the seat of the experimental syphilitic inoculation by means of a calomel ointment (calomel 1, lanoline 2). Metchnikoff's and Roux's experiments on apes and on a medical man, Dr. Maisonneuve, who volunteered to undergo experimental inoculation, were successful in preventing further developments.⁴⁰ Doubts have been thrown on the value of this experiment, however, and failures cited by Lévy-Bing⁴¹ and Gaucher. In another case⁴² a hard chancre and a macular rash appeared in due course, notwithstanding the use of the calomel ointment immediately after copulation. Neisser, it is stated, has also investigated this point, and inoculated no less than 200 monkeys, the ointment being applied from one to eighteen hours after the inoculation of the syphilitic virus, with the result that he failed in 100 instances, a primary chancre developing in the usual way.⁴³ The value of the ointment as a prophylactic, therefore, is doubtful, but one should try it nevertheless, and every medical man, dental surgeon and midwife, liable as they are to accidental infection, should have a pot or a tube of it handy in case of need, so as to apply it with as little delay as possible.

Another consideration of importance is: When should mercurial treatment be commenced? Undoubtedly immediately the primary chancre is diagnosed with certainty, and this is possible in a good many cases. Where there is any doubt, one should of course wait for corroborative symptoms.

This brings me to another point, namely, for how long after its appearance is a primary chancre auto-inoculable? The experiments of Queyrat in this connexion, with histological examinations by Levaditi positively revealing *Spirochaeta pallida*, assuming that micro-organism to be the *fons et origo mali*, appear to show that a successful auto-inoculation can be carried out up to the eleventh day, on condition, of course, that the patient undergoes neither local nor general treatment.⁴⁴ This also agrees with what is known as "successive syphilitic chancres,"⁴⁵ and with the results recorded by Duhot, who treated a number of cases by pushing the injections of grey oil at an early stage. Clinically, he found the twelfth day after the appearance of the primary chancre to be the limit within which one might expect, by the intensive method he advocates, to prevent the appearance of the so-called secondary symptoms, which by their presence show us that the infection has become general.⁴⁶ The auto-inoculability of chancres may, perhaps, be compared with what has been observed in vaccination, in which condition auto-inoculation may be carried out up to the ninth, and sometimes the tenth, day.⁴⁷

Duhot further insists that in his cases (134) cerebro-spinal lymphocytosis did not occur. I would call your attention to the important part played by an examination of the cerebro-spinal fluid obtained by lumbar puncture,⁴⁸ in the matter of syphilis, by revealing at a period when proper treatment may do so much the early insidious stages of severe syphilitic affections of the brain and spinal cord.⁴⁹

With regard to the manifestations of the early or secondary period, they may vary greatly as far as the cutaneous lesions are concerned. In bad cases these may be severe and gummatus, and therefore require careful treatment and judgement. No rule can be laid down, but if it is borne in mind that all the facts of the individual case require to be taken into account, good and not harm will come of such an attitude.

The secondary rash may be preceded by a high temperature, which should be no bar to mercurial treatment if a positive diagnosis can be made on the evidence of primary chancre or chancres.

In the case of iritis, atropine must be exhibited to prevent synechiae. It is a curious fact that early syphilitic iritis will make its appearance, although the patient is under mercury. Iritis is a symptom which usually means a severe infection, and indicates that treatment should be pushed and the nervous system watched, for it has been shown by Trousseau, the ophthalmologist, that a large proportion of the cases he followed up developed serious brain and cord affections.⁵⁰ Where the eye is threatened seriously, as in a case of central retinitis which developed in a syphilitic patient under my care, intramuscular injections of solzopdolate of mercury, which I employed as soon as the diagnosis of the eye condition was made by Mr. Fleming, no doubt saved the eye.⁵¹ Whilst on this subject I may be permitted to allude to two cases of syphilitic optic neuritis, in which Jullien, a determined partisan from early days of calomel injections, was able to save the sight by this method.⁵²

It is important to remember that serious nerve symptoms may arise in the earlier periods of the syphilitic infection.⁵³ Take the case of syphilitic hemiplegia in young men. The importance of immediate and vigorous mercurial treatment of such cannot be overrated. A few pills are of no use whatever. It is here that intramuscular injections of mercury are indicated, commencing with an insoluble preparation such as calomel and following up with a soluble mercurial salt when the case is out of danger.

As to syphilitic affections of the nails⁵⁴ and hair, specific treatment gives very good results.

With regard to the later manifestations, included under the term tertiaries, the keynote of treatment must still be mercury, either with the usual iodide treatment or following on the latter.

I would like to call your attention to the importance of combining mercurial inunctions or injections with larger

doses than the ordinary pot. iodi gr.v ad 3j in rebellious serpiniginous gummata, and also in bony lesions. Gummata infiltrations and broken-down gummata also do well with scraping *plus* the mercurial and iodide treatment. A great deal of time can be saved by surgical means under an anaesthetic.

Another gummatus affection frequently lost sight of is syphilis of the myocardium, which often leads to sudden death.⁵⁵ The importance of the early recognition and specific treatment, that is, with mercury, of such cases is obvious.

Late syphilis of the uterus is sometimes overlooked. It is here that proper specific treatment may be of the greatest value, not only in leading to a cure but in possibly preventing the development of malignant disease.⁵⁶

In severe lesions of the tongue, looking like epithelioma and becoming so if left alone, excellent results have been recorded with intramuscular injections of calomel when other treatment has failed. Such conditions do well with sulphur waters as auxiliaries.

I must now deal with congenital syphilis. The first thing to note is that infants stand mercury very well. There should be no hesitation in prescribing pulv. hyd. c. cretâ gr. j ter in die p. c. Another method is to smear ung. hydrarg. on the binder.

The syphilitic coryza of infants should receive more local attention than it usually does, for it brings in its train various complications, one of the chief being the cachexia so frequently met with in infants with the snuffles. Histological examination has shown that this condition is not a syphilitic infiltration of the nasal mucous membrane but a polymicrobial, mainly streptococcal, infection.⁵⁷ Therefore every care should be taken to keep the orifices as clean and aseptic as possible.

Another point to remember is that the mother of a congenitally syphilitic infant is herself syphilitic, although she may display no symptom of the infection, and be unable to give a history of any symptom. Of course, in women a negative history goes for very little. That Colles's law was right and that Colles's law is a law, I have myself no doubt whatever. The alleged exceptions when examined cannot hold water.⁵⁸ It is obvious, therefore, that the mother should also be treated, especially from the point of view of future pregnancies.

This leads me to a consideration of the treatment of the pregnant syphilitic woman. Of course, mercury is required and should be given, but it will not unusually happen when the infection is of recent origin that the first child will be born dead whatever is done in the way of treatment. No doubt much depends on the kind of treatment, and how it is carried out by the patient.

Again, in women suffering from congenital syphilis, miscarriages are frequent.⁵⁹ In some cases of this kind appropriate mercurial treatment might be of value from the point of view of a living child.

One word now, in conclusion, as to prevention. We are all agreed on the seriousness of the morbidity and mortality brought about by syphilis. There is no doubt whatever that syphilis is on the increase in London, judging from hospital work alone.⁶⁰

Again, all medical students and hospital nurses should be warned of the dangers of accidentally contracting syphilis, and told of the precautions to take to avoid extragenital infection.

In the time at my disposal my survey has necessarily been a rapid one. I have purposely omitted to touch on certain details of treatment which are a matter of common knowledge, preferring to deal with points of interest germane to the subject. But at the same time I cannot but see how incomplete this paper is, and acknowledge that I have merely skimmed the surface of a vasty deep.

REFERENCES.

- ¹ Metchnikoff, *The New Hygiene, Harben Lectures*, 1906, p. 25.
- ² Tschiriew, *BRITISH MEDICAL JOURNAL*, vol. ii, 1905, p. 246.
- ³ Okamura, *Monats. für prakt. Derm.*, xxviii, pp. 296-300.
- ⁴ Cooper, Samuel, *Surgical Dictionary*, 1838, p. 1410.
- ⁵ Rollet, *Traité des Maladies Vénériennes*, 1865.
- ⁶ Fox, G. H., *Photographic Atlas of the Diseases of the Skin*, vol. iv, p. 197.
- ⁷ Von Düring, *Arch. f. Derm. u. Syph.*, Band 61, 1902.
- ⁸ Neisser (with Siebert and Schucht), *Deut. med. Woch.*, 1906, No. 13 (reprint).
- ⁹ Finger, 1906, p. 10 (reprint).
- ¹⁰ Bunge, *Physiologie des Menschen*, vol. ii, p. 487.
- ¹¹ Justus, *Proceedings of the International Congress of Dermatology*, London, 1893, 1898, p. 756.
- ¹² Finger, *op. cit. supra*, p. 6; also Herxheimer und Opificius, *Münch. med. Woch.*, No. 7, 1906 (reprint).

- 13 Mayer, *Ueber die Prognose der Syphilis*, 1904, p. 12.
 14 Private Case-book, D., fol. 452.
 15 Daniel Turner, *De Morbis Cutaneis*, A Treatise of Diseases Incident to the Skin. Fifth Ed., 1756, p. 60.
 16 Audry, *Ann. de Derm. et de Syph.*, 1906; also loc. cit. 1905, p. 793.
 17 Soffiantini, *Trans. Int. Derm. Congress*, London, p. 375.
 18 Emery, *Traitément de la Syphilis*, 2nd Ed., 1906, p. 41.
 19 Neisser, *Allgem. med. Central. Zeitung*, 1904.
 20 Lafay, *Pharmacologie de l'huile grise*, 1906 (with many details of great interest), *Ann. de Derm. et de Syph.*, 1906.
 21 Lambkin, *The Treatment of Syphilis in the Public Services*, 1899.
 22 *The Treatment of Venereal Disease and Scabies in the Army*, Final Report (no date, but issued in 1906).
 23 Duhot, *Int. Med. Congress*, Lisbon, 1906.
 24 Claude et Dobrovici, *Ann. des Mal. Vén.*, No. 2, 1906.
 25 Kretting, *Berl. klin. Woch.*, No. 38, 1905 (reprint); also Nicolas, *Lyon Méd.*, July, 1906.
 26 Jullien, *Journ. des Mal. Cut. et Syph.*, August, 1902 (reprint); Kobert, *Lehrbuch der Intoxicationen*, vol. ii, 1904-6, 2nd Ed., for a general review with very full bibliography of mercurialism in all its forms.
 27 Emery et Druelle, *Presse Méd.*, No. 12, 1905.
 28 Chatin, *Les Syphilitiques aux eaux minérales, Traitement intensif de la Syphilis à Urriage*, 1904, p. 18.
 29 Discussion on Intravenous Injections in Syphilis, *Trans. Int. Derm. Congress*, London, 1896.
 30 Abadie, vide Emery, *Traitément de la Syphilis*, p. 48.
 31 Martin, Paul, *Le Lépideol*, Lyons, 1905.
 32 Nicolas, Joseph, *Assoc. française pour l'Avancement des Sciences*, Lyons, 1906. See also Nagelschmidt, *Ueber Immunität bei Syphilis*, Berlin, 1904.
 33 Nicolas, loc. cit. supra, p. 14 (reprint); Metchnikoff, *The New Hygiene, Harben Lectures*, 1906, p. 84.
 34 *Trans. of the Life Assurance Medical Officers' Association*, London, 1904-5 (1906), pp. 266, et seq.
 35 Chatin, op. cit. supra (28).
 36 Bertier, *Paris Thesis*, 1905.
 37 Ferras, *Paris Thesis*, 1901.
 38 Cooper, op. cit. supra (4), p. 132.
 39 Neisser (with Baermann and Halberstädter), *Deut. med. Woch.*, 1906, Nos. 1-3.
 40 Maisonneuve, Paul, *Paris Thesis*, 1906.
 41 Lévy-Bing, *Ann. des Mal. Vén.*, No. 2, 1906, p. 115.
 42 Gaucher, *Ann. des Mal. Vén.*, No. 3, 1906, p. 219.
 43 Lévy-Bing, loc. cit. supra (41), p. 120.
 44 Queyrat, *Soc. de Derm. et de Paris*, March, 1905.
 45 Sabareanu, *Paris Thesis*, 1905.
 46 Duhot, loc. cit. supra (23).
 47 Trousseau, *Clinique Médicale de l'Hôtel-Dieu*, 1865, vol. i, p. 64. Jenner was acquainted with this. See Pernet, *Vaccination Rashes and Complications*, *Lancet*.
 48 Abbé, Marcel, *Le Cytodiagnostic*, etc., Paris, 1903.
 49 Ravaut, *Ann. de Derm. et de Syph.*, 1904; Ross, *Trans. Path. Soc.*, Ivii, 1906, p. 361.
 50 Trousseau (the ophthalmologist), *Ann. d'Oculistique*, May, 1900, p. 458; also Pernet, abstract in *Brit. Journ. Derm.*, xiii, 1901, p. 70.
 51 Pernet, *Berl. med. Woch.*, No. 37, 1904.
 52 Jullien, *Journ. des Mal. Cut. et Syph.*, July, 1904. Also see *Injections Mercurielles* (26), December, 1904.
 53 Nonne, *Syphilis und Nerven System*, 1902, many references.
 54 Pernet, *Diseases of the Nails*, *Encyclopaedia Medica*, vol. viii.
 55 Stockmann, Wilh., *Ueber Gummisknoten im Herzfleisch bei Erwachsenen*, 1904.
 56 Franceschini, *Ann. des Mal. Vén.*, No. 4, 1906, p. 241.
 57 Gastou, *Rev. d'Hygiène et de Méd. Inf.*, vol. iii, No. 3, 1904.
 58 Matzenauer, *Arch. f. Derm. u. Syph.*, 1903. Also Matzenauer, *Wien. klin. Woch.*, 1903.
 59 Jullien, *Int. Cong. of Derm.*, Paris, 1900. Also Pernet, *Brit. Journ. of Derm.*, 1899, p. 459.
 60 Pernet, *BRITISH MEDICAL JOURNAL*, vol. ii, 1904, p. 1423; Gregory, *Report of Medical Officer of Health for the Colony of the Cape of Good Hope for 1903*; also for 1904 (especially pp. xcv and following).
 Also Fournier, *Le Traitement de la Syphilis*; Gaucher, *Le Traitement de la Syphilis* (a concise review), etc.
 In preparation, a very full treatment of the subject, Emery and Chatin's *Traitément de la Syphilis*.

Researches

ON THE

BACTERIOLOGICAL DIAGNOSIS OF CHOLERA,

CARRIED OUT BY MEDICAL OFFICERS OF THE SANITARY,
MARITIME AND QUARANTINE COUNCIL OF EGYPT,
UNDER THE DIRECTION OF
MARC ARMAND RUFFER, M.D.,
PRESIDENT OF THE COUNCIL.

IN 1897, during the return of the pilgrimage from Mecca, Dr. Galvani showed me microscopical preparations from the intestinal contents of a pilgrim, who had been found dead on a ship returning from Jeddah. No history of the man's illness could be obtained.

I was greatly astonished to find in these preparations a large number of micro-organisms, not to be distinguished microscopically from cholera vibrios. At the autopsy of this pilgrim, dysenteric lesions were found, together with fibroid kidneys and heart. Cultures from the intestinal contents, made first in peptone water and then in gelatine, showed the presence of comma-shaped, monociliated,

motile, non-phosphorescent vibrios, which were extremely virulent for guinea-pigs, did not coagulate milk, and gave a marked indol reaction. In fact, the cultures could not be distinguished from those of cholera.

The agglutination test with the serum of a horse repeatedly injected with cultures of cholera obtained from Professor Pfeiffer, showed that the vibrios agglutinated and gave Pfeiffer's reaction, exactly like those isolated from cholera cases. No quantitative or qualitative differences were noticed.

My first idea was that the patient had either suffered from, or had been in contact with, cholera. After careful inquiries, this theory had to be abandoned, for it was found that no cases of cholera had occurred among the pilgrims in the Hedjaz, nor on the return journey. A sharp look-out was kept at El Tor for cases of sudden diarrhoea, vomiting and cramps, but in vain. No disease resembling cholera was observed.

On the days following this discovery, the intestinal contents of every pilgrim who died in the camp were examined bacteriologically. I superintended the autopsies and examined all the patients in hospital, together with Dr. Zachariadis Bey; who, having seen several epidemics, was well acquainted with the clinical signs and lesions of cholera. Nevertheless no case of cholera was discovered, though in no less than five typical cases of colitis and dysentery we isolated cultures not to be distinguished from those of cholera, even by the agglutination test and Pfeiffer's reaction. The pilgrims finally left El Tor, five days after the finding of the vibrio, and no cases of cholera occurred either on the ships or after the pilgrims reached home.

During the four following years, the work of reorganization and the lack of skilled assistance prevented the systematic prosecution of these researches; though I frequently observed vibrios in the stools of pilgrims free from all symptoms of cholera.

In 1902, the pilgrims brought back typical cholera from Jeddah and Yambo to El Tor. The observations performed at the time showed three facts quite clearly:

1. The stools of almost every pilgrim suffering from diseases other than cholera—namely, pneumonia, rheumatism, dysentery, constipation, diarrhoea, etc.—contained vibrios numerous enough to be recognized microscopically.

2. Vibrios agglutinating with cholera serum were isolated from patients showing no symptoms of cholera. On the other hand, some vibrios isolated from typical cases of cholera did not agglutinate with cholera serum.

3. Although it was unavoidable that pilgrims carrying vibrios should mix with other pilgrims, yet only one fresh case of cholera occurred in the camp; all the others were imported. In the general hospital, where the majority of patients were excreting vibrios in every stool, not a single case of infection occurred among the patients, the European or native attendants. Further, not a single case of cholera occurred on the ships leaving El Tor after the period of quarantine was over.

BACTERIOLOGICAL INVESTIGATIONS.

In 1905, after the Hedjaz and El Tor had been free from cholera for nearly two years, Dr. F. Gotschlich examined systematically for vibrios the stools of every patient who died at El Tor. The autopsies were made by myself, and it may be stated once for all that no lesions resembling cholera were found in any case.

The results of these bacteriological examinations may be summed up as follows: Vibrios were found in 38 patients out of 107 cases examined. Thirty-two of these vibrios did not agglutinate, but six agglutinated readily with cholera serum. The characteristics of those which agglutinated with cholera serum were as follows: they were monociliated, non-phosphorescent, very virulent (with one exception) for guinea-pigs, and not virulent for pigeons, did not coagulate milk, liquefied 10 per cent. gelatin and gave a well-marked indol reaction. The morphological characteristics were not the same in all, but the differences were not greater than those existing between cholera vibrios isolated from different cases.

The results of the agglutination test are shown in the accompanying tables.

Five of these vibrios therefore agglutinated with specific serums just like cholera vibrios, and did not agglutinate at all with ordinary serums. One of them agglutinated far less than the others, but similar differences occur among vibrios isolated from typical cholera cases.