

in seven minutes, and did not vomit or suffer from any after-effects. The bronchitis was not increased, and he made a good recovery.

CASE 177. Female, aged 32, who had previously had a gastro-enterostomy for gastric ulcer; as the trouble recurred it was decided to do a gastrectomy. She was anaesthetised with this anaesthetic combined with gas and oxygen, and good relaxation was obtained; operation very difficult owing to adhesions from the previous gastro-enterostomy, and lasted 2 hours 40 minutes. At the end of two hours she was becoming slightly collapsed and a gum saline infusion was given intravenously. Her condition then greatly improved, and remained good until end of the operation. After recovering consciousness the patient vomited four times, the material being blood in each case. She had no further vomiting and made a good recovery.

Summary.

To recapitulate the advantages claimed for this anaesthetic:—

1. It is less toxic than chloroform or ether, and the safety margin is greater than with either.

2. It is less irritating to the respiratory passages than ether, and consequently there is less risk of subsequent bronchitis and pneumonia; the induction of anaesthesia is also rendered easier.

3. Post-anaesthetic vomiting is less than with chloroform or ether.

4. The taste and smell noticed afterwards by the patient are very much less than with ether, and are generally entirely absent.

In conclusion I should like to express my thanks to those surgeons who have afforded me opportunities for taking blood-pressure readings, and to Mr. B. B. Sharp, late resident anaesthetist to St. Bartholomew's Hospital, for his help in taking the readings.

CHAULMOOGRA OIL IN LEPROSY AND TUBERCULOSIS.

THE SUCCESSFUL TREATMENT OF LEPROSY BY INJECTIONS OF SOLUBLE PREPARATIONS OF THE FATTY ACIDS OF CHAULMOOGRA AND OTHER OILS AND ITS BEARING ON THE TUBERCULOSIS PROBLEM.¹

By SIR LEONARD ROGERS, Kt., C.I.E., M.D.,
F.R.C.P. LOND., F.R.S., I.M.S.,

EXTRA PHYSICIAN FOR CLINICAL RESEARCH, LONDON
SCHOOL OF TROPICAL MEDICINE.

ALTHOUGH the disease of leprosy is mainly of historical interest in this country, it presents an important and difficult problem in the tropics, especially in India and China; so a method of treatment which brings about destruction of the leprosy bacilli in the tissues is thus of great interest apart from its possible bearing on tuberculosis. Chaulmoogra oil has long been the best known remedy for the disease, but, owing to the nausea produced by large doses, it has only an ameliorative effect in typical cases, although Hopkins of Louisiana obtained some apparent cures in incipient cases by persevering with use of the oil. In 1913 Heiser reported apparent cures of a few cases by the prolonged use of chaulmoogra oil intramuscularly, which was a distinct advance. Power and others had obtained chaulmoogric and hydnocarpic acids from chaulmoogra oil and from hydnocarpus oils, while the name of gynocardic acid had been given by Moses to a mixture of the lower melting-point acids of chaulmoogra oil.

Use of Gynocardic Acid.

I myself early used gynocardic acid orally in the place of chaulmoogra oil with promising results, one severe case having nearly cleared up on very large doses in the course of a year, and in 1912 I attempted unsuccessfully to obtain a soluble compound of it for injection; returning to the subject in 1915, after Heiser's results had been published, I began giving

subcutaneous injections of sodium gynocardate, which resulted in more rapid improvement than that following the oral use of gynocardic acid. These injections, however, were rather painful and slow in their action, so I next used sodium gynocardate intravenously in small doses, which were painless, being followed in some cases with much thickening of the tissues, indicating the presence of very large numbers of acid-fast bacilli, by febrile reactions accompanied by swelling up and softening, with subsequent more rapid absorption of the lesions. Microscopical examinations in such cases showed large numbers of red dots of disintegrated bacilli with but few remaining rods, proving that the reactions resulted in rapid destruction of the bacilli in the tissues. Repeated microscopical examinations of cases not showing febrile reactions demonstrated that a similar more gradual breaking-up and absorption of bacilli occurred under the new treatment, until the lesions became bacteriologically negative.

Occasionally, in advanced cases of the disease, more severe reactions with prolonged fever occurred, followed as a rule by great improvement. Two remarkable cases were noted, in one of which extensive lesions of 20 years' duration with ulceration almost completely cleared up, with healing of all ulcers, during a period of about a year following a single small intravenous injection with prolonged febrile reaction; whilst in the other case very extensive lesions on the face and body completely disappeared, becoming bacteriologically negative after a similar reaction, although no further injections were given—a fact indicating that the extensive breaking-up of the bacilli during such reactions had led to curative formation of antigens in the body. Such reactions took place only after intravenous, and not after subcutaneous, injections of sodium gynocardate; the improvement was also much more rapid and satisfactory under the former method of administration, although it had the drawback that irritation of the vein at the site of injection sometimes caused strictly local obliterative phlebitis, producing difficulty in continuing the intravenous injections in certain patients.

Activity of Hydnocarpic Acid.

The next step in the investigation was to separate different melting-point unsaturated fatty acids of chaulmoogra oil by fractionation, and to test their sodium salts or soaps in cases of leprosy, to ascertain which were most active in the disease. As the result of prolonged observations it was found that the lower melting-point preparations, consisting mainly of gynocardate of soda, were less active than those made from fractions with melting-points of about that of hydnocarpic acid—namely, 58° C.; but that chaulmoogric acid, with a melting point of 68° C., formed sodium salts too insoluble for injection alone; the latter could be used in combination with sodium gynocardate, but without presenting any advantages. The conclusion was, therefore, arrived at that hydnocarpic acid was probably the most active constituent of the oil; it can be obtained more readily and in large quantities from hydnocarpus oils than from true chaulmoogra oil derived from the seeds of the Indian tree, *Taraxiogenos kurzii*. Later observations, however, have shown that active preparations can be made without laborious fractionation, from the whole of the fatty acids of these oils, which will simplify the production of the soluble active portions of the oil for the new injection method of treating leprosy.

Use of Sodium Morrhuate in Tuberculosis.

The successful treatment of leprosy by soluble derivatives of chaulmoogra oil led me to consider the trial of a similar line of treatment in tuberculosis, due to the other important human acid-fast bacillus, but the induration, pain, and slow effects of subcutaneous injections of gynocardates, and the severe febrile reactions sometimes produced by their intravenous injections, which might conceivably lead to a generalised infection, made me hesitate to use

¹ An abstract of a paper read before the Section of Therapeutics and Pharmacology of the Royal Society of Medicine, April 19th, 1921.

that preparation in tuberculosis, so I made a similar sodium salt of the unsaturated fatty acids of cod-liver oil, which I called sodium morrhuate, and first tested it in leprosy cases which had become stationary on gynocardates, or in which the latter could not be given intravenously for any reason. The preparation proved to be non-toxic, very soluble and unirritating to the tissues or veins, so was much easier to administer than the gynocardates and hydnocarpates; it soon became evident that leprosy patients who had ceased to improve on gynocardates might once more progress and completely clear up under sodium morrhuate. Moreover, even advanced cases treated by simple and almost painless subcutaneous injections of sodium morrhuate might recover completely; the very important fact was established that other oils besides chaulmoogra and hydnocarpus may be effective in leprosy.

Testing of Other Oils.

A wide field of investigation was thus opened up and explored; oils with a high iodine value, indicating a large content of unsaturated fatty acids, were selected for testing. One made from linseed oil proved to be irritating to the tissues, while another derived from Japanese sardine oil was very toxic to animals, but a third preparation made from soya bean oil, which is an excellent food largely used in China, was found to be very suitable for injection purposes. In a short trial before the author left India, a severe case, with a very extensive lesion on the face, cleared up and became bacteriologically negative within the exceptionally short time of six weeks; proving that yet another oil may yield active products, although further cases did not clear up so rapidly. These several preparations may be advantageously used alternately or mixed together, a change being made if progress is not satisfactory under one of them.

Duration of Treatment.

The duration of treatment required to obtain complete clearing up of typical leprosy cases is considerable, a year or more often being necessary, although comparatively early cases may show apparent recovery in a shorter time. The results of five years' investigation were summarised at the Calcutta Leprosy Conference in February, 1920, when of 51 cases treated with sodium gynocardate and hydnocarpate, 1 was not improved, 9 slightly improved, 20 greatly improved, and in 21 the lesions had completely disappeared, all cases treated as long as three months being included. Thus, 80 per cent. showed either great improvement—with a good prospect of complete clearing up after further treatment—or had already become bacteriologically negative. If cases treated for a year or longer were considered alone, 9 out of 13, or 65 per cent., showed complete disappearance of the lesions. Of 20 further cases treated with sodium morrhuate, 3 were slightly improved, 12 greatly improved, and in 5 the lesions had disappeared, none of the cases having been treated for over one year: 85 per cent. were thus classed as greatly improved, or "lesions disappeared."

After-Results.

The after-results were next discussed in the light of 26 gynocardate and 8 morrhuate cases, which had been followed up for another year subsequent to an earlier report on their condition. Of the former class, 5 had shown further improvement, in 5 the lesions had disappeared, and 10 remained well, bringing the latter class up to 65 per cent.; 5 had relapsed—all patients who had discontinued the treatment against advice as soon as their visible lesions had disappeared, although some of them subsequently cleared up again under further treatment. Stress was laid on the importance of relapses in emphasising the necessity for prolonged treatment and justifying the caution of the author in not speaking of cures. Still, four cases had remained well for two and a half years, and six more for over one year; in certain of these cases an additional

year can now be added, so that some may eventually prove to be cured. Confirmatory results reported by a number of observers were quoted, the most important being a trial in 13 Indian leper asylums of hydnocarpates in 183 and morrhuate in 117 cases reported on by Dr. E. Muir (who is now carrying out much more extensive trials in connexion with the Calcutta School of Tropical Medicine) with improvement in 72 per cent. and great improvement in 32 per cent. The trials were only of from two to 12 months' duration in most of these cases; while of those treated for six months and over, 100 per cent. showed improvement and 52 per cent. great improvement, including disappearance of the lesions in some cases. Moreover, sodium morrhuate gave exactly the same results as hydnocarpate of soda. Dr. M. Carthew, in 14 cases followed up in a Siam jail, also reported 2 improved, 8 greatly improved, and 4 with lesions disappeared for from six to 18 months. Ethyl ester chaulmoogrates and morrhuates were also made, but the former was rather painful on injection, although it has the advantage that it can be given subcutaneously or intramuscularly; in the Sandwich Islands, Hollmann and Dean, in 1919, and McDonald, in 1920, have reported very good results from its use, 78 patients having been discharged on parole by a medical board by the latter date. Moreover, patients were voluntarily seeking admission to the leper hospital for treatment, which should help in the segregation of early cases. There is thus no doubt that a great advance has been made in the treatment of leprosy by the researches in Calcutta and those of more recent date in Honolulu.

Age and Susceptibility to Leprosy.

Figures were next adduced to show that there is an especial susceptibility to infection by leprosy during the first two decades of life as compared with later decades. Denny, in the Philippines, has shown that no less than 44 per cent. of children living for seven to ten years with leper parents became infected, and that no less than 73 per cent. of cases in which the source of infection was traced, were among children and young adults, as compared with 1 to 2 per cent. between husband and wife in later decades of life. The frequent infection of children with tuberculosis is closely parallel, and attention was drawn to a recently published report showing the success of the Grancher Institute in Paris, which by permanent removal of children from exposure in overcrowded families containing adults with open tuberculous lesions, has greatly lessened infection among children. The great value of such protection of early life against infection of both leprosy and tuberculosis was emphasised.

Variable Results in Tuberculosis.

The trial of sodium morrhuate and sodium gynocardate in tuberculosis was next dealt with, the use of the former by six medical men in India having been reported in 1919, when the author concluded that the treatment was harmless and worthy of further trial, in view of five out of the six observers having reported favourably. Since that time variable results have been recorded, a trial among Indian sepoys in the dry, cool climate of Quetta having been very favourable, as well as the use of sodium morrhuate in tuberculous gland cases and in four cases of lupus, in one of which a new preparation, mercury morrhuate, was applied locally. On the other hand, trials in America had not given favourable results in phthisis. Attention was next drawn to the remarkable experimental investigation of gynocardates and morrhuates on acid-fast bacilli by Walker and Sweeny, who found that the chaulmoogra-oil preparations were lethal to acid-fast bacilli as a class on long exposure to their action in fluid media in dilutions of 100,000, having an especial selective action on them, although not on other classes of bacilli; they suggested that in leprosy these soluble preparations of chaulmoogra oil might have a direct destructive effect on the leprosy bacillus. On the other hand, sodium morrhuate had no such action on acid-

fast bacilli, and I wish to point out that the interesting American observations do not explain the undoubted value of sodium morrhuate in leprosy; and that some chemical reaction with the fatty envelopes of the acid-fast bacilli, so weakening them as to allow the body cells to deal with them, best accounts for their destruction in the body under the action of my preparations; but much more research is required in the wide field now opened up.

Conclusion.

A recent experimental investigation has been made of the three new preparations, which had proved effective in the treatment of leprosy, in animals infected with tuberculosis; but in the acute general tuberculosis produced in the very susceptible animals used the results were entirely negative, except for an early febrile reaction followed by temporary fall of temperature, in two goats, who eventually succumbed to the infection at about the same time as a control animal. It was pointed out that these animal infections were equivalent to acute general tuberculosis in man, so that the failure in such cases did not prove the drugs to be useless in the more chronic forms of tuberculosis which form the great majority of human cases. I conclude that, whilst there is doubt at present as to the advisability of treating pulmonary tuberculosis with sodium morrhuate, except in the hands of experts with control cases, these drugs are worthy of further trial in the more chronic forms of the disease, and especially in lupus and surgical tuberculosis, where any changes will be visible and easily observed.

A CASE OF JAUNDICE FROM LATE SALVARSAN POISONING.

By JOHN ELLIOTT, O.B.E., M.D., B.S., B.Sc.LOND.,
F.R.C.S. ENG., F.R.C.P. LOND.,
PHYSICIAN, CHESTER GENERAL INFIRMARY.

IN September, 1918, I was asked by a colleague to see a patient who was suffering from locomotor ataxia with severe root pains; he had previously had two intravenous injections of salvarsan with inunction of mercury administered. The second injection was followed by violent vomiting and purging and alarming general symptoms. At that time I was in the habit of administering novarsenobillon by the "deep subcutaneous" method into the fascia covering the gluteus medius. As I had seen no untoward effects from this procedure I concluded that the slower rate of absorption of the drug made for comparative safety. Accordingly I administered 0.45 g. by this method dissolved in a few minims of distilled water. It caused no pain and he went to business the same day and also on the next day. On the evening of this day, however, he was taken ill with vomiting and purging, the stools containing blood. The illness lasted two days. As the injections gave him great relief from the lightning pains I decided to repeat them, guarding (if possible) against after-effects by the administration of adrenalin chloride (1 in 1000) \mathfrak{M} 25 in water twice daily, with intermediate doses of calcium lactate, gr. 20, commencing on the day of injection and continuing for three days. This procedure was completely successful; the injections caused practically no pain (no doubt due to the diminished deep sensibility from *tabes*), and he suffered neither discomfort nor malaise but continued his work uninterruptedly. Since that time I have given him several prolonged courses of novarsenobillon and inunction of mercury ointment, always with the accompanying medicinal treatment as above, and with marked benefit to his condition.

In the course of the three years during which I have been connected with the venereal clinic at the Chester Royal Infirmary I had seen no case which

gave me the slightest anxiety from after-effects, with the exception of one very severe case of acute dermatitis, which came to us after treatment at another clinic, and the case of jaundice which I am about to describe—and this in spite of the fact that many of the patients live in the mountainous districts of Flintshire and Denbighshire, and have to travel to their homes after receiving an injection. I make it a rule never to give an injection if the patient is not in good health, from any cause other than his specific complaint. The urine is tested before each treatment, and all patients undergoing a course of salvarsan and mercury treatment take a teaspoonful of sublimed sulphur in treacle or syrup at bedtime to assist in the elimination of the mercury and thus also, indirectly, of the organic arsenic compound. They are also encouraged to drink freely of simple diuretics such as barley water or whey. I had seen no case of jaundice from delayed salvarsan poisoning, but decided that I would treat such a case with intravenous injections of normal saline (which I had found efficacious some years ago in treating a case of acute yellow atrophy), and also with adrenalin and calcium, after my experience of the effect of these drugs in the case of *tabes* mentioned above.

On Jan. 22nd of this year a patient attended the clinic with the following history:—

A man, aged 39, employed on a farm. Rheumatic fever in 1913; laid up 12 weeks. Joined army February, 1918; served in the R.E. in Kent; never abroad. Had a venereal sore when he joined army; slight rash on the arms, no sore-throat; had no treatment.

1919.—Glands in the neck enlarged; discharged from army on this account. May to September, 1919, in Chester Royal Infirmary. Lymphadenoma diagnosed; treated with arsenic and X rays; no improvement. July 21st, 1919, Wassermann test positive +; treatment, potass. iodid. and mercury ointment inunction; lost sight of until March, 1920, when he appeared at the venereal clinic. March 20th, 0.45 g. novarsenobillon intravenously, inunction; 27th, not well, injection omitted. April 3rd, 0.45 g.; 10th, omitted. 17th, 0.6 g.; 24th, 0.6 g.; May 8th, 0.6 g.; not well after the injections; these omitted until June 5th, 0.45 g. June 12th, 0.45 g. Injections discontinued again; 24th, Wassermann positive + +. July 28th, 0.45 g. August 4th, 0.45 g. August 11th, 0.6 g. and hyd. 1 gr. intramuscularly. 18th, 0.6 g. Sept. 1st, 0.6 g. and hyd. 1 gr. 8th, 0.6 g., hyd. 1 gr. 25th, 0.6 g. and hyd. 1 gr. Oct. 2nd, 0.6 g., hyd. 1 gr. 9th, not well. 16th, 0.6 g. 23rd, Wassermann positive + +. Nov. 20th, 0.45 g., hyd. 1 gr. 27th, 0.6 g., hyd. 1 gr. Continued to attend at the clinic, but felt unwell.

He always felt ill after the injections; shivering, giddiness, sometimes sickness, feeling of prostration and distaste for food. The specific treatment was entirely discontinued and tonics were administered from time to time. It is noteworthy that intramuscular injections had the same effect as those given intravenously.

Jan. 22nd, 1921: Came to the clinic complaining that he had been vomiting after everything he took; had noticed that he was yellow. Pain coming and going in the stomach; urine had been a deep colour. At once admitted as an in-patient; put on low, fat-free diet; sulphur, a teaspoonful at bedtime, and barley water ad lib. Did not vomit during the first two days in hospital. 24th: 4.30 P.M., one pint of normal saline given intravenously. 6 P.M., severe rigor, patient faint and collapsed; 6.30 P.M., hæmatemesis, about 5 oz. bright blood vomited; diarrhoea; severe pain in epigastrium and under right ribs, shooting to back and up right side. Temp. 103.4°F., pulse 128. 9 P.M., I saw him at the infirmary; deeply jaundiced, pulse 140; collapsed and feeling very ill; right upper rectus abdominis rigid; tenderness in epigastrium and over gall-bladder region. Gall-bladder could be felt distended; spleen not felt; liver dullness normal. (I formed the opinion that the gall-bladder was distended with blood.) Ordered liq. adrenalin chlorid. \mathfrak{m} 25, and calcii chlorid. 10 gr., in alternate doses 4 tis. 25th: Much better, no further vomiting or diarrhoea; pain not so severe; 20 oz. of dark-coloured urine had been passed during the preceding 24 hours. Fæces clay-coloured. 26th: 10 oz. normal saline, given intravenously; slight shiver followed and temperature rose to 99°. Gall-bladder diminished in size, liver and spleen normal, less pain. (The distilled water used in preparation of the normal saline was not above suspicion, so I had it doubly distilled, and no further ill-effects followed the injections.) Saline administered per rectum in addition to the intravenous. 27th: 10 oz. saline intravenously; the same quantity per rectum;