

## TOXIC EFFECTS OF ARSENOBENZOL PREPARATIONS.

REPORT BY THE SALVARSAN COMMITTEE.

THE Salvarsan Committee appointed by the Medical Research Council has recently issued its Report\* on the toxic effects following the employment of arsenobenzol preparations. The committee was established in 1918 on account of a peculiarly high incidence of fatal jaundice following the use of "606" or "914" in certain military hospitals receiving syphilitic cases. However, in spite of the fatalities occurring about that time, accidents following the use of salvarsan and its congeners have, on the whole, been very much rarer in this country than on the Continent. Especially numerous have been the deaths recorded in Germany, and public opinion was so seriously disturbed at one time in that country that two separate official inquiries were made in 1914 and 1917 concerning the value of salvarsan treatment and the injurious effects which were alleged to follow its use. The findings of these German committees of inquiry were of importance, and they receive full consideration in the report issued by the British Salvarsan Committee.

The chief statistics available to the Salvarsan Committee have been those obtained from military hospitals, as, for various reasons, less reliance can be placed on the records of civil venereal clinics. As a result of its investigations the committee has arrived at the conclusion that no special arsenobenzol preparation must be regarded as more likely than another to produce ill effects. Moreover, when accidents have occurred errors in technique in administration have seldom been found to be responsible. There have been fatalities even under the most careful control, and in large and well-equipped hospitals.

The most important ill effects which may end fatally were found to be encephalitis haemorrhagica, acute yellow atrophy of the liver, and exfoliative dermatitis and its complications. Encephalitis haemorrhagica usually occurs within two or three days after an injection, and most frequently after the second injection of the series. Disorders of the liver provide a very large number of the ill effects following arsenobenzol treatment, and may occur as an early jaundice or as a late and more dangerous lesion. The pathology of the latter lesion is still in some doubt, and it has even been suggested, especially in Germany, that it is not directly due to arsenobenzol. Skin reactions following salvarsan are fairly common, but fortunately they are light and transient as a rule, the only reaction or lesion of serious significance being exfoliative dermatitis. There exist certain other ill effects which may end fatally, but fortunately these are but rarely encountered; they include acute renal damage, ulcerative enteritis, polyneuritis, and aplastic anaemia.

Some of the ill effects which are recognized as being due to salvarsan may without hesitation be ascribed to the arsenic which it contains. The lesions capable of such explanation are gastritis, enteritis, and exfoliative dermatitis. The so-called "crises nitritoides," vasomotor phenomena, and liver lesions are, on the other hand, probably produced by arsenobenzol poisoning rather than by arsenic. An interesting point in connexion with the latter is the observation that cases of severe jaundice and liver atrophy appear to have occurred in the form of small outbreaks localized to one or another hospital, and restricted in time to a few months of its practice. This fact has led certain observers to suggest that these liver lesions are not directly due to poisoning but are caused by an intercurrent microbic infection of the liver. The committee does not, however, favour this view. Before stating its conclusions as to the relation of arsenobenzol compounds to the occurrence of jaundice and acute yellow atrophy of the liver, the committee has made an exhaustive study of the literature and the experimental work on the subject. A brief examination of this is sufficient to show that a great diversity of opinion still exists as to the pathology of the condition, many observers believing strongly that salvarsan is not responsible for the condition. It is, however, impossible to get over the fact that before salvarsan came into general use in the treatment of syphilis comparatively few cases of jaundice were encountered. It is difficult therefore to accept the view that the spirochaete rather than the salvarsan is responsible for the hepatic lesions. For the view that it may be produced by an infective cholangitis arising from the intestine there would

appear to be more foundation. This supposition relies for support on the bacteriological findings of Stuart Macdonald and Fraenkel, who claim to have found organisms in the hepatic tissues of fatal cases. It is obvious, however, that little reliance can be placed on bacteriological examinations carried out after death and unsupported by blood cultures made during life.

But quite apart from the results of morbid histology, evidence is gradually accumulating that a course of arsenobenzol treatment is followed in practically every instance by a certain degree of hepatic insufficiency, not enough to give rise to active symptoms, but capable of recognition by means of special tests. Such tests have been carried out at St. Bartholomew's Hospital by Dr. Mackenzie Wallis, and by Spence and Brett elsewhere. For this purpose two tests have been employed—namely, lactulose toleration tests and the estimation of the lipase or fat-splitting ferment normally present in the blood. The main results obtained so far by Mackenzie Wallis may be summarized as follows: (1) The effects of one or two injections of arsenobenzol preparations are almost always very slight, and little evidence of hepatic damage may be found at the end of a course of six injections. (2) The most striking results are obtained when the tests are applied three months after the last injection. Evidence of hepatic insufficiency is then detected almost invariably, although no clinical signs of hepatic disorder may be discovered. Six months after the last injection all evidence of hepatic insufficiency has gone, in cases where three months before it was clearly in evidence. It is obvious that the importance of these findings, if widely confirmed, may be very great in connexion with the safe spacing out of courses of arsenobenzol treatment.

Whilst recognizing the importance of exercising great care in the administration of "606" and "914," the committee is completely in accord in expressing the view that arsenobenzol preparations are more efficacious than any other drug yet available for the cure of syphilis:

"Although it is true that even this preparation cannot be guaranteed to effect an absolute cure, except in the early stages of the disease, it is now well established that a considerably larger proportion of cures can be effected by salvarsan and its allies than by any other form of treatment."

The committee's report ends with the following conclusions:

"It is believed that the very small number of unavoidable deaths due to this treatment are immeasurably outweighed by the deaths and disabilities which would arise if the older methods of treating syphilis were alone practised. At the same time the facts which have been brought together in this report no less strongly emphasize the importance of the most scrupulous care in the administration of a drug which is necessarily employed in doses not far removed from the danger line."

## MINISTRY OF HEALTH: ANNUAL REPORT.

### FIRST NOTICE.

THE third annual report of the Ministry of Health relating to the year ended March 31st\* has been issued. It consists of 166 pages, and embraces a large amount of information not covered by Sir Alfred Mond in his speech on the vote.

In the prefatory note on the conditions of economy mention is made of the appointment by the Government of a committee of inquiry under the chairmanship of Lord Meston, to report what system of Exchequer grants for locally administered services can be substituted for the percentage grant system wholly or in part. This year—as already announced—the course adopted in order to keep down expenditure is to give grants of fixed amounts for most of the services instead of percentage grants. In reference to National Health Insurance additional benefits it is stated that over twelve million insured persons in England were affected. The cash benefits of nearly four millions of these had been increased, over four million became entitled to new services, and nearly four and a half millions became eligible for advantages of both these kinds. Nearly £150,000 a year may be devoted to dental treatment, and nearly £300,000 a year to payments to hospitals or convalescent homes on behalf of members of societies which have included these additional benefits in their schemes.

### Tuberculosis.

The first section of the report treats of health administration in England. Great Yarmouth and the North Riding County

\* Cmd. 1713. Price 6s. To be obtained from H.M. Stationery Office or through any bookseller.

\* Reports of the Salvarsan Committee. II. Toxic Effects following the Employment of Arsenobenzol Preparations. Special Report Series, No. 66. H.M. Stationery Office. 1922. Price 2s. net.

Council having completed their scheme during the year, arrangements have now been made by all the county councils and county borough councils for dispensary and residential treatment of insured and uninsured persons suffering from tuberculosis. The number of dispensaries has been raised to 421, an increase of 10. The number of tuberculosis officers working under schemes of local authorities on March 31st was 339. The total number of institutions provided by local authorities and by voluntary arrangement was 433 and the number of beds 18,884, showing an increase of 1,492 beds. The number of additional beds which have been or are being provided under the term of the circular letter of November 3rd, 1919, will, under financial stringency, be limited to under 5,000.

The cost of residential treatment of ex-service men is borne by the Ministry of Pensions. The number receiving it on April 1st was 2,789, as against 3,559 on April 1st, 1921. The Public Health (Tuberculosis) Act, 1921, enables county and borough councils to arrange for the after-care of sufferers, and up to March 31st schemes of thirty-eight local authorities for setting up committees have been approved. In London interim committees were constituted in each borough during the war, and suggestions have now been given to them to organize permanent care committees to work in co-ordination with tuberculosis dispensaries. The matter of extra nourishment for persons under treatment for tuberculosis now devolves upon local authorities. The report says:

"It was not contemplated that extra nourishment should be provided by local authorities in other than limited classes of cases where the provision was likely to be of material assistance to treatment; or that more than limited expenditure should be incurred on this form of provision."

So far 119 local authorities have undertaken the provision on the lines of the circular letter of November 3rd, 1921. The expenditure of local authorities on this service ranking for Exchequer grants is limited to a maximum of £2 per annum per thousand of the population of the area of the authority.

#### *Veneral Diseases.*

The outstanding features in the campaign against venereal diseases in England during the year were a large diminution in the number of new patients attending the treatment centres and an increase in the total number of attendances of patients. The number of patients dealt with for the first time in 1922 was 79,000, as compared with 99,000 in the previous year. The number of attendances at treatment centres was 1,534,000, as compared with 1,434,000 in the previous year. The returns of the work done at treatment centres during 1921 show that, out of 52,000 cases which were recorded as having ceased to attend at the centres during the year, 13,000 were discharged after completion of treatment and subsequent observation, 14,500 ceased to attend after completion of one or more courses of treatment but before final tests as to cure, and 24,500 ceased to attend before completion of a course of treatment.

#### *Maternity and Child Welfare.*

The report states that the whole of England is now covered more or less completely by schemes for maternity and child welfare carried out by local authorities. It is part of the duty of the medical officer of health to supervise the scheme, but the executive medical work is generally carried out by whole-time medical officers or by general practitioners. The department has, in the past, urged each authority to appoint an assistant medical officer, preferably a woman, with special aptitude and experience, to supervise the work under the direction of the medical officer of health. Ninety-three local authorities have one or more assistant medical officers for the purpose. The work of such an officer is not necessarily confined to maternity and child welfare, but is very often combined with other duties, such as the inspection of school children. The total number of women acting as health visitors on March 31st was 3,378. Of the 48,618 women on the Midwives Roll (covering the whole of England and Wales), 12,052 gave notice of the intention to practise as midwives in 1921. Eighty-two per cent. of the total on the roll are now certificated. In 1920, the last year for which figures are available, the percentage of births notified by midwives was 47.7 in London, 66.9 in the county boroughs, and 47.1 in the counties. Over 100 new district nursing associations were started in England during 1921, and only 12 of the existing associations ceased work. Of the rural population of England 71 per cent. is now provided with the services of a trained midwife. On a rough estimate, 1,400 more district nursing associations were needed to provide a complete service in rural districts, and it was hoped that as financial circumstances improved these associations would gradually be established, while others had authorized the medical officer of health to employ a nurse when necessary. Grant was payable in respect of the home nursing of maternity cases and for certain infectious diseases in young children,

such as measles, whooping-cough, epidemic diarrhoea, poliomyelitis, and ophthalmia neonatorum. About 140 local authorities had contracted with the local district nursing associations. The trustees of the Carnegie United Kingdom Trust gave £100,000 to provide model centres at a cost of £25,000 each in Liverpool, Birmingham, Shoreditch, and Rhondda. It was a condition that the local authority should maintain the centre, and the department was unable to make a definite promise of grant in aid of maintenance until the estimates of expenditure on this service had been examined. It has now been found that a margin of public money is available, and steps are being taken to establish these institutions.

#### *Welfare of the Blind.*

Under the Blind Persons Act, 1920, which came into operation on September 10th, 1920, those who had reached the age of 50 were entitled to pensions as they would have been under the Old Age Pensions Act if they had attained the age of 70. On March 31st, 1922, nine thousand one hundred and seven blind persons in England and Wales between the ages of 50 and 70 were in receipt of old-age pensions. From the date of the operation of the Act to March 31st, 1922, 3,267 appeals relating to claims were received. Of these, 1,423 were referred to the regional medical staff and 45 to ophthalmic specialists on the question of the degree of blindness. The two inspectors are carrying out investigations into the voluntary agencies and are assisting local authorities to prepare schemes. The advisory committee has made numerous recommendations to the department. The committee appointed to investigate and report on the causes of blindness expects to conclude its deliberations at an early date.

#### *Other Services.*

Other sections covered in the report under the heading "Public Health" include the inspection and supervision of food, sanitary administration, housing and town planning. The report deals also with local government and local finance, the administration of the Poor Law, old-age pensions, and National Health Insurance. To this last-named part we shall recur on another occasion.

#### *Welsh Board of Health: Public Health.*

In regard to tuberculosis treatment it is stated that in Wales all the councils act for this purpose through the Welsh National Memorial Association. The contributions which the County and County Borough Councils have agreed to pay to the Association amount in the aggregate to £68,442, approximately equal to a rate of 1.34d. This represents an increase of 0.34d. on the rate agreed for the previous year. The residential institutions of the Association on March 31st consisted of four sanatoriums with 600 beds, and 10 hospitals with 501 beds. Arrangements are also made for the treatment of patients in 14 institutions belonging to other authorities or bodies. The conversion of Craig-y-Nos Castle, Brecknockshire, into a hospital with 300 beds was nearing completion, and hospitals at Sealyham, Pembrokeshire, with 30 beds, and at Machynlleth, Montgomeryshire, with 30 beds, were also nearly completed. The Association had been offered a mansion midway between Cardiff and Newport for conversion into a hospital with 100 beds, and had been authorized to proceed with the scheme. Approval had also been given for the acquisition of property at St. Bride's, Pembrokeshire, to provide accommodation for 100 children. When these hospitals were completed, two at Newport would cease to be used. There were now established in the principality 14 central dispensaries, round which were grouped 89 visiting stations.

#### **IMPERIAL CANCER RESEARCH FUND.**

The annual meeting of the Imperial Cancer Research Fund was held at the Examination Hall, Queen Square, Bloomsbury, on July 19th, with the DUKE OF BEDFORD, K.G., President, in the chair. Amongst those present were Sir William Church, Sir Humphry Rolleston, P.R.C.P., Sir Anthony Bowlby, P.R.C.S., Sir George Makins, Sir John Bland-Sutton, Dr. William Bulloch, Sir D'Arcy Power, Sir Charles Ballance, Sir Thomas Barlow, Sir Frederick Andrewes, Dr. J. A. Murray (Director), Dr. Russell, and Mr. F. G. Hallett (Secretary).

Sir WILLIAM CHURCH, in moving the adoption of the twentieth annual report of the Fund, sketched the principal researches which had been carried on, as stated in the Director's report published in full below. The motion was seconded by Sir JOHN BLAND-SUTTON and carried.

The DUKE OF BEDFORD, in moving a vote of thanks to the executive and other committees and the treasurer (Sir