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ANTI-SYPHILITIC TREATMENT AND HEPATIC CIRRHOSIS

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JAUNDICE occurring in the course of syphilis has been recognised since Paracelsus first directed attention to the association some four hundred years ago. In spite of the intervening centuries the diagnosis of syphilitic hepatitis, in the individual case, is by no means easy. The clinical differentiation between the non-syphilitic causes of jaundice and that resulting from the invasion of the liver by *Treponema pallidum* presents many difficulties, and even modern laboratory tests are of little help due largely to the multiplicity of functions served by the liver and its great physiological reserve. The introduction of the arsphenamine series of drugs in 1910 with their hepatotoxic propensities has further increased the diagnostic dilemma of the syphilologist faced with jaundice in a case undergoing, or following upon, anti-syphilitic treatment. Prognosis in such cases is equally difficult and, although many patients apparently recover completely and may tolerate further intensive arsphenamine therapy, increasing interest is being focussed on the late results of the hepatic damage of which jaundice may be the only manifestation. In the latter connexion the case-findings reported in this communication together with a brief examination of the relevant literature may be of interest.

CASE REPORT

The patient, a marine fireman, aged 29, was first seen in Liverpool in April, 1937. He presented the genital sore and bubo typical of chancroid, and, apart from dental sepsis, thorough clinical examination revealed no other abnormality. So far the patient had received no treatment and exposure had occurred six weeks previously in a South American port, the sore appearing

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five days later. On examination in Liverpool the serum from the sore proved negative for *T. pallidum* on three consecutive days. The Wassermann reaction and Meinicke tests were also negative. The Wassermann reaction was repeated three days later and as a positive result was now obtained treatment with neoarsphenamine and a bismuth preparation was substituted for the Dmelcos vaccine which had been administered following the negative serum tests on admission. He received 3.75 gm. neoarsphenamine and 2 gm. bismuth, given in bi-weekly injections over a period of one month, before returning to sea with sore and bubo completely healed. One month later, on his return to Liverpool, both clinical and serological examinations were negative and he received 2.55 gm. neoarsphenamine and 1 gm. bismuth before sailing again after four weeks ashore. No evidence of intolerance was noted during these two intensive courses of anti-syphilitic treatment.

On 3-9-37, five months after his first attendance, he was landed from his ship in Liverpool in a distressed state with a history of jaundice and increasing abdominal distension for the past eighteen days. On admission to hospital he was afebrile and presented marked ascites and moderate icterus. The abdominal wall was drum-like, free fluid was easily detected by percussion and the diaphragm was pushed upwards causing compression of the lower lobes of both lungs and upward displacement of the heart. Tachycardia was marked but the cardiac rhythm was normal. In addition, dental sepsis and gonococcal urethritis were present. The Wassermann reaction was negative and the icterus index was 30. Examination of the urine gave the following results: specific gravity, 1.020; reaction acid; minute trace of albumin; a trace of pus and no renal elements. Milk, glucose, a salt-poor diet and pil. Guy were prescribed and on 4-9-37 abdominal paracentesis resulted in the removal of fourteen pints of straw-coloured fluid. Following this procedure clinical examination was facilitated and it was noted that the lower border of the liver was just palpable beneath the costal margin. From 7-9-37 pot. iodide, 30 gr. daily, was given, and by 11-9-37 the patient was able to receive daily urethral irrigation with potassium permanganate 1:8000 solution, tab. hexamine gr. 5 t.d.s. being also prescribed.

The jaundice had now abated but the production of ascitic fluid proceeded rapidly and a second and a third abdominal paracentesis was performed on 17-9-37 and 28-9-37 respectively. On 29-9-37 mild pyrexia and a crop of petechial spots developed. Clinical examination of the heart revealed no abnormality, blood culture remained sterile and serological tests excluded infection by organisms of the typhoid, paratyphoid and salmonella groups or by *Brucella abortus*. The white cell count was 15,000 per c.mm., comprising 80 per cent. polymorphonuclear leucocytes and 19.3 per cent. lymphocytes. On 1-10-37 a fresh crop of spider-shaped, petechial spots, characteristic of cirrhosis of the liver, appeared and the latter diagnosis now seemed definitely established. The general treatment adopted at the beginning was continued and mercurial diuretic treatment with salyrgan was also tried with such small benefit that paracentesis was required on 19-10-37, 26-10-37 and 10-11-37. On 15-11-37 the liver and spleen were noted to be impalpable, the petechiæ had increased in number and the Wassermann reaction was again negative. Blood examination revealed a hypochromic anæmia and a leucopænia of 5,000 white cells per c.mm. and pil. Blaud gr. 15 t.d.s. was commenced.

The possibility of hepato-recurrence of the syphilitic infection had been kept in mind and although the negative serology and the nature of the previous anti-syphilitic treatment made this an unlikely explanation of the pathological process it was decided that any possibility of ameliorating the patient's condition, however remote, should not be neglected. Accordingly, bi-weekly injections of bismuth and 10 per cent. sodium iodide solution were commenced on 16-11-37, 20 gm. sodium iodide and 1 gm. bismuth being administered in all. No improvement, however, resulted from this therapy and abdominal paracentesis was required on six further occasions between 19-11-37 and 10-1-38. During this latter period the general condition deteriorated; the complexion became sallow and earthen in appearance; the number of petechiæ progressively increased; the blood pressure remained within normal limits and muscular tremors were noted.

On 16-1-38 the patient developed acute cholæmia manifested by vomiting, drowsiness and epileptiform

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seizure followed by unconsciousness. Some improvement followed lumbar puncture and a large, concentrated dose of mag. sulph. introduced into the stomach after a wash-out with sod. bicarb. solution. Clinical examination, after consciousness had been restored, revealed delayed cerebation, inability to concentrate and disorientation

FIG. 1.—Appearance of patient in terminal stages of hepatic cirrhosis. Osler's spider-shaped petechial hæmorrhages can be seen on the right forearm and over the line of the left sterno-mastoid.

in respect of time. The pupils were normal, superficial reflexes were exaggerated and incontinence of urine and involuntary tremors of muscles were present. Rombergism was marked and the gait was unsteady. The cerebro-spinal fluid was sterile and of normal composition. The illness pursued its course with intermittent attacks of cholæmia and the patient died on 4-4-38 after terminal coma. Ascites continued to the end although, as is usual

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in the late stages of this condition, the fluid formed more slowly. Altogether abdominal paracentesis was performed on eighteen occasions throughout the whole illness and approximately forty-five gallons of ascitic fluid were removed in this way. In the last few months of the illness the gastric disturbances, characteristic of hepatic cirrhosis, were a prominent feature and contributed to the emaciation evident in the photograph illustrating the spider-shaped petechial hæmorrhages.

FIG. 2.—Macroscopic appearance of the liver at autopsy showing coarse atrophic cirrhosis. Weight of liver, 24 oz.

An autopsy was performed four hours after death with the following findings: The liver, which weighed 24 oz., showed advanced, coarse cirrhosis (see photograph 2). The spleen was enlarged and somewhat fibrotic, weighing 12 oz., while the pancreas also showed some fibrosis. The kidneys weighed 5 oz. each and had narrowing of the cortex and an adherent capsule; while the heart presented myocardial degeneration and terminal dilatation of the right auricle. The brain appeared normal except for slight œdema. Microscopic findings were as follows: Liver, definite coarse cirrhosis. Spleen, fibrosis and great

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congestion. Kidneys, marked degeneration of the cells lining the tubules and atrophy of some of the glomeruli associated with hæmorrhage into the kidney substance.

DISCUSSION

I believe it is impossible to present, in dogmatic and definite steps, a statement of the pathological and ætiological processes involved in this case because it is probable that the final condition of hepatic cirrhosis was the resultant of several contributory factors. The liver and spleen undoubtedly sustained severe parenchymatous damage which rapidly produced generalised hepatic and splenic cirrhosis but the relative importance of the parts played by syphilis, arsenic, bismuth and other potential factors is difficult to assess. Moderate beer-drinking was admitted but the consumption of more potent spirits was denied. Some degree of dental sepsis was present but this focus of infection and potential intoxication must have been operative for a considerable time before the syphilitic infection occurred and there is, therefore, nothing to suggest that the liver was other than normal when subjected to spirochætal invasion and subsequent anti-syphilitic treatment. Splenic anæmia was considered in the differential diagnosis but there was no family history of Banti's disease and the course of the illness was atypical of such a condition. The features of the case which are considered of interest include the occurrence of cirrhosis of the liver in the third decade ; the relationship of early syphilitic infection, and its treatment, to the development of this condition ; the involvement of the spleen in, and rapid course of, the cirrhotic process ; and the opportunity which the case presented of studying the sub-cholæmic and acute cholæmic stages of the disease. Osler's " spider-shaped " petechial hæmorrhages, characteristic of hepatic cirrhosis, were well demonstrated and are illustrated in photograph 1.

A syphilitic lesion of the liver may give rise to jaundice. Stokes gives an excellent description of the various clinical types under the following categories : 1. Early acute benign hepatitis. 2. Syphilitic destructive hepatitis or acute yellow atrophy. 3. Subthreshold hepatic syphilis detected by functional tests. 4. Hepato-recurrence. 5. Mild chronic hepatitis of latency. 6. Diffuse

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and localised gummatous hepatitis. 7. Chronic interstitial pericellular cirrhosis of heredosyphilis. 8. Perihepatitis. Wile and Sams found that syphilis of the liver occurred in only 0·18 per cent. of syphilis cases treated at the University Hospital Clinic, Michigan, and general experience, with adult cases, confirms this low incidence of clinically recognisable hepatic syphilis. Milian maintains that hepato-recurrence is responsible, in many cases, for the hepatitis, especially where treatment, in the early stages of syphilis, has been inadequate and claims that dramatic improvement may follow active arsenical treatment. This theory, although receiving the support of some venereologists, has not gained universal acceptance.

Chronic alcoholism was formerly accepted as a common cause of cirrhosis of the liver. More recent opinion, based on clinical and experimental work, contradicts the old view and this pendulum-like swing coincides with an era of increased temperance. Stokes, however, believes that the heavy and regular drinking of alcohol exerts a deleterious influence on the course of syphilitic hepatitis, increasing the incidence of ascites and the gravity of the prognosis.

The rôle of bismuth in producing hepatic damage has been considered by Lane, who recalls that bismuth, in the presence of fresh organ extracts, is converted into a new bismuth compound which Levaditi called "Bismoxyl." This latter compound is stated to be therapeutically more active than in its original form and it is thought possible that its toxic effect may be likewise increased. There appears, however, to be no unequivocal evidence that bismuth therapy is responsible *per se* for permanent liver disease. In combination with other deleterious agents it is possible that bismuth may prove to be the proverbial straw which breaks the hepatic resistance.

That arsenical preparations, taken therapeutically or by accident, may be incriminated as a cause of hepatic cirrhosis has been suggested in the literature. Thus, Sturrock and Reynolds concluded that the epidemic of hepatic cirrhosis occurring in England during 1900 and 1901 was due to the accidental contamination of beer by arsenic. O'Leary, Snell and Bannick reported the development of hepatic cirrhosis in cases which had

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received inorganic arsenic over a prolonged period and O'Leary, Green and Rowntree reported one non-alcoholic case which, being suspected of suffering from syphilis, received treatment with arsphenamine and mercury during a period of ten years, the patient then dying of hepatic cirrhosis. Paul O'Leary has records of ten fatal cases of cirrhosis of the liver, all of which had suffered from post-arsphenamine jaundice. Baldrige has reported twelve cases of cirrhosis of the liver with portal obstruction which followed treatment with arsphenamine and mercury and in these cases clinical evidence of disease of the liver was not detected prior to treatment and jaundice did not occur at any time. Lane in an analysis of 100 cases of jaundice which occurred in the Dermato-Syphilologic Clinic of the Massachusetts General Hospital among 3,186 cases of syphilis, treated between 1929 and 1935, reported a case of acute yellow atrophy of the liver with a fatal issue four months after the beginning of treatment with neoarsphenamine and bismuth and also another case which died of atrophic cirrhosis following treatment with tryparsamide and bismuth. Traenkle and Dolce have also reported two fatal cases of acute liver necrosis. The first case followed some six weeks after the completion of a third course of ten weekly injections, each of 2 gm. tryparsamide, each course being separated by a rest period of two months. The second case developed after 28 gm. tryparsamide and two injections of bismuth salicylate. The former case had received trivalent arsenical therapy seven years previously and had also suffered from malaria but the latter case had received no previous anti-syphilitic treatment.

It will be noted that in all the reports mentioned above arsenic is the common factor and that its inorganic as well as its trivalent and pentavalent organic preparations are incriminated. The parts played by such factors as alcohol and syphilitic infection appear to be of a subsidiary nature.

Laboratory evidence of the toxic effects of arsenical preparations on the liver parenchyma is also forthcoming. Gerrard reported that the van den Bergh reaction detected a definite increase in the blood bilirubin in 89 of 370 cases of syphilis undergoing arsenical treatment and that, in spite of the cessation of treatment, clinical icterus later developed in four of these cases. Dixon, Campbell and

Hannah have also obtained similar results. Lewin investigated the possible impairment of liver function by determining the change in the urinary bile salts during anti-syphilitic treatment. He showed that of all urinary constituents only the bile salts influence surface tension and in thirty-three of eighty-eight patients receiving from 0.45 gm. to 0.6 gm. neoarsphenamine a fall in surface tension was recorded twelve to twenty-four hours after injection. This increased secretion of bile salts persisted for from one to seven days and, in several instances, became more marked and tended to be permanent with repeated doses of neoarsphenamine. Campbell and Soffer carried out the bilirubin test in about forty cases which had recovered from post-arsphenamine jaundice and concluded that, in many such patients, there is a definite, permanent interference with the bilirubin excreting function of the liver.

A further factor which may be operative in the production of permanent liver damage is some non-specific infection occurring during the course of anti-syphilitic treatment. Ruge found such a close parallel between the temporal incidence of arsphenamine and epidemic jaundice that he considered the two diseases to be identical and concluded that the arsenic reduces the resistance of the liver to epidemic infection. Soffer (1937) found similar evidence in a study of the Johns Hopkins Hospital cases. In this connexion the experimental work of Opie appears, by analogy, to be of interest. He showed that the administration of chloroform and the concurrent injection of living bacteria produced greater hepatic damage than occurred with chloroform alone.

While the appraisal of the individual parts played by multiple factors prohibits dogmatism, the culpability of the arsenical preparations in producing hepatic damage appears to be established from the above consideration of published work. What is the magnitude and importance of the problem arising out of this conclusion? The estimates of the incidence of arsenical jaundice, as reported in the literature, vary from 0.6 per cent. (Harrison) to 5 per cent. (Clement-Simon and Vulliemoz) and Soffer (1939) stated that 0.87 per cent. of 18,250 patients, treated for syphilis at the Johns Hopkins Hospital from 1919 to 1934 inclusive, developed jaundice. Acute yellow atrophy occurred in 6.3 per cent. of these

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latter cases, while Strathy, Smith and Hannah assess the incidence of this grave complication as 14 per cent. following the use of "606" preparations. As an increasing proportion of cases now report for anti-syphilitic treatment it will be seen that this problem of persistent hepatic damage arising out of arsenical therapy is of practical importance. Such a conclusion confirms O'Leary's statement that "the problem concerning the ultimate prognosis of patients with post-arsphenamine jaundice is assuming increased importance in view of the fact that some of these patients are said subsequently to develop outspoken cirrhosis of the liver."

SUMMARY

A case is described in which fatal hepatic cirrhosis developed during the treatment of early syphilis.

The possible factors concerned are discussed with reference to published work.

In patients developing jaundice during the course of anti-syphilitic treatment it is concluded that the importance of ultimate prognosis is commensurate with the difficulty such a prognosis presents.

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