mental enfeeblement, and who is now doing a full day's work and taking his full share of responsibility.

Conclusion

A definite conclusion cannot be drawn from such a small group of cases with comparatively short periods of observation, but the evidence so far accumulated indicates that further trial of the methods described is amply justified.

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JAUNDICE IN SYPHILITICS*

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The following survey summarizes my general observations on an investigation of cases of jaundice occurring in syphilitics, treated and untreated, in the past two years, and reviews the main points in our present knowledge of the subject.

War-time increase in jaundice

I first noticed a local increase in the incidence of jaundice occurring in my syphilitic patients about two years ago, and in April, 1941 the numbers were high enough for me to circularize my colleagues in other Commands to see whether they had noticed a similar increase. None of them, at that time, was aware of any notable rise in incidence, but two people reported a slight increase. From small beginnings the increase has continued until it now constitutes a major problem.

I have felt from the first that jaundice during arsenical treatment was not a distinct clinical entity, and have always tried to compare my cases with those of infective hepatitis patients who were not syphilitic. It now seems to me that the jaundice coincident with arsenical treatment is only a small, but not insignificant, part of what is really a pandemic of jaundice, occurring in many different types of individuals and having different predisposing factors, but due essentially to a disturbance of liver function leading through various pathological states of the liver cells either to necrosis of these cells or to their recovery. All my observations have supported this view and I have seen in the last two years about 600 patients with jaundice, half in cases of treated syphilis and half in otherwise healthy individuals.

During the whole of the present war period the antisyphilis treatment used in the area from which most of my cases came has been the same. Early syphilis is treated with a minimum of four courses of neoarsphenamine and bismuth. Courses are of ten weekly injections of 0.6 gramme of neoarsphenamine and 0.2 gramme of bismuth with a month's rest between the courses. The therapeutic results in syphilis have been very good with this dosage.

We know that the incidence of syphilis has increased, and that treatment complications must obviously also increase. Although the incidence of dermatitis and other complications which are directly due to arsenic have appeared subsequent upon the increase in syphilis, the incidence of jaundice has gone far above the highest previously quoted average. As jaundice and hepatitis can occur for a variety of reasons in the course of syphilis and its treatment, I think it wise to consider all the types that may be encountered, for they are important in differential diagnosis.

The varieties of jaundice in untreated syphilis

Hepatitis with or without jaundice can occur at any stage of acquired or congenital syphilis.

* An address to the Medical Society for the Study of Venereal Diseases, March, 1943.

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(1) *Congenital*.—A clinical enlargement of the liver can be found sometimes at any stage of the disease, but clinical jaundice is uncommon apart from treatment. Hutchinson described it as almost unknown.

(2) *Acquired*.—(a) *Early*. A mild hepatitis has long been noted as occurring in the primary and secondary stages of syphilis before treatment is begun. Clinical jaundice is rare, various authorities giving the rate as between 0.1 and 3 per cent. I should put the incidence nearer the first quoted figure. The jaundice in such cases usually coincides with a severe florid secondary syphilis. The work of Irgang and Sala suggests that symptomless hepatitis is quite common in cases of early syphilis. They found that up to 25 per cent of cases had a positive direct or direct delayed van den Bergh reaction. They did not find any evidence that such cases were more liable to jaundice later on, after treatment had begun. All such cases clear up quickly with arsenical treatment, although there may be an initial reactionary deepening of the jaundice. Acute yellow atrophy has been noted by a number of observers, including Hutchinson (1909), as occurring in patients with untreated early syphilis. Arsenical treatment has been advised in such cases.

(b) *Late*. Clinically obvious liver damage is not very common in the late stages of syphilis. This view was also held by Hutchinson in the pre-arsphenamine era. Clinical signs include enlargement of liver and spleen with jaundice and ascites, one or other being most prominent. Latent hepatic involvement is probably commoner.

Recurrence.—Milian considers that many cases of jaundice are due to a later involvement of the liver after inadequate early treatment. Clinically, such involvement resembles the hepatitis of early syphilis, and in the case of a patient I have seen recently, jaundice preceded a muco-cutaneous relapse and cleared up after treatment with arsenic. The patient was a defaulter. The jaundice was at first thought to be an ordinary intercurrent jaundice and treatment with bismuth only was restarted but muco-cutaneous lesions supervened. This was not the first patient I have seen who relapsed during bismuth treatment after inadequate arsenic treatment. I consider this an instance of an important type in differential diagnosis.

Incidence of hepatic syphilis

Clinical diagnoses of hepatic syphilis are very uncommon, for example at the Johns Hopkins Hospital, Baltimore, such a diagnosis was made in only thirty-four out of 6,420 cases of late syphilis. At post-mortem examinations at the same hospital, thirty-three cases were found at 8,500 necropsies. Latent hepatic involvement is probably commoner, according to Stokes (1936) and other observers.

Jaundice and hepatitis coincident with arsenic treatment

This is the type with which we are now primarily concerned and which can be put into four main categories.

- (1) Acute or mild hepatitis (clinical and sub-clinical).
- (2) Chronic and more severe hepatitis.
- (3) Sub-acute yellow atrophy.
- (4) Acute yellow atrophy.

Types (1) and (2) tend towards complete recovery; type (3) leaves residual damage which is clinically obvious; and type (4) is usually fatal. I consider that these four main types have a common pathological basis but develop in different ways.

Incidence of jaundice after arsenical treatment

This has been given in the past as between 0.6 per cent and 8 per cent by different people, but at the present time the figure is generally higher. I have found it impossible to find accurate figures for various reasons—movements of patients into or out of my area, patients under treatment at civil clinics and jaundice treated in civil hospitals or in hospitals without a venereologist and in which, consequently, the cases were not notified.

The best I can do is to give the percentage of those who have had jaundice out of the total number of patients attending at the three main centres in my area at the present time.

	Under treatment	Jaundice
(1) Woolwich	248	34 (or 14 per cent)
(2) Colchester	232	42 (or 18 per cent)
(3) Military Isolation Hospital, London	460	197 (or 42 per cent)
Total	940	273 29 per cent

The patients at these hospitals had not all been treated throughout in the same centre, nor had they had jaundice while being treated there. The figure for the Military Isolation Hospital is very high as most jaundice patients are sent there and kept in the hospital area for observation and investigation. The method of treatment, preparation of the drug, sterilization of syringes and brands of neoarsphenamine were the same at all three hospitals.

Analysis of the cases at the Military Isolation Hospital shows that two had had jaundice in 1940, nineteen in 1941, and 160 in 1942. The admission figures of jaundice patients to the hospital were sixty in 1941 and 120 in 1942, but there was also a 100 per cent increase in the number of new cases of syphilis and of patients attending for treatment at the same time.

I have not had much personal experience with Mapharside, but I will give two recent opinions. In an article, Lieutenant Colonel H. S. Mitchell of the Canadian Army (1943) has given the incidence of jaundice in a group of patients under treatment for syphilis as 5.84 per cent. Of these, 90 per cent were treated with neoarsphenamine and 10 per cent with Mapharside. The incidence of jaundice was relatively three times as great in the neoarsphenamine cases as in the Mapharside. The same ratio was given by Dr. Anwyl-Davies (1943) of the St. Thomas's Hospital Clinic, who says that in the six years he has used Mapharside the incidence of jaundice and dermatitis has dropped to about one-third of the previous level when neoarsphenamine was used.

The clinical types

The cases seen have not shown any clinical point of difference from the types of infective hepatitis seen in the non-syphilitic population. I have been permitted by colleagues in civil and military hospitals and in private practice to examine a very large number of cases of infective hepatitis, and I am confident on this point. The same four broad categories can be recognized.

(1) *Mild or acute hepatitis*.—Patients with this form usually begin with indigestion, nausea, vomiting and anorexia. The patient may complain that his urine has become dark or his stools pale. Sometimes the disease is only diagnosed when the patient becomes yellow. General joint pains are quite a common prodromal symptom, and urticaria has been seen in a few cases. Jaundice may appear at any time from a few days to several weeks after the first symptoms, but abortive cases which never become jaundiced are quite common. Urobilinogen can be found in the urine for some days or weeks before clinical jaundice appears. In mild cases there is usually some slight clinical enlargement of the liver, and the spleen is sometimes palpable. Such patients are not very ill. Some, in fact, have been treated as out-patients as a test, and all generally recover in from one to three weeks.

When subclinical jaundice is suspected, arsenic treatment is stopped but bismuth is continued in heavier doses. About half the cases progress to those of clinical jaundice. In a few test cases arsenic treatment was continued in spite of warning signs, and about 80 per cent of the patients became jaundiced although some still escaped.

(2) *Chronic hepatitis*.—Here the onset is very much the same as in the mild type but the symptoms are more obvious, the jaundice is deeper and the liver is usually larger. I have thought that such cases sometimes tend to occur later in the treat-

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ment of the syphilis, after the second course of arsenicals, but I would not care to be dogmatic. Loss of weight is a prominent feature and the patients are often very depressed. Sometimes a little ascitic fluid has been detectable for a short time in the worst cases, and Dr. J. McMichael of the British Postgraduate Medical School tells me that he has sometimes found a little in the course of making punctures to obtain biopsy material. In such cases the patients take from four to eight weeks to return to normal colour and may have transient periods of deepening of the jaundice. In the chronic cases the patients eventually recover completely, although it may be months before they are quite normal in health and appearance.

(3) *Subacute yellow atrophy*.—This is uncommon. I have seen only two patients with this type of hepatitis and both, I am glad to say, have recovered. The disease starts in the usual way, but after a week or two the patient becomes very ill. There are two types, one in which there is deep jaundice and cholaemic symptoms, the other in which ascites is the prominent feature. One of my patients, who had great ascites, developed a clubbing of his fingers in fourteen days. A liver biopsy, performed after his resumption of duties as a clerk, showed marked cirrhosis, but the man is still fairly well a year after his illness.

The other patient, who was a case of the cholaemic deeply jaundiced type, has unfortunately gone from my area, but when last I saw him he appeared to show signs of early cirrhosis.

(4) *Acute yellow atrophy*.—I have had only one such case in my series. The man had a rapidly deepening jaundice, passed into cholaemia and died about fourteen days after the onset of symptoms.

Treatment

A specific treatment has not yet been found which causes much alteration in the speed of recovery. I advise rest in bed in the early stages but have not found it harmful to allow patients up for a little gentle exercise once they begin to recover. The best diet contains a minimum of fat with plenty of carbohydrate and protein, and the patient is allowed to choose what he wants as far as possible. Glucose is given, but some patients who did not have it have done just as well as the others. Sodium thiosulphate has been used but I have abandoned it completely for about eighteen months. I have also tried Hepatex T liver extract, vitamin C, sodium salicylate and sulphanilamide without finding special merit in any of them.

Convalescence.—It takes a long time for a patient with even a mild attack to get really well after jaundice. I have found it best to send soldiers to their homes for a week or two after they leave hospital for they do much better at home than in convalescent camps where exercise is usually too heavy. Patients who have had more severe attacks often remain lethargic and sallow for months after the jaundice has faded, and often a trace of urobilinogen persists in the urine. Eventual clinical recovery is the rule however. Patients should be kept off full duty for at least a month after returning to their jobs. Alcohol is absolutely contra-indicated during at least three months after an attack.

For ultimate recovery.—Rankin and Marlow (1940) studied cases up to nineteen years after jaundice and found signs of subclinical liver damage in some cases, although cirrhosis was rare. The liver gradually improves in function, but this can be retarded by alcohol. Rankin and Marlow say also that arsenic should be given again only if the danger of syphilis outweighs the danger of further liver damage.

O'Leary indicates a graver outlook and considers subsequent cirrhosis more likely. The ultimate prognosis in present cases will not be known for some years. Cirrhosis may develop after hepatitis in cases of patients treated with arsenic and in severe infective hepatitis cases. The mortality rate for acute yellow atrophy in both types is probably about the same.

The treatment of syphilis must not suffer because of jaundice and it is important to continue bismuth in heavy doses throughout the course of the disease and not to give any rest periods until arsenic is resumed. Several authors, including Stokes, describe cases in which arsenic has been given throughout the course of

jaundice without ill effect. I have treated subclinical cases of jaundice and even one or two mild clinical cases with neoarsphenamine without incident.

The danger of syphilis relapse must be remembered, and in most cases arsenic treatment should be resumed as soon as possible. It is usual to give only bismuth for three months after jaundice and this is just as long a delay as is permissible in cases of early syphilis. Most of my patients have resumed neoarsphenamine treatment after such a time lapse without ill effect. I have seen only four cases in which there was a return of jaundice after arsenic treatment had been resumed. Relapse or recurrence is also possible in infective hepatitis. I have also used Mapharside or Acetylarsan when resuming treatment in the more severe cases in which neoarsphenamine has not been well tolerated.

Provided that treatment is not seriously interfered with, jaundice has little effect on the ultimate prognosis of syphilis, but clinical and serological relapse may occur if return to arsenic is too long delayed.

Predisposing causes

It is a common observation that the great majority of cases of jaundice are noted about the beginning of the second course of arsenical treatment, that is at the time of the eleventh to the sixteenth injection or the fifteenth to the twentieth week after treatment begins. There is a similar interval when Mapharside is used, the jaundice occurring at the fourteenth injection according to Anwyl-Davies. About 80 per cent of my cases have occurred at a comparable time. Of the remainder, most occurred after this critical period, only a few being seen at the end of the first course of treatment or during the first rest period. In three cases jaundice occurred up to six months after treatment had ceased.

Drug.—The type and batch of neoarsphenamine does not appear to matter. I have used Stabilarisan, N.A.B., neoarsphenamine, Novostab, and neo-Kharsivan and have not found any difference in their effects. I have also seen jaundice develop in patients treated with tryparsamide, Mapharside and Sulfarsenol.

There is good evidence to show that jaundice is less likely to occur with Mapharside treatment than with the arsphenamines. This may be due to the decreased amount of arsenic or possibly to impurities in neoarsphenamine, or to breakdown products of neoarsphenamine.

Jaundice also occurs in patients treated by massive arseno-therapy with neoarsphenamine or Mapharside, and it occurs in patients treated with "606."

The occurrence of jaundice during bismuth therapy has been described too, but since most of the patients have had arsenic also at some time or another, it cannot be proved that bismuth has been the responsible factor. Hutchinson described a type of jaundice which occurred during the treatment of syphilis with mercury and considered it to be identical with infective hepatitis.

Geography.—In the early days of the present war I thought that my cases were localized in certain areas. In 1941, in the Guildford area, and later in Croydon, I found most cases, but with the passage of time and the increase in numbers, I found that I could not positively confirm my theory of selective localization. Now the bulk of the cases occur in or near London. In the last few months Colchester has had a rising incidence of jaundice.

Distribution amongst population.—I think I am correct in saying that the amount of jaundice seen in civilians at venereal diseases clinics is negligible in most areas, yet soldiers who receive their after-treatment at civil clinics develop jaundice no less frequently than those treated at military hospitals. I also believe that the Royal Air Force has a lower jaundice rate than the Army, although treatment is essentially the same. The Royal Navy, however, has also had a high incidence of jaundice in the past.

Time of year.—I thought at first that the incidence was highest in winter, but this is not borne out by later figures.

Spread.—Droplet infection is believed to be the method of spread of infective hepatitis. The possibility of spread in crowded waiting-rooms at clinics has been suggested, but I have not been able to substantiate this. The soldier, of course, in his communal life, has every opportunity of catching any infectious disease.

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Contact.—I have now seen many cases in which two men in the same unit have become jaundiced at the same time. In some cases both men were being treated for syphilis; in others one man was otherwise healthy. I have also had a case of a soldier and his wife, both under antisyphilitic treatment, developing jaundice at the same time, and have heard of similar cases. The orderly who helps me in my syphilis treatment room has had jaundice. Local epidemics of infective hepatitis in hospitals are well known, as are epidemics in army units.

Alcohol.—The alcohol factor is a difficult thing to assess, but it can be said that alcohol increases the liability to jaundice. Stokes believes that alcoholics are more liable to ascites if liver damage occurs, and he thinks that the ultimate prognosis is worse in alcoholics.

Diet.—This is a possible causal factor, yet the soldier, who is better fed in most respects than the civilian, is more liable to jaundice. Stokes, quoting Craven, states that jaundice is more likely on a high carbohydrate diet than on a high fat and protein diet. Starvation is also a predisposing factor.

Sex.—Men are infinitely more liable to jaundice than women. To the best of my knowledge the incidence of jaundice among women in the Forces and among the civilian wives of soldiers, under my care, is under 2 per cent. Congenital syphilitic children do not often get jaundice.

Type of syphilis.—Jaundice is equally common to, and does not show any difference in type in, treated cases of early, late, latent or congenital syphilis. Syphilis may be a predisposing factor in itself and what we call the jaundice of early syphilis may only be a superinfection. The biopsy findings in one such case, unfortunately after two injections of arsenic, were indistinguishable from those in cases of hepatitis in treated patients.

Epidemiology.—It has been shown notably by Ruge (1927, 1932) that increases in the jaundice rate in syphilitics are similar to the rise in the infective hepatitis rate in the general population, but at a much higher figure. Probably the patient under arsenical treatment is anything from twenty to forty times as liable to jaundice as a healthy person. The present increase of jaundice in syphilitics is again only an incident in a general epidemic.

Pathology

The blood biochemistry does not show any really significant changes which can be used to differentiate infective from so-called toxic jaundice. Apart from a rise in the serum phosphatase and bilirubin and a slight rise in cholesterol, there is nothing of note. The blood is usually quite normal in erythrocyte, leucocyte and differential cell counts.

Liver biopsy.—Investigations made by Professor Dible and Dr. J. McMichael of biopsy material from patients with infective hepatitis and from those with hepatitis occurring after treatment for syphilis, have not shown any difference between the two types.

Virus.—The character of infective hepatitis suggests that it is probably due to a virus. I do not think this has been definitely proved, but experimental work is proceeding on this point, and cases of jaundice occurring in treated syphilitics are being included in investigations by Dr. MacCallum of the Wellcome Research Foundation.

Prevention

(1) Routine glucose before injections does not seem to have much effect. It was being used at the outset in the Guildford clinic where the first cases occurred, and is still used in one hospital.

(2) The possibility of spread by infectious material in inadequately sterilized syringes has been suggested. Anwyl-Davies (1942), in a recent article, did not consider that boiling syringes between injections had any effect on the incidence of jaundice.

(3) Increasing the dosage of neoarsphenamine increases the amount of jaundice. Curtis (1942) gives figures from the Whitechapel Clinic records in support of this. Up to 1937 the dosage employed there was 7.5 grammes of neoarsphenamine

in a thirteen weeks' course and the incidence of jaundice was from 7 to 8 per cent. After 1937 the dosage was increased to 13 grammes in thirteen weeks and the jaundice rate was from 25 to 30 per cent. Reducing the amount of arsenic by the use of Mapharside appears to reduce the incidence of jaundice.

I have records of ten patients treated with neoarsphenamine in doses of only 0.45 gramme weekly but they did not develop jaundice at the critical period. As their treatment is not yet complete, this finding is inconclusive.

Summary

The present increase in jaundice as a complication of the arsenical treatment of syphilis is coincident with an increase of infective hepatitis in the general population, but people under treatment for syphilis are much more apt to be affected.

The same clinical types can be observed in cases in which arsenical treatment has been given, and also in those patients who have not been given any treatment. As yet obvious pathological distinctions cannot be made. There are five factors which possibly increase the liability to liver damage in syphilitics.

(1) The use of arsenic in treatment. The fact that the bulk of cases of jaundice occur at about the same time in the course of treatment may suggest that a threshold amount of an arsenical drug is necessary to produce damage.

(2) Syphilis itself.

(3) Environment. Some people may live in conditions which are more conducive to the spread of an infection, if this is a factor.

(4) Diet. The absence of some constituent of the diet, particularly in war-time, may reduce the resistance of the liver.

(5) Sex. Males are infinitely more liable to jaundice than females.

With regard to the essential cause of jaundice, our present evidence suggests that the liver has only one way of reacting to a variety of infecting or toxic agents.

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JAUNDICE IN SYPHILITICS*

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I do not intend to deal with the whole question of syphilitic jaundice, but will confine myself to cases of jaundice due to, or concurrent with, treatment by the arsphenamines.

Although infective hepatitis or catarrhal jaundice is occurring in epidemic form in various parts of Great Britain, I have been unable to obtain evidence of an incidence among non-syphilitic men in the Forces in Scotland even remotely approaching the percentage I have encountered among members of the Forces undergoing antisyphilitic treatment.

*An address to the Medical Society for the Study of Venereal Diseases, March, 1943.