Major J. Marshall said that in regard to the necessity for local treatment for women he had found that the sulphonamides appeared to be just as effective in the absence of local treatment. He had found trichomonas infestation to be of very frequent occurrence, 30-35 per cent of cases, and it was his routine to add Stovarsol treatment for all women with gonorrhoea so that any missed infestations with trichomonas were dealt with.

As to Dr. Nabarro's objection to a change to another member of the sulphonamide compounds, Major Marshall had found that in resistant infections it was always better to effect a change in the sulphonamide compound. Sometimes it had been necessary to make two or three changes in the variety of sulphonamide in order to attain success. With regard to the necessity for local treatment in women out-patients who were being given sulphonamide treatment he had not seen any additional improvement in a series of patients so treated.

Dr. Mary Gordon said that her present treatment for gonorrhoea in women was a course of sulphathiazole of 5 grammes daily over a period of five days. She inquired whether or not Major Bolton advised any special diet during sulphonamide treatment and whether or not these compounds were given after meals.

Wing-Cdr. McElligott said that every woman with relapsed gonorrhoea that he had seen, wherever she had been treated, had always been treated with more than one course of a sulphonamide. This suggested that the case in which more than one adequate course of a sulphonamide compound was required was a case of which to beware. Much had been heard of "cures" following one, two, three or four courses and he began to wonder whether they really happened.

Major Bolton in reply said that she had great confidence in her pathologist and she herself had seen many of the tests made. In cases in which closed foci were present resolution was established in many during sulphonamide treatment but sometimes and especially when pus was present, surgical drainage was needed. As regards the number of cases treated with sulphapyridine and sulphathiazole the change-over was made about half-way through the series; the results were apparently identical. There were not any short-period courses used in the series. All patients received a five-day treatment. She preferred sulphathiazole because it caused less distress to the patient. With regard to the tests for cure patients were tested immediately after a monthly period if they lived within a reasonable distance of the hospital, otherwise they were admitted for a night and a provocative used. Lubricants were not used prior to taking specimens for assessing cure; the urethra was swabbed with dry swabs and the cervix treated in the same manner.

As regards diet the patients did not receive large quantities of meat when they were not feeling well, but otherwise they were not restricted. Sulphathiazole was given in doses of 7.5 grammes the first day, 5 grammes during the second day, and 1 gramme each day for the remaining three days. Patients who had had sulphonamides previously for gonorrhoea or pneumonia seemed to be tolerant to additional sulphathiazole.

Dr. Shanson had inquired as to why it appeared necessary to give sulphonamides throughout the night as well as by day when treating pneumonia whereas this was not the custom in treating gonorrhoea. Major Bolton presumed that to maintain the high blood level of sulphonamide (10 milligrams per cubic centimetre) necessary for the effective treatment of pneumonia the dosage had to be given round the clock. In gonorrhoea the desired effect appeared to be achieved with a blood level of 3 milligrams per cubic centimetre.

THE PATHOLOGY OF ARSENO-THERAPY JAUNDICE*

By J. H. DIBLE, M.B., Ch.B., F.R.C.P.

Professor of Pathology, British Postgraduate Medical School, London

and J. McMICHAEL, M.D., F.R.C.P.Ed.

Reader in Medicine, British Postgraduate Medical School, London

The evolution of opinion regarding the causation of jaundice occurring during the arsenical treatment of syphilis has passed through several phases. It was quickly recognized that syphilis *per se* was not the cause, and the occurrence of epidemic waves of the disease indicated that some additional factor was responsible. The dosage or particular arsenical compound seemed to have no relationship to the condition, and in every respect the clinical course of the jaundice closely resembled that of so-called catarrhal jaundice or epidemic hepatitis. By developing the technique of liver biopsy, the Copenhagen workers, Roholm and Iversen (1939), gave us a new method of approach to the problem. We have been able to apply this technique to thirty-five cases of arsenical jaundice and we have in addition studied cases of ordinary epidemic hepatitis and the jaundice which follows serum infusions, which may be regarded as controls. The only biopsy work on arsenical hepatitis other than that of Roholm and Krarup (1940) was

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

THE PATHOLOGY OF ARSENO-THERAPY JAUNDICE

carried out by Hanger, Jun. and Gutman (1940). The former workers demonstrated a hepatitis and the latter work was used to argue that many of the cases had an obstructive element in their causation.

In the material available for our study we have had an opportunity to observe patients from the first day of appearance of the jaundice onwards. In every instance the histological appearance has been that of a hepatitis, i.e. an inflammatory condition of the liver lobule associated with degeneration and destruction of liver cells. The lesion may be zonal or diffuse in its main incidence. The diffuse form may vary in severity and in some instances a picture has been encountered which falls little short of acute liver necrosis. In other instances the inflammation is relatively mild. Complete histological recovery can occur even in cases where the histological appearance is of great severity. In the zonal forms degeneration may predominate in the peripheral or central parts of the lobule, or in both. This is the appearance usually seen after the second week of the jaundice, but frequently it may be present from the beginning. The association of intense zonal inflammation with "diffuse" changes in the less affected part of the lobule suggests that an initial diffuse inflammation has taken on a more severe character in the peripheral and central parts of the lobule; this leads to a more intense degeneration in these parts with consequent cellular connective tissue, histiocyte and round-celled infiltration especially in the periportal zone. This may pass on to the condition of "zonal scarring." Chronic cirrhosis may occasionally develop as a sequel to these pathological changes; we have encountered one such case in the arsenical series and one in the epidemic hepatitis group.

Fig. 1 (x 130). Soldier aged 29. N.A.B. jaundice for twelve days. Plasma bilirubin 5.6 milligrams falling from 8.9 milligrams five days previously. Clinical cure a month later. Section shows a diffuse hepatitis with fragmentation of liver cell columns and histiocytic and round cell proliferation between the remaining cells.

THE BRITISH JOURNAL OF VENEREAL DISEASES

The main pathological sequences and their clinical correlations may be represented as follows.

ACUTE HEPATITIS

	PATHOLOGICAL COURSE	CLINICAL CORRELATION
Diffuse inflammation	Complete, often rapid, restoration to normal	Short course, or up to 6 weeks, with complete recovery
	Acute liver necrosis (? 0.2 per cent)	Rapid deterioration with shrinkage of liver and cholaemia
Zonal inflammation	Restoration to normal	Short course. Jaundice often mild
	Residual zonal scarring	Grumbling course up to 2-3 months
	Subacute necrosis	Severe course complicated by ascites, haemorrhage, etc.
	Cirrhosis (2 per cent)	May follow subacute atrophy or zonal scarring. Ascites frequent

Fig. 2 (x 160). Soldier aged 21. N.A.B. jaundice for four days. Serum bilirubin 10 milligrams. Clinically cured in a month. Section shows a periportal and central zonal damage with bile duct proliferation and much new cellular connective tissue.

THE PATHOLOGY OF ARSENO-THERAPY JAUNDICE

The Histological changes

Diffuse form.—On the day the jaundice appears, usually after a week or so of upper abdominal discomfort, anorexia, vomiting and other symptoms, the liver is already intensely inflamed. The liver cell columns are fragmented and many liver cells are lying apparently isolated from their neighbours. Other cells are in the process of degeneration and disappearance. The loose lobular structure which remains is infiltrated with round cells and histiocytes which are often somewhat heavily clumped round the portal and central zones.

In those cases which last into the second and third weeks with deepening jaundice the inflammatory changes may intensify (Fig. 1). A still greater number of liver

Fig. 3 (x 75). Civilian aged 37. N.A.B. jaundice six weeks recovering after five weeks and then relapsing. Bilirubin 1·8 milligrams. Clinical cure three weeks later. Section shows zonal scarring in central and periportal regions.

cells may have disappeared with marked trabecular fragmentation and a further increase in cellular infiltration. Plugs of bile-pigment are found here and there as though trapped in the neighbourhood of the cells which secreted them.

It is readily seen that cases of greater severity may give transitions towards the picture of acute liver atrophy. On the other hand, we have seen complete histological restoration of the liver following lesions much more intense than that in Fig. 1.

Zonal form.—This type of appearance is usual from the second week after the onset of jaundice. Degenerative changes become intense in the periportal and central regions of the lobule. In the central zone the changes resemble those described for diffuse inflammation in its severest forms. Round the portal tracts cellular connective tissue accumulates and sometimes isolated liver cells may be

seen trapped in its meshes. New bile-duct formations are often noted in this connective tissue (Fig. 2).

The processes of healing

We have already mentioned that the diffuse forms may be followed by complete restoration to normal in the course of a few weeks. The reticular framework of the liver cell trabeculae remains intact and the regenerating liver cells may be thus "guided" to form a normal anatomical structure.

In the zonal forms the more intense destruction of parts of the lobule is followed by a more persistent formation of new connective tissue. As the process illustrated in Fig. 2 subsides the wide zones of connective tissue become less cellular and more fibrous (Fig. 3). The preservation of regular lobular structure in contrast to cirrhosis must, however, be noted: This histological appearance is compatible with clinical cure. The rarity with which this form of connective tissue increase is found in routine necropsies suggests that the connective tissue may disappear almost completely in the course of time. The condition is probably comparable to the pre-cirrhotic reversible fibrosis produced experimentally by Cameron and Karunaratne (1936).

The development of subacute atrophy and cirrhosis

An important feature of permanent cirrhosis is the loss of regular lobular structure and its replacement by islets or nodules of regenerated liver cells. In the majority of cases of hepatitis the lobular pattern is preserved and liver cell regeneration can lead ultimately to restoration of a histologically normal liver. When, however, destruction has proceeded one stage further and connective tissue formation has become more permanently established, regeneration may be possible only in nodular form. In some such way the picture of permanent cirrhosis may

Fig. 4 (x 80). Soldier aged 29. N.A.B. jaundice four months before, followed by ascites, with recovery. Not jaundiced at time of biopsy. Section shows classical cirrhosis with nodular areas of liver cells, new bile duct formation in the fibrous tissue. For further details refer to the article by Major J. Marshall in the June number of this Journal.

THE PATHOLOGY OF ARSENO-THERAPY JAUNDICE

develop ; in the more acute stages it may take the form of subacute atrophy with nodular hyperplasia.

Control observations in relation to aetiology

Infective Hepatitis ?—The lesions described are duplicated in all their aspects in our observations on seven cases of jaundice following serum injections and on fourteen cases of epidemic hepatitis. In each group, however, there is a wide range of possible histological appearances and it would be unwise to conclude that, because they resemble one another very closely, they are of exactly identical aetiology. On the other hand, the similarity of histological appearances conforms with the identity of clinical course in all three groups.

Syphilitic Jaundice ?—It is to be noted that no lesions which could be called gummatous or syphilitic have been seen in this series. Jaundice in secondary syphilis is a rarity. We obtained good biopsy material from one patient who had developed jaundice coincidentally with secondary syphilis and before N.A.B. therapy was started. The liver showed appearances identical with those in other forms of hepatitis. There does not seem to be any reason why a syphilitic patient should not occasionally develop epidemic hepatitis during an epidemic. The liver of one patient with florid secondary syphilis was biopsied and it could be passed as normal.

Arsphenamine Jaundice ?—A suggestion still lingers that arsphenamine compounds may themselves produce liver damage, and that such chemical injury may be precipitated by another unknown factor (dietetic, infective, or other causes), thus accounting for the epidemic incidence. It is therefore incumbent on us to compare the histological lesions with those produced in animals by arsphenamine.

Kolmer and Lucke (1924) produced in rats a picture of intense necrosis and haemorrhage in the central parts of the liver lobule with fatty and hydropic vacuolation of liver cells and pyknosis of nuclei. Similar lesions have been produced in dogs (Messinger and Hawkins, 1940) and Soffer (1936) adds to the histological description in dogs that the lobules are surrounded by punctate haemorrhages, the cells in the periportal region being well preserved. Sometimes necrosis also affected the portal vein.

The histology of these lesions is that of chemical injury similar to chloroform and phenyl hydrazine poisoning in the sharp delimitation of the central zone (Hurst and Hurst, 1928). Similar central sharply defined lesions follow poisoning by O-dichlorobenzene (Cameron and Thomas, 1937).

The following points are against arsphenamine poisoning.

(1) *Dissimilarity of the histological lesion.*—In our material : Distribution of lesions is diffuse and often periportal. The central lesion is encountered quite as frequently in other forms of acute hepatitis which have not received organic arsenicals. Fatty degeneration is conspicuously absent. There are no haemorrhagic lesions.

(2) *Dosage of arsenicals.*—The animal lesions are only produced by massive doses equivalent to five to fifteen times the normal human dose. The incidence or severity of the lesion in man bears no correlation with the total quantity of arsenicals given.

Milian, Stokes and Ruedemann (quoted by Soffer, 1937) have continued arseno-therapy during the jaundice without ill effects.

Recent work on the intensification of chemical liver damage by high fat diets and the beneficial actions of certain components of a high protein diet (Miller, Ross and Whipple (1940), Miller and Whipple (1940), Messinger and Hawkins) has been discussed by others in this *Journal*. We feel that while this line of approach may possibly give a guide to useful therapy in the presence of liver damage it is unlikely to give a solution to the problem of causation of jaundice in the course of arseno-therapy for the reasons outlined above.

Conclusions

(1) Every case of arseno-therapy jaundice shows one of various forms of hepatitis.

(2) The histological picture and the sequence of pathological developments do not show any significant differences from the appearances seen in epidemic hepatitis or the hepatitis after serum injections.

(3) The histological appearances do not support the suggestion that either syphilitic lesions of the liver or arsenobenzol poisoning play any part. The appearances are more compatible with damage by an agent similar to that causing serum jaundice or epidemic hepatitis.

Acknowledgments

We are indebted to Brigadier T. E. Osmond and Major J. Marshall for the opportunity to study many of the arseno-therapy cases. Dr. Sheila Sherlock and Dr. E. Singer (house physicians) gave valuable aid in the clinical investigation. Messrs. Baker and Griffin devoted much care to the histological preparations. The work was carried out with the aid of a research grant from the Medical Research Council.

REFERENCES

- Cameron, G. R., and Karunaratne, W. A. E. (1936) *J. Path. Bact.*, **42**, 1.
 — and Thomas, J. C. (1937) *J. Path. Bact.*, **44**, 281.
 Hanger, F. M., Jun., and Gutman, A. B. (1940) *J. Amer. med. Ass.*, **115**, 263.
 Hurst, E. W., and Hurst, P. E. (1928) *J. Path. Bact.*, **31**, 303.
 Kolmer, J. A., and Lucke, B. (1924) *Arch. Derm. Syph., N.Y.*, **9**, 321.
 Messinger, W. J., and Hawkins, W. B. (1940) *Amer. J. med. Sci.*, **199**, 216.
 Miller, L. L., Ross, J. F., and Whipple, G. H. (1940) *Amer. J. med. Sci.*, **200**, 739.
 — and Whipple, G. H. (1940) *Amer. J. med. Sci.*, **199**, 204.
 Roholm, K., and Iversen, P. (1939) *Acta path. microbiol. scand.*, **16**, 427.
 — and Krarup, N. B. (1940) *Arch. Derm. Syph., Wien.*, **181**, 521.
 Soffer, L. J. (1936) *Proc. Soc. exp. Biol., N.Y.*, **35**, 160.
 — (1937) *Amer. J. Syph.*, **21**, 309.

THE USES AND LIMITATIONS OF THE SERUM TESTS FOR SYPHILIS*

BY

L. W. HARRISON, F.R.C.P.Ed., BREVET-COLONEL (LATE R.A.M.C.),
Adviser in Venereal Diseases to the Ministry of Health

and T. E. OSMOND, M.B., BRIGADIER
Consulting Venereologist to the British Army

We have ventured to change the title of this paper from that originally selected to the present one because the great increase in the practice of serum-testing for syphilis as a matter of routine in medical examination, which has occurred in the last few years, has made it important that someone in this country should stress the limitations of these tests and emphasize the fact, almost a commonplace with serologists, that a positive reaction with such a test is not a verdict on the question of syphilis in the donor of the blood specimen.

We propose to discuss the serum tests for syphilis under the headings of their uses and limitations in diagnosis and of their use as a guide to the management of syphilis. In doing so we do not intend to present anything approaching a complete review of the literature, but merely to present evidence, either in our own or in other workers' experience, sufficient to prove the points which seem important.

First as to the use of these tests in diagnosis.

The use and limitations of serum tests for diagnosis of syphilis

We think it would be profitable to discuss particularly the causes, prevention

*Based on an address in opening a discussion by the Medical Society for the Study of Venereal Diseases on 26th June, 1943.