TWO UNUSUAL PHASES OF HEPATIC SYPHILIS*

UDO J. WILE, A.B., M.D.

ANN ARBOR, MICH.

The gross and microscopic pathologic features of hepatic syphilis are in the light of our present knowledge well recognized and easily determinable. The close resemblance of these pathologic pictures to those of nonsyphilitic origin, particularly in the group of cirrhoses, is reflected in the clinical aspects of liver disease. Syphilis, the great imitator, is perhaps never seen in a more advantageous rôle as such than in hepatic disease.

The incidence of liver syphilis is second only in frequency to that of syphilis of the heart. McCrae is authority for the statement that syphilis of the liver occurring late is as frequent as late involvement of the nervous system. Considering that a fairly advanced degree of cirrhosis or cicatrization may be present without giving rise to clinical symptoms, and that such involvement is not frequently an accidental postmortem finding, it is evident that the incidence of hepatic syphilis is higher than would be indicated by figures drawn from clinical experience. The special predilection for spirochetal invasion in the substance of the liver is held by some as accountable for the great frequency of involvement of this organ. However this may be, liver syphilis is a predominating clinical and pathologic finding in both the inherited and acquired forms of the disease.

The whole subject of liver syphilis covers far too large a field to be covered by me in the time allotted, and such a review is moreover apart from the purpose of this paper. I should like to emphasize merely two phases of liver syphilis: The first — "icterus gravis syphiliticus," also known as "icterus syphiliticus praecox," merits description by reason of the fact that it is hardly mentioned in American literature. The second, syphilitic cirrhosis, deserves a detailed description by reason of the apparent lack of correlation of its pathologic and clinical features and because of peculiar therapeutic considerations bearing on it.

ICTERUS GRAVIS SYPHILITICUS — "ICTERUS SYPHILITICUS PRAECOX"

Jaundice, occurring as a rare complication at the outset or in the early secondary period of syphilis, was recognized as early as 1585 by Paracelsus. It is also mentioned by Portal, Monti, Botallus, Fallopius and other writers of the latter part of the sixteenth century, in accord-

* Read at a stated meeting of the Chicago Medical Society, March 18, 1920.

ance with the early belief that the liver was the site of election for venereal disease. At a much later date Ricord described icterus in two cases of early syphilis, and ventured the statement that the syphilis was the cause of the jaundice. Gubler, in 1853, substantiated the observation of Ricord, adding seven cases which, by clinical observation at least, were those of true syphilitic jaundice. Still later Lancereaux was able to collect twenty cases of true syphilitic icterus.

Jaundice in early syphilis is now recognized as occurring in two forms — mild jaundice and severe jaundice or icterus gravis. I shall pass over the subject of mild jaundice, as it has no further place in this essay. Suffice it to say in passing, that it differs in no way symptomatically from the simple catarrhal jaundice, and that its incidence in early syphilis is recorded in about five-tenths of one per cent. of all cases. This mild form has been shown to have a varied pathology. The jaundice may actually be obstructive from the pressure of lymph glands on the common duct, as recorded by Engel-Reimer. In other cases, on the other hand, it has been shown to be due to a more diffuse inflammatory reaction of the biliary ducts and portal lymph vessels. Mauriac reported an active inflammation of the liver with hyperemia and stopping up of the biliary ducts.

With the grave form, or syphilitic gravis icterus, we are dealing with a parenchymatous hepatitis, and as it occasionally supervenes on a milder form it is not unlikely that some cases of the mild icterus, at least those in which we are dealing with a mild hepatitis, differ only from the grave form in degree.

Of far greater importance than mild icterus is the graver form. Occasionally supervening on the former, it may often arise with a stormy onset and a rapid course. The tendency, if unrecognized and untreated, is for the condition to go on clinically and pathologically to acute yellow atrophy.

In 1854 Lebert, from a collection of seventy-two cases of acute yellow atrophy, recorded seven as associated with early syphilis. Tierfelder found that eight out of eighty-one cases of acute yellow atrophy occurred in old or recent syphilitic patients. Recognition of the syphilitic nature of certain cases of acute yellow atrophy is found in Osler's *Modern Medicine* in which it is stated that 10 per cent. of all cases occur during early syphilitic diseases.

Up to 1898, thirty-nine cases of icterus syphiliticus gravis had been garnered from the literature by Richter, with an addition of two cases in his own experience. This number was increased to fifty as collected by Umber in 1911. In 1894 the condition was well recognized by Lasch and described by him under the name of icterus syphiliticus praecox. Many cases were subsequently reported under this title.

From all recorded cases the condition seems to be much more common in women than in men, the ratio being about five to one. For the most part the icterus occurs coincident with the exanthem. It may, however, precede this. In practically all cases the condition occurs during the first year of the infection.

Cause of Icterus Gravis.—The cause of icterus gravis has been carefully studied by Buschke and Zernick in 1911, who concluded that it is due to a syphilitoxic parenchymatous hepatitis, a jaundice of the nonobstructive type. This view was earlier advanced by Buraczinski and Vespremi and Kanitz, and is generally accepted today as the correct explanation of the pathology of the disease. Such incidental factors as pregnancy, abortion, gonorrhea and sepsis may play a minor rôle. In none of the recorded cases was previous liver disease present or demonstrable. The administration of mercury does not play a part in the causation of the condition.

Symptomatology.—The symptomatology of icterus gravis syphiliticus is that of acute yellow atrophy, differing only from other cases in that it yields to specific treatment when recognized early. The onset is variable, generally insidious. A mild icterus usually appears as the first objective sign, accompanied by malaise, vomiting and constipation, but usually without marked gastro-intestinal symptoms. There may be a slight rise in temperature, although it often becomes subnormal. The pulse is usually accelerated. Lumbago and muscular pain are common and there may be severe abdominal cramps. Often debility and a toxic condition similar to that seen in typhoid fever are present. Cases with ascites are reported. While not a uniform finding, hemorrhagic symptoms are reported by many authors. These are manifested by gingivitis, purpura, bloody vomitus, melena and occasionally hemoptysis, hematuria and metrorrhagia.

The second stage of the disease is far more definite. In onset it is marked by a change for the worse in the general condition, by rapid decrease in the size of the previously enlarged liver, the appearance of maniacal symptoms associated with intense headache, disturbance of vision and the occurrence of leucin and tyrosin in the urine. Pupillary disturbances and amblyopia are common. Marked psychic depression, restlessness with insomnia, convulsions and delirium are among the associated mental factors. Apart from the jaundice the clinical symptoms may often resemble meningitis, and indeed partial paralysis and strabismus have occasionally been noted. Marked dyspnea occurs late. A persisting constipation extends throughout the condition, and such dejecta as occur are extremely offensive. Death usually occurs in coma, with accompanying complete sphincter relaxation.

The urine is diminished in amount and highly colored with bile pigment. There is no glycosuria, but small amounts of albumin and

casts are a frequent finding. Crystals of leucin and tyrosin are invariably present, often in so great an abundance that they spontaneously precipitate. This finding is regarded by Senator, Buschke and Zernik as pathognomonic of liver atrophy. Rolleston, however, does not regard it so. There is no characteristic blood picture.

The liver is enlarged at the onset in all cases. The enlargement is smooth, both lobes being equally involved. Tenderness is recorded in one third of the total number. After a variable period reduction in size comes on suddenly, associated with the severe symptom enumerated above and heralding a rapidly fatal outcome.

Necropsy Findings.—At necropsy the liver presents the typical picture of acute yellow atrophy, often being reduced to one third of normal size and weight. The more slowly progressing cases reveal areas of acute yellow atrophy interspersed among areas of red atrophy, the latter representing early destruction. In some cases the entire liver is not affected, while in others not a single normal cell remains.

Of great interest is the negative finding of spirochetes at necropsy, as recorded by Buraczinski, Vespremi and Kanitz, Fischer and Bendig.

Prognosis.—Unrecognized cases are invariably fatal. The course is somewhat longer than that of acute yellow atrophy from other causes, the average duration of the recorded cases being eighty-four days. Many cases, however, ended fatally in less than two weeks. In one of Bendig's reports a mild icterus with indefinite prodromes extended over three days, followed by a stormy exacerbation and death within twenty-four hours.

The older writers regarded the condition as invariably fatal. Compared with other types of acute yellow atrophy, however, if the syphilitic nature of the case be recognized, the prognosis for the recovery is fair. Isolated cures even in advanced cases are recorded by Duhot and Umber. In Senator, Buschke, Zernik and Lasch's case recovery is recorded even after an appreciable decrease in the size of the liver had taken place, with the findings of leucin and tyrosin in the urine. Purgation with calomel, intensive mercurialization and arsphenamin are indicated by most authorities.

To the cases of recovery after correct diagnosis I may add one observation by myself at the University Hospital in 1916.

In this case, studied by Hewlett and myself in our wards, there occurred in a man of 38, shortly after the appearance of syphilis, the acute onset of a fulminating type of jaundice. The liver was enormously enlarged and excessively tender. The spleen was likewise enlarged and firm. The stools were clay-colored. The urine contained large amounts of albumin, casts and numerous crystals of leucin and tyrosin. The abrupt onset, without gastro-intestinal symptoms, the absence of fever, the enlargement of the spleen, the intensity of the jaundice, the leucin and tyrosin in the urine, all pointed to the syphilitic nature

of the disease, rather than to a simple catarrhal jaundice. Added weight to the presumptive diagnosis was given by the associated nephritis. During the first few days of observation the patient's condition became much worse, the liver appreciably decreased in size day of day, confusion and delirium set in and we were faced with the clinical picture of acute yellow atrophy. Under vigorous mercurialization, together with large doses of iodid of potash administered at this stage, the patient made a rapid recovery and was apparently restored to complete health.

Since the employment of arsphenamin and its derivatives in the treatment of syphilis, a new type of jaundice has been added to those hitherto known. This jaundice may be mild in type, in which case it is apparently due to the retention of arsenic in the liver. Severe cases leading to death, however, are reported in the German and French literature, in which, according to Milian, the condition is a hepato-recidive analagous to that occurring in the nervous system. From a study of these cases, of which I have seen five, I am inclined to believe they are in no way related to the condition just described.

Icterus gravis syphiliticus, unrecognized, carries with it the prognosis of acute yellow atrophy. Recognized and differentiated from other forms and intelligently treated, it presents a clinical picture carrying a gratifying prognosis in the face of a seriously grave destructive process.

SYPHILITIC CIRRHOSIS

If I have had the temerity to bring up a subject, the clinical aspects of which are no doubt thoroughly familiar to clinicians in general, it is because I am convinced that great confusion exists in the correlation of the pathologic and clinical features of late syphilis of the liver. The pathologic status of liver syphilis, moreover, is today a confused and debatable field among pathologists. From the pathologic side it may be accepted that late syphilitic hepatitis is due to direct involvement of the parenchyma on the one hand, and primary involvement of the blood vessels with secondary changes in the parenchyma on the other. Undoubtedly most cases combine both features.

Various types of hepatic syphilis are described as pathologic entities which do not in fact have their clinical analogues. The attempt to differentiate clinical forms of liver syphilis, so that they shall correspond to the kaleidoscopic pictures of the pathologist leads to confusion. The entire status of the cirrhoses, syphilitic and otherwise, is today a matter of debate and polemic. In the gross and microscopic pathology of liver syphilis certain facts stand out which, if recognized and emphasized, would lead to a clearer understanding of the clinical phases of the disease.

Two Forms of Late Syphilis of the Liver.—Late syphilis of the liver is either diffuse or circumscribed. The diffuse forms, consisting

of multitudinous infiltrates and miliary gummas, lead to an extensive interstitial fibrosis. The more circumscribed form, consisting of isolated infiltrates and larger gummas, leads spontaneously and under treatment to localized fibrosis. The end-result in either case is identical—a cirrhotic liver. A combination of these two forms is perhaps more common than either one alone. Reconstructing the pictures clinically, therefore, one has a small atrophic liver, with or without ascites, and resembling the Laennec type as a result of diffuse infiltration, and a lobulated, either hypertrophic or atrophic liver, cirrhotic in patches, resulting from the more circumscribed type. The latter is the so-called "hepar lobatum."

The reason one or the other type predominates in a given case would lead us into the realm of speculation. It is not impossible that previous liver injury or disease, and the predominance of syphilis of the hepatic blood vessels, are causative factors.

Alcohol as a Predisposing Factor.—Among other factors which are emphasized as predisposing the liver to syphilis, alcohol stands out. McCrae asserts that it is an important factor, and in only five of his seventy cases was alcohol not used freely. In my own series of closely studied cases I cannot subscribe to this view. Alcohol played a minor, if any, rôle in the causation of the disease in my cases. Interesting in this connection is the fact that certain pathologists today deny the existence of an alcoholic atrophic cirrhosis and are inclined to regard this as always syphilitic.

Size of Liver.—The question of the size of the liver is a matter of much confusion to clinicians but of little moment. It depends not so much on the difference of form of cirrhosis present as to the time when the patient is seen. I have repeatedly seen hypertrophic livers become distinctly shrunken and gradually recede during the period of treatment, underneath the costal border. In about half the cases in my series the liver was extensively enlarged at the first examination. In practically all at a later date hypertrophy became less marked. Enlargement of the spleen is an early and constant finding, and I believe of great differential diagnostic importance.

Symptomatology.—It is a well established fact that an advanced degree of either one of the two types of hepatic syphilis or their combination may be present without any symptoms, and may be an accidental necropsy finding. In this connection I have been impressed by the frequency of symptomless hepatic syphilis, associated with tabes and with other forms of visceral syphilis.

The morphology, then, of clinical hepatic syphilis depends on the appearance in the one case of tumor, in the other of obstructive portal circulation leading to ascites and the combination of these two con-

ditions. There is no reason for a detailed description of the various symptoms that may or may not be present with interstitial syphilitic cirrhosis. These are familiar to all clinicians of experience. In the light of biologic laboratory tests and in the more close observation and study of syphilis less and less mistakes occur in the diagnosis of this condition. There are certain therapeutic considerations associated with liver syphilis, however, to which I beg to direct your attention.

Prognosis.—The consensus of opinion is that, compared with other forms of hepatic disease, syphilitic hepatitis has an admirable prognosis. I wish to concur in this view in so far as it applies to the focal types, i. e.: gummous hepatitis, *hepar lobatum*, and to certain cases of the interstitial type.

During the past eight years I have had a very unusual opportunity of studying many cases of hepatic syphilis in its various forms at the University Hospital. Given equal conditions, I have been struck with the great difference in the prognosis as worked out in various cases. I have been able to separate my cases broadly into three classes. The first type is syphilitic cirrhosis, in which gummous tumors were the predominating features. In a general way the prognosis of this condition stands out as the best of the three types. The second type consists of combined gummous hepatitis and interstitial cirrhosis, in which not only tumors are present, but there are associated cirrhosis symptoms. In this type, as well as in the third class, that of the pure interstitial and diffuse type, an apparent paradox in the treatment occurs. Patients improve with regard to syphilis and become worse or die from cirrhosis.

The reason for this is not difficult to understand. Hepatic syphilis in any case is but one phase of a widespread constitutional infection, one phase of an extensive visceral syphilis. Improvement in general health, improvement in associated anemia, in the not infrequent nephritis and in general vascular tone may be expected and is usually noted, following specific treatment.

What happens, however, to the liver? The gummatous masses in the combined form disappear rapidly. They are replaced by scar tissue. The associated multitudinous microscopic syphilomas are likewise rapidly dispersed. In both instances the replacing scar tissue produces a more advanced degree of cirrhosis than was caused by the gradual attrition of the disease process. At the end stage, therefore, one has to do not only with the disease itself, but with the mechanical factor of pressure from scar tissue.

In this type of case my experience has been that there is an immediately apparent improvement in the patient's general condition, soon dispelled, however, by the more rapid onset of ascites.

Indeed in not a few cases the ascites has first appeared following the improvement in the general condition. In a case under my care at present it has been necessary to perform paracentesis twenty-six times at weekly intervals, a total amount of over one hundred and fifty liters, more than twice the patient's weight, being removed. In this type of case there can be no question of a collateral circulation being established. Indeed this in itself could lead to no improvement in the condition. The graveness of the condition is due rather to the throwing out of function of the liver as a secreting organ than to the ascites. Exhaustion and death are the rule in this type and occur as a direct result of disturbed metabolism.

Correlation Between Pathologic and Clinical Findings.—In conclusion may I be permitted to emphasize the fact that an easier correlation between pathologic and clinical findings would be possible if it were remembered that the differences in the pathologic and clinical features are rather those of degree, size and time than of morphology? The determining factors in recovery in the last analysis that are likewise the determining factors in the differences of the clinical and pathologic features are: First, that unknown factor which determines the circumscription or diffuseness of the process—in other words, the extent to which complete fibrosis and inclusion of liver tissue in scars occurs; second, the extent to which compensatory hypertrophic lobules of liver tissue can find access through the scar tissue to the circulating blood. Alcohol, in my experience at least, plays a minor rôle, if it is of any significance, in the pathology and clinical features of this form of the disease.