Disseminated lobular necrosis of the liver with jaundice (hepar necroticum cum ictero of Curschmann and H. Oertel) : and a case of acute hepatic atrophy in secondary syphilis / by F. Parkes Weber.

Disseminated Lobular Necrosis of the Liver with Jaundice (*Hepar Necroticum cum Ictero* of Curschmann and H. Oertel), and a Case of Acute Hepatic Atrophy in Secondary Syphilis

BY

F. PARKES WEBER

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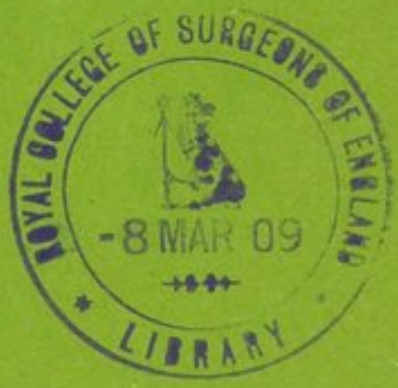

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Disseminated Lobular Necrosis of the Liver with Jaundice (*Hepar Necroticum cum Ictero* of Curschmann and H. Oertel), and a Case of Acute Hepatic Atrophy in Secondary Syphilis.

By F. Parkes Weber.

(I) Disseminated Lobular Necrosis of the Liver.

D. S., aged 35, a shoemaker, was admitted at the German Hospital on February 25, 1908. At first he was on the surgical side under Dr. Michels, but was afterwards transferred to the medical side under Dr. Parkes Weber. The present illness was said to have commenced gradually sixteen months before admission with pains, vomiting and jaundice. The jaundice had persisted since then, though the pains and vomiting had left him. For the last four weeks he thought that he had had fever. There was no history of syphilis or other previous diseases.

On admission the patient was deeply jaundiced, of a greenish colour, not very emaciated. His fæces were colourless. His urine was bilious, of specific gravity 1022, acid, free from albumin, but yielding a cloud of nucleo-proteid with acetic acid. There was ascites, and the liver could be felt below the right costal margin. The spleen could not be palpated. There was considerable fever, the temperature rising to 102° F. in the evenings. On February 28 a small incision was made and the ascitic fluid evacuated; nothing abnormal was felt, except that the liver was enlarged. After this there was less fever in the evenings, and after March 5 there was no fever at all. But the patient continued to lose weight and strength, and became greatly emaciated. The ascitic fluid accumulated again, and was evacuated by paracentesis on March 7. *Blood examination* (March 9, 1908): Hæmoglobin (by Haldane's method), 55 per cent.; red cells, 2,000,000 in the cubic millimetre of blood; white cells, 11,920. Microscopic examination of a blood-film showed polymorphonuclear leucocytosis; one nucleated red cell was seen. The urine (March 9) was bilious, of specific gravity 1019, and free from albumin and sugar. Death occurred on March 12.

The *post-mortem examination* was practically confined to the abdominal organs. A hard tumour of the size of a walnut was found in the

head of the pancreas pressing on the common bile-duct. The gall-bladder and all the extra-hepatic and intra-hepatic bile-ducts were dilated with green bile. The liver was enlarged, weighing 91 oz., and was greenish in colour. Pieces were removed for microscopic examination. There were several moderately enlarged lymphatic glands in the neighbourhood of the head of the pancreas and in the mesentery, but otherwise no metastatic tumours were seen. The spleen was somewhat enlarged, weighing 16 oz. The kidneys did not appear diseased.

Microscopic Examination.[1]—The growth in the head of the pancreas was carcinomatous, and the enlarged lymphatic glands were found to be secondarily infiltrated. The splenic swelling seemed to be due, at all events in part, to engorgement of the organ with blood.

The Liver.—Microscopic sections showed a decided increase of interacinous tissue, fibrous rather than cellular, constituting a kind of sclerosis of interacinous (monolobular or rather unilobular) distribution. Within the acini the columns of liver-cells appeared somewhat shrivelled and abnormally separated from each other, the spaces between them being occupied by dilated blood-capillaries. Many of the liver-cells and bile capillaries were crammed with bile pigment (or rather, inspissated bile). But what chiefly attracted one's attention was the presence in the hepatic parenchyma of multiple, scattered, sharply defined, circular "islands" of tissue which had undergone some necrotic change (*see* plate). These necrotic islands mostly occupied the whole of a lobule (acinus); their average diameter probably equalled that of the lobules. The liver-cells in these areas seemed to have faded or "melted away," leaving a scanty "cobwebby" meshwork of degenerated ground substance (capillary walls, &c.), containing a few nuclei and fat globules. In the central portions of these areas the necrotic debris was often either deeply stained with bile pigment, apparently by imbibition, or evidently replaced by an actual extravasation of bile from the over-distended bile capillaries. In some of the necrotic areas, however, especially in their central zones, a subsequent small cell-infiltration had succeeded the changes just mentioned. The central portions of these areas were filled with round cells, and the bile-stained debris had been more or less completely absorbed or formed a narrow zone around the central mass of round cells. Outside this zone there was a clearer zone occupied by the meshwork left by the atrophied liver-cells—*i.e.*, consisting of degenerated remnants of capillaries, fat globules, &c. Outside this

[1] For the microscopic sections in this case I am greatly indebted to Mr. E. H. Shaw, and also to Dr. Chapuis, one of the House Physicians at the German Hospital.

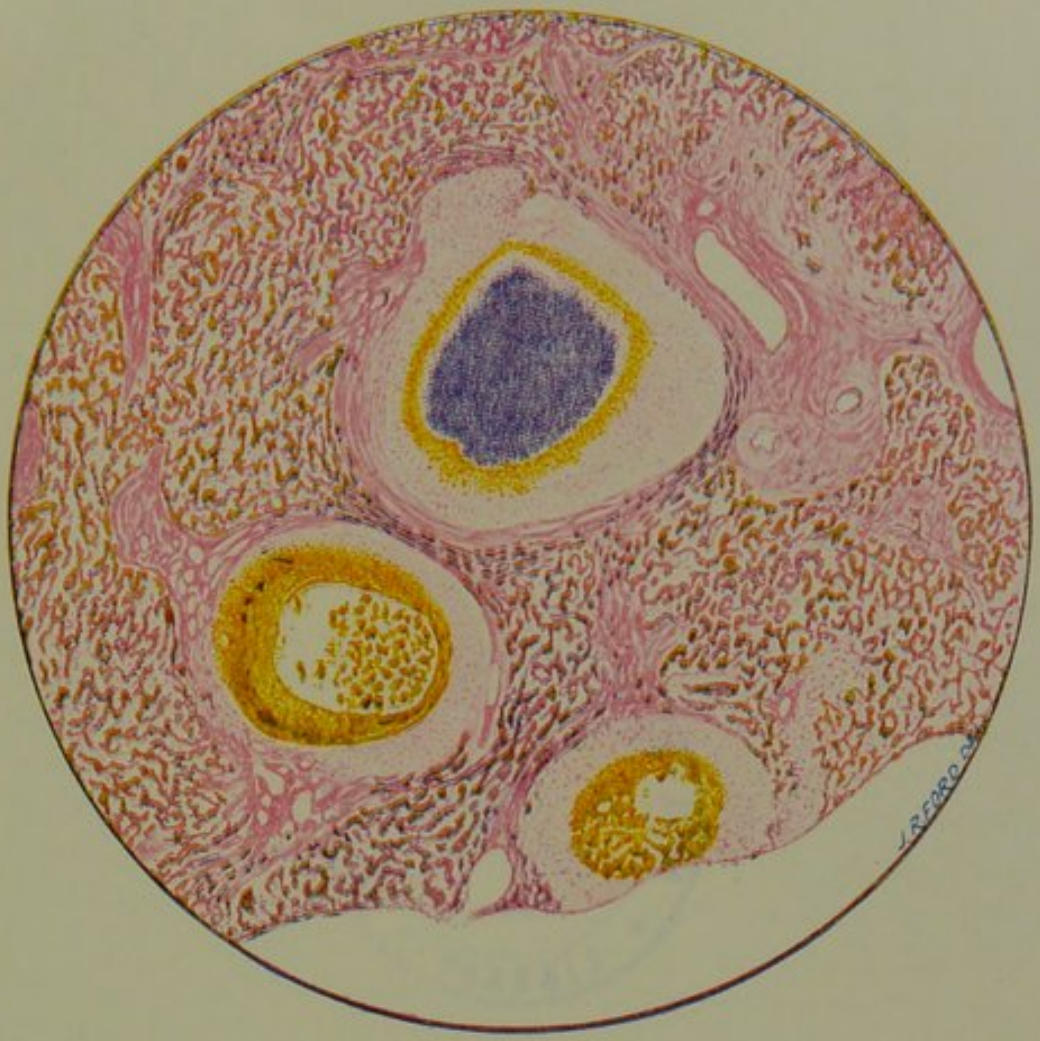


FIG 1.

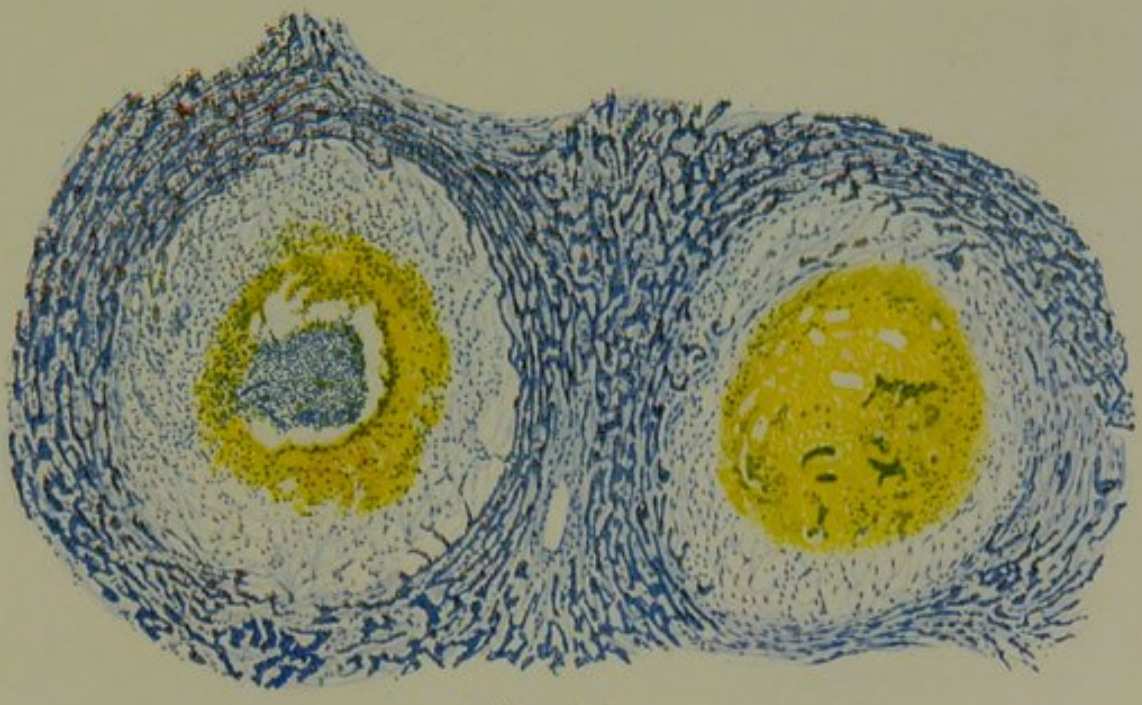


FIG. 2.

The figures (magnification × 60) show several of the necrotic areas in the liver. In two of them (one in each figure) the central bile-stained debris has been partially replaced by small cell infiltration. The stains employed were Jenner's eosinate of methylene blue for figure 1, and Loeffler's alkaline methylene blue for figure 2.

again, and enclosing the whole island of necrosis, there was usually a more or less complete capsule formed from the surrounding tissue, especially by the interlobular fibrous tissue already referred to. In specially stained sections no microbes could be discovered, either in the necrotic areas or elsewhere. The small cells of the areas of cell-infiltration mostly contained irregularly shaped, branched, or broken up nuclei.

I cannot here enter into the whole subject of focal, zonal and diffuse necroses of the liver, a subject which has been much investigated, especially in America (Walter Reed, F. B. Mallory, S. Flexner, E. L. Opie, R. M. Pearce, Horst Oertel, J. McCrae, and O. Klotz, &c.), both by post-mortem observations in human beings and by experimental researches in animals. The small focal necroses, which as seen in the later stages of cellular infiltration have been termed "lymphoid nodules," chiefly met with in typhoid fever cases, differ considerably from the relatively large scattered islands of necrosis found in our case, but hepatic lesions in jaundiced patients identical with those in our case have been carefully described by H. Curschmann (1899)[1], and Horst Oertel (1904 and 1906)[2]. Curschmann described the process as a "peculiar form of necrosing hepatitis"; whilst Oertel, though giving all due credit to Curschmann, described it as a "multiple non-inflammatory necrosis of the liver with jaundice (*hepar necroticum cum ictero*)." I would prefer to term it a "disseminated lobular necrosis of the liver," since there is a decided tendency for the necrotic process to affect whole lobules, in which respect it differs from the ordinary focal necroses of typhoid fever.

In Curschmann's first case the patient was a woman, aged 51, with vomiting, jaundice, irregular fever and bed-sores. At the necropsy the liver was seen to be of dark brown colour and about usual size. A rough ("mulberry") calculus obstructed the common bile-duct, which was dilated behind the obstruction. Between the gall-bladder (which was contracted) and the liver was an encapsuled abscess filled with bilious purulent matter and detritus. The whole liver substance was studded with minute (miliary to pea-sized) spots. Microscopic examination of different parts of the organ showed a disseminated necrotic change tending to be of centro-acinous distribution. Bile-imbibition in

[1] Curschmann, "Ueber eine eigenartige Form von nekrotisirender Hepatitis," *Deut. Arch. für Klin. Med.*, Leipzig, 1899, lxiv., p. 564.

[2] H. Oertel, *Journ. Med. Research*, Boston, 1904, xii, p. 75; and *Journ. Exper. Med.*, New York, 1906, viii, p. 103.

the necrotic areas was a striking and characteristic feature. The minute (miliary) spots visible to the naked eye were due to a whole acinus being filled with bile-stained necrotic material. The largest spots (those up to the size of a pea) were apparently due to the fusion of several necrotic acini. There was no true suppuration in the hepatic parenchyma. The portal spaces in Curschmann's case showed a decided sclerotic change, as they have done in most of the cases subsequently examined.

The description of Curschmann's two other cases and Oertel's four cases help to confirm and elaborate the features of this peculiar liver change. More or less jaundice and a toxic condition of some kind or other are probably essential pathogenic factors in the production of the characteristic microscopic appearances. In our case a toxæmic factor was evidenced during life by the intermittent pyrexia. Probably the degeneration of the hepatic cells in these cases, a form of degeneration which Oertel would like to term "cytolysis," commences usually but not always in the central region (centro-acinous zone) of the affected acinus, but soon affects the whole acinus, and several neighbouring acini may become necrosed and coalesce, as described in Curschmann's first case. The central portion of each necrotic "island" is generally at first deeply stained with bile pigment, by imbibition or extravasation of bile, but afterwards is infiltrated with round cells which clear away or replace debris and bile pigment. Sections through a necrotic "island" at this stage show a central area of small cell-infiltration, around which is a narrow zone of bile-stained debris. Outside this in our sections is a pale zone, which appears to be occupied by a mesh of "groundwork" substance (degenerating capillary walls, &c.), from which the hepatic cells have faded. A kind of capsule, made up of compressed hepatic parenchyma and interacinous fibrous tissue, constitutes the outermost zone of the necrotic islands. The margins of these necrotic areas are always sharply defined. More or less interacinous sclerosis seems to be generally present, and in some cases there may have been a certain amount of preceding cirrhotic change. Our case differs somewhat from the others in that the jaundice was due to cancerous obstruction of the common bile-duct, but it seems to us that the essential factors in the production of the histological picture in all these cases are: (1) some toxæmic condition giving rise to patchy necrosis of the hepatic parenchyma; (2) increase of bile-pressure (from some kind of obstruction to the flow of bile) favouring extravasation of bile into the necrosed areas.

(II) Acute Hepatic Atrophy in Early or Secondary Syphilis.

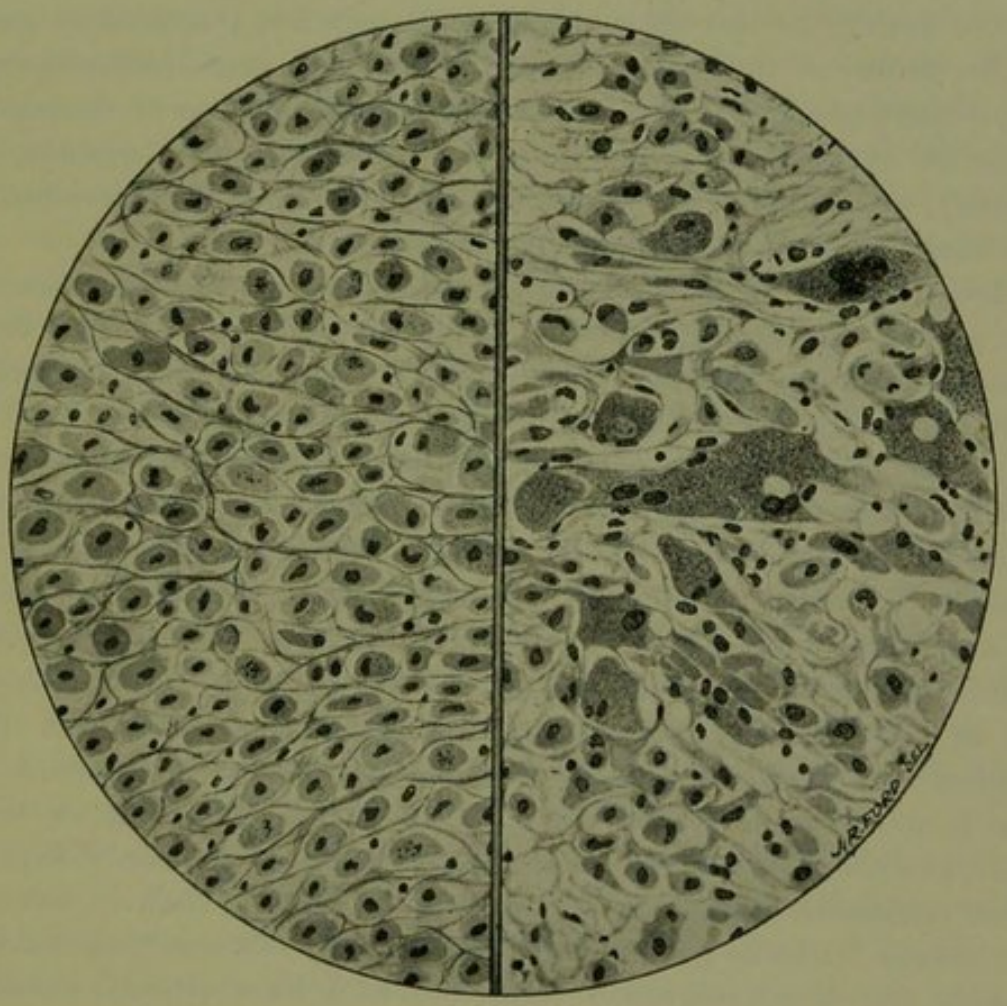
M. V., aged 22, was admitted to the German Hospital in the afternoon on March 25, 1902, under the care of Dr. Fürth. He was a tolerably well-nourished man of medium size, a German waiter in London. The history was that two months previously he had had a hard chancre, for which he had been treated by mercurial injections. The jaundice from which he was suffering had commenced fourteen days before admission. During the last days he had felt worse, but was able to walk to the hospital. Soon after admission, however, he became mentally dull and drowsy. His temperature was 97° F. and his pulse about 68 in the minute. During the following night he vomited, uttered peculiar cries and became unconscious. On the next day (March 26) he was passing urine and fæces into the bed. The limbs were rigid and the knee-jerks were excessive. Temperature 96° F. The jaundice was very deep. There was no pain by palpation in the hepatic region. The liver could not be felt. A hundred cubic centimetres of blood were removed by venesection from the right median cephalic vein and two litres of normal salt solution were injected subcutaneously. On the following night there was Cheyne-Stokes respiration and recurrent tonic contraction of the muscles of the limbs with trismus. The patient died early in the morning of March 27. The urine passed on March 25 was very bilious, slightly acid, of specific gravity 1015, free from sugar, but apparently containing a trace of albumin or nucleo-proteid; in the sediment some bile-stained tube-casts were seen, but no crystals of leucin or tyrosin.

Necropsy.—The brain, except for jaundice, presented no macroscopic evidence of disease. The heart weighed 10 oz. and appeared normal except for some ecchymoses below the epicardium; the cardiac muscle was pale. Nothing abnormal was noted in the lungs, kidneys, pancreas, or alimentary canal. The spleen weighed about 9 oz. and was rather soft ("pulpy"). The liver was decidedly too small, weighing only 39 oz., and was too flaccid. The capsule could be "crinkled up," as in cases of atrophy of the hepatic parenchyma, but it appeared otherwise normal. The biliary passages were free. The cut surface of the organ had lost its characteristic normal markings, but the division into red and yellow areas, so often seen in acute atrophy, was not noted. Microscopic sections from two portions of the organ showed no normal hepatic parenchyma. The lobular arrangement could, however, be still made out by using the

blood-vessels as landmarks. In some parts, especially in the marginal zones of the lobules, the liver-cells had practically disappeared, leaving only a meshwork of "ground substance" ("Stützgewebe," made up of the walls of the blood-capillaries, &c.). In most parts the hepatic cells seemed shrivelled, with their nuclei small and pycnotic or altogether absent—that is to say, apparently absent—because they had undergone karyolysis, or at all events were not differentiated from the cytoplasm by the stains employed; the cells appeared to be lying in but not filling compartments, separated from each other by the meshwork of the "ground substance," or "supporting tissue," already mentioned. Some of the cells contained globules, probably fatty in nature, but no special stains for fat were employed. In other parts a more acute process of degeneration of the parenchyma was indicated, the cells were necrosing, often apparently without preliminary shrinkage; their cytoplasm had undergone a fine granular ("woolly") change, and their nuclei were fading (that is to say, stained badly), or had already disappeared (karyolysis), or were breaking up and setting free the chromatin-particles (karyorrhexis) (*see* figure). The bile canaliculi generally appeared to be increased. In some parts there was very little evidence of inflammatory reaction, but in other parts there was considerable small cell-infiltration around the interlobular vessels; but there was no evidence whatever of preceding cirrhosis or any kind of earlier disease in the liver. At some spots, chiefly centro-acinous in distribution (*i.e.*, around the central veins of the lobules), were groups of fairly well-preserved liver-cells, and some of these contained more than one nuclei, as if an attempt at cell-regeneration was already in progress. No vascular changes were observed, such as are associated with the lesions in various organs met with during later periods of syphilis. An old section of the liver was kindly re-stained (Levaditi method) for spirochætes by Dr. J. C. G. Ledingham, but with negative results.

A benign form of jaundice is well known to occasionally associate itself with the ordinary symptoms of secondary syphilis, accompanied perhaps by a little fever, but soon passing off with (or possibly without) antisyphilitic treatment. In two of the cases referred to by Arnheim jaundice accompanied the secondary rash and recurred during a relapse with condylomatous sore throat. A malignant type of jaundice—that is to say, "icterus gravis"—though much rarer than the benign form, has likewise been repeatedly observed during secondary syphilis. At first the jaundice may not appear very threatening, but then come great

weakness, vomiting, cerebral symptoms (stupor, delirium, convulsions, coma), and rapid diminution in the size of the liver, and death soon follows. In all such cases in which a post-mortem examination has been made a condition of hepatic atrophy has been found present, usually described as acute yellow (or red) atrophy of the liver. The number of such cases already described is so considerable that in my opinion it is



Showing, in the observer's left half of the figure, shrinkage of the hepatic cells, which lie in a fine mesh of ground substance. In the right half of the figure some of the cells retain their size, but are in various stages of granular change. (Magnification, Zeiss, obj. D, oc. 4.)

impossible to doubt that a causal connexion of some kind exists between the atrophy of the liver and the syphilis, even though the hepatic disease does not seem to be associated with the local presence of spirochætes in the affected organ. In some cases of icterus gravis in secondary syphilis the liver has shown relatively chronic changes in addition to the

acute degeneration of the parenchyma. Thus, in Hilton Fagge's case (a woman aged 23) and in Siredey and Lemaire's (a girl aged 19) there was much cell-infiltration and "fibroid" change, said to recall appearances met with in the pericellular cirrhosis of congenital syphilis.[1] Similar hepatic changes were met with by H. D. Rolleston in A. H. Wilson's case, a girl aged 17, with a secondary syphilitic roseola, who became jaundiced six weeks before her death; her mental condition was affected during the last three weeks, and leucin and tyrosin were present in the urine at the end. Icterus gravis with acute parenchymatous degenerative changes in the liver may doubtless also occur during later stages of syphilis, as it did in a boy with congenital syphilis, aged 9½ years, whose case was recently described by F. J. Poynton; but with such cases we are not at present concerned.

According to W. J. Calvert, the occasional association of jaundice with syphilis was already noted by Paracelsus in 1510, and according to Neumann, Ribeiro Sanchez (1699-1783) believed that the jaundice was causally connected with the syphilis in such cases. That such a causal connexion of some kind exists in regard to the jaundice of secondary syphilis ("icterus syphiliticus") has in modern times been long maintained in France—namely, by Ricord, Gubler, Lancereaux, Cornil, Mauriac, Fournier, &c., though the actual proportion of cases showing the association is not great. S. Werner (1897), in 15,799 cases of early syphilis, found that jaundice was observed in only fifty-seven (that is to say, in only 0·37 per cent.), and according to O. Goldstein (1904) jaundice was noted in only twenty out of 7,462 early syphilitic cases (that is to say, in only 0·26 per cent.) in E. Finger's clinic at Vienna. It is quite possible, however, that slight jaundice in secondary syphilis is rather commoner than these statistics would seem to show.

Cases of "icterus gravis" and acute atrophy of the liver in secondary syphilis are, of course, much rarer, but, as I have already mentioned, many examples have been recorded. It was a paper by Engel-Reimers in 1889, with a careful report on three cases, which first seems to have attracted attention to the subject on the Continent. Senator, at the German Medical Congress of 1893, added accounts of two more cases, and in the discussion on Senator's paper Naunyn spoke of another case. In 1895 Meder succeeded in collecting accounts of twenty cases of acute

[1] Diffuse or circumscribed areas of pericellular cirrhosis recalling the changes met with in inherited syphilitic cirrhosis of infants have been occasionally noted in livers from cases of acquired syphilis in adult life. *Vide* Adami, "On the Stages and Forms of Syphilis," *Montreal Med. Journ.*, June, 1898; and F. P. Weber, "Diffuse Syphilitic Change in the Liver," *Trans. Path. Soc. Lond.*, 1899, 1, p. 42.

atrophy of the liver in secondary syphilis, so that Quincke, in his article on Diseases of the Liver in Nothnagel's great "System," vol. xviii, wrote: "In the secondary stage of syphilis, particularly at the commencement, acute atrophy of the liver has been sometimes recorded, following the jaundice which may occur at that period."

In 1898 P. F. Richter was able to collect forty-one cases, to the admission of some of which Veszpremi and Kanitz have recently objected, wrongly, I believe, in regard to the case described by J. Andrews (a man aged 20, who contracted syphilis five months before his death from acute atrophy of the liver) and Hilton Fagge's case (a woman aged 23) in the *Transactions of the Pathological Society of London*, 1866-67, xviii, p. 136. I find, however, that Richter did actually make two cases out of Hilton Fagge's single case, apparently having seen an abstract in which the patient's age was given as 32, instead of the real age, namely, 23 years.

Amongst other observations are those by Talamon (1897, a girl aged 17), Goldscheider and Moxter (1898, a girl aged 18), Thurnwald (1901, a man aged 24), van Niel Schuuren (1905, a woman aged 29), Nikolski (1906, a girl aged 16), and C. Fletcher (1906, a man aged 21). In regard to the last case Fletcher himself does not attribute the hepatic disease to the syphilis, but he mentions it as a fact that the patient had acquired syphilis six months before his death from acute yellow atrophy of the liver. Miller and Hayes, likewise, in their recently published investigation, mention that the patient (a girl aged 19) was supposed to have had a secondary syphilitic rash about five months before she died of acute hepatic atrophy.

In 1905 came the famous discovery by F. Schaudinn and E. Hoffmann of the (*Spirochæta pallida*) (*Treponema pallidum*) as the probably essential cause of syphilis, and as this parasite was found to be present in children's livers[1] affected by congenital syphilis (congenital syphilitic cirrhosis), it was supposed that it might likewise be present in the livers from adults with icterus gravis and acute hepatic atrophy in secondary syphilis. In all such cases, however, the search for the local presence of spirochætes in the liver has given a negative result. Buraczynski (1907) searched in two cases, Veszpremi and Kanitz (1907) in one case; also W. Fischer (1908, a man aged 22), P. Bendig (1908, a

[1] That the liver is one of the chief sites of the *Spirochæta pallida* in cases of inherited syphilis was demonstrated soon after the discovery of the organism in question—*see* especially, amongst the more recent papers on the subject, J. McIntosh, "The Occurrence and Distribution of the *Spirochæta pallida* in Congenital Syphilis," *Journ. of Path. and Bact.*, Cambridge, 1909, xiii, pp. 239-247.

girl aged 17), and A. Sézary (1908, a woman aged 25), each in one case; but always with negative results. Moreover, three apes of the genus Macacus were inoculated with pieces of the liver, spleen and bone-marrow from Fischer's case, but likewise with negative result, though later on a positive result was obtained in these same apes by inoculation with syphilitic condylomata lata. Altogether, up to the present time, fatal acute hepatic atrophy has been recorded in about fifty-three or fifty-four cases of secondary syphilis.

This brings us to the question of the *pathogeny of jaundice and acute hepatic atrophy in cases of secondary syphilis.* That there is some connexion between the liver affection and the syphilis one can hardly doubt, and it is quite possible that in many of the cases published as examples of idiopathic acute yellow atrophy of the liver a preceding syphilitic infection has escaped detection. Many still think that acute atrophy of the liver cannot be connected with syphilis, and they are therefore less likely to search for evidence of the latter. It is probable that the icterus gravis, accompanied by acute hepatic atrophy in these cases, is to be regarded as an exaggeration of benign "icterus syphiliticus"; and that the jaundice in such cases is really causally connected with the syphilis is evidenced by the cases (already referred to) in which persons whose earliest syphilitic exanthem was accompanied by jaundice became again jaundiced when they suffered from a secondary syphilitic relapse.

Amongst the theories that have been, or may be, suggested to explain the occurrence of mild or grave jaundice and acute hepatic atrophy in secondary syphilis are the following: (1) That the jaundice is of nervous origin ("emotional jaundice") and due to the mental worry and anxiety connected with the syphilitic infection; (2) that the jaundice is due to syphilitic enlargement of lymphatic glands, pressing on the extra-hepatic bile-ducts; (3) that the jaundice is due to venous congestion; (4) that the jaundice is due to a specific duodenal catarrh obstructing the bile-flow; (5) that the jaundice is due to a kind of syphilitic exanthem or erythematous swelling of the lining of the bile-ducts, analogous to the cutaneous roseola of secondary syphilis; (6) that the jaundice is due to obstruction of some kind in the biliary canaliculi; (7) that the hepatic atrophy is due to a specific change in the small blood-vessels; (8) that the hepatic atrophy is brought about in some way by the local presence and local action of spirochætes in the liver; (9) that the hepatic atrophy is due to toxins produced elsewhere in the body by the vital or metabolic activity of spirochætes and carried to the liver

in the blood-stream ; (10) that in some cases it is due to the action of the mercurial treatment in addition to that of the (hypothetical) syphilitic toxin ; (11) that it is due to counter-infection of the liver with B. coli or other microbes at a time when the resistance of the hepatic parenchyma is temporarily depressed by the syphilitic toxin circulating in the blood.

Simionescu refers to observations of Lioubimow and others showing that an enlarged lymphatic gland in secondary syphilis may actually press on the common bile-duct and give rise to obstructive jaundice. Naturally very few post-mortem examinations have been made in cases of secondary syphilis with jaundice (other than "icterus gravis"), and doubtless in many cases the jaundice is partly obstructive in origin and the fæces may be more or less acholic, but at least in some cases, according to O. Goldstein and F. Samberger, the fæces do not lose their colour, and bile still enters the duodenum.

In regard to the onset of "icterus gravis" with acute atrophy of the liver during secondary syphilis the theories which seem to suit best are those which I have numbered 7, 8 and 9. Though Tileston has recorded a case of acute hepatic atrophy in an apparently non-syphilitic boy after mercurial treatment, I do not think there is much to be said in favour of his suggestion that mercurial treatment (with or without the help of syphilitic toxin) plays a part in the causation of acute atrophy of the liver in syphilitic cases. If this were so, one ought almost to regard the appearance of jaundice in early syphilis as a contra-indication for mercurial treatment, whereas W. J. Calvert concludes his paper on "Icterus in Secondary Syphilis" (1904) as follows:—"Even the grave cases if properly treated are rarely fatal. Treatment consists in ordinary treatment for syphilis in this stage."

In regard to theory seven I believe that no evidence of specific disease of the hepatic blood-vessels has been discovered in the fatal cases, certainly not in the recently examined cases of Buraczynski, Veszpremi and Kanitz, and Sézary.

In regard to theory eight it has been already stated that in several cases diligent search for the local presence of spirochætes in the liver gave a completely negative result. In the present case likewise spirochætes were apparently absent from the liver, if the results obtained by re-staining old sections can be relied on.

Theory nine, which is upheld by recent authors, seems on the whole to afford the most probable explanation. It is maintained, in fact, that in secondary syphilis a toxin is produced by the spirochætes in the skin,

&c., which is carried to the various parts of the body by the blood-stream and that this toxin may more or less readily (in particular individuals) give rise to parenchymatous degenerative changes in viscera, such as the liver[1] or kidneys.

It would furthermore appear that the livers of women are far more susceptible to the harmful action of this hypothetical toxin than are those of men, since of those who succumb to acute atrophy of the liver in secondary syphilis there are about four females to one male. A possible analogy may be found in rheumatic chorea if that disease be regarded as a manifestation of the injurious effect of a toxin on the brain—that is to say, of a toxin produced by the rheumatic microbes in the joints or elsewhere and carried in the blood-stream to the brain. One would then have to suppose that the brains of girls were more sensitive (vulnerable) to that particular toxin than the brains of boys.

In regard to the term "acute" atrophy of the liver it appears from microscopic examination that the rapidity of the process varies in different cases and in different parts of the same liver, and that the process is not always so rapid as the acuteness of the final clinical symptoms ("icterus gravis") would lead one to suppose.[2] In some parts of an affected liver the parenchymatous cells seem to have had time to shrink or show fatty degeneration, whilst in other parts they have undergone a more rapid change, an acute necrosis of the parenchyma having occurred. In some cases (Siredey and Lemaire, &c.) a more chronic or fibroid change (preceding the icterus gravis doubtless) seems to have been present, a kind of intercellular sclerosis somewhat resembling the changes in congenital syphilitic cirrhosis, and one case (a woman aged 20) is recorded by Neumann in which apparently an acute (or subacute) atrophy of the liver in secondary syphilis was followed by regenerative changes in the form of adenoma-like nodules (post-mortem examination by Kolisko). Such decided regenerative changes, though rare, have been repeatedly observed in cases of acute (or "subacute") atrophy of the liver not connected with syphilis, and on the whole it is best to retain the term "acute" atrophy, unless the clinical course is decidedly subacute.

[1] An interesting question arising is whether this hypothetical toxin (produced in the body by the spirochætes or otherwise) has a more or less specific cytotoxic action on the hepatic secretory cells analogous to the more or less specific (hæmolytic) action of the toxins on the red blood-corpuscles in cases of hæmoglobinuria (? blackwater fever, paroxysmal hæmoglobinuria, &c.), or whether the liver in cases like the present one is selected merely as a "locus minoris resistentiæ."

[2] Doubtless the normal liver, like other organs, is endowed with a considerable reserve of functional power. Progressive destruction of the hepatic cells is tolerated by the organism until the "breaking point" is reached. Then symptoms of "icterus gravis" suddenly arise and are usually quickly followed by death.

I am indebted to Mr. S. G. Shattock and Dr. Ledingham for kind assistance in the microscopic examination of these cases and to Dr. Rolleston for several references to the literature of "focal" and other necrosis of the liver, and I have especially to thank my colleague Dr. Fürth for his great courtesy in handing over to me the material of the second case.

REFERENCES ON ATROPHY OF THE LIVER IN SYPHILIS.

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