

ACUTE HEPATITIS SIMULATING STONE IN THE COMMON DUCT AND LIVER ABSCESS.

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THE studies of recent years in the pathology of the liver have resulted in a revision of the early conceptions of both parenchymatous and interstitial hepatitis. The disease has gradually been proven not susceptible to the simple classifications so long in use, and the various processes of inflammation, degeneration, necrosis, and regeneration have been so often found in one liver that the attempt to assign to a symptom complex, constant and characteristic lesions has been abandoned. Ideas have been modified very much, as in the case of nephritis. Experimental work has demonstrated the complex nature of liver changes and the part played in them by the various factors of infection, intoxication, autolysis, and regeneration; and autopsy findings have demonstrated how varied are the lesions associated with a given clinical picture. The terms "acute" and "chronic," "intralobular" and "interlobular" are no longer favorably regarded; cirrhosis is not considered a disease *sui generis*; still less is it admitted that the various forms of liver cirrhosis are distinct diseases. "All ground," says Kretz,¹ "for regarding cirrhosis as an entity, disappears." A place is reserved by some pathologists for the smooth, hypertrophic form with jaundice, which is regarded as sufficiently characteristic to deserve separate consideration. But Meyer,² and with him many modern pathologists, is unwilling to make even this concession, denying the existence of Hanot's cirrhosis as a distinct disease.

The newer views affect our conception not only of the interstitial but also of the parenchymatous lesions. It is now recognized that these, too, may be present in a given liver in the most varied form; and that there is no ground for ex-

pecting to find associated with a given symptom complex a constant, or even a characteristically predominating, parenchymatous lesion. Rokitansky's acute yellow atrophy seems to have survived criticism, as do the various types of syphilitic cirrhosis. But there is reason for the belief that even these types are not so sharply differentiated as had once been supposed.

In view of these facts there is no ground for the hasty assumption that new diseases have been established by finding "hitherto undescribed" hepatic changes.

The present cases, though associated with unusual lesions in the liver, are reported because of their clinical importance. They are examples of an uncommon disease and are of a good deal of diagnostic interest.

CASE I.—Weakness and loss of appetite, with vague abdominal pains for two years; jaundice and cough for three weeks; diurnal and bidaily chills (97.5° to 106.5°), with sweats and some pain in the right side; complete obstructive jaundice, unchanging in degree; enlarged, slightly tender liver; some nausea; negative Wassermann and Widal; purpura of the ankles; no malarial parasites. At autopsy, gall-bladder and ducts normal; no stones; liver enlarged; moderate degree of cirrhosis with diffuse necrosis of the parenchyme; no organisms (smear, sections, and blood culture): no syphilis.

The patient was a married woman of fifty, who had suffered for two years with vague pain in the right side. She had gradually grown weaker and had lost her appetite. Three weeks before admission she had "taken cold," and since then had been troubled by a cough. During this time jaundice had appeared and had gradually increased. She had complained of "uneasy feelings" in the stomach, but there had been no sharp pain, nausea, or vomiting. The bowels were regular. She gave a not very clear history of "some chills and fever." On the night of admission she had a shaking chill, accompanied by pain in the right side, and followed by a profuse sweat. The temperature rose to 105° , pulse 95, leucocytes 11,880. No malarial parasites could be found. The patient was extremely jaundiced and much emaciated. The tongue was heavily coated,

but there was no herpes. The abdomen was everywhere soft, but was fuller below the costal margin on the right than on the left side. The liver dulness reached 3.5 cm. below the costal margin in the R.M.L. During the next few days, the patient continued to have diurnal and bidaily chills, with sweats, headache, nausea, and palpitation. There was a muttering delirium when the fever was at its height. The jaundice persisted unchanged. The stools, which were acholic and fatty, contained

CHART I.

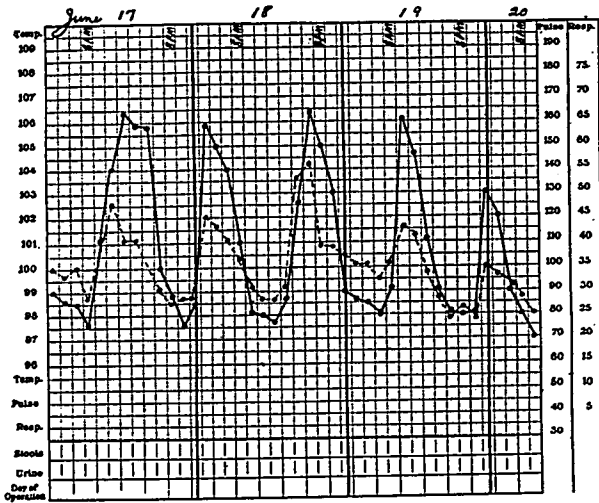


Chart showing pulse and temperature for a few days of the illness in Case I.

no blood. There was abundance of bile in the urine. Over the abdominal fulness in the right upper quadrant there was slightly increased resistance, but no marked tenderness or muscle spasm. The Wassermann reaction was negative. No variations in the jaundice or attacks of gall-stone colic occurred. The character of the fever is shown in the temperature chart (Chart I). At the time of the chills there was no particular abdominal pain, but tenderness was present in the right upper quadrant and extended into the flank. The gall-bladder could not be felt.

The Widal reaction was negative. Haemoglobin 38 per cent.; coagulation time 6 min. Two weeks after admission purpuric spots appeared on both ankles. The patient was rapidly going down hill, and, though evidently too ill for an exploration of the common duct, it was felt that a palliative drainage of the gall-bladder might relieve the symptoms if due, in part, to infection of the bile-passages. At operation, the peritoneal cavity was found to contain a small quantity of bile-stained fluid. The gall-bladder and bile-ducts were normal. On the under surface of the liver there were numerous whitish-gray spots, which looked like minute abscesses and reminded us of a case of acute hepatitis seen shortly before (the second case here reported). Rapid closure was done. The down-hill course continued, uninfluenced by the operation, and the patient died two days later. At the autopsy the only findings of interest, aside from the liver lesions, were a slight excess of peritoneal fluid, firm adhesions about the spleen, between the liver and duodenum, and between the duodenum and right kidney. There was an acute splenic tumor, and a vegetation on the aortic valve, smears from which failed to show organisms.

The liver weighed 2800 Gm. and measured $31 \times 24 \times 7.5$ cm. The outline was well preserved and the enlargement was uniform. There were dense adhesions on both diaphragmatic and lower surfaces. The capsule was not thickened, and through it one could see depressed scars. The lobulation was much obscured, in places could not be made out at all. Jaundice of the liver tissue was quite marked. The organ was like rubber in consistency and cut with some difficulty. On section the picture was pretty uniform throughout. The architecture was obscure; and in general the picture suggested a certain amount of cirrhosis. There were depressed scars with conspicuous raised areas of parenchyme, some of which measured 2 to 3 mm. in diameter. These nodules of parenchyme were of various colors (gray, yellow, red, green), or were quite opaque. There was apparently acute inflammation and necrosis of the liver tissue, with staining of all the elements with bile pigments. Cultures made at autopsy from the heart's blood showed no organisms either aerobically or anærobically.

Microscopically, the fat stains showed a large amount of fat. In parts of the liver, greenish or bronze-colored pigment was abundant. There was a wonderful grade of parenchymatous degeneration. This had affected all parts of the liver and almost none of the liver cells were normal. Some of them showed a granular or hyaline necrosis involving a part or all of the protoplasm. Others contained many vacuoles. Others were represented by a pink granular detritus. Poly-

morphonuclear neutrophiles were abundant, and there was much oedematous new-formed connective tissue. There were enormous numbers of new-formed bile-ducts. The capillaries were greatly congested, and large numbers of red blood-cells were present throughout the section.

CASE II.—*Malaria 25, syphilis 10, and pneumonia 8 years before admission. Onset of present illness two weeks before admission, with malaise, asthenia, and nausea; dull pain in right hypochondrium; fever (99.5° to 104.2°) and night-sweats; loss of twenty pounds; liver enlarged; tenderness in right upper quadrant of abdomen; Wassermann reaction positive; Widal reaction and blood culture negative. At autopsy, syphilitic aortitis; gall-bladder and ducts normal, no stones; diffuse cirrhosis of liver and necrosis; no abscess.*

The patient, a man of forty-two, had had a primary luetic infection with secondary symptoms ten years before admission. An attack of pneumonia eight years, and of tertian malaria twenty-five years, before were (with the exception of moderate constipation) the only other points of interest in the previous history. The present illness began suddenly fourteen days before admission, with general malaise, dizziness, weakness, and nausea following exposure to the wet. The following morning a dry cough developed and the patient began to experience a dull, aching pain in the right hypochondrium. He vomited once on the second day of the illness but not again. Fever, night-sweats and great weakness were the chief symptoms during the next few days. His appetite was fair, bowels irregular. A constant dull ache, worse at night and on deep inspiration, persisted in the right side. The pain did not radiate and there had been no attacks of colic. He had lost twenty pounds since the onset of the illness. He was moderately well nourished, with flushed cheeks, cyanotic lips, and a slight jaundice. Numerous medium râles were heard throughout the chest. The abdomen was quite tense throughout. At a point about 5 cm. to the right of the umbilicus there was tenderness, but none elsewhere. The respiratory movements were free and there was no muscle spasm. The spleen was not felt and there were no rose spots. The Wassermann reaction was positive, the Widal reaction and blood culture negative. There was a trace of albumin, but no casts in the urine. The liver was enlarged,

its border rounded. The character of the fever is shown in the temperature chart for the early days of the illness (Chart II). The symptom complex, together with a slight rise of the border of the lung on the right side, justified a probable diagnosis of liver abscess. At the exploratory operation, there was no fluid in the peritoneal cavity. The gall-bladder and ducts were normal. The liver was large, succulent, and covered with small grayish-

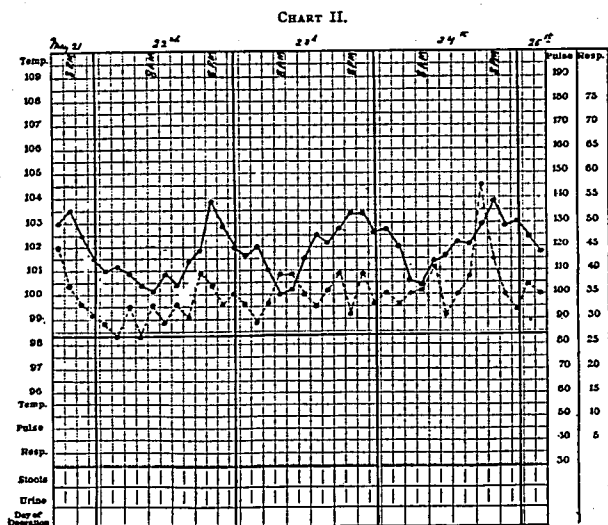


Chart showing the temperature and pulse for the early days of the illness in Case II.

white specks resembling abscesses. The liver was thoroughly explored with a needle but no pus encountered. During the ten days following operation there was extreme weakness, profuse perspiration, some distention, but no vomiting, and death occurred in extreme prostration.

At the autopsy, except for the liver lesions, the only features of interest were a slight enlargement of the spleen and a definite syphilitic aortitis. The gall-bladder and ducts were normal and there were no stones. The liver weighed 4000 Gm. and measured 30 x 20 x 9 cm. The capsule was thin. The organ was uniformly enlarged and its architecture

perfectly preserved. It was pretty uniformly mottled with opaque yellowish dots about $\frac{3}{4}$ mm. in diameter. The liver cut with some difficulty. The surface was not quite smooth, showing here and there irregular depressions evidently due to increase of connective tissue in the portal spaces. The liver lobules varied much in size, some being quite large and swollen and standing out beyond Glisson's capsule, others small and distorted. In many places the gross picture suggested pretty extensive necrosis. Smears made from a few small pockets, which contained grumous material suggesting pus, showed no pus-cells or organisms, and cultures made from the liver were sterile. Microscopically, the connective tissue of the portal spaces was everywhere increased and infiltrated with leucocytes, chiefly polymorphonuclears. The bile-ducts were much increased in numbers; all of them were dilated and filled with leucocytes and coagulated serum. In some places the ducts were so numerous as to suggest adenomatous growth. There was no degeneration of the lining epithelium of the ducts and no desquamation. The liver cells for the most part stained well, although they were swollen and granular. In many places they were atrophied, apparently by the pressure of the connective tissue. In places there was much brown pigment. In general, the pathological picture was not so striking as in the first case. Destruction of the parenchyme was less marked, increase of connective tissue more marked. More noticeable too was the great proliferation of the bile-ducts.

A small number of cases somewhat similar to these have been reported and the conclusion drawn that a separate clinical entity had been established. Curschmann,³ in 1899, described a specific form of hepatitis, with necrosis, based on the observation of two carefully reported cases.*

CASE I.—Woman of fifty-one, attacks of gall-bladder colic for one year; ten weeks before admission a mild attack, with loss of appetite, nausea, and almost daily vomiting; three weeks before admission jaundice, which had not been previously present even after the attacks of colic. Liver not enlarged, not tender; jaundice constant in degree; stools brown; moderate amount of bile in urine; irregular fever, only twice exceeding 39° ; pulse about 110; death ten days after admission. Autopsy: common duct thickened and enlarged; stone lying loose in common duct; abscess about cystic duct, with which it communicated by a perforation; liver slightly enlarged and showing numerous whitish spots, which looked like abscesses but contained no pus; diffuse central and midzonal necroses, with cirrhosis about the enlarged and proliferating gall-ducts.

CASE II.—Woman of forty-three, typhoid 12 years before admission; attacks of gall-stone colic, with jaundice, for two years; sharp attack.

* Incomplete reports of one or two other cases are also given.

with chill, three months before admission, followed by loss of appetite, frequent vomiting, alternating diarrhoea and constipation; temperature irregular, seldom much above normal; stools slightly colored; small amount of bile pigment in urine; jaundice practically unchanging in degree. At autopsy, gall-stones in gall-bladder. Cystic duct closed by a scar. Loose gall-stones in common duct, which was much dilated. Gall-bladder thickened and shrunken.

What Weber⁴ regarded as a similar condition, he reported under the title "*Hepar necroticum cum ictero*" (of Curschmann and Oertel). His patient suffered from deep jaundice, colorless stools, much emaciation, and ascites. There was a septic temperature. At autopsy a tumor of the head of the pancreas and dilated gall-ducts were found.

Extensive liver necrosis has been the feature common to the cases of Curschmann, Weber, and the author. The constant exposure of the liver to injurious agencies from the intestines, its double blood supply, the susceptibility of its cells to many mineral and proteid poisons, and its exposure to the effects of mechanical obstruction in the bile passages make such necroses not uncommon. The importance of infection in these processes has long been understood, but the part played by other factors is becoming clearer. Evidence is accumulating to show that the site of the necrosis within the lobule may be some indication of the cause of that necrosis. The association of a peripheral necrosis with pregnancy, for instance, is well known. Midzonal necrosis is regarded as so frequently connected with intense bacterial infection that the latter must be considered the most important factor in its production. In central necrosis, too, some form of acute infection must be regarded as the essential factor, though vascular disturbance may predispose to the lesion. The picture seen in a liver may, however, be altered by a combination of these factors. Opie,⁵ for instance, using a poison which *alone* would not cause midzonal necrosis, in combination with a relatively non-virulent organism (*B. coli*), was able to produce typical midzonal lesions. He thinks it probable that the organism retards the parenchymatous regeneration after destruction by the poison. Moreover, the picture has been shown

to change with the intensity of the intoxication and the time during which it acts on the liver. Flexner, using large doses of ricin and abrin, produced hepatic cell destruction without proliferative changes in the connective tissue; while smaller repeated doses of the same drugs led to the new formation of connective tissue and proliferation of the bile-ducts. Naunyn also showed that organisms introduced in large quantity into the ligated common duct might cause liver necroses, without any sign of suppuration, and that this rapid death of the liver cells might result fatally in seventy-two hours. Certain digestive or autolytic processes probably also play a part in the final pathological picture in some instances of hepatic disease. Salkowski⁶ and others have shown that the albuminous bodies of liver and muscle, under conditions in which bacterial action is excluded, are split into leucin, tyrosin, purin bodies, and albumoses, that this process may go on during life, and that it is probably of importance in explaining liver necroses.

The liver under conditions of disease may thus be exposed to the action of a large number of injurious agents. These agents may act singly or in combination; they may act intensely for a short, or mildly for a long, period; and a great variety of lesions therefore results. Many of these changes may be observed at one time in a given liver. If the common duct, for example, be occluded for some time, changes in the liver will be produced by the long-continued bile stasis. But infection may also be present and additional lesions be produced by the organisms. Finally, absorption of albuminous toxins from the intestines may modify the final picture. A liver examined at various stages in such a disease would present the most varied pictures—no one of which could be regarded as the "typical picture of biliary cirrhosis."

It is for reasons of this sort that attempts to establish sharply demarcated groups of hepatitis are unwarranted, and there is no evidence for the belief that the hepatitis described by Curschmann was a specific form. Both his patients had stones in the common duct. The first had a perforated cystic

duct with abscess; the second, gall-stones in the gall-bladder. Both had had repeated attacks of colic; jaundice was present in both cases, of long duration in the first case. The clinical picture was that of long-continued cholelithiasis, the liver changes probably contributing, as they often may, to the symptom complex in the last stages of the disease. The moderate degree of the jaundice and the fact that the stone was loosely lodged in the common duct hardly justify Curschmann's conclusion that the final clinical picture represented a distinct entity, referable to the liver rather than to the gall-stones. The effects of bile stasis on the liver are variable and the human liver is thought to be relatively resistant to this factor. Yet Janowski,⁷ in a study of the liver in ten patients dead of cholelithiasis, described one case which showed central necroses scattered throughout the liver—changes quite similar to those in Curschmann's cases. Experimentally, the effects on the liver of ligation of the common duct have varied with the animal used.

No bacteriological study of Curschmann's cases was made. Yet infection was obviously present and cannot be disregarded. Naunyn was able experimentally, by injection of *B. coli* into the ligated common duct, to produce extensive liver necroses. Curschmann's communication is only of value because it calls attention to the rôle played by the liver in the late clinical picture of cholelithiasis—a rôle often overlooked in the interest in the stones themselves. A similar criticism must be made of Weber's communication. His patient showed obstructive jaundice, ascites, enlarged liver, and fever; but inasmuch as an obstructing tumor of the head of the pancreas and dilated gall-ducts were found at the autopsy, the mere presence of multiple disseminated lobular necroses hardly justifies the consideration of the disease as a separate clinical entity.

In 1908 Oertel⁸ described in some detail four cases associated with a multiple, non-inflammatory necrosis of the liver, which he thought to be characteristic of the condition and similar to the lesions described by Curschmann. He applied

to the disease the name "*Hepar necroticum cum ictero*." The clinical picture, so far as one can gather from the meagre histories, was not characteristic. Jaundice and symptoms of intoxication (fever, mental disturbance, and delirium) seem to have been the chief features. All the patients were in a state of generally lowered nutrition, showed marked degenerative changes throughout, and had been exposed for some time to unhealthy modes of living. Common to all the cases was a peculiar and characteristic multiple and irregular destruction of the liver tissue, with more or less pronounced bile and blood stasis and fatty change. There was entire loss of the liver markings. The organ was leathery and pale yellow. There was a complete lack of inflammatory reaction within the liver tissue, and the sclerosis was confined to the portal spaces. The parenchymatous lesion appeared to be an unusual fading and gradual disappearance of the liver cells, with complete retention of the cell-outline, so that ultimately only "ghosts of cells" persisted.

Whether the changes described by Oertel are to be regarded as characteristic enough to entitle them to separate consideration is open to grave doubt. But, on the other hand, there is no doubt whatever that the clinical significance of extensive and relatively acute liver destruction—as illustrated by his cases and the cases reported in this paper—deserves emphasis, and this emphasis may be made without attempting to establish "hitherto undescribed" forms of hepatitis.

One of the interesting features of the cases here reported was our complete inability to demonstrate any cause for the hepatic change. The character of the temperature suggested an infectious origin, but blood cultures were negative, and no organisms could be found either in smears from the liver or in sections. The failure to obtain positive cultures from the liver has, however, only relative value. It was shown years ago by Babes⁹ that in patients dead of streptococcus septicæmia with extensive liver necroses, the organisms, though present in the blood, could not be grown from the liver; and that, in experimental streptococcus septicæmia, if the animals

lived longer than eight days after the injection, the organism could not be cultivated from the degenerated internal organs. There seems to be some reason for believing that this fact is due to the production of bactericidal properties from the albuminous molecule in the liver (Conradi).

Nor did the absence of signs of suppuration in the liver exclude infection, for the observation has been repeatedly made that organisms in large quantity may produce destructive parenchymatous lesions without the usual suppurative changes. It seems, indeed, altogether likely that these cases of destructive liver lesions, with fever and symptoms of intoxication, are often due to absorption from the intestines even when an infection cannot be absolutely demonstrated (Chauffard's toxi-infection).

In the second case here reported, the large, ulcerated, and thrombosed hemorrhoidal vessels must be thought of as a possible source for the infection. In some of the greatly dilated veins softening and ulceration of the thrombi had occurred, whereby the thrombus connected, through the ulceration, with the lumen of the gut. There was no sign of ileocolitis.

Syphilis cannot be disregarded in a discussion of acute destructive hepatitis with fever. The clinical features of this form of syphilis have been referred to by Gerhard, Frerichs, Hirschberg, Klemperer, and others, who have reported cases with fever either of the continuous or the irregularly remittent type; and Nasarow¹⁰ has made the point that the liver in these cases is almost always hypertrophic. Mannaberg¹¹ reported a patient who, on the basis of a malarial temperature chart, was treated for that disease for one and a half years; the fever disappeared rapidly with antiluetic treatment and complete recovery occurred. Osler and Churchman¹² include under Group 5 of their classification of luetic hepatitis cases resembling liver abscess. Unfortunately not a great deal is known of the pathology of these conditions, and the part played by lues has not been made absolutely clear by post-mortem examinations. In the cases reported in this paper, the pathological picture was quite different from that seen in

syphilis, but it is to be recalled that the old ideas in regard to luetic hepatitis are undergoing some change, and the ability to recognize the disease more often, by the Wassermann reaction, seems likely to make further changes still. Adami,¹³ for instance, while acknowledging the relative infrequency of the extensive diffuse liver lesions in the acquired form of the disease, states that "the lesions occurring in the congenital and in the acquired disease are identical, and that the same processes are at work in the secondary and tertiary stages; no sharp line between them can be drawn." Unfortunately, the failure to find the *Treponema pallidum* in the liver is of little value in excluding syphilis. Cases are reported (Veszprémi and Kaniz¹⁴ and Buraczynski) in which the organisms were present in considerable numbers in the specific skin lesions, but could not be found in the liver; and failure of this sort has been the general experience. Specific luetic liver changes have not been found in these cases, the diagnosis resting on the presence of other definite syphilitic processes or on the recent syphilis. The question might therefore be raised whether these were not cases of acute toxi-infectious hepatitis occurring in the course of syphilis, rather than instances of true luetic hepatitis. The complete response of symptoms to specific treatment in a group of clinically similar cases establishes the existence of syphilitic hepatitis with fever; but it unfortunately precludes the possibility of post-mortem evidence as to the liver changes in the cases known to be syphilitic.

In the two patients here reported the lesions in the liver were quite unlike those usually associated with syphilis. Sections stained by the Levaditi method failed to show the organisms of Schaudinn. In the first case, syphilis could be absolutely excluded, on the absence of infection, the negative Wassermann reaction, and the absence of syphilitic lesions in any of the organs at autopsy. In the second case, the patient had undoubtedly had syphilis, as shown by the positive Wassermann reaction and the presence of specific aortitis; but there is no evidence whatever that the liver lesions from

which he died were of specific nature. In view, however, of the unsettled state of knowledge in this respect, the Wassermann reaction is essential in patients exhibiting the symptom complex here described, and the therapeutic test should always be tried.

Acute yellow atrophy, though now recognized as occurring in a number of conditions, is still regarded as a definite pathological entity, and the early stage of the disease is sometimes associated with enlargement of the liver. This disease could be positively excluded in my cases by the gross and microscopic appearance of the liver, as well as by the absence of diminution in the size of the organ even in the late stages of the disease. Certain of the symptoms corresponded with those seen in the second (cholæmic) stage of acute yellow atrophy. Fever is not, however, a characteristic symptom of this disease; it is often, indeed, described as afebrile.†

The cases here reported illustrate the importance of a grave, acute disease associated with enlargement of the liver, some increase in the connective-tissue elements, and a high grade of parenchymatous destruction. The symptoms produced are jaundice, complete or nearly complete absence of bile pigment from the stools, fever like that seen in common-duct stone or in liver abscess, and manifestations of profound intoxication. Although the clinical picture suggested a bacterial origin, none could be demonstrated. Syphilis was excluded; but this disease, though usually producing changes in the liver quite different from those seen here, is known to cause hepatic lesions varying all the way from the common catarrhal jaundice to the "acute yellow atrophy of syphilis"; and some of the reported instances of luetic hepatitis have resembled clinically the cases in this paper. In view of the fact that liver changes of varied kinds—both as regards pathological picture and etiology—have been found in asso-

† Fever is often present during the initial catarrhal icterus, but later the temperature is, as a rule, normal. In the second stage it may become subnormal, though an agonal rise (sometimes very high) is often seen. Quincke in Nothnagel's System, Volume on Liver, Pancreas, and Suprarenal Glands. See also Kelly in Osler's "Modern Medicine," Vol. V.

ciation with this grave clinical condition, it is unwise to attempt to classify it pathologically and equally unwarranted to attempt to establish a close connection between this symptom complex and a "characteristic" liver change. Clinically, the condition is a very acute one, but in many cases chronic cirrhosis undoubtedly exists for a long time without producing symptoms, and is only recognized when (probably owing to some complication) grave symptoms supervene. So that even the word "acute" must be used cautiously in this connection. Icterus gravis primitivus describes, though somewhat vaguely, the clinical picture and takes account of the absence of demonstrable cause. Degenerative, productive hepatitis with enlargement indicates the main lesions and correctly emphasizes the element of destruction. Both names rightly imply the existence of an acute disease of the liver distinct from acute cloudy swelling, acute yellow atrophy, suppurative cholangitis, and liver abscess. The fact of the existence of such a disease is of more importance than its name; and its resemblance to liver abscess or stone in the common duct is of some importance in diagnosis.

Both cases were treated in the surgical service of Dr. Halsted, whose accustomed generosity with his clinical material it is again a pleasure to acknowledge. The second case was under the care of Dr. Thayer and Dr. Finney, who kindly allowed me to use it for study.

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