Pathogenesis of So-called Intrahepatic Cholestasis Based on Three-dimensional Analysis of the Cholangiolar System

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Liver specimens from three cases of the so-called intrahepatic cholestasis were submitted to graphic reconstructions of the cholangiolar system by means of serial histological sections and were examined for obstructive changes of the system. The results were evaluated in comparison with those obtained with a normal liver.

Although routine histological examinations failed to demonstrate any significant change of the bile duct, the three-dimensional analysis revealed a striking disturbance in the continuity of biliary pathways. Remarkable structural derangements of the cholangiolar system were found in all the examined cases. This was interpreted as a result of disseminated cholangiolar lesions followed by regeneration of bile ductules, which was, however, unsuccessful to restore sufficient passage to bile flow.

The same pattern of cholangiolar derangement was also demonstrated in cases of subacute serum hepatitis. This indicated that viral hepatitis was commonly accompanied by a cholestatic mechanism, which was exaggerated in intrahepatic cholestasis. The so-called intrahepatic cholestasis, characterized by jaundice of obstructive character and by absence of other serious functional impairment of the liver, was regarded as a sequela of hepatitis, most frequently of viral origin, when the cholangiolar derangement persisted long after recovery of liver cell injuries. Consequently, it was not acknowledged as an independent pathological entity, and ‘cholangiolar derangement syndrome’ was proposed to designate the condition.

The intrahepatic cholestasis, or the intrahepatic obstructive jaundice, has long drawn attention of both clinicians and pathologists, mainly because of the difficulty in giving reasonable explanation for its cause and mechanism. The puzzling problem lies in the peculiar characteristics of the condition, in which jaundice of obstructive character occurs without mechanical obstruction of gross bile ducts. It is therefore with reason that the disorder has been regarded

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as bearing a discrepancy between the function and structure of the liver in regard to bile secretion. In fact, the site and nature of the obstruction remain unsettled and are still under debate.

Eppinger described first the periacinar or cholangitic form as a clinical and histological variety of 'catarrhal jaundice'. Its clinical findings correspond fairly well with those of what is known today as intrahepatic cholestasis. He assumed that the jaundice might well be attributed to a cholangiolar damage which was caused by perilobular inflammation. There is little doubt that Eppinger was more or less influenced by the studies of experimental jaundice of Ohno and his associates and by the view of Aschoff who considered the junctional area to be the "Achilles' heel" of the biliary system. Nevertheless, this concept should be appreciated as a reasonable explanation of the syndrome, and really it has found wide-spread favor.

In recent years, however, as information about intrahepatic cholestasis has been accumulated along with increasing use of needle biopsy, a criticism has appeared against the concept of Eppinger. As stated in the report of Watson and Hoffbauer, the criticism is based on a striking paucity, at least in some cases, of histological changes in the liver, especially on the absence of such periportal inflammation as was once emphasized by Eppinger. On the icterogenic mechanism, Watson and Hoffbauer advanced a hypothesis of bile diapedesis through damaged cholangioles and designated the syndrome as 'cholangiolitic hepatitis'. Since then, a variety of concepts have followed one after another, attributing the bile stasis to compression of bile capillaries with swollen liver-cell cords, to certain electron-microscopical changes of bile capillaries, or to some damage to the liver cell. It must be accepted, however, that these concepts or views are based on scanty and rather indirect evidence. In any case, the classical theory of cholangiolitis appears currently to have been abandoned. Dubin asserts that there is little need for continued consideration of 'cholangiolar damage' as a causative factor of intrahepatic cholestasis.

It will not necessarily be fruitless, however, to re-examine the problem by means of elaborate histological examinations of the liver. The liver with intrahepatic cholestasis of long duration exhibits invariably a conspicuous intralobular bile stasis which differs in no essential manner from that of extrahepatic obstruction, except that bile stasis in the former is definitely restricted to the lobular parenchyma, while in the latter total segments of intrahepatic biliary system are simultaneously involved (compare Fig. 1-a with 1-b). From this characteristic distribution of bile stasis, it is quite obvious that the mechanical obstruction to bile flow, if any, can only be located in the place where bile canaliculi join with interlobular bile ducts, i.e., in the cholangiolar area. As will be mentioned later, however, the cholangiolar system as a whole constitutes a tree-like structure with complicated individual pathways. Therefore, it is practically impossible to conclude the continuity or discontinuity of
Fig. 1. Intrahepatic cholestasis (1-a) and extrahepatic obstruction (1-b) for comparison. Bile stasis is restricted to lobular parenchyma in the former in contrast with the latter, where interlobular ducts are distended by mass of stagnant bile.
the entire system from two-dimensional examinations on a single histological slide. Whether there exists any derangement in the system would properly be evaluated only after a three-dimensional analysis, which needs a reconstruction of serial histological sections. Such an attempt has not yet been reported.

Secondly, there has been an argument that the cholangiolar area cannot be the main site of icterogenic process, because the area is often free from inflammatory reactions. However, inflammatory reactions once present may disappear with the course of the disease. On the other hand, intrahepatic cholestasis has been taken for a variant of hepatitis all the while since the time of Eppinger. Recent advances in clinical research suggest all the more that there are not a few cases of viral hepatitis, in which cholestatic aspects are pushed to the foreground. Therefore, if exaggerated intrahepatic cholestasis is associated with a particular course of hepatitis, its histological findings must represent a certain stage of the disease. Thus, absent pericholangiolar inflammation at the time of biopsy excludes by no means an inflammatory origin of the condition. In fact, pericholangitis is an invariable finding in the earlier stages of hepatitis, and a damage to cholangioles by the inflammation may well be expected.

The above review gives the fundamental principle to the present analysis. In an attempt to elucidate the icterogenic mechanism of intrahepatic cholestasis, it is first of all necessary to know about the three-dimensional architecture of the cholangiolar area. Troublesome reconstruction is an unavoidable procedure.

The term ‘intrahepatic cholestasis’ is used today in a rather broad sense. Wewalka, for instance, includes ascending cholangitis in the category of intrahepatic cholestasis. In this case, the mechanism of jaundice is quite easy to understand, but this entity does not belong to the problem which is to be discussed here. Apart from this, the term intrahepatic cholestasis is employed under various definitions and causes a certain confusion about its implications. This confusion, originating in part from the obscure character of the disease itself, makes it impossible to prescribe a clear diagnostic standard beforehand.

The concept of the disease will be made clear only after the mechanism of jaundice is elucidated. Since the problem lies in the character of jaundice which has been susceptible of no convincing explanation, cases with this characteristic will be adequate for the present purpose. They correspond to the cases described by Eppinger, and Watson and Hoffbauer, or to those classified by Popper as intrahepatic cholestasis without structurally demonstrable causes. The authors selected three cases which satisfy the following requirements and are regarded for the time as having intrahepatic cholestasis.

1) There is sufficiently prolonged jaundice.
2) The liver function studies reveal obstructive nature of the jaundice, but little evidence of liver cell damage for a long while, except at the
onset of the disease.

3) It is proved by means of cholangiography, laparotomy or autopsy that the extrahepatic as well as gross intrahepatic bile ducts are free from obstruction.

4) Histological examination of the liver reveals a marked intralobular bile stasis, but apparently no pathological process which might cause ductular obstruction, for instance liver cirrhosis, tumor infiltration along the portal spaces, and so on.

**MATERIALS AND METHODS**

The reconstruction of the cholangiolar system was performed on three cases with intrahepatic cholestasis in view of the demonstration of obstructive changes in the system. Further, two cases of serum hepatitis in the subacute phase were treated in the same way in order to study possible development of intrahepatic cholestasis from hepatitis. Neither clinically nor pathologically hepatitis processes were of particular severity in both cases. Besides, the liver of a young adult was used as the control.

Liver specimens of four out of the six cases were obtained at autopsy. In the other two cases surgical liver specimens obtained at laparotomy were used. They were fixed in Zenker-formalin or formalin solution, embedded in celloidin-paraffin, and serial sections were prepared. Each section was 6μ in thickness. The requirement of the present study was sufficiently satisfied with 200 to 300 sections for each case. A large part of the sections were stained with Heidenhein-Mallory stain which ensured the best discrimination of the cholangioles from surrounding tissues. A small part of the sections were stained with hematoxylin-eosin and Goldner’s trichrome. A randomly selected portal area about 200μ in breadth was projected under high magnification, and all the ducts and ductules within and around the portal space including the limiting plates were drawn on tracing paper. The drawings were placed one upon another in series, and the

Fig. 2. A cardboard model of cholangiolar area constructed for Case 3.
Fig. 3. A graphic reconstruction of the normal cholangiolar area. A to B: main interlobular duct. C: lateral branches running in reverse direction. A pair of
architecture of the cholangiolar area was examined. Through this process we could prepare a chart of the cholangiolar system. However, since the chart was usually too complicated for intuitive understanding, we summarized the results in a stereogram, a side-view of the portal tract. Furthermore, a cardboard model (Fig. 2) was made for Case 3. The troublesome reconstruction with a plastic three-dimensional model was not absolutely necessary, for the graphic reconstruction met satisfactorily the requirement of the present study.

It must be noticed here that the reconstruction thus performed reveals not the architecture of the lumen, but the outside contour circumscribed by the basement membrane of ducts and ductules. The lumen appears on histological sections often indistinct, and it is not feasible to perform its reconstruction.

**RESULTS**

**Normal Liver**

A considerable number of researches have been reported on the normal architecture of intrahepatic bile ducts and ductules. Elias22 gave a detailed description on the range where the architecture could be demonstrated on gross anatomical or roentgenological methods. There are, on the other hand, numerous reports23-25 on the mode of junction between the limiting plate and the final segment of the biliary system. However, observations are quite limited in number on the cholangiolar area which covers the extent from limiting plates to a certain order of the ramifications of the biliary tree. It is just this area, of which information is needed for the present study.

An apparently normal liver specimen was obtained from a male, aged 22, who died one week after the onset of his illness. The clinical diagnosis was Japanese B encephalitis. The autopsy performed three hours after death revealed cerebrospinal lymphocytic meningitis. The liver was 1,250 g in weight, with no gross anatomical or histological change.

Fig. 3 is the sketch illustrating the arrangement of ductules in and around a segment of portal tract. It presents a view when the liver cell plate surrounding the portal tract—the limiting plate (Elias23)—was disconnected from the ductules at the junctional place and removed. The direction of bile flow is indicated by several arrows, along which one can note a prominent pathway continuous from A to B. This will be called henceforth main interlobular duct of the portal tract. The main interlobular duct takes a remarkably meandering course with several abrupt deflections. More complicated are the courses of lateral branches which connect the limiting plate with the main interlobular duct. They change their courses often in a reverse direction (C). Sometimes, two ductules, originating from closely adjacent sites of a limiting plate, follow entirely different directions and terminate in the main interlobular duct at places far apart from each other (see two ducts marked with D). Anastomoses are formed among some terminal ductules (E). Thus the cholangiolar system as a whole constitutes a structure which is hardly comparable to a tree-like pattern. One may be reminded of an injection preparation of hepatic artery, where peripheral routes take in general roundabout ways as well. The ductules interrupted with two dotted lines in the figure are the branches going
continuously into the ramified segments of the portal tract; they were omitted in the diagram for the sake of easy perspective.

The endings marked with $F$ indicate the junctions of terminal ductules and the limiting plate, the latter having been taken away from the sketch. The border was recognized with the characteristic staining property of the cytoplasm of lining epithelial cells. The mode of junction has been a much debated point, in reference to the cytological features of lining epithelium on the one hand, and to the presence of the so-called ampulla on the other. But we have no intention to occupy ourselves in these problems, for our attention is mainly focused on the continuity of the system in general. Besides, the terminal ductules have been referred to as bearing some special meaning under the name of 'canal of Hering' or 'Schaltstück' of Clara.24 As is shown in the figure, however, each excretory route passes through different numbers of ramifications and segments in its course from the limiting plate to the main interlobular duct, so that there is no reason to treat the 'Schaltstück' as a specific structure, except that it represents the last segment of bile ducts. Nor any definite boundary of the cholangiolar area to large bile ducts is demonstrated in the above results. In this study, therefore, the terms denoting the parts of bile ducts were adopted without strict definitions; ducts or ductules for individual branches, and cholangiolar system or cholangiolar area for the total structure.

Intrahepatic Cholestasis

In comparison with the results mentioned above, typical examples of intrahepatic cholestasis are presented as follows.

Case 1. Y.S., female, aged 49.

This patient developed high fever late in December 1964, followed by cough with sputum. She was admitted to a private hospital where a diagnosis of pneumonia was made. Pyrogenous staphyloocci were cultured from the sputum. After their tolerance was examined against a variety of antibiotics, she was given Achromycin and chloramphenicol continuously until January 10, 1965, when her condition was much improved. Slight jaundice was first noted on January 20. It increased in intensity rapidly within a few days. There were no available data of liver function tests of this stage. The serum transaminase, first estimated on February 10, was moderately elevated and declined thereafter to a relatively low value in 20 days. But jaundice persisted without any improvement, and the patient was referred to the City Hospital of Mizusawa on March 27 and was immediately admitted to the hospital.

On admission the patient appeared somewhat under-nourished but otherwise in a relatively good condition. Severe jaundice was visible and there were widespread excoriations. The stools were light in color. The liver was palpable two fingerbreadths below the right costal margin. The spleen was not palpable. There was no fever upon admission or later. Examination of the blood disclosed nothing particular. Routine urinalysis revealed only a large amount of bilirubin. The results of blood analysis were as follows: total protein, 9.4 g/100ml; total cholesterol, 378 mg/100ml; total serum bilirubin, 23 mg/100 ml; and direct reacting bilirubin, 16 mg/100 ml. The liver function tests are entered in Table 1.
TABLE 1. Liver function tests in Case 1

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<td>278</td>
<td>50</td>
<td>82</td>
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<tr>
<td>1965, Mar. 9</td>
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<td>(-)</td>
<td>99</td>
<td>67</td>
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<td>Mar. 29</td>
<td>175</td>
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<td>(-)</td>
<td>178</td>
<td>188</td>
<td>46.9 (K. A. unit)</td>
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<tr>
<td>May 10</td>
<td>114</td>
<td>1.1</td>
<td>(-)</td>
<td>157</td>
<td>136</td>
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<tr>
<td>Aug. 19</td>
<td>143</td>
<td>2.7</td>
<td>(-)</td>
<td>129</td>
<td>55</td>
<td>63.5 (K. A. unit)</td>
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<tr>
<td>Oct. 12</td>
<td>166</td>
<td>(-)</td>
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The liver function pattern having been regarded as suggestive of cholestatic hepatitis, 20 mg of Betamethasone were orally given daily from March 30 for the following fifty days. It is to be noted that during this period icterus index fell from 175 on March 29 to 114 on May 10. But at the same time there appeared a marked elevation of serum alkaline phosphatase level, which indicated possible extrahepatic obstruction. Exploratory laparotomy was performed on May 21. No changes of the extrahepatic bile ducts or of the gallbladder were detected. The liver was intensively green in color, smooth on its surface and was without any cirrhotic appearance. External biliary drainage was established by means of a catheter inserted into the gallbladder. A liver specimen was taken for histological examinations. After the operation the amount of drained bile averaged only about 20 ml daily. A cholangiography was carried out via the drain on June 20; the intrahepatic biliary tree was well demonstrated.

Thereafter, the condition of the patient remained entirely unchanged. Though occasional administration of corticosteroids appeared somewhat effective against jaundice, no general improvement was achieved until the end of November, 1965.

The histological structure of the liver is shown in Figs. 4 and 5. There was no fibrosis stretching out of the portal space, much less cirrhotic change. The

![Fig. 4. Case 1. Intrahepatic cholestasis. Remarkable bile stasis is observed in the lobular parenchyma. Lobular architecture is well preserved.](image-url)
liver cells were arranged in regular cords, though a few acidophilic bodies were sparsely scattered in the lobular parenchyma. Sometimes focal monocytic infiltrations were found in sinusoids in the form of so-called 'Spätknöchen'. But it might safely be said from the general appearance, that liver cell damage was only slight in degree. There was, on the other hand, conspicuous bile stasis in the lobular parenchyma, especially accentuated toward the center of the lobules. Some terminal portal spaces were diffusely infiltrated with round cells, and it was of great interest that no distinct bile duct was made out in most of them. It was found on the contrary, that bile ducts were well preserved in larger portal spaces of 500μ or more in breadth. There was no periportal ductular proliferation throughout the liver. Nor was there any sign of ascending cholangitis.

Though a mild liver cell damage is suggested both clinically and histologically, the outstanding feature of this case consists in severe obstructive jaundice. Now, the result of bile duct reconstruction is shown in Fig. 6. The figure represents a segment of portal tract in such an orientation as bile flows downwards. One can realize at first sight, that the portal tract has no well-defined main interlobular duct. Within the limit of the figure, all ductules from the limiting plate terminate in the portal space in the middle of their courses. Such blind terminations are marked with rounded closed ends in the figure; these will be called blind endings of the ductules. There are also ductular pieces that have lost communication both with other ductular segments and with limiting plate (ductular fragment). Thus the ductules are, as a whole, broken up into fragments and are incompatible with the function of an excretory system. A plausible explanation of this condition would be that multicentric foci of ductular destruc-
Fig. 6. Cholangiolar area of Case 1. No bile-excretory route in this portion of the portal tract.
tions have seriously impaired the functional integrity of the terminal bile ducts. It is of course impossible that the liver is entirely deprived of the route for bile excretion, but our result clearly demonstrates serious mechanical obstruction of the biliary conductive system.

Besides, there is no predilection of the lesions in a certain anatomically definable part. Interruptions of ductules appear to have occurred indiscriminately in the whole system. There is no reason to regard the 'Schaltstück' as the most vulnerable structure.

Case 2.  H.K., male, aged 1 year and 7 months at death.

The patient was admitted to the 2nd Surgical Clinic of the Tohoku University Hospital on November 21, 1962, with a complaint of jaundice. He had been born on June 5, 1962, as a 9-month premature. Labor was normal. Birthweight was 2,300 g. The pregnancy was uneventful. Jaundice was noticed on the third day of birth and it was gradually intensified. Acholic stool appeared occasionally after the middle of August. Otherwise, he was in a good condition with a fairly good appetite.

On admission, the patient was a rather poorly nourished boy with severe jaundice. The abdomen was not distended, and there was no fluctuation. The liver was palpable three fingerbreadths below the right costal margin. Examination of the blood disclosed 70% hemoglobin, 3.51 million erythrocytes and 18,000 leukocytes with 63% lymphocytes. The level of total serum protein and A/G ratio remained throughout the subsequent course 7.0 to 8.6 g/100 ml and 0.71 to 0.90, respectively. The stool was generally acholic, though occasional faint yellowish tint was observed. The results of liver function tests are summarized in Table 2.

<table>
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<th>Date</th>
<th>Bilirubin (mg/100 ml)</th>
<th>CCFT</th>
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<th>SGPT</th>
<th>Alkaline phosphatase (Bessey unit)</th>
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<td>1963, Jan. 14</td>
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<td>(―)</td>
<td>51</td>
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</tr>
<tr>
<td>Jun. 8</td>
<td>7.8</td>
<td>4.4</td>
<td>(―)</td>
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<td>Nov. 1</td>
<td>15.6</td>
<td>8.8</td>
<td>(―)</td>
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The liver function tests suggested extrahepatic obstruction. Parenchymal liver diseases as the cause of jaundice were rather improbable, and the pre-operative diagnosis was congenital anomaly of the extrahepatic bile duct. Because of the incomplete nature of obstruction, partial narrowing of the common duct was suspected. Surgical exploration was performed on December 26. The common duct as well as the cystic duct was patent on its entire course. The gallbladder was of normal size. The liver was deep green in color, but without signs of cirrhosis. Direct cholangiography via the common duct at operation revealed no obstructive change of gross intrahepatic ducts. A catheter was inserted into the gallbladder and the bile was led outside the body. An explorative liver specimen was obtained.

Jaundice persisted with undiminished intensity even after the operation. On January 21, 1963, the child was referred to the pediatric clinic of the hospital on account of measles. He remained in this clinic for the following 10 months under the diagnosis of intrahepatic cholestasis. Several kinds of corticosteroid preparations were intermittently given until he was discharged late in November, 1963, without any improvement of jaundice. Two months later, he died of pneumonia following influenza. Permission of
Fig. 7. Case 2. Intrahepatic cholestasis. Bile plugs filling the bile canaliculi (arrows). No sign of liver cell damage.

Fig. 8. Case 2. 'Ductular budding' along the limiting plate (arrows).

autopsy was not obtained.

Histological examination of the liver specimen (Figs. 7 and 8) disclosed regular arrangement of lobules without cirrhotic change. Numerous bile plugs were scattered in the distended bile canaliculi, but there was no sign of liver cell
Fig. 9. Cholangiolar area in Case 2, including the ramification of a portal tract into three branches. No bile-excretory route in the two branches, left and upper right. Abundant ductular buds regenerating from the limiting plate (ductular budding).
damage in the lobules. Portal spaces, partly infiltrated with lymphocytes, were surrounded by limiting plates along which one could make out a number of duct-like proliferations, a finding regarded as one of the characteristics of cholestatic hepatitis.\(^26\)

Fig. 9 shows the result of reconstruction. The sketch of bile ducts is made in the same orientation as in the first case. It includes the ramification of a portal tract into three branches. Main interlobular duct can be recognized in only one of the branches located in the upper center of the figure, but not in the remaining two, left and upper right; the latter two branches seem to be deprived of bile excretory routes. There are besides numerous fragments of ductules of various lengths, which represent duct-like proliferations from the limiting plate. Most of them are still in contact with the limiting plate as the primary buds of ductules and indicate ductular regeneration.

They play in this condition a very minor role in conducting bile flow. They will be hereafter referred to as ductular buddings. In association with this one may be reminded of the well-known term ‘pseudoductule’ which has been under debate for a long time, particularly on the point whether one should make a discrimination between ‘pseudoductules’ and ‘true’ ductules. But we have no reason to make such a discrimination or to employ the term ‘pseudoductule’, for we are interested only in the continuity of ductules, but not in their origin.

Case 3. K.I., male, aged 71.

The patient was admitted to the 1st Surgical Clinic of the Tohoku University Hospital on January 30, 1962, with complaints of jaundice and pruritus. He had been well until five weeks prior to admission, when he became jaundiced. The jaundice was aggravated and was associated with pruritus from its onset. He was treated by a practitioner, who recommended laboratory studies and made some preliminary prescriptions, but no improvement was attained in his condition. The patient had previously received neither transfusion nor administration of drugs which might cause jaundice.

On admission, the patient was severely jaundiced. The liver was palpable three fingerbreadths below the costal margin and slightly firm. Urinalysis revealed neither albuminuria nor glucosuria. The stools were almost acholic and were negative for occult blood. The red blood cell count was 3.11 millions, with a hemoglobin level of 62%. The white blood cell count was 6,300. The differential count was normal. The total protein amounted to 8.3g/100ml. The results of liver function tests are shown in Table 3. On the basis of laboratory studies carcinoma of the common bile duct was suspected, and laparotomy was performed on February 7.

The operation disclosed no particular change either of the common duct or of the hepatic ducts. The gallbladder was not distended and contained no stone. The liver was

<p>| Table 3. Liver function tests in Case 3 |
|-----------------|-------|-------|-------|</p>
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<td>Feb. 19</td>
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<td>108</td>
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Alkaline phosphatase (Bodansky unit)
intensely jaundiced and its surface was smooth. A T-drain was inserted into the common duct, and a liver specimen was obtained. After the operation, 20 to 100 ml of bile were drained daily to the outside, but jaundice remained unchanged in degree. Cholangiography was made via the drain on the 13th day of the operation, but no obstruction in the gross branches of intrahepatic biliary tree was demonstrated. On February 22, the patient

Fig. 10. Case 3. Intrahepatic cholestasis. Surgical specimen.

Fig. 11. Case 3. Specimen obtained at autopsy. Marked intralobular bile stasis in both specimens. No change in lobular architecture.
vomited about 1,000 ml of dark blood, and intermittent hematemesis of smaller amounts together with discharge of tarry stool was noted thereafter. This was attributed to peptic ulcers induced by corticosteroid administration. After March 9, urinary output declined gradually and at the same time there came an increasing disturbance of consciousness. The condition became worse and he died on March 19 in a comatose condition. Blood N.P.N. was 168 mg/100 ml on that day.

The autopsy was performed two hours after death. The liver was 1,350 g in weight.

Fig. 12. Cholangiolar area in Case 3. In the upper half of the figure a complicated ductular plexus with numerous bile plugs is demonstrated. This is isolated from communication with the main interlobular duct.
with intensive jaundice accentuated at the lobular center. There was no disorder in lobular arrangement, still less cirrhotic change. These findings corresponded to those of ordinary obstructive jaundice. However, no obstruction was demonstrated in the gross biliary pathways even by careful examinations. Acute renal failure due to hemorrhages from peptic ulcers of the stomach was the cause of death.

The histological picture of the surgical liver specimen is shown in Fig. 10, and those of the autopsy specimens in Figs. 1-a and 11. In the latter, liver cell plates appeared to be atrophied probably because of the terminal shock, and intralobular bile stasis was somewhat more advanced than in the former, but no essential difference was present between the two cases. Some portal spaces had focal lymphocytic infiltrations, accompanied by rudimentary perilobular ductular proliferation.

Fig. 12 shows an essential part of the sketch. A main interlobular duct may be traced in the vertical direction of the figure. There is a complicated, somewhat labyrinth-like ductular plexus in the upper half of the figure, where several bile plugs fill up ductular lumina. The plexus has in fact no connection with the main interlobular duct which runs at some distance behind the plexus. One segment, marked with A stretches from the plexus upward outside the figure, finally terminating in a limiting plate. At the place marked with 'ductular interruption' one can find a pair of blind endings faced closely against each other. The upper one leads to the plexus and the lower to the main interlobular duct. The gap between them is filled with dense infiltration of round cells. It is suggested from the topographical relation that a ductular segment was disconnected at the place and caused bile stasis in the upper region. Of particular interest is the obvious relation between bile stasis and discontinuity of the biliary pathway.

Viral Hepatitis


The patient was admitted to the 3rd Medical Clinic of the Tohoku University Hospital on May 4, 1963. Four weeks prior to admission he had got a sore throat with some fever, and 5 days later he noted that his face was edematous. Edema was generalized within a few days. On admission, urinalysis revealed heavy albuminuria. The blood pressure was 190 mm Hg systolic and 110 mm Hg diastolic. The urine volume was between 300 and 500 ml daily. Renal function studies performed four days after the admission disclosed GFR of 50 ml/min and blood urea nitrogen of 42.5 mg/100 ml. The diagnosis of nephrotic syndrome was made and corticosteroid therapy was instituted immediately. There was on the other hand a considerable hypoproteinemnia of 4.2 mg/100 ml in total protein, so that intravenous drip infusion of human plasma, 400 ml daily, was started on May 12, and was continued for the next ten days.

The clinical condition showed little change until July 22, ten weeks after the start of plasma infusion, when jaundice appeared. Liver function studies were carried out consecutively thereafter, and the outline of the results is given in Table 4. Of particular interest is that certain cholestatic signs were noted clinically in close relation in time with the peak of the serum transaminase level, namely, disappearance of urine urobilinogen
Intrahepatic Cholestasis

was noted during 8 days from July 29, and a discharge of acholic stools on August 1 and 2. The serum transaminase decreased and reached a normal level on August 12. Diabetes mellitus was pointed out at about the same time. This was accounted for by the longstanding corticosteroid administration. An extensive phlegmonous inflammation of the left thigh developed on August 14 with signs of septicemia, and the patient died on the next day.

TABLE 4. Liver function tests in Case 4

<table>
<thead>
<tr>
<th>Bilirubin (mg/100ml)</th>
<th>SGOT</th>
<th>SGPT</th>
<th>Alkaline phosphatase (K. A. unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Direct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1963, Jul. 22</td>
<td>3.14</td>
<td>2.7</td>
<td>125 × 5</td>
</tr>
<tr>
<td>Jul. 29</td>
<td>175 × 5</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Aug. 5</td>
<td>360 × 5</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>Aug. 12</td>
<td>150 × 5</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>6.75</td>
<td>5.10</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

The autopsy was carried out 1 hour after death. The liver was intensively jaundiced, 1,120 g in weight, without irregularity in lobular structure. There was no obstructive change in the gross biliary tracts. The cause of death was a generalized infection from the phlegmon with multiple pyemic embolisms involving both kidneys. Concomitant chronic glomerulonephritis was demonstrated histologically.

Microscopical appearances of the liver are presented in Figs. 13, 14 and 15. The liver cell plates had already restored their normal arrangement. Regeneration of parenchymal cells was apparent from the varying sizes of liver cells with large nuclei. There were a few necrotic foci. Cellular infiltrates were scanty in sinusoids. These histological characteristics were in good agreement with the results of liver function tests, especially with decreasing serum transaminase, and indicated

Fig. 13. Case 4. Serum hepatitis. Marked bile stasis of central lobular region. Bile plugs are indicated by arrows.
a convalescent stage of serum hepatitis. A predominant feature of this liver was marked bile stasis in the intralobular parenchyma (Fig. 13), accompanied in part by foci of the so-called feathery degeneration (Fig. 14). There were furthermore a small number of portal spaces, in and around which striking proliferation of distended ductules containing inspissated bile was demonstrated.
Fig. 16. Cholangiolar area in Case 4. Cholangiolar derangement quite similar to that in the foregoing cases.
This made it probable that even a larger order of biliary tree might have been involved.

From the above descriptions we can visualize a histological picture of otherwise ordinary non-fatal viral hepatitis with extremely accentuated cholestasis. The result of the reconstruction shown in Fig. 16, discloses again a remarkable derangement of the cholangiolar architecture, the individual constituent changes differing in no way from those described in the foregoing cases. Besides, there are places in the system where ductules are so attenuated as to become cord-like structures composed of epithelial cells; the cells are piled up without regular arrangement as ductular lining epithelial cells. The term 'ductular stenosis' will be proposed for such a finding.

Case 5. Y.A., female, aged 34. Pemphigus vulgaris and serum hepatitis.

The patient developed a small number of bullae on her back toward the end of April 1963. The bullae increased progressively in size and number, and were generalized on the whole body. She was admitted to the Dermatological Clinic of the Tohoku University Hospital on January 17, 1964. The diagnosis of pemphigus vulgaris was established, and a therapy with 8 mg of dexamethasone per day was immediately started. The dosage was maintained until February 25, when urinalysis revealed distinct glycosuria. In addition, 100 ml of human plasma had been given intravenously daily for eight days from January 21, because of considerable hypoproteinemia at the admission, the total serum protein being 4.8 g/100 ml with an A/G ratio of 0.53. Jaundice appeared on March 3, 41 days after the beginning of plasma administration and rapidly increased its intensity. This was accompanied by a severe epigastric pain which lasted until her death. The patient lost appetite, her condition gradually deteriorated, and she died on March 20. Table 5 shows the results of liver function tests, including those obtained before the onset of jaundice.

### Table 5. Liver function tests in Case 5

<table>
<thead>
<tr>
<th></th>
<th>Bilirubin (mg/100 ml)</th>
<th>CCPT</th>
<th>SGOT</th>
<th>SGPT</th>
<th>Alkaline phosphatase (K. A. unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Direct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1964, Jan. 20</td>
<td>0.2</td>
<td></td>
<td>(--)</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Mar. 5</td>
<td>19.1</td>
<td>11.8</td>
<td>(H#)</td>
<td>210 × 5</td>
<td>570 × 5</td>
</tr>
<tr>
<td>Mar. 8</td>
<td>22.2</td>
<td>13.9</td>
<td>(--)</td>
<td>130</td>
<td>350</td>
</tr>
</tbody>
</table>

The autopsy performed 2 hours after death revealed deeply jaundiced liver, 1,150 g in weight. The gross biliary pathways were kept free from obstructive changes. There were multiple peptic ulcers on the duodenal mucosa and a large amount of tarry mass in the intestinal tract anal to the lesions. The massive hemorrhage was regarded as accountable for the death of the patient.

Histologically, the liver was characterized by an irregular arrangement of partly disrupted liver cell plates (Fig. 17), scattered with the so-called eosinophilic bodies and mitotic figures. Dense cellular infiltrates were found in sinusoids as well as in portal spaces. Cholestatic signs were quite scanty.

The laboratory and histological examinations of this case revealed an
impressive contrast to those of the preceding case in showing far less cholestatic and more typical features of viral hepatitis. A portal tract with especially conspicuous signs of bile stasis was selected for reconstruction. The result (Fig. 18) demonstrates all kinds of structural changes mentioned in the above cases. There is a branch of portal tract, to the right of the figure, which is devoid of bile-excretory routes; here budding ductules are seen in a large number with marked bile inspissation.

**DISCUSSION**

1) The anatomical basis of 'intrahepatic obstruction'. The mechanical-obstructive origin of the so-called intrahepatic cholestasis is clearly demonstrated through the observations on Cases 1 to 3. It is plainly visible that there exists a marked discontinuity in the biliary pathways in all the cases, brought about by the derangement in the architecture of the cholangiolar system. The pattern of derangement suggests random and indiscriminate lesions affecting the cholangiolar system and subsequent irregular ductular regeneration, which is still unsuccessful for restoring effective continuity of the system. There are often portal tracts with no patent excretory route as shown in Cases 1 and 2. This would not necessarily imply a complete deprivation of every bile-draining route, since bile canaliculi constitute as a whole an extensive network where bile flow may be maintained to some degree, if some routes are still kept open in the liver. It is certainly beyond the scope of this study to deal quantitatively with the grade
Fig. 18. Case 5. Remarkable cholangiolar derangement with ductular buds, blind endings and ductular stenoses. No bile-draining route in the rightward branch of this portal tract.
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either of the ductular discontinuity or of the impediment to bile flow. At any rate, the above results are regarded to furnish an explanation on the nature and the place of 'intrahepatic obstruction', which will sufficiently account for the protracted obstructive jaundice in the cases of intrahepatic cholestasis.

2) Cholestatic feature in viral hepatitis. It deserves further attention that cholangiolar derangement of exactly the same character is found in typical viral hepatitis. Cholestasis of this origin is rather a common feature in viral hepatitis, since the disease is expected to involve the cholangiolar system as a rule, although the intensity of the lesion may be quite different from case to case. Our results will support in this regard a number of preceding clinical reports.16-18 On the other hand, 'hepatocellular' origin of jaundice in viral hepatitis has been advocated by the majority of pathologists. The concept of hepatocellular jaundice, however, is still ambiguous and susceptible of controversies. Anatomically, it is hardly acceptable that jaundice should develop as a result of liver cell damage alone. We are of the opinion that obstructive mechanism also plays an important part in the development of 'hepatocellular' jaundice on the ground of the above results.

Overt jaundice usually disappears in non-complicated acute hepatitis after a duration of several weeks. This is due to sufficiently restored patency of the cholangiolar system by active ductular regeneration. The regenerative process is indicated by abundant budding ductules or labyrinth-like arrangement of ductules, as seen in Cases 4 and 5.

The length of time necessary for the restoration may be different from case to case. On the other hand, there may be wide individual variations in the degree and extent of cholangiolar damage itself. Therefore, the variations in the outcome of viral hepatitis depend not only on different grades of liver cell injuries, but also on the difference in the behavior of the cholangiolar system. It is easily conceivable, that there may be cases in which derangements of the cholangiolar system persist long after the complete reparation of liver cell lesions. Prolonged jaundice of obstructive character is in such cases the sole manifestation of the pathological processes which have once involved the liver.

An exact etiological inquiry was not possible in our three cases of intrahepatic cholestasis. Administration of some antibiotics was found in the record of Case 1 before the onset of the disease, but it is not likely that the hepatitis in this case was induced by drugs. In any way, etiological differences are of little importance so far as pathological processes randomly affect the cholangiolar system.

3) The concept of intrahepatic cholestasis. From the foregoing discussions, it is established that intrahepatic cholestasis is nothing but a phase or sequela of hepatitis which involves the cholangiolar system, of whatever origin it may be (Fig. 19). There is no reason to regard the condition as an independent entity in

liver diseases. In this respect, we cannot advocate the use of the term ‘cholangiolitic hepatitis’. To avoid confusions in the concept and terminology, we would like to propose ‘hepatitis with cholangiolar derangement’ for hepatitis with remarkable bile stasis, and ‘cholangiolar derangement syndrome’ for the condition designated preliminarily as intrahepatic cholestasis.

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