The Adrenal Glands in Liver Disease
Histopathological Studies on Functional Zonation
and Venous System of the Adrenals

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Hyperestrinism in liver cirrhosis has been known to occur for many years. Concerning the source of aldosterone production in the adrenal cortex, Sasano regarded it the outer margin of the fasciculata and proposed the term, zona glomerulosa adulta. The results of the present investigation would also confirm his concept. It will be further taken into consideration, that adrenal lesions in liver diseases are induced not only by endocrine disturbance including stress, but also by certain other factors of topography of the organ, particularly direct effects of abnormal portal circulation.

MATERIALS AND METHODS

Both adrenals of 141 autopsy cases of liver diseases with minimum or slight post-mortem changes were selected for the examination. After Zenker-formol fixation, the tissues were embedded in paraffin, and sections were stained with hematoxyline and eosin, Goldner's trichrome combined with Weigert's elastica stain and Pap's silver impregnation. Frozen sections stained with scarlet red for the demonstration of lipid were also prepared. Weil's spirochetes were demonstrated by Dieterle's silver impregnation. The pituitaries were also available in 61 of the cases and stained with PAS-methylbule-organe G, aldehyde fuchsins and performic alcian blue (Adams and Pearse). With the latter staining, basophil cells could be divided into two types, S and R, as the original authors observed.

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For the exact evaluation of histologic findings, the width of the adrenal cortex was measured by micrometer on the silver impregnated sagittal sections through the central part of the adrenals. The adrenal cortex could be divided into four layers according to Sasano39), the fetal glomerulosa (FG), the adult glomerulosa (AG), the fasciculata (F) and the reticularis (R). The average of several measurements of each section was calculated and relative thickness of the adult glomerulosa to the total cortical thickness was determined. The results were compared with those of groups of heart diseases and of the control.

In order to confirm hypertrophy of the venous wall, perfect cross-sections of the medially vein were magnified and projected for camera lucida drawings. The exactness of the cross-sections was most reliably checked by the histologic features of the longitudinal muscle bundles in the venous wall. The total surface area $S$ and the surface area $L$ of the venous lumen were planimetrically determined on the magnified camera lucida drawings. The internal circumference of $IL$ of the vein was determined likewise on the magnified drawings with a curvimeter. The surface area of the cross-section of the venous wall $W$ was then obtained by using the formula $W=S-L$. The ratios $W/S$, $W/L$, $W/IL$ and $L/IL$ were taken into consideration in the evaluation of the thickness of the venous wall.

RESULTS

1. Adrenocortical lesions

1) Fulminating liver diseases. In cases of acute fulminant hepatitis, Weil's disease and acute phosphorus poisoning disarrangement of cortical cell cords, cytolysis, vacuolization, pseudolumen formation, edema of the FG and focal cell dissociation of the R with occasional hemorrhage were observed. The lesions were marked in the F and accompanied by lipid depletion. Such cortical changes were observed in both adrenals, particularly evident on the right side. The findings, in general, suggested the nonspecific fundamental characteristics as severe acute damages but certain differences of detail were demonstrated in various diseases: e.g. in acute phosphorus poisoning peculiar lipid accumulation was noted in the cortical cells, suggesting metabolic disturbances. In Weil's disease severe coagulation necrosis and distinct inflammatory cell infiltration with hemorrhage and edema were observed in the adrenals. Spirochetes were demonstrated in 2 cases out of 7.

2) Chronic hepatitis. The findings were generally milder than those observed in acute fulminating hepatitis. Reparative hyperplasia of the outer cortex became distinct, and accordingly the site of alarm reaction in the final stages was reduced and shifted to the deeper portion of the F. Cortical cells were generally eosinophilic usually with differentiation of light and dark cells, and
lipid was fairly well preserved. Edema in the FG was more or less absent and beginning fibrosis was noticeable not only in the FG but sometimes throughout the whole cortex. ACTH or cortisone administration produced no detectable histologic changes. In a case with adenomatous hyperplasia of the anterior pituitary, the F was thickened.

3) Liver cirrhosis, hepatoma and other chronic liver diseases. In the majority of cases with liver cirrhosis, evident hyperplasia of the AG transposes the site of alarm reaction in the F to the deeper portion, where slight cortical damage represented by degenerating cells with densely stained with eosin were frequently observed. Severe cortical damage comparable to those observed in acute liver disease were occasionally found particularly in the F. Also focal fibrosis was sometimes observed. However, acute injuries were generally less conspicuous than those observed in chronic hepatitis and about 1/4 of the examined cases had no detectable cortical damage. In cases with primary liver cell carcinoma, the findings were even less severe and more frequent than those observed in liver cirrhosis. The acute cortical injuries in liver cirrhosis and hepatoma were generally ascribed to the accidents in the final stages and different in their severity according to the clinical signs to death. The most distinct lesions were observed in cases with bleeding to death. Complicating acute pancreatitis followed this and the slightest lesions were observed in cases with hepatic coma or acute infection. No distinct correlation was found between the severity of adrenal lesions and the degree of abnormal liver chemistries. Exceptional cases with extremely high Meulengracht index over 150 were accompanied by severe adrenal damages. No difference in the adrenal histology was noted with various types of liver cirrhosis but fibrosis of the FG was more evident in postnecrotic and active posthepatitic than in inactive posthepatitic cirrhosis. No differences in sex or aging process of the adrenal cortex were observed. Hemorrhagic diathesis and gastric or duodenal peptic ulcers had a positive relation with adrenal injuries. Administration of corticosteroids induced attenuation of the cortex particularly of the F.

Regressive cortical changes were most evident in biliary cirrhosis, less prominent in carcinoma of the extrahepatic bile ducts, and the least severe with cholangioma and metastatic liver cancer. In cholangitis and liver abscess moderate vacuolar degeneration, necrosis and hemorrhage was observed mostly in the F. Lipid depletion was distinct in the majority of the cases. It was noticeable that cortical lesions were accentuated in the right adrenal only in liver cirrhosis and fatty cirrhosis, while no distinct difference between both adrenals was generally observed in other diseases.

2. Hyperplasia of the outer cortex

1) Histology. Hyperplasia of the outer cortex, mainly consisting in that of
the AG, was generally diffuse and/or nodular in appearance and sometimes accompanied by mitosis. This was usual in chronic hepatitis and liver cirrhosis, even in cases with reduced thickness of the whole cortex. Nodular hyperplasia of the AG was observed in 2/3 and pericapsular cortical nodules were detected in 1/3 of the examined cases except acute hepatitis. The findings occasionally made difficulty in distinguishing from intra- or extracortical adenoma. Nodular hyperplasia was more conspicuous in the left than in the right adrenal. (Table I)

### Table I. Hyperplasia of the Outer Cortical Zones

<table>
<thead>
<tr>
<th>Diseases</th>
<th>No. of cases</th>
<th>Pericapsular cortical nodule</th>
<th>Intracapsular cortical nodule</th>
<th>The adult glomerulosa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nodular hyperplasia</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>12</td>
<td>2</td>
<td>7</td>
<td>4 (0)*</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>11</td>
<td>4</td>
<td>4</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>31</td>
<td>9</td>
<td>20</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Fatty liver cirrhosis</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Hepatoma without cirrhosis</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hepatoma with cirrhosis</td>
<td>20</td>
<td>7</td>
<td>7</td>
<td>16 (7)</td>
</tr>
</tbody>
</table>

* Marked hyperplasia is registered in parenthesis.

A patient with chronic hepatitis with distinct cortical adenoma had clinically detectable hypokalemia and hypoproteinemia. Furthermore, in patients with particularly evident hyperplasia of the outer adrenal cortex clinically hypokalemia was detectable.

2) Histometry. The material was divided into two age groups, those under and over 40 years. In the younger age group, the increased width of the AG in liver cirrhosis and hepatoma was confirmed histometrically. This tendency was also noticed in the chronic hepatitis but could not be found in carcinoma of the extrahepatic bile ducts nor metastatic liver cancer. In the older age group, the width of the AG was increased in almost every liver disease group except metastatic liver cancer. (Table II, Fig. 1).

The AG was significantly thicker than in the control in both age groups in which ascites exceeded 2000 cc at autopsy (Fig. 2). In liver cirrhosis and/or
Table II. The Width of the Adult Glomerulosa

| Diseases                          | Age  | No. of cases | The mean width of AG* | $t=\frac{|m_c-m|}{\sqrt{\frac{n_c n (n_c+n-2)}{(n_c+n) (S_x^2+S^2)}}} $ |
|----------------------------------|------|--------------|-----------------------|---------------------------------------------------|
| Control                          | 20-39| 23           | 3.01                  |                                                   |
|                                  | 40-  | 23           | 3.42                  |                                                   |
| Chronic hepatitis                | 20-39| 5            | 3.82                  | 3.04**                                            |
|                                  | 40-  | 11           | 3.82                  | 6.53**                                            |
| Liver cirrhosis                  | 20-39| 12           | 3.69                  | 3.99**                                            |
|                                  | 40-  | 23           | 3.89                  | 3.21**                                            |
| Hepatoma                         | 20-39| 7            | 3.71                  | 4.06**                                            |
|                                  | 40-  | 30           | 3.65                  | 1.04*                                             |
| Carcinoma of the extra-          | 20-39| /            | /                     |                                                   |
| hepatic biliary passages         | 40-  | 22           | 3.87                  |                                                   |
| Metastatic carcinoma of the      | 20-39| /            | /                     |                                                   |
| liver                            | 40-  | 13           | 3.51                  | 0.51                                              |
| Heart diseases                   | 20-39| 17           | 3.55                  | 3.46**                                            |
|                                  | 40-  | 17           | 3.39                  | 0.19                                              |

** Significant at 1–0.1% level
* Significant at 5% level
† The width of the whole cortex is assumed to be ten.

Fig. 1. The width of the adult glomerulosa is given in reference to the width of the whole cortex which is assumed to be ten.
hepatoma the left adrenal was predominant over the right in total cortical width due to hyperplasia of the outer cortex, while in groups of control and of metastatic liver cancer no difference was detected between the two sides.

3. Histology of the inner cortex

The R had variable width and in cases with low serum protein it was generally thick and contained much pigment. The pigment content was generally increased in all forms of chronic liver disease and particularly marked in fatty cirrhosis. Hypertrophic cortical cells with dense granulation were observed in the juxtamedullary zone in about half the cases.

4. The adrenal medulla.

No abnormalities were generally detectable in the medulla. In acute liver disease inflammatory cell infiltration was frequently observed; hyperemia and hemorrhage of the deeper cortex occasionally involved the medulla. In chronic liver disease, hyperemia, hemorrhage, clear cells and vacuolar degeneration were reduced, but inflammatory infiltration was more frequently observed in the medulla than in the cortex. The width of the medulla remained unchanged, even when the cortical width was reduced in chronic liver diseases.

5. The adrenal venous system.

1) Dilatation and proliferation of the capsular vein. In acute hepatitis and phosphorus poisoning, dilatation of the capsular and pericapsular veins was
observed in about a half of the examined cases without distinct tendency of proliferation. No difference was confirmed between both adrenals. In chronic hepatitis, proliferation of small veins besides dilatation was observed in more than a half of the cases, particularly in the left adrenal. The findings were quite distinct in liver cirrhosis and more evident on the left side than those observed on the right side in 3/4 of the cases. In cases with hepatoma the difference between both sides was not as distinct as in cirrhosis. The results are shown in Table III. Close relation was confirmed between the above findings and signs of portal hypertension. For example, the majority of the cases with more than 3000 cc of ascites had marked venous dilatation and proliferation, which were particularly evident in the left adrenal.

**TABLE III. Dilatation and Proliferation of Pericapsular Veins of the Adrenals**

<table>
<thead>
<tr>
<th>Diseases</th>
<th>No. of cases</th>
<th>Difference between both adrenals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$R_{&lt;L}$</td>
</tr>
<tr>
<td>Control</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Acute poisoning</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>10</td>
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</tr>
<tr>
<td>Chronic hepatitis</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Fatty liver cirrhosis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Biliary liver cirrhosis</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Carcinoma of the biliary passages</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Metastatic carcinoma of the liver</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Cholangitis, liver abscess</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Portal thrombosis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Weil's disease</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

2) Dilatation of the cortical veins. Only slight dilatation of cortical veins was observed in about a half of the cases with acute and chronic hepatitis, while distinct findings were confirmed in 2/3 of the cases of cirrhosis and/or hepatoma.
The findings had no general relation with signs of portal hypertension, although two cases of portal thrombosis showed highly distinct dilatation of cortical veins, particularly on the left side. Intensively eosinophilic, homogenous material was sometimes observed in the dilated veins.

3) Quantitative evaluation of medullary veins. (Table IV, Figs. 3–7) In the control groups the ratio W/S increased with increasing diameter of the vein. In the younger age groups of liver diseases, no distinct abnormalities were observed in histometrical results. In the older age groups, all but cases of acute hepatitis showed an increase in the ratio W/S of the veins smaller than 0.4 mm in diameter.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>No. of cases</th>
<th>Mean W/S</th>
<th>t =</th>
<th>m - m</th>
<th>t =</th>
<th>m - m</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>R</td>
<td>L</td>
<td>Total</td>
<td>R</td>
<td>L</td>
<td>Total</td>
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<tr>
<td>Control</td>
<td>22</td>
<td>35</td>
<td>57</td>
<td>0.3994</td>
<td>0.3940</td>
<td>0.3961</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>23</td>
<td>27</td>
<td>50</td>
<td>0.6119</td>
<td>0.5335</td>
<td>0.5695</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>28</td>
<td>22</td>
<td>50</td>
<td>0.5733</td>
<td>0.5058</td>
<td>0.5436</td>
</tr>
<tr>
<td>Heart diseases</td>
<td>26</td>
<td>21</td>
<td>47</td>
<td>0.6049</td>
<td>0.5285</td>
<td>0.5705</td>
</tr>
</tbody>
</table>

*Significant at 0.1% level

Fig. 3. Cases with chronic hepatitis show an increase of W/S of the veins smaller than 0.4 mm in diameter.
Fig. 4. W/S increases in hepatoma, but there is no manifest difference in liver cirrhosis in comparison with the control.

Fig. 5. W/S of the veins smaller than 0.4 mm in diameter increases in liver cirrhosis and in hepatoma.

The results showed a partly similar tendency as those of heart diseases. Statistical treatments revealed a difference in the mean W/S at the level of 0.1% between each group of liver diseases and the control group. The mean W/S was seemingly
higher in the right than in the left adrenal, but the difference was not statistically significant. No relationship was found between the mean W/S and the amount of ascites.
6. The anterior pituitary

Edema, hyperemia with occasional hemorrhage and cell infiltration were observed in acute fulminating hepatitis and Weil’s disease. Abnormalities were evident in chromophil cells, particularly in the basophils.

1) Basophil cells. In acute fulminating liver diseases degranulation of S cells was detected, while vacuolization and hyaline degeneration frequently induced in R cells. Amphophil cells were not affected. In chronic hepatitis many S cells were degranulated and adenomatous hyperplasia mainly of R cells was observed in 2/5 of the cases. Amphophil cells tended to increase in number. In atrophic liver cirrhosis S cells were increased in number in a third of the cases particularly in cases of younger age group. R cells were increased in number and their granulation was relatively well preserved. In about 1/3 of the cases of liver cirrhosis amphophils were increased in number and occasionally showed hyaline degeneration. About a half of the cases with hepatoma had an increase of S cells in number. The majority of the cells was enlarged and densely granulated but some showed degranulation. Amphophils showed hyaline degeneration and an increase in number in a half and in a third of the cases, respectively. In other types of liver disease generally no definite pituitary changes were noted. The administration of ACTH or adrenocortical steroids induced degranulation of S cells and an increase of R cells in number. Hyaline changes were frequently observed in R cells.

2) Acidophil cells. Degranulation was evident in both acute hepatitis and Weil’s disease and was also accompanied by vacuolization in the latter. These findings were only rarely observed in liver cirrhosis or hepatoma, but were prominent in fatty liver cirrhosis.

3) Chromophobe cells. No definite changes were found.

DISCUSSION

Adrenocortical lesions in acute fulminating hepatitis and Weil’s disease can be regarded as nonspecific and are common in various acute infectious diseases; Murakami in his discussion interpreted the adrenal cortical lesions in acute hepatic damage as signs of exhaustion in stress. Swelling and degranulation of S cells in the anterior pituitary would support this theory. In Weil’s disease spirochetes could be found in the adrenals with fairly high incidence as observed by previous authors. Analogously, it is possible that some of the adrenal cortical damage in acute infectious hepatitis is caused by the virus itself although the presence of the virus in the adrenals could not be demonstrated.

The close topographic relation between the liver and the right adrenal, would explain the predominance of adrenal cortical injuries in acute liver disease on the right side. Acute inflammation and/or other damage of the liver involves the
right adrenal more readily and severely than the left. Popper\textsuperscript{34}) suggested that part of the cortical lesions might be postmortem autolytic changes with autolytic enzyme diffusing from the nearby injured liver into the right adrenal. This possibility requires further evidence. In chronic hepatitis and cirrhosis, focal fibrosis with atrophic or disarranged cortical cell cords is regarded a result of cortical damage in acute liver damage and was predominant in the right adrenal. Therefore, it is concluded that acute adrenocortical lesions in liver diseases occur mostly in vivo and only partly postmortem.

Adrenocortical lesions in chronic hepatitis were the sequence of injuries in the acute stage, reparative processes or recurrence of the liver disease.\textsuperscript{5,17}) Regressive changes were predominant in the right adrenal, while reparative and progressive changes were marked in the left. Liver cirrhosis with and without hepatoma showed generally less marked acute cortical lesions than those observed in chronic hepatitis; sometimes any appreciable changes were missing, as previous investigators\textsuperscript{28,32}) indicated. As for the relationship between the direct cause of death and adrenal glands, the most severe cortical changes were seen in patients with cirrhosis who died of hemorrhage from varicose veins.\textsuperscript{6}) The adrenal lesions even in such cases were predominant on the right side. This might be explained by the difference of "reserve capacity" between both adrenals. As a result largely of the difference in degree of cortical injuries between both adrenals in the acute phase of hepatitis, the right adrenal shows relatively distinct fibrosis and a retarded or imperfect reparatory process compared with those of the left. The difference in the development of collateral circulation in the right and left adrenals should also be considered. Consequently, the "reserve capacity" of the right adrenal would be smaller than that of the left.

The width of each cortical zone was quantitated at first by Hammar\textsuperscript{20}) (1924). von Lucadou\textsuperscript{51}) (1935) calculated the ratio of the medulla to the cortex in cases of heart disease, liver disease, hypertension and glomerulonephritis. He concluded that the medulla increased its width in heart diseases, but other diseases induced cortical enlargement. The present investigation revealed that increase of AG in width was observed in chronic hepatitis, liver cirrhosis, hepatoma and cholangiocarcinoma, but could not be found in extrahepatic bile duct cancer and metastatic liver cancer. Diffuse and nodular hyperplasia of the AG are not only reparative processes as far as adrenocortical damages are concerned, but are significant functionally, too.\textsuperscript{35,36}) According to Sasano\textsuperscript{39,40}), the AG is regarded to be the source of aldosterone production; its hyperplasia or adenoma is usually found in hyperaldosteronism. Increased urinary aldosterone excretion is generally observed in liver disease with a large amount of ascites.\textsuperscript{13,16,33,48,50,52,53}) This is explained by increased aldosterone secretion from the adrenal and/or reduced aldosterone inactivation in the injured liver.\textsuperscript{8,9,16,46}) This is supported also by the fact that adrenalectomy\textsuperscript{18,29}) or the administration of aldosterone antagonists is effective
in the management of ascites.\cite{8,13,31,46} Davis reported that aldosterone level in the venous blood from the adrenal was elevated in experimental ascites of dogs, and that adrenalectomy promoted diuresis.\cite{15} Wolff observed that removal of ascites generally induced increased aldosterone production.\cite{23} According to Sherlock\cite{44} aldosterone sustained ascites rather than induced it. The results of the present investigation indicated that AG was thicker in cases with a large quantity of ascites than in cases with little or no ascites. In cases with hypokalemia the AG was distinctly enlarged.\cite{14} It was also increased in width in the younger age group with heart disease. Hyperplasia of the AG is usually accompanied by an attenuation of the F, the site of glucocorticoid production and of the alarm reaction. The reduction of the volume of the F would enhance the effect of aldosterone, because glucocorticoids act as aldosterone antagonists.\cite{41,46,49}

The observations on adrenal veins in various types of liver disease are interesting and significant. It has been a question for a long time whether the adrenals have some efferent vein other than v. suprarenalis.\cite{22,25,30} The problem is not only of anatomical but also of endocrinological importance (Bachmann\cite{6}). Kutschera-Aichbergen\cite{26} came to the conclusion that venous blood both from the medulla and from the cortex flowed via capsular veins into the portal vein due to the "Verschlussmechanism" of central veins. His opinion was shared by Heil, although Tammann\cite{47} failed to confirm this. Donath\cite{15} demonstrated the inflow of adrenal venous blood into the portal system on dogs by the injection of fluorescent dyes. Present study revealed conspicuous dilatation and proliferation of the adrenal capsular veins in chronic hepatitis and in atrophic liver cirrhosis. Intracortical veins were also dilated. Hypertrophy of the adrenal medullary veins smaller than 0.4 mm in diameter was distinct in the age group of more than 40 years. No significant difference was confirmed in larger veins between liver cirrhosis and control. The results were in accordance with those observed by Heinivaara\cite{21} in the adrenals of hypertensive patients. Concerning the function of adrenal veins in hypertension, renal disease or heart disease two opposite opinions are popular (Allen\cite{4}, Goldzieher and Sherman\cite{19}, Liebegott\cite{27}, Guichard and Heinivaara\cite{21}). One attributes some "Sperrmechanismus" to the longitudinal muscles, the other proposed by Heinivaara ascribes a suction and pressure pump mechanism to the activity of venous wall. It is believed by the majority of authors that hypertrophy of the wall of adrenal veins is not only a sign of elevated venous pressure, but rather a result of enhanced functional demand on the venous wall. In the present study, the findings of muscular hypertrophy of medullary vein wall, together with dilatation and proliferation of cortical and capsular veins, were explained by collateral circulation, i.e. reverse flow of the portal blood into the adrenal veins due to abnormal portal circulation (Fig. 8). This assumption is supported by the findings in two cases of portal thrombosis.
Fig. 8. The relationship of the adrenal venous system, v. portae and v. cava inferior. Physiological direction of blood flow, indicated by arrows, is regarded to be reversed in portal hypertension.

with distinct dilatation of adrenal capsular veins and hypertrophy of the wall of the medullary vein. It seems significant that dilatation and proliferation of the capsular vein were particularly evident on the left side, while hypertrophy of the wall of medullary vein was rather prominent on the right side.

Hyperestrinism in liver cirrhosis is an interesting problem. It is suggested by histologic findings of the anterior pituitary, in which S and R cells were increased in number although Crooke cells could not be detected.\textsuperscript{7,10,23,38,43,45,54} Hyperestrinism cannot be simply attributed to increased hormone secretion or to reduced liver function, but also to abnormal adrenal circulation. In physiological conditions, blood flow from capsular veins of the adrenal to the portal system results in inactivation of adrenal steroids in the liver. In portal hypertension the blood flow is reversed and the adrenal hormones are released in large quantity into the systemic circulation, bypassing the liver. Even if inactivation of corticosteroids through the hepatic artery may normalize the hormone balance to some extent, the effect must be a limited one and as a result the hormone level in the peripheral blood is elevated.

**SUMMARY**

The adrenal glands of 141 cases with various liver diseases were histologically investigated with particular attention to the zona glomerulosa adulta (Sasano) and the adrenal venous system.

Hyperplasia of the outer cortex, particularly of the adult glomerulosa was observed in chronic liver disease, mainly in liver cirrhosis, and was prominent in the left adrenals. The findings are regarded as an expression of secondary
aldosteronism. Dilatation and proliferation of capsular veins with dilatation of the cortical veins were also confirmed in chronic hepatitis, liver cirrhosis and hepatoma. Again, the findings were prominent on the left side. Medullary veins smaller than 0.4 mm in diameter had hypertrophied muscular walls. These suggest that the adrenal glands are involved in the collateral circulation in portal hypertension.

The fasciculata was the main site of acute cortical injuries, which was prominent on the right side. The lesions are regarded to be induced not only indirectly by nonspecific stimulation via the pituitary gland, but also directly by local noxious influences from the diseased liver. In the anterior pituitary swelling and degranulation of S cells were found corresponding to acute injuries in the adrenal cortex. In chronic liver disease S cells were relatively well preserved and R cells were slightly increased in number. No pathognomonic lesions due to liver disease were found in the pituitary.

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Fig. 9. Acute hepatitis. Twenty-year-old female. Cytolysis, vacuolisation and coagulation necrosis are seen in the zona fasciculata and the zona reticularis. Hematoxyline and eosin.

Fig. 10. Chronic hepatitis. Thirty-nine year-old male. A marked hyperplasia of the adult glomerulosa. Hematoxyline and eosin.

Fig. 11. Liver cirrhosis. Fifty-nine-year-old male. Hyperplasia of the adult glomerulosa transposes the site of alarm reaction in the zona fasciculata to the deeper cortex. Hematoxyline and eosin.

Fig. 12. Liver cirrhosis. Forty-seven-year-old female. Dilatation of the cortical vein. Hematoxyline and eosin.
Fig. 13. Liver cirrhosis. Forty-eight-year-old female. Dilatation and proliferation of the capsular vein. Goldner's trichrome combined with Weigert's elastica stain.

Fig. 14. Liver cirrhosis. Forty-eight-year-old female. Hypertrophy of the medullary vein. Goldner's trichrome combined with Weigert's elastica stain.