

THE PATHOLOGY OF SUBCHRONIC ATROPHY OF THE LIVER*)

A Comparison with Cirrhosis hepatis Laennec.

By

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I. Introduction.

Subchronic Atrophy of the Liver in Denmark 1944-1947.

Details have already been published of a considerable number of fatal cases of hepatitis chronica (8, 21, 22, 1, 10) which arose in Denmark during the years 1944-1947. The patho-anatomical picture corresponded to what earlier literature

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described as subchronic atrophy of the liver (2) (synonyms: subacute diffuse necrosis of the liver—subacute yellow atrophy of the liver—toxic cirrhosis—necrotic hepatitis).

Consideration of the Problem.

The aim of this work has been to give a detailed description of the pathology of the liver in this rare disease on the basis of a considerable post-mortem material.

We found it of interest to make a comparison with the cases of cirrhosis hepatitis Laennec on which autopsies were made during the same period, since subchronic atrophy of the liver offers clinically a number of points of similarity with Laennec's cirrhosis.

As a few liver biopsies were made in the case of living patients, we have endeavoured to solve the problem of whether it is possible with the aid of liver biopsy at an early stage of the disease to distinguish subacute atrophy of the liver from acute hepatitis.

Finally, on the basis of both materials, we tried to discover if there is a connection between the size of the liver at autopsy and the occurrence of various symptoms, especially that of liver insufficiency.

History.

Only scanty reports concerning the pathology of subchronic atrophy of the liver have been published. In *Bright* (12) a typical case of the disease is described, but *Marchand* (26) was the first to recognise its relation to acute atrophy of the liver. *Wilson and Goodpasture* (45) describe a single case and refer to older publications dealing with the subject. (28, 30, 33, 34, 42). *Bergstrand* (2) discusses in his work on the acute and chronic atrophy of the liver 150 cases of these diseases. 11 of them had symptoms of the disease over a period of 3 months and were thus presumably of the same nature as those to be described here. In the years following, a few similar cases were described. *Lucké* (24) reports in a work from 1944 that among 125 fatal cases of hepatitis there were 7 of more than 3 months duration from the first symptom until death.

The following is a description of the liver in a condition of subchronic atrophy (see plate I):

As a rule the liver is greatly and uniformly reduced in size. The surface is smooth or wrinkled, and in cases of longer standing nodular. It is yellow and red in colour. In the areas corresponding to the yellow parts the surface is domed, and in those corresponding to the red parts it is depressed. On the surface of the section yellow "islands" are to be seen, separated by the red depressed parts. Under the microscope it is found that the liver parenchyma has completely disappeared in the red parts. Here there are only vessels and connective tissue

to be found, infiltrated with inflammatory cells with some "proliferation of the bile ducts". The yellow "islands" consist of cells of the liver parenchyma, to some extent with degenerative and necrotic changes. The trabecular structure is indistinct.

The Material.

a. Subchronic atrophy of the liver.

The material consists of 108 patients on whom autopsies were made at the pathological institute of the Kommunehospital during the period 1/1 1944-1/1 1948. Only 6 were men, while 102 were women. This considerable preponderance of women, which was shown by *Ryssing* (37) also to have existed formerly, cannot be explained. The age range of the dead subjects is shown in Fig. 1. It can be seen that the curve in the case of women rises steeply after the 45th year, a circumstance which cannot be explained.

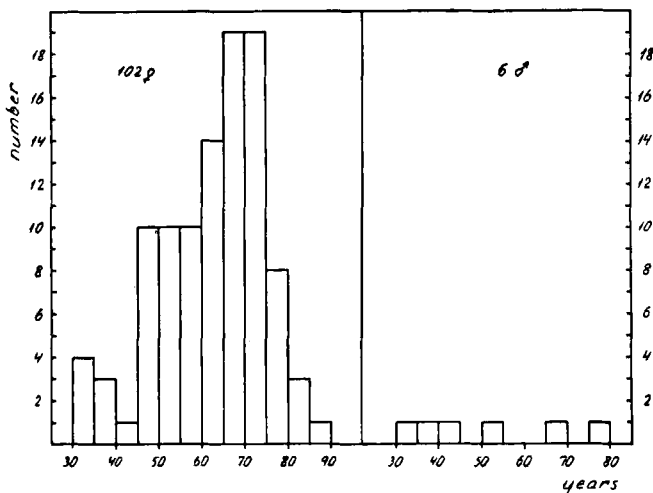


Fig. 1. Subchronic atrophy of the liver. Age and sex distribution.

With regard to the distribution of the material within the period 1944-1948, it must be noted that autopsies were performed on 78 of the 108 cases between 1/6 1945 and 1/10 1946.

There are included in this group all cases which correspond macroscopically to the picture of subchronic atrophy of the liver. In very few cases the diagnosis was in some doubt, as forms were noted which were in a state of transition towards cirrhosis hepatis Laennec. In one instance chronic atrophy of the liver was even seen in one lobe of the liver and Laennec's cirrhosis in the other. By far the greater part of the material showed, however, quite a typical and uniform appearance.

b. Cirrhosis hepatis Laennec.

This material consists of all cases of Laennec's cirrhosis (portal cirrhosis) on whom autopsies were made within the period 1/I 1944 to 1/I 1948, 76 cases in all (cases of biliary cirrhosis and chronic stasis of the liver were excluded). 33 were women and 45 men, thus a distribution between the sexes essentially

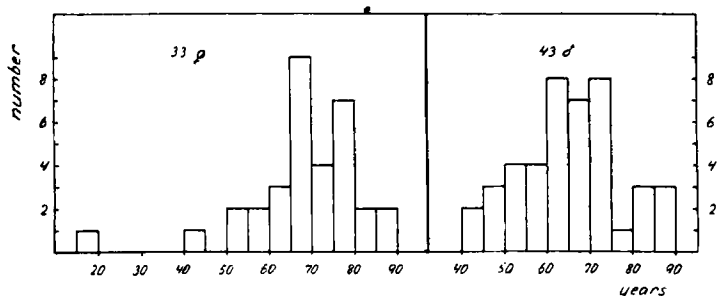


Fig. 2. Cirrhosis hepatis Laennec. Age and sex distribution.

different from subchronic atrophy of the liver. The age range is shown in Fig. 2 and indicates that the maximum falls within the age groups 60-80 years. No definite difference is seen between the distribution for men and women, nor does there appear to be any definite distinction in the age range between subchronic atrophy of the liver and Laennec's cirrhosis.

On examining the post-mortem material of cirrhosis hepatis Laennec and subchronic atrophy of the liver from 1928-1947 inclusive (Fig. 3), it can be clearly seen that the number of cases of Laennec's cirrhosis has been relatively constant over those years, about 20 per year (from 900-1000 autopsies), while the number of cases of subchronic atrophy of the liver shows an enormous increase be-

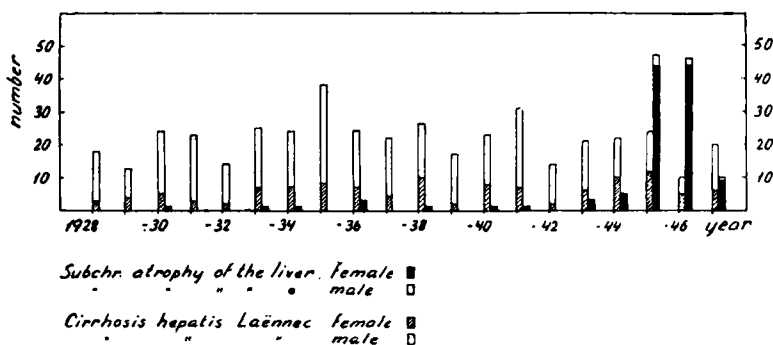


Fig. 3. The occurrence of subchronic atrophy of the liver and cirrhosis hepatis Laennec in post-mortem material of the Kommunehospital from the years 1928-1947.

ginning in 1944; formerly this type appeared only sporadically. With regard to the distribution between the sexes, it can be seen that former cases of Laennec's

cirrhosis occurred mainly in men (Fig. 3), while in the years 1944, 1945 and 1946 a relatively larger number of such cases appeared among women. We shall deal more in detail with this situation later.

2. Pathological Anatomy of Subchronic Atrophy of the Liver.

Macroscopic Pathological Anatomy.

Weight of the liver: In 28 autopsies of subchronic atrophy of the liver taken at random (25.9 %) the weight of the liver was measured. 7 weighed less than 700 gr., 14 between 700 and 900 gr., and 7 over 900 gr. In other words there was a very pronounced reduction of the liver parenchyma (normal weight: 1450-1750 gr. (43)).

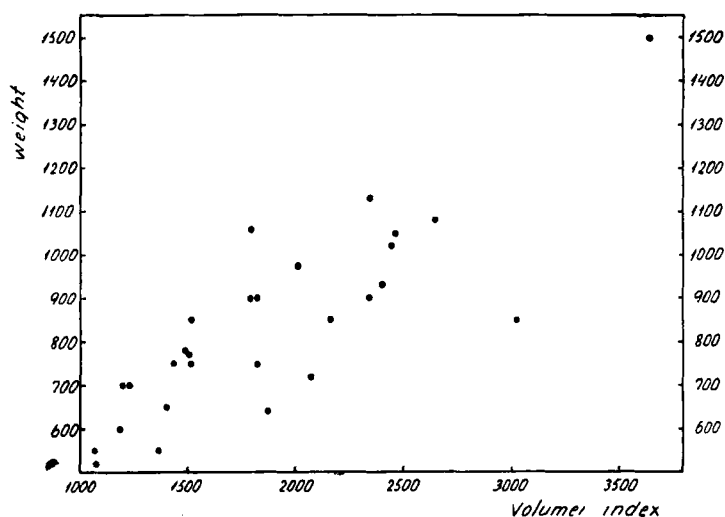


Fig. 4. Relation between liver weight and "volume index" in 28 cases of subchronic atrophy of the liver.

The size of the liver: In all autopsies the measurements of the liver are given in the three planes. We multiplied these three figures and on that basis formed an estimate of the liver's volume, knowing full well that this measurement can be at most a very approximate figure for the cubic content (hereinafter called the "volume index"). In Fig. 4 can be seen the relation between the weight of the liver and the volume index for the 28 patients mentioned above; a fair correlation can be noticed, and for that reason we felt ourselves at liberty later to use the volume index as measurement for the size of the liver.

In Fig. 5 can be seen the distribution according to the volume index for 104 cases of subchronic atrophy of the liver and 73 cases of Laennec's cirrhosis. Subchronic atrophy of the liver entails as a whole a considerably greater reduction of the liver than cirrhosis hepatis Laennec; 48 % of the cases of subchronic atrophy

of the liver have a volume index below 2000, while only 25 % of cirrhosis hepatitis Laennec have a volume index below the same amount.

Carcinoma hepatis: 5 cases of primary liver carcinoma were found (6.6 %) and 4 of hepatomata among the cases of Laennec's cirrhosis, while neither were found among 108 cases of subchronic atrophy of the liver. *Berk and Lieber* (3) found that 4.5 % of cases of liver cirrhosis had primary carcinoma, while $\frac{2}{3}$ of the cases with primary liver carcinoma were combined with liver cirrhosis.

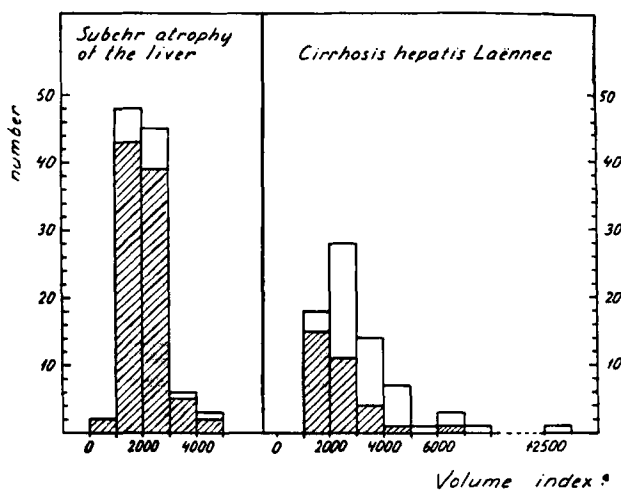


Fig. 5. "Liver volume index" for 104 cases of subchronic atrophy of the liver and 73 cases of cirrhosis hepatitis Laennec. Cases dying of hepatic coma are indicated //

Cholelithiasis: Among the cases of Laennec's cirrhosis there were 21 patients (28 %) having stone of the gall bladder (2 of these had undergone cholecystectomy directly before death), while 20 of the patients with subchronic yellow atrophy of the liver had gallstones (18.5 %). In all instances in subchronic atrophy of the liver it is a matter of small pigment stones, formed presumably during the course of the disease (41). It must be added that the cases taken beforehand to be biliary cirrhosis were not included in the material. The figures are scarcely higher than could be expected according to the age range and sex distribution of the types of material (38, 16, 46).

In both materials a few patients had a perihepatitis fibrillaris seq. as well.

Microscopic Anatomy.

Liver biopsy had been carried out according to the method of *Iversen and Roholm* (20) in 8 of the 108 cases of subchronic atrophy of the liver. Liver biopsy had been undertaken after 1, $1\frac{1}{4}$, $1\frac{1}{2}$, $1\frac{3}{4}$, 2, 3, 6 and 14 months' jaundice. The findings were the same in all instances and can be characterised as a violent

hepatitis (see plate II). The trabecular plan was indistinct. A number of the parenchyma cells appeared as strikingly large cells with large nuclei. An intense infiltration of inflammatory cells was found in the periportal spaces as well as interstitially in the parenchyma. The connective tissue in the periportal spaces was considerably increased in quantity. Bile pigment was found mainly intracellularly in the form of fine granules, but also various accumulations of bile pigment were found in the form of elongated globules. There was nothing in the microscopic appearance which distinguished subchronic atrophy of the liver fundamentally from severe acute hepatitis, but in no instance of benign hepatitis have we found such great changes (especially intralobular cell infiltration) at such a late stage after the inception of disease (see plate II).

Icterus.

By far the most patients with subchronic atrophy of the liver die with jaundice (94 patients out of 105 (90 %)), *while only 11 patients died without icterus and had never had icterus at any stage of the liver disease.* Compared with this, only 30 out of 74 patients with Laennec's cirrhosis had icterus at the time of death (41 %). This coincides with the fact that loss of liver function dominates the pathological picture to a greater extent in subchronic atrophy of the liver than in Laennec's cirrhosis.

As regards the degree of icterus, there was also a difference, since one half of 94 patients having icterus together with subchronic atrophy of the liver had an icterus index (Meulengracht) above 40, while only one third of 30 patients with Laennec's cirrhosis had an index above 40 (the index being reckoned at the time of death).

Ascites.

Ascites was found at the autopsies of 80 patients (74.1 %) with subchronic atrophy of the liver, while only 40 patients with Laennec's cirrhosis had ascites (54 %). As regards the degree of ascites, the distribution among the patients was as follows: 8 (10 %) had less than 0.5 litres, 48 (60 %) had between 0.5 and 2 litres, and 24 (30 %) had over 2 litres. The distribution was the same in Laennec's cirrhosis.

It will be apparent from Table 1 how often patients with subchronic atrophy of the liver and Laennec's cirrhosis, *complicated with ascites*, had at the time of autopsy: oesophageal varices, splenic enlargement, hydrothorax, oedema of the legs and of the lumbar region.

The cause of ascites in portal cirrhosis is generally considered to be partly portal hypertension, partly low colloid osmotic pressure. This hypothesis was first presented by *Iversen* (19). In an earlier work, *Bjørneboe, Brun and Raaschou* (9) investigated the colloid osmotic pressure in subchronic atrophy of the liver to decide upon the pathogenesis of ascites in this disease. They found that

TABLE I

Subchronic atrophy of the liver and Laennec's cirrhosis with ascites. The frequency of simultaneous oesophageal varices, splenic enlargement, hydrothorax, oedema of the legs and lumbar region compared in the two diseases.

	Subchronic atrophy of the liver	Cirrhosis hepatis Laennec
Oesophageal varices	40 (50 %)	29 (72.5 %)
Splenic enlargement	44 (55 %)	22 (55 %)
Hydrothorax	39 (48.7 %)	17 (42.5 %)
Oedema of the legs	48 (60 %)	25 (62.5 %)
Lumbar oedema	37 (46.2 %)	?

all patients with ascites and oedema had a colloid osmotic pressure below 220-240 mm. water, while the cases *without* ascites-oedema had a higher colloid osmotic pressure. Since also ascites occurs usually at the same time as oedema of the legs, and since ascites might again completely disappear, it was concluded that low colloid osmotic pressure must be the most essential factor in pathogenesis of ascites. It is still considered that low colloid osmotic pressure is the most essential cause of ascites occurring in subchronic hepatitis. Now, however, post-mortem findings show that oesophageal varices also appear in subchronic atrophy of the liver with ascites (50 %)—a certain degree of portal hypertension must therefore have existed in this disease. A closer analysis of the figures shows that the oesophageal varices are more frequent in Laennec's cirrhosis, just as their degree of development is greater (see below) in this disease. Thus there can be no doubt at all that *portal hypertension is more developed in cirrhosis hepatis Laennec than in subchronic atrophy of the liver.*

Splenic Enlargement.

Splenomegaly in the chronic diseases of the liver is considered in general to be caused by portal hypertension; *McNee* (29) considers, however, that the enlargement can arise on a toxic basis. But also the possibility must be taken into consideration that splenomegaly may be due to immunisation processes. Subchronic atrophy of the liver is presumably a virus infection, and splenomegaly in infectious diseases and experimental immunisation is a well-known phenomenon (17, 36, 11.).

In our post-mortem material of cases of subchronic atrophy of the liver 54 (50 %) had splenic enlargement, while it was not apparent in 54 patients. In the cases of Laennec's cirrhosis 56 % had splenic enlargement.

With regard to the degree of splenic enlargement in autopsies of subchronic atrophy of the liver, 33 patients had a slight degree of splenic enlargement ($> 12 \times 8 \times 4$ cm.), 20 had moderate splenic enlargement ($> 15 \times 10 \times 6$ cm.) and only one patient had a large splenic enlargement ($> 20 \times 12 \times 8$ cm.). The



Plate I
Subchronic atrophy of the liver. Woman, 71 years old. Duration of symptoms 5 weeks. Cut surface of the liver.

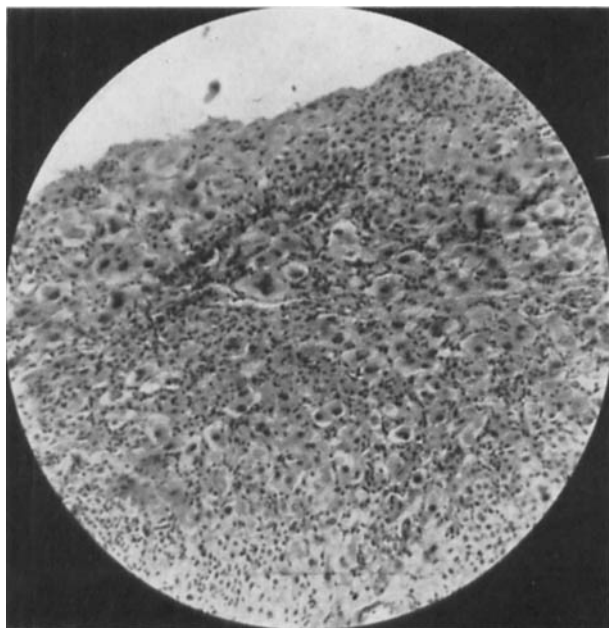
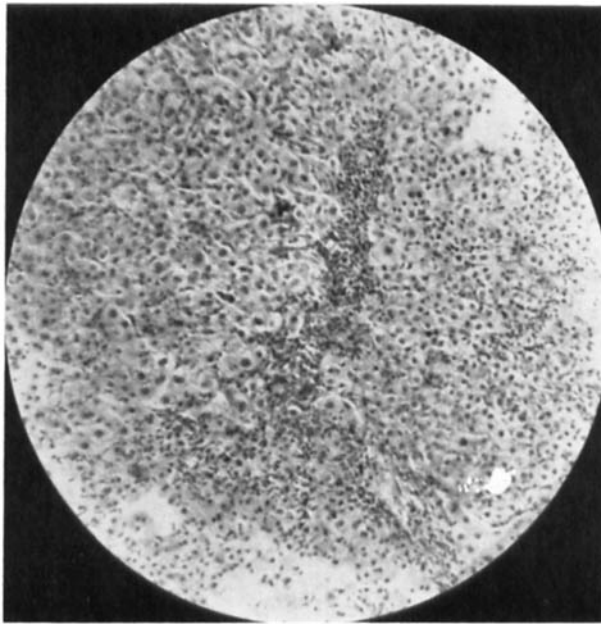
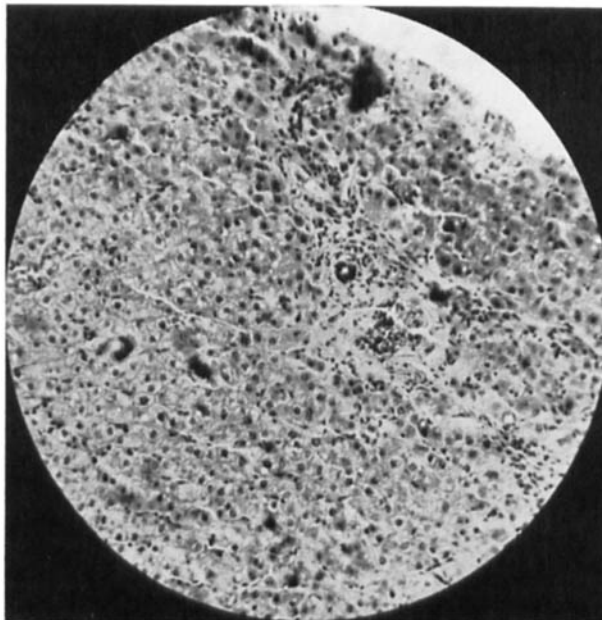


Plate II
A: Liver biopsy in a case of subchronic atrophy of the liver, taken after 2 months duration of symptoms. Woman, 56 years old. Duration of disease unto death $4\frac{1}{2}$ months.



B: Liver biopsy in case of subchronic atrophy of the liver, taken after $1\frac{3}{4}$ months duration of symptoms. Woman, 45 years old. Duration of disease unto death 14 months.



C: Liver biopsy in a case of acute hepatitis, taken after 2 months duration of symptoms. Man, 36 years old. Follow-up examination 1 month later: no symptoms or signs of liver disease.

distribution was the same in the cases of Laennec's cirrhosis, which in itself is very remarkable, since it must be presumed from above that portal hypertension is more developed in Laennec's cirrhosis.

32 of the 54 patients with splenic enlargement (51.8 %) did not have oesophageal varices. This figure permits the assumption that there really are other causes of splenic enlargement to be found apart from portal hypertension. Splenic enlargement without oesophageal varices appears only in 24 % of cases of Laennec's cirrhosis; on the assumption that there are only the three above-mentioned causes of splenomegaly, it is perhaps possible to deduce therefrom that splenic enlargement arising on a toxic or immunological basis plays a smaller part in Laennec's cirrhosis than in subchronic atrophy of the liver.

Nearly all patients with subchronic atrophy of the liver and splenic enlargement had at the same time ascites (44 patients (81.5 %)), while only 23 out of 41 patients with Laennec's cirrhosis (56 %) had ascites at the same time as splenic enlargement.

Oesophageal Varices.

Oesophageal varices were found in 48 patients (44.4 %) with subchronic atrophy of the liver and in 42 patients (58 %) with Laennec's cirrhosis. Only one patient with subchronic atrophy of the liver died after rupture of the varix with haematemesis (0.9 %), while 5 cases of Laennec's cirrhosis (6.6 %) died after rupture. This difference, too, indicates the greater degree of portal hypertension in patients with cirrhosis hepatis Laennec. This is also seen from the figures giving the degree of severity of oesophageal varices for the two illnesses in Table II.

TABLE II

*Subchronic atrophy of the liver and Laennec's cirrhosis with oesophageal varices.
The degree of oesophageal varices compared in the two diseases.*

	Subchronic atrophy of the liver	Laennec's cirrhosis
(+)	1 (2.1 %))	1 (2 %))
+	26 (54.2 %))	16 (38 %))
++	18 (37.5 %))	15 (36 %))
+++	3 (6.2 %))	10 (24 %))

Hydrothorax.

The occurrence of hydrothorax in liver diseases must be an argument for the existence and importance of low colloid osmotic pressure, if heart, kidney and lung diseases can be excluded.

In subchronic atrophy of the liver 42 patients had hydrothorax (38.9 %), in Laennec's cirrhosis 24 patients (32 %).

Of the 42 patients with subchronic atrophy of the liver, 13 had unilateral and 29 bilateral hydrothorax.

20 patients had under 0.5 litres, 21 between 0.5 and 1 litre, and one patient had over 1.0 litre. In Laennec's cirrhosis only $\frac{1}{5}$ had more than 0.5 litres.

Thus as regards the degree of hydrothorax, a considerable difference is to be found between the two liver diseases.

A pronounced correlation exists between the occurrence of hydrothorax and ascites-oedema, which points to the fact that low colloid osmotic pressure is a cause of ascites and oedema. Of 42 patients with subchronic atrophy of the liver and hydrothorax, 40 (95.3 %) had ascites at the same time; the great majority of them had oedema of the legs (69 %).

Oedema of the Legs and Lumbar Region.

Information about the occurrence of oedema of the legs in subchronic atrophy of the liver was given in 98 instances. With 52 patients (53.1 %) oedema of the legs was found during hospitalisation; 92.4 % of them had ascites and 55.8 % hydrothorax. Lumbar oedema occurred in 29 patients (41.9 %)—(out of 93 in whom the symptoms were known to exist). Of these, 94.5 % had ascites and 52.8 % hydrothorax. Similar figures were found for patients with Laennec's cirrhosis. These figures indicate a close connection between ascites and oedema.

Diathesis Haemorrhagica.

Indication of tendency to hemorrhages in subchronic atrophy of the liver was found at autopsy in 70 patients (64.8 %). Localisation occurred in the following organs (in order of descending frequency): pleura (43), pericardium (32), endometrium (25), intestine (17), skin (13), endocardium (8), nose (4), ovarium (1), meninges (1), bile duct (1).

In Laennec's cirrhosis 12 patients (16 %) had haemorrhagic tendency; thus there exists a distinct difference in this particular.

Since the prothrombin concentration was decreased in all patients with subchronic atrophy of the liver and haemorrhagic tendency, it is reasonable to assume that the haemorrhages are due to the decreased prothrombin production in the liver, another symptom in the condition mentioned above, that liver insufficiency is far more pronounced in subchronic atrophy of the liver than in cirrhosis hepatis Laennec.

Among other causes of haemorrhagic tendency in liver diseases thrombopenia (23) must be mentioned, and in so far as uterine haemorrhages especially are concerned, proliferation haemorrhage on the basis of the increased appearance of oestrogen hormone in the blood in liver cirrhosis (5).

The Gastro-intestinal Tract.

Gastric ulcer occurred in 11 cases of subchronic atrophy of the liver (10.2 %). As a rule, completely fresh ulcers or erosive gastritis were concerned, and in no case a chronic gastric ulcer. There is therefore little doubt that these gastric ulcers arise as a result of the disease of the liver. This connection has been suggested before, inter alia by *Schnitker and Hass* (39) in Laennec's cirrhosis, 19 % of 72 patients being found with gastric ulcer.

Of the whole material of hepatitis, 9 patients died of haematemesis and melæna; only one of these had rupture of oesophageal varices, while bleeding from the stomach in the others was due to gastric ulcer. In two cases the source of haemorrhage could not be established at autopsy.

In Laennec's cirrhosis only 2 cases of gastric ulcer with haematemesis (2.6 %) were found, and 2 cases of cancer of the stomach.

Lucké (24) mentions that he found phlegmonous enteritis in the ileocaecal part of the intestinal tract in 15 % cases of acute yellow atrophy of the liver. There was no case with this complication in our material.

Cerebrum.)*

The brain was examined microscopically in 8 cases of subchronic atrophy of the liver. In all patients oedema of the brain was found, in 2 cases degeneration of the ganglia cells. *Lucké* (24) found oedema of the brain in acute yellow atrophy of the liver, and perivascular and meningeal lymphocytic infiltrations in 15 %. *Decourt, Bertrand, Guilaumain and Grüner* (13) are similarly of the opinion that oedema of the brain and degeneration of the ganglia cells play an important part in hepatic coma in acute yellow atrophy of the liver.

These changes must be assumed to be patho anatomically the underlying factor for the neurological symptoms in the clinical picture. In our material this has been characterised by semiconsciousness to a varying degree over a period of several days, while no excitation nor convulsions were noted.

Bone Marrow.

Material was previously published by one of us on sternal punctures in 15 cases of chronic hepatitis (7)**) (of which some are included in this material, dealing with subchronic atrophy of the liver). The result can be seen in Table III.

The concentration of serum-globulin was determined by the method of *Henriques and Klausen* (18). The normal limits are found to be at 1.7-3.1 % by this method (4). *Gormsen* (15) indicates that by far the most normal have under 1 % plasma cells in the sternal marrow, but that amounts right up to 3 % can be seen

*) Microscopic examinations of the brain were made by Dr. med. Erna Christensen, to whom our thanks are due for permission to publish them.

**) Examinations of the sternal marrow were undertaken by Dr. med. H. Gormsen, whom we thank for permission to publish them.

TABLE III

*Examination of the occurrence of plasma cells in the sternal marrow of
15 patients with chronic hepatitis.*

*A comparison between the concentration of plasma cells and concentration
of serum-globulin.*

Plasma cells (percentage of nucleated cells in the sternal marrow	4.5	4	4	3	3	3	2	2	2	2	2	2	2	1	1
Serum-globulin (percentage)	5.5	6.1	3.8	5.3	5.1	5.1	2.9	4.3	4.5	5.5	3.2	3.5	4.1	2.8	2

in the normal. It can be deduced from the table that there is a tendency towards the increase of plasma cells in the sternal marrow among these patients, and that the concentration of serum-globulin shows a tendency to become greater with the increasing quantity of plasma cells in the sternal marrow. This discovery was compared with the hypothesis put forward by *Bjørneboe and Gormsen* (11) concerning the plasma cells as place of production for the globulin of antibodies. The opinion was formed that the investigations supported the view put forward previously (40), namely that the increase of serum-globulin in hepatitis is connected with the formation of antibodies. Material on the basis of 24 sternal punctures undertaken in patients with chronic hepatitis from the same epidemic (31) showed in a number of cases moderate hyperplasia of the marrow; also slight increase of plasma cells together with a more or less pronounced erythroblastosis.

3. Clinical Survey.

Clinical Aspect of Subchronic Atrophy of the Liver.

The duration of disease was known in the case of 98 patients (90.7 %) out of all the material. Far more of these patients can as a rule give an account of the duration of disease than patients with Laennec's cirrhosis. On the average the duration was 8.2 months (1-32 months) (Fig. 6). In 48 patients (49 %) it was under 5 months, in 21 patients (19.5 %) it was over 1 year.

The disease begins with a pre-icteric phase with anorexia, nausea, vomiting, lassitude and sometimes arthralgiae. *Jersild* (21, 22) has shown that the pre-icteric phase is as a rule longer than in acute hepatitis.

The patients then become *icteric*. The icteric phase is characterised in this disease by high icterus index and long duration. Often icterus disappears to recur later one or more times (in 55 patients there was 1 relapse of icterus, in 23: 2 relapses, in 9: 3, and in 5 > 3 relapses. As a rule the patients die icteric, while only 10 patients (10 %) had no icterus at autopsy. These patients had never had icterus at any time during the course of the disease.

Ascites is a very frequent complication and appears very late in the disease. With the presence of ascites the prognosis as a whole must be described as very poor, even if a few patients can improve nevertheless (6).

The duration of ascites was known in 49 patients with subchronic atrophy of

the liver (61.3 %); of these the duration was: 26 < 1 month, 13 < 2 months, 5 < 3 months and 5 > 3 months.

A relatively large number of patients with subchronic atrophy of the liver had at one time or another *pains* in the epigastrium or in the right upper quadrant. Out of 80 patients in which information about this symptom was available, pains were present in 36 (45 %). The existence of pains was not related to the occurrence of perihepatitis fibrillaris seq. at autopsy.

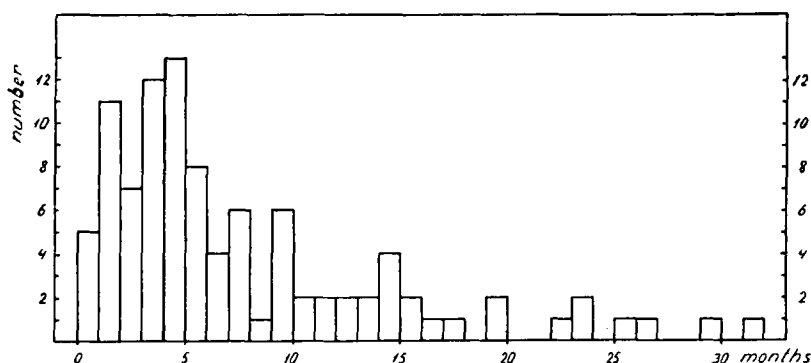


Fig. 6. Duration of symptoms in subchronic atrophy of the liver.

The clinical picture is moreover characterised by anorexia and lassitude. Oedema of the legs and the lumbar region frequently occur together with ascites. Sooner or later signs of haemorrhagic tendency arise, and finally semi-consciousness developing into coma.

Laboratory tests have shown that as a rule in this disease there is to be found a positive Takata-Ara reaction (8, 21, 22, 1), positive thymol turbidity test (25), low serum-albumin and high serum-globulin (6, 9), together with decreased prothrombin concentration in the blood unaffected by injection of preparations of vitamin K soluble in water (8). Furthermore in a number of cases an increase of iron in the blood serum (8), decreased colloid osmotic pressure in the blood when ascites is present (9), moderate anaemia often with increase in the diameter of erythrocytes and tendency to leucopenia (31).

Causes of death. Nearly all patients with subchronic atrophy of the liver died of loss of liver function with hepatic coma. 9 patients died—as already mentioned—of haematemesis and melaena, 15 with pneumonia as complication and 6 of other causes (hemiplegia, barbiturate poisoning, acute pancreatic necrosis, and complications following cholecystectomy and gastric resection).

We have attempted to relate the frequency of hepatic coma in subchronic atrophy of the liver and Laennec's cirrhosis with the "volume index of the liver" which was calculated as indicated above. It is apparent from Fig. 5 that the "volume index" for subchronic atrophy of the liver always lies, as it were, below

"3000", while only 63 % of cirrhosis hepatitis Laennec have a "liver volume index" below "3000". Hepatic coma appears, as already mentioned, as a cause of death for practically all patients with subchronic atrophy of the liver, while at most 43 % of patients with Laennec's cirrhosis died of hepatic coma. It can be seen from Fig. 5 that these cases occur mainly in the patients having the lowest "liver volume index".

According to this it is presumably legitimate to relate the occurrence of small liver volume and hepatic coma with each other, which appears moreover to be fairly obvious.

No relation is to be found between the duration of symptoms and the "liver volume index" in subchronic atrophy of the liver.

Clinical Aspect of Laennec's Cirrhosis.

Evidence of previous syphilis was found in 16 % of the patients. The corresponding figure for the material dealing with subchronic atrophy of the liver was 2.8 %. Alcoholism was found in 8 %. None of the patients with subchronic atrophy of the liver were alcohol addicts. Former icterus (i. e. at least a year before the first symptom of liver cirrhosis) was found in 6 cases (8 %), while none of the material for subchronic atrophy of the liver had had icterus previously. This figure must certainly be taken as a minimum, since the case-records are often incomplete on these points. An indication can be seen, however, of the well-known fact that syphilis and alcoholism are found relatively often among patients with cirrhosis of the liver. On this point subchronic atrophy of the liver seems to differ from Laennec's cirrhosis.

The duration of symptoms was only evident in 44 (58 %) of the patients with Laennec's cirrhosis (as against 90.7 % with subchronic atrophy of the liver), and the information offered is in many cases uncertain. This circumstance that it is difficult to determine the time of onset of the disease is characteristic of Laennec's cirrhosis, in contrast to subchronic atrophy of the liver. In 23 (30 %) the duration of symptoms was under 5 months, in 7 (9.2 %) it was over 12 months. Thus no striking difference in the duration of symptoms was discovered, even though among the patients with Laennec's cirrhosis there were relatively more in the group with a duration of symptoms of 5-12 months. There was information about the first symptom in 44 (58 %) of the cases. In order of descending frequency the first symptoms were as follows: icterus, ascites, lassitude, dyspepsia, oedema, pains in the region of the liver, diarrhoea, haematemesis. 10 of the cases (9 women and 1 man) occupied an exceptional position in regard to symptoms, since the course of their illness corresponded completely to a subchronic atrophy of the liver. If these patients are not included in the material, a different order is obtained in the symptoms mentioned, namely as follows: ascites, oedema,

lassitude, dyspepsia, icterus, pains, diarrhoea, haematemesis, hence an order in regard to frequency which corresponds more closely with what is generally indicated in the literature on the subject.*)

The 10 cases of Laennec's cirrhosis already mentioned, which clinically presented the appearance of subchronic atrophy of the liver, had a duration of symptoms which did not differ fundamentally from the duration of symptoms for subchronic atrophy of the liver ($5 < 5$ months— $3 > 12$ months). Thus we were not able in our material to find a basis for the assumption previously advanced (14) that *specially prolonged* cases of subchronic atrophy of the liver should present the appearance of Laennec's cirrhosis patho-anatomically.

As mentioned above, 40 (54 %) of the patients had ascites when autopsy was made. The duration was determined only in 21 cases. Of these, 7 had < 1 month, $6 < 2$ months, $4 < 3$ months, and $4 > 3$ months. On this point there is no difference in the two types of material. Also, in Laennec's cirrhosis the occurrence of ascites is a very bad sign for prognosis. This is a well known phenomenon.

In 20 cases there was evidence of pains in the epigastrium or in the right upper quadrant, that is scarcely half of the cases in which the symptom was known. In this there is no difference in the two materials.

Causes of death. Of the patients with Laennec's cirrhosis, at most 33 (43 %) died of hepatic coma, as previously mentioned. It has already been stated that this is a considerably lower frequency than for subchronic atrophy of the liver. In 9 of these cases the coma diagnosis was uncertain. In 8 of these patients there was found at the same time an infection, and the 9th died in connection with a cholecystectomy.

The other causes of death were: Bleeding oesophageal varices (5), bleeding from gastric ulcer (2), primary cancer of the liver (5), portal thrombosis (2), cardiac insufficiency (8), cancer with different localisations (6), resection for cancer of the stomach (2), pneumonia (4), different causes (9). The last group consisted of the following causes: nephritis with uraemia, tumour of the spinal cord, cholecystectomy complicated with peritonitis, fracture of the femur, fracture of the skull, cerebral hemorrhage, pulmonary embolism (1 of each), hypertrophy of the prostate with pyelonephritis (2 cases).

Heart diseases in the material will be dealt with more closely. As already indicated, 8 died of cardiac insufficiency. The frequency of pathological conditions of the heart was, however, much greater. If the milder variations are dis-

*) The distribution according to sex shows as in other materials for Laennec's cirrhosis a preponderance of men. It is not especially marked, however. As has already been mentioned, 10 of the cases occupied a special position in having a course of symptoms as in subchronic atrophy of the liver. If these patients are not included in the material, a sex distribution of 24 women and 42 men is obtained, more closely related to the sex distribution of other materials, and to material from previous years from the Kommunehospital (see Fig. 3).

regarded (as a slight degree of coronary arteriosclerosis, cardiac hypertrophy, sequels to endocarditis), the following figures are obtained:

TABLE IV

Patho-anatomical changes in the heart in Laennec's cirrhosis.

Cardiac hypertrophy	19 cases
Coronary arteriosclerosis	25 —
Coronary artery occlusion	2 —
Mitral stenosis	2 —
Aortic stenosis	1 —
Pericardial adherency	4 —
Acute pericarditis	4 —
Subacute endocarditis	1 —
Syphilitic aortitis	3 —
Myocardial fibrosis	1 —

In all, 46 were found to have these variations out of the 76 patients (61 %) with Laennec's cirrhosis. This is considerably more frequent than in the material for subchronic atrophy of the liver, in which the following variations were found for the heart:

TABLE V

Patho-anatomical changes in the heart in subchronic atrophy of the liver.

Cardiac hypertrophy	2 cases
Coronary arteriosclerosis	25 —
Coronary artery occlusion	1 —
Sequels to mitral endocarditis	1 —
Pericardial adherency	1 —
Myocardial fibrosis	2 —

These variations were found among 30 patients in all (28 %). The most striking difference in the two materials on this point is the difference in occurrence of cardiac hypertrophy, which is connected with the fact established by *Raaschou* (35), that there are strikingly few patients with arterial hypertension among the patients with subchronic atrophy of the liver. In the material for Laennec's cirrhosis $\frac{1}{3}$ had arterial hypertension (> 150 mm. Hg systolic pressure), a figure which corresponds with what is normally found in post-mortem material within these age ranges (35).

On the whole the impression is gained that the causes of death in the Laennec's cirrhosis material are distributed as might have been expected among people in this age group. Also, the impression is given that only in a minority (especially those with the smallest livers) was liver disease a direct cause of death through hepatic coma, rupture of oesophageal varices and portal thrombosis. Corresponding to this, the diagnosis in subchronic atrophy of the liver is nearly always made during the life, while only 23 cases (29 %) Laennec's cirrhosis was suspected before autopsy.

4. *Comparison Between Subchronic Atrophy of the Liver and Laennec's Cirrhosis.*

In conclusion we will now sum up quite briefly what differences there are, apart from the appearance of the liver, between the pathology and clinical aspect of subchronic atrophy of the liver and Laennec's cirrhosis.

a) Nearly all patients with subchronic atrophy of the liver are women, while there is a preponderance of men as far as Laennec's cirrhosis is concerned.

b) The impression is obtained that portal hypertension is more pronounced in Laennec's cirrhosis than in subchronic atrophy of the liver, since the oesophageal varices are more frequent and more pronounced in Laennec's cirrhosis, in the same way as the frequency of rupture of the varices is greater in this disease.

c) Furthermore it is our opinion that the low colloid osmotic pressure dominates the clinical picture more in subchronic atrophy of the liver than in Laennec's cirrhosis, since the frequency of ascites and the degree of hydrothorax found at autopsy are greater in subchronic atrophy of the liver than in Laennec's cirrhosis.

d) Pronounced damage of liver function is more frequent in subchronic atrophy of the liver; that is seen from the fact that haemorrhagic tendency and death from hepatic coma is far more frequent in this disease than in Laennec's cirrhosis.

The size of the liver expressed in its "volume index" is on the average smaller in subchronic atrophy of the liver than in Laennec's cirrhosis, which presumably is the cause of the greater frequency of hepatic coma. The frequency of hepatic coma is greater in Laennec's cirrhosis with low "volume index" than with high "volume index", which also supports this assumption.

e) In addition the following are allied with these differences:

1) A greater frequency of syphilis, alcoholism and previous jaundice (i. e. more than a year before the first symptom) in patients with Laennec's cirrhosis.

2) Greater frequency of gallstones, heart disease (especially cardiac hypertrophy) in patients with Laennec's cirrhosis. Primary carcinoma of the liver and hepatomata do not occur at all in subchronic atrophy of the liver, in contrast to the situation in Laennec's cirrhosis.

3) In the great majority of cases with subchronic atrophy of the liver, evidence as to duration of symptoms can be obtained from patients, while this happens far more seldom in Laennec's cirrhosis.

4) $\frac{3}{4}$ of the cases of Laennec's cirrhosis were not diagnosed during life, but since 90 % of patients with subchronic atrophy of the liver have jaundice, this disease can usually be recognised as a liver disease clinically.

5) The frequency and degree of enlargement of the spleen are identical in both subchronic atrophy of the liver and in cirrhosis hepatis Laennec. On the other hand, there are more cases of enlargement of the spleen *without* oesophageal varices in subchronic atrophy of the liver.

To sum up, we can state that subchronic atrophy of the liver leads to a greater degree of reduction of the liver parenchyma than cirrhosis hepatitis Laennec. From the clinical point of view, a greater frequency of symptoms of loss of liver function and a greater frequency of deaths by hepatic coma agree with this.

5. Summary.

The cases of subchronic atrophy of the liver described in literature up to the present time have been chiefly isolated cases appearing in materials of acute yellow atrophy of the liver.

This work is based upon autopsy material consisting of 108 cases of subchronic atrophy of the liver and 76 cases of cirrhosis hepatitis Laennec.

Subchronic atrophy of the liver. The material consists of 108 patients: 6 men and 102 women on whom autopsy was undertaken 1/1 1944-1/1 1948. Practically all the patients died after their 40th year.

Cirrhosis hepatitis Laennec. The material of 76 cases from the same period: 43 men and 33 women. The age range corresponded to that of subchronic atrophy of the liver.

An examination of the collected post-mortem material from the Kommune-hospital (1928-1947 incl.) shows that the number of cases of Laennec's cirrhosis has been more or less constant, while those of subchronic atrophy of the liver appeared only sporadically before 1944.

The macroscopic and microscopic pathological anatomy of the disease is described according to the literature.

The microscopic anatomy of the liver examined on liver biopsies corresponded to an acute hepatitis of severe degree.

The *weight of the liver* in most cases is found to be reduced to below half of the normal weight of the liver.

A fairly exact correlation is found between the weight of the liver and the "*liver volume index*" (determined by multiplication of the liver's three dimensions).

The liver volume index for subchronic atrophy of the liver shows a smaller variation than for cirrhosis hepatitis Laennec, and the reduction of the liver parenchyma is generally more pronounced in subchronic atrophy of the liver.

Icterus appeared in 90 % of the patients with subchronic atrophy of the liver at the time of death, while 10 % died without icterus and without having had icterus at any stage of the disease. Only 41 % of the cases of Laennec's cirrhosis had icterus at death.

Ascites occurred in 74.1 % with subchronic atrophy of the liver and in 54 % of the cases with Laennec's cirrhosis. No difference in the degree of ascites was found between the two diseases.

The pathogenesis of ascites is discussed, and it is emphasised that the reduced colloid osmotic pressure is regarded as the dominant factor in subchronic atrophy of the liver. The occurrence of mild oesophageal varices in half the cases, however, indicates that in this disease too a slight portal hypertension can be found.

Enlargement of the spleen was a symptom which appeared equally frequently in both diseases (in about half the cases), just as the degree of enlargement of the spleen was identical. Enlargement of the spleen without oesophageal varices was somewhat more frequent in subchronic atrophy of the liver, which is expressive of the fact that enlargement of the spleen arising on a toxic or immunological basis might possibly play a greater part in this disease.

Oesophageal varices were found in 44.4 % of patients with subchronic atrophy of the liver and in 58 % of patients with cirrhosis hepatis Laennec, in which disease they were more pronounced. This, together with the more frequent occurrence of rupture of varices in cases of cirrhosis hepatis Laennec, indicates that the portal hypertension is more pronounced in cirrhosis hepatis Laennec.

Hydrothorax is almost equally frequent at the time of death in the two diseases (38.9 % in subchronic atrophy of the liver and 32 % in Laennec's cirrhosis). Greater degrees of pleural effusion were found in subchronic atrophy of the liver than in Laennec's cirrhosis. In subchronic atrophy of the liver there is to be found a pronounced correlation between the occurrence of hydrothorax and ascites-oedema, which supports the assumption that low colloid osmotic pressure is a cause of ascites-oedema.

Oedema of the legs was found to be equally frequent at death in both diseases (in a good half of the number of cases).

Hemorrhagic tendency was found far more often in subchronic atrophy of the liver than in Laennec's cirrhosis (64.8 % as against 16 %). This is related to the reduced prothrombin content of the blood and the more frequent occurrence of loss of liver function in subchronic atrophy of the liver.

Gastric ulcer was found in 10.2 % of cases with subchronic atrophy of the liver and in 2.6 % of Laennec's cirrhosis. In many cases the ulcers bled and caused haematemesis and melaena.

In *microscopic examination of the brain* in subchronic atrophy of the liver, cerebral oedema was discovered and in some cases degeneration of the ganglia cells.

When the *sternal marrow* was examined, a slight tendency to increase was found in the plasma cells.

Hepatoma and primary liver carcinoma were not found at all in subchronic atrophy of the liver, while they appeared in some cases of Laennec's cirrhosis.

Stones of the gall bladder appeared more seldom in subchronic atrophy of the liver than in Laennec's cirrhosis.

The clinical aspect of subchronic atrophy of the liver. The duration of the symptoms was on the average 8.2 months, varying from 1 to 32 months. The

course of the disease is moreover characterised by a long pre-icteric period and by an icteric phase which consists of several waves of icterus in succession (in 37 cases there were more than one relapse of icterus in the course of the disease). Ascites occurs late in the disease. In more than half of the cases in which evidence was given of the duration of ascites, there was at most one month between the occurrence of ascites and death. Pains in the epigastric region or in the right upper quadrant were found in barely half the patients. Oedema occurred as a rule at the same time as ascites, sooner or later hemorrhagic tendency appeared and finally semi-consciousness developing into coma. Nearly all the patients forming the material died of hepatic coma (9 died of haematemesis and melaena, 15 with a complicating pneumonia and 6 of other causes). The frequent occurrence of hepatic coma and small "liver volume index" are to be related to each other.

The clinical aspect of Laennec's cirrhosis. Syphilis, alcoholism and former icterus (more than 1 year before the first symptom) were found to be more frequent in anamnesis among patients with Laennec's cirrhosis than with subchronic atrophy of the liver. Evidence as to the duration of the disease was given more seldom by patients with Laennec's cirrhosis than with subchronic atrophy of the liver. In the cases in which such evidence was given, there was no certain difference in the duration of symptoms between the two types of material. The initial symptoms were as follows (in order of descending frequency): icterus, ascites, lassitude, dyspepsia, oedema, pains in the region of the liver, diarrhoea, haematemesis. In Laennec's cirrhosis there was found also a short interval in time from the occurrence of ascites until death. Pains in the region of the liver were found with the same frequency as in the material for subchronic atrophy of the liver, viz. in almost half the cases. The causes of death were in 33 cases (43 %) hepatic coma; in 9 of these cases, however, the coma diagnosis was uncertain. The cases of coma were found mainly among patients with small "liver volume index", which strengthens the assumption that it is the reduction in quantity of liver cells which causes the loss of liver function. The remaining causes were distributed over a series of different diseases characteristic for the age groups included in the material. There is to be found a pronounced difference in the frequency of hypertrophy of the heart in the two materials. In Laennec's cirrhosis hypertrophy of the heart was found in a quarter of the patients, while it was only found in 2 of the 108 patients with subacute atrophy of the liver. This circumstance is due presumably to the fact that arterial hypertension is found remarkably seldom in patients with subacute atrophy of the liver.

To sum up, it can be established that subacute atrophy of the liver leads to a greater degree of reduction of the liver parenchyma than cirrhosis hepatis Laennec. Clinically a greater frequency of symptoms of loss of liver function is in favour of this, and also a greater frequency of deaths from hepatic coma.

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