Department of Pathology, Central Laboratory and Department of Medicine of the Hungarian State Railways Hospital, Budapest
(Director: L. Oó)

THE PATHOGENESIS OF FULMINANT HEPATITIS

I. Sümegi, L. Goreczky and I. Róth

(Received March 9, 1955)

Infectious hepatitis was the only ep demic to have attained almost pandemic proportions among the fighting units during World War II. The number of fulminant cases with a fatal course increased considerably towards the end of the war.

This paper presents 13 cases of the hyperacute form of this disease known in the literature as fulminant hepatitis. Lucké and Mallory, Werthemann and Bodóky, and other authors regard hepatitis as fulminant when the appearance of clinical symptoms is followed by death in about 15 to 20 days.

Of our 13 patients, 9 died within 10 days, and 4 within from 14 to 20 days after the first manifestations of the disease. In the 4 most acute cases death ensued as early as in 2 to 5 days.

Male and female patients were involved in equal proportions; of them 8 were under 50 years, including 2 children (3 months and 3 years, rsepectively), and 5 were more than 50 years old.

The disease invariably began with complaints of dyspepsia associated with slowly progressing jaundice. Later symptoms were on the whole similar to those encountered in yellow atrophy; all case records included more or less marked derangement, restlessness, insomnia, and excitement, which soon passed into drowsiness, depression and gradual coma.

Autopsy showed that the liver of adult patients was mostly smaller than normal, with weights varying between 600 and 1100 g; only in three cases was the liver of normal size. It was flabby, and the colour brownish-yellow or greenisch, depending on the degree of jaundice; the structure was usually well observable. The centre of the lobules was hyperemic and reddish, the margins were a yellowish brown. Many of the examined kidneys were larger than normal; their capsules stripped easily; they were found to be very fragile and of a yellowish brown colour. The cut surface showed a vivid pattern. Apart from incidental diagnoses, the general picture was completed by more or less grave haemorrhages all over the body, either under the mucous membranes or interstitially. Miliary tuberculosis without previous pulmonary lesion was encountered

in one of the cases, while atrophic disintegration was found to be present in the cirrhotic liver in another one.

The most striking feature revealed by histological examination was the rapid and nearly complete destruction of the parenchymal liver cells (Fig. 1). Sections were hardly recognizable. Not infrequently, the lobule was found to have been entirely destroyed, with no observable intact hepatic cell left. Haemorrhages variegated the picture. The proliferation of the biliary ducts was always intensive ; a widespread cellular infiltration was encountered in the periportal connective tissue, and frequently also at the site of the destroyed parenchyma, in which lymphocytes, a few plasma cells, and sometimes a fair number of eosinophils could be observed. The same types of cells could be seen accumulated in the often dilated capillaries. With Azan the cytoplasm of the degenerating hepatic cells stained purplish blue. The argentaffin structure remained on the whole fairly preserved and easily recognisable even in areas where destruction had been less complete and sometimes as much as one third of the lobule had escaped destruction. Necrosis in these areas was most marked in the centre of the lobules, where the cells took no nuclear stain and were devoid of fat. On the other hand, nuclear staining was more or less normal in the marginal cells where also finely or coarsely distributed fat was frequently seen, and regenerating hepatic cells could early be observed.

Following the law of hepatorenal compensation, the kidneys too revealed frequent and grave pathological changes. Faintly staining and finely granular exudate was found to have accumulated between the walls of Bowman's capsule, while the mesoangium and sometimes also the capsule of the glomeruli was thickened or, in some cases, grown together. The epithelial cells of the convoluted tubules were swollen, finely granular, with droplets of fat in most of them. Their nuclei did not take the stain, or only scarcely. In the lumina of the tubules there were frequently hyaline casts which stained red or blue with Azan. The general picture was that of glomerulonephrosis (Fig. 2).

The impulse to go into a detailed study of the cases briefly described in this paper had been given by a 24 year old patient who observed his symptoms clearly and died within 48 hours from the onset of the disease. This patient emphasized that he had no prodromal symptoms, and felt completely well until the sudden outbreak of jaundice and the accompanying great debility and general weakness. He became comatose 24 hours later and notwithstanding all the therapy applied died on the following day. Histological examination revealed complete disintegration of the hepatic parenchyma, while the kidneys were in the initial stage of developing the above-described pathological changes.

The histories of our patients were at once carefully restudied and wherever possible supplemented with information gained from their relatives. In this manner it was discovered that 10 out of the 13 patients had gone through previous illnesses damaging the liver. Four of them had suffered from lues and

had been treated with salvarsan, three having received the last treatment some years, and one 9 months ago. The revised history of three of these patients included also other diseases injurious to the liver, such as jaundice, grave food popisoning with urticaria, or Basedow's disesae with cardiac incompensation.

Table

No.	Name, sex, age, date	Earlier hepatic damage	Duration of present illness; special symptoms	Renal function	Results of post mortem examination
1	F. L. male, 24 years, 4, 7, 1950 (H 619)	2 years ago icterus for 4 weeks	2 days. — Intensive restlessness, delirium, coma, subicterus	Albumin, hyaline and granular casts	Total disintegration of liver. Renal lesion
2	B. B. female, 38 years, 4, 17, 1950 (H 754)	Antiluetic treatments	1 week. — Deranged, restless, coma. Wassermann negative	Albumin, hyaline casts erythrocyt.	Yellow atrophy. Renal lesion
3	F. K. male, 63 years, 12, 12, 1951	Antiluetic treatments 10 years ago. Hepatitis 7 years ago	10 days. — Deranged, restless, coma. Wassermann neg.	Neg.	Acute disintegration in cirrhosis
4	S. S. female, 41 years, 7, 10, 1951 (H 210)	Puerperal ecclampsia	10—12 days. — Deranged, unintelligible words, coma	Traces of albumin	Total disintegration of liver
5	T. J., 3 months, 2, 11, 1951 (H 233)	Purulent otitis	8—10 days. — Restless, later drowsy	Not examined	Total disintegration of liver
6	K. B. female, 28 years, 3, 11, 1951 (H 234)	«Meat poisoning» 1 year ago, urticaria. Wasserm. ++++ No treatment	5 days Febrile. Jaundice in the last 4 days. Restlessness, then coma	Traces of albumin, erythroc., casts	Total disintegration of liver. Renal lesion
7	A. F. 3 years, 10, 3, 1952 (H 72)	Otitis, pneumonias	4 days Restlessness, coma	Traces of albumin. Erythroc. cylinders	Yellow atrophy. Renal lesion
8	E. G. male, 46 years 14, 3, 1952 (H 76)	Basedow's disease, Krogh + 91%. Earlier incomp. Wasserm. +++	17 days Insomnia	Traces of albumin. Erythroc.	Yellow atrophy. Renal lesion

No.	Name, sex age, date	Earlier hepatic damage	Duration of present illness; special symptoms	Renal function	Results of post mortem examination
9	T. L. male, 63 years, 27, 5, 1952 (H 179)	Repeated pneumonia. Pleuritis	6—8 days	Traces of albumin. Erythrocytes	Acute hepatitis Renal lesion
10	M. J. male, 51 years, 6, 11, 1953 (H 389)	Jaundice 20 years and 1½ year ago. Jaundiced for the last 3 days	About 20 days Restless, later depressed; sopor.	Traces of albumin	Yellow atrophy Renal lesion
11	F. J. female, 78 years, 7, 9, 1953 (H 322)	Pneumonia 2 years, jaundice 1½ year ago	About 20 days Does not sleep	Traces of albumin. Erythroc.	Acute hepatitis
12	K. T. male, 59 years, 1, 8, 1953 (H 241)	Operation on the prostata, chronic heart failure	14 days Restlessness, coma	Albumin pos.	Total disintegration of liver. Renal lesion
13	F. V. female, 14, 7, 1954 (H 224)	Abdominal operations. Cardiac incomp.	9 days Intensive restlessness	Traces of albumin	Total disintegration of liver. Renal lesion

One of the other patients had previously ecclampsia with serious hepatic injury before delivery, while three had previously jaundice lasting several weeks. In the history of two further patients there were, besides old abdominal operations, other factors injurious to the liver, such as cardiac insufficiency, and conditions of incompensation. No direct hepatic damage was found in the two children and in one of the adults : their case histories contained only healed pneumonia, otitis and enteritis.

The history of GY. GÁL's infantile patients (from 4 to 14 months) with fulminant hepatitis likewise registered former otitis, pneumonia, and enteritis (personal communication).

In the aetiology of hepatic lesions, inadequate, protein-deficient nutrition must not be disregarded as a possible causative factor (LÜHRS, GRIESHAMMER, KETTLER, LUCKÉ and MALLORY). Hyperthyroidism is also known to damage the liver, especially in Graves' disease or during fast (BLACK—SCHAFFER, HABÁN, SEALY, SIEDE). *Szodoray* stresses the promptly damaging effect on the liver of syphilitic infections, and the present authors confirm having encountered in similar cases an increase in coproporphyrin I, as a symptom characteristic of hepatic lesion (SÜMEGI). Similar reports concerning the effect of syphilis and salvarsan were made by SIEDE, BARSKIJ, FINDLAY and WILLCOX. That pregnancy aggravates the course of hepatitis was observed by GOVAN and MCGILLIWRAY, DOZORETS and BELUSOVA, URANGA—IMEZ, ELLEGAST, and others. Also, various infections are known to have an

adverse effect upon the liver, such as typhoid fever, salmonellosis, brucellosis, malaria, etc. Hepatic injury or development of the hepatorenal syndrome following abdominal operations have been reported recently by DE LOYERS and TOUSSAINT, HARTL, NORDMANN, and RUNYAN. Cases of hepatic lesions due to statis were observed by WALLACH and POPPER, GLYNN and HIMSWORTH, HEUBNER.

On the strength of these reports, it appears justified to state that the above described cases of previous jaundice, ecclampsia of pregnancy, diverse infections, or abdominal operations in the history of our patients afford support for the assumption that the liver may have been injured many years before the present fatal disease. Equally, there is every reason to suppose that the old hepatic lesions had healed, since prior to the present disease none of the patients showed any symptoms which would have pointed to a hepatic damage.

It is therefore reasonable to regard the old hepatic lesions recorded with such a high percentage in the history of our patients, as pathogenic factors in the development of the fulminant hepatitis to which they succumbed (NISSEN).

SPERANSKY et al. found that injuries of the nervous system may have permanent, if not always visible, effects on the organism. It was proved in animal experiments that another lesion, even if it is of a quite different nature and occurs much later, may in a number of cases provoke much graver, sometimes fatal, dystrophic disease. For example, a small surgical intervention around the hypophysis may cause a tetanus, healed half a year before, to reappear and lead to death. The intervention in question has in this case furnished the so-called „Zweitschlag" — the second blow.

BERNARD holds that every focal lesion of the autonomic nervous system manifasting itself on the skin or in the viscera, has its particular central cause, and he regards this fact as a general law of pathology.

The relations between liver and nervous system have long been known. Adynamia, apathy, stupor, ataxia, or psychomotor excitement growing to delirium, and disturbed sleep are described by the authors in connection with acute hepatic insuffiency, and especially fulminant hepatitis (DOZORETS and BELUSHOVA, KOLBER, GAUPP, BODECHTEL). Organic symptoms such as Babinsky's sign, clonus and meningitis were found by LUCKÉ and MALLORY. Encephalitic symptoms were observed by THORLING, and extrapyramidal symptoms by SIEDE. All this goes to show that nervous lesions may manifest themselves in various forms during hepatitis and that although the descriptions of the morphological changes in the nervous system are still rather incomplete, it is quite probable that even the healing symptoms are rooted in anatomical changes.

As the experimentally induced second injury of the nervous system led to a positive result in SPERANSKY's said experiments, and as preceding hepatic injury had occurred in the majority of our cases, studies were undertaken with a view to establish the effect of such prodromal lesions and, in this manner, to approach the gist of the problem.

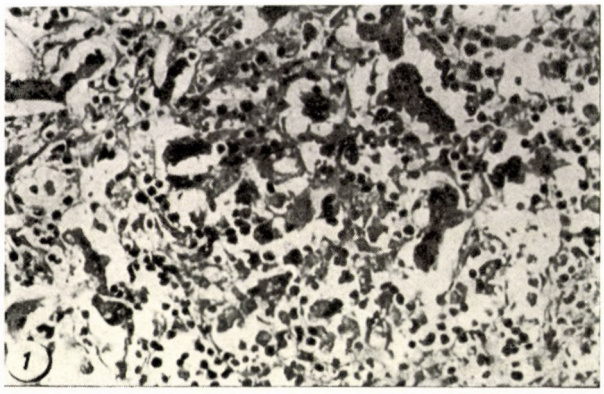
There are reports on occasional attempts of this kind in the literature, although they were usually made with other objects in view. For instance, *Opie* in his classical experiments administered to dogs pretreated with phosphorus and chloroform immediately after sensitisation, E. coli, proteus and streptococcus extracts. The liver of these dogs showed graver lesions than those of the controls ; the livers became exceedingly sensitive to bacterial toxins. BENNET, DRINKER and WARREN increased the effect of chlorinated hydrocarbons by the administration of various hepatic poisons. BLACK—SCHAFFER, JOHNSON and GOBBEL rendered the liver sensitive to chloroform by feeding thyroid and intensified the effect by starvation. HARANGHY could greatly aggravate lesions in the spleen and the reticuloendothelial system of animals by sensitizing them with Dick's toxin first, and treating with diphtheria toxin a few hours later.

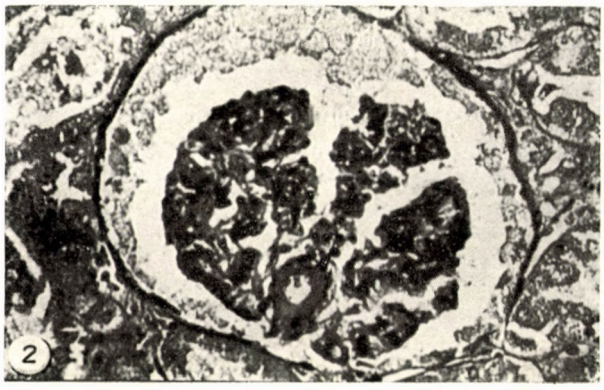
Substances injurious to the liver were administered to rabbits in our experiments. 25 animals were poisoned with phosphorus, phenylhydrazine, or hepatotoxic cat serum prepared with Masugi's method. The members of the first group received each 0,5 ml. of phosphorus oil through a gastric tube, while those of the second group were given 1 ml. of a 10 per cent phenylhydrazine dilution subcutaneously. The treatments were made at intervals of from 5 to 6 days, and each treatment had been preceded by the preparation of a nephelogram made with the blood of the animal according to Weltmann's method. The treatment was discontinued as soon as there was a marked deviation, which usually happened after 2 to 4 treatments. Some of the animals died nevertheless, while the complete recovery of the rest was controlled by nephelometry six weeks later. After a rest of four more weeks the experiments were continued with apparently perfectly healthy animals. Examination of the liver of those animals which had died, showed the well-known symptoms of phosphorus and phenylhydrazine poisoning, which will not be discussed here in detail. The kidneys invariably revealed the signs of glomerulonephrosis. A detailed report on these examinations was submitted to the Congress of the Hungarian Society of Pathologists held in 1952.

To prepare the hepatotoxic serum for the third group, 1 to 5 ml. of an emulsion made from saline-perfused rabbit livers was injected into the abdominal cavity of cats 5 to 6 times, at intervals of four days. A week after the last injection, the animals were bled and the serum was administered intravenously to rabbits every fourth day in doses of 8 to 10 ml. While some of the animals died with or without shock symptoms, the nephelogram of the rest showed a marked deviation after 3 to 5 injections. As soon as this was found to be the case, treatment was discontinued until the normalisation of the nephelogram. After a rest equal in duration to that given to the members of the preceding groups, the further experiments were resumed simultaneously in all three groups.

On examining the liver of the animals prematurely succumbed to the serum, fatty infiltrations were found which began at the centre of the lobule and covered about half of it ; further, a serious lesion which involved a few of the central cells and manifested itself in the lack of nuclear staining, or a nuclear fragmentation, and a granular disintegration of the plasma. The kidneys likewise showed pathological changes, revealed in Azan-stained preparations by the presence of accumulated serous or clotted exudate in many of the glomeruli, by the granular swelling of the epithelial cells in the convoluted tubules, and by the appearance of many blue-staining hyaline casts. The renal lesions were essentially similar to but less marked than those recently described in detail by BASERGA.

Ten of the animals pretreated according to one of the methods described, succumbed to the treatment but the remaining fifteen rabbits healed completely (5 treated with phosphorus, 4 with phenylhydrazine, and 6 with Masugi's method), and their blood recovered normal colloidal properties. After this, there followed a second treatment with another hepatic poison, meant as the „second blow". Seeing that the rabbit liver is very sensitive to chloroform, this drug





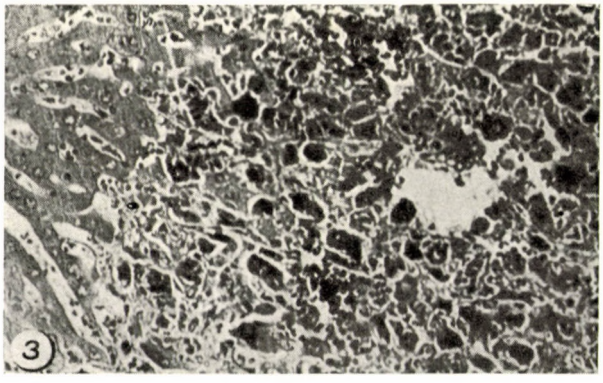


Fig. 1. Liver of case No. 1., under low power. Site of destroyed hepatic cells taken by reticular structure and inflammatory infiltration. Proliferating bile ducts

Fig. 2. Kidney of case No. 1. under high-power. Glomerular capsule thickened : granular exudate between the two walls

Fig. 3. Liver of pretreated rabbit died on 6th day. Centrolobular degeneration of hepatic cells with intact cells at the periphery. Low power magnification

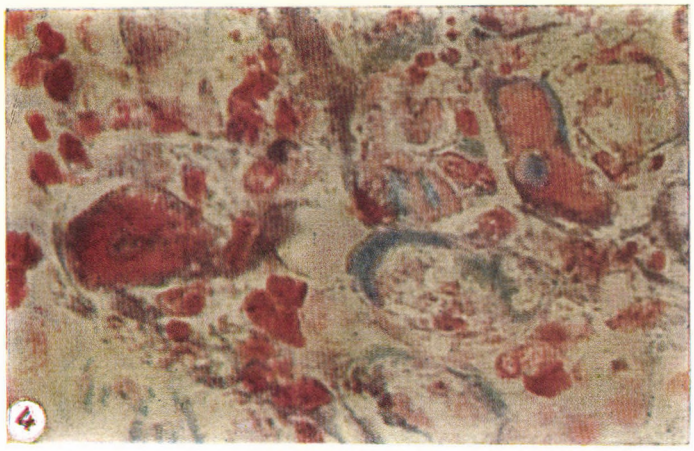


Fig. 4. Liver of pretreated rabbit died on 6th day. Coloured photomicrograph, high-power magnification, Azan stain. The cytoplasm of the destroyed cells stains bluish-violet, red or yellowish-red

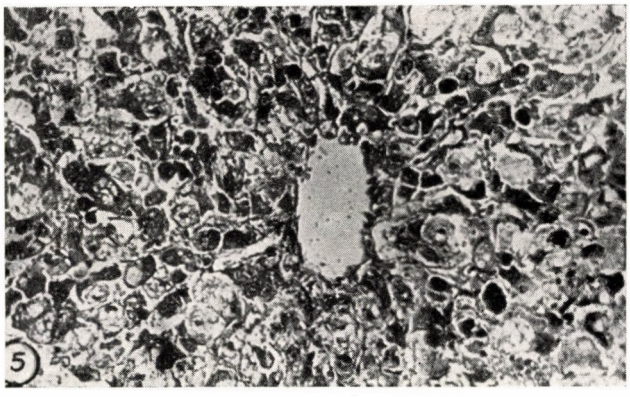


Fig. 5. Liver of pretreated rabbit died on 10th day. Low power magnification. Disintegration extending ower the whole of the lobule

was chosen for the purpose in question. Before using the chloroform, it had been exposed to daylight for 1 to 2 weeks and repeatedly irradiated with quartz light, so as to promote the formation of phosgene. The dose was one twelfth of that known as lethal from WHIPPLE's ZALKA's, and *our* own previous experiments, i. e. 0,1 ml/kg. Simultaneously, 11 controls received the same amount of chloroform without previous treatment.

The following results were obtained.

During the first 48 *hours* 3 animals, 1 pretreated with phosphorus and 2 with hepatotoxic serum, succumbed to the first injection of chloroform. Morphological changes in the liver were found to be slight. In the centre of the lobules around the central vein the cytoplasm of a few hepatic cells stained with eosin more intensively than that of the surrounding cells, and the nuclei in them were found to be pyknotic. Fairly extensive regeneration with many direct mitoses were observed in the intermediate and the marginal zones. The spaces of Disse were empty, and there was hardly any dissociation. The kidneys showed no change at all. No pathological changes could be seen either in the liver or the kidneys of the *controls* which had been sacrificed on the third day.

The situation was entirely different *three days later*, when one more of the animals pretreated with hepatotoxic serum died. Under low power it could be observed that at least three thirds of the lobules were destroyed by a necrotic process that was spreading from the central vein (Fig. 3). The cytoplasm of some of the necrotic cells stained intensively with eosin; their nuclei were pyknotic or fragmented, or covered with a fine granular substance precipitated in the cytoplasm. Occasionally, nuclear staining disappeared altogether. In other cells, biliary pigment and clots of calcium were observed. Under high power, Azan-stained preparations were conspicuous for the protein fragments in the necrobiotic hepatic cells with a swollen cytoplasm, which fragments precipitated in consequence of the gravely disturbed protein metabolism and stained pale blue, red, or orange yellow (Fig. 4). These hues were the same which, in some earlier experiments, had been observed by us in the staining of paraproteins adsorbed to the elastic fibres around malignant tumours. The precipitated proteins gave a positive Schiff reaction and stained bright red when treated according to ROMHÁNYI with toluidine blue and fuchsin at about pH 6,0, and black when treated with Haidenhain's haematoxylin or according to Kockel's fibrin staining method. Van Gieson's stain yielded a bright yellow, and Congo-red a reddish-brown colour. The picture described in the foregoing favours the conclusion that we have to do with Neumann's hepatic cell necrosis (fibrinoid necrosis) simply called eosinophil necrosis by some of the authors. Argentaffin fibres had been destroyed in the necrotic area, and only occasional thick bundles could be observed. (For similar cases in humans see SÜMEGI: 1922).

Examination of the kidneys of this same animal showed glomeruli markedly larger than normal, their capsule containing granular protein exudate, and the

mesoangium thickened. In the lumina of the tubules there appeared casts which stained blue with Azan.

On examining the *control* that was killed the same day, the acinous structure of the liver was seen to have remained fairly preserved and the dissociation not to have reached the markedly advanced stage observed in the animal which had succumbed. Centrolobular fibrinoid necrosis was found to be confined to the immediate vicinity of the central vein, and though pyknotic, the nuclei were invariably preserved. The cytoplasm, which stained a bright red colour with eosin, stained pale blue with Azan, in distinction to the purplish hue of the unimpaired cells but neither coloured proteins, such as had been found in the cells of the test animal, nor the presence of precipitated calcium could be observed. No renal lesions were encountered.

No aminal having died in the following two days, 1/6 of the lethal chloroform dose (0,2 ml/kg) was administered again subcutaneously to all survivals. Upon its effect six pretreated animals died with hepatargic coma and with jaundice between the *9th and 13th day* (2 with Masugi, 2 with phosphorus, 2 with phenylhydrazine pretreatment).Two controls were sacrificed on the 14th day.

The histological pictures of liver and kidneys were alike in all test animals, irrespective of the kind of pretreatment they had received. Half, three-thirds, or even the whole of the lobules was found to be necrotised in the liver of all animals with the exception of one that had been pretreated with phosphorus. Necrosis was in character similar to, though more extensive than, the lesions in the first week (Fig. 5). Symptoms of fibrinoid necrosis were seen in the centre of the lobules ; many of the cells were no longer visible, having undergone lysis. The cytoplasm of other cells stained blue with Azan but in these cells the nucleus did not stain. Some cells were small, their cytoplasm bluish violet, the nuclei small and pyknotic (cellular collapse, HELMKE). Dissociation was complete in this area, with no structure recognisable, the central vein being the sole guidance left. Necrosis spread to or beyond the intermediate zone which was followed by a layer of peculiarly changed, conspicuously large and swollen cells with finely granular, bluish, bluish-violet and red, or finely and uniformly vacuolated cytoplasm (Fig. 6). This layer extended either right to the edge of the lobule, or was followed by a thin marginal layer of intact cells. In the liver of the phosphorus-treated animal which formed the exception, there was hardly any necrosis ; vacuoles were predominant in it. The argentaffin fibres, too, were found to have been destroyed in the necrotic areas.

Apart from the one (phosphorus treated) exception changes were present in all the kidneys : exudate in Bowman's capsule similar to that seen in the first week ; a swelling of and a weak nuclear stain in the epithelial cells of the convoluted tubules ; the appearance of hyaline casts staining blue with Azan. Blue- and red casts, resembling those in myelomatous kidneys, were observed to appear in one of the phenylhydrazine-treated animals.

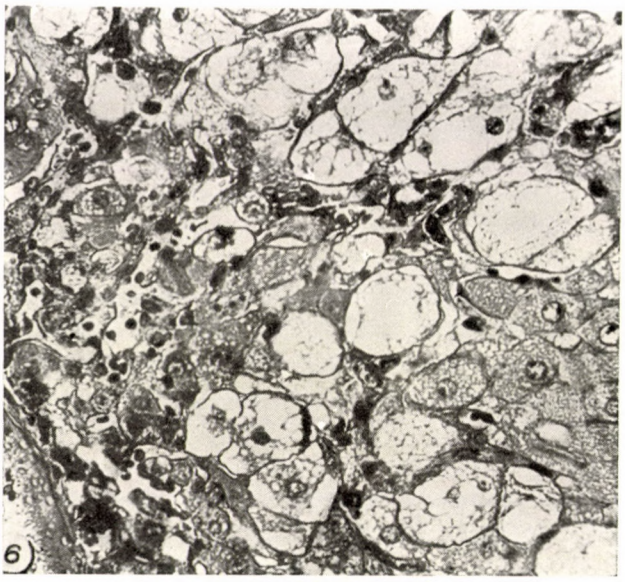


Fig. 6. Liver of pretreated rabbit died on 13th day. High power magnification. Observe „water-poisoned" big cells with vacuolated cytoplasm

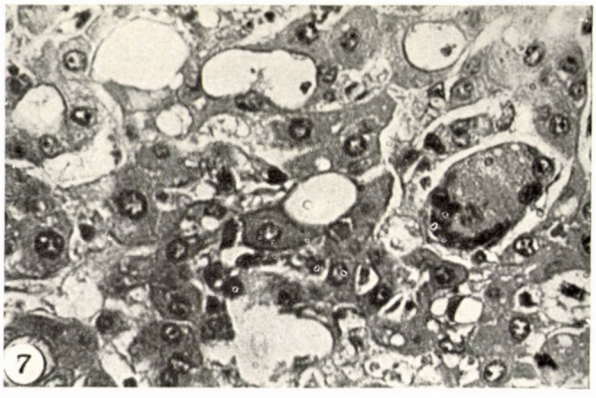


Fig. 7. Regeneration and formation of giant cells visible in control animal killed at the same time

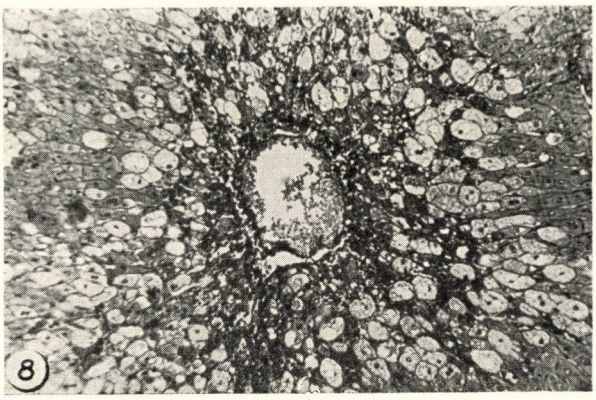


Fig. 8. Liver of pretreated rabbit died on 17th day. Low power magnification. Centrolobular regeneration; masses of cells with vacuolated cytoplasm in the intermediate zone

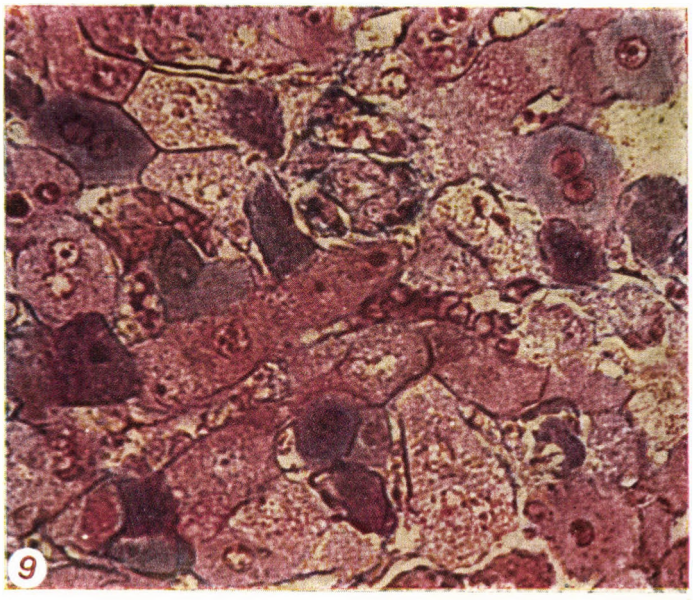


Fig. 9. Liver of preetrated rabbit died on 18th day. High power magnification; coloured photomicrograph, Azan stain. Hepatic cells in the regenerating area in mosaic arrangement. Cytoplasm of intact cells is reddish, that of vacuolated cells pale red, of not yet regenerated cells blue or bluish-violet

The liver of one of the two *controls* showed slight fibrinoid necrosis and marked vacuoles. It was conspicuous for its regenerative tendency at this early stage, displaying irregularly arranged masses of centrolobular cells which, small as they were and dark as their cytoplasm was, had a well stained nucleus, without as yet argentaffin fibres between them. From these central cells towards the lobule margins, numerous mitotic cells and the formation of multinuclear giant cells could be observed (Fig. 7). In the liver of the second control animal there was no necrosis, but the vacuoles and the regenerative tendency were unmistakeable. In the centre of the lobules regeneration even of the reticular argentaffin fibres was noticed to have begun. In the glomerular capsule there was exudate and in the tubuli a few bluish hyaline casts to be found.

At the end of the second week, one third of the lethal chloroform dose had been injected subcutaneously into the surviving animals, and this killed all but one of the pretreated rabbits within 3 days (2 phosphorus, 1 phenylhydrazine, 1 hepatotoxic). Two controls succumbed and three were sacrificed on the following day.

The liver of the *pretreated* animals was similar in appearance to that of the rabbits which died in the second week, with the difference that regenerative signs were clearly visible in all of them. Although necrosis was seen to had been at least as widespread as in the earlier animals, fibrinoid necrosis was no longer dominant, the destroyed centrolobular cells were already adsorbed, and their place taken by a reticular framework. In the same area the collapsed cells began to recover, and masses of regenerated fresh hepatic cells with small nuclei and narrow plasmatic margins began to show in their vicinity. These were either still lying in unarranged heaps, all but resembling hepatic adenoma, or were beginning to arrange themselves in rows. While hardly any reticular fibres were discernible among the unarranged cells, a rather thick argentaffine network could be seen commencing to regenerate among the rearranged cells. It was clearly visible that the fibres which had survived in the periportal space began to grow towards those spreading from the direction of the central vein. Vacuolated cells almost dominated the picture in some of the sections (Fig. 8). It was interesting to see how in the apparently healed areas the cells which had not yet quite recovered and the cytoplasm of which still stained a purplish or pale blue with Azan, arranged themselves in a peculiar, mosaic pattern among the red hepatic cells (Fig. 9). A fair number of giant cells was observed at the margins of the regenerated parts.

As regards the kidneys of these animals, they either presented a completely normal structure, or showed the above described lesions, though on a much smaller scale.

In two of the three *controls* which had died, hepatic lesions were similar to those in the pretreated animals ; in the third control centrolobular dissociation was very slight. The two controls sacrificed likewise showed but slight

hepatic lesions. Only one of these five animals had intact kidneys, the others presented renal lesions similar to those in the pretreated animals.

The one surviving animal, which it will be remembered had been pretreated with phenylhydrazine, and the last two control animals were given a lethal (1,2 ml/kg) dose of chloroform *at the end of the fourth week*, which killed them in 2 to 3 hours. Their liver showed almost complete restitution, with only the centrolobular dissociation, a few larger Kupffer cells filled with pigment, an occasional vacuolated cell, or a cell with violet cytoplasm pointing to the disease that had recently run its course in the animal. No traces were left of the changes in the kidneys.

In the following it is attempted to explain some of the described phenomena.

1. The *vacuolated cells* contained neither fat nor glycogen. It was demonstrated by WHIPPLE's, ZALKA's, and *our* own previous experiments that these cells presenting the picture of „water poisoning" are the morphological expression of extrarenal water retention of hepatic origin which accompanies serious hepatic damage and can be traced back to hypoxaemia. It was termed „Zellwassersucht" by FISCHER—WASELS, „acute hydrops" by APITZ, and „urticaria of the hepatic cells" by PRIBRAM and UPHAM. Some authors are of the opinion that these cells contain another substance besides water; however, SIEGMUND, for instance, does not identify it and only attributes importance to the physico-chemical disturbance. ATERMAN, on the other hand, takes the substance in question for glyco- or lipoprotein. Yet, in our experiments periodic acid fast substance were encountered only in necrotic and not in vacuolated cells. Very important is, however, ATERMAN's finding of ice crystals in vacuolated cells in sections which were frozen with Altman—Gersh's method. The increased uptake of water is attributed to hypoxaemia by most of the authors. Whether in consequence of the endothelial lesion, of the increased capillary permeability or of the dissociation, the circulation is disturbed in grave hepatitis, especially in the centre of the lobules, and this then causes the inner milieu to become acid and the cells to absorb water (VOEGT, BENDA—ELLEGAST—RISSEL). STATE, RAUCH and MÜLLER also emphasize the significance of circulatory conditions. On injecting hepatic poison intraportally, these authors observed increased portal pressure associated with oliguria and even anuria. ZISSLER and ZISSLER attribute even the cerebral symptoms associated with hepatitis to the escape of fluid through the damaged hepatic capillaries and the consequential diminution of plasma and blood volume. AXENFELD and BRASS lay stress upon the neurovascular point of attack in hypoxaemic parenchymal lesions. While all these data seem to favour the assumption that the pathologic water uptake of the injured hepatic cells is caused by circulatory disturbance and hypoxaemia, numerous other data in the literature point to the liberation of histamine-like substances as a possible factor in the development of the phenomenon.

2. The *renal lesions* found in experimental animals are frequently encountered in human subjects suffering from hepatitis.

BERMAN and POLAK, for instance, demonstrated such lesions in 22,2 per cent of their patients with infectious hepatitis, and in 19,4 per cent of those with serum jaundice. LESLIE, AMERIO, and VERCELLONE observed reduced urea clearance in 50 per cent of patients suffering from various diseases of the liver. Pathological changes largely identical with those described in this paper were observed by LUCKÉ and MALLORY in 80 per cent of their cases. It is, after all, more than a hundred years since ROKITANSKY described the cholaemic nephrosis which he invariably found in patients who had succumbed to hepatic disease. SIEDE believes the disturbances of fluid metabolism to be of extrarenal origin, and this theory seems to be confirmed by the capillary lesions, the increased permeability, and the frequently occurring cases of hypalbuminaemia observed by EPPINGER and other authors. SIEGLER and FALUDI found a reduced creatinine clearance in 80 per cent of their cases. SZABÓ, ZSOLDOS and RÉV reported a decreased glomerural filtrate and a low filtration fraction in acute hepatitis. They hold these changes to be consequential upon shock. Arriving at similar results, SÁRY, BRETÁN and B. RÓNA emphasized the significance of circulatory disturbances. Histological examinations by LÁSZLÓ and GAÁL revealed in every case of hepatitis the lesions which had been described by FAHR, ZOLLINGER, and RÓNA, and termed glomerulonephrosis. Similar lesions after burns and traumatic injury were observed by FARKAS and ENDES, respectively.

Of the case histories of our patients, 11 included previous proteinuria, and 3 previous haematuria. Urinary analysis was negative in one case, while no such analysis was made in another. The fulminant course of the disease left no time for thorough kidney function tests in any of the cases.

Considerations of space do not allow us to deal in detail with the pathogenesis of the renal lesions observed, or with their connection with the hepatorenal syndrome. Nevertheless, mention must be made of OETTEL's experiments, in which similar renal lesions were induced by the administration of homologous liver extract, and of those of LETTERER and SEYBOLD, who produced such lesions with foreign serum. Obviously, it is very probable that besides disturbed permeability and circulation, also disturbances of the protein metabolism have to be regarded as important factors. This assumption is justified not only by the findings of the said authors but also by our own earlier investigations, the observations of BINDER and MESTERHÁZY, and the present experiments, in which in the damaged cells broken-up hepatic proteins were present in the form of paraproteins, giving different colours on staining with Azan.

3. As regards destruction and regeneration of the argentophil fibres, this was discussed by one of us in 1934. (*Sümegi)*, when it was shown that, in contrast to viral hepatitis, the argentophil fibres die off within the area of centrolobular necrosis consequent upon the action of chloroform. On the site of the necrosis, first there appear fresh hepatic cells with no argentophil fibres demonstrable among them by silver impregnation. Thereafter new argentophil fibres begin to arise from the direction of both the centre and the periphery with a simultaneous arrangement of the fresh cells into trabecules. It is possible that this process is also connected with regeneration of the capillaries. It was found both in the earlier and the present experiments that newly formed hepatic cells are considerably more resistant to repeated and increasing doses of chloro-

form than cells treated for the first time. At the time it was assumed that the degenerating hepatic cells acted as antigens, against which antibodies were formed to protect the new cells from being poisoned.

We see no reason to abandon this hypothesis and still deem it probable that the newly formed argentophil fibres contribute to the development of the above-assumed protective mechanism, for the structures arising from the connective tissue ground substance readily adsorb immune substances. This has been shown by us in respect of elastic fibres adjacent to malignant tumours (BERNÁTH, SÜMEGI—GORECZKY—RÓTH).

One should keep an open mind on the subject until further investigations have been made, for even if viewed only in the light of the present experiments the disease induced in the rabbits appear to be partly an increased allergy-like sensitiveness of the liver to the second hepatic poison, and partly an increased resistance of the regenerated hepatic cells to the repeated, in fact growing, doses of the poison. The allergic process has no absolute morphological characteristics (BERGER, ALBERTINI). The results of our investigations make it highly probable that the chronically disintegrating hepatic proteins exert a sensitizing effect, and it is equally probable that the antibodies formed in the process offer protection against further disintegration (v. also BENKŐ, SCHEIFFARTH).

Surveying the experimental results we find that of the 15 animals, which after a preliminary hepatic injury had been given a renewed sublethal dose of hepatic poison, 10 died within 12 days of the intoxication. With the exception of the comparatively slight lesions in the three animals that died within the first 48 hours, all the rest presented the picture of hepatic necrosis of a partly fibrinoid character accompanied by the gravest desctruction, quite similar to the fulminant hepatitis encountered in human subjects. At the same time, none of the controls died, and the lesions seen in those killed were similar to, but considerably less extensive than, the changes in the test animals. Signs of regeneration were and remained evident in and after the third week, notwithstanding repeated doses of chloroform.

In our opinion, the model experiments described in this paper confirm the decisive significance of the sensitisation produced by previous hepatic damage mentioned in the history of our patients suffering from fulminant hepatitis and, further, they support the view of the probably allergic nature of the rapid hepatic disintegration consequent upon the antigen-like effect of the fresh injury during the second illness. Obviously, the essence of the process is to be sought for in the auto-antigen-antibody reactions. Experiments to demonstrate these reactions are in progress. The significant part attributed to the nervous system in the process seems to be substantiated by the fact that the „second blow" runs the course prepared by the first lesion almost with the speed of a conditioned reflex.

Summary

13 cases of fulminant infectious hepatitis have been described, of which in ten subjects the condition had been preceded by some earlier disease injurious to the liver. Animal experiments have proved these previous processes to be significant pathogenic factors. Hepatic damage had been induced in animals, and after this had subsided, they were again treated with sublethal doses of hepatic poison. The 2/3 part of the animals died within 12 days of the intoxication. Their liver showed gravest destruction similar to that observed in human patients, while the sacrificed controls displayed considerably less extensive pathological changes. In the authors' view the pathogenic significance of previous hepatic lesions consists in that the protein decomposition products, formed during the first illness and acting as autoantigens, sensitize the liver and bring about a rapid allergic disintegration during the fatal second disease.

REFERENCES

1. APITZ : (1940) Die Paraproteinosen. Virch. Arch. *306*, 631. — 2. ATERMAN : (1952) Some local factors in the restoration of the rat liver after partial hepatectomy. II. Watery vacuolation. Arch. Path. *53*, 209. — 3. AXENFELD and BRASS : (1943) Klinische u. bioptische Untersuchungen über den sog. Ikterus catarrh. Frankf. Ztschr. Path. *57*, 146. — 4. AXENFELD and BRASS : (1943—44) Weitere Beiträge zur Morphologie u. Pathogenese d. Hepatitis epid. ibid. *58*, 220. — 5. AMERIO and VERCELLONE : (1952) Significance of the urea clearance in liver diseases (Ital.) Exc. Med. VI. 6/9. 1328. — 6. ALBERTINI : (1954) Bedeutung der Allergielehre für die Pathologie. Schweiz. Ztschr. Allg. Path. Bakter. *17*, 1. — 7. BERGER : (1937) Discussion to Wätjen : Zentrale Läppchennekrose der Leber und Allergie. Verh. Dtsch. Path. Ges. : Zentralbl. Allg. Path. Path. Anat. *68*, 30. Tgg. Erg. Bd. S. 148. — 8. BENKŐ : (1954) Autoagressive Diseases (Hung.) Magyar Belorv. Arch. 7/6. 161. — 9. BERNÁTH : (1952) Amyloidosis in Malignant Tumours. Acta Morph. *2*, 137. — 10. BINDER : (1942) On the Treatment of Nonnenbruch's Hepatorenal Syndrome (Hung.) Orv. Hetil. *86*, 571. — 11. BERMAN and POLAR : (1951) A new outbreak of virus hepatitis. Exc. Med. VI. 5/5. 632. — 12. BENDA, ELLEGAST and RIESSEL : (1950) Zur Frage des Wasserhaushaltes bei akuten Leberparenchymerkrankungen. Wien, Ztschr. Inn. Med. 31/5. 177. — 13. BASERGA : (1949—50) Studio istopatologico della nefrite sec. Masugi nei ratti. Biol. Latina. III/1. 43. — 14. BENNET, DRINKER, WARREN : cit. Lucké and Mallory. — 15. BODECHTEL : (1952) Die Beziehungen der Leber zu neurologischen Krankheitsbildern. Dtschr. Ztschr. Verd. Stoffwkrkh. Sonderbd. (XV. Tgg.) S. 227. — 16. BERNARD : (1953) La lésion focale. Presse Méd. 61/42. 872. — 17. BARSKIJ : (1950) Clinical Problems of Acute Yellow Atrophy of the Liver. Exc. Med. VI. 4/8. 1239. — 18. BLACK—SCHAFFER, JOHNSON, GOBBEL : (1950) Experimental Total Midzonal Hepatic Necrosis. Am. Jour. Path. 26/3. 397. — 19. DOZORETS and BELUSHOVA : (1952) Neurological and physical lesions in acute hepatitis. Exc. Med. VI. 6/1. 38. — 20. DESLOYERS and TOUSSAINT : (1952) Étude des variations postopératoires de la bilirubinémie. Exc. Med. V. 5/1. 51. — 21. ELLEGAST et AL. : (1954) Virushepatitis und Gravidität. Wien. Klin. Wschr. 66/3. 42. — 22. ENDES and TAKÁCS—NAGY : (1952) Acute renal lesions developed on traumatic and toxic basis. Acta Morph. *2*, 417. — 23. EPPINGER : (1949) Permeabilitätspathologie. Springer, Wien. — 24. FINDLAY and WILLCOX : (1945) Infective hepatitis, transmission by faeces and urine. Lancet. *2*. 549. — 25. FISCHER—WASELS : cit. VOEGT. — 26. FAHR : cit. VOLHARD—FAHR (1914) Die beiderseitigen haematogenen Nierenerkrankungen. Springer, Berlin. — 27. FARKAS : (1952) Kidney injury in exp. burns. Acta Morph. *2*. 418. — 28. FARKAS and FODOR : (1952) Toxic lesions of the kidney. Acta Morph. *2*. 422. — 29. GLYNN and HIMSWORTH : (1948) The intralobular circulation in acute liver injury. J. Clin. Sci. *6*. 235. — 30. GOVAN and MCGILLIWRAY : (1950) Puerperal uraemia due to acute upper-nephron nephrosis. Lancet *2*. 128. — 31. GÁL : personal communication. — 32. GRIESHAMMER : (1950) Degenerative Veränderungen der Leberläppchen. Zbl. Allg. Path. *86*. 168. — 33. GAUPP : (1952) Leber und Psyche. Dtsch. Ztschr. Verdauungs- u. Stoffwechselkrkh. Sonderbd. XV Tgg. S. 237. — 34. HARANGHY : (1941) On the effect of continued infections on the ret.-end. system. Ann. Meeting of the Hung. Path. Soc. p. 45. — 35. HEUBNER : (1952) Toxische Leberschädigungen. Dtsch. Ztschr. Verdauungs- u. Stoffwechselkrkh. Sonderbd. XV. Tgg. S. 72. — 36. HARTL : (1952) Anatomische Untersuchungen von Nieren, Leber u. Pancreas bei postoperativen Todesfällen. Arch. Klin. Chir. *271*. 121. — 37. HABÁN : (1933) Lesions of the liver in Graves' disease. Ann. Meeting of the Hung. Path. Soc. p. 42. — 38. KOLBER : (1951) On the classification of epid. hepatitis in children. Exc. Med. VI. 6/9 (1952) 1259. — 40. KETTLER : (1949) Die Bedeutung path.ant. Befunde bei Eiweissmangel.

ernährung. Ztschr. ges. Inn. Med. *4*. 167. — 41. LUCKÉ: (1944) Pathology of fatal epid. hepatitis. Am. Jour. Path. *20*, 471. — 42. LUCKÉ and MALLORY: (1946) The fulminant form. of epid. hepatitis. Am. Jour. Path. *22*, 867. — 43. LÜHRS: (1950) Morphologische u. Bluteiweissuntersuchungen bei qualit. Nahrungsmangel. Ztschr. ges. Inn. Med. *5*, 1. — 44. LESLIE et AL.: (1951) Renal function as a factor in fluid retention in patients with cirrhosis of the liver. I. Clin. Invest. *30*, 1200. — 45. LÁSZLÓ and GAÁL: (1953) Renal changes in hepatic disease (Hung. only.) Orv. Hetil. 94/48. 1331. — 46. LETTERER and SEYBOLD: (1950) Bioptische und histologische Studien zur Masugi Nephritis am Forsch. Virch. Arch. *318*, 451. — 47. MASUGI: (1533) Über das Wesen der spez. Veränderungen der Niere u. Leber durch das Nephrotoxin bzw. Hepatotoxin. Zieglers Beitr. Path. Anat. Allg. Path. *91*, 82. — 48. MASUGI: (1934) Über die exp. Glomerulonephritis durch das spez. Antinierenserum. Zieglers Beitr. Path. Anat. Allg. Path. *92*, 429. — 49. MESTERHÁZY: (1943) Hepatorenal syndrome caused by gallstone ileus (Hung. only.) Orv. Hetil. *47*, 569. — 50. NORDMANN: (1952) Die toxische Nephrose. Ztschr. Allg. Path. Anat. *88*, 215. — 57. NEUMANN: (1896) Zur Kenntnis d. fibrinoiden Degeneration des Bindegewebes bei Entzündung. Virch. Arch. *144*, 201. — 52. NISSEN: (1954) Die akute gelbe Leberatrophie als zweite Krankheit. Ärztl. Wchschr. *9*, 149. — 53. NEUMANN: (1918) Zur Verständigung über Fragen der Entzündungslehre Zieglers Beitr. Path. Anat. Allg. Path. *64*, 1. — 54. OPIE: (1910) The relation of combined intoxication and bact. infection to necrosis of the liver. J. exp. path. *12*. 367. — 55. OETTEL: (1948) Degenerative Nierenerkrankungen, Thieme, Leipzig. — 56. PRIBRAM and UPHAM: (1950) Facts and Problems of Hepatitis. Rev. Gastroent. *17*, 469. Ref. Exc. Med. 1951. Sect. VI. 5/11. 1542. — 57. RUNYAN, WRIGHT and BEEBE: (1950) Homologous serum jaundice. JAMA *144*, 1065. — ROKITANSKY: cit. SIEGLER—FALUDY. — 58. RÓNA: (1952) Nephrosis. Acta Morph. *2*, 389. — 59. SCHEIFFARTH and BERG: (1953) Zum Nachweis von Autoantikörpern bei Leberparenchymerkrankungen. Klin. Wschr. 31/19—20. 441. — 60. SEALY: (1942) Role of infection in the pathogenesis of liver necrosis in hyperthyreoidism. Ann. Surg. *116*, 851. — 61. SIEDE: (1951) Hepatitis epidemica. J. A. Barth, Leipzig. — 62. SPERANSKY: (1950) Grundlagen der Theorie der Medizin. Saenger, Berlin p. 184, 235. — 63. SIEGMUND: (1952) Allg. Pathologie der Leberparenchymveränderungen. Ztschr. Verdauu. u. Stoffwechselkrkh. XV. Tgg. Sonderbd. S. 31. — 64. STATE, RAUCH and MÜLLER: (1952) The experimental production of the hepatorenal syndrome in dogs. Exc. Med. V. 5/7. 561. — 65. SÁRY, BRETÁN and BÓNA: (1953) The pathogenesis of the hepatorenal syndrome (Hung. only). Orv. Hetil. 94/48. 1328. — 66. SIEGLER and FALUDY: (1953) Functional investigation of the kidneys in patients with hepatic diseases (Hung. only). Orv. Hetil. 94/48. 1319. — 67. SÜMEGI, GORECZKY, LÁSZLÓ, GÁL: (1952) Experimental data to the hepatorenal syndrome. Acta Morph. *2*, 423. — 68. SÜMEGI, GORECZKY, RÓTH: (1954) Recent studies on the amyloid in malignant tumours. Acta Morph. *4*, 463. — 69. SÜMEGI: (1922) On the pathogenesis of liver changes in fatal cases with chloroform poisoning (Hung. only) Magy. Orv. Arch. *20*. — 70. SÜMEGI: (1934) Über die Neubildung der Gitterfasern. Frankf. Ztschr. Path. *47*, 123. — 71. SÜMEGI: (1935) Chlor- und Cholesterinstoffwechsel bei krebskranken Tieren. ibid. *48*, 386. — 72. SÜMEGI: (1935) Exp. u. Morph. Untersuchungen über den hepatorenalen Symptomenkomplex bei krebskranken Tieren. ibid. *48*, 398. — 73. SÜMEGI: (1954) On the porphyrins (Hung. only) Orv. Hetil. 95/30. 801. — 74. SZABÓ, ZSOLDOS, RÉV: (1953) The function of the kidneys in acute parenchymal liver diseases (Hung. only) Orv. Hetil. *94*/48. 1323. — 75. SZODORAY: (1942) Aetiology of the Hydroa aest. tarda (Hung. only) Orvostud. Közl. *3*, 216. — 76. SZODORAY: (1943) Porphyrin metabolism in patients with syphilis (Hung. only) Orvosképzés *33*, 140. — 77. THORLING: (1950) Neurological complications in acute infect. hepatitis. Acta Med. Scand. *137*, 322. — 78. URANGA IMAZ and GARCIA SIGUERO: (1952) Chronic hepatitis activated by pregnancy. Exc. Med. VI. 6/5. 687. — 79. VOEGT: (1952) Zur path. Anat. d. Hepatitis contagiosa. Dtsch. Ztschr. Verdauu. u. Stoffwechselkrkh. XV. Tgg. Sonderbd. S. 54. — 80. WERTHEMAN and BODÓKY: (1947) Die path. Anatomie der gehäuften Leberdystrophiefälle von Basel aus dem J. 1946. Schweiz. Ztschr. Path. Bact. *10*, 176. — 81. WALLACH and POPPER: (1950) Central necrosis of the liver. Arch. Path. 49/1. 33. — 82. WHIPPLE and HOOPER: (1913) Hematogenous and obstructive icterus. Exp. studies by means of the Eck fistule. J. exp. Med. *17*, 593. — 83. ZALKA: (1926) Observations on the effect of chloroform on the liver (Hung. only) Magy. Orv. Arch. No. 6. — 84. ZISSLER and ZISSLER: (1952) Zur Hämodynamik bei capillärer Betriebsstörung der Neber. Ztschr. Klin. Med. *149*, 448. — 85. ZOLLINGER: (1945) Die spontane und experimentelle Glomerulonephrose *12*, 23. — 86. ZOLLINGER: (1951) Histologische Befunde nach experimenteller Röntgenbestrahlung der Nieren. Schweiz. Ztschr. Path. Bact. *14*, 349.

О ПАТОГЕНЕЗЕ ФУЛЬМИНАНТНОГО ГЕПАТИТА

И. ШЮМЕГИ, Л. ГОРЕЦКИ и И. РОТ

Авторы дают описание 13 случаев фульминантного инфекционного гепатита, среди которых они выявили в анамнезе десяти больных предыдущие болезни с повреждением печени. Авторы доказывают патогенетическое значение этих предыдущих процессов опытами над животными. Животные, предварительно подвергнутые повреждению печени, после их выздоровления вновь получили сублетальные дозы гепатоксического яда, вследствие чего две трети их погибли в течение первых 12 дней после отравления. В печени этих животных наблюдался тяжелый распад, как и у человека, в то время как в печени убитых контрольных животных изменения были гораздо меньшего размера. Патогенетическое значение предварительного повреждения печени по мнению авторов кроется в том, что возникшие при предыдущей болезни продукты распада белков — в качестве автоантигенов — сенсибилизируют печень, и в течение фатального вторичного заболевания происходит на аллергической основе — бурный распад последней.

CONTRIBUTION À LA PATHOGÉNIE DES HÉPATITES FOUDROYANTES

I. SÜMEGI, L. GORECZKY et I. RÓTH

Ce travail étudie l'observation de 13 cas d'hépatite foudroyante ; 10 de ces malades présentaient dans leurs antécédents une maladie antérieure ayant entraîné une atteinte hépatique. Les auteurs mettent en relief l'importance pathogénique de ces processus morbides antérieures et les reproduisent sur l'animal. Ils avaient précédemment produit une lésion hépatique chez ces animaux et après guérison complète, ils leur administrèrent une dose non mortelle de poison hépato-toxique. Deux tiers des animaux ainsi traités succombèrent dans les douze premiers jours suivant l'intoxication et l'on constate dans leur foie une désintégration excessivement grave similaire à celle constatée dans les cas humains, tandis que les altérations constatées au niveau du foie des témoins sacrifiés étaient d'une étendue sensiblement moindre. L'importance pathogénique de la lésion hépatique préalable consisterait, dans l'esprit des auteurs, dans le fait que les produits de désintégration protéique mis en liberté à cette occasion agiraient comme auto-antigènes sensibilisant le foie et qui déclenchent sur terrain allergique la désagrégation foudroyante de celui-ci lors de la seconde maladie à issue fatale.

Dr. Prof. István SÜMEGI,
Dr. László GORECZKY,
Dr. Imre RÓTH,
Budapest, VI., Rudas L. u. 111. Hungary.