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EXPERIMENTAL MODELLING OF HEPATOGENIC ENCEPHALOPATHY*

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Hepatogenic encephalopathy in humans results from either chronic or acute liver insufficiency, from abnormal abdominal venous flow, bypassing hepatic portal circulation and from intolerance to gut proteins (Fischer, 1974). In most conditions all or at least two of these factors operate in combination. In a great proportion of cases, liver cirrhosis, being the most common cause of the chronic liver insufficiency, is accompanied by severe abnormalities in the portal intrahepatic blood flow expressed among others by the formation of the pathological extrahepatic venous collateral circulation. In addition Diemer (1978) had shown pathological intrahepatic shunting, being the result of liver cirrhosis. Clinical exacerbation resulting from dietary factors in cases of chronic liver cirrhosis or porto-caval shunting emphasizes the pathogenic importance of gut overloading with proteins. As great as the number of different factors precipitating the occurrence of the hepatic encephalopathy are, their final effects most likely fit into one of the three basic pathogenic mechanisms. Most of the clinical observations are clearly indicating that hepatic encephalopathy develops as a result of absolute or relative liver insufficiency, related with all probability to its "detoxicating" function. The possible role of an unknown active compound or compounds produced by healthy liver regulating the brain function and lacking in case of liver damage cannot be ruled out in the light of Geiger's studies (1958) and recently those of Egan and coworkers (1976).

Most of the experimental models, aiming at reproduction in animals of the pathological conditions corresponding to hepatogenic encephalopathy in

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humans are directed towards one of the above mentioned pathogenic mechanisms. They can be roughly divided into three following groups:

1. Porto-caval shunting, with many different surgical variants very often supplemented with additional precipitating factors.
2. Toxic liver damage, with a wide range of chemical compounds used.
3. Experimentally induced disturbances in the ammonia metabolism in animals with unchanged both liver and portal circulation, simulating the condition occurring in human in case of intolerance to gut protein.

All of the above mentioned procedures lead both to significant metabolic disturbances in the central nervous system and to its structural abnormalities.

In human material the most common pathological feature found in the brain in cases of liver disease are astrocytic abnormalities consisting in the concomitance of their progressive and regressive reaction. There is a widespread, generalized proliferation of astrocytic nuclei with a significant hypertrophy of individual astrocytes. These abnormalities appear against the background of regressive changes taking the form of more or less advanced klasmatodendrosis (Fig. 1). Numerous astrocytes lacking processes and their ameboid forms are seen. Alzheimer cells, type II in all their forms are present in practically all grey structures and in the subcortical white matter (Fig. 2). In a great majority of cases the intranuclear glycogen inclusions are to be found both in naked nuclei and in those of unchanged astrocytes (Fig. 3). Opalski cells (Fig. 4) occur in a great proportion of chronic cases, but they are absent from all acute ones.

The second feature common to most cases of hepatogenic encephalopathy is spongy degeneration of the brain tissue. Cortico-subcortical junction (Fig. 5), cerebral cortex, basal ganglia and cerebellar dentate nuclei are the sites of predilection for spongiotic changes. Relatively good preservation of myelin and neurons, as well as lack of either glial or mesenchymal reaction are fairly typical features of spongy degeneration observed in hepatogenic encephalopathy. Rare cortical necroses, neuronal abnormalities, taking the form of either non-specific degeneration or patchy neuronal loss, features of brain edema and hyperemia complete the pathomorphology of hepathogenic encephalopathy.

Aiming in reproduction of pathological changes typical for human hepatogenic encephalopathy, since several years two basic experimental models were used in our laboratory. They represented both the group of toxic liver damage and that of experimental porto-caval shunting. The toxic liver damage group comprises two subgroups. The first one most commonly used consisted in chronic carbon tetrachloride intoxication, in the second one alteration of the liver parenchyma was due to low protein in the diet, the content of protein in strictly standardized food being reduced to 10.8 per cent (Mossakowski, 1966; Mossakowski et al. 1970; Ostenda et al. 1976). The shunting

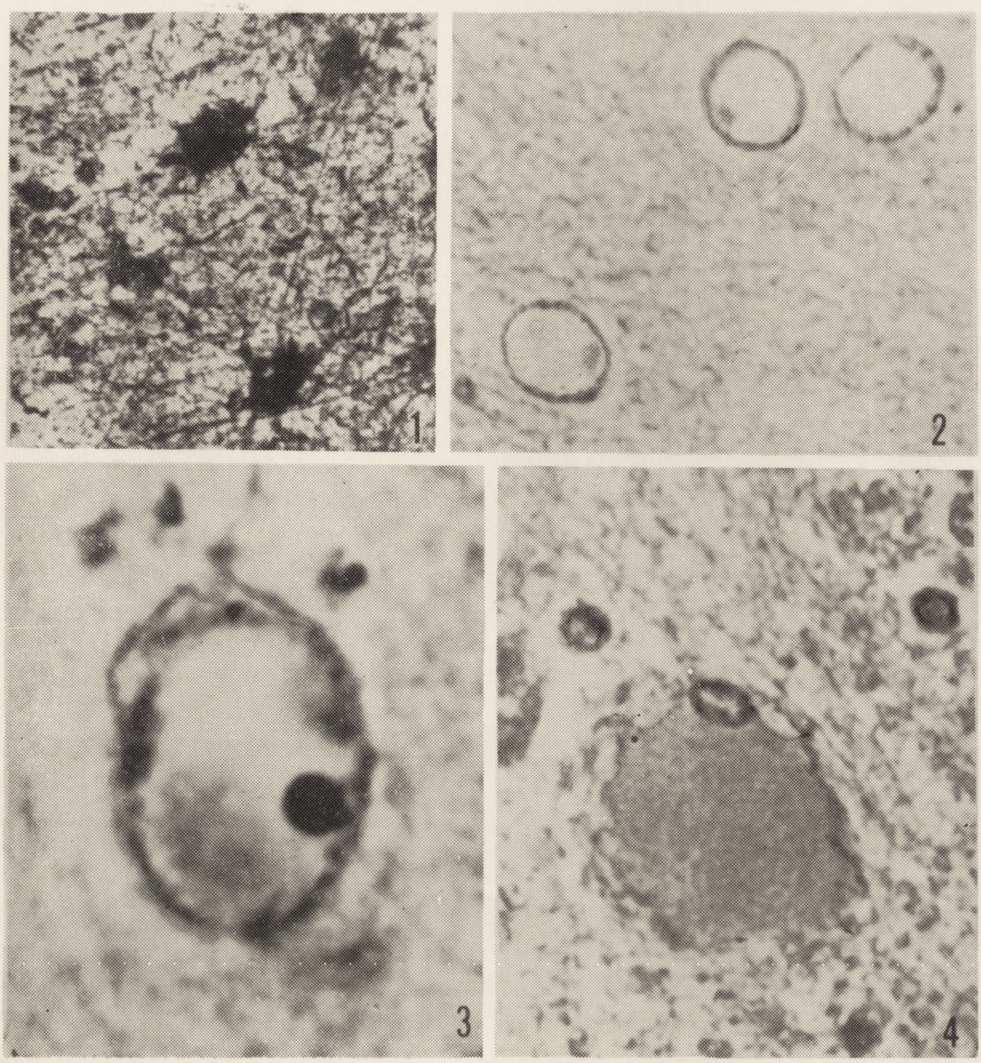


Fig. 1. Hypertrophied astrocytes with severe klasmatodendrosis in a case of hepatogenic encephalopathy. Cajal. X 400.

Ryc. 1. Zaawansowana klazmatodendroza przerosłych astrocytów w przypadku encefalopatii wątrobowej. Cajal. Pow. 400 X.

Fig. 2. Alzheimer II cells in a case of hepatogenic encephalopathy. H–E. X 600.

Ryc. 2. Komórki Alzheimera typu II w przypadku encefalopatii wątrobowej. H–E. Pow. 600 X.

Fig. 3. Naked nucleus with a glycogen inclusion in a case of hepatogenic encephalopathy. PAS. X 1500.

Ryc. 3. Nagie jądro z wtrętem glikogenowym w przypadku encefalopatii wątrobowej. PAS. Pow. 1500 X.

Fig. 4. Opalski cell in a case of hepatogenic encephalopathy. H–E. X 600.

Ryc. 4. Komórka Opalskiego w przypadku encefalopatii wątrobowej. H–E. Pow. 600 X

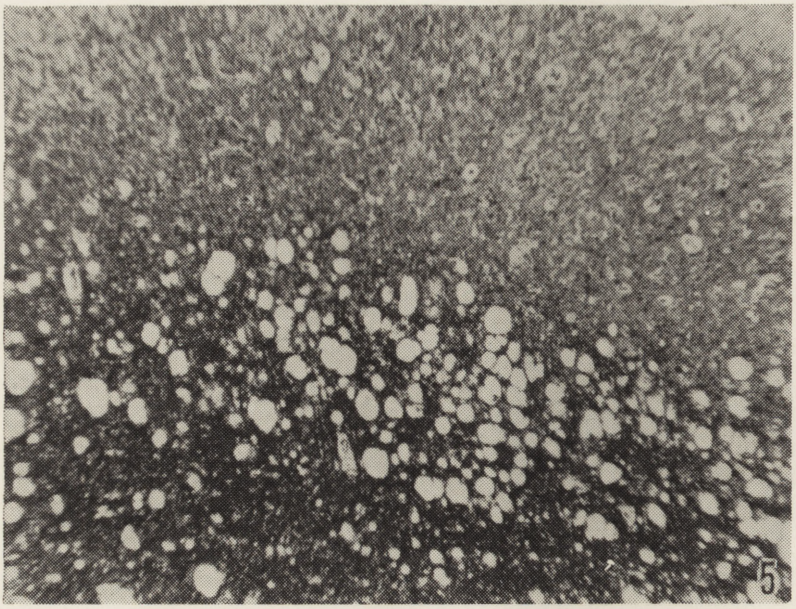


Fig. 5. Spongy degeneration of the cortico-subcortical junction in a case of porto-systemic encephalopathy. Good preservation of myelin is worth mentioning. Heidenhain. X 75.

Ryc. 5. Zwyrodnienie gąbczaste istoty białej na pograniczu korowo-podkorowym w przypadku encefalopatii wrotno-układowej. Zwraca uwagę dobre utrzymanie mieliny. Heidenhain. Pow. 75 X.

experiments have been performed in two species of animals, namely in dogs in which additionally meat intoxication was applied, and in rats (Mossakowski, 1966; Mossakowski et al., 1977). There was no increase of serum ammonia in either of toxic groups, which contrasts with Diemer's observations (1978). However in the carbon tetrachloride group, an increased concentration of ammonia within the brain tissue was shown by Hilgier (1980).

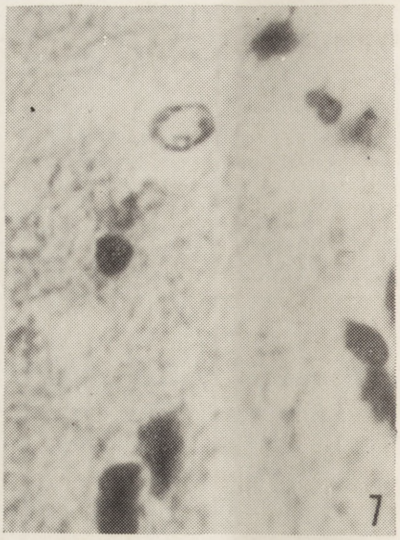
In both groups with porto-caval shunt a significant enhancement of serum ammonia was observed as a rule. In rats this was accompanied by its increase in the brain (Hilgier, 1980). In both dogs and rats ammonia level at the end of experiment was generally lower than in the first weeks following the performance of Eck's fistula.

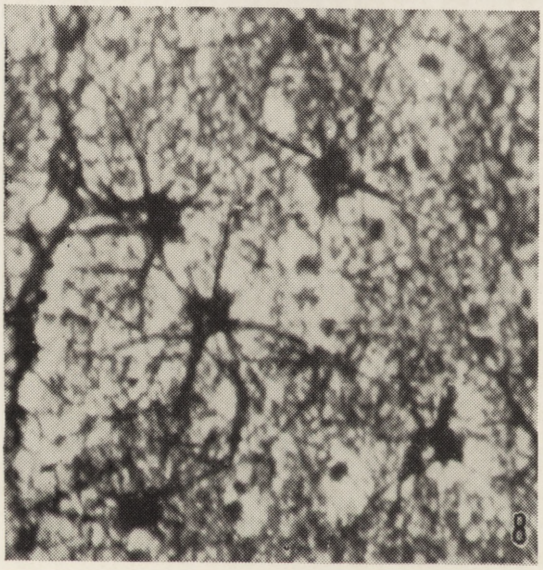
In rats kept on low protein diet for a period of nine month the most remarkable brain abnormality consisted in hypertrophy of astrocytes (Fig. 6) and occurrence of numerous enlarged astrocytic nuclei (Fig. 7) corresponding to typical Alzheimer II cells (Mossakowski, 1966). Glial abnormalities were generalized, involving both grey and white structures, with a predilection to the cortico-subcortical junction of the cerebrum and dentate nucleus of the cerebellum. Marked glial proliferation, although present in some animals, was not a striking feature, neither were pathological abnormalities of other

types of glia. Severe neuronal loss and nerve cells degeneration, taking the form of either chromatolysis or vacuolar degeneration completed the neuropathological picture of the brains of experimental animals. Neuronal abnormalities were mostly confined to the cerebral cortex and cerebellar dentate nuclei. Their intensity in other structures was much less. Slight spongiosis was present only in two of twenty five animals. It is worth pointing out that the astrocytic abnormalities were found only in those animals in which severe damage of liver parenchyma was present.

In rats with liver cirrhosis induced by carbon tetrachloride intoxication for the period of two, four and six months significant astroglial proliferation and hypertrophy involving most of grey formations of the brain were present (Fig. 8). These were accompanied by severe degeneration of astrocytes, seen both in the light and electron microscopy (Mossakowski et. al., 1970; Ostenda et al., 1976). Naked nuclei distributed troughout the central nervous system were the most striking feature (Fig. 9). Other types of glia were not involved. Slight spongy degeneration of the white matter was present only in two animals of the whole series. Abnormality in the capillary permeability for both silver nitrate, seen in the dark field microscopy (Mossakowski et al., 1970) and for horse radish peroxidase observed in the electron-microscope (Mossakowski et al., 1976) are worth mentioning. Cerebral blood vessels, though unchanged in light microscopy on the ultrastructural level revealed an increased number of pinocytic vesicles and abnormal localization of the activity of nucleoside phosphatases (Ostenda et al., 1975; Mossakowski et al. 1978). Nonspecific neuronal degeneration was a persistent supplementary finding. Notably, glial abnormalities and blood vessel permeability changes showed an evident dependence on the duration of the experiment.

In dogs with Eck's fistula there were some differences in the neuropathology between those with and without "meat intoxication" (Mossakowski, 1966). In both subgroups diffuse neuronal loss, mostly cortical and hyppocampal and severe nonspecific neuronal degeneration dominated the pathological picture of the brains (Fig. 10). Though most pronounced in animals with additional hypovolemic shock, considered as one of the precipitating factors, they were present in all animals of both experimental subgroups. Glial abnormalities were less evident; however, astrocytic proliferation and hypertrophy (Fig. 11), concomitant with klasmatodendrosis were observed throughout. Typical Alzheimer cells II were found only in some cases. Contrary to the previous experimental groups, spongy degeneration of both cerebral cortex and the white matter was present in almost all the examined cases in the subgroups without "meat intoxication" and in all with meat diet (Fig. 12). The intensity of these changes was similar in both subgroups, despite the significant difference in the duration of experiment, which was extended to 67—191 days in one subgroup and limited to 9—21 in the other.





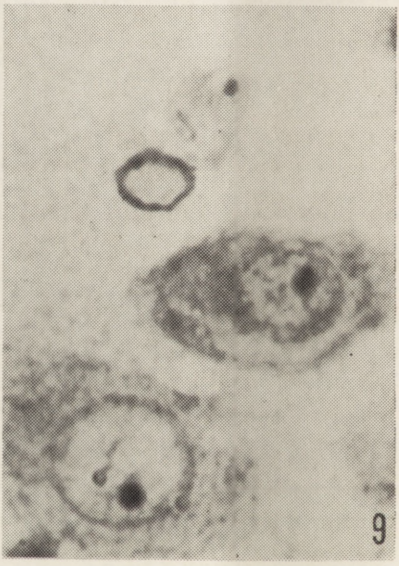


Fig. 6. Hypertrophy of the fibrillary astrocytes in the white matter in a rat kept for 9 months on low-protein diet. Cajal. X 300.

Ryc. 6. Przerost astrocytów włóknistych w istocie białej u szczura przetrzymywanego przez okres 9 miesięcy na diecie niskobiałkowej. Cajal. Pow. 300 X.

Fig. 7. Naked nucleus in the cortex of a rat kept for 9 months on low-protein diet. H–E. X 450.

Ryc. 7. Nagie jądro w korze mózgu szczura przetrzymywanego przez okres 9 miesięcy na diecie niskobiałkowej. H–E. Pow. 450 X.

Fig. 8. Increased number of hypertrophied astrocytes with some features of klasmatodendrosis within the white matter of a rat with carbon-tetrachloride intoxication. Cajal. X 600.

Ryc. 8. Zwiększona liczba przerosłych astrocytów z cechami klazmatodendrozy w istocie białej szczura z zatruciem czterochlorkiem węgla. Cajal. Pow. 600 X.

Fig. 9. Naked nucleus in the cortex of a rat with carbon tetrachloride intoxication. Cresyl-violet. X 600.

Ryc. 9. Nagie jądro w korze mózgu szczura z zatruciem czterochlorkiem węgla. Fiolet krezylu. Pow. 600 X.

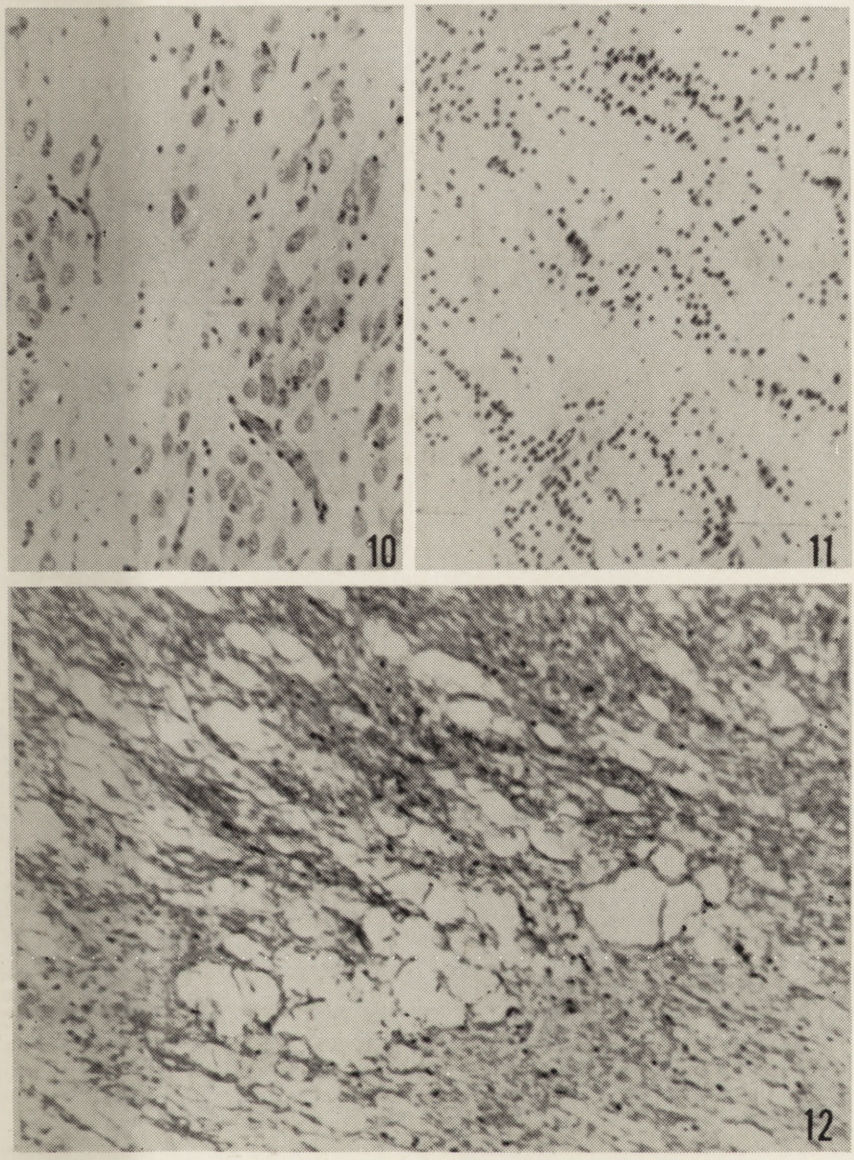


Fig. 10. Neuronal loss in the cortex of a dog with Eck's fistula. Cresyl-violet. X 600.

Ryc. 10. Ubytki neuronalne w korze mózgu psa z przetoką Ecka. Fiolet krezylu. Pow. 600 X.

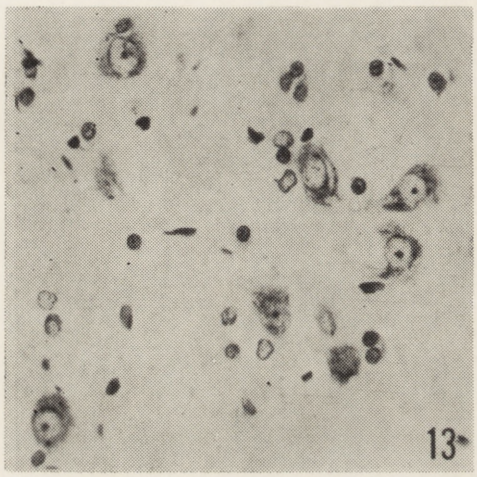
Fig. 11. Glial proliferation in the white matter in a dog with Eck's fistula. H–E. X 300.

Ryc. 11. Rozpem gleju w istocie białej u psa z przetoką Ecka. H–E. Pow. 300 X.

Fig. 12. Focal sporgiosis of the subcortical white matter in a dog with Eck's fistula. Klüver-Barrera. X 120.

Ryc. 12. Ogniskowe zgąbczenie podkomorowej istoty białej u psa z przetoką Ecka. Klüver-Barrera. Pow. 120 X.

In rats in which porto-caval shunt was performed for a period ranging from 7 to 10 weeks the typical abnormality was the appearance of enlarged light astrocytic nuclei (Fig. 13), some of them with irregular, lobulated outlines, overimposed over a slight glial proliferation (Fig. 14). The glial alterations in the earlier stage were confined mostly to basal nuclei, thalamus, some motor brain stem nuclei and dentate nucleus of the cerebellum. In later stage they also involved neocortex and Ammon's horn. Neurons and other types of glial cells were not altered, and so were the myelin sheaths. Spongy degeneration was absent.



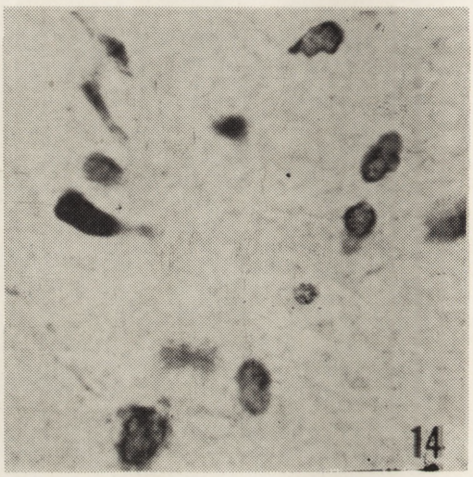


Fig. 13. Numerous naked nuclei in thalamus in a rat with porto-caval shunt. Cresyl-violet. X 400.

Ryc. 13. Liczne nagie jądra we wzgórzu szczura z przetoką wrotno-układową. Fiolet krezylu. Pow. 400 X.

Fig. 14. Alzheimer cells type II with lobulated outlines within the dentate nucleus in a rat with porto-caval shunt. Cresyl-violet. X 1200.

Ryc. 14. Komórki Alzheimera typu II z pofałdowanymi zarysami jąder w jądrze zębatym móżdżku u szczura z zespoleniem wrotno-układowym. Fiolet krezylu. Pow. 1200 X.

In none of the experimental group we were able to demonstrate intranuclear glycogen inclusions in astrocytes. Neither Alzheimer cells type I nor Opalski cells were present, except one case from the porto-caval shunt group in rats in which one cell with the morphological features of Alzheimer cell type I was seen within a glial scar of the traumatic origin.

The leading pathological changes found in all experimental groups are summarized in table 1. Their comparison clearly indicates differences between human and animal material on one hand and between various experimental models on the other. The most notable difference between both chronic and

Table 1. Comparison of brain abnormalities in different experimental models of hepathogenic encephalopathy

Experimental model, animals	Astrocytic abnormalities				Neuronal abnormalities		Spongy degeneration	Vascular abnormalities	
	proliferation	hypertrophy	degeneration	Alzheimer cells type II	neuronal loss	neuronal degeneration		morphology	permeability
Low-protein diet, rats	moderate	severe	severe	numerous	severe	severe	rare	not examined	
Carbon tetrachloride intoxication, dogs	severe	severe	severe	numerous	slight	moderate	rare	changed	increased
Porto-caval shunt, dogs	moderate	moderate	severe	occasional	severe	severe	frequent	not examined	
Porto-caval shunt, rats	moderate	moderate	not observed	numerous	not observed	not observed	not observed	not examined	

acute hepatogenic encephalopathy in humans and their experimentally induced counterparts in animals consists in the fact, that in each experimental model only some elements of the pathology typical for human cases are present. Hepatogenic encephalopathy due to chronic carbon tetrachloride intoxication, closest in its neuropathological picture to that seen in chronic human cases differ from them in an almost complete absence of tissue spongiosis. This abnormality fairly common to most of the human cases (Mossakowski 1966; Mossakowski et al., 1974) was on the contrary seen in dogs with Eck's fistula, in which glial abnormalities, mostly those taking the form of the so-called metabolic glia, were much less pronounced. On the other hand this type of tissue alteration was the only change in the brains of rats with portocaval shunt. The neuropathological picture of brains in rats kept on low-protein diet was dominated mostly by astrocytic hypertrophy concommitant with degenerative changes and naked nuclei formation, while glial proliferation seen both in human cases and in other experimental models, was much less pronounced. Intranuclear glycogen inclusions, fairly common in human pathology were absent in all experimental groups. So were Opalski cells occurring in a great proportion of chronic cases in humans, but not in the acute ones. Their presence in animals was described by Taraszewska et al.(1971) in a case of an aged dog with a primary cancer of the liver. In our human material, including both chronic and acute hepatogenic encephalopathy, Alzheimer cells type I were not seen. Contrary to this Cavanagh and Kyu (1976) demonstrated them in rats with porto-caval shunt. This type of cells was also seen in one of our experimental models. Neuronal losses and degeneration, which in most human cases, except the acute ones, are rather second rate features, dominated the neuropathology in dogs with Eck's fistula, regardless the survival duration of animals, being absent in rats with identical experimental pathology.

The above mentioned differences between various types of experimental models of hepatogenic encephalopathy are even more striking when the results obtained by other authors are taken into consideration (table 2—4), not mentioning the observations described by earlier authors, such as for instance encephalitis resulting from Eck's fistula in dogs (Balo, Kapasy, 1932) or basal ganglia necrosis due to hepatic artery ligation (Kirschbaum, 1923). Some of the more recent papers point out the involvement of oligodendroglia (Zamora et al., 1973; Diemer, 1978), myelin sheaths (Cavanagh, Kyu, 1971a), nerve cell processes and their endings (Rizzuto, Gonatas, 1974; Kornfeld, 1975).

Despite those variations, the general pattern of brain abnormality, consisting in the appearance of astrocytic changes seems to be common to most of the experimental models. The second feature characteristic for human hepatogenic encephalopathy, namely spongy tissue degeneration is less

Table 2. Brain pathomorphology in animals with toxic liver damage

Author, animals and damaging factor	Essential pathological changes in the brain
Lapham (1961), rats, CCl_4	astrocytic proliferation, Alzheimer cells II
Mossakowski (1966), rats, low-protein diet	astrocytic hypertrophy, Alzheimer cells II
Mossakowski et al. (1971, 1978), rats, CCl_4	astrocytic proliferation and degeneration. Alzheimer cells II, increased permeability of blood vessels (LM and EM), neuronal degeneration
Lahl (1974), rabbits, CCl_4	astrocytic proliferation, enlargement of astrocytic nuclei, hyperchromatic nerve cells, status spongiosus in the white matter
Hopper et al. (1974), sheeps, lasiocarpine	spongy degeneration of the white matter
Diemer (1978), rats, CCl_4	lobulated and enlarged astrocytes, decrease in number of oligodendrocytes and vacuoles in the white matter, neuronal degeneration

Table 3. Brain pathomorphology in porto-caval shunting

Author and animals	Essential pathological changes in the brain
Mossakowski (1966), dogs	astrocytic proliferation, Alzheimer cells II, spongy degeneration
Benson et al. (1970), dogs	astrocytic proliferation, Alzheimer cells II
Cavanagh, Kyu (1971a), rats	abnormal astrocytic nuclei in some cerebral structures
Cavanagh, Kyu (1971b), rats	abnormal astrocytic nuclei, Alzheimer cells I, while wounding, lesions of myelin and oligodendroglia
Norenberg et al. (1972), dogs	astrocytic proliferation and degeneration (ME)
Zamora et al. (1973), rats	astrocytic abnormalities and proliferation, lesions to capillary basal membrane and oligodendrocytes (ME)
Norenberg, Lapham (1974), rats	hyperplasia and hypertrophy of astrocytes, Alzheimer cells II
Laursen, Westergaard (1977), rats	increased permeability of blood vessels to HRP, astrocytic swelling (ME)
Kornfeld (1975), rats	abnormalities of dendrites, axon terminals and astrocytes (ME)
Mossakowski et al. (1977), rats	astrocytic hyperplasia, Alzheimer cells II
Diemer (1978), rats	lobulation and enlargement of astrocytic nuclei

Table 4. Brain pathomorphology in experimental disturbances of ammonia metabolism

Author, animals and noxious agent	Essential pathological changes in the brain
Cole et al. (1972), monkeys, ammonium acetate	astrocytic proliferation, Alzheimer cells II, glycogen deposition
Rizzuto, Gonatas (1974). rats, methionine sulfoximine	lesion to synaptic processes (after convulsions), swelling of glia
Gibson et al. (1974) mice, urease	astrocytic proliferation and hypertrophy, Alzheimer cells II, spongious vacuolization of neuropil (after convulsions)
Phelps (1975), mice, methionine sulfoximine	astrocytic accumulation of glycogen
Hooper (1975), sheeps, ammonium acetate	spongy degeneration
Diemer (1978), rats, urease	Alzheimer cells II

common. Like in humans it seems to be more inherent to cases with porto-caval shunting. Neuronal lesion in the sense of their loss and non-specific degeneration are the most fluctuating elements of the cerebral pathology.

Quantitative and qualitative differences in neuropathology of experimental hepatogenic encephalopathy may be due to numerous additional factors differing from one model to another. Some of them may act directly on the nerve tissue and thus modify the pathomorphology of the brain in each case. This may for instance explain differences in the extent and intensity of neuronal lesions between the groups where liver damage was due to low-protein diet and to carbon tetrachloride intoxication. The different brain tissue reaction to various pathogenic factors, having in common liver damage and/or bypassing portal-hepatic circulation, has also to be taken into consideration. This finds its support, among others, in the differences in metabolic abnormalities occurring in porto-caval shunting and in carbon tetrachloride intoxication in rats (Hilgier, 1980). The obvious species-related differences cannot be overlooked. It is well known that some animals are more, and some are less susceptible to the liver damage (Diemer, 1978). The time factor and severity of liver lesions are also of an utmost importance, as shown in the experiments with carbon tetrachloride intoxication (Mossakowski et al., 1970; Ostenda et al., 1976).

This short review of different experimental models of the hepatogenic encephalopathy showing the usefulness of each particular model for elucidating the pathogenic mechanisms underlying pathological process at the same time points out the necessity of simultaneous application of a variety of them; only such a complex approach offers the possibility to distinguish what is common, essential and primary from what is exception, incidental and secondary.

M. J. Mossakowski

DOŚWIADCZALNE MODELE ENCEFALOPATII WĄTROBOWEJ

Streszczenie

Omówiono stosowane typy modeli doświadczalnych encefalopatii wątrobowych wyodrębniając w oparciu o ich założenia patogenetyczne 3 grupy: a) doświadczalne uszkodzenie wątroby przy zastosowaniu różnorodnych substancji chemicznych; b) operacyjne wytworzenie pozawątrobowego przepływu krwi wrotnej; c) doświadczalnie wywołane upośledzenie metabolizmu amoniaku przy nieuszkodzonym miąższu wątrobowym i zachowanym krążeniu wrotnym. Przedstawiono zmiany patomorfologiczne w mózgu w dwóch stosowanych od szeregu lat modelach — toksycznym uszkodzeniu wątroby i wytworzonym zespoleniu wrotno-układowym. Zwrócono uwagę na podobieństwa i odrębności obserwowanych zmian neuropatologicznych w stosunku do patologii wątrobowo-mózgowej u ludzi i w innych typach doświadczalnej encefalopatii wątrobowej. Zwrócono uwagę na rolę dodatkowych czynników modyfikujących obraz uszkodzeń strukturalnych ośrodkowego układu nerwowego w doświadczalnej encefalopatii

wątrobowej. Wykazano, że równoczesne stosowanie kilku modeli doświadczalnej encefalopatii wątrobowej umożliwia wyodrębnienie zmian pierwotnych i istotnych dla procesu patologicznego od zaburzeń wtórnych i przypadkowych.

М. Я. Моссаковски

ЭКСПЕРИМЕНТАЛЬНЫЕ МОДЕЛИ ПЕЧЕНОЧНОЙ ЭНЦЕФАЛОПАТИИ

Резюме

Обсуждаются применяемые типы экспериментальных моделей печеночной энцефалопатии выделяя, основываясь на их патологические положения, 3 группы: а) экспериментальное повреждение печени при применении разнообразных химических веществ; б) операционное создание внепеченечного кровообращения воротной крови; в) экспериментально вызванное нарушение метаболизма аммиака при не поврежденной паренхиме печени и сохраненном воротном кровообращении. Представлены патоморфологические изменения в мозге в двух применяемых в течение ряда лет моделях — токсическом повреждении печени и образованном воротно-системном анастамозу. Обращается внимание на аналогию и отличие наблюдаемых нейропатологических изменений по отношению к печеночно-мозговой патологии у людей и в других типах экспериментальной печеночной энцефалопатии. Обращается внимание на роль добавочных факторов модифицирующих картину структурных повреждений центральной нервной системы в экспериментальной печеночной энцефалопатии. Показано, что одновременное применение нескольких моделей экспериментальной печеночной энцефалопатии делает возможным выделение первичных и существенных для патологического процесса изменений от вторичных и случайных нарушений.

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