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LIVER INJURY CAUSED BY ANTITUMOUR DRUGS

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It has repeatedly been observed in the course of our chemotherapeutic experiments that animals, cured of malignant growth by means of 1,6-bis (-chloroethyl-amino-1,6-desoxy-D-mannite-dihydrochloride) BCM (Degranol), died nevertheless after some time, although even their haemopoietic apparatus had become normal again. Autopsy usually failed to reveal the cause of death.

It is known that various cytocidal and cytostatic preparations — such as mustard nitrogen, — induce pathologic changes not only in tissues that show a high mitotic index (e. g. bone marrow, lymphatic tissue, sexual glands) but also in other organs [1, 2, 3, 4]. Such changes are, however, not sufficiently serious to explain the death of the animals. Preliminary toxicological tests had demonstrated that precisely from a toxicological point of view was BCM superior to the usual chemotherapeutical antitumour drugs [5], and that it was the one causing the least fatal organic lesions. Endeavouring to find an explanation for the subsequent death of apparently healed animals which had recovered their normal weight, we subjected their internal organs to a repeated analysis. In doing so we were led by the consideration that the lower tolerance of tumorous animals or the fact that chemicals are administered much longer in therapeutic experiments than in the usual toxicological tests might so modify experimental conditions as to provoke fatal organic lesions.

We focussed our attention on the liver not only because we knew the role this organ plays in the detoxification of various substances and chemicals [6], but also because DAVISON et al. [7] in mice, and BOURSNELL et al. [8] in rabbits, had found that a considerable part (50 per cent in the case of rabbits) of radioactive mustard nitrogen, a substance closely related to BCM, after being introduced into the organism, was concentrated in the bile by the liver within a very short time, as a matter of fact after the lapse of an hour. And, as was expected, we found sufficiently grave hepatic lesions in quite a few animals that, though cured of tumour, had nevertheless succumbed subsequently.

Encouraged by these observations we started systematic experiments with a view to studying the liver-damaging action of BCM. Our studies were extended to a simultaneous examination of the liver-damaging effect of mustard nitrogen, a drug related to but many times as toxic as BCM, as also of two other mustard derivatives, namely the N-oxide mustard (Mitomen) [9] and phenylalanine mustard (Sarcolysine) [10].

Method

Healthy, non-tumourous rats were used in the experiments. We performed experiments of three types, each in several parallels.

The first kind of experiments consisted in administering a single median lethal dose (LD_{50}) of the said drugs to the test animals ; its effect on the liver was then ascertained at various times (from 24 to 168 hours) following injection.

In the second series we tried to imitate therapeutic conditions by subjecting the animals to chronic treatment : we gave them 15 to 35 injections, distributed over an adequate period of time, in such doses as were known to inhibit the growth of tumours. The animals were killed after the last injection.

The third series of experiments was similar to the second, with the only difference that the animals were not sacrificed immediately after the treatment but allowed to live for 10 to 50 days after the last injection.

The experiments were repeated later and supplemented by liver function tests (bromsulphalein clearance). In making and evaluating the tests we adopted the method of *Ahmad* and *Frazer* [11]. The animals received intravenously 25 mg/kg of 0,5% bromsulphalein solution. Bromsulphalein determination was performed in 0,5 ml of serum. The colour reaction, obtained after the addition of 10% NaOH, was estimated by means of Pulfrich's photometer with an S_{53} filtre. The degree of bromsulphalein retention was expressed in per cents.

Results

The first morphological alteration observed in so-called acute experiments, *i. e.* those performed with median lethal doses was the initially partial and subsequently complete glycogen depletion in the liver. Partial depletion took place as early as from 24 to 48 hours after the injection of any of the four chemicals. Sections stained with the McMANUS—HOTCHKISS method revealed apart from the vessel walls and Kupffer's cells, only isolated and scattered PAS-positive cells, imparting a mosaic-like structure to the liver (*Fig.* 1). The disappearance of glycogen became complete after 72 hours : by this time, only the vessel walls and the Kupffer cells (the latter usually desquamated and swollen) remained PAS-positive. The liver of animals treated with BCM, after having lost its glycogen content, underwent in the majority of the cases a rapid fatty degeneration (within 72 to 96 hours) accompanied by the appearance of diffuse, large droplets, while — in some cases — it recovered its glycogen content. Treatment with any of the other three drugs (*i. e.* mustard nitrogen, Mitomen and Sarcolysine) was always followed after 96 hours by the reappearance of glycogen in the liver, and there remained only scattered foci of fatty degeneration with small droplets.

It should be noted that the described process was by no means the same in every animal. The liver of most animals gradually recovered its glycogen-

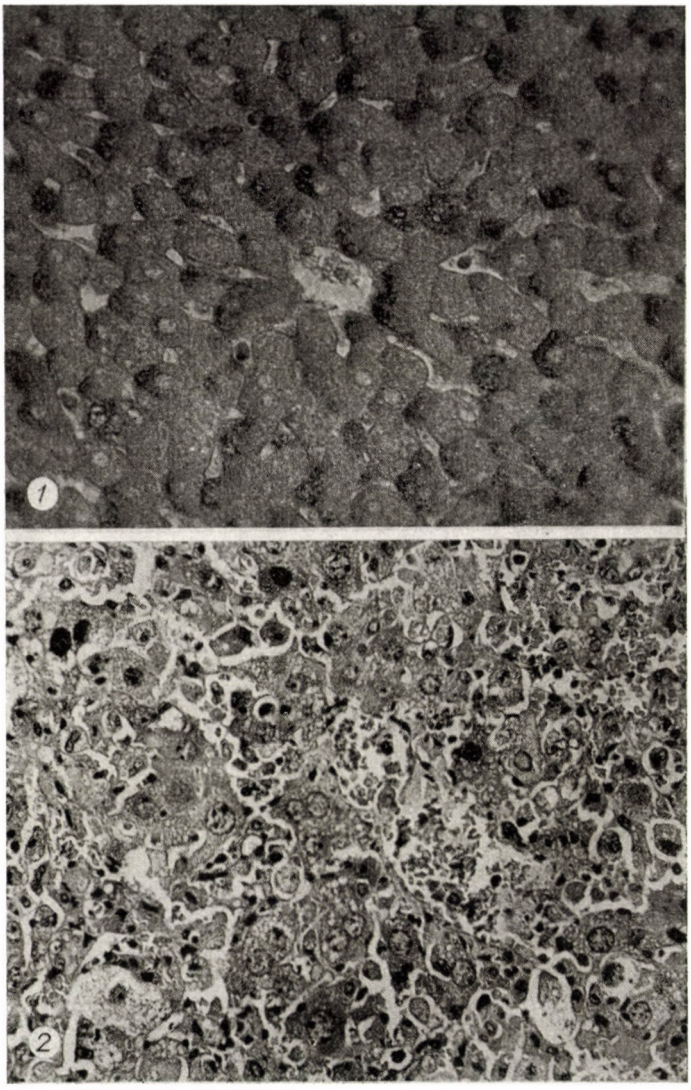

Fig. 1. Liver of rat injected with a single intravenous LD_{50}-dose of BCM (80 mg/kg), completely depleted of glycogen 72 hours after treatment. Apart from Kupffer cells, only occasional, isolated PAS-positive hepatic cells are observable. McManus-Hotchkiss stain ; ×240

Fig. 2. Liver of rat intravenously injected with 14×10 mg/kg of BCM (Lived 17 days after first injection). Lobular structure of liver no longer visible ; hepatic parenchyma dissociated ; hepatic cells swollen ; plasma vacuolised ; many disintegrating elements. Haematox. eos., ×240

storing power, so that 168 hours after the administration of the single large dose the liver was seen to be normal again. The individual sensitivity of the animals constituted a great — we can say a decisive — factor in influencing

the character, progress or regress, of hepatic alterations. Even a high standardization of experimental conditions (pure-bred animals of equal body weight, age and sex, standardized diet and fluid-uptake) did not eliminate differences in individual sensitivity.

The situation was essentially similar with chronic treatment. Groups of ten animals each were used for such experiments, which were repeated 2 to 3 times. There were never more than 2 or 3 animals in a group of ten to reveal serious hepatic lesions: the liver of the rest had either remained completely intact or — at the most — had lost some of its glycogen, undergone mild parenchymal degeneration or a desquamation of Kupffer's cells. After chronic treatment with Mitomen, mustard nitrogen or Sarcolysine, even the gravest symptoms did not go beyond a fatty degeneration with foci of small droplets.

Some of the animals that had been subjected to chronic treatment with BCM showed, however, very grave hepatic lesions. In these cases the lobular structure of the liver had disappeared, and most of the parenchyma was found to consist of large, bloated cells with pale eosinophilic cytoplasm. They were of varying size and situated side by side, without any regular structure. Between them we encountered many scattered cells in various stages of deterioration, pycnotic nuclear disintegration and karyolysis, with their cytoplasm more or less vacuolised. We found occasionally also multinuclear synplasm-like structures (Fig. 2). Some of the large swollen cells proved to be sudanophilic, and part of them displayed PAS-positivity at the same time. It was interesting to observe that, far from making these cells PAS-negative, salivary digestion rather increased their positivity.

Again, in other cases the liver had lost its lobular structure and was found to consist of greatly swollen cells with foamy vacuolised cytoplasm; these cells were closely packed in some places, while in others they appeared as solitary cells, isolated from scattered, proliferating bundles of bile-duct of Kupffer cells. Many of them had altogether ceased to take nuclear stains (Fig. 3). The majority of these large, pale cells proved to be sudanophilic and PAS-negative. Some of them were, however, less swollen, not vacuolised and not sudanophilic: the plasma of these hepatic cells contained PAS-positive globules (Fig. 4) which, on being digested with saliva, became still more positive.

However, in the majority of the cases, not even chronic treatment with BCM had induced hepatic lesions of such severity: the lobular structure did not disappear, but the cells became strongly inflated, their nuclei assumed different sizes, polynuclear cells were formed, and certain cell-groups developed pronounced sudanophilia. On the other hand, even in such livers there were occasional scattered hepatic cells which, detached from the cell bundles, were round, degenerative and showed all the symptoms of deterioriation.

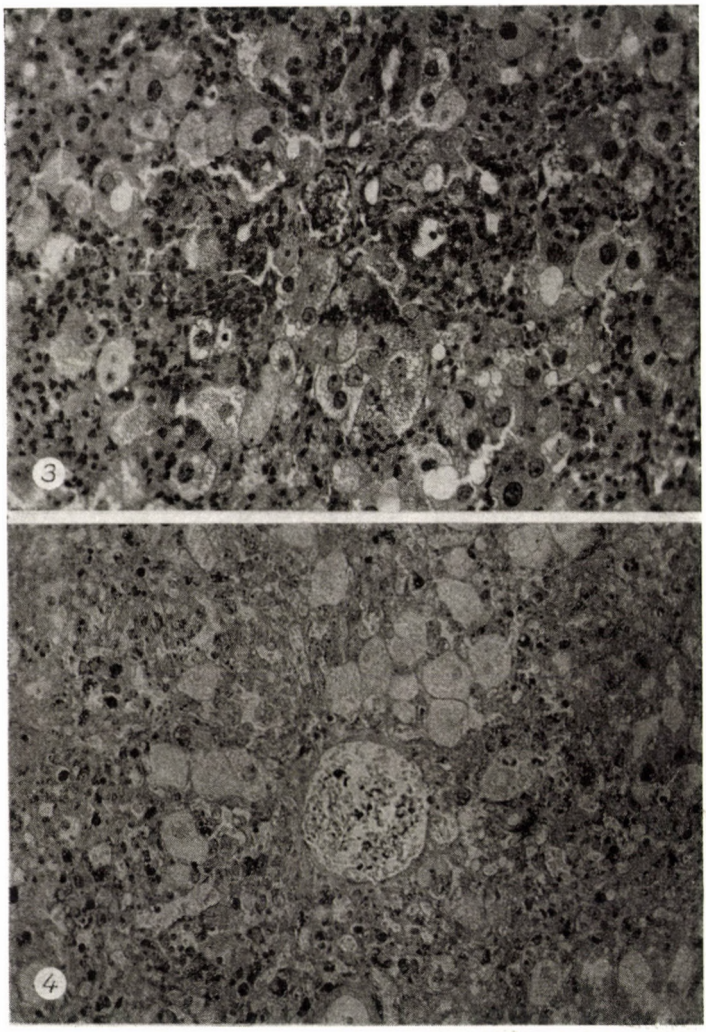

Fig. 3. Liver consisting of ballooned, foamy, vacuolised cells, many of which no longer take nuclear stains. A great number of Kupffer cells observable among the bloated liver cells. Dosage : 15 × 10 mg/kg of BCM in 28 days. Haematox. eos., × 240

Fig. 4. McManus-Hotchkiss-stained section of liver of same animal. PAS-positive globules in the cytoplasm of some liver cells. On salivary digestion, positivity of globules increased, × 240

We want to add that hepatic lesions were still more serious if tumorous animals had been subjected to chronic BCM treatment. Following the dissociation and necrosis of the hepatic parenchyma, a confluence of several cells gave rise to synplasm-like figures with a number of nuclei and nuclear fragments (Fig. 5). In some such animals we were able to observe intensive

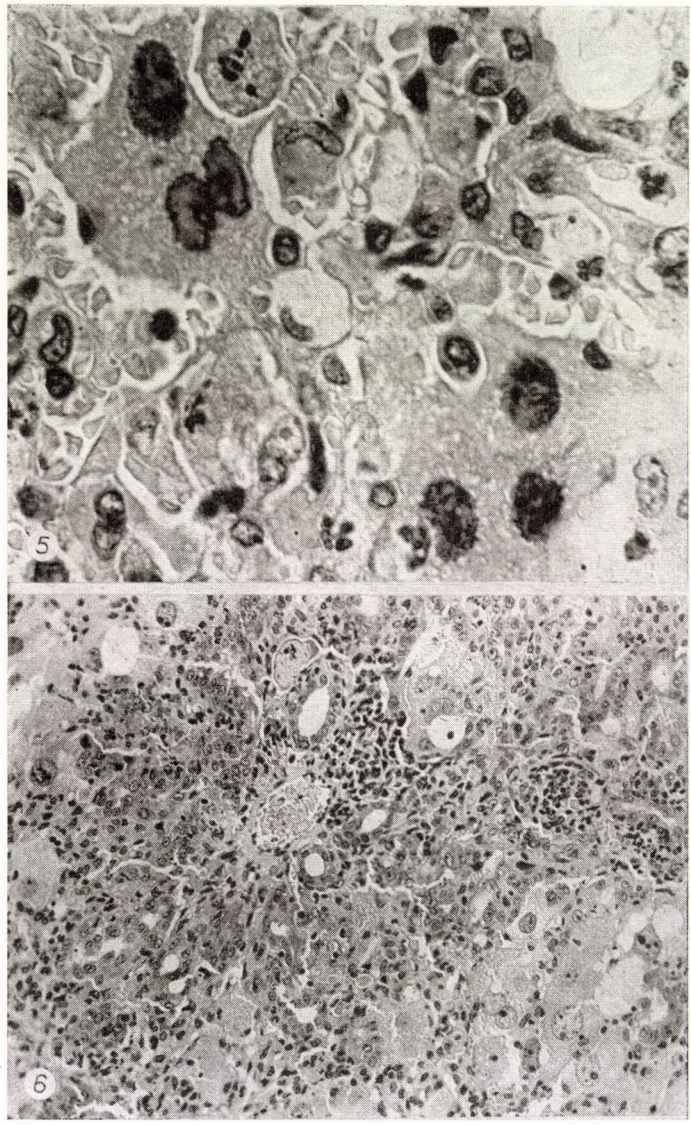

Fig. 5. Development of polynuclear synplasm-like giant cells with foamy, vacuolised cytoplasm in the liver. Haematoxylin-eosin ×820
(Liver of animal infected with Guérin's cancer; dosage: 50 mg/kg of BCM administered intravenously once a week; duration of treatment: 4 weeks)

Fig. 6. Focal proliferation of bile-ducts on the site of destroyed liver parenchyma. Haematoxylin-eosin, ×240
(Liver of animal infected with Guérin's cancer; dosage: 50 mg/kg of BCM administered intravenously once a week; length of treatment: 4 weeks)

focal bile-duct proliferation which was sometimes so pronounced as to make the whole picture similar to that presented by precancerous hepatic lesions in the early phase of butter-yellow carcinogenesis (Fig. 6).

As has been said above, the third series of our experiments had the purpose to ascertain wether or not alterations of the liver occasioned by chronic treatment are reversible. With this end in view, we refrained from sacrificing the animals after the termination of the treatment (from 25 to 30 injections) and allowed them — without any further treatment — to live for 10 to 50 more days. Killed after the lapse of this period, they revealed no pathological hepatic symptom, fatty degeneration or the formation of connective tissue, thus justifying the conclusion that the process in question is reversible.

It has also been mentioned that, in an additional series of experiments, liver function (bromsulphalein) tests were performed : their results are summarized in Table.

Table

	Control	CCl_4	BCM	Mitomen	Sarco-lysine	Mustard nitrogen
Total No. of animals	14	4	9	7	10	9
No. of animals with pathol. BS-retention	0	4	4	2	3	4
Mean BS-retention percents	2.3	16	32.2	9	25	15.5
Ratio of BS-retention and morphol. alterations	0/0	4/4	4/3	2/1	3/1	4/4

The table shows that while no pathologic retention was manifest in neither of the controls, in some of the experimentals, in keeping with the histological changes, abnormal BS-retention values are seen.

To control our method, the results of bromsulphalein tests in animals that had been poisoned with 0.5 g/kg doses of carbon tetrachloride over a period of 3 to 5 days, are separately indicated : it will be seen that BS-retention was abnormally high in all these cases. The second row of figures in *Table* indicates the average retention in per cents. That of the controls was 2.3%. This is in perfect agreement with the data given in the above quoted report of AHMAD and FRAZER [11], as also with the figures obtained by LAMM [12] in similar experiments performed on several hundred animals. Only a retention above 4% was regarded as abnormal. The last row of figures in *Table* expresses the ratio of pathological BS-retention to morphological alterations. It shows that a pathologically high value of BS-retention in animals poisoned with carbon tetrachloride was invariably associated with histologically demonstrable liver damage. Also, in the animals treated with various mustard

derivatives, pathological liver function (BS-retention) and morphological changes showed a good parallelism.

Independently of those described above, we made experiments in which the carcinogenic action of BCM was tested on mice [21] by administering the drug in weekly increasing doses (from 1 μg per mouse to 5 mg per kg) for a whole year [21]. Autopsy revealed in these mice conspicuous hepatic

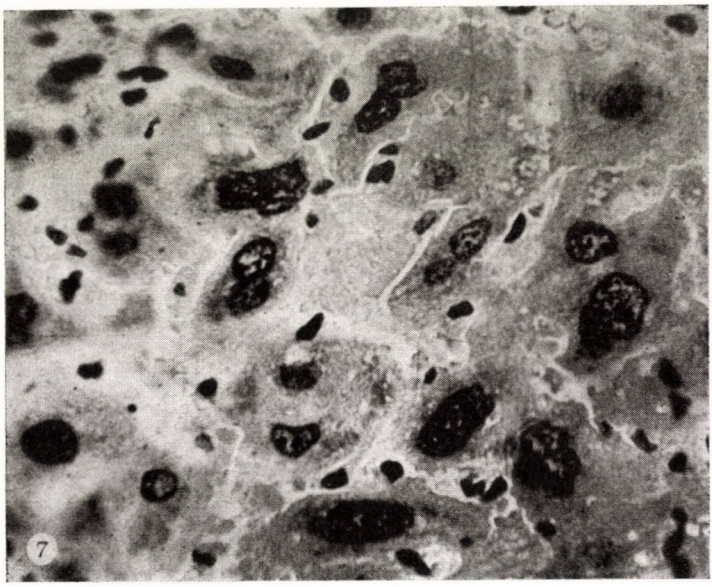

Fig. 7. Liver of mouse treated for a year with gradually increasing doses of BCM (from 1 γ per mouse to 5 mg/kg). Conspicuous variation of nuclear size ; many amitoses. Haematoxylin-eosin, ×560

changes. A variation of nuclear size was the most general symptom, with a frequent occurrence of extremely large nuclei and amitoses (Fig. 7).

Discussion

In the course of investigations into the clinical and pathological effect of mustard nitrogen derivatives, particular attention has been devoted to their action on the liver, especially since it was found that these drugs were secreted with the bile [7, 8].

Experiments made in mice and rats have led the majority of the authors (LANDING et al., 13, 14 ; GRAEF et al., 1) to the conclusion that, administered by the intravenous and intraperitoneal route, the said chemicals do not induce serious hepatic damage.

Although, following the administration of large doses to mice, GRAEF et al. [1] observed that the liver had lost all its glycogen content and had undergone fatty degeneration, they were aware of, and gave expression to, the fact that the liver is highly resistant to the said chemicals. This resistance seems to vary from species to species. While, for example, ZIMMERMANN [18] succeeded in producing focal necroses in the liver of cats, he found rat livers to be completely resistant to mustard nitrogen.

Certain authors hold that not even a direct injection into the portal vein is capable of inducing conspicuous hepatic damage, while URAM et al. [16] described focal and more extensive hepatic lesions to develop in rats and rabbits after direct intraportal infusion of the drug. The theory advanced to explain hepatic resistance to mustard derivatives was its attribution to the low mitotic rate. To solve the problem, LANDING et al. [13] studied the behaviour of the liver during regeneration following partial hepatectomy. What they found was that, although mustard nitrogen diminished the number of mitoses and retarded the mitotic process, it failed to induce serious hepatic lesions. Thus, the relative immunity of the liver to mustard nitrogen does not seem to depend on a low mitotic index, since it persists also when division of the hepatic cells is rapid.

Thus, the majority of the authors are in agreement as to the liver being resistant to mustard derivatives. We must, however, remember that what they examined was the effect of single large doses and that they practically neglected to ascertain the effect of prolonged treatment.

For some years past, SUGÁR and KELLNER of our Institute [3] have been studying the effect of mustard nitrogen on the organism — on the liver among others — of healthy animals : while they, too, failed to observe hepatic injury following the administration of single large doses, after prolonged treatment with repeated small doses they observed the appearance of abnormal mitoses, karyorhexis, fatty degeneration and sometimes focal necrosis in the liver. What they regarded as most characteristic in these cases was the great variation in the size of nuclei, a phenomenon verified by nuclear measurements by MATKÓ, HOLCZINGER and KERESZTURI [4].

The results of our investigations, together with the findings of SUGÁR and KELLNER [3], as also the hepatic lesions observed in the course of our carcinogenetic experiments during nearly a year, seem to furnish clear evidence that certain drugs — while perfectly harmless for the liver if administered in single large doses — may provoke liver damage if given chronically in therapeutic or, as proved by our carcinogenetic experiments on mice, even in still smaller — homeopathic — doses. Our findings have been confirmed by GARATTINI et al. [17] who found large doses of BCM to inhibit hepatic regeneration in rats. Immune as the liver appears to be to these drugs in acute experiments, hepatic lesions may be expected to develop in clinical condi-

tions, *i. e.* treatment is protracted or periodical through a number of years. This is of particular importance in view of the fact that the drugs in question are not infrequently prescribed to patients who already suffer from hepatic disease other origin. The available clinical data are rather contradictory. DAMASHEK et al. [18] observed serious disturbances of liver function in some patients and found miliary necrosis in three cases, 9 and 19 days after the termination of mustard nitrogen treatment. ZIMMERMANN et al. [19], on the other hand observed functional disturbances of the liver to improve under the effect of mustard-nitrogen therapy.

We have examined *post mortem* the liver of several patients who had been treated with BCM. None of them displayed significant hepatic injury especially no such changes as would have been attributable to a toxic action of the drug. According to the Department of Internal Diseases of our Institute [20], no disturbance of hepatic function has been found in any of several hundred patients treated with BCM.

Observations made in animal experiments give nevertheless rise to the question whether the possibility of a later, gradually developing hepatic damage does not counterindicate the repeated, prolonged administration of the said preparations, of BCM in particular. We do not think it does; the chief "point of attack" of the drugs under review is the haematopoietic apparatus, and it goes without saying that neither clinicians nor pathologists must cease to pay careful attention to it. The manner of therapy, its continuation or interruption, must be governed by the behaviour of the haematopoietic system. Our above-described findings must nevertheless be regarded as a warning that in no treatment with the drugs in question should physicians neglect to pay due attention to the condition of the liver. The question arises whether treatment with the said chemotherapeutic agents should be accompanied not only by a constant control and protection of the blood-forming organs but also by a simultaneous control of hepatic function and an adequate protection of the liver.

Summary

1. Comparative experiments have been carried out to ascertain the toxic effect on the rat liver of mustard nitrogen and of some of its derivatives (Mitomen, Sarcolysine and BCM — Degranol).

2. A single LD_{50}-dose of any of these preparations caused the liver almost completely to lose its glycogen content within 24 to 48 hours. This was followed by serious fatty degeneration with the appearance of large droplets in the animals treated with BCM, while the liver of animals that had received one of the other drugs regained its glycogen content within a relatively short time with no graver residual symptom than a mild, focal fatty degeneration in the liver of some of the animals.

3. Chronic treatment with doses sufficient to inhibit malignant growth was followed by grave hepatic lesions only in the case of BCM (disintegration of he liver's lobular structure, variation of nuclear size, fatty degeneration, focal necrosis and dissociation, formation of multinuclear, synplasm-like structures and — especially in animals infected with tumourous

substances — focal proliferation of the bile ducts). However, changes of this kind were observed only in a minor part of the animals (in 2 to 3 of groups of ten).

Treatment with the given doses of the other chemicals, even on chronic application, led to no more than a focal fatty degeneration with the appearence of small droplets in the hepatic cells of some of the animals.

4. An approximate parallelism was found to exist between the result of liver function tests (bromsulphalein retention) and the gravity of morphological alterations.

5. Although, in clinical practice considerably smaller doses are administered, our present experimental findings make it imperative that with protracted administration of antitumour drugs careful attention be paid not only to the control and protection of the haematopoietic system but also to the control of hepatic function and an adequate protection of the liver itself.

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ПОРАЖАЮЩЕЕ ПЕЧЕНЬ ДЕЙСТВИЕ ПРОТИВООПУХОЛЕВЫХ СРЕДСТВ

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1. Авторы проводили над крысами сравнительные исследования поражающего печень действия горчичного азота и некоторых его производных (BCM — Дегранол, Нитромин-Митомен и Сарколизин).

2. Однократная полусмертная доза всех четырех фармакологических средств после 24—48 часов вызвала почти полное выделение всего содержания гликогена печени. У животных, подверженных действию BCM последовало тяжелое крупнокапельное жировое перерождение, в то время как в случае остальных 3 средств печень животных вскоре восстановила свое содержание гликогена, и в крайнем случае в печени отдельных животных осталось слабое, очаговое мелкокапельное жировое перерождение.

3. В случае хронического воздействия дозами, эффективными с точки зрения задерживания роста опухоли, BCM также привело к более тяжелым изменениям (расстройство дольковой структуры печени, изменение величины ядер, жировое перерождение, очаговый некроз и диссоциация, развитие многоядерных синплазмаподобных образований, а в частности у животных, привытых опухолью, очаговое разрастание желчных путей). Однако, эти изменения развивались лишь у меньшей части крыс, как правило у 2—3 из 10 животных.

В ходе хронического воздействия остальными 3 средствами при одинаковых дозах развивалось в худщем случае только у меньшей части животных очаговое мелкокапельное жировое перерождение.

4. Функциональная проба печени (задержка бромсульфалейна) более или менее была параллельной со степенью морфологических изменений.

5. Хотя в клинике применяются значительно меньше дозы, авторы на основании своих опытов над животными все же того мнения, что при длительной дозировке противоопухолевых хемотерапевтических средств, наряду с проверкой и защитой кроветворной системы, необходимо проверять функцию печени и проводить соответствующую защиту печени.

DIE LEBERSCHÄDIGENDE WIRKUNG VON TUMORHEMMENDEN MITTELN

K. LAPIS, L. NÉMET, M. BÉKÉS und E. UNGER

1. Die leberschädigende Wirkung von Senfnitrogen und einiger seiner Derivate (BCM-Degranol, Nitromin-Mitomen und Sarcolysin) wurde an Ratten untersucht.

2. Die einmalige halbletale Dosis sämtlicher Mittel rief in 24—48 Stunden eine fast vollkommene Glykogenverarmung der Leber hervor. Bei den mit BCM behandelten Tieren trat hiernach eine schwere, grosströpfige Fettdegeneration auf, während im Falle der anderen 3 Mittel die Leber der Tiere ihren Glykogengehalt bald zurückgewann und höchstens eine schwache herdige kleintröpfige Fettdegeneration zurückblieb.

3. Bei chronischer Behandlung mit tumorhemmenden Dosen, führte BCM zu schwereren Veränderungen (Auflösung der Läppchenstruktur der Leber, Variierung der Kerngrössen, Fettdegeneration, Herdnekrose und Dissoziation, Entstehung von mehrkernigen synplasmaartigen Gebilden, und besonders in den mit Tumor geimpften Tieren eine herdige Proliferation der Gallenwege.) Diese Veränderungen entwickelten sich indessen nur bei einem kleineren Teil der Versuchstiere, in der Regel nur bei 2—3 von 10 Tieren.

Bei chronischer Behandlung mit den anderen 3 Mitteln entwickelte sich ebenfalls nur bei einem Teil der Tiere herdige kleintröpfige Fettdegeneration.

4. Die Leberfunktionsprüfung (Bromsulphaleinretention) ergab mit dem Ausmass der morphologischen Veränderungen mehr oder minder parallele Ergebnisse.

5. Obwohl im Klinikum bedeutend geringere Dosen zur Anwendung gelangen, sind Verfasser auf Grund vorliegender Tierversuche der Meinung, dass bei chronischer Verabfolgung chemotherapischer tumorhemmender Mittel, neben der Kontrolle und des Schutzes des hämopoetischen Systems auch für die Kontrolle der Leberfunktion und einen entsprechenden Leberschutz gesorgt werden soll.

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