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THE EFFECT OF ACUTE AND CHRONIC URETHANE TREATMENT ON THE RAT

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Since *Schmiedeberg* [41], the first to make use in 1886 of urethane as a narcotic, the tumefacient effect and the tumour growth inhibiting action of the drug have also become known. Therapeutical results obtained with it are difficult to evaluate ; nor is there any consistent view on the mode and course of its action.

From among tumour growth inhibiting agents, podophylline, colchicine and nitrogen mustard had been studied at this institute with respect to morphological changes inducted by them. The present study purposes to ascertain the respective similarities and dissimilarities of their effects and the action urethane.

Moellendorf [31], *Haddow* and *Sexton* [10], and *Heilmeyer* [12] consider urethane a mitotic poison. *Dustin* [7] listed it with karyoclastic substances. Its antimitotic effect was demonstrated by *Warburg* [50] in eggs of the sea-urchin. *Guyer* and *Claus* [9] found that mitosis in the cornea of the rat is almost completely inhibited by urethane, which, according to *Moeschlin* [33] inhibits all mitotic phases. *Küster* [23] drew attention to the absence of dispirema. According to *Haddow* and *Sexton* [10], and *Moeschlin* [33] et al., urethane inhibits enzymatic processes. *Todd*, *Plentl* and *Schönheimer* [46] ascribe the inhibition of mitosis to a disturbance of nucleoprotein synthesis. *Beickert* [3] suggests, instead of the selective cytostatic effect, that certain cell-types are hypersensitive to urethane. *Masshof*, *Heinzell*, *von Rom* and *Siess* [29] credit the drug with an inhibitory action on all forms of cellular activity, and particularly on proliferating cells. *Lasnitzki* [25] interprets the stimulation of tumour growth in tumour cultures as an increase in surface activity.

Most authorities consider urethane a poison. According to *Landschütz* and *Müller* [24], the substance reacts with the constituents of the cytoplasm. *Kirschbaum* and *Bell* [19] consider it a capillary poison. *Murphy* and *Sturm* [35] hold that urethane induces the adrenal gland to secrete a lymphocytolitic factor, *Dury* and *Robin* [6] found on urethane treatment an identical fall of the leucocyte count in adrenalectomized and normal animals and, accordingly, argue against the view that urethane would exert its action through

the adrenal gland. Urethane was found by *Andreyev* [1] to cause injury to the central nervous system, by *Leibetseder* and *Kwerch* [27] to influence sympathetic or parasympathetic reactions, and by *Klima* and *Wengraf* [22] to damage the «leucocytic centre». *Paterson*, *Haddow*, *Thomas* and *Watkinson* [37] were the first to administer urethane to a patient with chronic myelosis. The result observed by *Paterson* [38] in lymphoid leukaemia was far less favourable. *Sandkühler* and *Wagner* [40] observed not only the destruction of «leukaemic» cells but also damage to normal ones. *Vlados*, *Yourovskaya*, *Shamshina* and *Svedsky* [47] consider urethane as an inhibitor of pathological leucopoiesis which at the same time stimulates the maturation of granulocytes and the regeneration of erythrocytes.

Studying differential blood counts in mice, rats, rabbits, cats and guinea-pigs, *Moeschlin* and *Naef* [34] found rats the least sensitive of all the animals tested. They recognized the dual effect of urethane, its paralyzing action and its capacity to increase cell proliferation. In leukaemia, in the first days urethane provokes excitation in the leukaemic cells before exerting its inhibitory action. The same phenomenon was observed by *Tischendorf* and *Fritze* [45] in normal subjects. In experimental leukaemia, urethane controls pathological leukaemic cells without restoring the blood count to normal (*Moeschlin*, [32]). According to *Tischendorf* and *Fritze* [45], protracted urethane treatment has the effect of rendering the bone marrow immature and involves a fall in the erythrocyte count, a rise in the number of reticulocytes and granulocytes and a concurrent diminution in the lymphocyte count. A comparable change was observed by *Hawkins* and *Murphy* [11] in the rat, mostly 3 hours after treatment. *Kirschbaum* and *Lu* [20] reported a decrease in the number of mitoses in myeloid elements, *Berman* and *Axelrod* [4] a fall in the leucocyte count in mice. *Voit* and *Hodeige* [48] found in the rat that large doses of urethane induce toxic granulation in the leucocytes and an increase in the number of young forms.

Methods

A 10 per cent aqueous solution of urethane was administered by the intraperitoneal route to a total of 105 rats, mostly white males, weighing 120 to 180 g each. The resulting organic changes were examined in 34 animals, in two series. To study the acute action, 14 of the rats were each given one 100 mg dose per 100 g of body weight. The animals were killed 1, 2, 6, 12, 24, 48 and 72 hours after administration of the drug. For studying the chronic action, the former dose, found excessive in the acute phase of the experiment, was reduced to 70 mg for each 100 g of body weight, and this was administered to 20 rats twice a week through a period of 10 weeks. Two animals were killed each week, the last pair at the end of the tenth week, 24 hours after the last injection. As a control, animals from the same strain were used.

For microscopical examination, the spleen, thymus, lymph nodes, liver, kidneys, lungs, intestines and testicles were worked up. Fixation was made in 4 per cent formaldehyde, Susa's and Carnoy's solutions. For staining the sections, haematoxylin-eosin, occasionally Heidenhain's iron haematoxylin, van Gieson's and Mallory's dyes, Weigert's fibrin dye, methyl-green pyronine and Feulgen's stain were used.

The action of urethane on blood count and bone marrow count was studied in 71 animals, the effect of one dose having been observed in 35 animals, in 5 series, 1, 2, 6, 12, 24, 48 and 72 hours after the injection of 100 mg per 100 g of body weight. 20 rats were administered

70 mg per 100 g weight twice a week. Two animals were killed every week, each pair 24 hours after the last injection. The wide variations in the rat's blood count called for the use of a large number of controls. Blood was obtained from the caudal vein, bone marrow from the femur.

It had to be settled whether in protracted treatment, the response was the same to each administration of urethane. Therefore 8 rats each were examined 1, 2, 6, 12 and 48 hours after the last injection of the chronic course.

No pathological change in the organs was present on gross examination.

Histological changes

As early as after an hour, the sinuses of the lymph nodes are seen to be distended and to contain epithelial cells, lymphocytes, plasmocytes and a few eosinophils. The medulla is oedematous, the reticular cells are swollen ; somewhat later, the germinative centres are also damaged, along with symptoms of sinus catarrh. After 6, 12, or 24 hours the germinative centres are large, the dividing nuclei disintegrate into Feulgen positive globules and chromatin granules some of which are bare, while possess a thin cytoplasm border. There occur eosinophilic cytoplasm spheres free of nuclear substance (Fig. 1). The detritus fills the lymph sinuses. The number of dividing cells increases, and among them there are some which already show pyknomitosis. The cell destruction tends to narrow down the cortical substance. Some of the lymphocytes are shrunken. Most of the detritus is excreted within 48 hours.

In animals under chronic treatment it is again the germinative centres that react with gradual slight reticular hyperplasia, rarely with fibrosis. The changes correspond to those seen after repeated acute injury.

The thymus displays essentially similar changes which, however, are slighter than those in the lymph nodes. After 6 hours the number of dividing cells diminishes while disintegration becomes quite marked. Plasmocytes occur in unusually large numbers. After 48 hours restitution is nearly complete.

The spleen sinuses dilate in the first 2 hours ; their endothelium is swollen, the cells round off and come loose ; pyknotic nuclear substance, lymphocytes and leucocytes are present in the sinuses. The changes remain pronounced for 6 to 24 hours. The reaction in the germinative centre is as in the lymph nodes.

After 24 hours, the changes lose in severity ; cell disintegration in the follicles becomes less marked, the germinative centres resume their regular structure, there are less nuclear remnants in the pulp. Reticular giant cells occur sporadically.

Prolonged treatment induces an increase in the number of reticular giant cells, the follicles shrink. In certain cases there is incipient fibrosis in the trabecules and the sinus walls.

In the duodenum the covering epithelial cells of the mucous membrane become swollen in the first 2 hours. There is copious secretion ; the degenerated cells are forced into the lumen. The villose stroma is oedematous and infiltrated

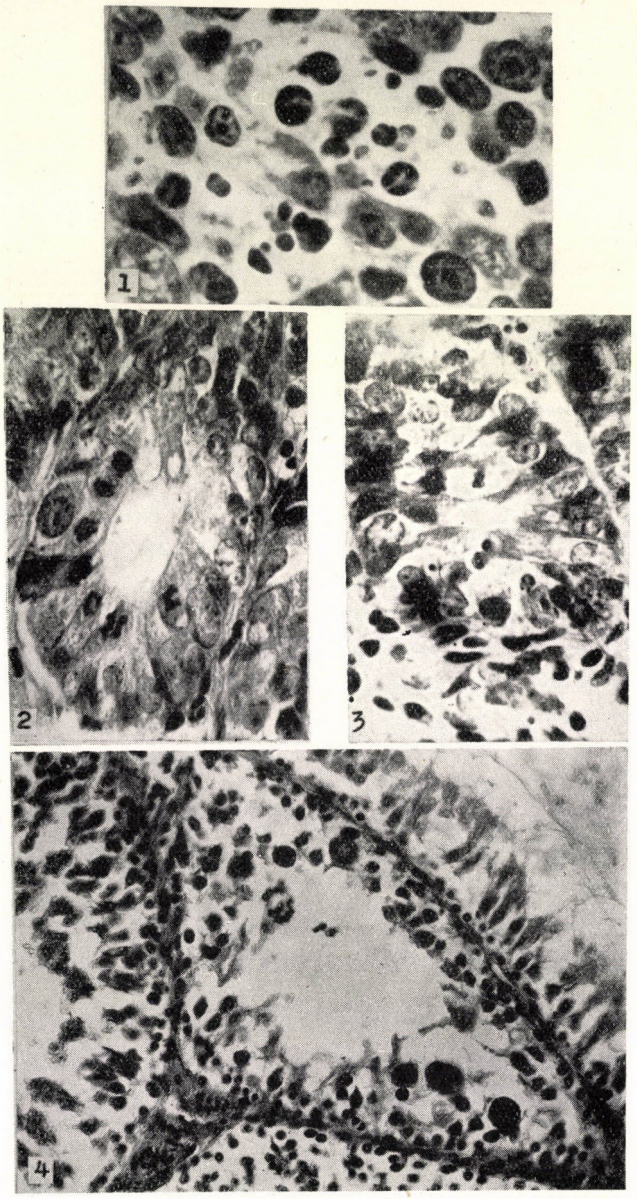


Fig. 1. Lymph node, dissociated cells in germinative centres. Disintegration of damaged cells, formation of chromatin granules and cytoplasm globules. (Acute, 12 hours, H. E. x 1600)
Fig. 2. Duodenum. Increased cell division, pyknomitosis in Lieberkühn's crypts. (Acute, 12 hours, H. E. x 820)
Fig. 3. Duodenum. Nuclear fragments, cytoplasm globules in Lieberkühn's crypts and in the interstices. (Acute, 12 hours, H. E. x 820)
Fig. 4. Testicle. Giant cells in testicular channels. (Acute, 6 hours, H. E. x 290)

with leucocytes. 6 hours later some increase occurs in the number of cells in Lieberkühn's crypts, followed by disintegration of damaged cells.

The change reaches its severest stage after 12 hours, with the covering epithelial cells swollen and their connections disrupted, the nuclear chromatin is finely granular, the cytoplasm light, vacuolated. The cytoplasm of the Paneth cells becoms coarse. Monasters preponderate among dividing cells which show all the stages of mitosis. Pyknomitosis is frequent (Fig. 2). Disintegration of injured cells results in the formation of chromatin globules surrounded with acidophilic cytoplasma, Feulgen-positive nuclear remnants of varying shapes and basophilic globules (Fig. 3). Destroyed cells are also found in the lymphatic spaces of the interstitial connective tissue. Large mononuclear cells phagocyte the detritus. There is marked siderophagy as well. In 72 hours the process has run its course.

After protracted treatment the histological changes correspond to those found 24 hours after a single injection.

Similar, though considerably slighter in degree, are the changes in other portions of the small intestine. The stomach shows no change of any account.

The damage to the testicles is demonstrable a little later, after the lapse of 6 hours. Spermiogenesis is generally maintained. In a few testicular channels the layers of germinative epithelium become indistinct, a loosening of internal cell layers, detachment and propulsion into the lumen of most prespermatids occurs, with consequent vacuolization in the cells that have become free. Chromatin dissolves in the nuclei, giving place to oval, crescent-shaped and kidney-shaped formations (Fig. 4). The vacuolized nuclei, disposed in the form of a wreath on the periphery of the cells, are more or less reminescent of Langhans type giant cells (Fig. 5). Return to normal sets in after 48 hours.

In chronic treatment the changes are often analogous, though on a more extensive scale.

Conditions in the liver are highly variable and, accordingly, difficult to evaluate. There is a low degree of stasis in the first hours, followed by slight cellular infiltration 2 hours later. After 6 hours a great number of Kupffer cells shrink and are found detached, or phagocyted by intact Kupffer cells. The cytoplasm of the hepatic cells turns granular, coarse and vacuolated (Fig. 6). Elsewhere there is conspicuous variation in the size of cells. The changes outlast even 72 hours.

Differences in nuclear size persist throughout chronic treatment.

The kidneys display hardly any change. As in the liver, there is no disintegration. The glomeruli are generally hyperaemic; endothelial cells are swollen. The basal membrane is oedematous in some of the glomeruli. In the primary convoluted tubules the epithelium is oedematous, in the collecting channels the epithelial cells contain vacuoles. The difference in nuclear size persists throughout chronic treatment.

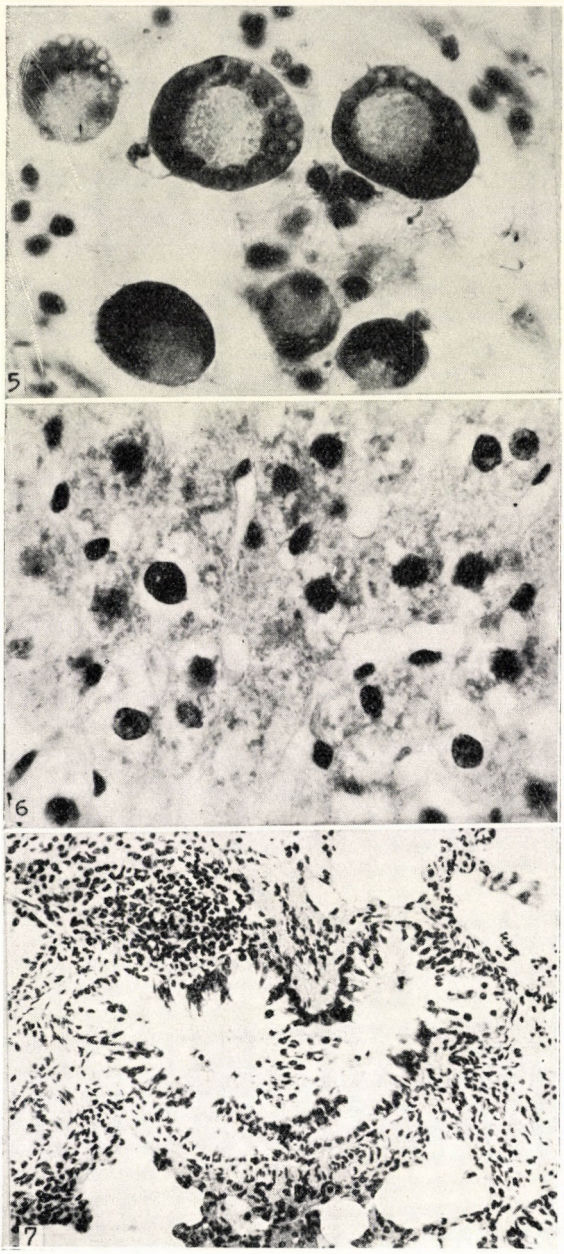
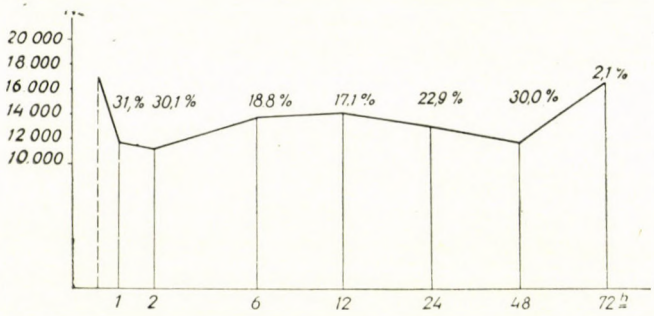


Fig. 5. Testicle. Cells reminiscent of Langhans type giant cells. (Acute, 24 hours, H. E. x 1600)
Fig. 6. Liver. Granular cytoplasm is droplets. Conspicuous variation in nuclear size. (Acute, 48 hours, H. E. x 940)
Fig. 7. Lung. Desquamated cells of signet-ring shape in the bronchi. (Acute, 72 hours, H. E. x 310)

In the lungs there are also few changes. After 2 hours, leucocytes, tissue eosinophils and macrophage cells replete with haemosiderin appear in the septa. The bronchial epithelium is loose and there is increased secretion. With their nucleus forced aside, the cells assume the shape of a signet-ring (Fig. 7). Elsewhere the bronchial epithelium shrinks. Some bronchi are dilated. The lymphatic follicles show the same behaviour as lymph nodes. The changes are still present after 72 hours.

The degree of secretion from the bronchial epithelium is considerably lower in chronic treatment. In the heart muscle there is no change apart from slight differences in nuclear size.

TABLE I.



Mean WBC values in 5 acute series. Above the tuble, percentual diminution. Dotted line, values before treatment

TABLE II

Acute series 1.

Leucocyte count before treatment	12000	14800	18200	20200	19600	12000	20200
Hours after injection	1	2	6	12	24	48	72
Leucocyte count after treatment	9600	9600	15200	16600	14400	10400	21400
Diminution %	20,0	35,1	17,5	17,8	26,5	13,3	—

Variations in differential count in acute series No. 1.

TABLE III

Acute series 1.

Lymphocyte per polynuclear before treatment	75/24	75/23	75/21	76/18	86/14	77/20	78/19
Hours after injection	1	2	6	12	24	48	72
Lymphocyte per polynuclear after treatment	55/41	63/36	72/27	61/36	69/28	71/27	77/21

Variations in differential count in acute series No. 1. : Percentage distribution of lymphocytes and polynuclear leucocytes.

TABLE IV

Acute series 1.

Lymphocyte per polynuclear before treatment	9000 / 2880	11110 / 3404	13640 / 3822	15352 / 3636	16856 / 2744	9240 / 2400	15756 / 3838
Hours after injection	1	2	6	12	24	48	72
Lymphocyte per nuclear after treatment	5280 / 3936	6048 / 3456	10944 / 4104	10126 / 5152	9936 / 4032	7384 / 2808	16478 / 4494
Decrease in lymphocyte count in per cent	41,3	45,5	19,7	34,4	41,0	20,0	—

Same as Table III in absolute values.

Under chronic treatment, the change appearing in the organs of animals killed 1, 6, 12 and 48 hours after the last injection coincide with those found at the same intervals following one injection.

The effect of urethane on blood count and bone marrow was studied in a separate series. In 5 acute series, the average WBC decreased by 17,1 to 31,1 per cent upon urethane treatment (Tables 1 and 2). The change sets in 1 hour after treatment and continues for 48 hours, to return to normal after 72 hours. We also made a study of the differential count (Table 3) 19,7 to 45,5 per cent absolute lymphopenia and relative leucocytosis were observable within the reduced WBC (Table 4). Acute treatment was found to bring about no change in the erythrocyte count.

In the course of chronic treatment there is no fall in WBC except in certain cases. The change seems transient; here again the damage corresponds to repeated acute changes. If after the last injection of prolonged treatment blood counts are made at the same intervals as after the single dose constituting acute treatment, variations in the WBC will be the same as after a single dose. Suspension of treatment results in return to normal.

We could trace no appreciable change in the bone marrow. In a few cases of acute treatment there was a rise in the number of erythroblasts and a fall in that of polynuclear leucocytes. No change was observed in the number of dividing cells. Increase in the number of reticulocytes was rare in chronic treatment.

Discussion

A single dose of urethane causes pronounced changes in the lymphoid organs after one hour already. The lymph nodes exhibit sinus catarrh in the first 2 hours. In the germinative centres there is some slight increase in the

number of dividing cells, soon followed by disintegration into chromatin fragments and globules of cytoplasm. The change is most marked between 6 and 24 hours ; thereafter the detritus is excreted and the lymph node regenerates. Contrary to *Berman* & *Axelrod* [4] we have observed a slight increase instead of a fall in the number of mitoses in the germinative centres. Their observation of pyknosis of lymphocytes coincides with our findings.

The process in the thymus is along the same lines, expect for a diminution in the number of dividing cells after the lapse of 6 hours.

The spleen exhibits comparable changes. Our investigations bear out *Voit* and *Hodeige*'s [49] and *Lennert*'s [28] description of a contraction of the follicles. *Sinclair* [43] emphasizes the increase in the number of giant cells.

Duodenal changes were very striking. According to *Green* and *Luchbaugh* [8], the tolerated dose of urethane does not interfere with mitosis, this being inhibited only by a next-to-lethal dose. *Klein* [21] found disturbance of mitosis in mice under the influence of minor doses (50 mg/100 g). As a result of medium doses (1500 mg/100 g) he reported sporadic pyknomitoses, which grow alldominating on administration of large doses (500 mg/100 g). We found the action to reach a marked degree after 6 hours, and to attain its peak in 12 hours' time, involving an increase in the number of dividing cells in the crypts. Pyknomitosis, however, was found to account for only a small fraction of the mitose. The damaged cells disintegrate and are converted, in Lieberkühn's crypts, into nuclear fragments and plasm globules, which make their way even into the interstitial connective tissue.

Cellular disintegration is at its highest between 6 and 24 hours ; in 72 hours the process is over.

The damage to the testicles becomes evident at the same intervals. In some of the channels the epithelium becomes loose and is cast off. The desquamated cells are vacuolated and soure transform into giant cells. The process runs its course in 48 hours.

In the liver, the first 2 hours make the Kupffer cells slightly to shrink. After 6 hours, the cytoplasm of hepatic cells becomes granular and vacuolated. The vacuolar degeneration has already been described by *Berman* and *Axelrod* [4]. *Voit* and *Hodeige* [49] found incipient necrosis, *Sinclair* [43] giant cells, *Klein* [21], in the liver of mice, granular hydropic swelling and pyknosis on administration of a 150 mg/dose and hydropic vacuolate swelling on injection of a 50 mg/dose of urethane. In our experience, the action in the liver is protracted, and we also observed variations in the nuclear size.

Dunn & *Larsen* [5] observed hyaline degeneration in the renal glomeruli of mice. *Kirschbaum* and *Bell* [19] described thickening of the capillary membrane of the glomerules, resulting in a picture resembling lipoid nephrosis. *Juhász*, *Baló* and *Kendrey* [17] found glomerular injury in the kidneys of mice. Our own observations revealed rarely changes in the kidneys. (Oedematous

infiltration of the glomerular basal membrane, variations in the size of epithelial cells.) *Nettleship & Henshaw* [36], *Henshaw & Meyer* [13, 14], *Sinclair* [43], *Baló, Juhász & Varga* [2] induced pulmonary adenoma in mice. *Jaffé* [16] observed also in addition to pulmonary adenoma liver tumour in rats. *Rosin* [39] described perivascular oedema and incipient proliferation of the bronchial epithelium 48 and 72 hours after injection and considered the extravasate to promote proliferation. We have found no substantial changes apart from epithelial desquamation and the reaction of lymph follicles ; no tumour had been formed in the course of a 10-week course of treatment, nor was there any sign of changes of a preadenomatous character. It must be assumed that our rat strain does not easily develop adenoma.

Tischendorf and *Fritze* [45] could discern no change whatever in the visceral organs.

We found urethane to decrease the leucocyte count over a period of 48 hours. With the lapse of 72 hours the count returns to normal. According to *Schoen* [42] urethane would act on leukaemic cells only. Our own findings show that on the effect of urethane the leucocyte count seemingly increases, while lymphocytes decrease in number, indicating that the drug has damaged even the unaffected lymphocytes.

On chronic administration of colchicine we had observed toxic panmyelophthisis to develop *(Matkó—Haraszti* [30]), a change which did not occur on prolonged urethane treatment.

As stated, changes arising during chronic treatment correspond to repeated acute reactions. This hypothesis is substantiated by the return to normal of the blood counts upon discontinuation of treatment and by the fact that the changes found in the blood of rats killed at various intervals after the last injection are identical with those observed at the corresponding intervals of acute treatment.

The bone marrow showed no appreciable damage. Single administration resulted in an increase in the number of nucleate erythrocytes and a fall in segmented neutrophils. The number of dividing forms did not change. Whereas chronic colchicine treatment had been found by us *(Matkó* and *Haraszti* [30]) to give rise to fibrosis in the bone marrow, apart from a few cases not even reticular increase was observed to develop on the effect of urethane.

A comparison of urethane-induced changes with those brought about by colchicine, podophylline, and nitrogen mustard shows urethane to bring about similar, but considerably slighter damage. The time factor in the process is likewise analogous. Colchicine exceeds urethane in its increasing cell division, pyknosis and cell disintegration in the duodenum. Disintegration in the lymphoid tissues and the testicles is equally more marked on the action of colchicine *(Kellner—Matkó* [18]), podophylline *(Holczinger—Kellner* [15]), and nitrogen mustard *(Sugár—Kellner* [44]) alike.

Lehman and *Hadron* [26] classify antimitotic agents into an inhibitory and a destructive group. The former acts on the cytoplasm, the latter directly on the nucleus. On administration of urethane there was nuclear damage in the duodenum, the lymphoid organs and the testicles. In the liver, the cytoplasm suffered the most conspicuously. This fact, however, still does not suffice to substantiate *Landschütz*' interpretation of urethane as a cytoplasmatic poison.

Increase in the number of dividing cells occurs in the very organs that show the highest rate of cell disintegration. While colchicine inhibits cell division in the metaphase, urethane leaves room for all the mitotic stages. We accordingly disagree with *Küster* [23] who claimed that mitosis is inhibited by urethane administration.

The varying nuclear size in the liver and the kidneys, the swelling of reticulocytes and the pyknosis of lymphocytes show that urethane affects not only dividing cells but resting ones as well. The changes concerned are, however, not widespread enough to justify the claim of *Masshoff* et al. [29] that urethane inhibits all forms of cellular activity.

It may further be asked how the quick rate of restitution is to be explained. The reason cannot possibly lie in mitosis there being no increase in the number of dividing cells in the restitution phase. It must therefore be assumed that amitosis is greatly concerned in restitution.

The changes brought about by urethane cannot be regarded as specific; they occur also in other types of poisoning. Repeated treatment leads to the recurrence of the injuries sustained on single administration. Discontinuation of protracted treatment results in return to almost normal of the morphological picture.

Summary

(i) The action of urethane on the organs, blood and bone marrow of rats has been examined.

(ii) The gravest damage is suffered by the lymphoid organs, the duodenum and the testicles.

(iii) The action in the lymphoid organs and the duodenum is at its peak for 6 to 24 hours, and is prolonged in the liver and kidneys.

(iv) Changes induced by chronic treatment correspond to recurrent acute injury.

(v) The changes caused are considerably less severe than on the effect of colchicine, podophylline or nitrogen mustard intoxication.

(vi) The white blood cell count keeps declining over a period of 48 hours and returns to normal after 72 hours.

(vii) In the differential count there develop absolute lymphopenia and relative leucocytosis.

(viii) Chronic treatment results in no aplastic destruction in the bone marrow as does administration of colchicine.

(ix) Urethane exerts its action on both resting and dividing cells.

(x) Our results do not suffice to throw light on all aspects of the mode of action of urethane.

REFERENCES

1. Андреев, Ф. А.: Cit. Кассирский И. А. (1950) Клиническая Мед. *11*, 11. — 2. **Baló, J., Juhász, J., Varga, Gy.:** (1953) Über durch Urethan verursachte Lungenadenome. Acta Morph. Hung. *3*, 101. — 3. **Beickert, A.:** (1950) Über die Affinität des Urethans zu verschiedenen Zellformen des normalen und leukämischen Blutes. Arch. exper. Path. Pharm. *210*, 473. — 4. **Berman, L., Axelrod, A. R.:** (1948) Effect of urethane on malignant diseases. Am. J. Clin. Path. *18*, 104. — 5. **Dunn, Larsen:** Cit. *Kirschbaum A. & Bell E. T.* — 6. **Dury, A., Robin, E. D.:** (1948) Urethane induced lymphopenia in normal and adrenalectomised rats. Endrocrinology, *42*, 320. — 7. **Dustin, A. P.:** Cit. *Leibetseder, F. & Kwerch, K.* — 8. **Green, J. W., Luchbaugh, C. C.:** (1949) Histopathologic study of the mode of inhibition of cellular proliferation by urethane. Effect of urethane on Walker rats cc. 256. Cancer Res. *9*, 199. — 9. **Guyer, M. F., Claus, P. E.:** (1947) Effects of urethane on mitosis. Proc. Soc. exper. Biol. and Med. *64*, 3. — 10. **Haddow, A., Sexton, W. A.:** (1946) Influence of carbamic esters on experimental tumours. Nature *157*, 500. — 11. **Hawkins, J. A., Murphy, J. B.:** (1925) The effect of ethylurethane anesthesia on the acid-base equilibrium and cell contents of the blood. J. exp. Med. *42*, 609. — 12. **Heilmeyer, L.:** Cit. *Beickert* (1944). 13. **Henshaw, P. S., Meyer, H. L.:** Minimal number of anesthetic treatments with urethane required to induce pulmonary tumours. J. Nat. Canc. Inst. *4*, 523. — 14. **Henshaw, P. S., Meyer, H. L.:** (1945) Further studies on urethane induced pulmonary tumours. J. Nat. Canc. Inst. *5*, 415. — 15. **Holczinger, L., Kellner, B.:** (1953) The effect of acute and chronic podophylline poisoning on the organs of the rat. Acta Morph. Hung. *3*, 306. — 16. **Jaffé, W. G.:** (1947) Carcinogenic action of ethylurethane on rats. Cancer Res. *7*, 107. — 17. **Juhász, J., Baló, J., Kendrey, G.:** (1953) Kísérleti glomerulosklerosis. Experimental glomerulosclerosis. Kísérletes Orvostud. *5*, 196. (Hungarian only) — 18. **Kellner, B., Matkó, L.:** (1953) The effect of acute and chronic colchicine poisoning on the organs of the rat. Acta Morph. Hung. *3*, 125. — 19. **Kirschbaum, A., Bell, E. T.:** (1947) Induction of renal glomerular lesions by urethane in imbred mice susceptible to spontaneous glomerulonephritis. Proc. Soc. exper. Biol. and Med. *64*, 71. — 20. **Kirschbaum, A., Lu, C. S.:** (1947) Effect of urethane on maturation of leukocytes of mouse myelogenous leukaemia. Proc. Soc. exper. Biol. and Med. *65*, 62. — 21. **Klein, H.:** (1951) Zur pathologischen Anatomie der Alarmreaktion nach Kerngiften, Virch. Arch. *320*, 93. — 22. **Klima, R., Wengraf, G.:** (1949) Über die Einwirkung von Urethan und andere Schlafmitteln auf die zentralnervöse Blutsteuerung bei Blutkrankheiten. Wien. med. Wschr. *99*, 43. — 23. **Küster, F.:** (1946—47) Urethan als Mitosegift. Klin. Wschr. *24—25*, 664. — 24. **Landschütz, Müller, D:** (1949) Zur Wirkung des Aethylurethans am Mäuse Ascitestumor. Zschr. Krebsforsch. *56*, 373. — 25. **Lasnitzki:** (1949) Some effect of urethane on the growth and mitosis of normal and malignant cells in vitro. Brit. J. Canc. *3*, 501. — 26. **Lehman, Hadron:** Cit. *Kellner—Matkó.* — 27. **Leibetseder, F., Kwerch, K.:** (1951) Urethanwirkung und vegetatives Nervensystem. Zschr. klin. Med. 148, 180. — 28. **Lennert, K.:** (1948) Über Morphologie und Mechanismus der Urethanwirkung. Klin. Wschr. 735. —29. **Masshof, W., Heinzell, W. von Rom, D., Siess, M.:** (1948) Experimentelle Untersuchungen über die Wirkung von Urethan auf Phagocytose, Speicherung und Entzündung. Klin. Wschr. *26*, 397. — 30. **Matkó, L., Haraszti, A.:** (1952) The effect of chronic colchicine intoxication on the blood count and on the bone marrow. Acta Morph. Hung. *2*, 219. — 31. **Moellendorf, S.:** Cit. *Moeschlin—Naef.* — 32. **Moeschlin, S.:** (1947) Zum Wirkungsmechanismus des Urethans bei Leukämien. Helv. Med. Acta. *14*, 279. — 33. **Moeschlin, S.:** (1948) Klinische und experimentelle Untersuchung zum Wirkungsmechanismus des Urethans. Schweiz. med. Wschr. *78*, 988. — 34. **Moeschlin, S.—Naef, A.:** (1948) Einfluss des Urethans auf das Blutbild der Laboratoriumstiere. Schweiz. med. Wschr. *78*, 458. — 35. **Murphy, J. B., Sturm, E.:** (1946) The effect of urethane on lymphatic leukaemia in rats. Science, *104*, 427. — 36. **Nettleship, Henshaw:** Cit. *Baló.* — 37. **Paterson, E., Haddow, A., Thomas, I., Watkinson, J. M.:** (1946) Leukaemia treated with urethane compared with deep X ray therapy. Lancet. *1*, 677. — 38. **Paterson, E.:** Cit. *Berman—Axelrod.* — 39. **Rosin, A.:** (1949) Early changes in the lungs of rats treated with urethane (Ethyl carbamate) Cancer Res. *9*, 582. — 40. **Sandkühler, S., Wagner, I.:** (1949) Über Urethanschäden an Leukocyten. Dtsch. med. Wschr. *74*, 912. — 41. **Schmiedeberg:** Cit. *Beickert.* — 42. **Schoen, R.:** (1946—47) Urethan im Lichte der Hämatologie. Klin. Wschr. *24—25*, 488. — 43. **Sinclair, J. G.:** (1949) Delayed action of urethane producing diverse tumours in mice. Texas Rep. Biol. Med. *7*, 456. — 44. **Sugár, J., Kellner, B.:** (1953) Effect of acute and chronic nitrogen mustard treatment on the organs of the rat. Acta Morph. Hung. *3*, 233. — 45. **Tischendorf and Fritze:** (1948) Tierexperimentelle Untersuchungen zur Wirkung auf das Blut und die blutbildenden Gewebe. Klin. Wschr. *26*, 11. — 46. **Todd, Plentl, Schönheimer:** Cit. *Leibetseder.* — 47. **Владос, Х. Х., Юровская, И. И., Шамшина, Е. В., Сведский:** (1949) Лечение хронических леукозов уретаном. Терап. Арх. *6*, 78. — 48. **Voit, K., Hodeige, H. J.:** (1949) Experimentelle Untersuchungen über die Urethanwirkung bei weissen Ratten. Med. Klin. *35*, 1115. — 49. **Voit, K., Hodeige, H. J.:** (1949) Nuclealstudien bei experimenteller Urethanvergiftung. Ärztl. Forsch. *3*, 387. — 50. **Warburg:** Cit. *Durr—Robin.*

ДЕЙСТВИЕ ОСТРОЙ И ХРОНИЧЕСКОЙ ОБРАБОТКИ УРЕТА́НОМ НА ОРГАНЫ КРЫС

А. ХАРАСТИ и Б. КЕЛЛЬНЕР

1. Авторы исследовали в опытах над крысами действие уретана на органы, картину крови и костный мозг этих животных.

2. Больше всего повреждаются лимфоидные органы, двенадцатиперстная кишка и семенник.

3. Максимум действия продолжается в лимфоидных органах и в двенадцатиперстной кишке от 6–24 часов, в печени и в почке действие более длительное.

4. При хронической обработки наблюденные изменения соответствуют повторным острым повреждениям.

5. Изменения проявляются гораздо слабее, чем в случае отравления колхицином, подофиллином или горчичным азотом.

6. В картине крови число лейкоцитов уменьшается в течение 48 часов, по истечению 72 часов оно становится нормальным.

7. В картине крови возникает абсолютная лимфопения с относительном лейкоцитозом.

8. В костном мозгу не проявлялось в течение хронической обработки апластического разрушения мозга, как это имеет место под действием колхицина.

9. Уретан оказывает действие не только на делящиеся клетки, но и на покоющие клетки.

10. Проведенные исследования авторов не выясняют в достаточной мере механизм действия уретана.

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