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EFFECT OF COLCHICINE, PODOPHYLLIN AND NITROGEN MUSTARD ON THE RESTING CELLS OF THE ORGANS

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(Received May 12, 1955)

It was observed in earlier investigations that colchicine, podophyllin and nitrogen mustard, besides affecting dividing cells, induce changes also in the non-dividing, so-called resting or inactive, cells of the various organs (KELLNER and MATKÓ, HOLCZINGER and KELLNER, SUGÁR and KELLNER). Such changes were seen to occur in the size of the nuclei and the fine structure of the chromatin substance. Although there exists an abundant morphological literature dealing with karyoklastic substances it contains but scanty data on the effect produced by these agents upon resting cells. Apart from the pyknosis and disintegration of mature blood cells no longer capable of mitosis (WIDMANN, MATKÓ and HARASZTI), some authors studied the effect of colchicine upon non-dividing hepatic and renal cells (HAMPERL, KANTNER, MISURSKY and DOLIANSKY, LAMBERS).

Since our earlier investigations had been concerned chiefly with the effect upon dividing cells, and since we had failed to find in the literature satisfactory reports on the behaviour of resting cells under the influence of the said agents, we have studied the effect of colchicine, podophyllin and nitrogen mustard upon organs with a low mitotic index, such as the liver, kidney, and the heart muscle.

Materials and methods

A total of 200 rats was used in the experiments. A single dose of colchicine (200 γ/100 g), podophyllin (3000 γ/100 g) and nitrogen mustard (200 γ/100 g), respectively, was administered. The effective dose of nitrogen mustard was given in some cases on each of three consecutive days. On the basis of experience obtained in experiments on organs possessing a high mitotic activity, part of the animals was killed in the incipient stage of the poisoning, another part at the time of the maximum effect, and the rest after its subsidence. Formaldehyde, Susa's fluid, sublimate with glacial acetic acid, and alcohol were used to fix the liver, kidney, and heart muscle. Staining the sections with haematoxylin-eosin, Heidenhain's iron haematoxylin and Best's carmin, they were also tested in some cases for the Feulgen reaction. Fat was demonstrated by Sudan III. Besides determining differences in nuclear size by histological methods, its variations were registered by curves based on direct nuclear measurements. We measured, at the above said critical moments, the diameter of the cell nuclei in the periglomerular tubules of the kidney and the central part of the lobules of the liver by means of a Zeiss eyepiece micrometer. Knowing that measurement of the diameter involves many errors, in some cases also the volume of the cell nuclei was determined. These values are shown in diagrams based on Hintzsche's logarithmic

scale. In order to evaluate deviations in nuclear size, significance computations as described below were made. Variations in the size of the nuclei of heart muscle cells were determined by planimetry.

Histological examinations

Histological changes in the liver, kidney and heart muscle consequent upon the administration of colchicine, podophyllin and nitrogen mustard have

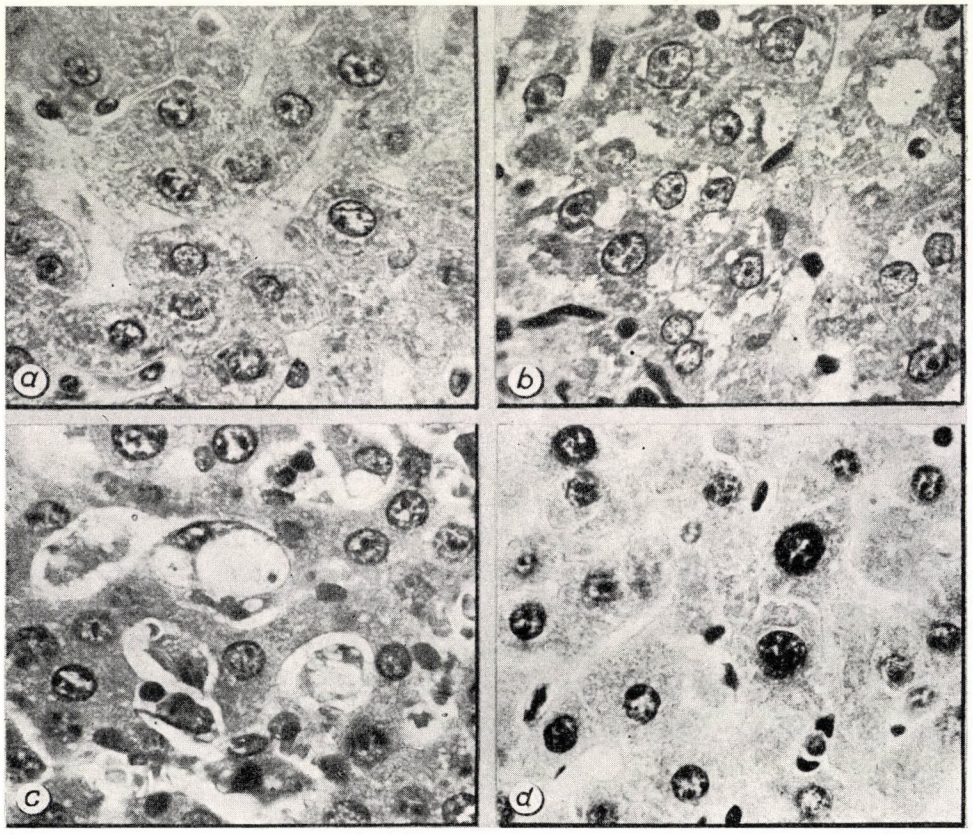

Fig. 1. Liver. Changes in structure and nuclear size. *a)* control, *b)* colchicine, *c)* nitrogen mustard, *d)* podophyllin. ×900 (Haematoxylin eosin)

been described in our earlier communications, so that we shall restrict ourselves to dealing with changes occuring in resting cells.

As regards the liver, all of the three said substances provoke notable changes in the size of the cell nuclei. Part of the nuclei was seen to have become smaller, with the chromatin condensed; the nuclear membrane was sharply distinct, and the nucleolus not infrequently missing. Another part of the cells

was seen to have grown, with the nuclear chromatin becoming irregular, powder-like or coarsely granular. The nucleolus in such cells is usually large, staining faintly and surrounded in some cases by basophilic granules. Nitrogen mustard and colchicine induce in many cells the development of large, circular, acidophilic, Feulgen-negative disklike bodies which take the place of the nucleolus.

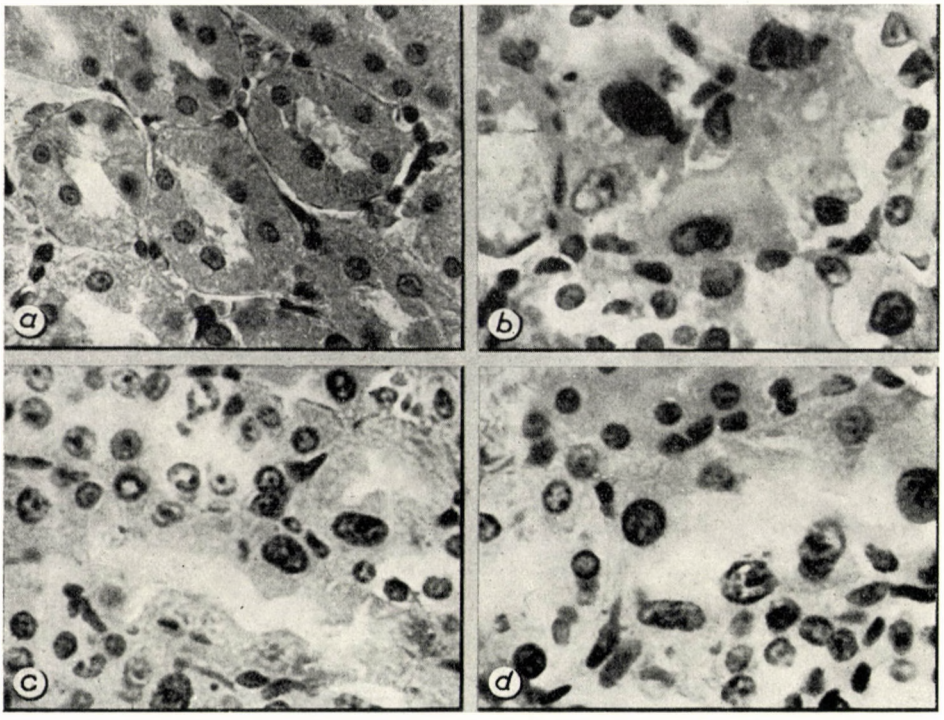

Fig. 2. Kidney. Nuclei of varying sizes and plasmatic injury in the periglomerular tubules *a)* Control, *b)* colchicine, *c)* nitrogen mustard, *d)* podophyllin. *a)* ×900, *b)*—*d)* ×1000 (Haematoxylin eosin)

No such intranuclear bodies appear in the liver of animals treated with podophyllin. The protoplasm of the cells becomes more or less swollen, coarsely granular, often vacuolated (Fig. 1).

As regards the kidney, all of the three poisons cause notable changes in the size of the cell nuclei of the tubular epithelium and induce the development of the said intranuclear disks.

Administration of podophyllin is followed by no other changes. Nor does nitrogen mustard seem to produce other significant structural changes, except — especially upon repeated doses — a fragmentation of the nucleus and often a complete desquamation of the tubular epithelium. Treatment with

colchicine occasions, on the other hand, tubular lesions of such a grave kind that the tubules become practically undistinguishable. All that can be seen in such cases is that the most gravely damaged tubules are those around the glomeruli and on the border between cortex and medulla (Fig. 2).

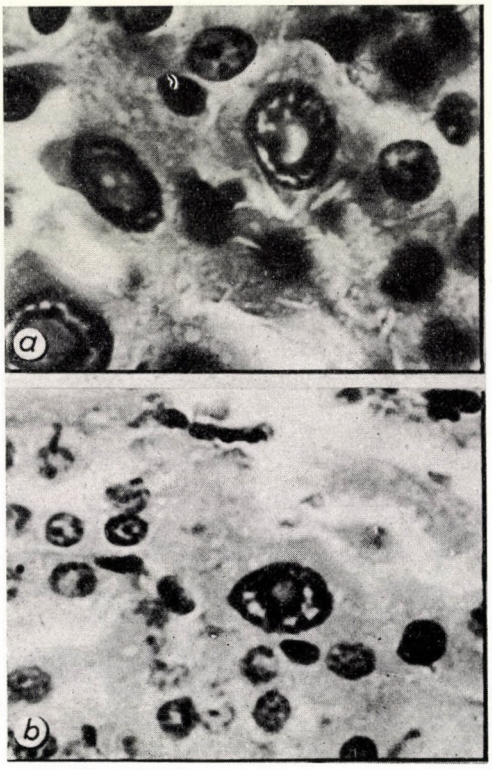

Fig. 3. Intranuclear disks in renal epithelial cells. *a)* Colchicine, *b)* nitrogen mustard. *a)* ×1500 *b)* ×1100 (Haematoxylin eosin)

The chromatin substance of the shrunken cells condenses, stains dark, and their nucleolus usually becomes unrecognizable. The enlarged cells stain faintly, and their chromatin displays a reticular pattern. The place of the nucleolus is occupied by a homogeneous, slightly acidophilic, disklike body which is Feulgen-negative like those described in the liver (Fig. 3).

As regards the heart muscle, treatment with colchicine was not seen to cause any damage to the fibres, all the change observable being a reduction or increase in the size of the muscle cells analogous to the changes described in the kidney and liver.

In contrast with the inhibition of mitosis, time and duration of the aforesaid, histological alterations are not specific.

Quantitative investigations

The maximum diameter of each of 500 hepatic and renal cell nuclei were determined with identical methods of fixing, embedding and staining.

The diameter of the cell nuclei varies between 3 μ and 9 μ in untreated rats, a diameter of 6 μ being the most frequent. One hour after the administration of colchicine, the curve becomes lower and is, in comparison with the control curve, seen to be displaced towards the larger cells. Its peak is at 6,5 μ. The curve is stretched left and right towards both the small and large cells, since the nuclear diameters vary now between 2 μ and 10,5 μ. At 72 hours the curve

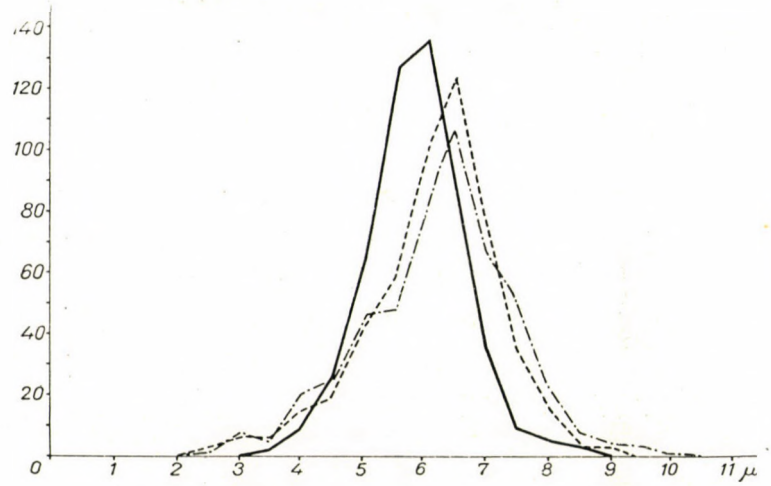

Diagram I. Change in nuclear diameters in hepatic cells under the action of colchicine.
————control ; —·—·— 1-hour acute ; — — — — 72-hours acute

is found to approach the control curve, its peak, although still at 6,5 μ, lying higher than that of the one-hour curve. There is a simultaneous decrease in the number of extremely large cells (Diagram I).

Treatment with podophyllin makes the curve shift towards the large cells : its peak is at 7 μ, and the nuclear diameters range from 2 μ to 10 μ. After 24 hours, the curve comes nearer to the control curve, its peak is at 6,5 μ, while the number of extremely small and extremely large variants increases. The nuclear diameter ranges now from 1 μ to 11,5 μ (Diagram II).

The diameter of the cell nuclei in the tubular epithelium of the kidney of untreated animals varies between 3 μ and 9,5 μ, with a maximum at 5 μ. 6 hours after the administration of podophyllin, the curve is markedly displaced towards the large cells, with a maximum at 6,5 μ. There is a significant increase in the number of extremely large cells, with the nuclear diameters varying

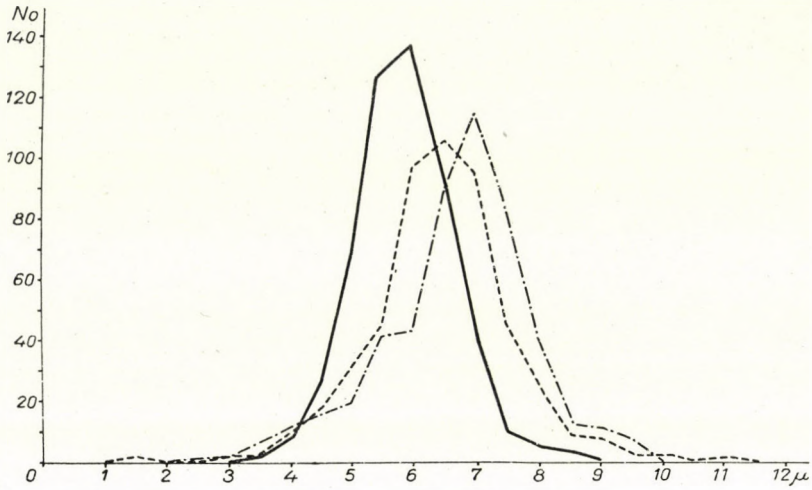

Diagram II. Change in nuclear diameter in hepatic cells on the action of podophyllin.
————control ; —·—·—·— 6-hours acute ; — — — — 24-hours acute

between 3,5 μ and 12,5 μ. After 48 hours, the curve shifts to the left, i. e. in the direction of the small cells, its peak being at 4,5 μ. The nuclear diameters range now from 3 μ to 10,5 μ, the number of large cells being extremely small. The majority of the diameters lies between 3 μ and 7 μ (Diagram III).

If nitrogen mustard is administered on three consecutive days, we find that 6 hours after the last injection the curve has markedly shifted in the direc-

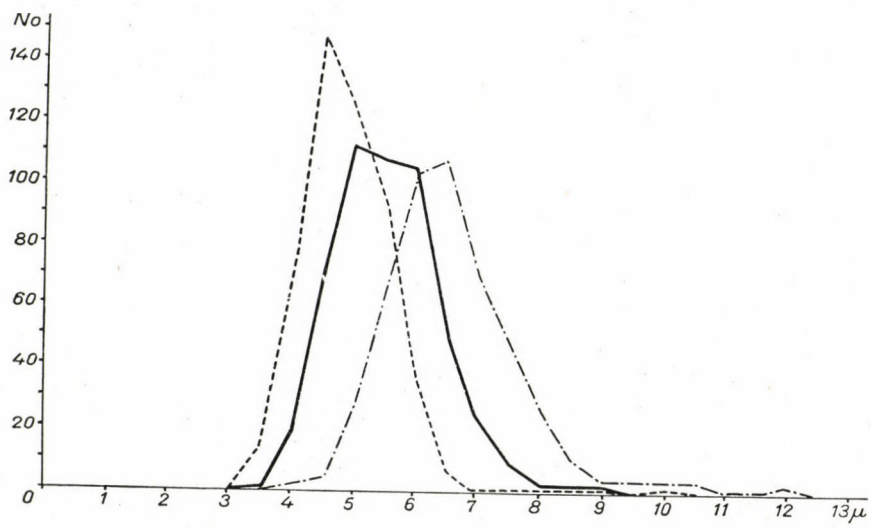

Diagram III. Change in nuclear diameter in renal cells on the action of podophyllin.
————control ; —·—·—·— 6-hours acute ; — — — — 48 hours acute

tion of the large cells, with its peak at 6 μ ; small cells are not observable. The length of the nuclear diameters varies between 3,5 μ and 12,5 μ. After an interval of 120 hours the cell nuclei become more uniform, with diameters between 3,5 μ and 7,5 μ, and with the peak of the curve at 5 μ like that of the control curve (Diagram IV).

It is known from the literature that by measuring diameters, it cannot be expected to obtain satisfactorily precise values for the size of the nuclei,

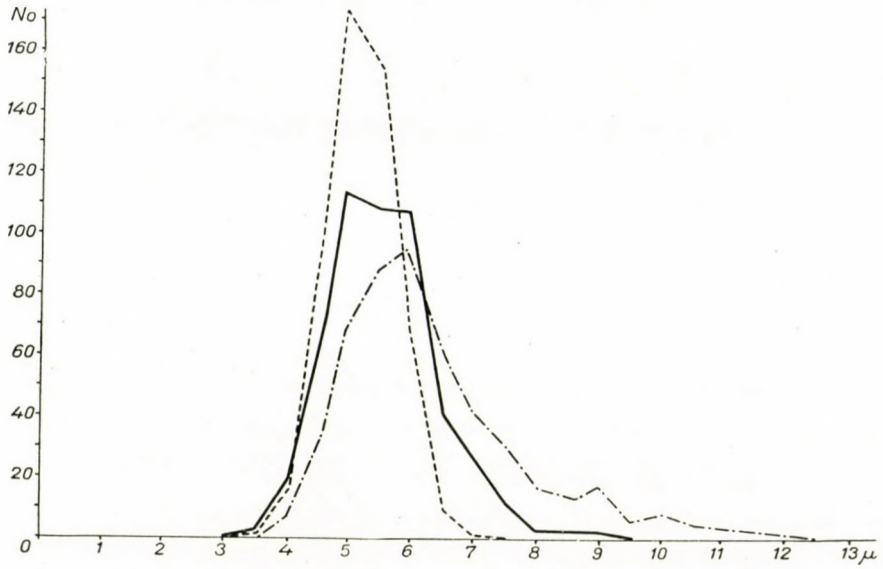

Diagram IV. Change in nuclear diameter in renal cells on the action of nitrogen mustard. ——————control ; —·—·—·— 6-hours cumulative acute ; — — — — 120-hours acute

especially if their shape is not at least approximately spherical. We have, therefore, in a number of cases, determined the nuclear volume of 200 cells each.

Since cell nuclei can be regarded on the whole as rotational ellipsoids, their volume was computed with the aid of the formula

$$V = \frac{4}{3} \cdot \pi \cdot a^2 \cdot b,$$

where a = half of the minor, and b = half of the major axis.

According to JACOBJ, the nuclear size in tissue cells does not vary at random. The nuclei can be divided into classes within which their volumes vary about a mean value. The class with the highest number of nuclei is termed «Regelklasse». Each class to the left and right of it contains less and less cells. Those classes which, contrary to this rule, contain a higher number of cells have

been found to be, together with the «Regelklasse», the terms of a geometric series with the number 2 as the common ratio.

JACOBJ demonstrates the nuclear volumes on a linear scale with the consequence that, as the size of the nuclei increases, the boundaries of the classes become more and more stretched, i. e. the curve lengthens out and becomes

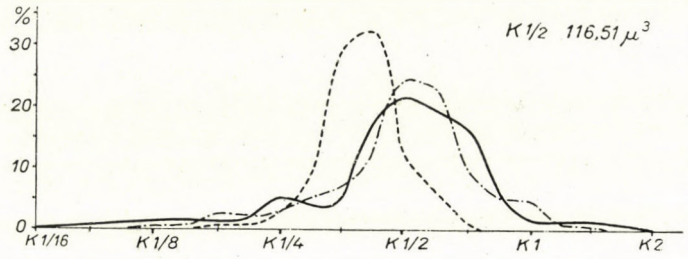

Diagram V. Change in nuclear volume in hepatic cells on the action of nitrogen mustard.
————control ; — — — — 6-hours acute ; —·—·—·— 120-hours acute

asymmetric. To be able to demonstrate biologically identical magnitudes, however, no class must stretch more than any other. This problem was solved by HINTZSCHE ; he substituted the logarithms of the volumes for their real values, and transformed thus JACOBJ's linear series into a geometric one.

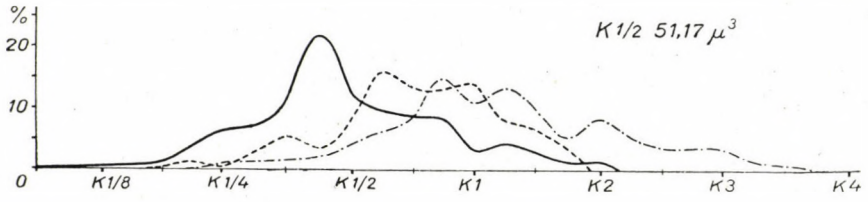

Diagram VI. Change in nuclear volume in renal cells on the action of colchicine.
————control ; —·—·—·— 30 minutes acute ; — — — — 72-hours acute

In order to plot the curve we had first to determine the «Regelklasse» (for which we use the symbol K ½) of the cell nuclei in the normal tissue. Having derived the further data, necessary for the class division, from the value of K ½ by HINTZSCHE's method, we transferred them to the ordinate of the graph, while the abscissa shows the distribution percentage of the examined cells.

The computations proved the value of K ½ to be 116,51 μ^3 for the control liver. According to the above definition, this is the point above which the peak of the control curve lies, i. e. where the number of cells is at the maximum (22,5 per cent). The nuclear volume of the hepatic cells varies between K 1/16 and K 2. It becomes less 6 hours after the administration of nitrogen mustard. The peak of the 6-hour curve is shifted to the left by the length of a «Zwischen-

klasse», and comes to lie higher than that of the control curve because 32,5 per cent of the cells belong to this class. It is remarkable that, on the whole, the cell nuclei have become smaller, large cells are no longer seen, and the curve only just reaches the lowermost limit of the class K 1. The effect of the poison entirely subsides by the 120th hour. The curve shows now hardly any deviation from the control curve, and we find the peak again above the K ½ point with a 25 per cent frequency maximum (Diagram V).

The value of K ½ is 51,17 μ^3 for the nuclear volume of the tubular cells in the kidney of untreated animals. The peak of the control curve (22 per cent of the cells) has shifted to the left of K ½ by exactly half the length of a «Zwischenklasse», since the frequency of the small cells is greater than that of the large ones. The value of the nuclear volumes varies between K 1/8 and K 2. A radical change is seen as early as 30 minutes after the administration of colchicine. The nuclei become markedly larger, so that the curve is displaced towards the large cells. Its peak comes to stand above the K 1 point. K 1/4 is the class with the smallest and K 4 that with the largest cells for this curve. We see the colchicine curve to become flattened after 72 hours, with its peak (12 per cent of the cells) above the point K 1/2, and a range of nuclear volumes between the points K 1/8 and K 2 (Diagram VI).

To complete the computations and diagrams regarding diameters and volumes, significance calculations were also made. Calculations concerning the kidney and the liver were each based on a series of three different observations of 200 cells each, as follows.

(i) *Kidney cells*

1. untreated,
2. 30 minutes after colchicine administration,
3. 72 hours after colchicine administration;

(ii) *Liver cells*]

1. untreated,
2. 6 hours after nitrogen mustard administration,
3. 120 hours after nitrogen mustard administration.

Nuclear volume was expressed in cubic micra.

Since the deviations of the poisoned cells from the untreated control seemed to be statistically significant, Wilcoxon's method was used in the calculations.

According to the calculations, no deviation is significant for which

$$37{,}118 \leq U \leq 43{,}082,$$

while a deviation is regarded significant if

$$U < 37{,}118 \quad \text{or} \quad U > 43{,}082.$$

The values of U derived from the data of the measurements were found to be

a) *Kidney :* 54,425 for the comparison of 1 and 2
49,272 « « « « 1 « 3

b) *Liver :* 50,724 « « « « 1 « 2
39,645 « « « « 1 « 3

Changes occuring in nuclear size both 30 minutes and 72 hours after treatment with colchicine were, therefore, significant in comparison with the normal values. A single dose of nitrogen mustard provoked a significant change in the size of the nuclei only 6 hours after the injection, while the change ceased to be significant after the lapse of 120 hours.

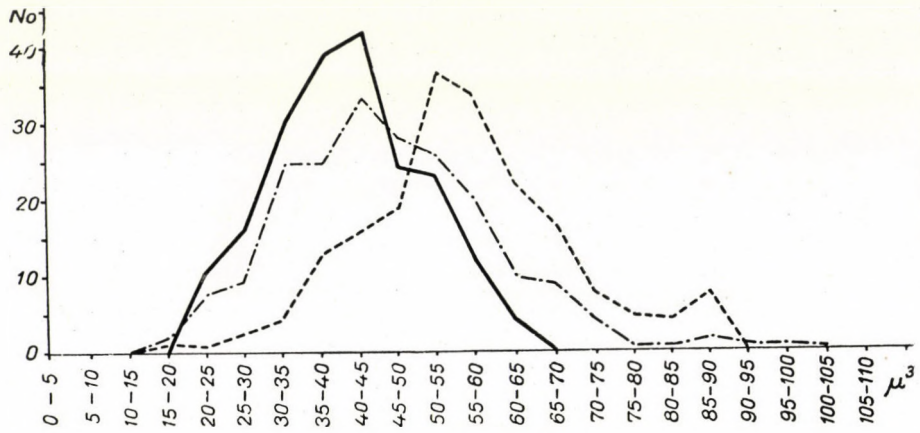

Diagram VII. Changes in planimetrically measured nuclear surfaces on the action of colchicine
——— control ; —·—·—·— 30 minutes acute ; — — — — 48-hours acute

Diagram VII illustrates the variations in the planimetric values of the cell nuclei of the myocardium under the influence of colchicine poisoning. The peak of the control curve is above a point between 40 μ^2 and 45 μ^2 with 42 per cent cells, the whole curve covering the range from 15—20 μ^2 to 65—70 μ^2. While after a lapse of 30 minutes the peak of the curve is still at the same point, only 33 per cent of the cells belong to this group, as the number of large nuclei has considerably increased, some of them reaching magnitudes between 100 μ^2 and 105 μ^2. A few small-sized nuclei are also observable (10—15 μ^2). The toxic effect is still more vigorous 48 hours after the treatment. The curve shifts further towards the region of the large nuclei, with a peak above a point between 50 μ^2 and 55 μ^2, to which category 37 per cent of the cells belong.

Discussion

We have found no report in the literature on investigations made with the object to offer mathematical comparisons between the changes in nuclear size caused by the action of different karyoklastic substances.

Although it has been pointed out by most of the authors that cell nuclei increase in size under the influence of colchicine (KANTNER, MISURSKY and DOLIANSKY, LAMBERS), exact measurements in this respect have not been made.

WACHTER, measuring the size of hepatic cells after the administration of CCl_4 and Perhepar, found the enlargement and diminution, respectively, of the nuclei to be frequent and notable in acute hepatic lesions. BUCHER, studying the effect of colchicine upon fibroblast cultures, evaluated his results mathematically and found that not only the average nuclear size had increased under the influence of colchicine but observed also a significant change in the shape of the distribution curve of the nuclear size.

The present experiments have proved that colchicine enlarges the nuclei of the hepatic, renal, and myocardiac cells. This enlargement manifests itself with an increase in nuclear diameter, volume, and surface alike. Measurements of nuclear diameter proved podophyllin to exert a similar effect, with even greater changes in the size of the nuclei.

The effect of nitrogen mustard poisoning greatly depends on dosage. If given in effective doses on three consecutive days, the curve shifts towards the large cells 6 hours after the last injection, as illustrated by the diagram showing the diameters of renal cell nuclei. If a single tolerated dose of the poison is administered, the 6-hour curve is seen to stretch out in the direction of the small cells (Diagram V).

Mathematical computations show the value of nuclear size to deviate significantly from those of the control values, the only exception being the change observed 120 hours after treatment with nitrogen mustard.

The above described observations allow, however, of further conclusions.

It is evident from the diagrams that all the three substances under review have a rapid effect, since the changes in nuclear size manifest themselves within a few minutes or hours. Also the changes in question are reversible, for the later the curves the more they approach the shape of the control curves.

It was shown in our previous communications dealing with the chronological sequence of the effect of antimitotic agents that the mitotic inhibition ceases after 72 hours in the case of colchicine, after from 24 to 48 hours in that of podophyllin, and after 120 hours in the case of nitrogen mustard. Comparing these data with those obtained in respect of non-dividing cells, it is found that the effect of the poisons under review, except that of the nitrogen mustard, is more protracted upon resting cells, since changes in the nuclear size still persist at a time when mitotic disturbances in the organs with a high mitotic index have completely subsided. It seems, therefore, that the changes in the nuclear size offer a much more precise method of measuring the effect of these agents upon the cells than the inhibition of mitosis.

We ascribe the temporary enlargement of the nuclei in some of the cells to the appearance of intranuclear «inclusion bodies».

These inclusion bodies were earlier thought to be of viral origin, and were even regarded as masses of elementary particles. Recent investigations seem to prove that these structures are manifestations of injury to the nucleus.

Structures of this kind were observed by HAMPERL and BUCHMANN to have developed under the effect of colchicine, while BLACKMANN observed them in connection with lead poisoning ; ZOLLINGER found them to appear under the action of ionizing rays and also in lead poisoning ; they occur, however, also in the spontaneous breast cancer of C_3H mice.

On the basis of histochemical reactions, BUCHMANN, BLACKMANN, ZOLLINGER, ALTMANN and other assume that these bodies contain nucleic acid and trace them from the nucleolus, that is, they regard them as pathologically transformed nucleoli.

Both their appearance and disappearance is rapid. Their development would be explained by the fact that, because of the changed conditions, the nucleolus is unable to pass its nucleoprotein to the cytoplasm, the retention causing enlargement of the nucleolus. As regards their disappearance, the opinions of the authors differ. BERG thinks that if the morbid proteins cannot be eliminated the cell must perish. SCHILLER is of the opinion, that cells containing inclusion bodies do not divide by mitosis, and that the daughter nucleus containing the inclusion body perishes along with the cell pertainig to it. ALTMANN and BUCHMANN suggest that, once the toxic effect has ceased, the nucleolus, resuming its usual function and regaining its normal metabolism, eliminates the accumulated ribonucleoprotein forming the «inclusion bodies». It is, however, quite possible that there exist also other ways in which the retained substances are eliminated.

In the course of the present experiments the inclusion bodies were first seen to appear in the epithelial cells of the renal tubules ; under the effect of colchicine and nitrogen mustard they appeared in the hepatic cells as well. Their occurrence is irregular and depends to a great extent on the manner of treatment. Their rapid disappearance is not so easy to explain. Although Altmann's theory seems to be more than probable, in other observations it was found that the toxic effect still lasts at the time when the inclusions have already disappeared. In addition the fact that extensive desquamation of the tubular epithelium can be observed at certain points of time makes it probable that the cells containing inclusion bodies die off.

Since the original nucleolus cannot be found in nuclei containing these structures, it may be assumed that the inclusion bodies are but transformed nucleoli. Histochemical reactions corroborate this theory. We attribute this pathological transformation of the nucleolus to a transitory disturbance of nuclear metabolism provoked by the poison.

The present experiments have made it evident that the development of the said inclusions bodies cannot be regarded as the sole cause of nuclear enlar-

gement, for also nuclei in which inclusion bodies are never seen (myocardium) invariably undergo enlargement. The enlargement or diminution of the nuclei is likewise the manifestation of a profound change in nuclear metabolism.

We regard the results of the present experiments as a confirmation of our earlier theory that the so-called karyoklastic substances affect not only dividing but also resting cells. Their effect manifests itself even more strikingly with a change in nuclear size than by the inhibition of mitosis. It seems that the effect is general, and that the said substances influence to a greater or lesser extent the metabolism of every cell nucleus in the organism.

Summary

Colchicine, nitrogen mustard, and podophyllin provoke considerable changes in the structure and in the size of cell nuclei in organs with a low mitotic activity (liver, kidney, heart muscle).

Karyometric investigations have proved that all the three said poisons significantly influence the size of the cell nucleus.

Changes on the nuclear size develop rapidly and are reversible. Their development takes about as much time as that of the early changes observable in dividing cells, but the durations of the effect is much longer in resting than in mitotic cells.

All of the substances in question are capable of producing «inclusion bodies» in the cells of the liver and especially the kidney. These «inclusion bodies» may be interpreted as pathologically transformed nucleoli. No such bodies could be observed in the nucleus of heart muscle cells.

The present investigations have made it evident that so-called karyoklastic substances affect both dividing and non-dividing cells, and that their effect manifests itself not only with an inhibition of mitosis but also with changes in nuclear size. The substances in question can therefore be regarded as poisons acting upon nuclear metabolism.

We are indebted to Dr. B. GYIRES, leader of the Debrecen Section of the Institute for Applied Mathematics of the Hungarian Academy of Sciences, and to Dr. I. JUVANCZ, leader of the Section of Medical Mathematical Statistics of the same Institute, for performing the mathematical computations.

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ДЕЙСТВИЕ КОЛХИЦИНА, ГОРЧИЧНОГО АЗОТА И ПОДОФИЛЛИНА НА ПОКОЮЩИЕ КЛЕТКИ РАЗЛИЧНЫХ ОРГАНОВ

Л. МАТКО, Л. ХОЛЦИНГЕР и Ш. КЕРЕСТУРИ

На действие колхицина, горчичного азота и подофиллина в органах с низкой частотой деления (печень, почки, сердечная мышца) возникают значительные структуральные изменения, как и изменения размеров ядер.

Согласно результатам кариометрических исследований авторов, все три упомянутые вещества в значительной степени влияют на размеры ядер.

Изменение размеров ядер быстро развивается и является обратимым. Его образование хронологически совпадает — с более или менее большими сдвигами — с выявляемыми на делящихся клетках ранними изменениями, причем оно сохраняется еще долгое время после прекращения нарушений процесса деления.

Все три вещества могут вызвать так называемые «клеточные включения» в печени, и главным образом в почках. Эти «включения» можно рассматривать как патологически преобразованные ядрышки. В ядрах клеток сердечной мышцы авторам не удалось выявить таких образований.

На основании своих опытов авторы считают доказанным, что так называемые кариокластические вещества оказывают свое действие не только на делящиеся клетки, но также и на клетки в состоянии покоя, и что их действие проявляется наряду с задержкой деления также и в изменении размеров ядер. Итак, эти вещества можно рассматривать как токсины общего обмена веществ ядер.

WIRKUNG VON COLCHICIN, PODOPHYLLIN UND SENFNITROGEN AUF DIE RUHENDEN ZELLEN VON ORGANEN

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Auf Einwirkung von Colchicin, Senfnitrogen und Podophyllin entstehen in Organen mit niedriger Teilungsfrequenz (Leber, Niere, Herzmuskel) bedeutende strukturelle und Kerngrössenveränderungen.

Laut den Ergebnissen von karyometrischen Untersuchungen üben alle drei gennante Stoffe eine signifikante Wirkung auf die Kerngrösse aus.

Die Entwicklung der Kerngrössenveränderung geht rasch vor sich, und ist reversibel. Ihre Entwicklung fällt zeitlich — mit kleineren und grösseren Verschiebungen — mit den an den sich teilenden Zellen nachweisbaren Frühveränderungen zusammen, und bleibt nach dem Ausbleiben der Teilungsstörungen noch längere Zeit bestehen.

Alle drei Stoffe können sogenannte «zelluläre Einschlüsse» in der Leber, und hauptsächlich in der Niere hervorrufen. Diese «Einschlüsse» können als pathologisch umgewandelte Kernkörperchen aufgefasst werden. In den Kernen der Herzmuskelzellen konnten solche Einschlüsse nicht beobachtet werden.

Auf Grund ihrer Untersuchungen glauben die Autoren bewiesen zu haben, dass die sogenannten karyoklastischen Stoffe ihre Wirkung nicht nur auf die sich in Teilung befindenden Zellen, sondern auch auf die ruhenden Zellen ausüben, und dass ihre Wirkung sich ausser in der Teilungshemmung auch in der Veränderung der Zellengrösse zeigt. Infolgedessen können diese Stoffe als Toxine des allgemeinen Kernstoffwechsels aufgefasst werden.

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