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THE EFFECT OF CHRONIC COLCHICINE INTOXICATION ON THE BLOOD COUNT AND ON THE BONE MARROW

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In previous investigations (Kellner and Matkó : Tissue Changes Observed in Rats Poisoned with Colchicine ; presented at the Congress of Pathologists, 1949) we tried to find such a dosage of colchicine that facilitates longer viability of the animals, in spite of the fact, that the poison exerts an action on cellular division. This method of administering colchicine was found in the chronic administration of sublethal doses. Detailed studies of the organs revealed that characteristic changes are given rise to in the bone marrow, as well as in the blood. We wished to determine whether the blood count showed changes which would draw attention to the danger of treatment in the case of chronic administration of colchicine. In tumor therapy only such dosages are practicable that render prolonged administration of colchicine in effective doses possible. When administering various doses of colchicine, changes of the blood count and of the bone marrow have been observed, but in accordance with our primary aim it was the changes brought about by the chronic administration of colchicine that have been considered in the first place.

The changes occuring in the blood count and bone marrow of rats after a single injection of colchicine were first noted by *Dixon* (5), who observed that the initial decrease in the number of leucocytes was followed by a marked leucocytosis within a few hours. Beside the increase in the number of the polymorphonuclear leucocytes he found nearly no change in the number of lymphocytes. He explained the decrease and increase of the leucocyte count the following way : these cells first stream back into the capillaries of the lungs and spleen and into the marrow, later they reappear in the peripheral circulation. According to this author, large doses of colchicine have a destructive effect on the bone marrow, a small dose, on the other hand, exerts a stimulative effect thereon. Beck (1) determined leucocyte counts at 2 to 4 hours intervals following a single injection of 0.1 mg/kg of colchicine. He did not consider the initial reduction in the number leucocytes to be significant, but he also registered an increase in the leucocyte count. He found no appreciable changes in the differential blood count. In 1939, *Borsetto* (2) reported data on changes in the blood counts of dogs. After the administration of 3 mg/kg of colchicine, the animals died within a period of 15 to 16 hours. He obtained blood from the heart at four-hour intervals by puncture. After an initial decrease in the number of leucocytes he found leucocytosis, mainly due to the increase in the number of granulocytes. There was a rise in the hemoglobin values that could be explained with the increase in number and volume of red cells. The effect on human blood of therapeutic doses was studied by *Levison* (8), he found, however, no marked effect on the bone marrow. The effect of single and repeated doses of colchicine on the normal blood count in man was studied by *Landolt* (7), in 1943. He found a slight decrease in the number of leucocytes after 2, 5, 7 or more hours in a few cases only, which was followed by a slight leucocytosis of short duration. The sternal punctate showed no marked changes. The kariorhexis of red cells was conspicuous and so was the vacuolisation of the nuclei and plasma

in the myelopoetic cells. *Widmann* (9) in 1949, found that in case of colchicine poisoning the bone marrow was exhausted, the number of immature myeloid elements was increased and these latter cells showed signs of toxic degeneration. Cells in the state of mitotic division and resting cells — both belonging to the haemopoetic system — are equally lesioned.

Methods. In our experiment we used vermin-free white (albino) rats of 150 to 200 g body weight. Twenty-four of the animals were poisoned acutely and 48 chronically with a 0,2 per cent solution of Colchicinum purissimum cryst. (Merck.) The lethal dose was 300 gamma per 100 g. In acute experiments we injected a single sublethal dose (200 gamma/100 g) subcutaneously; following the injection, blood was obtained from the tail vein at 1, 2, 3, 6, 12, 24, 36, and 48 hours, or later. Parallel with the examination of blood the bone marrow was also studied. In chronic experiments the animals were given 2/3 to 1/2 part of the sublethal dose (130 to 100 gamma/100 g) every third day. The animals thus treated survived for 10 to 12 weeks and received approximately a total of 3 to 6 mg of colchicine. Sometimes treatment was discontinued for a longer period of time then it was resumed again. Blood was always taken prior to the administration of colchicine. The bone marrow was studied depending on the changes of the blood count. In the beginning, bone marrow was obtained from the distal one-third of the femur with a technique similar to that of sternum puncture. The bone, however, often became fractured and bled freely, thus rendering smears useless. Later the femur of the animal was prepared, cut up, the bone marrow was curetted, and, dropping natrium citrate solution to it, smears were prepared, which then were stained with May-Grünwald-Giemsa's solution. In many cases the bone marrow was also embedded.

Rats are not very suitable for the purpose of haematological experiments, owing to the great variations in blood counts and bone marrow findings of these animals. Having used rats in our previous colchicine experiments, however, we did not want to change the species. Considering the high variability of the findings, 20 control animals were used. In addition to this precaution, the haemostatus of each animal was determined prior to treatment. Our data relative to results obtained in the controls (Tables I. and II.) are, in general, similar to those published by *Klineberger* [6] and *Cameron* and *Watson* [3, 4].

TABLE I.

Type of Cell	Variation	Average
Red Cells (million)	4,4—6,5	5,6
White Cells (thousand)	7,8—12,6	10,6
Metamyelocytes (Jugend)	0—1%	0,2%
Metamyelocytes (Stab)	0—3%	0,7%
Segmented forms (polymorphonuclears)	15—34%	22,9%
Eosinophils.....	1—4%	2,7%
Lymphocytes	60—79%	70,3%
Monocytes	1—6%	3,2%

Normal blood count of the rat based on data obiained from 20 control animals.

The blood count of the rat contains usually a great number of lymphocytes, these representing frequently 70 to 80 per cent of white cells. On administration of the sublethal dose of colchicine (200 gamma/100 g), the leucocyte count decreases slightly, reaching its lowest point in about 1 to 2 hours. If the changes in the differential count are given only in per cent, it is rather difficult to interpret the picture, therefore the leucocyte counts are represented in the graphs by absolute numbers, in the Tables, however, it is only the percentual values that are given, always presenting the total number of leucocytes as well. When the number of leucocytes decreases, it is the number of the granulocytes in the first place that is reduced. (Fig. 1.) Following the phase of leucopenia, leucocytosis occurs, reaching its peak between 12 to 36 hours, mainly due to the increase in the number of elements belonging to the myeloid series. This increase is considerable in the majority of cases ; instead of the normal 8 to 12 thousand even 30 to 50 thousand white cells may be found and a slight shift to the left may also be observed (Table III.). In such cases the number of leucocytes considerably exceeds that of the lymphocytes.

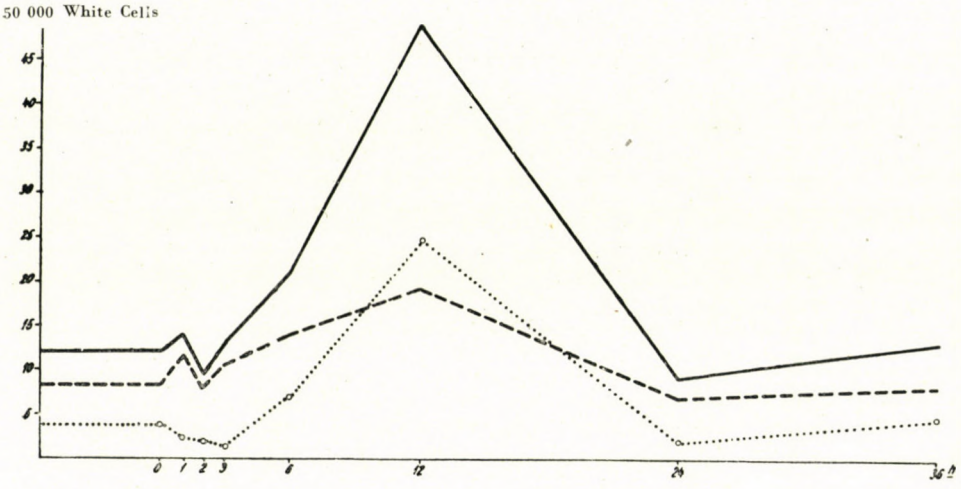

*Fig.*1 : Ac. I/8 dosis : 200 gamma/100 g.

In the 2nd hour mild leucopenia, in the 12th hour leucocytosis reaches its maximum, the number of granolocytes exceedes that of the lymphocytes. From the 24th hour original heamostatus develops again.

———— = white cells, — — — — — = lymphocytes. . . . . = segmented forms polymorphonuclears).

After colchicine injection the number of lymphocytes also varies, this variation, however, is not as regular as that of the leucocytes. The low grade anemia is indicative of the lesion of the erythrocytes. In the course of leucocytosis 1—2 nucleated red cells also appear in the peripheral blood count.

Due to the leucopenia occuring in the peripheral blood count the mature granulocytes disappear from the bone marrow and stream into the circulation, probably in order to replace the granulocytes destroyed peripherally by colchicine. In such cases a great number of leucocytes are seen in the interstitium of the lung in embedded sections. Myelogramms show a relative increase of erythroblasts, together with a marked reduction in the number of segmented forms. (Table IV.)

TABLE II.

Type of Cell	Variation %	Mean %
Immature erythroblasts	3,6— 7,8	5,2
Mature erythroblasts	19,6—23,2	21,6
Myeloblasts	4,2— 5,0	4,3
Promyelocytes	2,2— 4,6	3,2
Myelocytes	4,4— 7,6	6,0
Metamyelocytes (Jugend)	5,4— 7,6	6,6
Metamyelocytes (Stab)	6,2—14,0	10,0
Segmented forms	22,4—24,8	23,2
Immature eosinophils	1,6— 3,6	2,5
Mature eosinophils	2,0— 4,6	3,0
Basophils	0,0— 3,0	0,1
Megakaryocytes	0,2— 0,4	0,3
Lymphocytes	9,6—15,4	11,8
Reticulocytes	1,8— 2,8	2,2

Normal bone marrow finding in the rat as determined in 30 control animals.

Approximately 22 to 25 per cent of the cells of the normal bone marrow consists of segmented (polymorphonuclear) leucocytes (Fig. 2/A) ; in the phase of leucocytosis the number of young myeloid elements increases and one can observe many distorted mitosis resembling monaster and distorted giant cells which are similar to cell forms found in cases of colchicine poisoning (Fig. 2/B). Later these cells become stunted, take up the form of a rosette, then disintegrate with piknosis. (Fig. 2/C.) The toxic lesion of the bone marrow gradually increases, the cells become less resistant, are deformed and later disintegrate. (Fig. 2/B.)

These smears cannot be evaluated any more. Depending on the dose, the haemostatus either becomes normal again in about 48 to 72 hours, or, together with the deterioration of the toxic lesion, toxic panmyelophtisis develops and the animal dies.

Animals receiving chronic treatment were given 2/3 to 1/2 of the sublethal dose at three days intervals and thus acute toxic symptoms remained in the background. Blood counts and bone marrow had been examined once a week only and it was found that in chronic colchicine poisoning the changes of the blood count and bone marrow were principally similar to acute changes. The main difference is that the changes are of a lower grade and develop slowly. When smaller doses are given, the lesion is also of a lesser degree and the reaction of the bone marrow is not so excessive, either.

In the peripheral blood count at about the 30 th to 40 th day of treatment the leucocyte count shows a rise after minor variations, the number of leucocytes exceeds that of the lymphocytes, resembling acute changes. The sudden increase is, however, usually of a lesser degree (20 to 25 thousand). At this time nucleated red cells and hypersegmented leucocytes appear in the blood count and there is a slight shift to the left. After the reaction subsided, the number of leucocytes is reduced nearly to the normal value, but the nucleated red cells do not disappear. If treatment is continued, the characteristic changes in the blood count reoccur several times, but, due to the gradually increasing injury of the bone marrow, the reactions are less and less marked (Table V. and Fig. 3.). If treatment is discontinued, the animals regenerate. By this method it was possible to keep a number of animals alive, in spite of colchicine treatment, for a period of 1 to 1½ years. In the bone marrow of animals subjected to chronic treatment, at the time of the sudden increase in the number of leucocytes, changes similar to those seen in acutely poisoned animals could be observed. At first mature granulocytes disappear from the bone marrow, then a toxic lesion of the bone marrow develops. Due to repeated administrations of colchicine, no complete resting state develops in the bone marrow, either, not even after the leucocytosis subsided. (Table IV.) The number of lymphocytes is also markedly diminished. In the lymphoid organs (spleen, lymph nodes, thymus gland) marked disintegration of cells, increase of the number of reticulum cells and formation of giant cells is seen.

If treatment is continued for a longer period of time without interruption, the characteristic changes often reoccur. After the subsidence of the recurrent leucocytosis, the animals become more and more anemic and at the same time a condition similar to agranulocytosis develops. The number of red cells is reduced from 5 to 6 million to 1 million and many nucleated red cells appear in the blood count. The number of leucocytes drops from 8—12 thousand to 2—4 thousand. (Table VII.) In the smears, together with a more marked shift to the left, many over-mature, disintegrating granulocytes are seen. Due to the marked

disintegration of red cells, many cells containing iron pigment appear in the spleen, liver and lymph nodes.

No bone marrow smears can be prepared from the femur and sternum of the animals after this phase, the bone marrow is dry, crumby, similar to sawdust. In the sections at first the increase in the number of distorted giant cells is the most striking ; these cells possess a number of hyperchromatic nuclei of irregular shape (Fig. 4/B). The remaining bone marrow cells gradually disinte-

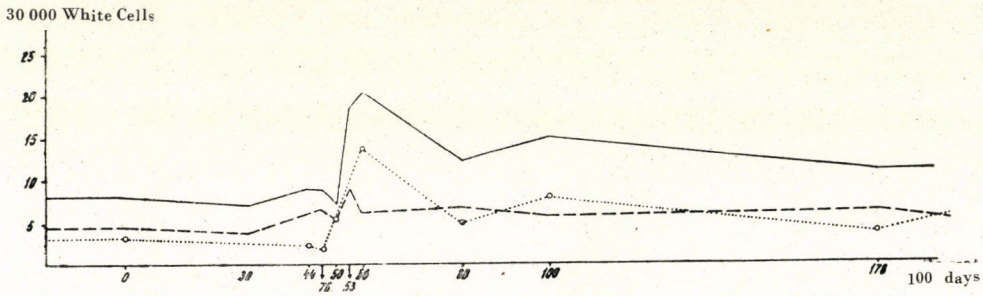

Fig. 3. : Chr. IV/5. Received a total of 6610 gamma of C. On the 56th, 100th and 190th day the number of granulocytes exceeds that of the lymphocytes. —— = white cells, . - - - - = lymphocytes, ... = segmented forms (polymorphonuclears).

grate with piknosis and together with the disappearance of giant cells, the number of reticulum cells increases ; these latter cells are later transformed into connective tissue cells (Fig. 4/C). Later extensive bone formation begins in the fibrous tissue and the whole picture is similar to that seen in ostitis fibrosa generalisata (Fig. 4/D). In this phase the process is irreversible, it is futile to discontinue the administration of colchicine, the animals die sooner or later, because myeloid tissue is replaced (substituted) by fibrous tissue everywhere.

*

In 68 of our experimental animals, changes showed a course similar to the one described above. Reactions of individual animals differed only in time and intensity. In four cases characteristic changes of the blood count were not observed ; the blood count of these animals was different prior to treatment already, inasmuch as no lympoid blood count was seen in these cases.

We consider colchicine effect to be a toxic lesion, which injures dividing cells in the first place and probably affects non-dividing cells as well. In the case of chronic administration, the regenerative power of the bone marrow appears to be exhausted after repeated destruction of cells and this leads to fibrosis. The lymphocyte system, of course, is injured not so much in the bone marrow, but rather in the lymphoid organs. By means of complete histological studies it could be shown that none of the vital organs was injured to such an extent as was the haemopoetic system. We are of the opinion that colchicine — at least in the case of chronic administration — destroys even the haemopoetic

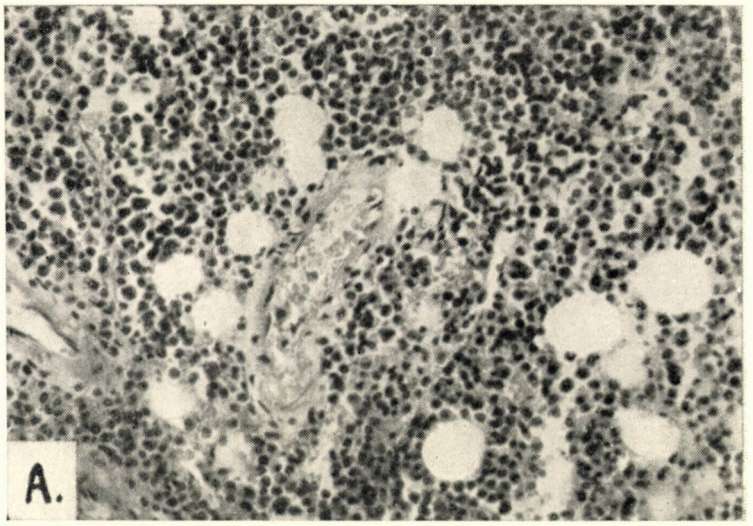

Fig. 4. *A :* Normal bone marrow

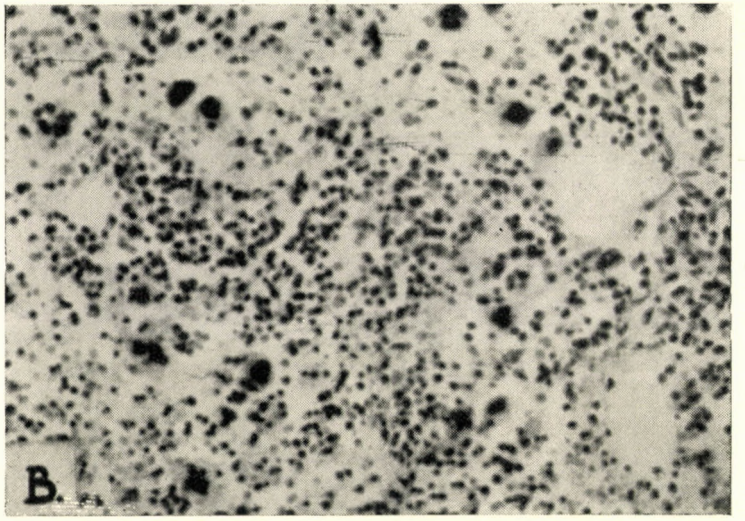

Fig. 4. *B :* Distorted giant cells in bone marrow (× 320).

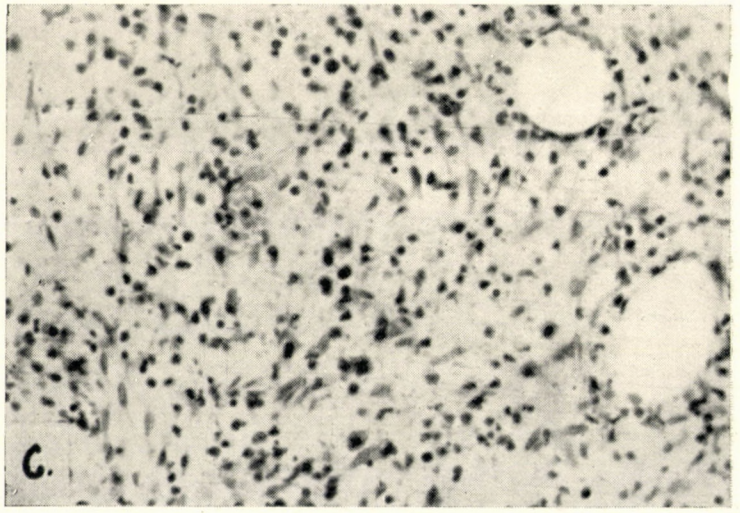

Fig. 4. *C :* Increase of reticulum cells among piknotically distintegrated bone marrow cells. (×320

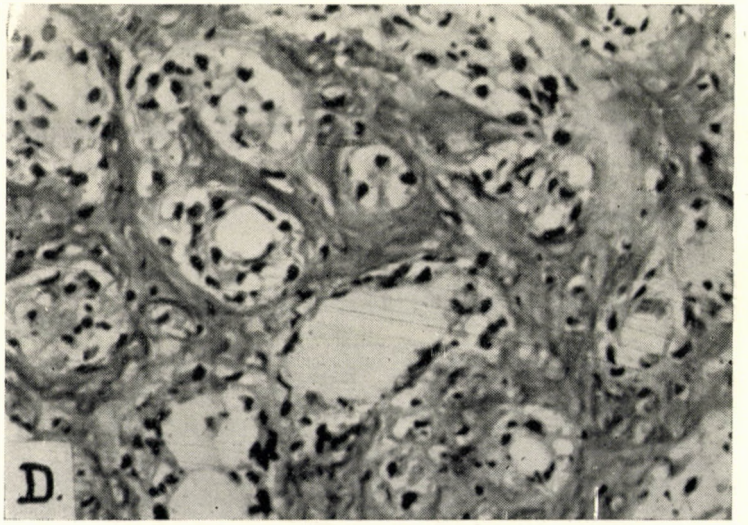

Fig. 4. *D :* Connective tissue bone formati on in the fibrous bone marrow

system and thereby kills the animal. This statement is rendered more probable by the fact that extramedullary haemopoesis cannot be seen anywhere.

Blood count changes seen in the case of chronic administration indicate that when the number of leucocytes decreases, nucleated red cells and hypersegmented leucocytes appear, treatment of the rats should be discontinued immediately. After a certain period of time the haemopoetic system regenerates and treatment can be continued again.

In our experiments in tumor therapy the greatest difficulty was caused by the toxic effect on the bone marrow of colchicine, therefore it should be determined whether injury to the haemopoetic system could be diminished if colchicine treatment were performed together with adequate support to the bone marrow.

Ac. No. II/2. TABLE III.

Hour	0	1	2	3	6	12	25	36
Red cells (million)	5,8	6,5	7,4	4,9	6,6	6,8	7,0	8,4
White cells (thousand)	11,2	7,8	8,7	14,2	7,5	16,6	20,4	40,0
Metamyelocytes (Jugend)	—	—	—	—	—	1	1	1
Metamyelocytes (Stab)	1	2	1	1	2	2	2	—
Segmented forms (polymorpho-nuclears)	34	32	16	27	27	23	51	66
Eosinophils	3	1	2	2	1	2	—	1
Lymphocytes	60	65	80	68	68	71	45	31
Monocytes	2	—	1	—	1	1	1	1

Ac. No. I/10.

Hour	0	1	2	3	6	12	24	36
Red cells (million)	6,3	6,2	5,8	5,4	5,7	5,4	5,9	6,2
White cells (thousand)	7,8	8,2	6,1	12,8	10,2	18,5	12,0	9,7
Metamyelocytes (Jugend)	—	—	—	—	—	1	—	—
Metamyelocytes (Stab)	3	2	1	2	2	3	1	1
Segmented forms (polymorphonuclear)	25	24	22	26	28	49	35	31
Eosinophils	1	3	1	2	3	2	2	1
Lymphocytes	65	66	69	62	59	39	53	58
Monocytes	6	5	7	8	8	6	9	9

Table III. 200 gamma/100 g of colchicin produces a mild leucopenia in 1 to 2 hours, followed by a marked leucocytosis at the 12th—36th hour. Leucocytosis is due to the increasing number of segmented forms (polymorphonuclears). At this time one-two young forms can also be seen.

TABLE IV.

Type of cell	Range of variation %	Mean %
Immature erythroblasts	3,4— 4,4	4,1
Mature erythroblasts	38,0—43,4	41,1
Myeloblasts	3,2— 7,2	5,4
Promyelocytes	3,4— 6,8	4,8
Myelocytes	5,8—18,4	12,6
Metamyelocytes (Jugend)	1,6— 6,4	4,8
Metamyelocytes (Stab)	1,2— 5,6	3,4
Segmented forms	7,8—14,6	11,0
Immature eosinophils	0,8— 8,6	3,8
Mature eosinophils	0,2— 1,6	0,8
Basophils	0,0— 0,3	0,2
Megakaryocytes	0,2— 0,6	0,4
Lymphocytes	3,6— 4,8	4,3
Reticulum cells	2,2— 6,2	3,9

Table IV. Bone marrow count after 2 hours, following the administration of 200 gamma/100 g of colchicin : The number of erythroblasts is relatively increased, the number of segmented forms (polymorphnuclears) is reduced (Based on data obtained from 5 animals).

TABLE V.

Chr. I/10. Received a total of 2560 gamma C.

Day	0	10	22	36	43	50	57	64	70
Red cells mill.	4,8	4,4	4,8	4,5	4,0	3,7	6,6	6,0	4,7
White cells thousand	8,3	12,1	10,6	16,2	17,4	14,1	15,6	26,7	10,8
Myelocytes	—	1	3	4	6	8	1	1	—
Metamyelocytes (Jugend)	—	3	3	5	12	6	2	2	—
Metamyelocytes (Stab)	1	3	2	2	11	9	1	5	3
Segmented forms	24	25	18	48	26	20	45	66	10
Eosinophils	4	2	2	2	1	5	2	1	2
Lymphocytes	67	64	68	37	42	46	43	22	84
Monocytes	4	2	4	4	2	6	6	3	1

From the 36th day nucleated red cells, max. : on 43th day : 100/12 ; from the 57th day toxic granulation of leucocytes.

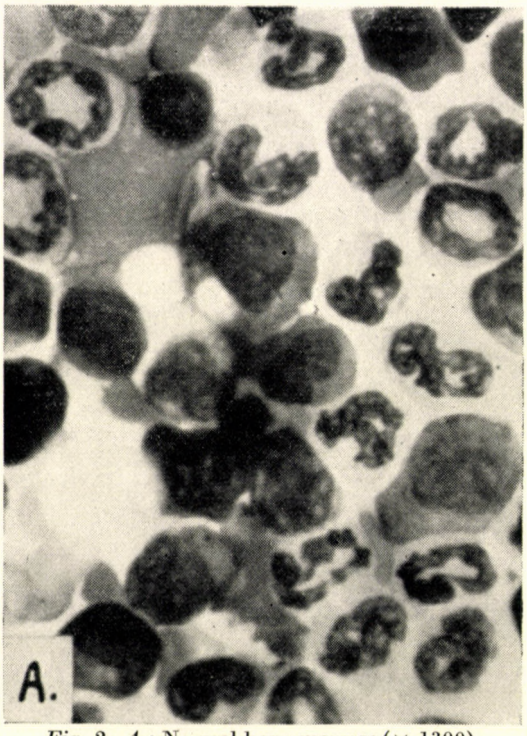

Fig. 2. *A* : Normal bone marrow (× 1300).

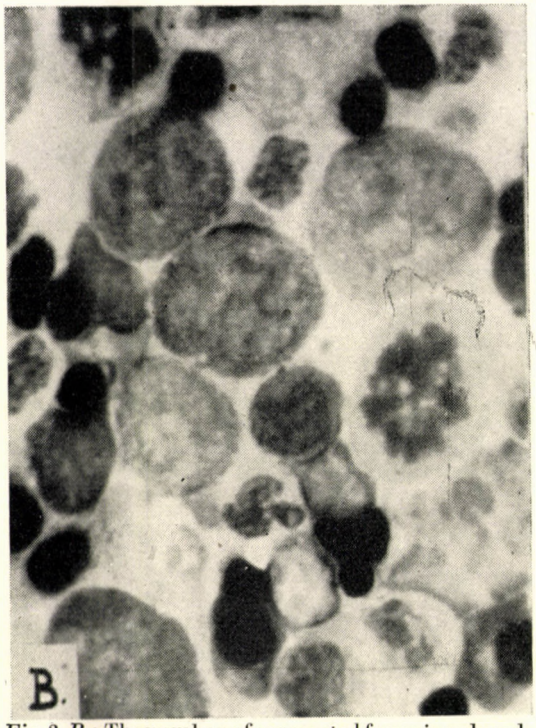

Fig. 2. B : The number of segmented forms is reduced, among young myeloid elements distorted mitosis can be seen. (× 1300)

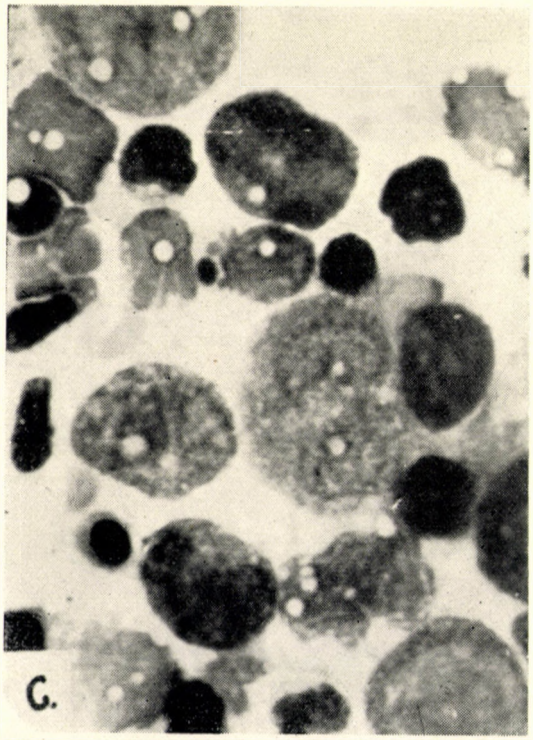

Fig. 2. C : Vacuolised myeloid elements with toxic granulation. (× 1600).

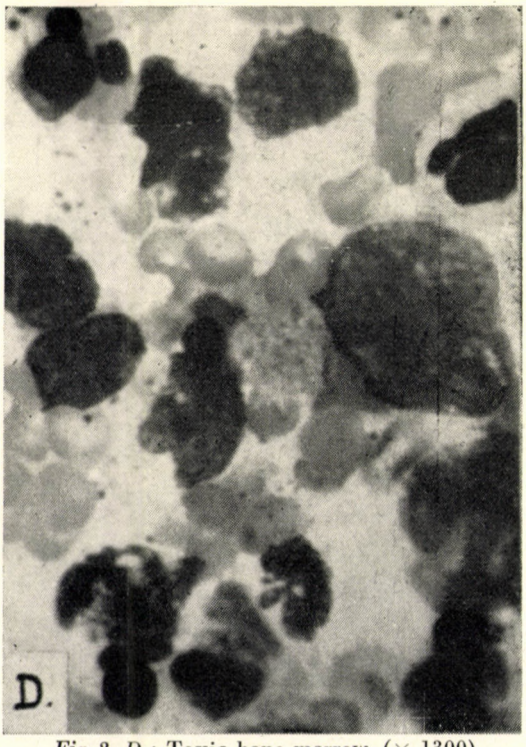

Fig. 2. D : Toxic bone marrow. (× 1300).

Chr. II/83. Received a total of 4672 gamma C.

Day	0	10	30	50	70	90	100	105	110
Red cells mill.	4,5	6,0	5,1	5,9	4,9	3,4	4,1	4,3	3,9
White cells thousand.....	11,7	13,4	13,2	18,6	12,8	5,1	11,2	18,3	6,0
Myelocytes	—	—	—	—	—	—	1	1	—
Metamyelocytes (Jugend)	—	—	—	1	—	2	3	4	1
Metamyelocytes (Stab) ...	—	1	—	1	1	2	2	3	2
Segmented forms.....	15	11	25	50	20	27	12	42	23
Eosinophils	4	1	4	4	4	2	3	—	—
Lymphocytes.....	79	84	69	43	72	61	77	49	74
Monocytes	2	3	2	1	3	6	2	1	—

From the 70th day nucleated red cells, max. on 90th day. Hypersegmented leucocytes.

Chr. II/95 Received a total of 5230 gamma of C.

Day	0	10	30	50	70	90	100	105	110
Red cells mill.	4,4	5,2	4,8	4,5	4,8	5,3	3,8	3,4	3,5
White cells thousand.....	12,6	12,4	9,5	11,5	17,3	8,4	14,0	47,6	17,3
Myelocytes	—	—	—	—	—	—	3	3	9
Metamyelocytes (Jugend)	—	—	—	3	—	—	3	3	2
Metamyelocytes (Stab) ...	—	2	1	1	1	—	5	3	3
Segmented forms.....	21	22	39	36	27	37	24	50	35
Eosinophils	3	3	6	9	6	6	—	—	1
Lymphocytes.....	74	69	53	46	64	53	62	39	49
Monocytes	2	4	1	5	2	2	3	2	1

From the 50th day nucleated red cells, max. on the 105th day.
Hypersegmented leucocytes with toxic granulation.

Chr. II./96. Received a total of 6840 gamma of C

Day	0	10	30	50	70	90	100	105	110	115	120	125
Red cells, mill. ...	5,5	4,5	4,1	4,4	4,1	3,9	3,8	3,5	4,3	3,8	3,2	3,1
White cells, thousand.....	11,1	12,7	11,8	15,4	8,2	11,9	8,3	16,7	7,0	6,0	10,7	8,2
Myelocytes	—	—	—	—	—	—	—	4	4	1	0	0
Metamyelocytes (Jugend).....	—	—	—	—	—	—	—	3	1	1	5	1
Metamyelocytes (Stab)	—	2	1	1	2	—	1	2	4	5	1	—
Segmented forms..	15	39	41	26	20	25	19	30	18	12	40	22
Eosinophils	3	3	2	4	2	1	2	1	2	2	1	3
Lymphocytes.....	78	51	49	68	71	69	77	56	68	72	51	72
Monocytes	4	5	7	1	5	5	1	4	3	7	2	2

From the 50th day nucleated red cells, max. on 90th day; to 100 leucocytes 12.

Table V.: Chronic changes in blood count.

TABLE VI.

Type of cell	First week		2nd week		3d week	
	Variation %	Mean %	Variation %	Mean %	Variation %	Mean %
Immature erythroblasts	4,2— 5,0	3,7	2,5— 3,0	2,8	1,4— 2,2	2,0
Mature erythroblasts	36,0—38,2	37,2	35,0—36,8	36,3	31,1—35,2	33,6
Myeloblasts	4,1— 7,0	5,3	4,2— 7,6	6,0	4,0— 4,5	4,3
Promyelocytes.....	1,5— 3,8	2,9	3,4— 8,1	5,7	4,2— 6,8	5,6
Myelocytes	6,1— 8,0	7,1	4,6— 6,1	5,4	4,6— 6,6	5,1
Metamyelocytes Jugend	4 — 6,1	5,1	5,6— 5,8	5,7	3,8— 4,1	4,0
Metamyelocytes (Stab)	6,5— 6,8	6,7	4,2— 4,5	4,3	5,3— 6,4	5,9
Segmented forms	18,5—22,0	20,1	19,6—21,0	20,0	18,0—19,6	18,8
Immature eosinophils	0,7— 2,6	1,7	1,0— 4,0	2,5	4,8— 6,3	5,5
Mature eosinophils	1,0— 1,3	1,2	0,8— 1,6	1,4	2,4— 4,7	3,6
Basophils	0,1— 0,2	0,2	0,0— 0,4	0,2	0,1— 0,5	0,3
Megakaryocyteos	0,1— 0,4	0,3	0,2— 0,5	0,4	1,0— 1,2	1,1
Lymphocytes.....	2,8— 5,4	4,6	2,4— 4,8	4,6	3,2— 4,2	3,8
Reticulum cells.....	3,6— 4,3	3,9	3,6— 4,9	4,7	5,8— 7,0	6,4

Table VI.: Data of bone marrow obtained from animals treated for a period of 1 to 3 weeks. The erythroblasts are increased in number, the number of segmented forms is reduced. Slight increase in the number of reticulum cells (Based on data obtained from 15 animals).

TABLE VII.

	Initial value	Maximum	Minimum
Chr. III/234-v	Lived 65 days	Received a total of 2248 γ of C	
Red cells	5 400 000	6 140 000	1 350 000
White cells	7 200	10 800	2 600
Lymphocytes	4 248	7 344	2 444
Segmented forms	2 520	3 348	156
Chr. II/83-b	Lived 109 days	Received a total of 4672 γ of C	
Red cells	5 480 000	6 120 000	3 990 000
White cells	11 700	18 300	6 000
Lymphocytes	9 243	13 908	4 440
Segmented forms	2 223	3 294	1 560
Chr. III/234-é	Lived 67 days	Received a total of 2670 γ of C	
Red cells	5 300 000	5 680 000	2 400 000
White cells	7 200	10 700	4 700
Lymphocytes	6 336	7 490	4 324
Segmented forms	504	2 782	376

Table VII.: Aplastic anemia occuring in the terminal phase.

Summary

1. In acute colchicine poisoning, after phases of milder leucopenia and more marked leucocytosis, toxic panmyelophtisis develops.

2. In chronic colchicine poisoning gradually progressing secondary aplastic bone marrow destruction is brought about, which finally leads to the complete termination of myelopoesis, as well as to the fibrous transformation of the bone marrow.

3. The development of the secondary bone marrow destruction can be prevented for a longer period of time by temporary discontinuance of treatment.

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ДЕЙСТВИЕ ХРОНИЧЕСКОГО ОТРАВЛЕНИЯ КОЛХИЦИНОМ НА КАРТИНУ КРОВИ И НА КОСТНЫЙ МОЗГ

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Резюме

При хроническом отравлении колхицином, исследование органов показало, что в крови и в костном мозгу возникают характерные изменения. Авторы ставили себе задачей установить: существует ли такое изменение картины крови, которое еще заблаговременно могло бы предупредить врача об угрожающей опасности длительного лечения колхицином.

Для своих опытов авторы использовали 20 контрольных животных; они отравили 24 крыс однократной сублетальной подачей, а 48 крыс хронической подачей колхицина.

В остром опыте они установили, что после впрыскивания колхицина число лейкоцитов несколько понижается, достигая самый низкий уровень через 1-2 часа. Затем возникает лейкоцитоз, который достигает свой максимум между 12—36 часов. В костном мозгу они одновременно наблюдали токсический панмиелофтиз. Картина крови стала опять нормальной приблизительно через 48—72 часа.

При хроническом отравлении изменения крови и костного мозга напоминают изменения, описанные при остром отравлении, но они менее выражены, так как костный мозг уже подвергался повреждениям вследствие первых доз колхицина. Приблизительно через 5—7 недель появляются ядерные красные кровяные тельца и гиперсегментированные лейкоциты. В костном мозгу число эритробластов относительно повышено по сравнению к молодым формам лейкоцитов. В том случае, когда авторы в этой стадии прекратили лечение, произошла регенерация костного мозга, однако, при продолжении лечения развивалась вторичная апластическая анемия, мозг подвергался волокнистому преобразованию и животные погибали.