COLCHICINE

III. Pathology and Hematology in Cats and Rats

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THE ACCUMULATED SCIENTIFIC REPORTS on colchicine have emphasized effects of this alkaloid on mitotic activity. Other possible morphological effects of the drug have been little studied in normal animals. Since this compound is an active mitotic poison and is still under consideration as a chemotherapeutic agent, it was thought that further toxicological and pathological data would be of interest. The present work represents part of a systematic re-examination of colchicine[3, 4] and describes the general morphological and hematological changes resulting from acute and chronic colchicine poisoning in cats and rats. The minutiae of mitotic changes have been ignored, since this aspect of colchicine activity has been adequately studied in the past.

METHODS

A total of forty-one rats and eleven cats were completely examined histologically. The rats were of the Wistar strain, equally divided by sex, and weighed 90 to 150 gm. The cats, most of them female, weighed 2.2 to 4.1 Kg. Colchicine was administered according to two dosage systems in each species: a single lethal intravenous dose or intraperitoneal doses repeated five times weekly, beginning with nontoxic amounts and doubling the dose each week until significant mortality developed. The single intravenous dose given to thirty-one rats was 4 mg. per Kg., with sacrifice seventeen hours after administration. The repeated injections in ten rats began with 0.1 mg. per Kg. per day and increased to 1.6 mg. per Kg. per day in the fifth week, with sacrifice during the fourth and fifth weeks. The single intravenous dose in seven cats was 0.5 or 5 mg. per Kg. per cat; they were sacrificed after eight to twenty-four hours. Repeated doses given to four cats, began with 0.025 mg. per Kg. per day and were increased to 0.2 mg. per Kg. per day in the fourth week, with sacrifice during the third and fourth weeks.

Autopsies were performed immediately after sacrifice. All organs were examined grossly and specimens for microscopic study were routinely taken from all abdominal and thoracic viscera, skeletal, muscle, bone, thyroid, parathyroid, and brain. In cats only, additional sections were made of the salivary gland, pituitary, spinal cord, and sciatic nerve. Routine histological methods, with fixation in 10 per cent formalin and staining with hematoxylin and eosin were utilized. Special techniques included stains for fat in frozen sections of kidneys, myelin stains in nervous tissue of cats only, and decalcification of bone-marrow sections.

For peripheral-blood studies, rats were sacrificed at various intervals after colchicine administration and heart-blood counts compared to those obtained in a separate group of nonintoxicated rats. Serial counts were made in cats on saphenous-vein blood. Standard hematological methods were used except for reticulocyte counts; saturated alcoholic brilliant cresyl blue was dried on slides, blood added under cover slips, and reticulocytes counted one to two hours later. This method usually yields higher values for reticulocytes than do other procedures.

Fluid-volume measurements were made on a third group of rats weighing 130 to 200 gm. Sodium thiocyanate (50 mg. per Kg.) and Evans blue (3 mg. per Kg.) were injected intravenously in etherized animals. After five minutes, blood was drawn from axillary vessels, plasma concentrations of injected materials determined colorimetrically, and dilution volumes calculated. The values obtained were

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compared with those of normal rats in the same weight range.

RESULTS

The lesions observed represent extreme degrees of colchicine poisoning. As observed in a previous toxicity study,[3] the single intravenous doses given to rats could be expected to kill half of a group by the time of sacrifice (seventeen hours) and the remainder within three days. The comparable single doses in cats were invariably lethal within eight to seventy-two hours. Repeated administration in both species was begun with doses not productive of toxicity, but no animals were sacrificed until fatalities had appeared in the groups. While the mortality rate was less than that

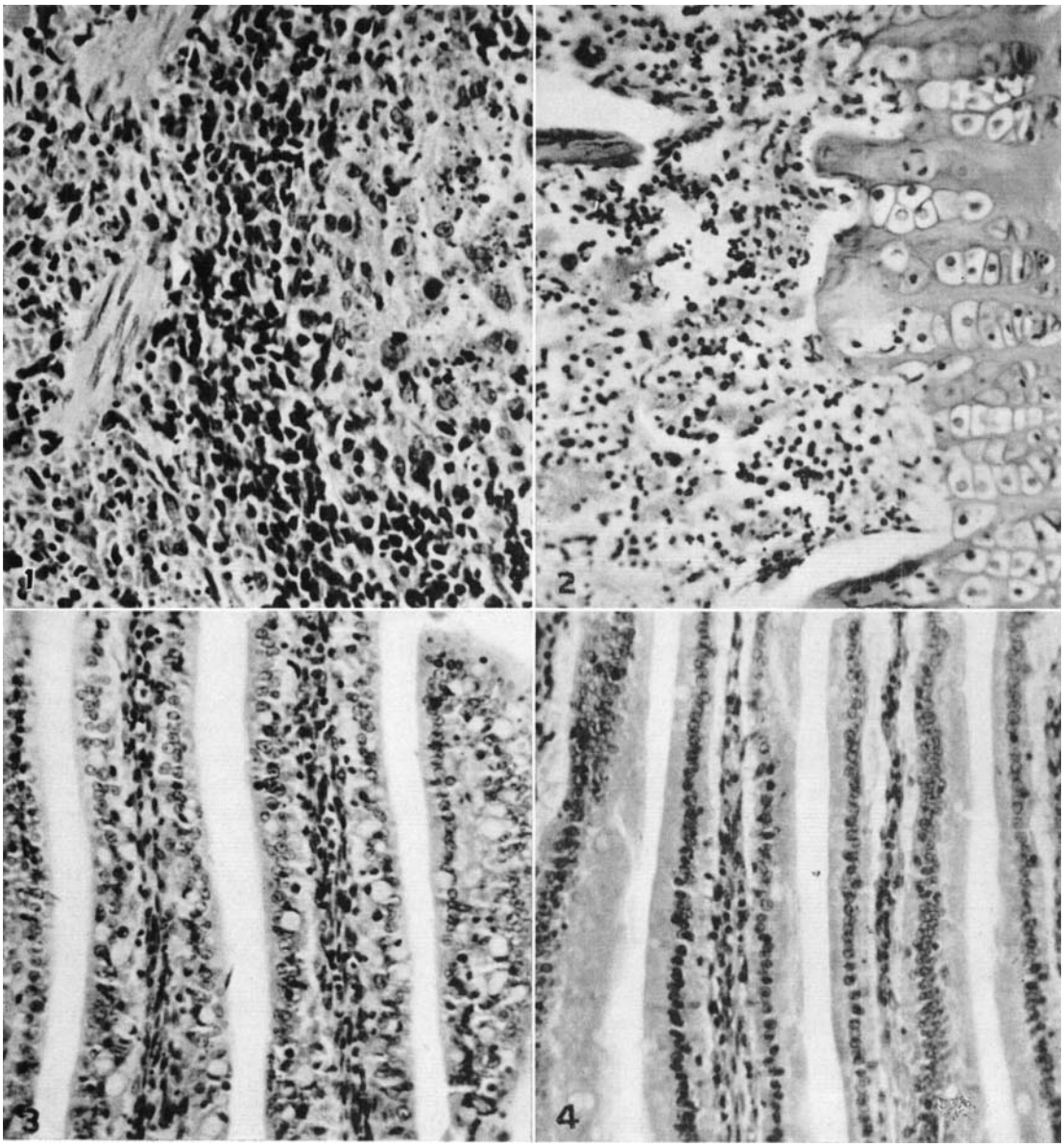

FIG. 1. Rat spleen; acute toxicity. Karyorrhexis of follicle and red pulp. Similar changes were observed in other lymphoid-containing organs in both rats and cats.
FIG. 2. Rat sternum; acute toxicity. Karyorrhexis, with depletion of cellular elements.
FIG. 3. Rat duodenum; acute toxicity. Villi showing loss of nuclear polarity, signet-cell formation, and stromal karyorrhexis.
FIG. 4. Rat duodenum; control. For comparison with Fig. 3.

obtained with single doses, approximately half the rats and a third of the cats had died by completion of the courses of administration (five weeks in rats and four in cats).

The only consistent finding on gross examination was hyperemia of the gastrointestinal mucosa. Cats and rats responded similarly to colchicine, and the effects of single lethal doses ("acute" poisoning) and of repeated increasing doses ("chronic" poisoning) were also similar. Accordingly, the detailed presentation of results will be confined to a general description of positive histological findings, with mention of any observed species or dosage differences.

Lymphoid Elements. In the lymph nodes and thymus of acutely poisoned animals, diffuse and extensive karyorrhexis was present, with maintenance of the basic differentiation of cortex and medulla. The powdering of nuclear debris was especially prominent in the follicular centers of the nodes and the medulla of the thymus. The same process was present in varying degrees of severity in other lymphoid-containing structures such as the spleen, bone marrow, and intestine. In the spleen the change was especially marked in the centers of the follicles but also present to a considerable degree in the red pulp, occasionally with diminution of cellular elements (Fig. 1). The splenic follicles did not appear enlarged or shrunken in rats but in cats were slightly reduced in size. Lymphoid elements in the bone marrow likewise showed areas with fragmented nuclei, most marked in the juxtaepiphysial zone (Fig. 2). In the intestines, the lymphoid patches showed marked karyorrhexis similar to that seen in the nodes. The nuclear debris frequently extended to the underlying muscle and the overlying mucosa.

Structural changes were much less marked in chronically poisoned cats and rats. Karyorrhexis was markedly less prominent in the thymus and virtually absent in lymph nodes. However, the thymus of rats showed involutionary changes with loss of corticomedullary demarcation, and the follicular structure of the nodes was lost. In the spleen little or no karyorrhexis was present, and the follicles appeared to be of approximately normal size with no change in configuration. The red pulp in rats was characterized by the presence of moderate numbers of small spindle cells resembling fibroblasts, a change similar to that described in nitrogen-mustard toxicity.[5]

Gastrointestinal System. Striking mucosal changes throughout the intestines were detected in all acutely poisoned animals. In the duodenum the epithelial cells covering the villi showed a loss of nuclear polarity. The uniform, even palisading of the nuclei was distorted by irregular displacement, often toward the luminal segment of the cell. Nuclei varied in size and shape and often were pyknotic. The cytoplasm showed increased vacuolization with prominent signet-cell formation. The number of inflammatory cells in the stromal cellular elements of the villi was increased and many manifested pyknosis and nuclear fragmentation (Figs. 3, 4, 5). The underlying glands showed the same loss of polarity, but with irregular swelling and distortion of individual epithelial cells, glandular ectasia, and flattened lining epithelium. Some of the dilated glands were filled with nuclear debris. In the remainder of the small intestines and in the colon, the changes in the surface epithelium, mucosal glands, and stroma were basically similar to those in the duodenum. In the colon, the mucosal goblet cells showed variations in size and shape of the vacuoles. Numerous foci were present in which the vacuolated epithelial cells were replaced by a granular pink cytoplasm. Some colonic glands were dilated, and the epithelium was flattened with the lumina containing degenerating epithelium and nuclear debris; other glands were frankly necrotic. The deposition of nuclear debris and the infiltration of inflammatory exudate into the stroma were focal and minimal, unlike the diffuse change seen in the small intestines.

No changes were present in the stomach except for foci of karyorrhexis and necrosis in glandular epithelium, restricted to the glands lying immediately beneath the luminal lining cells in the pyloric area (Fig. 6). This was associated with minimal glandular ectasia. The remainder of the stomach was unaffected except that, as in all segments of the gut, the capillaries were prominent and enlarged. Nowhere was ulceration detected and there was no appreciable edema. Foci of epithelial atypia were seen in the gallbladder, urinary bladder, and esophagus of cats. These changes will be the subject of a separate report.

The chronically poisoned rats showed intestinal changes similar to those described previously except that nuclear debris was no longer present. However, gastrointestinal abnormalities were virtually absent in the cats given repeated injections of colchicine. These chronically poisoned cats incidentally mani-

fested negligible functional disturbances, whereas vomiting and diarrhea had been extreme in those cats given single doses.

Liver. The hepatic effects of colchicine differed somewhat in cats and rats. Normal rats exhibited prominent basophilic granularity and cytoplasmic vacuoles in the liver cells (Fig. 7). Both characteristics were much less marked in all rats receiving colchicine. The hepatic cells appeared smaller in treated ani-

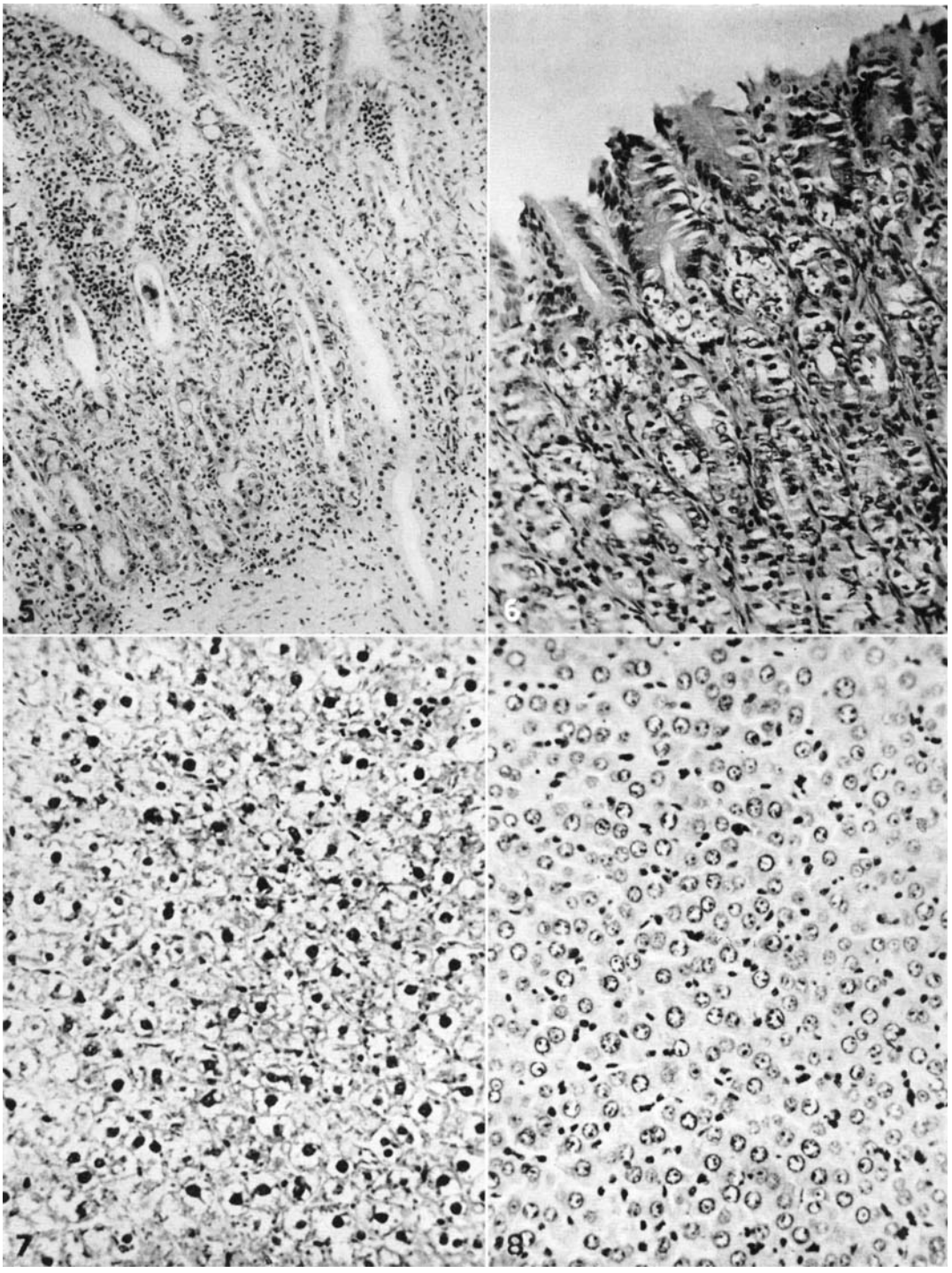

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TABLE 1

EFFECT OF COLCHICINE ON PERIPHERAL BLOOD OF RATS

Time after colchicine started	Total dose, mg./Kg.	No. rats	R. B. C., millions/ cu. mm.	Hb, gm./ 100 cc.	Hemato-crit, cc./100 cc.	Mean corpus-cular volume, cu. μ	Reticulo-cytes, % of R. B. C.	Leukocytes: Polymorphonuclear Neutro./ cu. mm.	Leukocytes: Polymorphonuclear Eosin./ cu. mm.	Leukocytes: Lympho. & mono./ cu. mm.
Control										
	0	14	7.4	16.4	52	71	6.2	800	90	3900
Acute Intoxication (Single Intravenous Dose, 4 mg./Kg.)										
2 hr	4	5	8.9	19.4	57	64	3.5	400	10	4000
6 hr.	4	5	8.4	18.8	52	62	4.1	1100	70	5800
17 hr.	4	10	10.4	22.1	60	58	5.3	1600	250	8000
Chronic Intoxication (Intraperitoneal Doses, 5 Times Weekly)										
4 days	0.4	5	6.9	16.2	48	71	6.7	600	10	3700
11 days	1.3	5	6.2	13.5	41	67	8.5	800	10	4300
18 days	3.1	5	7.1	14.3	52	73	6.9	600	80	4600
25 days	6.3	5	8.6	18.5	59	70	0.5	1000	90	3000
30 days	9.9	5	8.9	18.4	62	70	0	2000	0	4400

mals, with cell boundaries more sharply defined; the cytoplasm was relatively homogeneous (Fig. 8). Occasionally, areas of acute local necrosis were noted after colchicine. However, the same effect was observed in some control animals and it could not be considered significant. The liver in all cats was normal except for mild vascular engorgement.

Kidney. In rats receiving acute doses, the kidneys revealed subnuclear cytoplasmic vacuolization of the tubular epithelium. This was confined primarily to the proximal tubule, with inconstant extension to the distal segment. The vacuolization was especially prominent in the relatively aglomerular zone of the inner cortex, which opposes the medulla, and was least marked in the subcapsular tubules. The vacuoles were for the most part coarse and appeared on the basement-membrane side of the cell, elevating the nucleus (Fig. 9). Rarely, the vacuoles were fine and delicate, forming a network both in the luminal and basal portions of the cells. Frozen sections stained with oil red 0 revealed fine sudanophilic droplets in the cytoplasm of these cells (Fig. 10). Examination with polarized light revealed that the droplets were not doubly refractive. Tubular necrosis and glomerular changes were absent.

In the chronically intoxicated rats the fat deposits in the tubular epithelium were present but changes were more focal. The diffuse, evenly dispersed subnuclear vacuoles in the proximal tubules were rarely found. Scattered, isolated segments showed irregular and coarse vacuoles, causing marked distortion of the tubular nuclei and cytoplasm (Fig. 11). Intervening tubules either appeared normal or showed focal dilatation of the lumina. Fat stains showed this spotty distribution of fat; but, in any given segment that contained fat, the number of droplets was greater, and the droplets were often larger than those seen in the acute experiment (Fig. 12). Necrosis was again absent and the glomeruli and interstitial tissues were normal.

Renal changes in cats were the same in acute and chronic experiments. The principal effect of colchicine in both groups was revealed by fat stains. The tubular cells in normal cats contained large amounts of fat (Figs. 13, 14). After colchicine, there developed an increase in the total amount of fat present as well as an increase in the size of individual droplets. With the usual hematoxylin and eosin stain, the only suggestion that fat was present in larger amounts was indicated by a tendency for the tubular nuclei to be located closer to the lumen. In two cats (one acutely intoxicated and the other from the chronic group), however, there was widespread coarse vacuolization of the cytoplasm and the nuclei were almost uniformly pushed toward the lumen (Figs. 15, 16). These changes were confined principally to the proximal segment of

FIG. 5. Cat duodenum; acute toxicity. Changes similar to rat. Also dilated glands with necrotic debris, karyorrhexis, and inflammatory infiltrate.

FIG. 6. Cat pylorus; acute toxicity. Karyorrhexis, vacuolization, and necrosis of glands immediately beneath surface epithelium. Similar change seen in rats.

FIG. 7. Rat liver; control. Basophilic cytoplasmic granules and vacuolization.

FIG. 8. Rat liver; acute toxicity. Loss of basophilia, sharpened cell boundaries, and pale nuclei. (Same magnification as Fig. 7.)

the nephron. Glomerular and vascular lesions were always absent.

Bone Marrow. There was moderate to severe depletion of all cellular elements in the marrow after acute administration of lethal doses of colchicine (Fig. 2). Vascular congestion, focal areas of hemorrhage, and karyorrhexis were also noted. The effects were less marked in chronically treated rats and karyorrhexis was absent, though areas of fatty marrow were seen. Even less effect was apparent in chronically poisoned cats: two showed slight hypo-

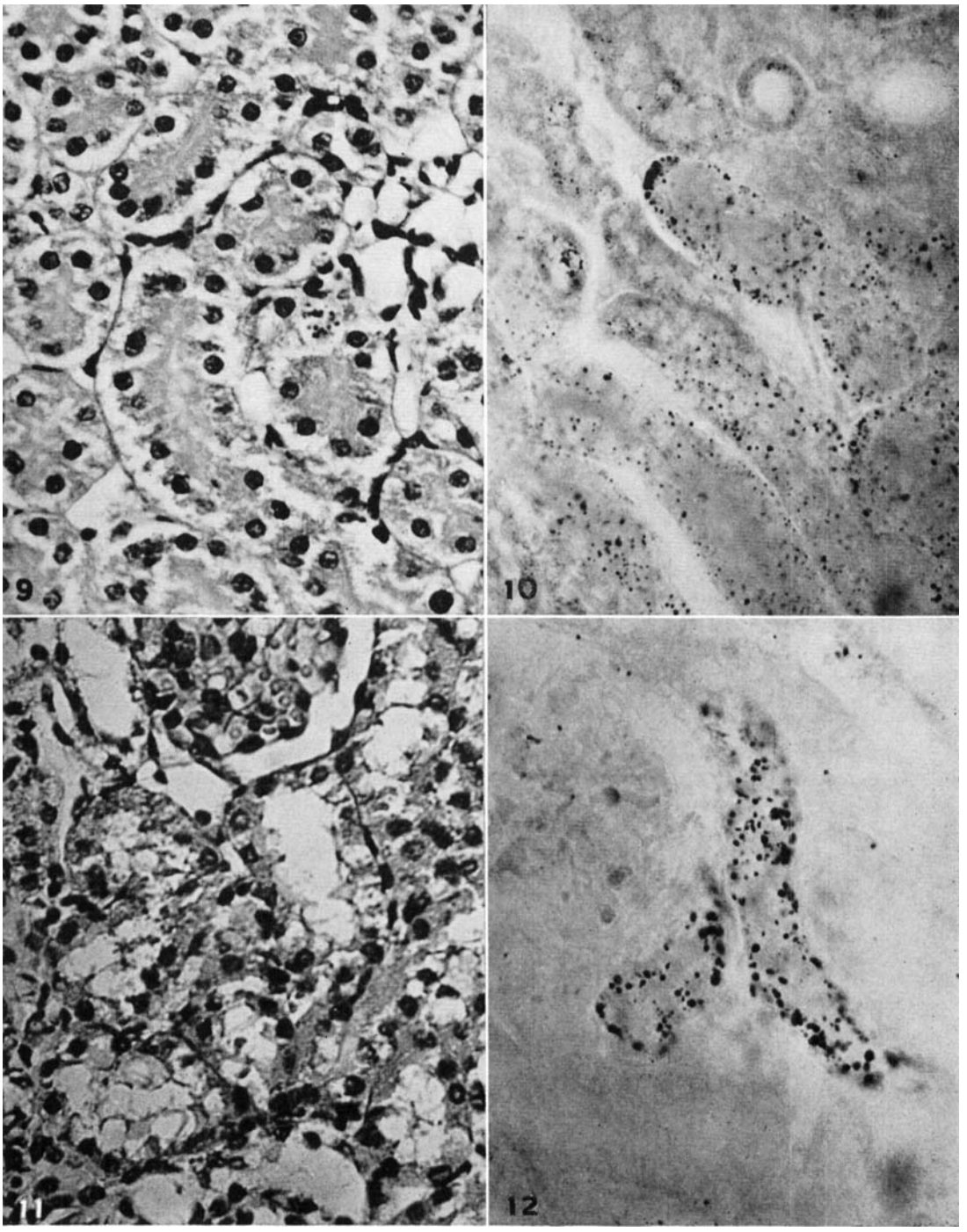

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TABLE 2

EFFECT OF COLCHICINE ON BODY FLUID VOLUMES OF RATS

	Control	Test	Change from control, %
Number of rats	8	7	
Original weight	160	166	
Final weight		154	
Thiocyanate space	33.0	20.4	−38
Plasma volume	4.7	3.3	−30
Circulating red-cell volume	6.3	4.8	−24
Total blood volume	11.0	8.1	−26

Test animals studied seventeen hours after administration of colchicine, 4 mg./Kg. intravenously. All values expressed in cc./100 gm. at time of sacrifice.

plasia and karyorrhexis; in the other two the marrow was normal.

Peripheral Blood. Table 1 presents hematological data obtained from groups of normal, acutely poisoned, and chronically poisoned rats. Acute administration of colchicine markedly elevated the values for red cells, hemoglobin, and all leukocytes. The hematocrit did not increase proportionately, owing to a concomitant decrease in mean corpuscular volume. The mean corpuscular hemoglobin content was unchanged, hence the concentration per cell increased slightly.

These acute changes must be considered in relation to disturbances in body water. Marked dehydration developed in these animals, owing to the starvation and diarrhea associated with colchicine activity. Measurements were made of the changes in body fluids, utilizing the dilution of Evans blue for measurements of plasma volume and the "thiocyanate space" as a guide to total extracellular fluid volume (Table 2). Colchicine administration produced a marked degree of hemoconcentration with a loss of about one third of total extracellular water. Surprisingly, the circulating red-cell volume was also reduced, despite the apparent increase indicated by the previous cell counts. Possibly this loss of erythrocytes occurred in part through the damaged intestinal mucosa.

Chronic administration of colchicine in rats produced only minor fluctuations in red-cell values for the first few weeks. By the end of the course, when the increased daily dose was productive of diarrhea, elevated red-cell values again appeared. The terminal rise in neutrophile leukocytes occurs in rats poisoned with many agents and can be given little importance. However, the disappearance of reticulocytes and eosinophile leukocytes in the final week of poisoning may represent specific actions of colchicine.

Table 3 presents comparable data in cats, based upon serial blood counts in acutely and chronically poisoned animals. Reticulocyte counts are omitted from this table because no significant numbers were ever seen in cats.

TABLE 3

EFFECT OF COLCHICINE ON PERIPHERAL BLOOD OF CATS (SERIAL COUNTS)

Time after colchicine started	Total dose, mg./Kg.	No. cats	R. B. C. millions/ cu. mm.	Hb, gm./100 cc.	Hematocrit, cc./ 100 cc.	Leukocytes: Polymorphonuclear Neutro./ cu. mm.	Leukocytes: Polymorphonuclear Eosin./ cu. mm.	Leukocytes: Lympho. & mono./ cu. mm.
Acute Intoxication (Single Intravenous Dose, 5 mg./Kg.)								
0	0	3	8.6	15.7	40	4300	250	5100
3 hr.	0	3	9.9	17.5	45	3300	90	5400
6 hr.	5	3	10.1	18.6	55	2700	40	6500
Acute Intoxication (Single Intravenous Dose, 0.5 mg./Kg.)								
0	0	3	9.6	15.6	42	4500	350	6700
3 hr.	0.5	3	10.1	16.3	45	2500	190	5300
6 hr.	0.5	3	10.2	17.0	47	2400	140	5100
24 hr.	0.5	2	12.1	18.2	48	2500	210	6200
Chronic Intoxication (Intraperitoneal Doses, 5 Times Weekly)								
0	0	4	10.2	16.4	44	3100	170	6000
4 days	0.1	4	7.9	14.0	38	10,300	380	5600
11 days	0.33	4	9.1	17.6	43	19,200	220	3700
17 days	0.68	3	7.9	14.4	34	10,500	400	3700

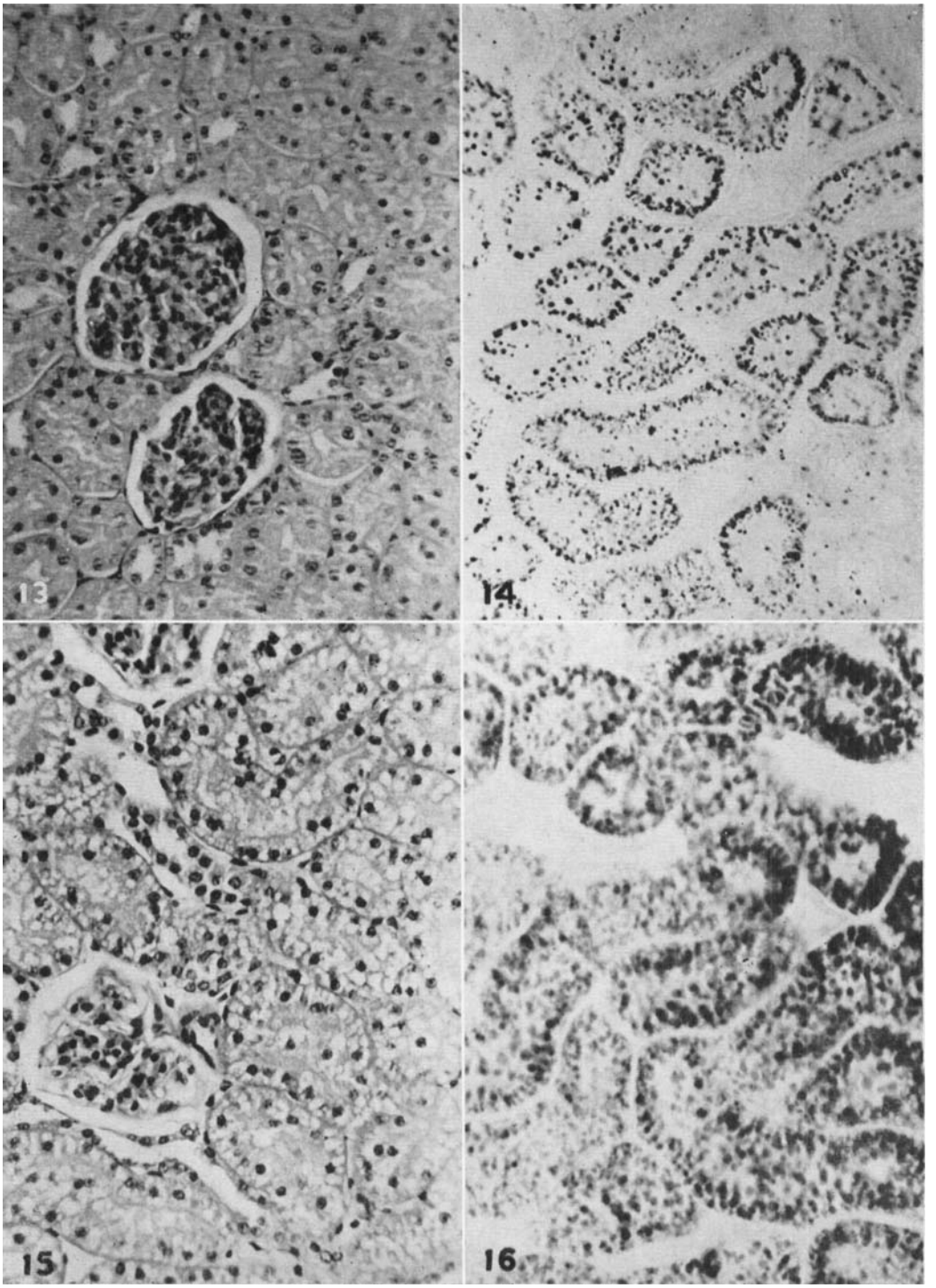
FIG. 9. Rat kidney; acute toxicity. Basilar vacuolization with elevated nuclei in proximal convoluted tubules.

FIG. 10. Rat kidney; acute toxicity. Fat stain showing fine droplets in tubules.

FIG. 11. Rat kidney; chronic toxicity. Coarse and irregular cytoplasmic vacuolization.

FIG. 12. Rat kidney; chronic toxicity. Fat stain showing single tubule with more and larger droplets.

Acute administration induced progressive increases in the erythrocyte count, hemoglobin content, and hematocrit, again in association with marked diarrhea, vomiting, and dehydration. There were no changes in mean corpuscular hemoglobin or volume. Unlike rats, cats did not manifest leukocytosis; there was in fact mild granulocytopenia. The failure of white-cell counts to rise, particularly in the face of hemoconcentration and erythrocytosis, may



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represent a species difference between rats and cats. However, the observed fluctuation was within the range of normal temporal variation and so cannot be proved significant. The only hematic effects of chronic colchicine poisoning were slight depression of erythrocyte values and an increase in polymorphonuclear leukocytes.

Nervous System. Special mention may be made of the fact that the brain, spinal cord, and sciatic nerve of treated cats exhibited no abnormalities, whether examined with routine methods or myelin-sheath stains. This is pertinent to the prior observation[3] that the peripheral musculature of chronically (but not acutely) poisoned cats developed physiological changes resembling chronic denervation. Some of the cats in which this "denervation-like" syndrome was demonstrated were in fact included in this histological study. Slight edema of the muscles was present and the muscles were obviously smaller than normal size but no organic basis for the functional derangements was detected.

Lungs. Treated cats, but not rats, showed moderate vascular congestion of the lungs. In two acutely poisoned cats, pulmonary edema was evident. No bronchial changes were seen.

Gonads. Chronically poisoned cats manifested some diminution of spermatogenesis. The testes in other animals and the ovaries in all appeared normal.

COMMENT

The renal changes in acutely intoxicated rats represent a toxic effect not previously recognized with colchicine. The pathological change observed in the kidney may be termed "fat nephrosis" as defined by Allen. A variety of agents (including phosphorus, carbon tetrachloride, and iodoform) produce an identical picture in humans and animals. With all these poisons (including colchicine), there develops throughout the proximal nephron cytoplasmic deposition of fat, not doubly refractive, with basilar vacuolization and nuclear elevation. The term "lipoid nephrosis" is reserved for conditions associated with the nephrotic syndrome and seen principally with certain forms of glomerulonephritis in which fat is deposited in the proximal nephron in a diffuse latticework rather than a basilar arrangement, anisotropism is usually seen, and deposition may occur not only interstitially but even in the glomeruli.[1] A single intravenous dose of 4 mg. per Kg. of colchicine will lead to the deposition of fat within seventeen hours. In chronic experiments the process is altered in that the deposition is not widespread and diffuse, although the isolated segments of the nephron that do become involved contain larger amounts of fat. Lits working with mice noted an elevation of the tubular nuclei from the basilar position but apparently did not recognize the change as possibly one due to the deposition of fat, since the material was not so stained.

The interpretation of the renal lesion in cats as that of fat nephrosis is not warranted in view of the fact that fat is normally present in the kidney of these animals. Apparently the fat content is relatively stable, being unaffected by starvation or high fat diets, although increased in pregnancy.[7] With colchicine it was noted that the amount of stainable fat was increased, with the formation of larger globules in both the acutely and chronically intoxicated animals. In addition, two of the colchicine-treated cats showed, with hematoxylin and eosin stain, diffuse nuclear elevation that mimicked quite closely the lesion of fat nephrosis in humans and animals seen with other poisons such as carbon tetrachloride. None of the five control cats showed this pronounced alteration.

The functional significance of the renal lesion in rats is unknown. Dicker observed various changes in tubular function after single doses of colchicine, but the studies were confined to the first few hours after drug administration and the kidneys were examined only grossly. It is not certain that the same actions of colchicine were involved in his findings, and analysis of renal function in conjunction with microscopic studies are needed.

Colchicine also exerted striking effects on the lymphoid and gastrointestinal structures that were quite similar morphologically to the changes seen with many other unrelated protoplasmic poisons. The nitrogen mustards, anti-folic acid agents, roentgen rays, and

FIG. 13. Cat kidney; control. Irregular vacuolization of convoluted tubules.
FIG. 14. Cat kidney; control. Fat stain showing diffuse distribution of relatively large amounts of fat.
FIG. 15. Cat kidney; acute toxicity. Marked basilar vacuolization with elevation of nuclei.
FIG. 16. Cat kidney; acute toxicity. Fat stain showing increased amount of tubular fat.

others have comparable actions. However, the several agents do vary in the severity of lesions produced as well as in the selectivity for certain tissues. For instance, although the nitrogen mustards in large doses produce intense fragmentation of lymphocytes in the lymph nodes and thymus, equivalent changes are not found in the stromal cells of the intestine.[5] Colchicine, on the other hand, produced severe necrotizing changes in the stromal elements. Antifolics, too, induce marked intestinal lesions primarily affecting the mucosa but without significant stromal karyorrhexis.[8] Unlike both colchicine and the mustards, however, the folic acid antagonists have only moderate effects on lymphoid tissues.[8] Radiation produces intestinal ulceration, a change not seen with colchicine; the antifolics and the nitrogen mustards may show only superficial desquamation or simple erosion.

Resistance of the stomach to the destructive processes in the digestive tract is a puzzling characteristic of all these agents. In this organ colchicine produced microscopic alterations that were minimal when compared with changes in the small and large intestine. The gastric changes with colchicine were localized to the glands immediately beneath the surface epithelium; the latter remained intact. Susceptibility of the glandular elements without involvement of the surface epithelium has also been observed in the case of radiation.[9]

The actions of colchicine on peripheral-blood cells have been the subject of numerous inquiries. Almost every possible hematological response has been reported: macro- and microcytosis, hypochromia, erythrocytosis, reticulocytosis and reticulocytopenia, leukopenia, lymphocytosis, and granulocytosis. These results have not in the main been confirmed. Possibly the differing effects were due to species differences, to differences in dose and time relationships of colchicine administration, or to the use of impure preparations of the alkaloid. Moreover, it appears that previous reports inadequately considered the normal variability of the blood picture in animals and particularly failed to appreciate the profound disturbances in body water induced by colchicine. The effects of acute poisoning were, with the exception of the questionably significant granulocytopenia in cats, entirely secondary to hemoconcentration and probable intestinal bleeding. The lack of more specific action is surprising in view of the destructive processes in the lymphoid organs and marow. Similarly, chronic administration of nontoxic amounts of colchicine produced but minimum anemia. Only when the dosage was raised into the lethal range did significant changes (granulocytosis in cats and absence of reticulocytes and eosinophilic leukocytes in rats) appear. It might be expected that such a potent mitotic poison as colchicine would induce more marked responses in the blood picture. Certainly the doses utilized were adequate to affect mitosis, for there have been many demonstrations that mitotic inhibition is effective at minimum concentrations of colchicine.

SUMMARY

The effects of single lethal and repeated increasing doses of colchicine have been investigated histologically in rats and cats. Similar findings were observed in both species by both dosage systems. Fat nephrosis, marked karyorrhexis of lymphoid structures, abnormalities in the gastrointestinal mucosa, and hypocellularity of the marrow were found. While these effects resemble those produced by several agents, certain differences between colchicine and other substances have been discussed. Colchicine produced only minor effects on peripheral blood cells, largely secondary to dehydration.

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