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The Natural Resistance of the Golden Hamster to Colchicine

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In the course of an investigation of the origin of tertiary giant cells in the pregnant uterus of the hamster, *Cricetus auratus,* it was decided to use colchicine to study proliferative growth. Doses varying from .1 mg up to 2 mg/100 g of body weight were injected, and the animals were killed 6–21 hr thereafter. No significant variation from the normal number of mitoses was observed, and the presence of anaphase and telophase stages with normal spindles in normal ratio suggested that these doses were ineffective. A review of the literature indicated that the effective dose in other rodents, mice, rats, and guinea pigs, and in rabbits, is usually just below the lethal level. In an attempt to establish the effective dose, and to test the potency of the colchicine used, a series of hamsters, mice, rats, and one rabbit were injected intraperitoneally from the same solution of colchicine, injections varying in concentration from 0.12 to 7.0 mg/100 g of body weight. Young mature males were used for this entire series. Time of injection, concentration, and subsequent history were recorded, the animals being checked in the morning, during the day, and in the evening. The results are recorded in Table 1.

Both rats and mice, and also the rabbit killed in this study by the lethal effects of colchicine displayed the classical symptoms of colchicine poisoning: diarrhea, bloody stools, lethargy, and progressive paralysis appearing first at the caudal end and extending cephalad. Several of the rats displayed bloody nasal hemorrhages.

The hamsters showed no effects whatever. All animals that were tested proved fertile. No attempt was made to check against the possibility of a certain post-treatment period of infertility, but some animals were tested and proved fertile as early as 5 days and others as late as 37 days after treatment, and hence there is no reason to believe that any infertile period occurs.

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Moreover, there was a normal increase in weight of 1.5–15 g/animal from the time of injection to the termination of the experiment, 4–8 weeks later.

Another series of 6 male animals (2 rats, 2 hamsters, and 2 white mice) was fed a mixture of one third *Colchicum autumnale* seed,[2] containing not less than 4.5 mg colchicine/g of seed, mixed with two thirds pulverized Purina laboratory chow blocks, in order to determine if the seed, too, affects rats and mice and not hamsters. Five g of this was fed daily to each rat, 3 g daily to each hamster, and 2 g daily to each mouse. From the third day the amount of food for each animal was doubled in order to ensure an adequate nutritive supply. The animals were kept in individual cages with water dishes; one of each pair had shavings for bedding; the other cage was left bare. The food was placed on a paper on the floor of the cage.

TABLE 1

APPROXIMATE LENGTH OF SURVIVAL FOLLOWING VARYING DOSES OF COLCHICINE

Dosage (mg)	Mouse	Rabbit	Rat	Hamster
.12			Lives	Lives
.25			2 days, 14 hr	"
.50	5 days		24 hr	"
1.0	3 days, 21 hr	8 hr	21 "	"
1.5	24 hr		10 "	"
2	24 "		4–4.5 "	"
3	10 "			"
4	10 "			"
5–10				"

Both mice died on the 7th day of the experiment. One had dropped in weight from 24 to 20 g; the mouse with no bedding dropped from 24 to 15.6 g.

The rat in the bare cage had dropped from 112 g to 69.2 g by the 6th day, when it died. The other rat had dropped in weight from 99 to 68.3 g by the 9th day, when it was sacrificed. Diarrhea could of course account for part of the weight loss, but the second rat seemed to be starving voluntarily. Large amounts of uneaten food were present in both the rat cages.

The two hamsters gained 1.5 g and .6 g during the same period.

A control mouse, fed identical gram amounts of pure chow alone, rose in weight from 25.5 to 25.7 g at the end of 9 days.

The injection series definitely indicates that the hamster possesses a natural resistance to the usual toxic effects of colchicine, a resistance which far exceeds that of other laboratory animals. Poe and Johnson (*1*) report the lethal dose of colchicine in the rat to be 1 mg/kg body weight injected intraperitoneally, with death in 51 hr. Sollmann and Hanzlik (*2*) give 1 mg/kg body weight injected intramuscularly as the lethal dose for the dog and cat. The lethal dose in man is said to be variable, but is about 8 mg/kg body weight (*3, 4*).

[2] Supplied through the courtesy of S. B. Penick & Co.

Perhaps no definite conclusions are justified by the colchicine feeding experiment, in view of the small number of animals used. It may well be that death in half the cases was from starvation rather than toxicity of the drug. However, the starvation must have been voluntary, since large amounts of food material were left untouched in the cage, and the duration of the experiment was not sufficient to suggest death from malnutrition.

The resistance to colchicine displayed by the hamster strongly resembles the natural resistance of the rabbit to aconite. In this respect, it is of interest to note that colchicine, which is usually extracted from the meadow saffron, *C. autumnale,* has also been isolated from other species of *Colchicum.* Although *C. autumnale* is distributed throughout Europe, the center of distribution for the genus (with 30 species) is in Asia Minor (*5*). This suggests that resistance in the hamster may have developed from close association with the plant in the natural habitat, *Colchicum* probably being used by the hamster as food. How high this resistance may extend, and what mechanism is involved, would be interesting to determine.

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The Turnover Time of Phosphorus in Normal, Sickle Cell Trait, and Sickle Cell Anemia Blood *in Vitro* as Measured with P^{32} [1,2]

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The close relation between oxidation and phosphorylation in the living cell would lead one to expect that a disease which affects one would have some affect upon the other. Thus in sickle cell anemia, sickle cell trait, or sicklemia (henceforth called trait), and normal blood, a study of rate of uptake of phosphate by the red blood cell under various conditions should give insight into the mechanism of phosphorus transfer and its disturbance in this serious blood dyscrasia.

In order to obtain comparable data with some statistical reliability, we secured blood samples from 10 normal, 9 trait, and 7 sickle cell anemia patients. The sickle cell patients were known cases which had been treated on the Pediatric Service of Freedmen's Hospital for typical crises of the disease. Four slides were made of each patient in the study, using the methods of Singer and Robin (*1*) and Daland and Castle (*2*). All the anemia and trait patients showed sickling. None of the anemia patients had received blood transfusions in the three months preceding this study. The trait cases were siblings or parents of known sickle cell anemia patients. The normal cases were asymptomatic and, of course, showed no sickling. The age distribution of the subjects is given in Table 1.

TABLE 1

	Normal	Trait	Sickle cell anemia
Lowest	9 years	4 years	2 years
Highest	14 "	49 "	10 "
Average	10.5 "	23 "	9 "

Approximately 23 ml of blood was taken from each patient. On 3 ml a complete hemogram was done. Exactly 20 ml was mixed with 0.8 ml of the ammonium potassium oxalate solution (2 g potassium oxalate and 3 g ammonium oxalate in 100 ml solution), following the method of Taylor *et al.* (*3*). This solution caused no swelling of the erythrocytes. The blood samples were incubated in stoppered brown bottles with 13.7 ml air above the sample. To each sample of a group, 0.5 ml of isotonic NaCl containing a tracer amount of P^{32} as PO_4 in weak HCl was added (e.g., 0.54 mc in 0.5 ml solution to each sample of normal blood). The activities were checked against the Tracerlab simulated P^{32} source.

The blood samples were incubated for 4 hr at $38° \pm 0.1°$ C. There was no sickling in the blood samples during incubation. After incubation, total, acid-soluble, and inorganic phosphorus were determined, following the method of Fiske and Subbarow (*4*), on the whole blood, the plasma, and red blood cells. The radioactivity was determined on an aliquot of each sample, evaporated to dryness and counted with a mica end window Geiger-Müller tube, thickness 3 mg/cm^2, feeding into a Nuclear Instrument and Chemical Corporation Model 172 scaler.

Blood samples were centrifuged for 15 min at 3000 rpm to separate the plasma from the red blood cells. The plasma was drawn off as completely as possible. The cells were resuspended in isotonic saline, centrifuged, and the supernatant saline was drawn off and discarded. This washing was repeated. The red cells were then frozen at $-20°$ C to produce hemolysis and to prevent hydrolysis of the organic phosphorus compounds. For analysis the frozen cells were thawed and diluted with distilled water.

The results are expressed in specific activities defined as the counts/sec/mg of phosphorus corrected for radioactive decay (Table 2).

In this preliminary report we shall consider only

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