

tion of that substance which is effective in the induction of remissions in pernicious anemia of human beings. Their only aim is to show that under proper conditions reticulocytes may remain at constant levels and that rises occur when liver extract is fed. Liver extract is a complicated and little-understood substance. It is rich in the vitamin B complex as well as in the anti-anemia factor. The question of which constituent is effective in the guinea pig must await further investigation.

Summary and Conclusions. 1. The number of circulating reticulocytes in the guinea pig increases after a variety of physiological disturbances. 2. By suitable care in handling and feeding stable reticulocyte levels may be maintained for as long as 3 months. 3. Rises of reticulocytes follow the feeding of liver extract. 4. Similar rises do not follow the feeding of charred liver extract.

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Effect of Colchicine on Human Tumors.

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The action of colchicine upon division of normal and malignant cells has been studied by several investigators. Dustin¹ described a remarkable increase in the number of mitoses in malignant growths in animals following the injection of colchicine. Ludford² found that colchicine applied to cultures of normal and malignant cells of animals brought about an arrest of mitosis for several hours, and that prolonged application destroyed the cells held up in division while the resting cells still survived, and that a single injection in animals produced an arrest of mitosis for several hours. The mitoses were arrested in the metaphase, which Ludford believes is due to the failure of the mitotic spindle to form and function in the normal manner. He also found that the largest accumulation of arrested mitoses occurred in tissue in which cell division is normally of frequent occurrence. This phenomenon has been utilized by others^{3, 4} as an index of the rate of cell growth. It, therefore,

¹ Dustin, A. P., *Bull. Acad. Med. Belg.*, 1934², **14**, 487.

² Ludford, R. J., *Arch. f. exper. Zellforsch.*, 1936, **28**, 411.

³ Brues, A. M., *J. Physiol.*, 1936, **86**, 63.

⁴ Allen, Edgar, Smith, G. M., and Gardner, W. U., *Endocrinology*. In press.

seemed that the method might prove of value in studying the growth characteristics of human tumors.

The colchicine effect on tumors was studied in a group of 21 patients who received the drug either subcutaneously or intramuscularly. Fifteen of the 21 patients had control biopsies before receiving the colchicine and of this group 11 showed definite arrest of mitosis in the metaphase. A biopsy was performed, when possible, to establish the diagnosis, and to serve as a control. Colchicine was then administered, and in most instances a second biopsy was performed or the entire tumor removed 9½ hours later. In certain inaccessible tumors it was impossible to perform a biopsy before the removal of the tumor. However, the colchicine effect could be observed and compared with similar tumors.

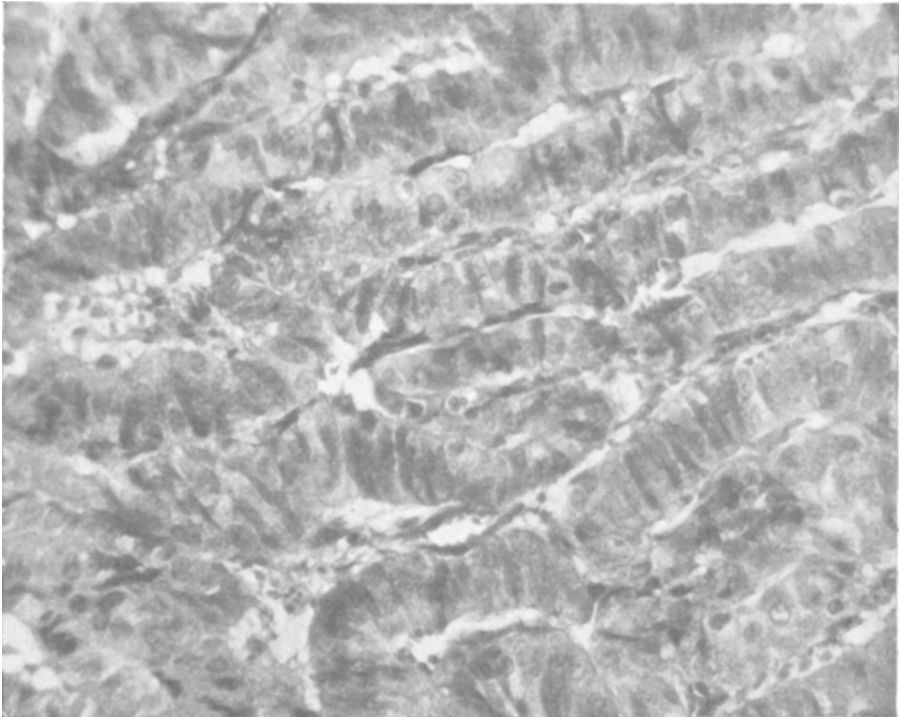


FIG. 1.
Adenocarcinoma of rectum. H&E. 200 X. Before colchicine.

In some cases, such as the one here reported, biopsies were taken at intervals varying from 4 to 18 hours after injection. The drug was diluted in saline solution, and administered either intramuscularly or subcutaneously. Doses varying from one to 4 mg. were

used, and as little as $1\frac{1}{2}$ mg. has produced a typical colchicine effect in some tumors.

The following case history is given as an example of the results obtained. A 50-year-old white male (A-67935) was operated on for a carcinoma of the sigmoid colon. The tumor was delivered on the abdominal wall according to the Mikulicz technique with its blood supply intact, and was readily accessible for biopsy. A portion of the tumor was removed as a control, following which 4 mg. of colchicine were administered subcutaneously. Biopsy of the tumor was performed at 5 and $9\frac{1}{2}$ hours after the injection of the drug, and at 12 hours the entire tumor and adjacent bowel were excised. The microscopic preparation revealed an anaplastic adenocarcinoma Grade III (Fig. 1). The biopsy before colchicine injection showed

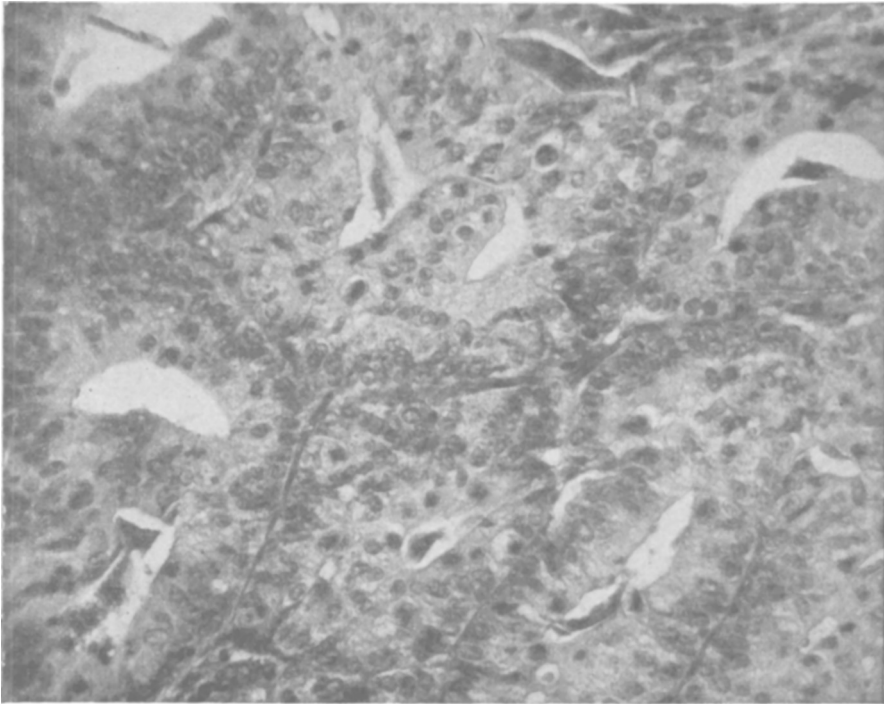


FIG. 2.

Same tumor. H&E. $200\times$. 12 hours after 4 mg. colchicine.

all phases of mitosis, whereas following colchicine almost all mitoses were in the metaphase. The mitotic figures present in 20 oil immersion fields selected at random in each biopsy were counted with the following results :

Control	Average	2.6	per	high	power	field
5 hr. after injection	"	7.3	"	"	"	"
9½ " " "	"	12.0	"	"	"	"
12 " " "	"	19.6	"	"	"	"

The number of mitotic figures was still increasing up to 12 hours, at which time there was an increase of over 700%. In some fields in the 12-hour specimen as many as 50% of the cells were in mitosis.

The accumulation of mitotic figures after colchicine cannot be attributed to delivery of the tumor on the abdominal wall, since control biopsies taken before and 10 days after the Mikulicz procedure showed approximately the same number of cells in mitosis per high power field. The repeated biopsies are probably not responsible for the changes noted, as similar accumulations of mitoses after colchicine have been observed in other intestinal tumors that were not subjected to multiple biopsies. It should be emphasized that the 12-hour specimen represents the entire tumor and a large portion of adjacent bowel. The sections of this tumor far removed from the sites of the small biopsy taken at the earlier period, as well as the normal mucosa beyond the tumor mass, showed the same striking accumulation of mitoses.

The subcutaneous and intramuscular injection of colchicine in the doses used has not been accompanied by any general toxic symptoms. Many patients, however, showed evidence of local irritation manifested by local soreness and redness, and in some instances by paresthesia. While these symptoms all disappeared spontaneously, nevertheless the discomfort in some patients was of such degree as to make it desirable to use some other method for administering the drug. At present, studies are being carried out on the effect of the drug by mouth.

There is insufficient data, owing to the small number of any one type of tumor, to permit us to draw conclusions as to its effect on tumors in general. It is, however, apparent that the colchicine technique makes it possible in some instances to obtain a more accurate index of the rate of growth of the tumor than can be obtained by ordinary methods.