Colchine, which was mentioned last week in the leading article about a secret remedy for cancer, is a mitotic poison which has been much used in research as a chemotherapeutic agent for cancer. This alkaloid, which is extracted from the autumn crocus, is probably the most powerful "radiomimetic" drug known—that is, it reproduces the cellular changes induced in cells by x rays. Even at dilutions of 1 in 100,000,000 it can bring about the typical mitotic arrest at the metaphase stage. Microscopically, areas of a tissue treated with colchine will sometimes show more cells in arrested division than in the resting state. Ludford, who has ably reviewed the literature on this subject, examined the mode of action of colchine on tissues grown in vitro and observed that the drug does not differentiate between embryonic and neoplastic tissue, which are equally sensitive to its mitosis-arresting activity. Other chemical and physical agents can inhibit mitosis, but, Ludford wrote, "colchine is unique in that it does not arrest the initial phase of division but brings the process to a standstill at the metaphase in a remarkably wide range of concentrations." There is little evidence that colchine stimulates mitosis as well as blocking it at metaphase, and, indeed, it has been reported that in high dilution it slows down the rate at which cells enter the mitotic cycle. Microscopically, the most obvious effect of the drug on a tumour is to induce haemorrhage of the kind also caused by polysaccharide fractions of bacterial filtrates—for instance, from Serratia marcescens. Even in minute amounts, of the order of 0.1 ju, these cause necrosis and haemorrhage.3 The similarity of the effects of colchine and bacterial filtrates is close enough to have suggested that they inhibit tumour growth by the same mechanism—by attacking the sensitive cells of the capillary system of a rapidly growing tumour. One of the principal conditions of chemotherapy is maximal injury to tumour cells with minimal effect on normal tissue, and the use of colchine appeared promising when examination by dark-ground illumination showed little alteration in the mitochondria and in the cytoplasmic granulation, indicating that the metabolic mechanism had escaped injury. Ludford found that mitosis could be blocked with dilutions of colchine far below that required for metabolic disturbance: in one experiment a thousandth of the concentration needed for metabolic effect sufficed to arrest mitosis. SEPr. 23, 1950 COLCHICINE IN CHEMOTHERAPY OF CANCER EDI¶SOH 719 Amoroso was one of the first to try the effect of colchine on tumours in animals. He found that transplantable mouse carcinoma No. 63 responded by complete regression, and he successfully treated a carcinoma of the buccal mucous membrane in a dog. Among other early experiments with colchine in animals the regression of multiple skin tumours in a mare has been recorded, and also of the Shope rabbit papilloma after the injection of a few milligrammes of the drug. In the latter case the treatment induced immunity to further infection by the virus. Colchine has been used with success in experiments on the regression of a lymphoid tumour of the C3H strain of mice and on the Flexner-Jobling rat carcinoma. Ludford, after studying 17 different strains of transplantable tumours and 47 spontaneous mammary carcinomas, concluded that the lethal and chemotherapeutic doses are close to one another and that soft, highly cellular, rapidly growing tumours are the most responsive, the reaction of slow-growing tumours being negligible. In a detailed investigation of the factors determining the action of colchine on tumour growth he used a rapidly growing carcinosarcoma of the Strong A strain of mice. The transplants were treated with a 1 in 10,000 solution of the alkaloid, the total dose of 0.7 mg. being divided and spread over a few hours. The injections were repeated on the 26th
and 35th day. After a sudden decline in the size of the
tumour grafts growth was resumed, and on the 50th day
after transplantation the experimental tumours were the
same size as the controls on the 30th day. A spindle-celled
sarcoma growing in Strong A mice was treated
with a total of 0.154 mg. of colchicine. Two out of
three tumours regressed completely. Nevertheless
Ludford considers such success exceptional, the more
typical result with colchicine being regression followed
by recurrence. Among other factors which influence
the effect of colchicine, he found that young adult mice
are more resistant to the toxic action of the drug than
very young or old mice, and that tumour regression is
more obvious in strain A mice than in C57 mice. The
results of treatment of mice bearing carcinoma 63—a
soft, highly cellular tumour with a large number of
mitotic figures—was to produce total regression in 5
mice out of 10. Three died of toxic effects, and the
tumours of 2 continued to grow. The tumours which
regressed showed extensive haemorrhage, just as in the
case of tumours treated by bacterial filtrates. It has been
suggested that the haemorrhage may be caused by pressure
exerted on the newly formed capillaries by the
tumour cells, which become swollen after colchicine treatment.
Bass and Probet in the U.S.A. recently reported
the satisfactory treatment with colchicine of C3H hybrid
mice bearing lymphosarcoma, the drug being given in
doses of 0.5–0.75 mg. per kg. of body weight daily for
2 to 23 days. The regressions, expressed as fractions,
were 8 out of 10 mice, 4/9, 12/20, and 10/28 in different
experiments. The mice whose tumours regressed were
observed for five months; immunity lasted at least 173
days after the original transplantation.
Although there is a close parallel between the nucleotoxic
action of colchicine and of x rays—for instance, in
the acquired tolerance of tumour cells to the drug and
the acquired radio-resistance of tumours which were
previously radio-sensitive—yet there are certain differences
in the toxic effects on the nuclear chromatin.
Colchicine is much more specific in its action on the
nuclear structures. Ludford states that one of the outstanding
difficulties, in the colchicine treatment of
tumours is the lack of cell-type specificity. Tests with
the aim of supplementing the action of colchicine with
radiotherapy have been, on the whole, without success.
Several workers have investigated the action of colchicine
in the treatment of cancer in man, but it was
found that the drug caused very unpleasant symptoms,
and sometimes death from colchicine poisoning. One
woman was treated with colchicine combined with x rays
for an adenomedullary carcinoma of the breast. The
tumour at first shrank to a third of its original size, but
then rapidly began to grow again, with fatal results.
Another patient with an anaplastic carcinoma of the
neck reacted in much the same way; the central portion
of the tumour necrosed, but the peripheral layers grew
with increasing speed.
Seed, Slaughter, and Limarzi, after investigating the
action of colchicine on human subjects and on laboratory
animals, concluded that, "although the rapidly
growing cancer cells are much more susceptible to the
poison, the concomitant general toxic effect is much too
great to expect any curative effect." 1 British Medical Journal, 1950, 2, 663.
3 See annotation in the British Medical Journal, 1950, 2, 32.
5 Brit. J. Cancer, 1948, 2, 75.