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Some Observations on the Cytological Effects of Antimitotic Poisons

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Recently discovered substances with antimitotic action fall in the two categories which have been defined since many years, i. e. spindle poisons and chromatin (or " radiomimetic ") poisons. The most recently studied are hydroxyurea — a powerful inhibitor of DNA synthesis — and the Vinca alcaloids — which destroy the tubular components of the spindle, bringing a prolonged arrest in metaphase.

The mechanisms of action of many of these drugs remain most obscure. In the field of spindle-poisons, there has been no explanation sofar of the relationship between their chemical structure and cytological action. While it is known that minor changes in the chemical structure of colchicine can prevent its specific action on the spindle, the precise relation which appears to exist between this complex molecule and the spindle structures remains obscure. The same remark applies to the Vinca alcaloids. Progress is being made however in this field. The ultrastructural aspects of the spindle have been analysed by electron microscopy, and a precise definition in chemical terms of the spindle may be close. These observations have shown the similarity between the tubules of the spindle and other tubular structures of identifical size: the neurotubules. Some recent observations indicate that these may also be destroyed by colchicine, a fact which may be related to the well-known and severe neurotoxicity of this alcaloid. What remains to be explained is the fact that the most effective spindle poisons are molecules of the size and complexity of those of vinblastine, while simple inorganic substances (arsenicals, heavy metals) may exert identical if not so powerful effects on the spindle structures. Another point which needs further research is the cause of the extensive cellular destruction which follows, in animal cells, any prolonged inhibition of the spindle function. The chemotherapic actions of spindle poisons are most probably related, not only to the growth inhibiting effects of these drugs, but most of all to the cellular breakdown which is observed in cells when they have been kept for several hours in metaphase.

The action of the poisons acting at interphase and producing cellular destructions similar to those observed after an irradiation ("radiomimetic" effect) is now better understood. Most, if not all, of these drugs prevent the replication of DNA. They act by various routes such as direct combination with DNA molecules as in

the case of nitrogen mustards or specific inhibition of the folic acid coenzymes. In most cases the period S of cell growth is the most sensitive. This action on DNA metabolism has been shown to be very similar to that of ionizing radiation, which also modifies the structures of DNA. However, it is not well understood sofar why this leads to extensive cellular destruction. It has been shown repeatedly that cells of germinative zones, in which the correct replication of DNA is prevented, undergo within a few hours a rapid destruction, the nucleus becoming pycnotic and the cytoplasm rapidly fragmented. From recent data on the action of ionizing radiation, these effects appear to start shortly (less than one hour) after irradiation. While it could be thought that any extensive change in DNA might disturb many cell functions by preventing the formation of messenger RNA and many cellular syntheses (this may be the case in the "radiomimetic" effects of actinomycin) such an hypothesis does not explain the remarkable fact that the "radiomimetic" drugs do not affect cells which are not preparing to divide. It appears as if some particularly sensitive mechanism was affected the cells which have started the process of cell replication and which have been inhibited at some step of this, falling rapidly to pieces. In fact, this cellular destruction may be closer than is usually believed to the similar destruction which follows the inhibition of the spindle-activity.

One last point is worth mentioning. In the use of antimitotic drugs in cancer chemotherapy some remarkable results have been obtained: prolonged remissions in acute leukemia, cures in choriocarcinoma. It is more and more apparent that with antimitotic poisons it is possible to arrest malignant growth without too serious effects on mitoses in other tissues, in particular bone-marrow, intestine and hair-bulbs. It is not well understood whether this represents a true differential effect, the poisons acting more powerfully on malignant cells than on normal cells, or if other factors play a role. Most experimental work appears to indicate that all substances which have proved to be of some use in cancer chemotherapy are mitotic poisons: this is known since more than twenty years (and more: Fowler's solution, used in the past in the treatment of leukemia, acts as a mitotic poison on the spindle of leukemic cells) and most new discoveries have confirmed this fact. It does not appear that neoplastic mitoses may have some special sensitivity towards mitotic poisons. Another explanation of some remarkable therapeutic actions, even in tumors in which the number of dividing cells is not so great, is that between the tumor and the host there exists in many cases some equilibirum, which may be displaced in favor of the host by a slight change in the rate of growth of the tumor. Remarkable chemotherapic results have been obtained in Burkitt's tumor, which is a lymphosarcoma in which many cells appear to be phagocitized continually by large macrophages (hence the typical "starry night" appearance of sections of this tumor). In Hodgkin's disease also, mitotic poisons may considerably modify the size of hypertrophied lymph-glands, in which the number of dividing Sternberg cells is not so great. In this condition, it can be imagined that the inflammatory reaction which accompanies the Sternberg cell growth has the character of an immune reaction. Any change in the growth of the truly malignant fraction of the hypertrophied lymph

glands, i. e. the Sternberg elements, would be followed by a sharp decrease of the inflammatory reaction, which may be related to immunological reactions.

In conclusion, it appears more and more evident that the study of mitotic poisons and their action on tumors is bringing interesting information in two quite different fields: in the analysis of the mechanisms of mitotic division, and in the study of the complex reactions which exist between host and tumor. The cure of choriocarcinoma by antifolic drugs is the most striking of these facts: the tumor differs immunologically from the host, being of embryonic origin. There are reasons to think that there are often minor immunological differences between tumors and host; the modification of the rate of growth of the malignant cells by non specific mitotic poisons would permit a better inhibition of tumor growth by the normal immunological reactions. This leads to another most important conclusion, which should be mentioned here: good antitumor agents having an action on mitosis should not, as many mitotic poisons do, belong to the group of so-called " immunosuppressive " drugs.