50 (2282)

Studies on cancer.
IV. Factors regulating the production of cancer in the organism.

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Recent and older careful studies of cancer have shown that this disease may be induced by a variety of substances and conditions; such as coal tar, various lipoid solvents, arsenic, various animal parasites, X-ray, radium, etc. In mice it occurs most frequently in certain families (Maude Slye). In man it may arise in certain congenital defects and tumors and in old inflammatory processes.[1]

These same studies have further indicated that cancer unlike the inflammatory processes when once induced is not dependent any longer upon these original exciting agents. Cancers once induced by coal tar may be transplanted through many generations of animals.[2]

From observations cited in the three preceding papers of this series it is evident that an independent growth of body cells is dependent on a crowding of these cells together and a relative decrease in their blood supply. It became thus of interest to see what might be the nature of the changes induced by these various excitants of cancer. This work was just begun three years ago. It has been described in part in other papers.

Ross[3] in discussing the action of these various substances which lead to cancer thought them direct excitants of cell division. It seemed evident to me from my studies of the factors regulating cellular growth in the organism that their action might be otherwise. Fischer[1] many years ago had already shown that when drops of olive oil containing Sharlach R are introduced just beneath the epidermis the epithelial cells are attracted to these drops. These cells surround the drops of oil to form

1 Ewing, J., *Neoplastic Diseases*, 2nd ed., 141.

2 Woglom, W. M., and Murray, J. A., 7th *Sci. Rep. Imp. Can. Res. Fund*, 1921, 45.

3 Ross, H. C., *J. Can. Res.*, 1918, 111, 321.

dense cell masses not unlike those of cancer. Jorstad[4] working in my laboratory has found that coal tar acts in the same manner. Drops of this substance attract the cells to them and away from their blood vessels and thus they build a dense mass of cells peculiar to the normal organism and with a relatively poor blood supply. These masses as they grow larger become autonomously growing systems.

Whether the coal tar in itself may induce division in these cells has not been fully determined. In Jorstad's preparations no division-figures were seen until the masses themselves were of a size consistent with such changes as deduced from their occurrence in the cultures.

In the same manner I have found that the tape-worm described by Bullock and Curtis[5] attracts connective tissue cells to it. It does not induce the densely fibrous capsule peculiar to the ecchinococcus for instance but a very cellular one. The spirotera of Febiger[6] shows a similar attraction for the epithelial cells of the stomach.

These substances act, therefore, quite differently from those which produce inflammation. These latter substances induce primarily an exudate from the blood vessels. The cells react secondarily to organize and become scattered in the exudate. The cancer producing substances act on the cells directly to attract them away from their intercellular substances and blood vessels. The tissue built in the former case is a richly vascular tissue with a large bulk of intercellular substance. In the latter instance it is a densely cellular tissue poor in intercellular substances and in blood vessels.

As Ross has clearly pointed out it is not injury that produces cancer, it is the action of specific substances. Our studies have indicated that these substances attract cells to them, away from their intercellular material and blood vessels and form a dense local mass free from ready avenues of escape for the soluble products of their normal metabolism.

A soluble stimulus placed in the tissue can have no such effect. It must escape by way of the blood stream. It is a viscid mass which remains fixed and attracts cells to it that act in this regard, like certain animal parasites, thick drops of coal tar, drops

[4] Jorstad, L. H., PROC. SOC. EXP. BIOL. AND MED., 1923, xxi, ?

[5] Bullock, F. D., and Curtis, M. R., *Trans. N. Y. Path. Soc.*, 1920, xx, 149.

[6] Febiger, J., *J. Can. Res.*, 1919, iv, 367.

of olive oil or better, olive oil containing substances like Sharlach R. One of the Swedish observers has noted that only drops of coal tar having a high boiling point induce cancer.

The exudates of chronic inflammatory processes attract cells to them as Hertzler's[7] studies have indicated and the work of the cultures have proven. In the body these same conditions also are associated with the development of blood vessels and exudates become coagulated and deposited as extracellular fibrils between the cells. Primarily these processes lead away rather than towards any cancerous process. The epithelial cells of the glands and other parts do not, however, react readily to these exudates. They become imbedded in this mass of newly formed connective tissue. Later this mass of connective tissue changes. The blood vessels become obliterated. The connective tissue becomes hyaline. The cells degenerate. With this change in the blood supply the separated epithelial lined ducts suffer atrophy to a greater or less extent. At the same time their environment becomes more suitable for an active proliferation. Carcinoma is a disease of old age. It develops frequently in the epithelial cells of the skin which are undergoing atrophy. As it is well known the breasts of women and probably other tissues suffer periodic stimulation from the sex glands and other internal secreting glands. As it is evident from the above laws of growth laid down, such atrophying epithelium must respond quickly to any stimulant for cellular growth or as the culture-experiments indicate such a tissue may begin to grow independent of such a stimulation. To prove this it becomes of interest to study the effect of a soluble stimulant upon tissues of adult animals. The stimulant used was the one produced by the tissue as noted above. It was extracted from the Jensen sarcoma with normal saline solution. The solutions of this stimulant were made sterile of sarcoma cells by passing them through a Berkfeldt filter. When introduced into the normal skin of an adult rat this solution had no noticeable effect. It was evidently removed by the blood stream. When injected into areas of skin suffering pressure atrophy this solution produced carcinomatous proliferation[8]

We have not investigated as yet the action of X-ray and radium. Members of families of mice which frequently develop

[7] Hertzler, A. E., *The Peritoneum*, 1919, 1, Chap. V.

[8] Burrows, M. T., *Mo. State Med. J.*, 1923, xx, 145.

cancer have also not been investigated. From the above observations it seems evident, however, that cancer may result from any condition or substance which can build a dense mass of cells in the organism; to a proper reduction in the blood supply of any cellular tissue so that the growth stimulus may accumulate and the nutrition remain unchanged. The simple pigmented mole is such a mass of cells. These moles as it is well known may become malignant after injury or disturbances in their blood supply or in the course of their normal development in the aging organism. Such age-changes are associated with a decreased vascularity and atrophy of the superficial tissue. The relation between senile keratoses and cancer has long been recognized by dermatologists.

Further studies of the mechanism of cell-division which have just been completed in the laboratory have shown that an orderly division of cells to form columns and to line the ducts of glands is directly related to the circulation and position of the blood vessels. Decrease this circulation and stimulate the cells, lateral division and dense masses may develop.

While it is true that many authors, such as Child,[9] have assumed that differentiation is the normal outcome of all cellular growth it is possible to show quite definitely as I have indicated in an accompanying article[10] that is not true. Such a cellular system as cancer once developed in the animal organism reproduces itself.

The striking peculiarity of body cells which distinguishes them from unicellular organisms is not in that part of their general organization which has to do with their growth and function but it is their inability to utilize the crude materials from nature as food. They again have no protection from external influences in the form of membranes. Much more crowding is necessary to obtain growth in body cells than in the unicellular organism.

These body cells cannot even burn sugar without the intervention of the pancreas so the whole developing animal depends absolutely for its nutrition on the yolk and the mother. True yolk is formed by the parent body. In man as in animals all the

[9] Child, C. M., *Senescence and Rejuvenescence*, 1915.

[10] Burrows, M. T., read before the Southern Med. Soc., Washington, Nov. 15, 1923.

essential organs are formed before it is possible to remove the animal from its yolk or its mother. The cells are nourished always by foods which have first passed through a fully formed organism.

Differentiation like growth is not a primary phenomenon in all periods of life but in the early stages. It is hastened as many previous experiments have shown by removing parts of the yolk or by accelerating the metabolism of the developing organism through the feeding of thyroid.

Cancer as we have seen it, therefore, may be the normal outcome of any substance or condition capable of building a densely cellular tissue in the organism associated with an orderly decrease in the blood supply. It is not the result of any primary changes in the cell but to a specific rearrangement of cells, intercellular substances and blood vessels in the organism.

ABSTRACT OF COMMUNICATIONS.

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Experimental infection of culture rats and mice with the common intestinal amebae of man.

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The present investigation was undertaken in order to check on the previous reports in which attempts were made to infect rats and mice with *Endameba dysenteriae* and also to infect these rodents with the other common intestinal amebae of man.

Infections of five species of human intestinal amebae, *Endameba dysenteriae, Endameba coli, Councilmania lafleuri, Endolimax nana,* and *Iodameba büttschli* have been experimentally transferred to rats by feeding them human feces containing cysts of these amebae. Mice have been experimentally infected with *Councilmania lafleuri* and *Endameba dysenteriae.*