already shown that the stimulating substance for the growth of cells is soluble in salt solution. The studies reported in paper No. 1 of this series, indicate clearly that it may be washed away from the tissue with serum. These observations show that this stimulating substance is a product of the normal metabolism of the cell. These cells can grow only when they are crowded together in an environment where this product of their metabolism is not rapidly removed from them.

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### Studies on cancer.

### III. Cellular growth and degeneration in the organism.

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As it is well known an active independent growth of cells in the body is peculiar alone under normal conditions to the earlier periods of development. At first this growth is quite generalized. Later it becomes localized, first in one part and then another. In man it ceases entirely with the laying down of the last kidney tubule and glomerulus at about 10 days after birth. Subsequent to this time all growth is merely the enlargement of pre-formed organs and tissues. It is like the hypertrophies and hyperplasias of later life.

In later life it is again well known that hypertrophy and hyperplasias are related directly to the functional activity of the part. Increase the work of the heart, it grows. Decrease its activity, it atrophies. So, in the same manner, the removal of a part of any organ or another organ of the same kind leads to an active enlargement of the remaining parts. This enlargement continues to the re-establishment of a certain size which corresponds to the functional demand made upon the part.

As a moderate increase in the functional demand made upon an organ or a part is associated with the growth of that organ

or part so further or excessive work is associated with a degeneration of these same cells. Such a degeneration is also seen in certain structures during development. The pronephros and the metanephros of higher animals suffer such changes as they give way for the development of the kidney.

Cancer represents a return of the property of independent active growth to certain cells or rather to groups of certain cells in the organism. This independently growing tissue also often suffers extensive degenerative changes in part. While these degenerations resemble ordinary autolytic changes they differ from those seen in the infarct, for instance, in that they are not harmful for the organism. The disappearance of the pronephros or the metanephros does not disturb the nutrition of the whole; so it has been shown that large tumors may disappear in a few days without evident toxic symptoms to the animal.[1]

Closely associated with this loss of independent active growth in the developing organism marked morphological and chemical changes also take place in the tissue. The various cells peculiar to the different organs and tissue are differentiated. The blood vascular system develops. The cells become separated by a rich vascular network and by a deposit of extracellular reticular fibres, the connective tissue fibrils. In early embryonic life, the cells are closely packed together. The number of capillaries per unit cell-area is small. In later life one sees great variation in the number of cells per unit area in any tissue. In the most cellular tissue of this period all cells are closely beset with capillaries. The cells of the liver for instance are separated into columns no more than 2 cells thick. The circulation is active in these capillaries. These conditions are in contrast to the slow sinisoidal circulation of the embryonic liver.

Such an arrangement of cells peculiar to the adult is strikingly different, therefore, from the dense cells-masses of cancer and early life. Cancerous tissue is peculiar not only in that it grows actively and independently of the whole or of any functional demand made upon its cells but it again, like the tissues of early embryonic life, is a densely cellular tissue. It is peculiar not that its cells are like the embryonal cells—they are not—but that they are arranged in dense masses. They have lost in many instances the shape peculiar to them in the normal tissues. Oth-

[1] Ewing, J., *Neoplastic Diseases*, 2nd ed., 1922, 141.

erwise they are not embryonal. The cells of the cancer of the skin are skin epithelial cells. So the cells of the sarcoma are connective tissue cells. The only demonstrable change they have suffered is in their arrangement, their ability to grow and their shape.

For many years it has been known that increased functional activity in the organism is associated with an increased circulation to the part. Growth quite the reverse may follow a decrease in the circulation. The clubbing of the fingers with disturbance in the general circulation illustrates clearly this fact. In an unpublished paper on the circulation of the nail I have found that the circulation of the growing bed is very much less than along the whole of the outer parts of this structure.[2] The entire growth of the developing nervous system takes place along the central canal. The blood vessels invade the outer peripheral portions. In the light of these facts it may not be surprising, therefore, that the heart hypertrophies when it is overloaded, its cavities dilated and its walls compressed. Such compression of the wall must impede the circulation about the muscle fibres.

Correlating the above observations of the cultures, cited in the two preceding papers, with conditions as they exist in the body it became evident, therefore, that the disappearance of an active independent growth of cell in the developing organism may be none other than the direct result and orderly laying down of intercellular materials and the development of a rich vascular supply. Cancer looked at in this sense may be the direct result of any change in the organism which leads directly to the accumulation of dense masses of cells free from intercellular substances and having a reduced blood supply or to an orderly disappearance of the normal vascular supply.

To give further proof for this conception it became of interest to study more carefully and quantitatively the action of this growth stimulus on the cells. Devloo[3] in analyzing the active growth stimulating substance noted by Wildiers in cultures of yeast came to the conclusion that it is either a phospholipin or is associated with or dissolved in lecithin. In my studies of the cells of higher animals I have identified a substance liberated by these cells which is an active blood coagulant and otherwise has many of the physical properties of a phos-

2 Proirer and Charpy also note this fact (*Traité de Anat. hum.*, v, 184).

3 Devloo, R., *La Cellule*, 1907, xxiii, 359.

pholipin. This substance I have been able to quantitatively show produces the energy for the migration of these cells, for the development of tension or the energy for muscular contraction and combines to form the extracellular fibrils of connective tissue. In growing tissues it is formed in excess and disappears in the presence of food so it may be retained in the reaction forming protoplasm of certain parts of the cell. This is not the stimulating substance. The stimulating substance is soluble in normal saline solutions and in body fluids. It acts in lower concentrations to the excessive formation of the energy producing substance. In higher concentration it acts to break down the proteins of the cells. The degeneration produced by this substance is histologically like autolysis. Physiologically these degenerating cells act quite differently. They are utilized as food by the other cells while autolyzing tissue inhibits activity in these cells. The degeneration seen in the centers of the small fragments in the culture and later in other cells of the cultures well supplied with oxygen and in the crowded cell area of cancer is of this type. It is not a primary autolysis. It is the result of a greater accumulation of that same substance which in lesser concentration leads to an active growth of these cells.[4]

Again I have not found any evidence to show that this stimulating substance combines in any of the reactions of the cell. It acts as a catalyzer of other reactions of the cells. Whether it is a product of the same reactions which it accelerates I have not fully determined.

Its activity at all times is wholly dependent on its concentration. Its concentration at all times is directly proportional to the rate of its production and indirectly proportional to the avenues for its escape by way of the blood stream.

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