

CHANGES IN THE TISSUE SURROUNDING A GROWING  
TUMOR AND THE SIGNIFICANCE OF THE  
"PRECANCEROUS STATE."\*

By ISAAC LEVIN, M.D.

*(From the Department of Pathology of Columbia University, College of  
Physicians and Surgeons, New York.)*

PLATES II AND I2.

One of the characteristics very frequently encountered in the early development of a malignant tumor is a certain degree of abnormality in the organs and tissues surrounding the growth. This condition very early attracted the attention of pathologists and for purely technical reasons the subject was studied almost exclusively on the epithelioma of the skin. The epithelial layer of skin is supported by subepithelial connective tissue, and since any change in the latter resembles an inflammatory condition, the impression was created that a developing malignant growth is surrounded by newly formed inflammatory connective tissue.

Ribbert (1), Bonney (2), Borrmann (3), and others consider this condition of paramount importance in the genesis of cancer and believe that the changes found in the connective tissue always precede the formation of the tumor. As the subject is stated in recent writings, a "precancerous state" in the surrounding tissue is essential for the formation of a cancer. von Hansemann (4) and his followers, on the other hand, hold that the connective tissue changes are secondary to the formation of the tumor and are influenced by the latter.

In the material derived from human cancer one usually sees the tumor and the changed surrounding tissue side by side, and it is impossible to declare with certainty which condition precedes and acts as a causative agent on the other. The solution of the problem

\* Conducted at the expense of the George Crocker Special Research Fund. Read before the meeting of the American Association for Cancer Research, April 3, 1912. Received for publication, April 22, 1912.

may be expected only from an experimental study by the aid of which we may create artificially either an abnormality in an organ or the growth of a malignant tumor. In such experiments we may cause at will either the changes in the tissues to precede the growth of the tumor or the growth of the tumor to precede the changes in the tissues.

In a recent investigation the writer (5) succeeded in producing artificially a true "precancerous state," *i. e.*, an abnormality within an organ of the white rat which favored the subsequent growth of an inoculable cancer. The following is a brief statement of the experiments.

The work was conducted with an adenocarcinoma of the white rat described by Flexner and Jobling (6). This tumor grows readily in the rat when inoculated subcutaneously or when introduced into any of the parenchymatous organs with the exception of the testicle. In the latter the inoculation does not succeed. But when an abnormality is created within the testicle by an injection of two to three minims of Scharlach R-oil or by an injection of an emulsion of ether in water, then a subsequent inoculation with the tumor is successful. Thus an instance is found experimentally where a change in the tissue of an organ is absolutely essential to the success of a subsequent inoculation of a tumor, since the latter does not grow in the normal organ. In other words the creation of a "precancerous state" is indispensable for the success of the development of the inoculated tumor.

It is important to note here that the "precancerous state" created in this instance does not consist primarily of an inflammatory formation of new connective tissue. The growth of the inoculated tumor was influenced by the degenerative changes in the parenchymatous cells of the testicle and not by the newly formed connective tissue, as would have been claimed by Ribbert's school. The connective tissue formation could have been very profuse, but the tumor would not grow while the parenchymatous cells remained in a fair state of preservation.

But from these experiments the conclusion cannot be drawn that in every case the growth of tumors is aided by the changed surrounding tissues. Indeed, the experiments to be described later will show that instances occur in which no relationship exists between the growth of the tumor and the changes produced in the surrounding tissue.

The aim of the present investigation was to determine experimentally whether an abnormality in the tissue surrounding a growing tumor may be created under the influence of the tumor and subsequently to its development. The following method was employed.

## INOCULATION OF TUMORS INTO MUSCLE AND LIVER.

A study of intracellular fatty infiltration affords the best means for detecting slight changes within a cell. Any impairment in the normal metabolism of the cell causes an increased accumulation of its fat contents. The question whether the accumulation of fat within the cell is an indication of a true degeneration, or whether it is due simply to nutritional causes, is of no consequence for the subject under consideration. The main point is that any undue accumulation of fat droplets in a cell is an indication of the beginning of a cell injury.

In order to detect the possible fatty changes in the tissue surrounding a growing tumor the following series of experiments were undertaken. A rat sarcoma was inoculated into the livers and muscles of a number of perfectly normal rats. At various intervals after the inoculations, the grafts were excised together with some of the tissue surrounding them and the excised pieces were placed in a 5 per cent. solution of formalin. Twenty-four hours later the tissues were cut by means of a freezing microtome and stained with Sudan III and hematoxylin. The examination of the specimens showed that while most of the tissue appeared normal, there was a zone of cells in the immediate neighborhood of the growing tumor, which was filled with an excessive amount of fat.

Figure 1 shows the condition in the liver in which a sarcoma was inoculated, and in figure 2 are seen a number of muscle fibers surrounded everywhere by tumor cells. Most of the muscle fibers are filled with fat. Although some of the liver cells and some of the muscle fibers surrounding the tumor show no fatty changes, the fact remains that a great many of the neighboring organ cells appear to be abnormal. The tumor graft had been placed in perfectly normal tissue, but then under the influence, mechanical or chemical, of the proliferating tumor cells the tissue cells became impaired in their normal metabolism and, as a consequence of this, had degenerated. An abnormality was here induced in a tissue that was previously healthy, but the sequence of events in this experiment is different from that in the experiments with the testicle. While in the experiments with the testicle the abnormality had to be created by some artificial means before the tumor could be made to grow,

in the present experiments the changes in the tissue were caused by the growth of the tumor and developed subsequently to this growth.

If the name "precancerous state" is to be applied to the condition described in the testicle of the white rat, then it may be permitted to give to the condition described in the present experiments the name "postcancerous state."

INOCULATION OF TUMORS INTO ANIMALS TREATED WITH  
PHOSPHORUS.

The previous series of experiments have shown that the cells of the organ surrounding a growing tumor undergo a fatty infiltration before they disappear and are replaced by tumor cells. Undoubtedly this fatty change aids the growth of the tumor to a certain extent. This second series of experiments was undertaken in order to ascertain whether a similar fatty change induced artificially in the parenchymatous cells of the liver would enable a tumor to grow in an organ of an animal known to be resistant to the growth of the same tumor.

As is well known, phosphorus poisoning induces in the cells of the liver an abnormal accumulation of fat, which is followed by necrosis and then by the formation of new connective tissue. This condition induced in the liver may resemble cirrhosis, and this was another reason for performing this series of experiments, for cirrhosis of the liver is very frequently followed by the development of a primary carcinoma in the liver. Indeed, some authors (Ribbert (7), Wheeler (8), and Huguenin (9)) believe that the primary cancer of the liver originates from a cirrhosis. According to their ideas, the cirrhosis induces the formation of an adenoma of the liver, and the adenoma is then transformed into a carcinoma.

Our experiments were conducted as follows: An injection of two to three minims of a 0.25 per cent. suspension of phosphorus oil was made subcutaneously into rats which were previously shown to be immune against the inoculation of the rat sarcoma. The injection was repeated three times at intervals of three days. Four days after the last injection the sarcoma was inoculated into the livers of these immune rats. In none of the twenty animals operated upon did the tumor grow, though the fatty changes in the liver cells were a

great deal more pronounced than in the cellular zone of the liver surrounding the tumor growth in a normal animal.

#### SUMMARY.

An analysis of the results of the experiments reported in this investigation shows that the changes so frequently observed in tissues surrounding a growing tumor may be caused by different conditions. The development and growth of a malignant tumor depends upon a local interaction between tumor cells and organ cells. When the cells of a normal organ are capable of inhibiting tumor growth, then an impairment of the normal state of the parenchymatous cells of this particular organ is essential for the growth of the tumor. This "precancerous state" does not consist primarily of an inflammatory change in the adjacent connective tissue, as Ribbert and his followers maintain, but in a degeneration of the parenchymatous cells of the organ.

If, in another instance, the cells of the normal organs are unable to inhibit the proliferation of the tumor cells, then no preparation of the cells of the organ for the tumor is necessary, *i. e.*, no "precancerous state" is needed to enable the tumor to grow. On the other hand, the proliferating tumor cells injure normal cells, either mechanically or chemically, producing a condition that appears on superficial examination like that described as the "precancerous state." In reality, however, this condition is the resultant effect of the tumor growth and may be more correctly designated the "post-cancerous state." In these conditions, then, von Hansemann's explanation of the phenomenon, and not Ribbert's, seems to be the correct one.

Of still greater importance is the fact demonstrated in the last series of experiments; namely, that the general condition of resistance or immunity to cancer growth exerts a greater influence on the organism of the animal than any of the local conditions described above. The local resistance of a testicle to tumor growth in a generally susceptible animal may be overcome, but if an animal is made generally immune to the growth of cancer, neither the animal as a whole nor a single organ or tissue in it can be made susceptible to the growth of the tumor.

BIBLIOGRAPHY.

1. Ribbert, H., *Das Karzinom der Menschen, sein Bau, sein Wachstum, seine Entstehung*, Bonn, 1911.
2. Bonney, V., *Lancet*, 1908, i, 1389.
3. Borrmann, R., *Ztschr. f. Krebsforsch., Ref.*, 1905, iii, 339.
4. von Hanseemann, D., *Virchows Arch. f. path. Anat.*, 1893, cxxxiii, 147.
5. Levin, I., *Jour. Exper. Med.*, 1912, xv, 163.
6. Flexner, S., and Jobling, J. W., *Monographs of The Rockefeller Institute for Medical Research*, 1910, No. 1, 1.
7. Ribbert, H., *Deutsch. med. Wchschr.*, 1909, xxxv, 1607.
8. Wheeler, F. J., *Guy's Hosp. Rep.*, 1909, lxiii, 225.
9. Huguenin, B., *Centralbl. f. allg. Path. u. path. Anat.*, 1911, xxii, 241.

EXPLANATION OF PLATES.

PLATE II.

FIG. 1. To the left of the drawing is sarcoma tissue; to the right, liver tissue. Sudan III and hematoxylin. High magnification.

PLATE 12.

FIG. 2. Muscle fibers surrounded with sarcoma cells. Sudan III and hematoxylin. High magnification.

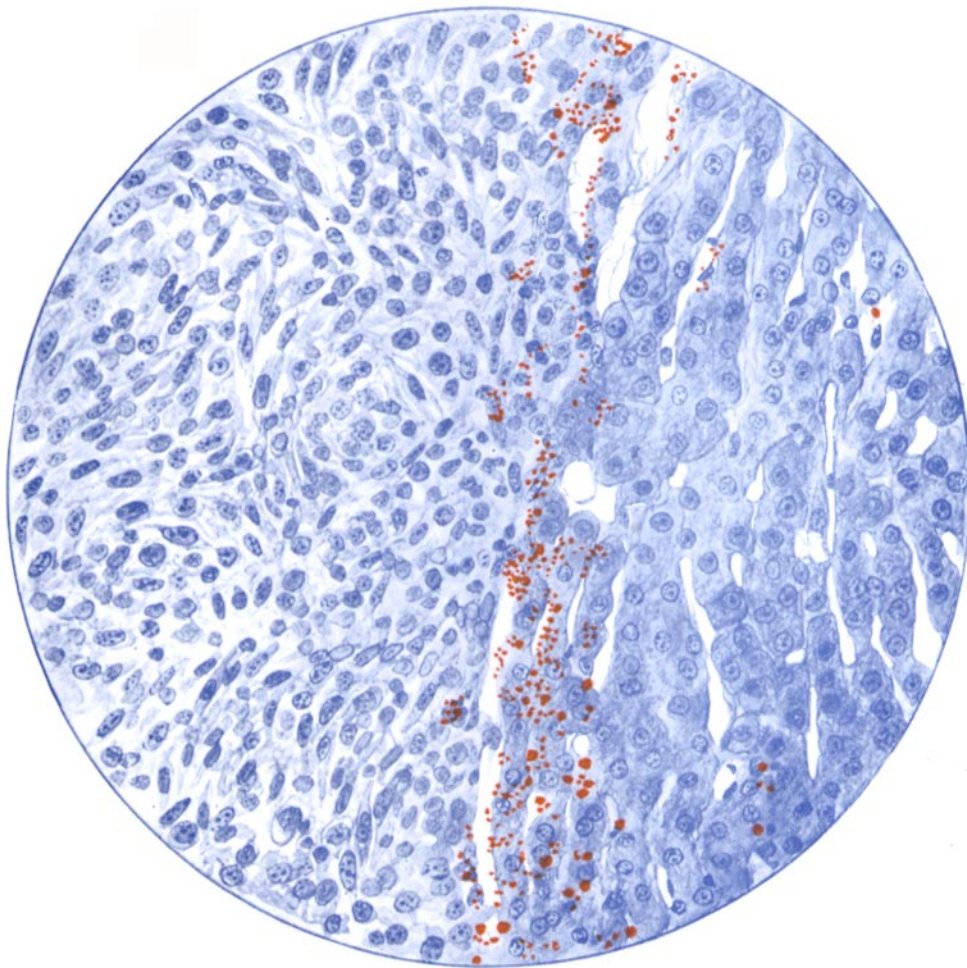


FIG. 1.

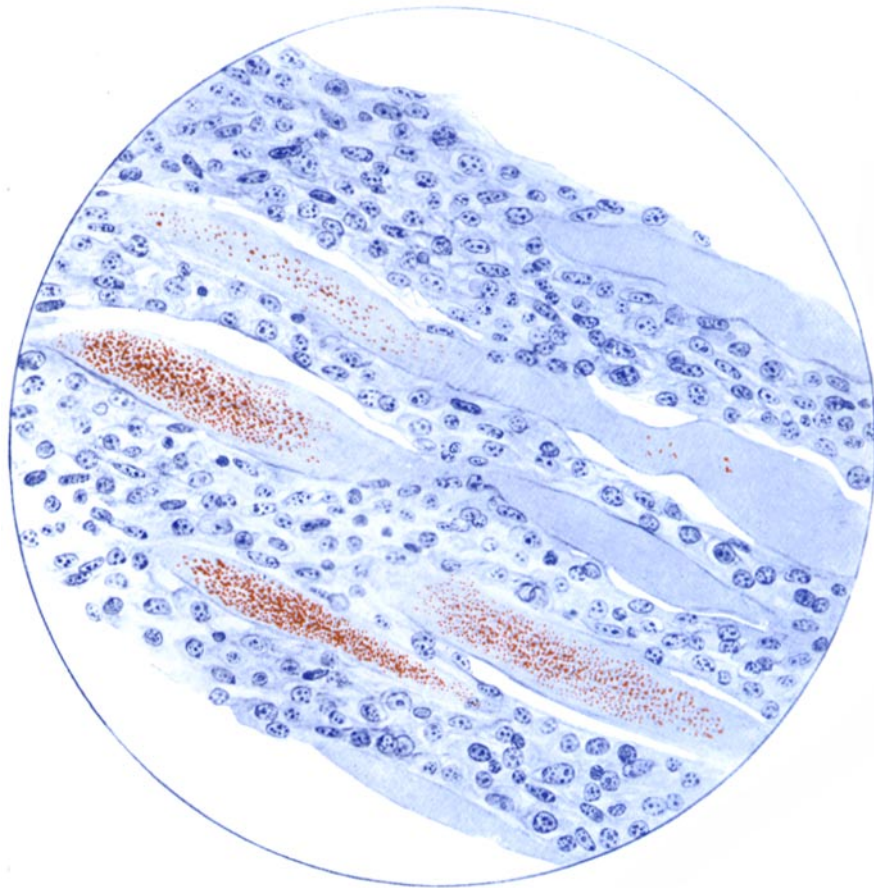


FIG. 2.