CANCER CELLS IN THE BLOOD STREAM

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It is generally accepted that cells from malignant growths are at some stage in the progress of the growth carried by the blood stream from the primary tumor to other parts of the body. Some lodge and form metastases; presumably the larger number are destroyed by lytic properties of the blood stream or tissues and many potential metastases are thus prevented. Possibly large numbers of such cells are present in the blood stream. On this assumption we have studied the blood in cancer cases.

The picture of a patient with carcinoma of many months duration, riddled with metastases, is too well known to need detailed description. In such cases cells have been seen in fixed tissues, filling the lumen of vessels, and in many instances invading the vessel walls. Schmidt in 1903 made microscopic examinations of the lungs in 41 cases of advanced malignant disease, and in 15 found tumor emboli in the pulmonary arteries. Pathologists use the evidence of blood vessel invasion as one of the criteria in establishing the diagnosis of carcinoma of the thyroid gland. In a case of carcinoma of the stomach studied by Quensel a small tumor embolus the size of a pea was found in the right auricle of the heart.

Many investigators have attempted to demonstrate the presence of tumor cells in the circulating blood stream. Marcus in 1917 reported "abnormal cells" in the blood taken from the finger of a patient with bronchiogenic carcinoma. Schleip described cells varying from the normal in a case of gastric carcinoma. Quensel examined the blood of 50 cadavers with malignant tumors, finding cancer cells in 6; of these 6 cases 4 were carcinoma of the stomach.

Our efforts have been directed toward ascertaining whether cancer cells may be identified in the circulating blood of living subjects, in the hope that a method might be developed of value in the differential diagnosis and prognosis of malignant growths.

In view of the fact that probably only occasional cells are dislodged from the primary tumor, it was believed that a study of smears alone would be unsuccessful. Consequently a variation of the method described by Mandlebaum in 1917 was used. Five c.c. of venous blood were withdrawn from the patient and "oxalated" to prevent clotting. The specimen was then hemolyzed with 15 per cent acetic acid, this concentration being used to obtain a rapid and maximum hemolysis with a minimum volume. The hemolyzed specimen was then centrifuged at a high rate for half an hour, the supernatant liquid was poured off, and

the specimen fixed by over-laying with 10 per cent formalin in alcohol. The specimen was then dehydrated and embedded in paraffin in the usual manner. Multiple sections were cut at intervals through the block and mounted under a cover-slip.

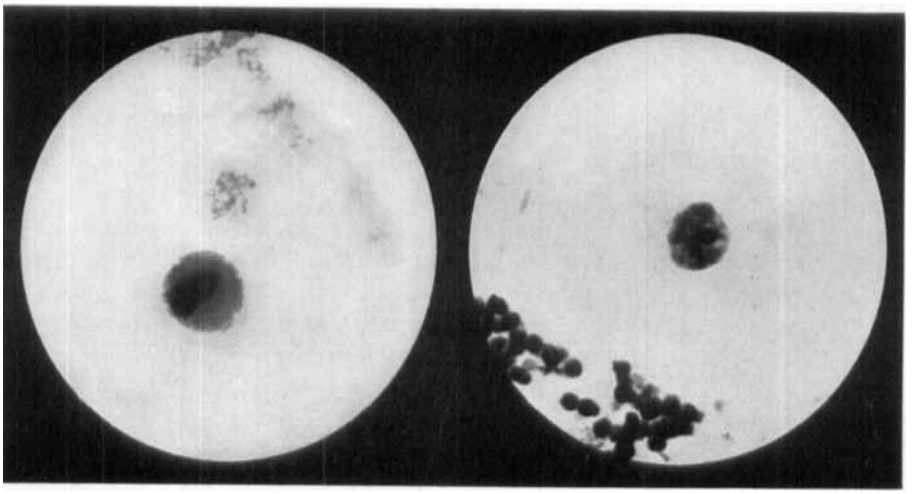

FIG. 1. SINGLE LARGE CELL FOUND IN A CASE OF CARCINOMA OF THE STOMACH, SHOWING THE HYPERCHROMATIC NUCLEUS AND EARLY DISINTEGRATION OF THE CYTOPLASM
FIG. 2. SINGLE LARGE CELL SEEN IN A CASE OF CARCINOMA OF THE STOMACH, WITH LYMPHOCYTES IN THE PERIPHERY OF THE FIELD

In an attempt to determine the effect of this treatment on any cancer cells that might be present in the blood specimen, scrapings from an adenocarcinoma of the breast were mixed with normal blood and prepared as described above. The cancer cells were easily recognized and revealed no significant injury. The leukocytes were well preserved, and the erythrocytes were completely hemolyzed.

Specimens of venous blood from 40 cases of advanced carcinoma of the breast, colon, stomach, rectum, and other sites, were prepared as has been described and the sections were studied for suggestive cells. In almost every instance a normal blood was run through as a control. In a few cases blood was withdrawn from the femoral artery or from the left ventricle just after death. In one case of inoperable carcinoma of the sigmoid, blood was withdrawn, during operation, from a mesenteric vein coming from the tumor.

Specimens of normal blood were mixed with the scraped exudate from proved carcinoma and the sections studied with a view of familiarizing ourselves with the appearance of known cancer cells in blood treated by this method. To eliminate the possibility of mistaking endothelial cells from the wall of a vein, dislodged by the needle, for tumor cells, a piece of vein wall was ground in a mortar and the residue mixed with normal blood to serve as a control. In the beginning numerous bizarre and atypical cells were seen both in normal blood and in blood from cancer patients (Plate I, d; Fig. 3). These were early eliminated as insignificant. Observation soon centered on a large spherical cell

with a round, elongated, or slightly curved hyperchromatic nucleus (Plate I, a, b, c; Figs. 1 and 2). These cells were seen only in the blood from cancer patients and were followed with interest until one was found in a case of gastric ulcer in a seventy-two-year-old patient with

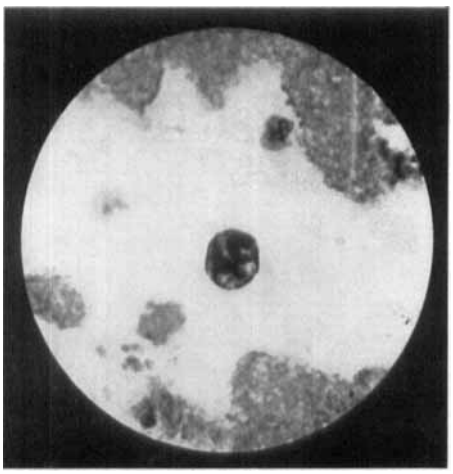

FIG. 3. SINGLE ATYPICAL CELL SEEN IN A CASE OF CARCINOMA OF THE STOMACH

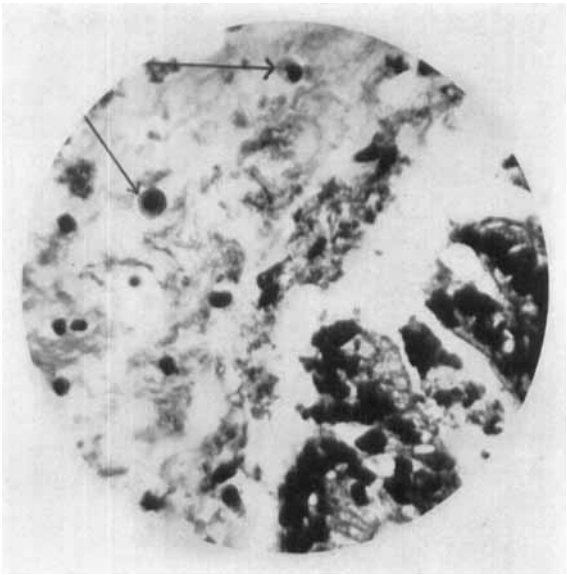

FIG. 4. SCRAPINGS FROM AN ADENOCARCINOMA OF THE BREAST, SHOWING SEVERAL DISCRETE CANCER CELLS WITH A PORTION OF THE TUMOR AT THE PERIPHERY

no anemia and a normal free hydrochloric acid. His symptoms were those of pyloric obstruction. The lesion was thought to be a carcinoma of the pylorus when a first stage gastro-enterostomy was done. When the abdomen was opened again, for pylorectomy, the tumor mass was found to be half its original size. Sections showed a chronic ulcer with-

out malignant change. Blood from ten other ulcer patients was examined without discovery of another of these cells.

Of the 40 cases studied such significant looking cells were found in 17. The cells were from two to ten times the size of a large monocyte, with round or elongated hyperchromatic nuclei. Often the cell membrane was irregular, suggesting beginning disintegration. No mitotic figures were seen. Of the 17 cases with positive findings, 7 were carcinoma of the stomach.

It is well recognized that there are many difficulties associated with the identification of individual tumor cells, especially when never more than one or two are seen in a section. Zadek, in describing the appearance of cancer cells in cytodiagnosis, emphasizes four points:

1. The rapidity with which cancer cells take a stain.
2. The agglomeration of cancer cells in compact, sharply outlined masses, whereas cells from a serous membrane lie in sheets one cell thick and have indeterminate and frayed edges.
3. The tendency to form giant vacuoles, 40 to 90 μ in diameter.
4. The nucleolus-nucleus ratio, as emphasized by MacCarty.

Needless to say the identification of a single and often partly degenerated tumor cell, surrounded by blood elements, proves a more difficult problem than the recognition of clumps of tumor cells in ascitic and pleural fluid.

The results of our investigation may be summarized as follows.

A large, hitherto undescribed cell was found in smears of the blood in 17 out of 40 cancer cases. Apparently the same cell was found in one non-cancer case. The significance and origin of the cell are not established.

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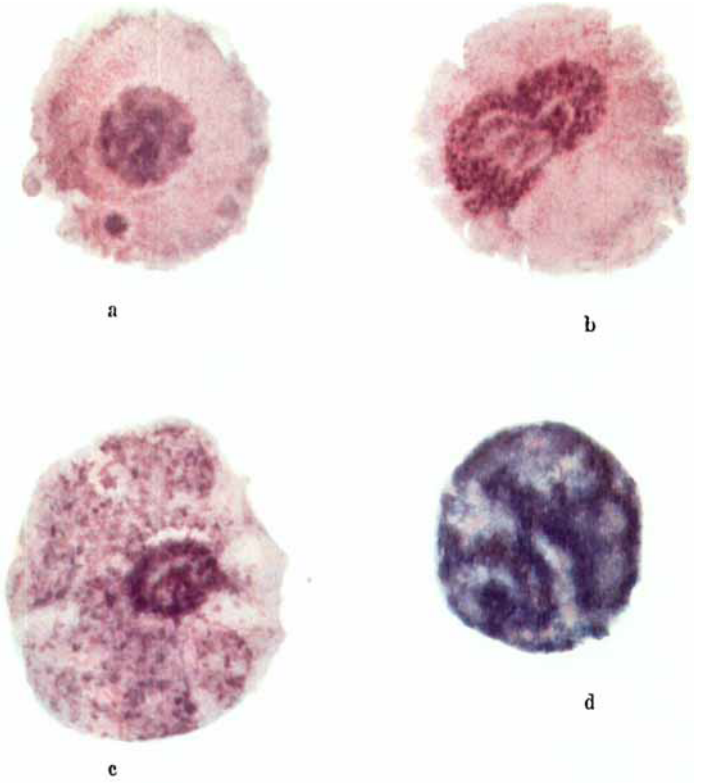
PLATE I



a, b, c. Typical cells observed in carcinoma cases. d. Atypical cell.