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Human Cancer, the Primary Target: *Guest Editorial*

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The burgeoning interest in chemotherapy as an area of cancer research has stimulated greatly increased drug screening and has also given rise to expanded biochemical investigations. Essentially all these studies are being carried out in transplanted rodent tumors. We have been concerned that the convenience of these tumors as research tools tends to obscure the need for cancer research in man. Although the assay of drug activities is being extensively pursued in human cancer, there appear to be many other areas where laboratory science, particularly biochemistry, could contribute importantly to cancer research in man. We are persuaded that greater attention to biochemical studies in human cancer could provide improved yields in clinical investigations, challenging problems for biochemical efforts, and information of importance in understanding human cancer.

The happenstance that certain enzymes leak from their cellular confines into extracellular fluids where they can be more readily studied may make them less representative of the true state of intracellular biochemical affairs than enzymatic activities determined directly in biopsy specimens. Since a common hindrance to chemical studies with human tissues is the macromethodology frequently presented in biochemical papers, the development of micro-methods is urgently needed. Human tissues are ordinarily available only in micro-quantities; in those quantities, however, certain tissues are repeatedly available for study. Micromethods adaptable to cylinders of tissue removed by needle biopsy approximately 5–10 mg. wet-weight would be helpful for the determination of cell functions and constituents. Enzymatic functions and other biochemical reactions to be studied would vary from tissue to tissue, but it is hoped that those reactions thought to be associated with the cancer process in experimental tumors could be studied in man. Postulated abnormalities in glycolysis and pyrimidine and purine anabolism and catabolism serve only as examples of broad areas in which specific enzymatic functions have usually been assayed in and interpreted from non-human tissues.

Since human tumors contain widely varying amounts of connective tissue, blood vessels, and necrosis, the feasibility of carrying out such studies as mentioned above depends on the development of suitable methods for the separation and differential analysis of tumor and stroma. The development of such methods, under strict histological control, should be given high priority.

Clinicians could be helped by learning more about the biochemical pharmacology of drugs of established usefulness in cancer chemotherapy. Our knowledge of the intracellular fate and activities in man of methotrexate, 6-mercaptopurine, stilbestrol, testosterone, and a few alkylating agents is unfortunately small in comparison to the accepted place these agents enjoy. Early availability of technics concerned with the activation of a drug in man to its physiologically important form might permit biochemical assays *in vitro* of tumors to be treated. The reactions of 6-mercaptopurine to 6-mercaptopurine ribotide and of 5-fluorouracil to fluorodeoxyuridylic acid have been reported to occur in experimental tumors sensitive to these

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compounds. The possibility of predicting responsiveness by studies of this sort is inviting, and pilot studies are now under way in the latter case. Similarly, enzymes are known to exist which are affected by particular drug action, e.g., orotidylic decarboxylase by azauridine and folic acid reductase by methotrexate. Workable technics for measurement of these enzymes are in hand, and activities in different tumors and drug effects thereon may permit chemical classification of tumor responsiveness in man.

The eventual ineffectiveness of a previously effective cancer chemotherapeutic drug occurs with tragic inevitability in man as the disease and treatment continue. Although much information has been gained from laboratory models of the phenomenon of resistance, the demonstration of a presumed biochemical mechanism for its occurrence in patients treated with any drug is remarkably rare.

Three other aspects of human cancer biochemistry are independent of chemotherapy but may exercise profound influence on drug response. The metabolic disease which man acquires from progressing metastatic cancer is essentially irreversible and, in the absence of other catastrophe, leads to cachexia and death. Differential responsiveness to drug treatment among metastatic lesions is commonplace, suggesting that biochemical differences exist among metastases. Any information such differences might contribute to understanding the phenomenon of metastasis would be a singular gain. The natural means of growth promotion and control in normal and neoplastic tissues are, in large part, obscure. These three areas are fundamental to an understanding of human cancer; they constitute obstacles of ignorance to progress in chemotherapy and are worthy challenges to the most serious students of cancer.

Finally, we, among others, have growing reservations about the validity of the generalization that cancer represents a biochemical convergence to a typical protoplasmic pattern, with enzymatic activities more characteristic of cancer than of the parent tissue. Nearly all of Greenstein's magnificent pioneering work, and most that has followed has been performed on transplanted rodent tumors. In the few spontaneous rat or mouse tumors that have been studied there appear to be many exceptions to the generalization. Certain enzymatic activities have remained essentially unchanged or have increased as compared with the tissue of origin. We doubt the wisdom of accepting biochemical information derived from transplanted tumors when the data apparently are not consistently applicable to spontaneous neoplasms in the same species. Certainly, it is imperative to investigate the validity of the Greenstein hypothesis as it applies to primary and metastatic neoplastic disease in man before it can serve as a basis for the planning of rational therapy. Indeed, Greenstein's studies of human cancer demonstrated a reasonable similarity of cytochrome c and cytochrome oxidase activities in human tumors and their corresponding tissue of origin.

More studies on the biochemical characteristics of *human* tumors are imperative before we accept the unitarian concept of a primitive, convergent, enzymatically depleted cancer tissue, which appears to fit many of the transplanted rodent tumors. Since it is conceivable, indeed even likely, that a systematic enzymatic exploration of human tumors with recent and refined technics may demonstrate a substantial degree of divergence of tumors—among organs, among tissues, and among tumors—it appears important to us that this information be gathered. Divergence, if it exists, might be exploited to increase our understanding of cancer in man and, hopefully, to improve therapy.

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