Summary of Informal Discussions of Second Day*

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This meeting was called to ascertain whether cancer is one or many diseases in the opinions of a number of experienced scientists of different disciplines. It was hoped that a well documented answer to this question would serve either to confirm the wisdom of the present policy governing the use of funds for cancer research, or to provide a useful base for a new and different one.

An adequately succinct report must be directed not alone to the question asked, but also to the reason, real or assumed, which led the Society to ask it. Hence, this statement is formulated in the belief that we are to provide support for, or denial of, a program of cancer chemotherapy.

To expend research funds in such an orderly and concentrated procedure requires reasonable evidence that chemotherapy is feasible; that leads exist which render the desired goal probably attainable. The question posed, “Is cancer one or several diseases?,” is really asked because the contention that it is several is the objection most commonly raised to extension of the present efforts to improve our existing chemicals for cancer control. It is said, either overtly or by implication, “Cancer appears in an infinite number of forms, perhaps thousands, and so a program seeking a cure for cancer of any one is utterly absurd, the goal unattainable, and the money expended on it wasted.”

Many prefer to expend in medical education these moneys given to eliminate cancer as a problem to society; to expend them in the support of the natural sciences in the universities; to give permanent salary tenure to generally talented investigators.

The questions to be resolved in this report, then, are: (a) Have these biochemists and biologists here assembled presented evidence that biochemical, morphological, and therapeutic characteristics set apart neoplastic from normal cells either quantitatively or qualitatively? (b) If proof of differences has not been advanced, do suggestions of them exist which justify further or more intensive search? (c) Do any differences, even slight, exist now which can be exploited, converted, into better therapy under a more vigorous program? (d) If proof of differences is not at hand, is it because they do not exist or because the efforts to find them have been inadequate? and (e) Are all cancer cells alike or different?

The detailed presentations of the biochemists certainly leave one with the conviction that biochemical species and tissues specificity do exist. Indeed, since the cells composing different tissues obviously look, function, and react differently, and since the cells are complex chemicals, it is hard to conceive of anyone seriously questioning the fact that they are chemically different. If this rather obvious reasoning be accepted, the question becomes, “Are cancer cells, which look, function, and react in many respects as differently from any normal tissue as normal tissues do among one another, also different chemically from any normal cells?” Clearly, if our first assumption is correct, the second must also be true.

The evidence presented by the biochemists appears to bear out this assumption. Greenstein summarized well those facts which define the biochemical specificity of normal tissues, as well as those which differentiate them from neoplastic ones. Moreover, his data on the relative uniformity of the enzymes of neoplastic tissue indicate at least a quantitative, if not qualitative, difference between the normal and the cancer cells.

The data presented by Weinhouse and Potter support adequately these conclusions. One states that the neoplastic tissues studied can do everything chemically which normal tissues can do, but they do not do everything so well. The other defends convincingly the thesis that there exists a specific biochemical defect in the cancer cell—a term applied, of course, to the particular type of cells he works with. One can only conclude, therefore, that differences exist regularly, definable by the chemists in the material studied.

Two questions then remain: (1) Is the proof of differences between normal and neoplastic cells adequate, or is this only a possibility? (2) In either case, is the evidence strong enough to justify vig-

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orous efforts to obtain more or to use the existing findings as the basis for efforts to convert them to practical use in therapy?

Clearly, it has been assumed that the evidence is not conclusive, and so the cancer biologists have been asked to present their views. Berenblum has reviewed the data which indicate five different types of etiological mechanisms, and he implies that the tumors derived from them are indistinguishable one from the other. His fascinating data bearing on tumor initiation and promotion, including the ability to sensitize systemically to a promoting agent, provide no evidence in support of the view that tumors resulting from different inducing mechanisms differ correlatively, either biochemically or in their sensitivity to specific controlling agents.

Steiner, on the other hand, as one who has been principally concerned with the study of spontaneous neoplasms in man, has presented conventional, but convincing, data concerning the morphological dissimilarities between normal and neoplastic cells of different tissues and refers to the tendency of the neoplasm to maintain a likeness to the tissue of its origin. He concludes that the type of neoplastic response reveals less about the etiology than it does about the cell type upon which the agent has exerted its cancer-producing effects. I am forced to conclude from this that he finds little evidence for, or against, the thesis of chemical specificity of the neoplastic cell sufficient in extent to justify vigorous chemotherapeutic efforts.

The presentation of Law supports very adequately the contention that neoplastic cells differ from normal ones. The examples studied are, in many instances, susceptible to selective destruction, even to the extent of being curable in some instances. I hardly see how there could be more convincing evidence of the chemical difference of certain neoplastic cells from similar normal ones, of the variety of differences which may exist among neoplastic cells, and of the ability of these cells to change. No evidence either for or against the possibility of a common different characteristic of the neoplastic process is presented, however.

It is remarkable how completely the facts presented by Karnofsky can be superimposed on those of Law, if one substitutes human neoplastic cells for those of the animal. Here, once again, one finds adequate evidence for differences between certain neoplastic cells and their normal analogues, for differences among individual neoplasms, and finally for the ability of individual neoplasms to change in sensitivity. Moreover, there is a suggestion, from these studies, that similar neoplastic cells in different locations may vary biochemically, as indicated by variation in susceptibility to injury by therapeutic agents.

One must conclude, therefore, from this mass of data in both the presentations and the discussions, the following:

1. Neoplastic cells do not differ according to the inciting agent.
2. They do differ in some instances from their normal relatives.
3. The consistency of these differences and their specificity still wants more adequate definition.
4. Sufficient difference exists to justify vigorous further study, designed to achieve the practical goal of cancer therapy.

We may, then, regard two questions as answered. Differences between cancer and normal tissue exist, of an extent to justify further exploration and serious efforts to convert them to means for more adequate therapy. Furthermore, there can be no doubt that, at present, cancer is many diseases in terms of the sensitivities of its various types to restraint, injury, or even cure by chemical agents. Nevertheless, no proof or even evidence has been advanced that there may not be also a chemical defect, or quality, which characterizes many types of cancer if not all.

Good evidence on this point has been advanced, however, by Skipper: In a study of a very large number of transplantable neoplasms, including two of human origin, he has demonstrated a consistent inability of the neoplastic tissues to incorporate certain precursors of nucleic acid, in sharp contrast to the normal tissues employed. These data, coupled with the fact that cellular specificity is controlled by nucleic acid and that all of the interesting therapeutic agents act on that cellular constituent, make a strong case in support of further study of nucleic acid antimetabolites in therapy.

If we grant the weight of the evidence advanced for the chemical specificity of the neoplastic cell and for its consequent sensitivity to selective growth restraint, we should, from the evidence here presented, recommend procedures which will permit the acquisition of even more convincing evidence. The following possibilities merit consideration:

1. For biochemical study, directly comparable normal and neoplastic tissues reproducing at the same rate should be employed. Many of the data now available have not been obtained from comparable tissues.
2. Studies of human tissue, normal, hyperplastic, preneoplastic, and neoplastic, are required. The procurement of such material is perhaps one of the most important activities which could be conducted.

3. Standardized normal and neoplastic cell lines in tissue culture are urgently needed on a scale which would permit adequately reproducible biochemical studies.

4. Further information on the requirements of human neoplastic tissue for nucleic acid precursors is essential.

5. Knowledge of the mechanism by which human neoplastic cells become resistant to therapeutic agents is almost entirely wanting. Its procurement should have a high priority.

6. Data on the resistance of the human host to the growth of neoplastic cells are almost incomplete. Studies of both cellular and humoral immunity should be encouraged.
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