Differences between Cancers in Terms of Therapeutic Responses*

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The report I have been asked to prepare, to quote Dr. Weaver, "is not so much to document progress" (not a review, in other words) "as it is to point up problems that must yet be solved and to re-evaluate concepts which may or may not be entirely valid." I am forced to note at the outset the profound inadequacies in information and thought which I bring to this enormous problem. Members of this committee have reviewed the cancer problem from one end to another; they have constructed theories; they have appropriated information from many scientific disciplines; and they have wrestled with the problems of cancer in solitude, in the laboratory, at the hospital bed, and in committees. Yet all are still waiting for the concept, the experiment, the clue, which can vitalize and orient the vast machinery of cancer research toward purposeful, productive, and practical ends. The signal for this activation cannot be provided by any presently known combination of words. This committee is seeking for something that continues to elude us, no matter how many the corners that have been swept, the drawers opened, the memories searched. Nevertheless, the search must go on, and somehow, from the experiments of the laboratory scientist and the experiences of the clinician, ideas extracted which, in Dr. Weaver's words, "might effect a practical solution of the cancer problem."

Because of the specific title of my assignment, I shall try to adhere closely to the subject. To cover the area it is necessary to make some general observations, and then to turn to the responses of cancer to therapeutic agents.

GENERAL OBSERVATIONS

Is There a Unified Concept of Cancer?

A major goal of cancer research is to discover a unifying abnormality common to all forms of cancer—a fundamental etiologic mechanism or a biochemical derangement as the motivating force in the disease. In other words, a discovery for cancer as unifying as that concerned with the roles of bacteria and viruses in infectious diseases. The demonstration of a common primary etiologic mechanism or functional disturbance could well provide the key to a chemotherapeutic attack on all forms of cancer, wherever it occurs. Nothing has been shown at this meeting, thus far, to indicate that we are nearing this objective.

While we can hope that the ultimate understanding of cancer will be in terms of unified concepts, one is presently impressed with the great and obvious diversities among the many different forms of cancer, in their appearance, their clinical courses, and their response to known therapeutic agents. It can be concluded at the outset of this talk, and without much thought, that cancers differ greatly among themselves. This categorical conclusion is not a promising one to the therapist, but, if true, it is so important that it should be arrived at only at the completion of a laborious analysis. It is this great diversity among cancers, particularly in the unpredictability of the therapeutic response in individual cases and in the invariable development of resistance to treatment in the responsive cases, that I am discussing today.

Some Tumor Characteristics

Neoplasms occur throughout the plant and animal kingdom, and the variety that has been found or produced, and studied in some manner, is truly enormous. Table 1 lists a few species and representative tumors that have been observed in each species, and in some instances the apparent etiologic agent is also included. The list is long, and each tumor has its students and proponents. Do extensive taxonomic descriptions of neoplastic diseases or separate studies on specialized features of a great variety of cancers divert attention from the more pressing fundamental problems? This is a question of emphasis in research that merits discussion.
Certain features are important in describing the nature and biologic behavior of cancers, and they clearly emphasize the great differences that exist among them.

Species of origin.—The characteristics of a tumor will obviously bear histologic, metabolic, and immunologic relationships to the species from which it arises; e.g., chicken, fish, bird, mouse, hamster, etc.

Site of origin.—A tumor will often retain certain histologic and functional characteristics of the normal tissue from which it arises; e.g., stomach, thyroid, bone, blood-forming tissues.

Causative agent.—The cause of most forms of cancer is unknown. For certain cancers, however, known inciting agents exist; e.g., viruses, chemicals, radiation, hormonal imbalances.

Histologic appearance.—Tumors vary greatly in the microscopic appearance and arrangement of the tumor cells, their blood supply, and the nature and degree of the host tissue reactions around the tumor. The same tumor also may show important variations in structure in different areas, and metastases may differ in appearance from the primary lesion. Tumor cells may show structural arrangements and histochemical reactions indicating specific functional activity related to their normal tissues of origin.

Malignancy.—It is sometimes difficult to draw a fine line between a benign and malignant tumor. Certainly the growth rate of a tumor can be independent of its invasiveness and metastatic properties. Tumors may grow rapidly and remain localized; others, while slowly growing locally, will disseminate widely. This separateness has been emphasized in our experiences with two transplantable human tumors, Toolan's H.Ep.#8 and H.S.#1. Both tumors grow rapidly when explanted to the chorioallantoic membrane of the chick embryo, the H.S.#1 actually producing larger tumors in most instances. The H.Ep#8 metastasizes widely from its site of inoculation on the chorioallantoic membrane, and such chicks on hatching show metastatic foci of H.Ep.#8 which continue to grow and finally kill the host. H.S.#1, however, has not metastasized under identical circumstances of transplantation (10, 11).

Specific functional capacity of tumor cells.—It is apparent that tumor cells have many of the fundamental attributes of normal cells as far as synthetic activity and the mechanics of cell division are concerned. Neoplasms may originate from practically any tissue and often retain structural similarities and functional activities from their tissues of origin. Some produce acid phosphatase (prostatic cancer), make thyroid hormone (thyroid

### TABLE 1

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology, when known</th>
</tr>
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<tbody>
<tr>
<td>Plants: Crown gall (6)</td>
<td>Agrobacterium tumefaciens</td>
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<tr>
<td></td>
<td>Fiji disease of sugar-cane, Wallaky-ear disease of corn, club root of tobacco, wound-tumor disease (4)</td>
</tr>
<tr>
<td>Animals: Insects: Fruit-fly</td>
<td>Melanoma (36)</td>
</tr>
<tr>
<td>Amphibians: Frog</td>
<td>Kidney tumor (51)</td>
</tr>
<tr>
<td>Azotol</td>
<td>Melanoma (44)</td>
</tr>
<tr>
<td>Fish:</td>
<td>Lymphosarcoma (85)</td>
</tr>
<tr>
<td></td>
<td>Melanoma (94)</td>
</tr>
<tr>
<td>Birds: Chicken</td>
<td>Chicken sarcoma (48), Fowl lymphomatosis (8), RPL 12 (87),</td>
</tr>
<tr>
<td></td>
<td>Erythroleukemia (8),</td>
</tr>
<tr>
<td>Duck</td>
<td>Sarcoma (14)</td>
</tr>
<tr>
<td>Parakeets</td>
<td>Pituitary tumors (48)</td>
</tr>
<tr>
<td>Mammals: Mouse</td>
<td>Breast cancer, leukemia, lymphosarcoma, melanoma, hepatomas, osteogenic sarcoma, ascites tumors (Ehrlich, Krebs 9, Sarcoma 180)</td>
</tr>
<tr>
<td></td>
<td>(87)</td>
</tr>
<tr>
<td></td>
<td>Tumors of endocrine glands (81)</td>
</tr>
<tr>
<td>Rat</td>
<td>Sarcomas, bladder, liver and breast cancers, leukemia, Yoshida ascites tumor (81)</td>
</tr>
<tr>
<td></td>
<td>(81)</td>
</tr>
<tr>
<td></td>
<td>Physiological disturbance</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Vx, Brown-Pearce papillomas (82)</td>
</tr>
<tr>
<td>Horse</td>
<td>Variety of carcinomas and sarcomas (80)</td>
</tr>
<tr>
<td>Dog</td>
<td>Many types; common varieties include skin and mammary cancers, sarcomas, and melanomas (38)</td>
</tr>
<tr>
<td>Man</td>
<td>Many varieties; common types include breast, uterine, cervix, lung, stomach and large bowel, prostate, leukemia and lymphomas (1, 18)</td>
</tr>
</tbody>
</table>

carcinomas), secrete mucus (large bowel carcinomas), etc. The retention of these specific activities indicates clearly that tumor cells are not entirely aberrant cells, but to varying extents they attempt to mimic the behavior of their normal analogs. Some endocrine tumors remain responsive to or dependent on pituitary secretions for their functional activity, whereas others produce excessive hormones in the absence of any known stimulation. These latter cells thus exhibit autonomy not only in growth but in specific function.

**Rate of tumor growth.**—The growth rate varies with each tumor and may change at different stages in the evolution of a cancer. Thus, a cancer may remain indolent for long periods and then suddenly show an explosive increase in growth. The mass of a tumor is the remainder of new cells formed minus the cells dying. Some tumors apparently grow by the continuous addition of long-lived cells. Other tumors, however, may have a high rate of new cell formation, but these new cells have a short survival time. Thus, in the presence of intense cellular activity (cell division and destruction), the mass of the tumor may increase slowly, and, if the equilibrium is upset by briefly interrupting cellular multiplication with treatment, the tumor may promptly regress. The latter situation is seen in some cases of acute leukemia, in which the untreated case there is chemical evidence of rapid cell growth and destruction while the leukocyte count and size of the enlarged organs remain constant. The rate of new cell production and destruction is important in measuring the response of cancer to carcinostatic agents, since tumors which slowly produce long-lived cells would show far less immediate or transient response to a chemotherapeutic agent than tumors in which cell turn-over proceeds at a rapid rate. This will be the result, despite the fact that prior to treatment the apparent rate of enlargement of the two types of tumors we are contrasting appears to be the same. This phenomenon may be analogous to the hematopoietic disturbance produced by radiation or nitrogen mustard. Under normal circumstances, leukocytes survive about 6 days and erythrocytes about 120 days, and the supply of these cells is replenished at an appropriate rate from the bone marrow. Following an effective dose of one of these agents, the bone marrow is temporarily severely depressed. The leukocyte count falls promptly to low levels, but in the absence of bleeding there is only a slight decrease in the hemoglobin level because of the long-lived erythrocytes. Within 2–3 weeks the bone marrow recovers. The leukocyte count slowly rises to normal, and the slight anemia is promptly corrected by recovery of the erythroid tissue. While the insult to granulocytic and erythropoietic elements in the bone marrow is practically the same, the depression in the leukocyte count is far more conspicuous. Thus, information not only of the rate of tumor growth but of rates of cell turnover is important in characterizing tumors.

**Evolution of individual tumors.**—As tumors grow and metaostasize, they may change their histologic appearance and functional activity, presumably owing to the natural evolution of the disease. Chronic myelocytic leukemia may become more ‘blastic,’ Hodgkin’s disease may develop sarcomatous features, and carcinomas may become more anaplastic. Certainly the functional capacities and responsiveness of a tumor may change, and tumors previously responsive to hormonal control, radiotherapy, or nitrogen mustard may become refractory. This is probably a process of tumor maturation rather than the survival of cells resistant to previously effective therapeutic agents. On the other hand, some tumors show more differentiation, and spontaneous regressions have been reported. This has been noted, for example, in neuroblastomas, where histologic maturation to a ganglioneuroma and regression have been observed in an appreciable number of the cases. We must consider, therefore, that some tumors will alter their appearance, growth rate, and functional activities during their evolution in a manner analogous to some normal tissues.

**Effects of tumors on the host.**—Tumors may affect the host in various ways. In many instances disturbances are produced by infiltration or mechanical displacement of vital structures in the host, resulting in ureteral obstruction, hepatic insufficiency, respiratory embarrassment, etc. Some tumors mimic to excess the function of their tissue of origin, producing thyroid hormone, adrenal cortical hormones, serotonin, etc. Some tumors produce such a multitude of short-lived cells that the body metabolism rises; others may produce fever, itching, anorexia, possibly due to a toxic factor or by inducing an unusual response in the host tissues; some tumors, by metastasizing to bone and eroding it, liberate large amounts of calcium, with resultant hypercalcemia and hypercalcuria leading to neuromuscular disturbances and renal damage. The variety of local and systemic derangements produced by specific forms of cancer indicate the many specialized tumor properties that exist. Chemotherapeutic agents may modify or relieve these secondary disturbances without necessarily acting on the underlying disease. An important aspect of the evaluation of a chemotherapeutic agent is to demonstrate that it is truly carcinolytic or carcinostatic and not acting only to relieve the...
secondary disturbances produced by the cancer.

**Development of resistance.**—The clinical course of some tumors may be appreciably altered by treatment. An inevitable consequence, even of a favorable response to the available forms of treatment, is the appearance of resistance. This resistance may be attributed to the “maturation” of the tumor. There is good evidence in animals that strains of cells which are no longer inhibited by previously active chemotherapeutic agents may appear by selection. This phenomenon has been discussed by Dr. Law.

It seems clear from this discussion that each form of cancer has its own characteristic properties which distinguish it from others, and these characteristics are numerous and varied.

**TABLE 2**

**Transplantable Tumors Commonly Used in Chemotherapy Studies**

<table>
<thead>
<tr>
<th>(15, 22, 26, 28, 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chicken</strong></td>
</tr>
<tr>
<td>Rous sarcoma, Leukosis RPL-12</td>
</tr>
<tr>
<td><strong>Mouse</strong></td>
</tr>
<tr>
<td>Crocker sarcoma 180, Sarcomas T341, Ma887, 637, 1, 37</td>
</tr>
<tr>
<td>Leukemias AK, A/K, AK4, AK417, AK4, L1210, C1498, H8276, P1654</td>
</tr>
<tr>
<td>Lymphosarcoma Mecca, 6CSHED, P1654</td>
</tr>
<tr>
<td>Harding-Passey melanoma, S91 melanoma</td>
</tr>
<tr>
<td>Mammary carcinomas E 0711, Bashford ca63, ca755, RC tumor, CSHBA, 15001a, Miyono adenocarcinoma, Ehrlich carcinoma</td>
</tr>
<tr>
<td>Carcinoma 1025, hepatoma C574, Twort carcinoma</td>
</tr>
<tr>
<td>Ridgway osteogenic sarcoma, Wagner osteogenic sarcoma</td>
</tr>
<tr>
<td>Aspects forms of Ehrlich, Sarcoma 180, and Krebs 2</td>
</tr>
<tr>
<td><strong>Rat</strong></td>
</tr>
<tr>
<td>Flexner-Jobling carcinoma, Walker carcinosarcoma, Jensen sarcoma, Murphy-Sturm lymphosarcoma, Yoshida sarcoma</td>
</tr>
<tr>
<td><strong>Rabbit</strong></td>
</tr>
<tr>
<td>V5 and Brown-Pearce carcinomas</td>
</tr>
<tr>
<td><strong>Human</strong></td>
</tr>
<tr>
<td>Transplantable human tumors grown in conditioned hamsters or rats, and in the chick embryo and chick. These include Toolan’s H.Ep. #8 and H.S. #1. (48)</td>
</tr>
</tbody>
</table>

In the search for effective chemotherapeutic agents it is desirable to have a continuous supply of tumors which have a regular growth rate and respond in a reproducible manner to various procedures. For these reasons, transplantable tumors are widely used in chemotherapy research. There are many transplantable tumors available, the number is increasing, and it can be extended almost to infinity. The tumors in general use are summarized in Table 2. It is clear that, while these tumors differ greatly among themselves, they are individually more constant in their behavior than spontaneous tumors of a given type. Gellhorn and Hirschberg in their recent report entitled Investigations of Diverse Systems for Cancer Chemotherapy Screening (22) have demonstrated the variations in the responses of fifteen different tumors to 27 potential chemotherapeutic agents. The results of this study are summarized in Table 3. Whereas thirteen of fifteen tumors showed some response to 6-mercaptopurine, only six of fifteen responded to A-methopterin. Daraprim seemed to have a marked effect on only the Sarcoma 180, whereas 6-mercaptopurine inhibited eleven of fifteen tumors to a similar extent. The Sarcoma 241 was almost unresponsive to the drugs tested, whereas mammary carcinomas, Ca-755, Ca-1025, and Sarcoma 180 were susceptible to a variety of chemicals. Gellhorn and Hirschberg conclude: “The present results confirm and extend previous observations on the variability of response among experimental neoplasms to chemotherapeutic agents.” Thus, even among reliable and reproducible systems, differences in response to chemotherapeutic agents exist, and, as Dr. Law has already noted, tumors which respond to an effective chemotherapeutic agent can be made resistant to the drug without alteration of their neoplastic activity.

**WHAT IS THE CANCER CELL, AND HOW IS IT INFLUENCED BY CHEMOTHERAPEUTIC AGENTS?**

Is any single concept of the cancer cell an abstraction, a universal cell that does not exist in reality and, therefore, does not present a real target for chemotherapy? Or is the cancer cell many different kinds of cells, as varied and as complex as the normal tissues from which it arises? Or is there a common basic defect in all cancer cells which is thus far obscured by the many settings in which cancer can occur? We shall try to present our answer to these questions by a simple analogy.
### TABLE 3

**Summary of Results of Experimental Chemotherapy Study Testing Chemical Agents Against a Variety of Experimental Neoplasms (Gellhorn & Hirschberg [28])**

| NAME                                  | S-180 | PHEL. | WALE. | CA.  | S-741 | CA.  | MECA  | CA.  | RAME | CA.  | BROW. | GLUL. | LEDG. | LIII-S | ERLICH ASCITES* | EF | ELD |
|---------------------------------------|-------|-------|-------|------|-------|------|-------|------|------|------|-------|-------|-------|-------|-------|-----------------|----|-----|-------|
| 5-Mercaptopurine (Primethol®)          |       |       |       |      |       |      |       |      |      |      |       |       |       |       |                 |    |     |       |
| 5-Fluorouracil                         |       |       |       |      |       |      |       |      |      |      |       |       |       |       |                 |    |     |       |
| N-Methylformamide                      |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       |       | ±               |    | ±   |       |
| Methylthiochloroethyl amine (nitrogen mustard, HNII, Mustargen®) |       |       |       |      |       |      |       |      |      |      |       |       |       |       |       | ±               |    | ±   |       |
| 8-Azaguanine (8-Amino-7-hydroxy-1H-   |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| triazolo[1,5-a]pyrimidine, Guanadin)   |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Hydrocortisone (Compound F)           |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Urethan (ethylcarbamate)               |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| 5,6-Diamino-2,3-dichlorophenyl-2,4     |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| ethylpyrimidine                        |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Amcetacin (O-Diaacetyl-L-serine,      |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Bovaril®)                              |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| 1,4-Dimethanesulfonylbutane (Myle-o-  |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| ray® GT741)                            |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| A-methylterpin (4-Amino-N-methylpyra-  |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| zynothamic acid, Methotrexate®)        |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| N-Methylacetamide                      |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| 5,6-Dithionine                         |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Colchicine                             |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Diethylstilbestrol (Stillbestrol)      |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Potassium arsenite                     |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Nitrogen                               |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| 5,6-Diaminopenazine                    |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| 5,6-Diamino-2,3-dichlorophenyl-2,4     |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| ethylpyrimidine (Dacromycin®), Pyrimetham-  |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| plene®)                                |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| 4-Methoxytetraquine                    |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| 5-Aminolevulinate                      |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Benimidazole                            |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Methylbarbital                          |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Chloramphenicol (Chloromycetin®)       |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| 6-Azathioprine                          |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| D-Glucosamine                           |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| 5-6-Thiouracil                          |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |
| Desoxyxpyridoxine                       |       |       |       |      |       |      |       |      | ±    | ±    |       |       |       |       | ±               |    | ±   |       |

* EF—fast-killing dose. ELD—hyperdiploid.
Normal cells.—Cells may be regarded as separate factories, with a similar basic organization, but each has its special operational pattern, including the requirements for certain raw materials and the machinery for the formation of specific products. Also, each factory has its maintenance service for the repair of worn out and damaged equipment, and, to strain the analogy, when necessary each factory can duplicate itself. Furthermore, each factory unit may join with other functional units into an integrated complex body, and under certain conditions the activity and number of units can be either increased or decreased. It must be noted also that certain factory units can be consumed in the production of their own product and thus lose the capacity to form new units or to continuously produce materials. Thus we have a system whereby raw materials are being supplied to a factory where they are converted into complex substances by specific machinery under the guidance of a controlling area; the complex substances are fabricated into the unit product, but they are also used as needed for factory maintenance and for new unit formation.

Examples of neoplastic cells.—The normally functioning factory may be diverted in a variety of ways to an abnormal neoplastic state.

a) The factory may take in an excess of raw materials, produce the usual product, but divert a greater amount of its effort to the formation of new units, e.g., functional thyroid carcinomas.

b) It may stop serving a useful function in the community, take in an excess of raw materials, and divert its entire activity to the production of new units, e.g., anaplastic carcinomas.

c) It may continue to produce a product, but it is abnormal, and thus it may have a harmful influence on its total environment (possibly illustrated by the systemic toxicity in Hodgkin’s disease).

d) It may continue to manufacture its product in increasing and excessive amounts without responding to normal controlling factors, e.g., carcinoma of the adrenal cortex, malignant carcinoids.

In these and many other ways, the neoplastic cell may approach to various degrees the patterns of activities of normal cells. Where is the defect in the cancer cell? Is it in the functional disarray, which is of almost infinite variation, or in the controlling mechanism of the cell, which may be more universal in character but, at the same time, more difficult to define?

The clinical effects of presently available chemotherapeutic agents.—The basic machinery in the normal and abnormal units may be very similar, and, in the use of systemic agents to damage or destroy the neoplastic units, some of the normal structures may suffer sufficiently to disrupt the entire body economy. The situation in regard to the agents used in current therapy is shown in Chart 1. The chart presents the variety of drugs in use, some concept of their mechanisms of action, the types of normal tissues and physiologic processes affected by the drugs, the forms of cancer which show some response to these drugs, and the probable locus of action of the drugs on the cancer complex. This intricate chart furnishes graphic evidence of the great differences between cancers in terms of therapeutic responses.

Tumor resistance.—Among a group of factory units exposed to an adverse situation, certain units can apparently survive and be resistant to the destructive agent. While the development of permanent resistance to an antimitabolite is readily demonstrated in leukemia, it has not been described for normal cells susceptible to antimitabolite action, such as the bone marrow and intestinal mucosa. How can the resistant unit continue to function despite the presence of an ordinarily effective blocking agent? Do the surviving resistant units (a) have different machinery, (b) operate with different raw materials, or (c) have different portals of entry and transport for raw materials? Are these resistant cells qualitatively different from the susceptible strain of cell? Is it now possible to develop new agents to damage the devices of resistance with less severe injury to the normal tissues than that produced by conventional agents?

RESPONSES OF HUMAN CANCERS TO THERAPEUTIC AGENTS

Neoplastic diseases in man bear many resemblances to the disease in laboratory animals. Human cancers grow locally, infiltrate normal tissues, metastasize, and in some cases they have been grown on transplantation into other patients (after growth in an intermediate host or in tissue culture) (45), and several cancers are being maintained by continuous heterologous transplantation (48). While information derived from the study of various forms of cancer in animals has been, in many instances, applicable to man, such inferences must be confirmed by clinical tests. The great variation in the appearance and biological characteristics of animal tumors and in their response to chemical agents has already been noted. It has been shown, however, that a number of drugs effective against transplantable animal tumors also produce therapeutic effects in certain forms of human cancer (46). Recognizing the great variety in human and in animal cancer, these correlations may seem sur-
CHART 1.—Legends on following page
prising or a manifestation of providence, but this feeling of wonder diminishes when we consider how general and fundamental the actions of these agents are on a great variety of growing tissues.

In this report we are primarily concerned with human cancer in terms of its clinical variations, and with an analysis of its response to established chemotherapeutic agents.

**Characteristics of Human Cancer**

The same criteria are observed in describing cancer in man as in other species. These include: site of origin, histological appearance, rate of tumor growth and cell turnover, tissue infiltration, local metastases, pattern of evolution of the disease, metabolic features of the tumor, effects of tumor on the host, and evidences of the host reaction to the presence and growth of the tumor.

**Reproducibility of Therapeutic Responses**

The type of response to chemotherapeutic agents will be described later, but an important criterion that must be emphasized is the reproducibility of response. A specific drug may sometimes be associated with remarkable benefit to an isolated patient, in contrast to its failure in a number of other patients with the same disorder. The isolated case may be presented in dramatic terms,

**Chart 1.** A diagram demonstrating the interrelationships of chemotherapeutic agents, normal tissues and physiological processes of the host, and the cancer complex. The categories of agents used in clinical cancer chemotherapy and their effects on normal tissues are shown in the outer portion of the diagram. They are:

1. Polyfunctional alkylating agents (80, 89, 41): of which the prototype is methylbis(β-chloroethyl)amine hydrochloride (HN2). Other alkylating agents, including triethylene melamine (TEM), triethylene thiophosphoramide (ThioTEPA), and 1,4-dimethanesulfonyloxoybutane (Myleran), are available for clinical use. In vivo, these agents are presumed to react in a highly selective manner with certain components of the cell nucleus. The blood-forming organs are particularly sensitive to their cytotoxic action.

2. Antimetabolites: Compounds of current clinical interest include the folic acid antagonists (19)—4-aminopteroyl-N10-methyl glutamic acid (A-methopterin), 6-mercaptopurine and related 6-substituted purines (6, 9), O-diazoacetyl-5-mercapto-

serine (aza-sarcurine) (18), and 6-diazo-5-oxo-l-norleucine (DON). These compounds, in various ways, interfere with the synthesis of the precursors of nucleic acid and thus possibly interrupt certain essential cellular functions and the production of nucleic acid for new cell formation. 6-MP and A-methopterin can consistently damage the normal bone marrow, as well as produce lesions in the mouth and intestinal tract, whereas azaserine principally causes oral lesions with only an inconstant depressant effect on hematopoietic function.

3. Sex hormones: The androgenic and estrogenic steroid hormones exert a physiologic action by altering the hormonal balance in the host, by inhibiting the pituitary gland, and by an inhibitory effect on the action of the reciprocal hormone. The sex steroids act on tissues dependent for their full growth and function on hormonal stimulation (40).

4. Adrenal cortical steroids: There are a number of active adrenal steroids in use including cortisol, hydrocortisone, and the 1α and 9α fluoro-analogs of cortisone. These compounds appear to damage lymphocytes and interfere with inflammatory reactions and the growth of certain mesodermal tissues (12, 38). Excessive dosage may cause fluid retention, hypertenion, hyperglycemia, and mental changes.

5. Radioactive isotopes (40): While radioactive isotopes produce their therapeutic effects by irradiation, their chemical properties will determine how they are metabolized by the body and in which tissue they localize. P32 is widely distributed, with some selective localization in bone and in multiplying cells. It produces effects on the host similar to those of total body irradiation, and bone marrow depression is an inevitable result of excessive dosage. I131 localized in high concentration in functioning thyroid tissue, but large doses also cause bone marrow injury.

6. Miscellaneous compounds: These include potassium arsenite, urethan, colchicine and its analogs, and the bacterial polysaccharides. Potassium arsenite may produce injury to the intestinal tract and skin; urethan has produced bone marrow depression, vomiting, somnolence, and occasional hepatic injury (20); colchicine analogs have caused intestinal injury, bone marrow depression, and shock; and the bacterial polysaccharides induce high fever.

7. Nontherapeutic toxic compounds: Host toxicity does not go hand in hand with therapeutic effects. Purine (51), 6-aza-

guanine (6), aminonucleoside (6), 6-azathiymine (17), methyl-ami-
mformamide (38), and ethionine (50), which exhibited some anti-tumor growth activity in laboratory animals, were without therapeutic effect in man at toxic doses.

In the center part of the diagram the several components of the cancer complex are shown.

a) Cancer cells, which will vary in appearance, rate of multiplication, and survival.

b) The stromal reaction, which is the supporting structure induced by the tumor cells. This may range from scanty to very dense.

c) The cellular response by the host, which is represented by lymphocytes, granulocytes, plasma cells, and macrophages. This reaction varies in intensity, and certain patterns of reaction may be specifically related to certain types of tumors.

d) The production by the tumor of specific toxic substances or excessive amounts of physiologic materials may cause important systemic alterations in the host; these are seen as increased enzyme levels in the blood (serum acid phosphatase in prostatic cancer), the fever and itching of Hodgkin's disease, the virilizing signs in adrenal cortical carcinoma, and the hypercalcemia in parathyroid tumors or in osteolytic bone metastases. Cancers can thus produce various disturbances in the host not necessarily related to its encroachment on normal structures. It is consequently evident that the secondary effects of the cancer may be modified and ameliorated without necessarily directly interfering with its growth.

e) Interference with blood supply: a tumor requires the development of a blood supply for growth. Damage to its blood vessels can result in necrosis in parts of the tumor.

While these several factors are operating in the cancer complex, they vary in importance in each cancer. There is ample evidence that some tumors, or some manifestations of neoplastic growth, respond to one type of agent but not to others. The components of the neoplastic complex affected by certain agents are shown by the arrows in the diagram.
whereas the failures are largely ignored. If the unusual response is attributed to the treatment, it emphasizes more than ever the great diversity in the response of cancer to specific drugs. The isolated successful response certainly does not appear to be a cause for optimism. An effective agent, if not generally curative, should exert a range of therapeutic effects in a group of patients from slight to marked, to indicate that it possesses a regular and predictable action against some facet of the disease. For example, Sykes et al. (47) reported a study on the effects of triethylene melamine (TEM) on ovarian cancer. In a series of 28 patients, approximately 54 per cent obtained some subjective improvement, and in 31 per cent there was objective evidence of tumor regression. The average period of improvement was 1—3 months, but one patient was benefited for 11 months before relapse occurred. A single case, treated 5 years earlier, was apparently cured, since there has been no sign of recurrent disease. While the evidence indicates that TEM has a slight but definite effect on ovarian cancer, the solitary 5-year case is not presented as evidence for the remarkable effectiveness of TEM. Either it was one of the rare spontaneous regressions reported in this disease, or the tumor, in showing such an unusual response to TEM, differed fundamentally from the great majority of ovarian cancers.

**Acute Leukemia**

This disease is characterized by an excessive proliferation of primitive bone marrow cells. These undifferentiated and multiplying cells metastasize readily and, in addition to involving the bone marrow, they can infiltrate numerous organs such as the liver, spleen, lymph nodes, skin, kidneys, etc. Generally the leukemic cells crowd out the normal elements of the bone marrow; as a result, anemia (due to interruption in red cell formation) and thrombocytopenia (due to displacement of megakaryocytes) occurs. The normal leukocytes of the blood diminish in number as they are replaced by primitive cells. Patients show hemorrhagic tendencies, develop a marked susceptibility to infection, and often exhibit a high fever. The response of acute leukemia to treatment differs in some respects in children and adults.

**Children.**—Acute leukemia is a progressive disease, although in about 5 per cent of the cases temporary spontaneous remissions have been reported. These spontaneous remissions presaged the fact that acute leukemia would respond to suitable chemotherapeutic agents. There are several criteria useful in measuring the response of acute leukemia to treatment, such as: improvement of the bone marrow picture with a return toward normal of the cellular components, decrease in size of the enlarged liver and spleen, rise in platelet count, spontaneous rise in the hemoglobin level, and decrease in fever. When a complete clinical and hematologic remission occurs, all manifestations of the disease disappear.

Several agents are temporarily effective in acute leukemia in children. The several types of acute leukemia are often impossible to differentiate, and in our experience such differentiation is only rarely of importance in therapy. Active drugs include:

a) **Adrenal steroids:** These agents inhibit the growth of some mesodermal cells and lymphatic tissue, and it seems likely that some strains of leukemia cells are related to lymphocytes or primitive mesenchymal cells. In favorable cases (about 70 per cent of the cases), the response to the adrenal steroids is usually prompt, with a fall in fever, decrease in bleeding, and rapid improvement in the bone marrow and peripheral blood picture. Improvement is usually brief, so that the drug is stopped when a remission develops. It may be restarted during relapse, and in this fashion several separate remissions may occur before resistance develops.

b) **Folic acid antagonists:** These agents interfere with the formation and function of citrovorum factor, a donor of single carbon fragments for purine synthesis. They produce hematologic remissions in about 35 per cent of children with acute leukemia, improvement occurring in some instances without host toxicity. Often, however, the patient must be brought to the verge of severe toxicity before a remission occurs. Hematological remissions may continue for several months, even if the drug is stopped as soon as improvement occurs, and several separate remissions may be produced before resistance develops. Another folic acid antagonist, diamino dichlorophenyl pyrimidine, while its toxicity is prevented by citrovorum factor in man, has not been so effective as A-methotrexate in acute leukemia; it produced greater host toxicity and fewer instances of hematologic improvement.

c) **Purine analogs:** These agents, such as 6-mercaptopurine, apparently interfere with purine synthesis. 6-Mercaptopurine (6-MP) has produced complete hematological remissions in about 50 per cent of children with acute leukemia. It is somewhat less toxic than the folic acid antagonists, but remissions are usually shorter (about 16 weeks), and resistance, when it appears, is marked, so that a second course of 6-MP is rarely effective.

d) **Azaserine:** This agent apparently interferes with purine synthesis, and adenine will prevent its
effects. Alone, it has a slight and inconstant action in acute leukemia, but when combined with the 6-substituted purines it may enhance their therapeutic action.

e) Other agents: The polyfunctional alkylating agents, as well as radioactive phosphorus and x-rays, can lower the leukocytic count in acute leukemia and destroy leukemic infiltrations. These agents do not produce hematologic remissions. They apparently depress the remaining normal bone marrow elements as well as the leukemic process, and their use may actually worsen the total picture. There is a contrast between the selective action of the adrenal steroids and anti-metabolites in favorable cases of acute leukemia, and their equally specific failure in other cases, as compared with the general suppressive action of the alkylating agents and radiation on both normal bone marrow and the cells of acute leukemia.

Adults.—Hematological remissions produced by chemotherapy in acute leukemia in adults is considerably less frequent than in children; in fact, the older the patient the less likely the response (15). The incidence of remissions produced by A-methopterin falls off rapidly after 10 years of age, the adrenal cortical hormones rarely produce remissions after the age of 40, and 6-mercaptopurine and related 6-substituted purines cause remissions in 10–15 per cent of the cases over the age of 40.

Even patients who respond to the initial treatment eventually develop resistance. Children responsive and then resistant to one agent still seem to retain their statistical chances of responding to one or more of the other agents.

The biochemical mechanisms responsible for resistance to therapy in initially responsive leukemias and for initial resistance to all forms of therapy in some previously untreated cases is unknown. Resistance appears to be inherent in the leukemic cells, since the cells survive while the host is developing toxic manifestations to conventional doses of the chemotherapeutic agent. The variety of responses seen in acute leukemia in children and adults to the various chemotherapeutic agents, and the alterations in the leukemic cell leading to resistance, are germane to the subject of this report.

It is assumed that the biochemical properties of leukemic cells can vary from patient to patient, and also that among the leukemic cell population mutations are a regular occurrence. In children, an effective agent will destroy or inhibit the proliferation of the susceptible leukemic cells. This interruption in the formation of leukemic cells permits the normal hematopoietic elements to regenerate.

While the dominant strain of leukemic cells is suppressed or destroyed in a satisfactory therapeutic situation, a resistant strain finally becomes manifest—a cell type which retains the virulence of the original leukemia and apparently differs mainly in its resistance to the therapeutic agent. This altered cell strain may or may not be susceptible to other classes of chemotherapeutic agents. In fact, a variety of leukemic cells may be described on the basis of their response to therapy. There are leukemias unresponsive to all available drugs; some which respond to cortisone alone, A-methopterin alone, or 6-mercaptopurine alone; some which respond to any two or three of these agents alone or in several combinations; and leukemias that are finally resistant to all of these agents. This suggests that a great number of biochemical variants to leukemic cells exist, as evidenced by their pattern of response and resistance to known chemotherapeutic agents.

Why are the adult leukemias less responsive to drugs than childhood leukemia? If the leukemic cells retain some metabolic patterns similar to normal stem cells, it would follow that drugs which inhibit the normal bone marrow may also selectively damage the more rapidly proliferating leukemic stem cells. Thus, 6-mercaptopurine and A-methopterin, depressants of normal bone marrow function, may selectively affect cells with qualitatively similar biochemical patterns. It is possible that in the child the leukemic cell may closely resemble the normal stem cell, functionally and biochemically. In older normal individuals spontaneous mutations may accumulate in the stem cells without necessarily impairing their function or survival. If one of these cells in an older person does become leukemic, it may be functioning by means of metabolic pathways not present in the normal cell and thus not susceptible to most conventional agents.

The mutation which leads to resistance in leukemic patients may occur rapidly, because so many leukemic cells are present and because they can so easily manifest themselves. A possible example of nests of leukemic cells mutating toward resistance to a drug is seen occasionally in patients with acute leukemia who have developed a complete hematologic remission on treatment. While the drug is continued and the bone marrow appears normal, small leukemic skin infiltrations or enlarged lymph nodes appear, suggesting that some of the cells in local foci of disease have mutated to produce independent colonies of resistant cells.

Do resistant cells differ qualitatively from normal cells in their metabolic pathways? Are resistant cells, by presumably developing metabolic sys-
tems not present in normal cells, now vulnerable to drugs which are not necessarily injurious to normal cells; in other words, can the development of resistance by the leukemic cell render it susceptible to drugs not toxic to the host?

**Chronic Myelocytic Leukemia**

This condition is due to the excessive production of granular leukocytes tending toward differentiation and maturity. It presents a considerably different picture from acute leukemia. The leukocyte count is markedly elevated, the spleen and sometimes the liver are enlarged, and there is general bone marrow stimulation. Lymphadenopathy is rarely present early in the disease. While a mild to moderate anemia is usually present, the platelet count is normal or elevated, and hemorrhagic phenomena are uncommon.

A number of agents, such as the polyfunctional alkylating agents, the antimetabolites 6-mercaptopurine and A-methopterin, urethan, potassium arsenite, colchicine analogs, and radioactive isotopes can suppress the manifestations of this disease. These drugs produce a fall in the leukocyte count, diminish the size of the enlarged liver and spleen, and the hemoglobin level rises to normal. Somewhat longer periods of improvement occur with the polyfunctional alkylating agents than with the antimetabolites. While the leukocyte may be brought down rapidly by the latter, relapse is often rapid when the drug is stopped. Also the normal bone marrow usually recovers more rapidly from A-methopterin or 6-mercaptopurine toxicity than from nitrogen mustard. The adrenal steroids have no beneficial action in chronic myelocytic leukemia.

The frequent development of almost qualitative resistance to treatment is not a conspicuous event in chronic myelocytic leukemia. As the disease progresses, usually over a period of 2–4 years, it gradually becomes less responsive to all agents, and the terminal event is often seen as an explosive exacerbation associated with an increased number of very immature cells. Some of these apparently terminal patients have shown a temporary response to 6-mercaptopurine, but the acute exacerbation of chronic myelocytic leukemia is possibly more refractory to treatment than acute leukemia in the adult.

Why does chronic myelocytic leukemia respond so readily to so many different drugs early in the disease? It seems likely that the differentiated leukocytes are reacting like normal ones. This may mean that these cells, which are being suppressed by treatment, are actually similar to normal cells and are being stimulated to proliferate by an underlying bone marrow disturbance. The high leukocyte count may be a secondary manifestation of the disease. As the disease progresses, the more primitive and resistant leukemic cells predominate.

**Hodgkin’s Disease**

This is a chronic disease which usually involves initially the lymph nodes, liver, and spleen. It is presumed that it is a neoplasm of the reticulo-endothelial system. The diseased nodes, however, usually show a vigorous cellular host response on microscopic examination, being infiltrated by lymphocytes, granulocytes, eosinophiles, and perhaps normal reticulum cells. Associated with the enlarged lymph nodes are frequent systemic manifestations, such as weakness, anorexia, fever, and itching, which suggest the presence of systemic toxic factors. The most effective drugs available are the polyfunctional alkylating agents. In favorable cases they produce, for varying periods of time, a decrease in size of the enlarged nodes, liver, and spleen, and a diminution in the systemic symptoms. The development of resistance is not related to the duration or frequency of treatment or to the type of the response obtained, but to the natural progression of the disease. In other words, the more rapidly progressive the disease, the brief the periods of improvement, and the more quickly the patient becomes refractory to treatment. What has been accomplished in this disease with nitrogen mustard? Are we modifying the basic disease or modifying the reaction of the host tissues to an underlying process? There is a little evidence that nitrogen mustard directly destroys the neoplastic cells in highly active disease. It is possible, however, as has been postulated in chronic myelocytic leukemia, that the normal tissue response is inhibited by nitrogen mustard, the enlarged nodes regress, and systemic symptoms disappear. Nitrogen mustard may stop the formation of noxious materials by the tumor; in any event, the rapid disappearance of the systemic manifestations of the disease is a common occurrence after nitrogen mustard therapy. While temporarily suppressing the manifestations of the disease, there is no evidence that the polyfunctional alkylating agents have substantially prolonged life.

Other drugs do not exert such a salutary action: the antimetabolites, adrenal steroids, and urethan are of little value, and only minor effects have been observed with colchicine or actinomycin C.

**Chronic Lymphatic Leukemia**

This disease is characterized by an elevated lymphocyte count, infiltration of the bone marrow,
liver, spleen, and lymph nodes, and, in many cases, a slow clinical course. The process may be favorably influenced by the polyfunctional alkylating agents and the adrenal steroids, and in some cases these agents have proved very effective and have temporarily eliminated all manifestations of the disease. In these cases the abnormal lymphocytes are even more sensitive than normal lymphocytes to the lympholytic drugs. Antimetabolites, such as 6-mercaptopurine, A-methopterin, and azaserine, have no useful effect in chronic lymphatic leukemia, and in some cases these drugs have apparently made the patient's condition worse.

The lymphocytes in chronic lymphatic leukemia may be extraordinarily long-lived, and the elevated lymphocyte count may represent a slow accumulation of long-lived cells (28). An alternate view is that, while cell turn-over may be rapid, new cells are constructed from large fragments of old ones, so that the metabolic blocks produced by available antimetabolites are ineffective. There is thus a striking difference between the response of chronic myelocytic and chronic lymphatic leukemia to drugs other than the polyfunctional alkylating agents.

Ultimately the lymphocytes become resistant to the alkylating agents and to cortisone, and these patients usually expire as a result of bone marrow replacement; complications include thrombocytopenia and bleeding, and increased susceptibility to infection.

Lymphosarcoma and Reticulum-Cell Sarcomas

These are localized tumors, and invasion of the bone marrow in adults is infrequent. Lymphosarcomas appear to consist almost entirely of neoplastic cells, but these cells in different patients show a wide range of response to polyfunctional alkylating agents, ranging from tumors which regress almost completely for long periods to highly resistant ones which continue to grow despite aggressive chemotherapy. The response to the adrenal steroids is also variable. We have observed patients apparently refractory to nitrogen mustard in whom the adrenal steroids produced rapid tumor regression. While the antimetabolites are only rarely and slightly effective in adults with lymphosarcoma, the disease in children often responds like acute leukemia, and marked temporary tumor regression may occur. Some of the same problems concerning the response of acute leukemia in children and adults to chemotherapy can be applied to lymphosarcoma in the different age groups.

Breast and Prostate Cancers

The principal methods for the control of disseminated breast and prostate cancers are the production of alterations in hormonal balance in the host. Approximately 50 per cent of breast and 80 per cent of prostatic cancer may respond to appropriate manipulations to reduce the level of stimulatory hormones sustaining the growth of the tumors. Breast cancers, in some instances, may respond satisfactorily to castration, to adrenalectomy, to hypophyseotomy, or to administration of androgens, estrogens, or adrenal cortical hormones. In some instances, breast cancer may be stimulated to grow by both androgens or estrogens, which suggests either that the tumor has lost its ability to discriminate between these steroids and responds to either one, or that the host, in some manner, converts the androgen to estrogen (34). Ultimately, breast cancer becomes resistant to alterations in the hormonal environment, although there is evidence that cancers that have been inhibited by testosterone and then recurred may show a second period of regression when testosterone is withdrawn. This may be one example of cells developing dependence on a previously inhibitory drug.

Prostatic cancers respond to castration or to estrogen administration, and, ordinarily, androgens will exacerbate the disease. Nevertheless, occasional patients are said to have improved on testosterone administration.

Some mammary cancers have also responded to the polyfunctional alkylating agents, presumably because of the general influence of these drugs on cellular growth. In our experience, however, probably not more than 10 per cent of the patients with far-advanced disease are temporarily benefited.

Miscellaneous Carcinomas and Sarcomas

The growth of these cancers is sometimes temporarily inhibited by the polyfunctional alkylating agents, and brief responses have been obtained regularly in carcinoma of the lung and ovary, and to a lesser extent in other cases. The antimetabolites, 6-MP, azaserine, and the 4-amino analogs of folic acid have not shown any consistent effect in carcinomas.

It is not feasible here to describe the many different clinical pictures produced by cancer and to analyze their response to available chemotherapeutic agents. The extent of the variety is all too apparent, and the effective drugs have different mechanisms of action and produce their effects on different components of the cancer complex in specific types of cancer. Increasing diversity con-
continues to be the result of the search for unity in the cause and treatment of cancer.

CONCLUSIONS
1. Cancers differ greatly in their appearance and biological behavior.
2. Cancer cells exhibit many normal activities, basic in terms of synthetic processes and mechanisms of cell division, and specialized in terms of retaining, to a greater or lesser degree, special functions and susceptibilities of their tissue of origin.
3. The available chemotherapeutic agents act on the basic or specialized functions of the cancer cell, which are qualitatively related to those of analogous normal cells. There is ample evidence of considerable differences in response among cancers to chemotherapeutic agents; for example, some breast cancers respond to hormonal control measures, and many acute leukemias of children respond to antimetabolites and to adrenal cortical hormones.
4. This diversity in therapeutic response is emphasized by the fact that some cancers fail to respond to agents effective in histologically related cancer and by the ability of cancer cells to develop resistance to a previously effective agent, without appreciable alteration in the virulence of the disease. This has been most clearly shown in acute leukemia in children.
5. It is possible that there is a qualitative common defect in all cancers which has not yet been discovered and which could provide the basis for the therapeutic response of all cancers to a single agent. This possibility has been neither proved nor disproved.
6. It is possible that the development of resistance of cancer cells to an antimetabolite may result in the appearance of metabolic pathways so distinctive from those in normal cells as to render the tumor cell susceptible to new types of chemotherapeutic agents not injurious to the host.

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Differences between Cancers in Terms of Therapeutic Responses

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