RECENT ADVANCES IN CANCER RESEARCH*

The Ludwig Kast Lecture

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IN 1913 H. G. Wells remarked, in *The New Machiavelli,* that to organize a laboratory expressly for cancer research was like issuing a license for a bath chair to scale the Himalaya Mountains. Yet already several such licenses had been issued; the laboratories were working valiantly; and now in 1946 the bath chairs are far up the slope of the mountains, and all about them, some in front, some behind, are other motley vehicles, not to speak of solitary climbers legging it along. The present is a good moment to speak of advances made.

Experimental cancer research is less than 50 years old, even younger than bacteriology; a few of the men who began it are still active. It got off to a start when the rewards of the close observational study of human cancer had become small. Then for the first time medical scientists paid attention to the fact that animals have tumors too—a fact previously known for some while. With the demonstration that these growths are true neoplasms and the maintenance of a few by transplantation, things got under way. At first hopes ran high that the cause of cancer would be found soon, but then it became clear that the transplanted tumors carried the secret along with them in host after host. Nothing could be procured from the tumor cells that would cause other growths, and anything killing them, in even the least disturbing of ways, brought the neoplastic process to an end. Furthermore, the transplanted tumors failed to call forth any resistance on which attempts at cure could be based in the human being; the new hosts reacted to the grafts merely as composed of tissue foreign to their bodies, not as tumor tissue. The cultivation of cancer cells *in vitro,* though occupying many workers, contributed no deep-going enlightenment, and until 1915, when tumors were purposely

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induced by means of tar, workers were unable to get at the conditions determining the occurrence of neoplasms. Until then, observations on the "precancerous states" of man had been the sole reliance of the investigator, since the spontaneous growths of animals had been too far along when first encountered to be informing. But now at last the conditions leading to cancer could be got at experimentally.

What are the recent advances? It will doubtless be agreed that when a fact or idea first attains recognition by scientists, this constitutes a recent advance though it may have been decades in the making. Perhaps the largest step forward of the last few years has been the very gradual comprehension, gained incidentally to the experimental production of tumors, that cancer is not a separate neoplastic entity, does not stand off by itself, but is merely one amongst the immense group of the true neoplasms, all these being expressions of a single general principle, the neoplastic principle as one might call it, however widely they differ in cellular make-up. To the practitioner this may seem an academic ruling; he knows but too well that every sort of tumor has its special characters, and even each growth an individuality of its own. For him the neoplasms cannot but be heterogenous diseases, and for the safety of his patients he must continue to look upon them as such. Until a little while ago experimenters did so too, and indeed when they first found themselves able to produce tumors they concentrated on getting cancers for study, disregarding almost entirely such other growths as happened to be elicited; they even applied the term "carcinogenic" to the agents which induce tumors, as if these gave rise to malignant epithelial tumors and no others—a usage which persists to this day. Now every investigator realizes that these agents call forth not only cancers but growths of all the main categories dealt with in the textbooks on human neoplasms. A single chemical carcinogen may elicit the whole diverse array, the precise kind of tumor which appears in a given experiment depending upon the kind of cells on which the agent is brought to bear. Not only this, but they call forth the leukemias as well, and almost insensibly these latter have come to be acknowledged as within the neoplastic fold. Every now and then leukemias have been encountered in animals, or elicited, consisting of cells which give rise to tumors if injected into the connective tissue instead of into the blood. The investigator who tackles the cancer problem really tackles the tumor problem as a whole, and he can hope by studying one growth to learn something about those of many sorts. From here on, in the course of this survey, the terms "cancer" and "tumor" will often be used interchangeably.

Long before the first neoplasm was induced in an animal physicians had good reason to be aware that there are agents in man's environment which cause him to have tumors. But nobody had any conception of how widely distributed these agents are, or of how insidiously they work in some instances, or what a great host of them there can be—for chemists are now synthesizing new ones all the time to learn how they act, and more will be encountered as unforeseen hazards of new industrial processes. In the last few years we have come to know them in bewildering variety. We literally spend our lives amidst them; the very sunlight gives rise to cancer, and the only reason any of us go free from the disease is because the action of most carcinogens is occasional or weak.

Two British workers, the Kennaways, have found on scrutinizing English statistics that cancers of the skin, mouth, throat, esophagus, and stomach, all the way to the pylorus, are more frequent the lower the social scale of the human individual. Evidently the skin of poor people is more liable to be injured in ways that bring on cancer than of people in easy circumstances, and what they eat and drink is in all probability more likely to contain carcinogens. The thought that we may take in such substances with our food is disturbing. Recently it has been discovered that rats fed 2-acetaminofluorene develop tumors after a while, here, there or yonder, at spots far distant from the digestive tract, and some of the azo dyes have proved capable of giving rise to cancers of the liver when they are fed to rats placed on special diets. One such substance has been used in the past to color butter. They are harmless when given with certain food stuffs, and many workers attach great significance to this fact, though others discount it, pointing out that the dyes cannot make the liver cancerous unless they reach this organ, and that they become so strongly adsorbed to certain food stuffs as to be carried intact through the intestine, while in other instances they are degraded and rendered harmless by the bacterial flora of the gut, a flora which differs with the character of its contents. However all this may be, the findings to the present, and the fact that certain hydrocarbons are carcinogenic, have together suggested the possibility that the eating of superheated fats, such as may be formed when frying is bungled, may be responsible, at least in part, for gastric cancer. The evidence on this point is still equivocal, despite much experimentation.

A far more difficult problem than the carcinogens round about us—since these can be warded off in proportion as we perceive them—is that of carcinogenic agents arising within the body. There are reasons to suppose that they often do so. Some years ago the fact was brought out that tar produced by heating human skin may induce skin cancers when painted on the backs of mice. Of course this does not justify the conclusion that the skin elaborates tar under natural conditions: one might almost as easily suppose that because the body contains hydrogen, oxygen, and nitrogen, it produces fuming nitric acid. But gradually, as new hydrocarbons capable of inducing tumors have been synthesized, it has become plain that some of them are nearly related chemically to substances normally present in the organism, methylcholanthrene for example, almost the most powerful of chemical carcinogens, having a close structural relationship to cholic acid. Also in the last few years the discovery has been made that extracts of some diseased human tissues are capable of producing tumors in animals. The Negro miners of the Bantu race in the Witwatersrand of South Africa nearly all have abnormal livers; hepatic cancers are frequent amongst them; and extracts of their livers are capable of causing sarcomas when injected into the subcutaneous tissue of mice, and of evoking both papillomas and epidermoid cancers when painted on the skin. It might be argued that the chemical procedures employed in obtaining the extracts have resulted in the production of substances not existing naturally; but control extracts made in the same way from the normal livers of Europeans have a carcinogenic action less frequently. Furthermore, Schabad, who did the first experiments of the sort described, produced sarcomas in mice by the injection of mere benzene extracts of cancerous human livers. The fact that some extracts of normal livers have a similar effect does not lessen the significance of Schabad's finding; for, as already stated, it is not the presence of a carcinogen but its presence in effective quantity which determines whether a tumor will arise. The recognition of endogeneous agents and conditions, developing within the organism and capable of causing tumors, is one of the pressing tasks of the day.

For some years it has been known that certain normal substances, namely hormones, may give rise to tumors when they act too forcefully, as when they are injected in quantity over long periods of time. They are not true carcinogens themselves, but are indirect in their influence, bringing about such pathological states in the tissues they affect, getting the cells into such a disordered condition, that some of them undergo neoplastic changes after a while for reasons unknown. Repeated injection into mice or rats of the estrogens, for example, may render the tissue of the mammary glands so abnormal that cancers eventually take origin from it, and not only may such growths be thus produced but uterine carcinomas also, and lymphosarcomas, leukemias, testicular and pituitary neoplasms and bone tumors. It has become plain of late that most of the hormones influence other organs in addition to those to which they are obviously dedicated, and nobody knows to what kinds of tumors they may not give rise next if administered in sufficient quantity.

There is an obverse to these findings. Reducing the action of hormones may mean the prevention of certain tumors. It seems possible that enough estrogens may be elaborated within the bodies of some supposedly normal women to bring about the mammary disturbances out of which cancers come. If this is the case steps can be taken to lessen or combat the influence of these substances and the growths thus be warded off.

For nearly 75 years doctors have been aware that many cancers arise where there is chronic disturbance of the tissues, at flexures of the intestine for example, and now the accumulated evidence warrants the conclusion that this is the rule for tumors in general, that they appear only where pathological changes have taken place. Yet mere chronic inflammation is not enough in itself to cause growths; if that were the case, epidermoid carcinomas would arise wherever lupus existed, and cancer would follow upon every leg ulcer present for years. Some special factor there is which precipitates the neoplastic change. Ordinary histological techniques have failed to disclose its character; they are bankrupt in this connection. But of late, new methods have been devised, notably that of Caspersson, a Swedish worker. He has utilized ultraviolet rays of special wavelengths to take photographs of microscopic sections of tissue, and has thus obtained detailed pictures which tell large new facts about the happenings in cells.

At the time when neoplastic changes first appear in response to a carcinogenic agent the tissue acted upon is in a hyperplastic state. But often the hyperplasia is secondary to injury—as for instance in skin injured with Roentgen rays; and certain workers, notably Haddow of the Royal Cancer Hospital in London, have concluded that the cells become neoplastic while they are faring badly and that the chemical carcinogens act through the depression of cellular activities that they bring about. The injection into animals of some of these substances causes transplanted tumors to grow more slowly, and knowing this fact a European surgeon, just before the War, actually painted operable human cancers of the skin with a powerful carcinogenic hydrocarbon, ignoring the danger that other growths might arise later on as a result of its action. He reported that the tumors disappeared, and in the present state of Europe the end-results of the treatment may never be known. Haddow himself has synthesized numerous hydrocarbons nearly related chemically to those of carcinogenic sort, hoping to obtain some which would check established tumors while giving rise to none on their own account. His results in animals encourage further work and he has now begun clinical trials on inoperable cases. Laboratory observations made in our own country during the War on the effects of the nitrogen mustards to retard cell activity have led to the utilization of such substances in the treatment of lymphoid tumors and leukemia in human beings. There cannot be too many well-reasoned efforts such as these.

What can the cause of tumors be, the actuating cause which keeps them going? One favorite idea went out the window during the first years of experimentation with carcinogenic agents, the idea that cells run amuck and form tumors because of a relaxation of some governing influence exerted by the organism, which had kept them in order previously and all doing what they should. On painting the skin of an animal at different places successively with a chemical carcinogen, it has been found no easier to induce a second tumor, or a third or a fourth, than the one which had arisen at the spot painted first; if the body really exercises a control this is as tight as ever. The conclusion that tumor cells are not mere ordinary cells which have seized an opportunity to go on the loose, but differ from them in some distinctive way—a way yet to be ascertained—underlies all the present-day searchings for chemical traits peculiar to cells in the neoplastic state. The hope that they may elaborate some specific antigenic substance and thus provide a serological test for the presence of a neoplasm goes back to the first years of immunology. Very recently a distinctive antigenic substance has been demonstrated to exist in the Brown-Pearce rabbit carcinoma; but further work has shown it to be peculiar to this neoplasm, quite different serologically from another antigen encountered in a second kind of epidermoid carcinoma of the rabbit. On the basis of these findings one might perhaps look forward to a galaxy of blood tests, each for some tumor of special sort, but not to a single test which would help in the generality of human instances, those in which the doctor wants to know whether there is any tumor at all in his patient, its precise nature coming afterwards. And even the possibility of special tests is problematic, since in rabbits carrying the tumors above mentioned the antibody formation essential to a serological reaction often fails to take place, although the tumors themselves regularly contain the specific antigen.

Most of the agents which are effective in producing tumors, the Roentgen ray and Bilharzia ova, to cite extreme examples, cannot possibly be the actuating causes of the growths. Their part is played when they have produced neoplastic change; the tumor flourishes on its own, just as a fire does which has been kindled in any one of a myriad ways. But the fact that certain hydrocarbons have proved capable of inducing tumors has led investigators to ask whether substances having similar effects may not be continually formed within cells after these become neoplastic, and maintain them in their abnormal state. Even if this is not the case a knowledge of precisely what the synthetic carcinogens do should prove broadly enlightening. Gifted chemists are now concerned with these possibilities, trying to learn whether there is not some radical or bond or configuration common to carcinogenic molecules which is responsible for their singular effect on the cell. The most widely different carcinogens may give rise to growths of identical sort.

Large opportunities for studies on tumor causation have been provided of late through a feat of the geneticists. By mating mice, brother to sister, year after year, for as many as fifty generations they have untangled the hereditary traits which exist interwoven in the ordinary animal. They are now in possession of breeds of mice consisting of individuals which are not only homogeneous, in that their normal tissues, and their tumors as well, can be transplanted from one to another as successfully as if transferred within the same organism, but which exhibit special characters that are ordinarily obscured by a mixed inheritance and hence find expression only now and then. Some of the pure-bred strains of mice have striking liabilities to spontaneous tumors of one sort or another, while others have equally remarkable freedoms from these growths. Nearly every animal of certain breeds may develop lung tumors, or liver tumors, or leukemia, or every ageing female may have mammary cancer, whereas in other strains such neoplasms never appear. And back of the primary tumor liabilities there may be secondary ones; an animal escaping the mammary carcinoma which kills most individuals of its strain may in all likelihood die of leukemia later.

What are the reasons for these differences? At first it was supposed that the various tendencies to tumors are hereditary, passed on through the chromosomes. For most of them this may indeed be true. But a worker in Holland and others at Bar Harbor, Maine, who studied crosses between mice of strains having marked and slight liabilities respectively to mammary cancer, found simultaneously that the tendency to such tumors is handed down through the mother. There followed startling discoveries by Bittner, one of the Bar Harbor group. He took young mice of strains highly liable to mammary cancer away from their mothers as soon as they were born; had them suckled by females of a strain with no such liability; and found that thus they were rescued from having mammary cancer in later life. By carrying out the experiment in the opposite direction the tendency to mammary cancer was conferred upon breeds not having it ordinarily. The tendency is passed along from one generation to the next by something in the mother's milk, the "milk factor" as it is now called. A single nursing just after birth is enough not only to establish the factor in the young female itself but in its descendants as well. And most important, whole races of mice can be rescued from having mammary cancer by preventing the milk factor from reaching the original mother of the race.

The factor does not produce its effect at once. It somehow reaches the mammary tissue from the gut, increases in quantity as the glands develop, and when the mouse grows old, one adenocarcinoma or several make their appearance in the breast tissue. This happens in practically every individual of some breeds. Yet nothing can be got from the mammary glands, or from the cancers, which will cause tumors directly on injection into other ageing individuals, only the milk factor, though this in great amount. Titrations have shown that one-millionth of a gram of mammary tissue yields enough of it, on extraction with salt solution, to confer the tendency to mammary cancer on an endless series of animals. A great deal has been found out about the factor in recent years and everything, its size, its physical character, its antigenicity, its continual increase in association with living tissue, its infectivity—for it sets up what must be regarded as a postnatal infection—all puts it in the category of the viruses save the fact that it does not induce disease directly. The most reasonable explanation for the way it works is that it is a harmless virus, thriving and increasing in the mammary tissue, and varying to become a tumor-producing virus when its cellular environment undergoes pathological alteration, as in the breasts of female mice which have grown old.

These discoveries have caused many surmises as concerns human cancers of the breast. One cannot doubt that within the human species there are hidden liabilities to tumors which find individual expression now and again, but statistics show that only very rarely is the layman's fear justified that there is "cancer in the family." Perhaps, on the analogy of inbred, pure-strain mice, brother to sister matings of human beings during a thousand years might bring out pronounced familial differences as concerns the incidence of tumors; but we can be thankful that, as matters stand, we are a mixed lot. A few workers with the milk factor have lately urged that new-born babies of human families in which mammary cancer has occurred should be taken away from their mothers before they have nursed at all, and be raised on the bottle; but this would be to subject such children to very real dangers because of fears that are ill-grounded in the generality of instances, as the statistical evidence proves.

A great deal of experimentation has been done to learn whether other tumor liabilities in mice besides the mammary are transferred through the milk, but the results have been negative save perhaps in the case of certain leukemias.

The existence of the milk factor has brought new support to the conception that tumors in general may be due to viruses. As is well known, many of the neoplasms occurring spontaneously in chickens yield such agents, with which growths of identical sorts can be produced. Most of the theoretical objections to viruses as the general cause for tumors have been done away with by this finding, but it has not lessened the practical ones. Despite persistent efforts during the last thirty years no viruses capable of directly causing neoplasms have been procured from rat or mouse tumors—the common currency of the laboratory—though a few out-of-the-way growths have yielded them. Lucké has demonstrated that an adenocarcinoma of the kidney which occurs often in the leopard frogs of American swamps is due to a virus, and the huge papillomatous growths frequently present on the skin of Western cottontail rabbits are also virus-induced, as Shope showed. The papillomas behave like true tumors at the brink of malignancy, and after they have grown for some months metastasizing squamous cell carcinomas often arise from them by secondary changes in their virus-infected cells. These cancers would never happen were it not for the action of the virus, and they appear so soon that the latter rates as the most powerful of known carcinogens for the rabbit. Yet nothing can be extracted from the cancers that will cause such growths, or even papillomas in other individuals; and it is possible that the virus does no more than start off a process with which, like the ordinary physical and chemical carcinogens, it has nothing further to do. The great majority of workers at the cancer problem see little in the idea that the generality of tumors are due to viruses, and recent experimental evidence, into which there is not time to go, speaks against the assumption that agents of this sort, passing from one individual to another, can be their cause. But decisive evidence in the matter may be available soon, for much can be expected of the new techniques for visibility now under development. Already Claude and Porter have obtained pictures of chicken tumor viruses within the cells of the sarcomas they induce, being enabled to do this because the cells spread out so thin in tissue culture as to permit photography with the electron microscope. In a few years at most it should be possible to search the cells of mammalian growths with the same instrument.

One might think that pathologists would now be possessed of a thorough knowledge of the natural history of tumors as result of the diligent observations made on human growths during the last hundred years; but the very definition of a tumor misses the mark, as proven by recent discoveries. The conception has long been axiomatic that a tumor is an autonomous new growth. But Huggins' demonstration that many prostatic cancers, including some which have metastasized, stand still for years or disappear after removal of the patients' testicles shows that even the cells of malignant growths, of cancers ordinarily fatal, are not always truly independent in their behavior. The cells of the prostatic cancers which behave in this way have been spurred on by the male sex hormone elaborated within the gonads and responsible for the normal activities of the prostatic epithelium. When, after orchidectomy, they are no longer thus urged, they cease to proliferate and sometimes they are actually incapable of maintaining themselves. By combatting the influence of testosterone with natural or synthetic estrogens similar results have been obtained.

The significance of this discovery far transcends its practical application; for it means that thought and endeavor in cancer research have been misdirected in consequence of the belief that tumor cells are anarchic. As every medical student knows, the extent to which these cells deviate from the normal varies from tumor to tumor over a wide range, and the greater the divergence the more likely is the growth to be malignant, by and large. It has been known too that the cells of nearly all cancers make some attempt at the customary tasks of normal elements of the same sort, perhaps forming gland-like structures, or making more or less successful attempts to differentiate like the stratified squamous epithelium from which they derived. But no one had realized that neoplastic cells making such attempts at differentiation might also respond in line of duty to normal physiological influences such as the hormones exert. How widely this principle finds expression in the behavior of tumors has yet to be learnt, and how successfully it can be utilized in repressing them. The course of events with prostatic cancer has seemed to justify the expectation that many mammary cancers would dwindle when the influence of the female sex hormone was lessened by removal of the ovaries or by injections of testosterone. The results with women have not been very promising thus far, but the paradoxical fact that cancers of the male breast yield to orchidectomy, or to stilbestrol, is encouraging; for it makes sharply plain the existence of critical factors which have yet to be understood and pressed into service.

A priori one might suppose that the prostatic cancers composed of cells which have lost all the morphological characters peculiar to the gland elements from which they come, which are wholly anaplastic in other words, would be those which would fail to respond to orchidectomy or to the neutralization of the influence of testosterone with estrogenic compounds; and this has turned out to be the case. But Huggins has shown that even the most anaplastic cells still elaborate acid phosphatase, a normal function of the prostatic epithelium. Evidently they are not lost to all good, and it may be possible to find ways experimentally to play upon what might be called their better impulses.

There are other instances in which the formation and the success of tumors is consequent on the stimulating influence of hormones. Certain testicular neoplasms of mice will not grow after transplantation unless the new hosts are injected with estrogen. A few years ago it was noted that uterine myomas develop in guinea pigs thus injected, and Lipschütz, working in Chile, has now demonstrated that testosterone will prevent the growths from appearing. Whether this has a practical bearing remains to be seen.

It is a curious fact that while hormones play a large role in tumor production and behavior little has been found as yet which the vitamins do. This is not for lack of tests with them.

The dependence of some tumors on hormonal influences for success justifies the inference that the change of a normal cell to a tumor cell does not necessarily mean that a growth will arise; and proof in the matter has been accumulating recently. Most of the tumors which appear on skin exposed to carcinogenic agents require favoring conditions if they are to grow, and the carcinogen itself provides these by setting up a chronic local inflammation productive of hyperplasia. After the carcinogenic applications are stopped many or all of the induced growths, including squamous cell carcinomas, may disappear rapidly as the local disturbance wears off. The course of those growths that progress and later prove highly malignant is often hesitant in the beginning. If the caloric intake of mice is cut down somewhat, so that the animals appear fit instead of fat, though slightly smaller than usual, the carcinogenic hydrocarbons induce relatively few tumors on their skin and these appear much later. This is not because the agents have failed to bring about neoplastic changes; for if the animals are full-fed later, tumors rapidly start forth although the carcinogen has not again been applied. The "spontaneous" pulmonary growths to which mice are liable can also be prevented from appearing by moderate restriction of the food intake. It would be worth while to know whether the incidence of cancer has fallen off in the starving populations of Europe. At the moment much work is under way to learn whether modifications of the diet which involve no caloric reduction will hinder tumor growth.

In proportion as a tumor continues to grow, cutting down the food is less effective in hindering it. This is in part because the best equipped cells tend to come to the fore as proliferation goes on, and in other part because secondary neoplastic changes, superimposed on the first and always for the worse, may render the tumor more aggressive. Often cancers seen in the clinic are the end result of a series of untoward happenings and have been "babied along" by this influence, or that circumstance. It is no accident that most of the precancerous states observed in man provide conditions notably favorable to cell proliferation. And yet most of the cancers seen by the surgeon are not doing all of which they are potentially capable, as witness the stimulating effect upon them later of trauma, necrosis, ulceration, bacterial infection. Ultimately however, some of them become superior to their circumstances; many cancers grow with exceeding swiftness in their final stages, though the patient wastes. Much has still to be found out concerning the adjuvant influences which make clinical cancers worse. Without doubt some of these influences can be excluded or combatted.

These facts lead on to a conclusion of large practical import, namely, that the cells of not a few malignant growths can be held in check, kept from dividing, if steps are taken while they are in the early, hesitant stage; and to hold them in check is, in effect, to prevent the cancers. The systematic examination with the microscope of human prostates has shown that carcinomas are frequently present in them which never cause trouble. Not only should a tumor be got at early because then it is small, but because then it is different, a far less capable threat intrinsically. Even the smallest details in the previous history of cancer patients, no matter how far back, may prove vital for other human beings, as giving hints about where the chain of events can be broken which leads on to the disease. Too much pains cannot be spent in eliciting such histories. There should be specialists in every cancer hospital whose duty and ambition it is to learn precisely how each patient's tumor has come about. For just beyond such knowledge lies prevention.

Numerous discoveries might be mentioned which perhaps have a greater claim to attention than those here dealt with; the years will show. But at the moment most of these have only the status of random facts, facts with no setting, what might be called knick-knacks of knowledge because how they fit into it is not yet clear. What is the meaning, for example, of the discovery made in France by Lacassagne that Roentgen rays applied in very small amount to the leg muscles of rabbits, at spots where a pyogenic infection has healed a year or two previously, often lead to the appearance of sarcomas? There is more here besides a hint to practitioners of radiology. And what of the finding that general anesthesia with urethane, lasting only a few hours, is followed by the rapid appearance of multiple lung tumors in mice of the breeds liable to occasional growths of the sort? And why should urethane, though provoking lung tumors in mice, actually hinder the course of human leukemia? Each of these well-attested observations means something, perhaps something large, but no one can say now what it is. Any new fact about cancer is worth while, and the growing heap of knick-knacks assuredly holds treasures. The authenticated advances themselves have been largely episodic in character. Yet there is a feature common to most of them which bodes well for the future; they are not the reward of random strivings but of intent and purposeful head-work. They give the physician good reason to look forward to the day when knowledge of cancer will come to be power.