even with existing machine programs is *not* being made, simply because available funds to pay for machine time are far too limited. Computing time is rather expensive, yet the amounts of time needed to make adequate use of existing and future machine programs would be trivially small compared with the amounts now being spent on nuclear and high-energy problems and on outer space.

References and Notes

1. See the reprinted 1913 papers with a valuable historical introduction and discussion by L. Rosenfeld (Munksgaard, Copenhagen, and W. A. Benjamin, New York, 1963).
2. In view of the fact that a set of orbitals which are only approximate can still correspond to a self-consistent field which is, however, like the orbitals, only *approximate*, many people (including my Chicago colleagues) commonly designate true exact (or almost exact) self-consistent-field orbitals by the name Hartree-Fock orbitals. In the case of atomic or molecular states with nonzero spin, there are additional complications.
3. A. C. Wahl, *Science* **151**, 961 (1966); W. M. Huo, *J. Chem. Phys.* **43**, 624 (1965).
4. To speak of the "valence-bond method" places the emphasis in chemical bonding on a few pairs of electrons holding atoms together in the Heitler-London manner, whereas actually the interactions of many of the other electrons often have very important effects on the stability of molecules.
5. Ø. Burrau, *Det. Kgl. Danske Vid. Selskab.* **7**, 1 (1927).
6. For some simple diatomic examples, see G. Das and A. C. Wahl, *J. Chem. Phys.* **44**, 87 (1966); G. Das, *ibid.* **46**, 1568 (1967).
7. Details and references are given in an article entitled "Molecular scientists and molecular science: some reminiscences" [*J. Chem. Phys.* **43**, S2–11 (1965)].
8. See the introduction to "Report on molecular orbital theory," *J. Chim. Phys.* **46**, 497 (1949) and references given there.
9. The major structural features of diatomic spectra are dominated by the existence of molecular vibrations and rotations, but the detailed structures depend on the interaction of molecular rotation with electronic orbital and spin angular momenta, and of the two latter with each other.
10. To be sure, often some (or even most) of them turn out to be mainly (or, in some cases, almost wholly) concentrated near particular atoms or groups of atoms.

10a. G. G. Hall and J. E. Lennard-Jones, *Proc. Roy. Soc. London* **205A**, 357 (1951) and other papers of the same series; J. E. Lennard-Jones, *J. Chem. Phys.* **20**, 1024 (1952).

11. F. Hund, *Z. Phys.* **73**, 1 (1931).
12. According to their original definition, valid for diatomic (or linear) molecules, π orbitals are twofold degenerate. That is, there are two varieties of π orbitals which (if real rather than complex orbitals are used) differ only by a 90° rotation around an axis of cylindrical symmetry. But in the case of double bonds, only one of these is used, and the other no longer exists as such but is mixed with σ orbitals. The "π" orbitals of double bonds and of aromatic molecules really ought to have a different name.
13. These figures have been borrowed from my 1965 Silliman Lectures at Yale.
14. Perhaps the first example of the LCAO type of description was its use by Pauling for H_2^+, which, however, can be considered as an example of the AO equally as well as of the MO method.
15. On the classification of molecular states, see *J. Chem. Phys.* **23**, 1997 (1955).
16. R. S. Mulliken, *J. Phys. Chem.* **6**, 2306 (1962).
17. ———, *Chem. Rev.* **41**, 201 (1947).
18. ——— and C. C. J. Roothaan, *Proc. Nat. Acad. Sci. U.S.* **45**, 394 (1959).
19. For a review of Slater's work, see R. S. Mulliken, in *Quantum Theory of Atoms, Molecules, and Solid State* (Academic Press, New York, 1966), pp. 5–13; also see J. C. Slater, *Int. J. Quantum Chem.* **1**, 37 (1967).
20. See R. S. Mulliken, *J. Chem. Phys.* **36**, 3428 (1962), Sec. II, 1–3; **43**, S39 (1965).
21. P. E. Cade and W. M. Huo, *ibid.* **45**, 1063 (1966); detailed papers to be submitted for publication shortly.
22. P. E. Cade, personal communication.
23. M. Cohen and A. Dalgarno, *Proc. Roy. Soc. London* **77**, 748 (1961).
24. R. S. Mulliken, *J. Chem. Phys.* **23**, 1833, 1841, 2338, 2343 (1955).
25. Up to now I have used mainly a different procedure [R. S. Mulliken, *J. Amer. Chem. Soc.* **74**, 811 (1952); *J. Chim. Phys.* **60**, 20 (1964)] with a wave function corresponding partly or largely to an electron configuration of MO's of the free donor and acceptor, but with some mixing in of a second configuration in which an electron has been transferred from the donor to the acceptor. For loose complexes the two procedures are roughly equivalent, but the whole-complex method is becoming advantageous now that all-electron SCF computations are becoming feasible for relatively large molecular systems.

The Challenge to Man of the Neoplastic Cell

Peyton Rous

Tumors destroy man in an unique and appalling way, as flesh of his own flesh, which has somehow been rendered proliferative, rampant, predatory, and ungovernable. They are the most concrete and formidable of human maladies, yet despite more than 70 years of experimental study they remain the least understood. This is the more remarkable because they can be evoked at will for scrutiny by any one of a myriad chemical and physical means which are left behind as the tumors grow. These had acted merely as *initiators*. Few situations are more exasperating to the inquirer than to watch a tiny nodule form on a rabbit's skin at a spot from which the chemical agent inducing it has long since been gone, and to follow the nodule as it grows, and only too often becomes a destructive, epidermal cancer. What can be the reason for these happenings?

Every tumor is made up of cells that have been so singularly changed as no longer to obey the fundamental law whereby the cellular constituents of an organism exist in harmony and act together to maintain it. Instead the changed cells multiply at its expense and inflict damage which can be mortal. We term the lawless cells neoplastic because they form new tissue, and the growth itself a neoplasm; but on looking into medical dictionaries, hoping for more information, we are told, in effect, that *neoplastic* means "of or pertaining to a neoplasm," and turning to *neoplasm* learn that it is "a growth which consists of neoplastic cells." Ignorance could scarcely be more stark.

The chemical and physical initiators are ordinarily called *carcinogens*; but this is a misleading term because they not only induce the malignant epithelial growths known as carcinomas but other neoplasms of widely various kinds. In the present paper the less-used term *oncogens* will be employed, meaning thereby capable of producing a tumor. It hews precisely to the fact.

Some may exclaim on reading what comes next that it consists mostly of truisms. This does not make these the less vital to my theme.

Tumors occur in vertebrates of so many kinds that it would not be surprising if neoplastic changes took place in them all. Normal cells of any sort capable of multiplying in response to ordinary stimuli are liable to become

The author is Member Emeritus of The Rockefeller University, New York. This article is the lecture he delivered in Stockholm, Sweden, 13 December 1966, when he received the Nobel Prize in physiology or medicine, a prize which he shared with Charles Huggins. Minor corrections and additions have been made by the author. The article is published here with the permission of the Nobel Foundation and will also be included in the complete volume of *Les Prix Nobel en 1966* as well as in the series, Nobel Lectures (in Enlgish), published by the Elsevier Publishing Company, Amsterdam and New York. Dr. Huggins' lecture appeared in the 26 May issue, page 1050.

neoplastic if acted upon by an initiator. It follows that the growths they form are almost incredibly multifarious, and this not only because of their widely various, cellular sources but because tumors of several kinds may derive from a single one. Nevertheless the changed cells are all alike in the basic respect that they disobey the law of organism. Obviously, what has to be understood is not the tumor but the neoplastic state of its cells. These are all animated by some principle exploiting their capabilities. In this respect the problem they present is a coherent entity.

The range in effectiveness of neoplastic changes in tumors is exceedingly great. Often the obvious alterations undergone by neoplastic cells are so slight that they look scarcely different from the normal and function in a similar way, retaining the task of storing fat for example. Yet even such cells, when forming tumors, possess an abnormal power to multiply, however slowly they divide. They are euphemistically termed "benign." The cells of some not only retain the normal ability to form hormones needed by the body but may produce these in such quantity as to disturb it greatly; and the hormones themselves are sometimes changed to a pathological extent.

In proportion as neoplastic cells diverge from the normal they ordinarily function less well. As time goes on their ability to multiply usually increases, and often they undergo such alterations in their state as to render them lawless and a threat to life. For the tumors they then produce we again use a humanistic term, "malignant." The changes for the worse undergone by the cells are not gradual but are the result of discontinuous steps according to their magnitude, sometimes several of them following one another at intervals; and they may take place in differing directions with result in heterogeneous growths. With each change in this *decensus averni*—"*progression*" as I've ventured to term it—the cells leave behind more of the specialized features which have distinguished them when normal, until at last they may have wholly lost all of their normal aspect, becoming so completely "anaplastic" that one cannot tell their source. As the consecutive changes go on they tend to lose their adherence to one another, and not infrequently they become a disorderly mob, penetrating the adjacent normal tissue in groups or individually, and destroying it. They frequently enter blood vessels or lymph channels and, coming loose within, are borne along on their fluid to lodge in distant organs and there form secondary tumors of the same sort, "metastases." Sometimes it's every cell for itself! Not infrequently a primary neoplastic change resulting in malignancy makes the affected cells so fatally ill that they would form no tumors did not their rate of division exceed that of their death. Here one is inclined to ask whether drastic neoplastic changes may not sometimes kill cells at once.

Many of the chemical and physical initiators already mentioned must be brought to bear for quite a time before their oncogenic effect becomes perceptible. Often those of different kinds, when applied successively, have cumulative action. Since neoplastic change manifests itself by tumor formation as a culminating event the assumption is generally made that it occurs abruptly; but facts speak decisively against this view. Epidermal carcinomas of the penis almost never occur if circumcision has been done at birth, whereas if delayed until adolescence in persons of the same race, penile cancers not infrequently arise when the man grows old, for no reason that is perceptible then. Evidently in these instances some initiating oncogen must have acted upon the epidermal cells prior to circumcision, though not sufficiently to bring about neoplastic changes at that time, but only what can be termed a *pre-neoplastic condition* which has persisted in the cells' descendants and has come to completion, or been brought to it at last by some imperceptible, initiating factor. Similar longtime culminating events have been observed in my laboratory during study of rabbit skin exposed many months previously to an initiating oncogen without any growth occurring in the interval.

Tests have shown that single, living cells, taken from notably vigorous tumors and transferred to other inbred animals of the same stock, will give rise to growths of the same sort; yet the traits of neoplastic cells cannot easily be discerned by studying them singly. When many are proliferating together in tumors though, much can be learnt about them.

An exceedingly important trait of most neoplastic cells is their unnatural excitability which sometimes renders them extremely active on what seems slight encouragement. Infection with inflammatory bacteria often has this effect. Indeed merely the healing of a hole a centimeter across, punched through a rabbit's ear that had been swabbed on its smooth, innner surface with an oncogenic tar some weeks before, may cause several tumors to start forth from the epidermal sheet which is extending in to close the hole, although elsewhere on the tarred ear none has arisen. Some of the growths thus elicited actually behave as if malignant, their cells invading and replacing those of the new connective tissue underlying them, and building up into what appears to be a genuine tumor. But this activity only lasts as long as they are exposed to reparative stimulation. When this ceases, on closure of the hole, the growths gradually disappear, leaving an epidermal layer which looks normal microscopically but is not, as shown by recurrence of the spurious malignancy when a new hole is punched inside the boundaries of the old. The hidden cells rendered neoplastic by the tar had not been altered one whit; they had been merely exploited by the stimulus of healing. Many initiating chemicals possess the power to act in a similar way on the cells that they have caused to undergo neoplastic change, but they do so only during the period of their application. *Promotion*, as Dr. Friedewald and I termed it, can have a great deal to do with the behavior of tumors.

Neoplastic cells never get well if they are self-assertive, meaning thereby capable of forming a tumor without any extraneous help such as promotion. The great majority are of this kind, as made plain by their success on transplantation. Those that have got worse by steps never retrace these. Were this not the case one would find at autopsy now and then residual nodules composed of cells to all appearance normal, marking the place where once there was a tumor. Neoplasms occasionally get smaller for one intercurrent reason or another, and often they are forced to disappear when subjected to strong irradiation. Yet in both instances the cells languish and die as the same neoplastic elements that they previously were. They never revert to the normal but are potentially immortal by way of their progeny if transferred to compatible new hosts before they have killed the old. Not a few rat and mouse tumors have been maintained in this way for study throughout more than 50 years.

A striking trait of actively multiplying, neoplastic cells is their ability to evoke from the adjacent tissue the blood vessels and structural support needed for the production and maintenance of the growths they are capable of forming. In proportion to the rate at which these latter enlarge, their demands of this sort become peremptory, unless indeed their cells have become capable of actively invading and replacing the normal tissue next to them, and hence are capable of "living off the country." One can perceive how crucial help of this kind is for most growths by scattering, amidst the subcutaneous tissue of a mouse, tiny fragments of a murine, mammary carcinoma, containing several mingled neoplastic components of widely differing capabilities. This can be done by rapidly injecting a suspension of the fragments in salt solution under the dorsal skin, together with sufficient air to split the underlying connective tissue horizontally, thus "plating out" the tiny bits of tissue on its broad expanse, much as bacteria are purposely scattered for colony formation on an expanse of nutritive agar. Many of the fragments thus implanted soon give rise to tumors because their cells call forth blood vessels and stroma swiftly from the tissue on which they lie, whereas others do no more than survive because their cells are devoid of these evocative powers. It is as if the normal tissue were acting as a school for iniquity and rapidly promoting its worst scholars.

However slowly neoplastic cells divide they must of course obtain additional food if they are to multiply; and however "benign" the growing tumors, their demands can be peremptory. During old times in China, when surgery was seldom done, benign tumors sometimes reached a prodigious size, whereas the body serving them emaciated because of their first claim upon its food. One can witness the same course of events after implanting a small piece of a benign, mouse tumor at a subcutaneous spot in another mouse, where it can grow big without damaging the adjacent tissue. The resulting growth gets huge while the body wastes.

With the sole exception of the tumor cells initiated and actuated by hormones and viruses—which have yet to be discussed—neoplastic cells neither give off any telltale substance indicative of their presence nor elicit any specific reaction from the body, whereby they can be certainly discerned, nor do they form any injurious substance characteristic of themselves, even while flourishing in great number or undergoing necrosis. True, the body often reacts against them while they are small, as it does against grafts of incompatible normal tissue, destroying them; yet so rarely do established tumors disappear that such happenings seem miraculous. The generality of them, while growing, do away so completely with the initial resistance the body offers to strange cells that even grafts from animals of alien species may succeed. Pig skin has been known to flourish when transplanted to the skin of volunteers having inoperable, lymphoid cancers.

Confronted with the dire challenge offered by neoplastic cells the physician does what he can. Fortunately he is sometimes aided now, and to a life-saving extent, through the discoveries of Dr. Huggins, an experimental oncologist though a practicing surgeon, who has shown that the existence of not a few cancers in the human body, namely those of the prostatic gland, are initiated, actuated, and promoted by hormones formed within the patient's body; and that many of them can be made to disappear by bringing a female sex hormone, or a closely related, chemical agent to bear upon them. Their cells, like those of other regressing neoplasms, never get well. They die.

The medical consultant who has found a tumor makes the tacit assumption, based on the experience of his innumerable predecessors, that the presence of this growth does not ordinarily imply any significant liability in the same individual to others of differing sorts, unless indeed his patient has tissues ultrasensitive to initiating agents through inheritance, as in the case of those unfortunates who are albinos or who are subject to intestinal popyposis, both of which render the affected tissues abnormally susceptible to oncogenic changes. The physician's attitude in this relation signifies how dependent most neoplastic changes are on intercurrent, episodic initiation.

What can be the nature of the generality of neoplastic changes, the reasons for their persistence, their irreversibility, and the discontinuous, step-like alterations that they frequently undergo? A favorite explanation has been that oncogens cause alterations in the genes of the ordinary cells of the body, as distinct from the generative, somatic mutations as these are termed. But numerous facts, when taken together, decisively exclude this supposition (*1*).

The number of viruses realized to cause disease has become great during the last half century, but relatively few have any connection with the production of neoplasms. Yet it should be said at once that what these few have been found to do has surpassed imagination.

Two Danes, Ellermann and Bang, reported the first tumor virus in 1908 (*2*). It caused leukemia in chickens, and they made six successive passages of it from fowl to fowl, producing the same disease each time. They studied it until 1923, meanwhile reporting upon a second virus causing a chicken leukemia of a differing sort. Yet though their work was convincing it was written off because the leukemias were not then realized to be neoplastic diseases; nor indeed did this happen until after 1930.

In 1910 I described a malignant, chicken sarcoma which could be propagated by transplanting its cells, these multiplying in their new hosts and forming tumors of the same sort. In other ways the growth showed itself to be a neoplasm of classical type yet, as reported in 1911, its cells yielded a causative virus. Numerous workers had already tried to get extraneous causes from transplanted mouse and rat tumors, but the transferred cells had held their secret close. Hence the findings with the sarcoma were met with downright disbelief, though soon several other, morphologically different, "spontaneous," chicken tumors were propagated by transplantation, and from each a virus was got causing growths of precisely its kind. Not until after some 15 years of disputation amongst oncologists were the findings with chickens deemed valid, and then the growths were relegated to a category distinct from that of mammals because from these no viruses could be obtained. Only in 1925, through the efforts of a British worker, W. E. Gye, was much attention given them by scientists.

The virus causing the chicken sarcoma studied first, now generally termed the RSV, has been maintained for more than 55 years and it is still busily investigated in many countries. Throughout most of this time it would engender growths only in chickens and closely related fowls; but of late several extraneous, non-neoplastic viruses have become associated with it, during its passage in unusual avian hosts and through their action as adjuvants its scope has been so enlarged that now not a few mammals, including monkeys,

have been found to develop tumors as result of inoculation with it.

After working out the complex relationships existing between the original RSV, the cells it affects, and their hosts, I tried for several years to get causative viruses from the transplantable tumors of rodents, but with the same failure as previous investigators, and hence I quit the neoplastic problem for others in pathology yielding positive results. Not for years did a virus opportunity come my way again. But in 1933 Richard Shope of the Rockefeller Institute (a worker already renowned for discovering animal diseases with human implications) reported on a virus causing the giant warts often present on the skin of wild "cottontail" rabbits in the southwestern U.S.A. This virus, on inoculation, proved effective only in rabbits; and it produced far more vigorous warts on animals of domestic breeds than on its native host, the cottontail. When describing the growths of both species Shope remarked that they might be true tumors. He knew of my fruitless search for a mammalian tumor virus, and he and I had long been friends. Hence he asked me to determine the character of the warts, asserting that he knew nothing about tumors and already had more than he could do, what with possessing four new viruses responsible for animal diseases of other sorts. Thus it came about that I experimented as his deputy throughout many later years. Now and again he reported on the peculiarities of the papilloma virus as such, but never did he concern himself with its relationship to tumors until after the work in my laboratory had come to a close. He died—and of cancer—less than a year ago. One of his last papers, written while ill, ranks as a classic (*3*). It is concerned with "the many sly and devious ways that viruses may behave in causing tumors"; and he stressed, as example, an extraordinary finding reported by him early, namely that the papilloma virus can rarely be recovered from the prodigiously active growths it yields in domestic rabbits, although immunological tests show it to be present and it can regularly be got in quantity from those of cottontails.

Experimentation carried out in my laboratory, together with Beard, Kidd, Friedewald, and MacKenzie, showed the "warts" produced by the virus to be genuine tumors, benign epidermal papillomas in which the virus persists although eliciting an antibody capable of neutralizing it on direct exposure. The same anomalous state of affairs had previously been found to exist in chickens carrying the first tumor that had yielded a virus, and collateral experiments had disclosed the fact that the phagocytic cells of normal blood can protect ingested bacteria from antibodies present in the surrounding medium as long as they themselves remain alive, and will even shield ingested red cells of a foreign species from a markedly hemolytic serum. Later work with Hudack and McMaster showed that rabbit fibroblasts separated from one another with trypsin, and placed in a suspension containing vaccina virus would, on becoming infected with this, protect it from a strong antibody placed in the surrounding fluid, but only while they were living.

These findings enable one to understand why the Shope papilloma virus flourishes in the proliferating cells of cottontail growths despite the strong antibody that it engenders, and why it never causes the adjacent normal cells to become neoplastic but instead produces tumors which grow by intrinsic cell multiplication, *aus sich heraus,* to use the German phrase, as do the neoplasms of unknown cause.

After some months carcinomas arose from most of the actively proliferating virus papillomas of both cottontail and domestic rabbits, owing to further changes in their cells which resembled those that take place now and again in benign papillomas initiated in rabbits by chemical agents and actuated in some way unknown. Yet the two changes were unlike in certain distinctive, cytological respects; and when the papilloma virus was injected into the blood stream of domestic rabbits carrying papillomas due to chemical initiation it localized in these and urged them on, rendering them much more vigorous, and altering the cells of some in such wise that they became mongrel growths exhibiting merged features referable to both agents. It also rendered others carcinomatous forthwith. Furthermore when fragments of the epidermal carcinomas, arising from papillomas induced by oncogenic hydrocarbons in cottontail rabbits, were exposed to the Shope virus *in vitro* and reimplanted in the animals from which they had just been procured, their cells, on proliferating anew, exhibited the mongrel aspect indicative of viral influence, and their malignancy was also greatly enhanced.

Later tests showed that after the brief application of a powerfully oncogenic hydrocarbon to the lightly scarified skin of domestic rabbits, into which the papilloma virus had just been rubbed, the "warts" that arose looked and behaved like those induced as controls elsewhere on the same scarified skin; and yet they underwent carcinomatous changes much sooner than these latter did. The inference seemed justified that the hydrocarbon had acted on the same cellular mechanism as the papilloma virus.

Some of the carcinomas arising from the papillomas of domestic rabbits were serially transplanted, and one that soon became anaplastic and exceedingly malignant has now been maintained for 28 years by transfer from rabbit to rabbit. Never has it yielded a virus of any sort, and tests of the blood of its early, successive hosts showed that the antigen inducing an antibody against the papilloma virus was gradually disappearing. Now it has been gone for many years. This cancer, known as the V2, is studied in many laboratories today because, like the generality of those in mammals, that are due to other causes, it yields no sign of what actuates it. Obviously the Shope virus had been merely an initiator when producing the V2, though some antigenic remnant of it had persisted for a while. In this relation a remarkable recent discovery by the Kleins of the Royal Caroline Institute of Sweden deserves mention, namely that certain polycyclic hydrocarbons initiating mouse tumors put a specific, antigenic mark on these growths, which persists despite their repeated transplantation.

Nature sometimes seems possessed of a sardonic humor. In the 1930's a group of American geneticists, long concerned with the incidence of "spontaneous" tumors in rodents, undertook to determine how a pronounced liability of female mice of certain strains to develop mammary carcinomas as they grow old is inherited; and through breeding tests they came upon the astounding fact that this liability reaches the young from their mothers. How could this be? Was it passed on through the ovum, the placenta, or what? A member of their group soon afterwards made a revealing test. He arranged for some of the young of the strain under study to be suckled from birth by mice of a breed in which the cancers did not occur; and the mice thus wet-nursed never had any! His later work showed that the liability to these cancers had been due to a virus passed on to the

young in their very first milk. This virus lay latent within them until they matured, and then it caused orderly, benign tumors in the breasts of females; and from these growths carcinomas derived by step-like changes like those described some pages back. To this day no virus directly responsible for the cancers has been got from these, but only the "milk virus" producing the benign growths. The problem of the actuating cause of the cancers remains unsolved like that of the V2 carcinoma of rabbits (see *4*). In both instances the virus causing the benign tumor has been no more than an initiator of the malignant growths deriving from them.

In 1953 Gross (*5*) discovered a neoplastic virus that has greatly widened knowledge. He obtained it from a carcinoma arising spontaneously in the parotid gland of a mouse, and on inoculation into other mice it proved capable of producing tumors of more than 20 kinds, and some in rats, rabbits, guinea pigs, hamsters, and ferrets as well. Because of these widely various neoplastic effects it has been aptly termed the polyoma virus. The growths it induces can be maintained indefinitely by transplantation, and nearly always the virus disappears from them as time goes on; yet the activity of the tumor does not lessen. Obviously in such instances its role is no more than that of an initiator, comparable in such respect to the chemical and physical oncogens. Very occasionally though, it is an actuating agent as well, persisting and multiplying in a parotid cancer like the one originally providing it; and from this favorable growth it can be recovered anew and started again on its polyomatous career. Under natural conditions the virus maintains itself as an infectious agent widely prevalent in mice, but causing only a trivial, scarcely perceptible illness of non-neoplastic sort, save in those rare instances in which it produces a neoplasm.

No virus has as yet been found that indubitably actuates tumors in man. Yet this is not to say that viruses play no part in initiating them occasionally. Now and again a human cancer arises where a virus has persistently wreaked other cellular injury. The virus causing "fever blisters" repeatedly next to the mouths of persons notably susceptible to its action provides an instance in point, cancer sometimes arising after a while from the epidermal tissue long kept in a disturbed state. One sees the same course of events occasionally on skin where the severe virus causing herpes zoster ("shingles") has left tissue permanently damaged. Yet these instances tell no more, as concerns causation, than do the cancers that now and then arise on the skin of old people where this was burned in youth. Sunlight provides yet other examples, cancer arising from skin that it has kept inflamed instead of tanned. In all these instances the tumors have been merely initiated. No virus actuating any of them has been found.

Of late many gifted investigators have sought new neoplastic viruses with the aid of technics recently devised, and not a few have been disclosed in rodents. Certain adenoviruses of man fail to cause any tumors in their human hosts, yet do this in small mammals to which they are foreign. Some viruses of both chickens and mammals, which cause no tumors when acting alone, do it when they are inoculated together. The possibilities in both these directions are boundless, opening vistas of complexity. Yet they will not be dealt with today because a far greater problem presses, namely that of man's mortality from cancer. About one person in six is now killed by neoplastic cells. Can nothing be done to combat them?

During the present century we have learnt enough to undertake this task. First there was the observation that the tumors of mammals closely resemble our own. Then they were maintained by transplantation for study. Next came the realization that what one discovers by experimenting with rodent tumors throws light on what happens in man. And then in 1918 came the epoch-making discovery by Yamigiwa and Ichikawa that tarring rabbit skin will cause tumors to arise. This opened an era of rewarding search for other chemical agents—and physical as well—which are oncogenic. It is an era so far from done as to have been the main theme a few months ago of the International Cancer Congress held in Japan, a theme chosen with urgent reason since some of man's habits, many of the occupations through which he earns his living, and the mischances taking place in his own body can prove fatal through the growths they induce unless something is done to ward them off. All such oncogens are initiating in character, and some can be dangerous promoters too, if the exposure to them is long. The wider and closer one looks the more clearly does one see that chemical and physical agents start off nearly all human tumors, and that these latter are occupational diseases resulting from the exceedingly hazardous occupation of living out a life in this world. Despite strong admonitions and active preventive steps—many are now taken in civilized lands—deaths from cancer have not as yet been markedly lessened.

What can be the character of the alterations which render a cell and its progeny permanently neoplastic, and so self-assertive in behavior as to kill? On these matters we have only the meager information provided by the neoplastic viruses of animals. Innumerable attempts have been made to obtain evidence of the action of similar agents in human tumors, and recently to discern them with the electron microscope. Yet such attempts have drawn blanks save in a few highly dubious instances.

In the enormity of our ignorance we have now resorted to "try-and-see" tactics on a large scale, attempting to destroy the tumors of animals, because of what success with these may mean for man. In all the larger, civilized countries efforts with this aim are made, and they are amply supported, in some instances, with governmental funds. Already more than half a million chemicals and materials of biological origin have been tested in the U.S. Several institutions exist for this special purpose, and there is much cooperation by manufacturing concerns. The most encouraging results thus far have been those provided by Dr. Huggins, whose rescues of patients with prostatic cancer have been prodigious. The leukemias of children have been overcome by chemotherapy in some instances, and the singular, highly malignant lymphomas occurring in African children and known as Burkitt's disease. Yet the successes have been episodic thus far. Save in the case of the relatively small, though slowly increasing, number of viruses, no inkling has been obtained of what happens when a cell becomes neoplastic, nor of how its power is passed on when it divides. Man must and *will* find out.

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