THE CHALLENGE OF CANCER

A RESEARCH STORY THAT INVOLVES THE SECRET OF LIFE ITSELF
THE CHALLENGE OF CANCER

by LESTER GRANT

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FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

1950
CONCURRENTLY WITH THIS PUBLICATION, a documentary film, entitled “Challenge: Science Against Cancer,” has been produced by official agencies of Canada and the United States. The booklet and the movie complement each other in telling the story of cancer research—what it means, what it has accomplished and what direction it is taking. It is hoped that this dual presentation will enlighten the people of both countries as to the intricacies of the cancer research problem, and present a challenge to students interested in science and be helpful to those planning scientific careers.

The movie, sponsored by the National Cancer Institute, Public Health Service, Federal Security Agency, U. S. A., and the Department of Health and Welfare of Canada, was produced by National Film Board of Canada and Medical Film Institute of the Association of American Medical Colleges.
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ACKNOWLEDGMENT

THE AUTHOR WISHES to express his appreciation for the assistance he was given in preparing this series of articles by many of the nation's cancer researchers, including experts attached to the American Cancer Society and particularly by the scientists working at the National Cancer Institute in Bethesda, Md. Without the good wishes, wise counseling and exceptional objectivity of scientists and other staff members at the National Cancer Institute, the author would have found it virtually impossible to proceed systematically to an examination of much of the material covered by this report.

LESTER GRANT.
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A story was current recently about a man living in New York, who, on retiring at night, slept between two black sheets. He heard somewhere that cancer is caused by “emanations”—presumably some form of radiation—from the ground. The black sheets, it seems, would protect him in his sleeping hours.

Even to a layman unfamiliar with technical aspects of cancer, such a preventive measure against the disease sounds silly. And it is.

But it is no sillier than many other beliefs about cancer, beliefs compounded of quackery and ignorance, leaving the patient a prey to charlatans.

Cancer is indeed a mysterious process and one hardly dares
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generalize about it, so abundant are the exceptions to almost any rule that could be set down as sound doctrine.

For example, the following statement may be made about the disease: Cancer is incurable. Yet this can immediately be contradicted: Cancer is one of the most curable of all diseases.

Each statement is correct. The paradox is resolved very simply. Certain types of cancer, detected in time, are cured by surgery and radiation. In such cases the curability rate is high. Cancer is cured every day, cured simply, easily, quite painlessly. On the other hand, about 180,000 persons in the United States died of cancer last year and the number will probably mount this year and for the next several years unless methods are found to manage satisfactorily certain types of cancer in advanced stages, or to develop better detection to uncover the disease in early stages.

This would be particularly important in such a type as cancer of the stomach, which frequently does not betray its presence until it has a strangle-hold on vital organs.

Here is another paradox: The cancer process is often equated with the aging process, most cancer in man appearing after the age of 40. The aging process is a gradual and apparently inevitable process of disorganization and disintegration. Yet the disorganized cells known as cancer resemble, in many respects, youthful, embryonic tissue, rather than cells that are old.

One can make another paradoxical set of observations about the disease. One can say this:

In view of the fact that there is such a difference of opinion, even among the experts, about cancer, about the basic mechanism which sets off the process, this is presumptive evidence that little is known about the disease.

The statement is true and can be contradicted immediately as follows:

Probably more is known about cancer than any other disease which plagues man. This is also true.
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The reason for this seeming contradiction lies in the fact that when one gets down to the basic mechanism of disease processes, little is known about any disease.

Pneumonia is cured by penicillin, but scientists do not know how this comes about. Diabetes is managed by insulin, but the exact mechanism—the basic chemistry of this matter—is still one of nature's closely guarded secrets. Liver extract counteracts pernicious anemia, but if you ask a hematologist just how this is brought about, you will get an unsatisfactory answer.

This raises an important point about cancer research. It is this: The fact that the basic problem of growth—any kind of growth, normal or abnormal—is not understood certainly has delayed progress in the conquest of cancer, but it does not mean that the search for chemical agents against the disease is a hopeless one.

The layman often asks these questions: Why is cancer such a difficult disease to understand? What bogs down the scientist when he searches for treatment for it? These are questions which this booklet will attempt to answer. The answers will indicate that the difficulties in cancer research are staggering.

Yet there are other aspects to the problem, and much more hopeful ones, which it would be foolish to ignore.

For example, 15 years ago three forms of treatment for certain types of cancer—sex hormones, nitrogen mustard, and antifolic acid compounds, so called—were either unknown or not yet ready for widespread use.

Today all of these agents are used, with varying degrees of success, in the temporary control of certain forms of cancer, although it is true that they cannot be classified as cures. That there is disagreement among doctors about the value of these drugs, in special cases, is beside the point.

The fact is that 15 years ago the chemical control of cancer was still classified, in many circles, as an outlandish dream.
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It is not yet an accomplished fact, in the sense that one can take a pill with a guarantee that a tumor will vanish.

But there is good evidence that science is getting closer to it, getting closer to it without even understanding what cancer is. That is the most comforting paradox of all.

Cancer appears to be rising as a cause of death in America, due at least in part to the fact that people are living longer and cancer strikes mainly in age groups past 40.

On a purely relative basis, cancer jumped from eighth place to second in the mortality tables in the first 35 years of this century, as other diseases, such as pneumonia and certain common infections, succumbed to the skill of the research worker.

More than 200,000 Americans are expected to die of cancer this year. If recent trends continue, the annual death toll from cancer will double within the next 50 years.

Cancer, now the second cause of death in the United States, accounted for 13.5 percent of all deaths in 1946. This is in striking contrast to the situation a few decades ago. In 1900 cancer and other tumors accounted for only 3.7 percent of deaths reported nationally.

These statistics make a grim picture, but there are bright spots, too.

Recently the Metropolitan Life Insurance Co. reported that the death rate (as against the numbers dying) from cancer among women in 1947 continued the decline that has been in progress almost without interruption for the last 15 years.

The trend was viewed by statisticians as largely the result of the campaign of public education through which women have become more alert to early danger signals and have sought medical care earlier, when the chances of cure are more favorable.

That the American Cancer Society has played some role in this declining death rate, there can be no doubt. It would
The Paradox

appear that the society's effort is about to be intensified, rather than slackened, for the American Cancer Society and the National Cancer Institute, of the United States Public Health Service, have teamed up to teach women the basic facts about breast cancer.

The Metropolitan study of cancer mortality among women policyholders shows that every age group between 25 and 74 shared almost equally in the improvement in recent years, with the death rates at ages 35 to 64 now at the lowest level on record.

Evidence of the improvement in the cancer situation is also shown in reports of higher survival rates for cancer patients. In Connecticut, for example, the number of women who survived for at least 5 years increased from 25 percent for those treated in 1935, to 40 percent for those first treated in 1941.

The detection clinics, such as the Strang Clinic at Memorial Hospital, which was one of the first such clinics but is now only one of several in New York, also have played a major role in this aspect of the problem.

Unfortunately, the gains cited among women are not matched by gains among men and, in any event, the problem is still quite a serious one. More people are dying of cancer with the succeeding years, although the mortality rate may drop here and there.

This promises to continue for quite a while unless an accepted and highly effective chemical treatment for several forms of cancer is discovered.
2. The Problem:
To Understand Why One Animal Will Contract the Disease, Another Sidestep It

Cancer is one of the oldest diseases in the animal and plant kingdom.

It is neither a disease of man only, nor, in the broadest sense, of civilization only, although it has been shown that countries having high general death rates tend to have low specific rates for cancer, whereas countries having low general death rates have high cancer rates. It has been noted that a low general death rate is the result of such factors as high per capita wealth, high literacy rate, superior living standards with emphasis on nutrition, and high indices of medical practice.

Thus in countries with low general death rates, it becomes the happy custom to live on to 40 years and beyond, “then to die of the only things left to die from—cancer and heart disease.”

The Algire transparent chamber is shown above. The skin fold between the plates of plastic contains a growing tumor. Thus, cancer inside a living mouse can be studied under the microscope.
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The Java man had a bone tumor. Cancer is found in primitive peoples. Cancer is common in animals, tame and wild, in mice, cats, dogs, guinea pigs, rabbits, and horses, in sheep and goats, in frogs, fish, and birds, and in oysters, too.

It is a universal disease of vertebrate animals, particularly of the older members of the species; thus it is more common in domestic pets, which are kept alive beyond their natural span, than in farm animals, which are destroyed when their working life is over.

As far as is known, cancer is not due to any particular diet, but the nutritional aspects of cancer are just coming within man’s ken and there is evidence of a correlation between obesity and cancer.

Cancer appears most often after the age of 40 but no age is immune and it has been observed in new-born babies. Cancer occurs with equal frequency in vegetarian races, in meat eaters and in fish eaters. It is found in the herbivorous cow, the carnivorous tiger, the omnivorous pig.

Yet with all the mass of evidence about cancer, with the numerous agents available to produce it experimentally in animals so that the disease can be studied visually and chemically, it is an elusive foe.

It is possible, for example, to take a tiny bit of cancer and allow it to grow to a mass weighing perhaps seven grams in the body of an inoculated animal. This animal can then be killed, the seven grams of cancerous tissue cut into a hundred small bits and each of these may be inoculated into an animal from the same inbred strain.

Within 2 to 4 weeks, each of these 100 animals will have a cancerous mass weighing 7 grams. The original 7 grams of cancer tissue will thus have become 700 grams. Repeating the process, by the end of the next month the investigator would have 700 times 700 or 490,000 grams.

This gives the investigator a fine experimental tool and indeed, in this regard the man working in the cancer field is
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much better off than the man investigating a variety of other diseases, for example, multiple sclerosis, where the problem of producing the disease in lower animal forms seems to be much more formidable.

If this is so, one wonders, then, why it is not possible simply to induce cancer in an animal, say a dog, mouse, or guinea pig, study its development, subject it to chemical and other biological tests, smash it up, take it apart, filter it, put it under a powerful microscope, vary the conditions under which it will grow, add vitamins and proteins and other substances, and finally, walk into a meeting of experts and announce: "Gentlemen, here is the basic mechanism in this process."

Much has been learned by doing this sort of thing, but no one has found that mechanism. If the reader is confounded by such a state of affairs, some light may be shed on the reasons why the job is so difficult in the part of this booklet dealing with proteins and enzymes.

For the moment, and in much more general sense, here are a few ways to look at the problem:

Dr. Harry S. N. Greene, a Yale pathologist, has a viewpoint which boils down to this: Cancer is a problem involving a tumor-host relationship. What will produce cancer in one animal will not produce it in another.

He asks a penetrating question: How is it possible to transplant a certain type of tumor into, say, a Havana rabbit, with the tumor behaving like a cancer in the Havana rabbit, yet not possible to get the same cancerous growth by transplant into a closely related animal, a Himalayan rabbit? The transplant will "take" in the Himalayan rabbit, but it will grow only a short time and then will regress.

Moreover, Dr. Greene argues, autopsies may show that the body contains growths which appear to be quite similar to cancer—a point which would be disputed by many scientists—but which, for unknown reasons, do not develop into
cancer in most cases. Therefore, if the argument is sound, certain persons must have certain constitutional defenses against the disease and other persons lack these defenses.

If this is so, then the problem is to try to understand cancer not in terms of chemical generalizations about the disease or hard-and-fast doctrine about cancer-causing substances but in terms of the essential ingredients, whatever they may be, of one animal's constitutional ability to acquire cancer and another's physiological agility to sidestep it.

There is another way to look at the problem: For years chemists have been fascinated by the structural similarity among certain naturally occurring chemicals in the body and certain tar derivatives which are cancer-causing. Without going into the high-powered organic chemistry necessary to develop the argument, one can say that there is a rough similarity among cholesterol, a chemical found in the bile; the male and female sex hormones, and methylcholanthrene, a cancer-causing agent. The question is: Does the body, say, under certain disturbed conditions, convert its own products into cancer-causing agents? The theory is a plausible one, but the evidence is pretty thin.

There is another way, at a somewhat different level, to look at this problem:

Cancer is a series of diseases, each having something in common (i. e., loss of the cell's ability to run a normal life cycle) but each differing in perhaps some fundamental way. The fact that one type of chemical treatment is not effective for several types of cancer would indicate this. (There is no known or generally accepted chemical cure for cancer, but certain chemicals seem to have the power to abate the disease temporarily.)

If it is true that cancer is a variety of diseases, then it can almost be assumed that there never will be a single cure for all types of cancer. This is why it is probably silly to talk about a future "cure for cancer" in the same sense that one
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talks about a cure for, say, pneumonia (which has been brought under control by the sulfa drugs and penicillin). Therefore a discussion of cancer should be a discussion of "the cancers," although in this simplified review such distinctions usually will not be made.
3. The Control:
Surgery and Irradiation in Early Stages Found Successful Treatment

The danger signals of cancer are the danger signals of many other conditions. At the same time, they can be signals which have no special significance.

In general, these danger signals are listed as follows:

1. Any sore that does not heal—particularly about the tongue.
2. A painless lump or thickening, especially in the breast, lip, or tongue.
3. Irregular bleeding or discharge from any natural body opening.
4. Progressive change in the color or size of a wart, mole, or birthmark.

Highly magnified normal connective tissue cells in a healing wound (drawing on the left) can be compared with cancer cells from a connective tissue tumor. The nuclei of cancer cells on the right are larger, rounder, and less uniform, and the tissue pattern is disorganized.
5. Persistent indigestion.
7. Persistent hoarseness, unexplained cough, or difficulty in swallowing.
8. Any change in the normal bowel habits.

One of the reasons why cancer frequently is not diagnosed until it is too late to do anything about it is because there is no generally accepted, completely dependable diagnostic tool to give clews to various types of early cancer.

The keystone of diagnosis is tissue biopsy, which is the removing of a piece of tissue and the examination of it under a microscope. It is a valuable tool in the management of the problem but is not completely adequate because in many cases the doctor does not know there is a tumor to be biopsied until the growth is extensive. The biopsy of certain internal forms of cancer, moreover, may entail major surgery, often a necessary procedure but not an ideal type of diagnosis compared to, say, a simple blood test.

One of the most popular tools at the moment is the so-called Papanicolaou smear developed by Dr. George N. Papanicolaou of Cornell Medical College. This technique relies on the fact that a smear taken via various body openings will pick up a variety of cells, including exfoliated (stripped off) cancer cells.

The technique is regarded as a valuable diagnostic approach to the cancer problem, but there is a difference of opinion in the medical profession as to its exact value.

Simple cancer tests are announced with monotonous regularity, usually attended by some excitement and a great deal of hope, because a simple, cheap, sure test for cancer is one of the most sought-after goals in medicine.

The practical importance of such a test can hardly be exaggerated. If it is found, it might mean that cancer, or at least several forms of the disease, would vanish as a major medical problem, even though cancer as a disease might re-
main the terrible mystery that it is. With early diagnosis and adequate treatment, such as surgery, much of the terror can be eliminated from cancer.

A blood test for cancer announced last year by Dr. Charles Huggins, of the University of Chicago, grew out of a study of proteins in the blood. The test is not specific for cancer. It is hoped, however, that it will prove to be consistent enough so that positive results will put the doctor on guard and then, by a process of elimination, he may be able to arrive definitely at a diagnosis of cancer or eliminate it as a possibility.

The Chicago work awaits confirmation in other laboratories and it is too early to predict the ultimate role of the test in cancer diagnosis.

The urgency to find a good diagnostic test for cancer can be shown dramatically in the following table which compares the curability of cancer at certain sites if treated early and if treated when moderately advanced:

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Percent of cures if treated early</th>
<th>Percent of cures if treated when moderately advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>75</td>
<td>40</td>
</tr>
<tr>
<td>Cervix (neck of uterus)</td>
<td>75</td>
<td>15</td>
</tr>
<tr>
<td>Mouth</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>Lip</td>
<td>95</td>
<td>25</td>
</tr>
<tr>
<td>Skin</td>
<td>95</td>
<td>25</td>
</tr>
<tr>
<td>Rectum</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Bladder</td>
<td>50</td>
<td>10</td>
</tr>
</tbody>
</table>

As for treatment, there is general agreement in the medical profession that cancer is treated most successfully by surgery and irradiation, or a combination of both, when the disease is caught early.

To make this point, and the table above, more specific, one
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can cite many reports, among them recent results in the treat-
ment of cancer of the rectum at St. Mark's Hospital, London. Of
the patients operated upon when the cancer was confined
to the rectum, 81.9 percent were alive 5 years after operation,
compared with a 5-year survival rate of only 62.3 percent
when the cancer had already spread beyond the rectum be-
fore the condition was recognized.

As for radiotherapy, one of the limiting factors in this form
of treatment is that of access to the tumor. X-rays and
radium are harmful to normal as well as to malignant cells,
and one of the major problems facing radiotherapists has been
to produce a maximal effect upon the cancer cells and a
minimal one upon normal cells. This form of treatment, ac-
cording to Dr. William A. R. Thomson, of London, is best
suited for superficial or easily accessible cancer, such as that
of the skin, the throat, and the uterus. In the case of cancer
of the skin, results with radiotherapy have been excellent,
principally because cancer of the skin is so easily detected,
partly because often it is not very malignant and metastasizes
(spreads) late, Dr. Thomson points out. Results have also
been satisfactory in cancer of the uterus and neck of the uterus.
For instance, at the Marie Curie Hospital, London, 82.9 per-
cent of patients in whom cancer of the neck of the womb was
recognized at an early stage and treated by irradiation were
still alive 5 years later, while in the case of cancer of the uterus
itself, the comparable figure was 65 percent. On the other
hand, among the cases not recognized until a late stage of the
disease, the 5-year survival rate was only 7.4 percent for
cancer of the neck of the uterus, and 20 percent for cancer
of the uterus itself.

“During recent years there has been much discussion among
the experts as to the relative values of surgery and irradiation
in the treatment of cancer,” Dr. Thomson writes. “This has
been most acute in the case of cancer of the breast. Although
the problem has not yet been satisfactorily solved, the modern
The Control

tendency of opinion is to combine the two in varying amounts.

"On general principles there would appear to be much to be said for removing a malignant tumor and as much as possible of its spread, and then irradiating, either with X-rays or with radium, the remaining metastases which could not be removed. On the other hand, there is a definite school of thought among the experts that in certain cases radiotherapy alone is sufficient."

There are other ways to treat cancer, by radioactive substances (about which it is too early to draw conclusions), and by various drugs, including sex hormones, anti-fool acid compounds and nitrogen mustards, but none of these is regarded as a cure. Some of these will be discussed separately in subsequent chapters.

A mention might be made here of the fact that nitrogen mustard, which has a transient effect on such cancer-like conditions as Hodgkin's disease, was a wartime development, made first by the French between wars and then synthesized later by the Germans and Americans. As a weapon, it can cause severe burns and blisters.

Americans knew of the German work with the new form of mustard gas, in which various chemical components were combined with nitrogen instead of sulfur. America's fear that the Nazis might use it in the war provoked intense research on the substance here in the hope that by understanding its action, an antidote for it could be found.

As it turned out, a substance of fundamental importance in cancer was discovered, a substance which exhibits in some cases and for temporary periods only, a remarkably specific action on the cancer cell.

Down through the years, almost everything has been tried in cancer, a point made rather nicely by Dr. William H. Woglom, of Columbia, a few years ago. He picked up a 100-year-old quote from a man named Volker, who said: "The degree to which a disease is open to therapeutic attack is in-
versely related to the number of remedies that we possess.”

Nowhere is this more true than in cancer, for which treatments have been advanced by the thousand.

Dr. Woglom pointed out that the older ones included, among others, crabs or crab soup (cancer is the Latin word for crab); purgation; black and red salves; plasters; pipe clay, blood-cleansing teas, silver and gold, mercury, copper, phosphorus, arsenic, externally and internally; narcotics, compression, cold, acids, alkalis, metals in the colloidal state, electricity, diuresis (abnormally great excretion of urine), vegetable products of all sorts, including violet leaves; toads, and snake venoms.

The list of metals that have been tried in cancer, in addition to those named above—all with conflicting or negative results—include calcium, magnesium, caesium, barium, iron, cobalt, platinum, aluminum, thallium, samarium, neodymium, lanthanum, yttrium, scandium, rhenium, tin, tungsten, bismuth, and lead.

According to the American Medical Association, cancer quacks do a brisk business in parts of the United States, offering nostrums to desperate people.

One of the reasons for this is that if a patient thinks that his case is hopeless, so far as established therapy is concerned, he is likely to try anything. If he didn’t, he wouldn’t be human. Therefore, it will take more than laws to eliminate quackery. It will take the chemical control of the disease, or something equally effective.
The basic unit of animal and plant life is the cell.

Most animal cells are small and the unit chosen for their measurement is the micron, which is 1/1000 of a millimeter (a millimeter being 1/1000th of a meter, or 0.03937 of an inch).

Human red blood cells average 7.5 microns in diameter, and many other cells are 10 to 50 microns in diameter, but certain nerve cells in large animals are several feet in length.

Life in higher animals starts with the union of two sex cells, which combine to form a body cell, or somatic cell. In man, in the nine-month period following this union, this single cell multiplies, the 1 cell forming 2, the 2 forming 4, the 4 forming 8, etc., until, at the birth of a child, the single cell has developed into an organism of about 200 billion cells.

A new advance in the cultivation of cells outside of the body is illustrated here. The cells are growing from a fine glass tube in which a single cell had been placed. These cells will produce a large culture in a flask.
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This is a basic fact of growth in higher organisms—the development from one cell to billions—yet one might say, without meaning to be whimsical, that one outstanding aspect of normal growth is not that it continues, but that it stops. Cancer, on the contrary, continues unchecked, a point we shall come back to later.

One thinks of the human body, which contains billions of cells, as being a complicated organism, but any one of these cells—taken from any tissue of the body—is so complex that the cell has defied the most astute efforts of science and the probing of the most exact instruments to determine how it is put together.

The single cell is a world of its own, so to speak, carrying out in the most extraordinary way basic functions compatible with life.

In the last century it was barely suspected that a body cell was capable of independent life. In 1907, Dr. Ross Harrison, then at Johns Hopkins, completed an experiment later carried further by the late Alexis Carrel and many other workers.

Dr. Harrison took a minute fragment of tissue, embedded it in clotted lymph, kept it moist and free from bacteria, and discovered that it grew by itself, that its cells multiplied, that they lived in an existence independent of the body from which the tissue had been cut.

Recently Drs. Virginia Evans and W. R. Earle at the National Cancer Institute have found that by growing tissue cultures under sheets of perforated cellophane, the cultures can reach a far larger size than those grown in clotted lymph. One bit of tissue grew to cover an area of 24 square inches in a few weeks, and this size could probably have been exceeded if the container had been larger.

This technique may well open the way for even larger scale growth of cultures, a development that will probably have many uses in cancer research and in other fields.

At the other end of the scale, in the same laboratory, Drs.
The Cell

Katherine Sanford and Earle for the first time have been able to grow tissues from cells isolated in glass capillary tubes, and have been able to produce large cultures from the progeny of one such cell.

Today biologists look upon cells as potentially immortal. Death, as man knows it, is not due to the death of the body’s cells but rather to the failure of co-ordinated action among cells, and cells may live on after the individual’s death, some for minutes, some for hours, a few perhaps for days, until they are ultimately asphyxiated or starved.

The cell has a number of features, among them the following:

- It has a nucleus which contains chromosomes. The chromosomes according to generally accepted beliefs, contain genes. Genes presumably are self-duplicating particles transmitting hereditary characteristics, but how the gene acquires this attribute is not known. The nucleus is inclosed in a nuclear membrane and beyond this lies the cytoplasm, or cell plasm.

- In cancer, the cell (perhaps the nucleus, the chromosomes, the cytoplasm, or all three) is disturbed in some way which causes it to become what we call a cancer cell. This cell divides and the resulting tissues grow, remorselessly, until death is caused by their interference with the normal healthy functions of the body. It is generally agreed among members of the medical profession that the only way to avoid such an outcome is by removal of these abnormal cancer cells from the body. Such removal is done by surgery or the cancer is killed by irradiation.

- In the loosest sense (from a scientist’s viewpoint), there are two outstanding facts about normal growth. First, that it is organized. That is, the cells divide and differentiate to form bones, arteries, skin and other elements that make up the amazingly efficient mechanism that is the living body. Second, this growth stops at the right time. There seem to be brakes on it.
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Either these brakes are missing from the cancer cell or, perhaps saying the same thing in a different way, the cancer cell is able to overcome whatever it is that regulates normal cell growth. Thus the cancer tissue will grow in a disordered fashion, forming a mass that serves no useful function, but serves only to interfere with normal bodily functions.

Unquestionably some chemical transformation is involved in this problem, but exactly what it is is not known, although there are clews here and there and some of these will be discussed in later sections.
5. Regeneration:
Experiments Seek to Learn Why Some Abnormal Tissues Grow Remorselessly

AT THE NATIONAL CANCER INSTITUTE, Dr. H. W. Chalkley has performed an interesting experiment. Dr. Chalkley works with hydra, a member of a fairly low order of animals which are the lowest animals with definite tissues.

Dr. Chalkley takes a cubic millimeter of hydra tissue, minces it up, pours it into a mold so that it fuses, and in 5 or 6 days the essential elements will reorganize themselves so that on an average four hydra will appear.

The number of hydra that come out of this mixture seems to have nothing to do with the number of hydra that went in; the important consideration is the over-all amount of hydra tissue that is used. So 5 large hydra, so to speak, will produce about 4 hydra from the mixture, and so will, say, 20

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The planarian is useful in cancer studies because of its remarkable capacity to regenerate new parts. Generally speaking, the smaller the portion removed, the more complete the regeneration as shown above where white parts represent regeneration portions.
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small hydra, so long as the volume of tissue is 1 cubic millimeter.

The question might be asked: How do the hydra that come out of this mixture relate to the hydra that went in? Are they brothers, sisters, cousins, nephews, sons, daughters, or what? A biologist cannot answer this question, but a philosopher might take a stab at it.

The Chalkley work bears on cancer in a most interesting way.

Certain tissues in the body, and therefore the cells of which they are composed, have the remarkable ability to regenerate—or to be "reborn." In higher animals, such as man, this regeneration is limited. For example, if a man loses an arm or a leg or a foot by amputation, another limb will not grow to replace the lost one.

Yet if a man breaks a bone, new bony tissue usually regenerates and knits the ends of the broken bone together. In the same way, skin tissue regenerates if one removes the outer layer of skin without damaging the underlying tissue. This is what happens to you many times in a lifetime, for when you wash your hands, and dry your hands, you scrape away dead tissue. If new tissue did not replace the dead tissue scraped away, your hands would be rubbed raw early in life.

If this appears to be a remarkable attribute, it is hardly even exciting compared with the ability of certain lower animal forms to regenerate. Take the case of the planarian, known to laymen as a flatworm.

This animal is about a half inch long, dark brown or deep brownish green in color, with a rounded head, a flat, unsegmented body and a tapering hind end or "tail." The animal has no limbs. Two crescent-shaped eyes usually help to give the head a jack-o'-lantern appearance. It also looks a little like a shmoo.

If one cuts one of these worms in two just in back of the head, both cut surfaces begin to regenerate new tissue.
Regeneration

The body remnant also regenerates a complete and functional head, which begins where the former head left off and which enables the worm to continue a successful existence.

A worm cut in two at a line a little behind the center of the body is more versatile. It frequently regenerates a tail on the part needing it, and a head on the other part, thus producing two worms where before there was one. When the dividing line is close to the rear end of the body, the part retaining the head regenerates a tail. The small portion, where the old tail remains, may also partially regenerate.

Many other animals have similar properties, although the flatworm appears to be the Olympic champion in the regeneration competition. Even when one gets as high on the evolutionary scale as the salamander, which is a vertebrate (man is also a vertebrate), this power of regeneration exists. Salamanders can regenerate limbs or a new tail when those are removed.

This remarkable ability of regeneration—the ability to produce an exact duplicate of a missing part—has never been fully explained, although experimental work on one aspect of the problem won for Dr. Hans Spemann, a German, a Nobel Prize in 1935. He discovered that there are “organizers” in the embryo which direct the form and substance which certain tissues are to take.

In work on frog and newt eggs, he found what he called an “organizer” in a portion of the embryo which underlies in the embryo the part that, at maturity, becomes the forebrain. This organizer appears not to be present at the fertilization of the egg but develops shortly thereafter. This is a puzzling situation and one wonders what kind of a chemical transformation is necessary to evoke the organizer which in turn acts, as one writer describes it, as a master builder which organizes the stuff of life—whatever that means—into its various tissues and organs.

The problem of tissue organization, and the controls neces-
The Challenge of Cancer

ecessary to insure that cells will combine in a way that will produce normal tissue and only normal tissue, at birth and later in replacement of worn-out tissues, is one which obviously bears on cancer. For the cancer cell has shot free of the normal controls and instead of reproducing the kind of normal tissue from which it is derived, it joins with other cancer cells to form tissues which ultimately, if they go unattended, strangle normal tissues.

There are two fundamental points here, and in order not to confuse them, let's put them this way: In one case, the question turns on the organizer in the embryo, the master builder so-called, which directs the activities of various cells, causing them to combine into proper tissues, such as kidney, spleen, liver, and so on. Moreover, once having produced tissue of this type, each tissue, in regenerating after injury, produces characteristic cells, so that, for example, injured skin can be replaced by normal skin, or by a scar which will cover the injury.

The second point grows out of the first; it concerns the problem of cancer which might be looked at this way: Something happens to normal cells which perverts them and imparts to them the ability to reproduce, inevitably and remorselessly in many cases, more abnormal cells until finally the abnormal tissue overpowers the normal tissue.

Some embryologists believe that there are several organizers, forming a hierarchy with the embryo at the base, one organizer depending on the activity of the organizer operating at a level immediately behind it. There is no general agreement as to the extent to which organizers are involved in the regeneration process.

In any event, Dr. Chalkley is trying to determine how cancer-causing agents affect the organization of tissue. His animal is the hydra. His cancer-causing agent is methylcholanthrene, a coal-tar derivative. His preliminary experiments indicate that certain profound changes may be produced in the organizing and reproductive abilities of the
Regeneration

hydra under the influence of methylcholanthrene, causing anomalies, such as, for example, the formation of too many tentacles on the animal.

This led him to the mincing experiment with the hydra. He proposes now to do the same experiment over again, with the exposure to methylcholanthrene of the one cubic millimeter mixture, and other mixtures. What effect would this cancer-causing agent have on the organizing factor in hydra? If there is an effect, in such an experiment, will it give a clew as to the action of methylcholanthrene? Can this clew be used to understand better the process known as cancer? Only future experiments can answer these questions.
6. The Environment:

Science Has Isolated, by Hundreds, Substances That Can Induce the Disease

Through chemical studies in the last 25 years, a few hundred cancer-causing substances have been isolated in the laboratory.

Study of chemical carcinogens, or cancer-causing agents, dates from the days of Percival Pott, a London surgeon, who commented in 1775 on the incidence of scrotal cancer among chimney sweeps and suggested a connection between the disease and the accumulation of soot on the bodies of the sweeps.

But it was not until 1915 that the Japanese produced cancer of a rabbit’s ear with tar and it was not until 1930 that the English isolated a substance known as 3,4-benzpyrene from coal tar and synthesized other cancer-causing agents.

Such investigations have given research workers an opportunity to produce, at will, enormous amounts of animal cancer.

Numerous physical and chemical agents in man’s environment are potential carcinogens. For example, excessive exposure to X-ray and sunlight may cause skin cancer and cancers of this and other tissues may result from certain chemicals.
The Challenge of Cancer

tissue for study. Much significant evidence has been gleaned from these studies, yet the exact mechanism whereby a normal cell is converted into a cancer cell is shrouded in the thickest of fogs.

As for the immediate inciting cause of the disease, for years it was generally believed that irritation or injury could incite cancer and this is a point which still arises in forensic, or legal medicine. Yet Dr. I. Berenblum, Special Research Fellow of the National Cancer Institute, points out that a careful analysis of the recorded examples of “traumatic cancers” indicates that, in the great majority of cases, the evidence is unacceptable.

Also, from a study of occupational tumors, it is clear, he reports, that few irritants with which workmen come in contact are cancer-producing. But the most crucial verdict comes from carefully controlled experiments on animals. Since mice are particularly sensitive to cancer-producing action, and since the agents known to be cancer-producing to man are even more potently cancer-producing to these animals, it is reasonable to suppose that if ordinary irritation were responsible for cancer in man, it should also be demonstrable in mice.

"Yet none of the ordinary irritants tested on mice have been found to produce cancer," Dr. Berenblum reports. "On the contrary, some irritants when added to known cancer-producing agents, actually inhibited cancer production."

Most irritants are incapable by themselves of inducing tumors in man or in animals. Those irritants that do possess cancer-producing properties owe their action to highly specific effects on the tissues, and not simply to their irritative action. But recent studies have shown that when a precancerous lesion exists, then certain kinds of non-specific irritation may sometimes “precipitate” the appearance of a tumor. Thus, concludes Dr. Berenblum, in the rare cases when an ordinary irritant does seem to have produced a
cancer, the probable explanation is that the tissue was already in a precancerous state.

Between the two extremes of true cancer-producing agents (such as tar and X-rays) on the one hand, and non-cancer-producing factors (such as physical injuries and the majority of chemical irritants) on the other, there seems to be an intermediate group which is anomalous in character.

This group includes severe burns, the prolonged action of arsenic, and certain forms of chronic inflammation. The anomaly lies in the fact that tumor-production may occur, but is so rare as to constitute the remote exception rather than the rule.

For instance, the fact that a severe burn is sometimes followed by a cancer has been fully substantiated, Dr. Berenblum reports; yet, when it is remembered how often a human being burns himself accidentally, and how seldom such a lesion becomes converted into a cancer, one wonders whether some additional factor must not be implicated before the process of cancerization can occur. But if this is so, the “additional factor” must be of a very elusive character.

Despite a wealth of data indicating cancer-causation from crude mixtures, only three unadulterated agents have thus far been proved to be carcinogenic for man.

These are (1) radiation, such as ultraviolet rays, X-rays and rays from radioactive material; (2) beta-naphthylamine, a compound associated with the manufacture of certain dyes, and (3) arsenic. As far as environmental cancer is concerned, Dr. W. C. Hueper at the National Cancer Institute summarizes this problem as follows:

Medicine: Preparations containing arsenicals and coal tar have been known to cause cancer of the skin; medicinal exposure to X-rays and radium, in the treatment of often non-malignant diseases, has resulted in cancers of the irradiated tissues in some patients.
The Challenge of Cancer

Diet: Dietary deficiencies, particularly of proteins and vitamin B factors, are thought to be responsible for the excessive incidence of cancer of the liver among a certain kind of African Negroes and some inhabitants of Java. Thyroid cancer seems to be related to the occurrence of endemic goiter in population groups suffering from a dietary iodine deficiency.

Habits: There is no definite evidence that tobacco is carcinogenic when smoked or chewed. There is, however, an abnormal incidence of cancer of the mouth in India and the Philippines, where the people chew tobacco-betel nut quids, or place tobacco-lime quids in the groove behind the lower lip. Mouth cancers are unusually frequent in a certain tribe in India which smokes cigars with the lighted end in the mouth.

The natural environment contains only a few recognized carcinogens. Of these, solar radiation is one of the best proved, particularly as it affects light-skinned people who become over-exposed for long periods of time to the carcinogenic ultraviolet radiation in southern dry and sunny climates and at high altitudes. An abnormally high arsenic content in drinking water has been shown to cause cancer of the skin in Germany and Argentina. Infections with the parasite Schistosoma hematobium, common among the fellahs of Egypt, are apparently related to the high incidence of cancer of the bladder found there.

In the artificial environment created by an industrial civilization an appreciable number and variety of agents have displayed carcinogenic properties for producers, users, and consumers of these agents. The occurrence of cancer of the bladder in dye workers, for example, has followed closely the establishment of large-scale dye industries in different countries.

There is evidence that contact with some of the distillation and fractionation products of coal, oil shale, lignite and petro-
The Environment

leum causes cancer of the skin and, possibly, even cancer of the lungs, Dr. Hueper reports.

Reports from Japan and Canada suggest that the inhalation of hot tar fumes by stokers of gas generators of steel mills may result in an excessive incidence of lung cancer among these workers.

Observations in several industries have added several inorganic, metallic chemicals to the list of suspected carcinogenic agents. During the last 15 years more than 100 cases of cancer of the lung have been reported from German and American sources in workers who inhaled chromate dust for a number of years.

Cancer of the nasal sinuses and of the lung were found by English observers to afflict, at an excessive rate, workers engaged in the purification of copper-nickel ores. Recent reports from England suggest that the inhalation of arsenical dust during the production of sheep-dip seems to increase the liability of the exposed workers to both cancer of the skin and cancer of the lung.

Occupational cancer of the lungs is to be found among the miners of radioactive ore in Schneeberg, Germany, and Joachimsthal, Czechoslovakia. Many of the miners have died at an early age from a lung ailment variously termed "mountain disease," "miner's phthisis," or "metal sickness."

Carcinogenic hazards from radiating energy should not be confused with conditions existing during the diagnostic use of X-rays in medicine. So far as is known, there is little, if any, danger from examination of the chest or other organs with X-rays, by competent technicians, in diagnosis of medical complaints.

The question of solar cancer, so called, is an interesting one. Significant results on the relation of solar cancer to the intensity and duration of sunlight have been obtained in recent years. The chart of skin cancer incidence in certain American cities shows important variations in proportion to differences in total annual solar radiation.
The Challenge of Cancer

Such a study, on the relation of intensity of sunlight to skin cancers among whites, shows the following:

<table>
<thead>
<tr>
<th>Skin cancers per 100,000 population</th>
<th>City</th>
<th>Percent of total possible sunlight</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>Dallas</td>
<td>60–80</td>
</tr>
<tr>
<td>129</td>
<td>New Orleans</td>
<td>62–64</td>
</tr>
<tr>
<td>37</td>
<td>Pittsburgh</td>
<td>50–57</td>
</tr>
<tr>
<td>24</td>
<td>Detroit</td>
<td>40–25</td>
</tr>
</tbody>
</table>

The fact that all of these agents are at work in the environment does not necessarily mean that workers, in any given industry, are exposed to such hazards and are certain to develop occupational cancer. On the contrary, if adequate control measures, preventing effective contact of the workers with the carcinogenic agents, are instituted and rigidly observed, dangers can be minimized or perhaps completely eliminated, according to Dr. Hueper.
7. Stable Isotopes

One of the most useful tools available to the scientist for investigating cancer—or any other disease—is a substance known as a stable isotope.

The use of stable isotopes in medical research is assuming greater and greater significance, as laboratory after laboratory applies these incredible chemical detectives to the problem of tracing down the secrets of human physiology. It is the purpose of this discussion to show, in a very simple way, how a scientist would go about using a stable isotope in a research problem and what he could hope to achieve by doing so.

Let's take carbon as an example. Let's start out by stating that natural carbon has an atomic weight of 12.01. That's a frightening statement. Don't let it throw you. What it means is that by a certain arbitrary numbering system, the carbon atom is given a weight of 12.01.

The mass spectrometer is used to trace the course of compounds, such as cancerogens and amino acids, through the animal body. The compounds are first enriched with stable isotopes. These are later recovered from the organs and measured by this instrument.
The Challenge of Cancer

How does one arrive at such a weight? It is arrived at by figuring out—and there are ways to figure it out—that there are units in the nucleus of the carbon atom which, when added up, turn out to have a weight of 12.01. The units in the nucleus which, when added up, give this figure are known as neutrons and protons. We won’t worry about what neutrons and protons are. We’ll just say that every neutron is 1 unit and every proton is 1 unit and if you should have 6 neutrons in a nucleus, and 6 protons, the total weight of the atom would be 12. It so happens that in the case of carbon that is exactly the fact. There are 6 neutrons and 6 protons. Add them up. You get an answer of 12.

But we have already said that the carbon found in nature has an atomic weight of 12.01. Where does the .01 come from? If you should pick up a handful of dirt, whether you pick it up in Brooklyn or Calcutta, you will find that the natural carbon in that dirt will have an atomic weight not of 12, which is what you would expect, but of 12.01. The reason this is so is in nature, carbon is a mixture of two isotopes: two kinds of carbon which are the same chemically, but differ only in their physical properties. In any 100 atoms of ordinary carbon, 99 will have an atomic weight of 12 (6 neutrons and 6 protons) and 1—and only 1—will have an atomic weight of 13.

Why this should be the case is not clear, but it is the case. It’s the nature of the beast. And it applies to all ordinary carbon. If you ask a geologist for an explanation of this, he will talk about the chemistry of the earth when the earth was formed. But let’s get back to the isotope.

If the chemist starts with an element—carbon, for example—where the natural carbon is composed of two isotopes, one with an atomic weight of 12, another with an atomic weight of 13, and if the proportion is 99 to 1 favoring isotope 12, then natural carbon must weigh 12.01. If your arithmetic is good enough, you can see why this must be so. In
other words, the mixture—at 99 to 1—is going to raise the atomic weight by .01—or by one one-hundredth.

What can a chemist do with such information? One thing he can do—and is doing—is to take a natural substance, change the mixture artificially and then follow the course of the substance through the body. He can follow the pattern through the body by capturing the changed substance at strategic points.

Take this example: sodium bicarbonate. The chemical formula is NaHCO₃. The Na stands for sodium, the H for hydrogen, the CO₃ for carbonate. Suppose one wanted to find out what happens to this substance when it is ingested; let us say, one wanted to find out if the carbon in the sodium bicarbonate comes out in the breath as carbon dioxide (which part of it does, by the way).

It would do no good to feed ordinary sodium bicarbonate, since on examining a person’s breath for carbon dioxide, one would not know whether the carbon in the carbon dioxide came from the sodium bicarbonate or from some other substance. In such an experiment, the carbon entering the body would have an atomic weight of 12.01 and the carbon in the carbon dioxide would have the same atomic weight. So would any other carbon taken into the body.

One could, however, conduct an experiment this way: one could change the mixture of the carbon in the sodium bicarbonate; change it, say, so that the ratio of carbon atoms is 10 to 1, so that the weight of the carbon is 12.10, instead of 12.01. And if, in the breath, the carbon dioxide turned out also to have a carbon isotopic ratio of 10 to 1, one would know then what is happening at least to some of the carbon entering the body by way of sodium bicarbonate.

Suppose it should turn out that in the normal course of events a certain chemical substance consistently follows a certain pattern in the body. But in disease, let us say, that pattern is changed.
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Here, then, one gets hold of a significant basic fact about a disease process. Knowing that such a critical chemical difference exists, one can try to find specific ways of altering the process in the direction of normal.

In this sense, the use of isotopes—both stable and radioactive—provides tools in biological research the value of which is almost impossible to exaggerate. They will enable scientists to find normal patterns in health, and to compare these with the patterns in disease.

Radioactive isotopes, too, are of great importance as research tools and, as has already been mentioned, of some significance therapeutically. The tell-tale signs of radioactivity, rather than the changed atomic weight (as in the case of stable isotopes) will reveal the pathway through the body of various chemicals.

In one case—in the case of the stable substances—one would make one’s calculations with an instrument known as a mass spectrometer, which reveals the isotopic concentrations of the substance under investigation. In the case of radioactive materials, calculations are made with a Geiger counter.

Radioactivity offers a more sensitive indicator. But the stable isotope has the advantage that it can be used, almost under all circumstances, in human experiments without raising the danger of subjecting the body to radioactivity.
8. Radioactive Isotopes:  
A Hitch-Hiker With a Walkie-Talkie

The several hundred thousand billion cells in the human body ride a fantastic biochemical merry-go-round. At any single instant, they are extracting energy from carbon compounds, expelling waste material, getting born in huge numbers and dying in huge numbers. With all this racing activity, the body as a whole—each of its organs, tissues, and separate fluids and compounds—remains substantially the same in volume and weight.

This paradox is the core problem in biochemistry—to learn how this endless round of breakdown and renewal of body materials proceeds, and to explain how it is so finely regulated. Exploration of cancer is the next step: What disrupts the merry-go-round? Why does a group of cells grow wild, tip over the normal balance and finally destroy the body itself?

Some knowledge of these processes can be gained by du-

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Geiger counters of various types are used to measure the distribution of radioactive materials introduced into animals. In the illustration, the radioactive tissue under study is surrounded by lead bricks to protect the operator.
The Challenge of Cancer

plicating a few of the simpler aspects in a test tube, or by chemically assaying laboratory animals that have been fed various elements and then cut up. But test tubes and dead animals are a far cry from the living body. For a deeper understanding, biochemists have long known that the trick is to follow each of the essential compounds—vitamins, amino acids, carbohydrates, fats, and others—from the time it goes into the living body, watch it being mobilized as a source of energy or incorporated into the body structure, and analyze it when it comes out as waste.

That's why a great and growing number of scientists today are excited about isotopes, especially radioactive isotopes. The latter are nearly identical twins to natural elements—the body cannot tell them apart. But before they were manufactured and shipped from Oak Ridge, Tenn., they were bombarded by particles in an atomic reactor, and the nuclei in their individual atoms were transformed into unstable forms. To regain stability they emit particles or radiations, which can be picked up by a Geiger counter, amplified in a loud speaker, and say, “Here we are” to anybody who cares to listen.

A few months ago the National Cancer Institute put on a television show. One of the stars was a cooperative mouse in whom some radioactive material had been implanted. As he was brought to the Geiger counter, the distinctive sound of emanations—a weird cross between radio static and the nicks on a battered phonograph record—floated into many of the homes and assorted taprooms of Washington.

To the trained technician the sounds of radioactivity tell a coherent story. They mean that a tagged element, hitched onto a stable compound, is making its way through the body, participating in body processes, and sending out a running walkie-talkie account of where it is, what it is doing, and in what amounts. Its rate of disintegration is distinctive—the technician is in little danger of confusing it with stable or with other radioactive elements. It can be heard even in
Radioactive Isotopes

small amounts: A small fraction of a billionth of a gram, sometimes even a relatively few radioactive atoms, will make its whereabouts known. Most radio-isotopes go through the body without upsetting body processes, and hence can be traced for as long as necessary in the live laboratory animal or human patient.

Although radio-isotopes were long available in tiny quantities at high cost, the Atomic Energy Commission now supplies them in ample amounts and without a price tag, to any qualified cancer investigator.

This new and powerful means of perception has been a shot in the arm for cancer research in a great variety of basic ways. At Massachusetts General Hospital, for example, carbon 14 is taking investigators on a guided tour through protein metabolism of normal and cancerous tissue in experimental animals. (Radioactive carbon is about 14 times as heavy as hydrogen, which is given a weight of 1; natural carbon is about 12 times as heavy.) Among the facts learned is that a rat liver cancer builds amino acids into protein faster than normal rat liver. (The same experiment referred to in the chapter on proteins.) Nucleic acids, which are thought by many scientists to play an essential role in cell division and hence in cancer growth, have been made with radioactive components, for study in a number of laboratories.

Researchers are studying what happens to carcinogens when they enter the bodies of laboratory animals, for example by tagging the cancer-causing chemicals methylcholanthrene and urethane with carbon 14.

A variety of food compounds containing isotopes are being fed to laboratory animals to determine which substances are essential to tumor growth. One possibility here is that withholding a key substance from the diet might starve the tumor without starving the patient and the isotope—radioactive or stable—may enable the scientist to measure with great exactness how a given food acts on the tumor.

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For a few types of cancer, clinics and hospitals are already using radio-isotopes both in diagnosis and treatment. The value of radiation in cancer therapy—whether applied with radium, X-rays or radio-isotopes—is due to its destructive effect on living cells, especially rapidly growing cells such as those found in most tumors. The problem is to deliver a strong enough dose without doing permanent damage to nearby normal tissue.

A beginning has been made in studying a phenomenon that may simplify this problem. Certain parts of the body have a definite lure for certain chemical substances: bone structure attracts and holds phosphorus and gallium; the thyroid gland absorbs iodine. Thus cancerous thyroid cells, including those that have broken away and spread through the body, often attract radio-iodine and hence radiation that may destroy them. Several hospitals are using other radio-isotopes to locate and diagnose breast cancer and brain tumors. Experiments at Harvard University have shown that brain tumors can absorb as much as 100 times more phosphorus than normal brain tissue, but that the radiation can be detected only by a needle-like counter inserted into the brain itself. Use of such a counter, as an aid in surgery, to distinguish the cancerous tissue from the rest of the brain, has resulted in an appreciable increase in surgical accuracy in brain tumor operations.

Despite various rosy forecasts, all this does not necessarily mean that radio-isotopes are going to solve the cancer problem. Radiocobalt will soon come into widespread use as a cheap and abundant substitute for radium, and a shower of small advances in the use of other isotopes in cancer diagnosis and therapy is the least we should expect. Meanwhile, radiologists are aware that they must go easy on the clinical use of radioactive compounds until more is known of the dangers as well as the benefits. A few medical men have seen the skulls of the luminous watch dial painters—skulls that can still be made to glow in the dark after 25 years and may remain radio-
Radioactive Isotopes

active for thousands of years to come. Fortunately, in tracer studies, short-lived isotopes are generally used, and the quantities needed are so small that the danger to normal human bodies is minimal.

Radio-isotopes may indeed provide a key to cancer. At the fundamental level of biochemistry and physiology, results of far-reaching importance are visualized by many researchers.
9. Proteins:

*Mystery in Creation of Molecules Poses One of Hardest Problems for Chemists*

Suppose some day the Empire State Building falls in a heap in Thirty-fourth Street. You bring a stranger to New York, a man who has never seen the Empire State Building. If you can imagine it, let's even assume he has never seen any building.

You say to this stranger: "There are the building blocks of the Empire State Building. Tell me, if you can, what the Empire State Building looked like before it was blown up." It doesn't take much imagination to appreciate the difficulties the stranger would be in.

Yet his job would be simple compared to what the chemist faces today in trying to reconstruct the protein molecule to find out not only what it looks like, but its chemical prop-

*The Van Slyke apparatus is used in enzyme studies of cancer. For example, the enzymes of a tumor extract are allowed to act on peptides and the rate at which amino acids are formed is measured by this instrument.*
properties as well as to determine, with exactness, the thousands of reactions into which it can enter.

In a discussion later on in this booklet covering the subject of viruses, it will be pointed out that if one were to lay about 17,000,000 small viruses end to end, the line would extend only 1 inch. Such a dimension is of an order that staggers the imagination. Yet the molecule of hemoglobin, which is a type of protein in the blood, is about one-eighth the size of the small virus.

The purpose of this discussion will be to show that when one deals with a problem such as cancer, which touches on the fundamental biological and chemical facts of life itself, and growth, and differentiation of cells, one walks into a no-man’s-land where the road signs are few in number, and darkness is heavy. It is true that a beam of light shines through here and there—just enough light to show that there is a mist on the horizon.

Let’s start with proteins. What is a protein? It is a chemical substance essential to growth. Without proteins, life would not be possible. That is one reason why you eat food containing proteins, such food as meat, milk, fish, eggs, and legumes. The body, the world’s greatest chemical factory, takes these proteins, breaks them down, reassembles and redistributes them and sends them shunting off into growth-promoting processes.

It is one thing to say that a protein promotes growth. This can be proved very simply. One merely runs experiments on animals, withholding critical elements in the diet and then making the proper comparisons with appropriate control groups.

But it is quite another problem, and a most difficult one to solve, to understand how the protein acts as it does. One of the most sought-after objectives in science today is a method to put together a protein artificially—synthesize it in the laboratory—so that the chemist, knowing the elements that went
Proteins

into the synthesis, will know exactly what kind of a substance he is dealing with.

Genes, the basic carriers of hereditary traits, contain protein. Viruses, submicroscopic agents which cause many diseases, are largely protein. Enzymes, which accelerate chemical processes in the body, are proteins. Some of the hormones are proteins.

Now let's come back to the point made earlier about the building blocks. The building blocks of the protein molecules are known as amino acids. A chemist knows this because he can knock a protein to pieces and get amino acids out of it. But he can't put them back together again.

What is an amino acid? It is a substance composed of carbon, oxygen, nitrogen, and hydrogen, formed in a way so that one amino acid can be hooked to another. If you hook enough of them together, you get a protein molecule.

Let's see how this thing works. Take an amino acid, for example the following: \( \text{CH}_3-\text{CHNH}_2-\text{COOH} \). It has a name, but let's not worry about it. Now we'll take another one: \( \text{HNH}-\text{CH}_2-\text{COOH} \). Let's forget the name of this, too. Line them up, side by each, and then try to put them together, this way: \( \text{CH}_3-\text{CHNH}_2-\text{COOH \ HNH-CH}_2-\text{COOH} \).

If you know the chemical formula for water, something may strike you about the above combination. Water is \( \text{H}_2\text{O} \)—two atoms of hydrogen and one of oxygen.

If one moves these two amino acids closer together, it can be seen that the two atoms of hydrogen and one of oxygen can be clipped off, forming water. That is exactly what happens. This way: \( \text{CH-CHNH}_2-\text{CO-OHH-NH-CH}_3-\text{COOH} \).

Water is removed and the rest of the substance becomes bound when a carbon atom and a nitrogen atom unite, thus forming a two-amino acid substance. If one repeats this
process, anywhere from say 500 to 50,000 times, a protein molecule will be formed.

Many other substances can be added to this protein molecule. It can become a molecule of such vast complexity that to try to understand exactly how it is put together (in order that one can put one together and thus manipulate it experimentally and antagonize it, if possible), is a task that, in the present state of knowledge, even makes a chemist's head ache.

It is not just putting the amino acids together that is tough—and that isn't easy—but it is getting them together in the precise order that will add up to a protein molecule. When one is dealing with a compound with, say, only 100 parts (the general run of proteins are much more complex), the possible combinations of these parts are almost unlimited.

Not only is it important to know how to put a protein together, but it is important to know how the cell does it. As a matter of fact, a protein can be made in only one place—in the living cell. Just what it is that enables the cell to perform this magic is something every chemist in the world would like to know.

Cancer appears to be a disease in which there is a definite derangement in protein synthesis, and one of the latest pieces of evidence for this comes out of Massachusetts General Hospital in Boston.

There it has been shown in experiments with rat liver tumor that the incorporation of amino acids into tumor protein is more rapid than in normal cell protein. This is what would be expected on the basis of the rapid growth and invasiveness of the tumor.

As far as a chemist is concerned, therefore, it is quite clear that since cancer is a disease associated with a derangement in protein synthesis, then an understanding of how proteins are put together and how they are constructed by the cell
Proteins would constitute an important finding in understanding cancer.

But it is a most difficult process to understand. This fact, a rather disturbing one but nevertheless a fact, is one reason why so little is known about the basic process of growth, including cancer, which is a type of growth.
The human body is the world's most remarkable chemical factory, conducting thousands of reactions every minute of the day. Many of these are in such delicate balance that the wonder is not that disease, such as cancer, overwhelms the organism but that the subtle interplay of chemical on chemical is not more often thrown out of adjustment.

Of all the chemical agents which participate in the life process—and in growth—none holds more fascination for chemists today than the enzymes, a group of protein substances which facilitate or accelerate chemical reactions.

One can think of an enzyme, rather crudely, in a number of ways. For example, if you chop a block of wood, the axe
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is the enzyme. Or, let’s say, you want to go from New York to Chicago. If you walk it will take perhaps a month. But an airplane will get you to Chicago in a few hours. The airplane is the enzyme. The enzyme participates in the reaction and then goes on about its business relatively unchanged. There are hundreds, perhaps thousands of enzymes in the human body, each performing a specific job.

Through wear and tear enzymes finally disintegrate and must be replaced by substances exactly like them. Where does the replacement come from? It probably comes from the combined efforts of many additional enzymes which are present in the cell to insure continued cellular formation.

But where do these enzymes which synthesize enzymes come from? This raises an age-old problem, as old as philosophy, of finding what caused the first cause. As far as most biologists are concerned, the ultimate control for the synthesis of each enzyme is the gene, an entity which is believed present in the nucleus of the cell. The gene is the basic carrier of hereditary characteristics. Where the gene gets this remarkable power of self-duplication no one knows.

Enzymes control digestion, respiration, muscular action and, in fact, all living processes in plants and animals. If one really wanted to get rhapsodic on this subject, one could define both life and disease—at a chemical level—in terms of enzymes and come out with a fairly respectable definition.

Not long ago, Prof. James R. Sumner, of the New York State College of Agriculture, Cornell University, who was a 1946 Nobel Prize winner in chemistry, did just that, making the following observation in a report before the central Pennsylvania section of the American Chemical Society:

“Life can be defined as an orderly functioning of hundreds of enzymes, and disease can be described as a disorder, lack, or inhibition of enzymes,” he said.

An enzyme known as urease, which decomposes urea to carbon dioxide and ammonia, was isolated and crystallized
Enzymes

by Dr. Sumner in 1926 and now more than forty enzymes have been obtained in pure crystalline form. Every one of these has been found to be a protein. Dr. Sumner believes that while not every protein has proved to possess enzyme activity, most proteins are enzymes.

No chemist has synthesized an enzyme, or, as far as that goes, any other substitute for a natural protein. It is possible to isolate these substances and work with them in the laboratory, and much has been learned about human physiology in doing so. But if one could put a protein together—and thereby learn what the step-by-step normal synthesis is—or if one could figure out how a cell puts a protein together, it might be possible to study the growth process with great precision, to learn how a cell grows and differentiates, and the forces which control these phenomena.

To say that an understanding of normal growth would provide clews about abnormal growth has become a cliché among scientists. It is a point of such surpassing importance in cancer that it cannot possibly be exaggerated.

Yet to come to grips with this problem, to get down to the fundamentals of growth, is one of the most difficult tasks facing science today. And it is one reason why—perhaps the only reason why—cancer at its most fundamental level is not understood.

There are clews here and there scattered through the millions of experiments which have been performed to try to decipher the baffling code of the cancer cell.

Some of these clews have come from enzyme studies. One which interests many chemists turns on the work of Dr. Jesse Greenstein at the National Cancer Institute in Bethesda. He showed that enzyme distribution in tumor and normal tissue has some interesting differences.

The enzyme distribution in different normal tissues is quite different; that is, liver is rich in certain enzymes and poor in others, whereas heart or brain may show the reverse as far as quantity of enzymes is concerned.
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In general, a given tissue can be characterized by its particular distribution of enzymes, a criterion which Dr. Greenstein refers to as the "enzyme profile." In general, the changes that a normal tissue undergoes as it becomes cancerous are toward a common enzyme distribution. As cells lose their characteristic profile, they adopt the new profile of a tumor which, in general, is the same for all tumors. In other words, tumors converge to a common type of biochemical existence.

This provides a unifying thread for thinking about tumor metabolism and raises the possibility that a form of treatment successful for one tumor may also be successful for others.

This is a point which chemists would not press too far, but it is one they think about, in a rather hopeful way.
11. Chemical Problems:

Scientists Change, Within Species, One Type of Organism Into Another

Suppose someone were to tell you that he could, by the use of a chemical, change a cocker spaniel into, say, a dachshund. Aside from the fact that such a person might worry all the cocker spaniels in the world, he would evoke a certain amount of astonishment even from people who don't own dogs.

No one is changing cocker spaniels into dachshunds. But at a lower level of animal life, a group of scientists has succeeded in changing, within a species, one type of organism into another type of organism. The scientists happened to be dealing with the micro-organism which causes pneumonia. At the level of micro-organisms, which is a fairly complex level, they have performed an incredible experiment with a type of chemical known as DNA, a type of nucleic acid which is being studied in cancer.

The Warburg apparatus is used in enzyme studies of cancer. The manometer measures the enzymatic activity in terms of gas exchange in a closed vessel submerged in the circular tank. Water in the tank is kept at body temperature to simulate natural conditions.
The Challenge of Cancer

The excitement in modern chemistry about nucleic acid in relation to cancer stems not so much from any single experiment involving the chemical but more from a host of seemingly unrelated investigations which, some scientists believe, are beginning to form a pattern of great significance. This sort of thinking happens periodically in cancer research and some scientists wonder if the current boom in nucleic acid, so to speak, represents the latest fad, or if, perhaps, there really is some significance to it.

In other words, is nucleic acid involved in the basic mechanism of cancer, or is the level of the chemical in the cell merely one of many side-effects—and perhaps not an important one—which cancer produces?

What is nucleic acid? Nucleic acids are substances which, in general, contain three main types of components: phosphorus, sugar and two classes of substances known as purines and pyrimidines.

The immediate significance of the nucleic acids lies in the fact that nuclei of all cells, as far as is known, have one type of nucleic acid, and the cytoplasm of the cell has another type.

Each of these nucleic acids has a ferocious name. One is desoxyribose nucleic acid (commonly called DNA)—found in the chromosomes, in the nucleus, of all known cells—and the other is PNA, pentose nucleic acid (or ribose nucleic acid), found in the cytoplasm. There is also some of the latter in the nucleus.

In working with these substances, scientists have come up with some exciting findings in recent years.

A group of workers at Rockefeller Institute was able to convert one type of micro-organism into another type of the same bug in the presence of DNA. This is an astonishing experiment which makes the alchemists of old look like pikers. It is the equivalent, at a level of micro-organisms, of a change within the dog species or, for that matter, a similar change within any given species.
Chemical Problems

The experimental material in this case was the germ which causes pneumonia, of which there are more than 75 types, each type identified by the chemical and immunological nature of a capsule which encloses the bacterium. The capsule is composed of a polysaccharide, which means that it consists of a complicated assemblage of sugar molecules.

There are still some technical points about the experiments which have not satisfied all scientists. But, basically, the work showed the following: in the presence of DNA, the experimenters were able to convert a mutant pneumococcus type, known as II R, into a type known as III S, and having made this conversion, the III S reproduced in kind. The DNA which did the trick was taken from the cultures of III S. The experiment represents a remarkable example of a change which is chemically induced and specifically directed by a known compound. Most mutations (changes) would appear to be random and in most if not all cases the mutation has the effect of depriving the organism of some desired faculty. In this experiment, however, the researchers were able to confer on one type of organism an ability to synthesize the polysaccharide. In other words, the directed mutation was a gain, not a loss. The evidence would indicate that this particular nucleic acid, in this experiment, directs the functioning, character, biological specificity, and the genetic pattern of the bug. It is a directed mutation which is predictable and reproducible in the hands of the experimenter.

There are a number of other ways in which one could show the importance of DNA, but for the purposes of this discussion they all add up, in general, to the following conclusion: There are certain chemical substances in the cell which are involved in some way with the hereditary mechanism, and in the ability of the cell to reproduce in kind. It is conceivable that an understanding of how these substances act is neces-
sary for an understanding of growth and differentiation—
either normal or abnormal.

Knowing this, it is conceivable that in certain abnormal
conditions—cancer, for example—one may be able by arti-
ficial means—that is, by the use of chemicals—to inhibit the
abnormal process and return growth and differentiation
toward the direction of normal.

There is some evidence that this reasoning may be applied
to cancer at this time and may produce powerful weapons
against cancer. For example, there is evidence that in cancer,
nucleic acid metabolism in the cell is proceeding at an ex-
cessive rate. There is evidence, moreover, that at least two
substances used in the treatment of cancer—nitrogen mustard
and certain anti-folic acid compounds—have their effect, at
least in part, because they inhibit nucleic acid metabolism.

In the present state of knowledge, one must not push this
reasoning too far. The expression “inhibit nucleic acid
metabolism” is based on the fact that these agents interfere
with mitosis (cell division) and the nucleic acids are impor-
tant, and perhaps the most fundamental, chemicals involved
in mitosis.

If compounds can be found which have a more selective
action on the nucleic acid levels of the tumor cell, it is pos-
sible that the search for a sound chemical treatment of cancer
will proceed at a rapid rate.

It may be too much to hope that the workers here have
come to grips with the critical problem in cancer: the inhibi-
tion or altering of nucleic acid groups, as exhibited by nitrogen
mustards, anti-folic acid compounds, and X-rays, all of which
seem to have therapeutic value in the disease. It may be naive
to state the cancer problem in terms of nucleic acid. Nature
still may be concealing the real mechanism, concealing it be-
because man’s instruments for probing the mysteries of the cell
are still inadequate, perhaps woefully so.

For the moment we’ll drop the discussion of the nucleic
Chemical Problems

acids and return to them in a later chapter dealing with
growth factors, where the problem can be approached at a
somewhat different angle, particularly in the light of certain
recent experiments, among them those of Dr. George Kidder
and his colleagues at Amherst.

There are a number of other facts about cancer which
fascinate the chemist. One of these concerns the tumor's
mechanism for getting energy, a fundamental property of all
living things.

Some biochemists believe that this property shows up one
of the most striking differences—at a chemical level—between
normal and cancer cells. Chemists hope, therefore, that by
exploring this problem, some chemical means may be devised
to disrupt the energy production system in the tumor cell and
thus inhibit or kill the cell, without at the same time destroy-
ing, or seriously affecting, normal cells and normal tissues.

Investigations by Prof. Otto Warburg, of Germany, re-
cently a visiting research worker at the National Cancer In-
stitute, brought this problem to the attention of scientists years
ago.

Simply stated, the difference boils down to the manner
in which cells use their carbohydrate foodstuffs. One might
look at it this way: there are two stages in the break-down of
sugar by a cell—with the release of energy—and the tumor
seems to rely, more than normal tissue, on one of these stages.
The scientist would describe this stage—the stage the tumor
relies on more than normal tissue—by the use of the word
glycolysis.

It happens that glycolysis—just as other biochemical trans-
formations—does not proceed except in the presence of
enzymes. One of the most important glycolytic enzymes goes
by the forbidding name of zymohexase. Without zymohexase
the tumor cannot get energy because glycolysis cannot pro-
ceed. The question is: How would one go about inhibiting
zymohexase?
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Here is a possibility:

One might extract the enzyme—zymohexase—from human material, then inject it into a horse. The enzyme, as a foreign protein, presumably would cause antibody production in the horse; that is, the horse would produce antibodies against the zymohexase, or in other words an antibody that might be described as an anti-enzyme. Then one might extract the antibodies from the horse serum, purify them and inject them into a human being with cancer.

Is it possible that creation of an antibody against a given enzyme, such as zymohexase, could inhibit the action of the enzyme in the intact organism? If so, can it selectively inhibit the action of the enzyme in tumor tissue without impairing carbohydrate metabolism in normal tissues? Professor Warburg and his former colleagues at the National Cancer Institute hope so. Experiments are projected along these lines.
12. Viruses:  
*The Problem*

One of the concepts used occasionally by some scientists to account for the origin of cancer is the virus theory. Whatever merit this concept may have in general biology, it should be made clear at the outset that there is little evidence, at present, that cancer in man is associated with a virus.

The main prop of the virus theory is the fact that certain animals—notably chickens—are prey to tumors caused by viruses, or what appear to be virus-like agents.

In recent years, experimenters connected with the United States Department of Agriculture and working at East Lansing, Mich., have discovered that a disease in fowls which appears to have some resemblance to cancer seems to be both infectious and contagious, but the full implications of this work are not yet clear. Beyond these findings it is difficult...
The Challenge of Cancer

to make out a case even for the contagious nature of even fowl cancer.

If a virus for cancer in man has not been found, one then wonders why a researcher considers this a profitable line of investigation in cancer. The answer as to why such an inquiry may help to explain human cancer depends on the viewpoint of the investigator. On this question—viruses and cancer—opinions range through a wide spectrum.

On one end of the spectrum there are those who state quite positively that viruses in man have nothing to do with cancer, except perhaps by the loosest definition of a virus. At the other end are those who maintain that the origin of cancer in man—or anywhere else—makes sense only in terms of a virus. This latter group argues that the only reason viruses have not been discovered in human cancer is that techniques are not available to uncover them. Besides, they hold, if the virus is specific for each species, as evidence in animals would make it appear, how would one go about finding this agent in humans unless he experimented on human material? If there are as yet undetected viruses at the root of cancer and if the viruses are specific only for human beings, then possibly the only way one could detect them would be to infect other human beings experimentally with tumor extracts. This is clearly beyond the pale of research in a democracy. The paradox that grows out of this problem will be touched on in a later discussion after an examination of the evidence.

The virus theory of cancer, as a general biological concept, clearly occupies a minority viewpoint in cancer research. But since so little about cancer really makes sense and so few of the findings fit together in a meaningful way, minority viewpoints, if for no other reason, are worth examining. This first part of the discussion will deal with viruses in general, the second with some of the things that have been learned in work with animal tumor viruses.

One can stir up a rather heated argument in some research
Viruses
circles over the question of viruses and cancer, and frequently it will develop that much of the argument is at a lofty academic plane, with the central point turning on the definition of a virus.

There are two schools of thought about this, one a more or less classical view that a virus is a self-reproducing organism, sharing an intimate relationship with the cell and that it is filtrable, as larger organisms are not. There is a newer view which takes into account these points and which holds that the virus is a type of protein molecule, or an assemblage of protein molecules, which seems to occupy some sort of a niche in that never-never land between the living and the dead. It would appear that this second concept is gradually replacing the first, at least in the thinking of some scientists. The virus, in other words, has become, in the theory of some persons, a self-reproducing protein, representing, as Dr. Berenblum described it, a sort of a half-way house between animate and inanimate matter, with emphasis on one or the other, depending on one's definition of "living matter."

Some scientists believe that the isolation in pure crystalline form of certain viruses affecting plants is probably one of the most fundamental discoveries of the age. Dr. Berenblum has gone so far as to say that in view of the implications of this work (the crystallization of tobacco mosaic virus), it may well come to rank with the outstanding discoveries of our generation. The work was done by Dr. Stanley and his colleagues at the Rockefeller Institute, using the purification methods worked out by Dr. Northrup. Both workers received the Nobel Prize.

In connection with the cancer problem the discovery is significant, it is held, because some of the animal tumor viruses, though not yet purified in crystalline form, appear to have the same type of constitution as the crystalline viruses of plants. Their constitution is that of a highly complex protein, containing certain groups (nucleic acids, discussed in the section un-
der this title) which relate them chemically to constituents of the nuclei of living cells, possibly to the genes themselves.

Therefore, the question of "infectivity" in relation to the cancer problem (as originally conceived by some supporters of the virus theory of cancer) is receding into the background, in some quarters, while new interest is being focused on the possibility of relating knowledge about tumor viruses with that of genetic influences, on the one hand, and the action of powerful cancer-producing agents, on the other.

One can call a virus a self-duplicating protein, which might be vague enough to cover a number of things. One can say that a virus is a minute organism, protein in nature, existing in a relationship with the cell which is so intimate that the very life of the virus is virtually inseparable from the life of the cell. One can add that this virus either has the ability to reproduce (a faculty which would be incorporated into most definitions of what is life) or it acquires this ability from the cell.

Viruses, which are very small, are extracted conventionally through fine filters, such as filters made of porcelain, which allow the virus to pass through but hold back such relative monsters as bacteria. Some workers isolate viruses by centrifugation.
13. Viruses:
Animal Tumor Viruses

The virus theory of cancer has excited controversy for 50 years or more. Among scientists today, the virus theory, its pros and cons, can produce more polemics, probably, than any single concept in cancer research. If no virus has ever been shown to cause cancer in man, one wonders then what all the shouting is about. It is the purpose of this discussion to review some of the evidence and to show the direction in which research in cancer viruses, which poses some of the most fascinating problems in biology, is moving.

Early in the present century, Dr. Borrel observed that sheep pox virus caused a proliferation of tissue, an observation later extended to other viruses. In 1908, Dr. Ellerman, a Dane, described a type of leukemia in chickens (leukemia is now considered a cancer-like condition of the blood) and he was able to transmit this disease from one animal to another by

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The electron microscope is about 100 times as powerful as ordinary microscopes. Instead of light rays, it uses a beam of electrons, and the "lenses" are electromagnets. Cancer viruses were seen for the first time with this instrument.
The Challenge of Cancer

cell-free filtrates; that is, by filtrates which contained a minute infectious substance, presumably a virus.

In 1910, Dr. Peyton Rous of the Rockefeller Institute, then a young medical researcher, was casting about for some productive type of medical research, when a chicken breeder sought him out. The chicken breeder was carrying a Plymouth Rock hen and the hen appeared to have a cancer of the breast. The problem of trying to understand what had caused this growth fascinated Dr. Rous and he went to work on it.

That decision was to result in one of the most widely discussed discoveries in biology in this century and today—40 years later—Dr. Rous is still wrestling with the implications of the finding he made in his youth. The examination of the chicken led Dr. Rous to the discovery of a typical sarcoma which was transplantable to other chickens.

That the sarcoma is caused by a virus or a virus-like agent, as Dr. Rous showed, has been corroborated by many other workers. Dr. Rous identified the growth by the rather unglamorous title of “Chicken Sarcoma 1” after he and his associates had procured other “spontaneous” fowl tumors (from several of which they got viruses); but in cancer research Dr. Rous’ finding is known simply as the Rous sarcoma. Though readily transferred in the laboratory, it has never been seen to pass from one bird to another spontaneously.

There is a gentle irony in the fact that the discovery probably has been responsible, to a greater extent than any single discovery, for the virus theory of cancer, yet later experimentation on mouse cancers by Dr. Rous himself has caused him to look upon the virus concept, which he helped initiate, with some misgivings. Dr. James B. Murphy, one of Dr. Rous’ early collaborators, also has some reservations about the virus theory. Dr. Rous does not exclude viruses as agents in certain cancers in certain mammals. But he is struck by the difficulties one can get into in broadening this theory to cancer in general.
Viruses

The Rous sarcoma, which is only one of a number of avian tumors, is a highly malignant growth that can be transplanted to other chickens. Dr. Rous found that if an emulsion of the ground sarcoma cells in a certain type of salt solution were passed through a fine filter, and if the cell-free filtrate were injected into other chickens, a sarcoma similar to the original could be produced. The filter does not permit the passage of sarcoma cells or of bacteria and this would be one reason to conclude that the virus was present in the filtrate. The agent can be dried, a procedure which would kill tissue cells, and can be kept in a dry state for years.

Further support of the virus theory has come from a number of findings in such animals as rabbits and frogs, although the evidence is not as extensive as in the case of avian tumors. More recently, a Japanese, Dr. Kinoshita, has presented evidence that a cancer virus may have been responsible for a tumor in a rat which the experimenter accidently came upon. Dr. Kinoshita himself says that the active agent of this tumor—which he calls factor O—cannot definitely be termed a virus without further study, and many informed researchers are not prepared to classify factor O as a virus.

In addition to this evidence, one might also mention the mouse milk factor (which is discussed under the chapter on genetics) as possibly implicating viruses in cancer. If the milk agent should prove definitely to be a virus and if factor O should prove to be a virus, then the evidence for viruses in cancer will have been carried into mammals, which, in a sense, brings the problem a step closer to man. Dr. Samuel Graff, at Columbia, has isolated what appears to be the virus of mouse mammary cancer.

But this does not dispose of the perplexities of the virus theory. Among these, as Dr. Rous has noted, is the fact that the viruses are quite specific for certain species and for certain types of cancer. To account for the scores of diverse tumors in the natural world, including tumors in man, in terms of
viruses, one might have to invoke so many different kinds of viruses that the theory would end in utter confusion.

This is a very important point. If the previous paragraph did not make it clear, the following one will.

For example, each cancer virus acts only on animals of the species from which it came, or at most on nearly related species, and each produces a cancer of a single kind, the frog virus causing kidney tumors of a special sort, and those only in leopard frogs, the chicken viruses producing growths like those from which they were procured originally, rarely doing so in other fowls than chicken, and the rabbit virus giving rise to warts of uniform appearance under the microscope after inoculation into the skin of cottontail and jack rabbits, swamp hares, domestic and snowshoe rabbits, but acting on no other animals of the many tested.

In man, just a description of the various kinds of tumors which plague him would fill a large volume, and if one must account for all of these differing growths in terms of a special virus for each, one is dealing with a subject so complex that it virtually defies analysis.

The fact that one and the same virus, or at least a few viruses, do not appear to account for the many types of cancer in the animal world has soured a number of investigators on the virus concept.

But instead of souring Dr. Francisco Duran-Reynals at Yale it has only served to stimulate his imagination. Dr. Duran-Reynals is one of the few workers in the cancer field who is willing to state—quite unequivocally—that the basic problem of cancer makes sense only in terms of viruses, or virus-like agents.

He brings powerful arguments to bear on his theory and even those who disagree with him—and there are many—will admit that his researches are inspired, offer considerable food for thought, and are not to be disposed of lightly.

In a series of experiments over the last 8 years, Dr. Duran-Reynals has attempted to show that in avian cancer, vi-
Viruses

viruses mutate (change) from host to host and that the virus has the ability to mask itself while being harbored in a certain host. At a theoretical level, his experiments cover some of the objections to the virus theory, but all the returns are not yet in and it is difficult to make a final appraisal.

Dr. Duran-Reynals tried, for example, to transmit the Rous sarcoma to adult ducks. He had no luck. But in young ducks the virus would take and the “take” would result in two types of response: in one case an immediate tumor in a couple of weeks; in the other case a tumor of somewhat a different type which appeared after a latent period of several months.

In the case of the first tumor one could extract a virus from this growth, but it was still a chicken virus, basically, because it would not take in old ducks, but could be transmitted back into chickens. In the case of the second tumor, extracts would yield a filtrable agent which was specific for ducks, but would not take in chickens (from which the virus came originally).

The net result of these and other experiments was to provide basis for the argument that a cancer virus can change, under certain circumstances, and therefore one need not invoke a multiplicity of viruses to account for the myriad forms of cancer. Within the limits of such a concept, one virus, or a few viruses, could, theoretically, account for many forms of cancer.

As yet, however, the changes induced in the avian viruses have given tumors not widely different from those they ordinarily produce.

An important observation made by Dr. Duran-Reynals was this: The virus causing the Rous sarcoma in adult chickens causes in young chicks a generalized destructive disease similar to the disease induced by the viruses of smallpox, encephalitis, etc. This established, to his satisfaction at least, that the virus of cancer is not the rare disease-causing agent that it was thought to be but an agent that, in the proper circumstances, can produce a disease not only completely unre-
lated to cancer but strikingly similar to many ailments, caused by well-known viruses, and typical of the young.

This happens in chickens and other birds and the question that worries Dr. Duran-Reynals is the following: It is well known that in many mammalian species, including man, the young suffer from acute generalized diseases produced by viruses and the adult has cancer; a connection, he thinks, between these two forms of disease has been found experimentally in birds, but can the same be found in mammals?

Take it easy, now. The question is: Can the same connection be found in mammals, if, indeed, there is a connection (which his theory dictates there is)? He has not yet found this connection in mammals, and many researchers think he is walking over desolate experimental terrain, doomed to failure.

His work poses a nice question, however, which most researchers find difficult to answer: Is this chicken virus a cancer virus of the adult that induces a destructive disease in young, or is it a destructive virus of the young that induces cancer in the adult?

Dr. Duran-Reynals is trying to answer these questions, and if his results are confirmed experimentally, the implications in cancer would be staggering; for the problem of viruses and cancer will have to be re-evaluated all over again. It is too early to draw any conclusions from the work.

For one thing, there may be error in the experiments. But Dr. Duran-Reynals’ work is being watched closely by many well-informed cancer workers, most of whom do not agree with his conclusions.

Dr. Duran-Reynals’ concept of cancer takes into account endocrine, nutritional and genetic factors but the crucial inciter of the disease, as far as he is concerned, is a virus, or a group of viruses.

This brings us back to a point made in the opening discussion on the virus theory, and one which furrows a brow occasionally among the researchers.
Viruses

It is this: If there is a cancer virus in human beings, and if it is specific for humans, how would it be possible to detect it? Presumably such a virus would not “take” in another species, if it is specific for humans. The crucial test for the activity of such a virus would, in our present state of knowledge, have to take some form of experimentation on human beings; in other words, the attempt to pass the virus from a cancer patient to a non-cancer patient. But this is out of the question, and properly so, in a democracy.

Since for moral, if not technical, reasons, such a type of experimentation would not be used, there is raised one of the most disturbing paradoxes in cancer research. It is this: If viruses are the cause of cancer in humans, and if it is not possible to show this, then it is not possible to prove what the cause of cancer is in human beings. To say that such a situation would complicate the problem of understanding cancer is to add an almost ridiculous understatement.

Therefore, one problem for research, to determine whether or not Dr. Duran-Reynals has hit on a question of fundamental importance, is to find means to “unmask” the virus in man (if the virus is there). That, in a phrase, is the whole point of Dr. Duran-Reynals’ work—finding methods to unmask a virus which he believes is hiding somewhere in the room, so to speak, but which most researchers suspect has not even gotten in the front door, as far as human cancer is concerned.

There is a hopeful angle to this: Microscopes of high power, such as the electron microscope, may enable man to see viruses within malignant cells and to identify them as such. (The electron microscope can magnify objects several hundred thousand times—the equivalent, roughly, of blowing a football up to the size of a city.) Such an instrument might show if there is a virus implicated in human cancer. This would help to solve part of the problem; at least it might show whether or not it is sensible to think of human cancer in terms of viruses.
14. Genetics:

The Problem

There are billions of cells in the human body, cells of many varieties, cells serving many purposes. These cells are acted on by many forces which, separately or in concert, affect in many profound ways the life histories of the cells, and of cell aggregates which are known as tissues.

For many years biologists have believed that the most profound influences at work on the cell were influences operating within the core—or nucleus—of the cell. It is within this nucleus that one finds chromosomes. The chromosomes carry the genes, which are the basic hereditary determiners.

The basic laws of genetics were formulated by Dr. Gregor Johann Mendel (1822–84), a monk and later abbot of the Augustinian monastery at Brunn, in Moravia. He recognized heredity as of major importance for understanding life and on the basis of his work with the pea, Pisum, which he

A cell is shown in the process of division. The chromosomes (U-shaped particles) have already divided and will soon form the two nuclei for the daughter cells. The hereditary properties are transferred by way of the chromosomes.
The Challenge of Cancer

studied in the monastery garden, he developed certain basic concepts about heredity which today form the foundation stones of genetics.

Later experimenters—Dr. W. E. Castle, Dr. T. H. Morgan, and others—added superstructure to Mendel’s work and in time it came to be recognized that certain thread-like structures in the nucleus of the cell, known as chromosomes, carried the basic units of inheritance. The units came to be known as genes.

The existence of the gene has been challenged from time to time and it might be pointed out that no one has ever positively seen a gene even under the highest power of the best microscope unless a recent report that an electron microscope may have identified this particle, proves to be correct. The gene has come into man’s thinking as a way of explaining how certain hereditary characteristics—such as eye color and other physical features—are transmitted from generation to generation. As a concept in biology, it has proved to be a pretty good one, explaining many things simply which otherwise could be explained only with the greatest difficulty, if at all.

At the moment, the gene is taking a beating from Russian scientists, (or the Russians are taking a beating from the gene), but it is not the purpose of this discussion to resolve, even if it were possible, the argument between Communist and non-Communist geneticists, if one can be permitted such a weird division of the animal kingdom.

Before looking into the question of heredity and cancer, one point should be made clear at the outset: In terms of generations a mouse-year is almost a man half-century, and for tendencies, such as cancer, to appear in man the way they appear in mice, brother-sister breeding would have to have persisted in one family without a break since the days of Abraham. With the haphazard inter-marrying of the human race, nothing comparable to such a cancer strain can appear.

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**Genetics**

In 18 years of operation—up to the tragic fire in October 1947—the Roscoe B. Jackson Memorial Laboratory in Bar Harbor, Maine, had built a collection of 90,000 rodents, including the oldest recorded strains in the world. One strain went back 210 generations to the year 1907 when the laboratory's director, Dr. Clarence C. Little, who has probably contributed as much as any man to an understanding of the cancer problem, had first become interested in mouse genetics. The year 1907 for mice is the same as tracing human ancestry back to 2252 B.C.

If this is so, then one can ask what the point of the mouse breeding experiments is, if they cannot be correlated directly with the human problem. The point is this: The geneticist, as any other scientist, wants to get as many variables out of experimental material as possible so that he can exercise some control over the experimental material. So he breeds strains of animals which are genetically pure (that is, the animals effectively have exactly the same genetic make-up; are all twins so to speak) and then he manipulates his material in such a way as to show the effects of, say, hormones or viruses or vitamins or other chemical agents on the animals. He knows that whatever results he achieves cannot be disrupted by genetic variables, because the genes—the basic carriers of hereditary traits—are exactly the same, or, at worst, almost exactly the same. This enables him to draw certain conclusions which he could not draw from human material, since he would not know, in the case of human material, what effect random inter-marrying down through the ages has had on the result.

Let's put it another way: If two parents were to possess identical genes, the offspring would also have the same genes and would, therefore, be genetically homogeneous. Under normal conditions of haphazard breeding (as obtains in man), this practically never happens, the only examples of genetic homogeneity being found in identical twins. (The reason for the homogeneity in twins is that the two members have developed from a single fertilized ovum.)
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The same lack of genetic homogeneity is also found in animals that are allowed to breed haphazardly. It is possible, however, to produce a strain of animals, all the members of which possess the same genetic make-up, and this is what is meant by a genetically "pure" strain.

This is done by consecutive brother-to-sister mating for some 20 to 30 generations. With each brother-to-sister mating, the genes that happen to be identical continue to be transmitted; the dissimilar genes have a 50-50 chance of dropping out, while no new types of genes are introduced. Thus, if this form of close inbreeding is continued for a sufficient number of generations, the ultimate offspring will all have identical genes.

The advantages to the geneticists of creating such "pure" strains of animals are obvious, for only under such conditions is it possible to establish with certainty that any particular characteristic is transmitted by the influence of a gene. By crossing a member of one pure strain with that of another pure strain, it is possible to predict the proportion of offspring that will display a particular characteristic, and from the manner of transmission it is even possible to determine whether only one single gene, or several different genes, are implicated in the hereditary transmission.

On the other hand, in a group of animals of mixed genetic constitution, hereditary transmission may not display such a simple mathematical pattern, and when one is dealing with a hereditary characteristic dependent on several genes, its actual occurrence among the offspring of mixed genetic constitution may be so irregular and sporadic as to appear to be independent of heredity.

This is more or less the position as regards cancer. Actually, the problem in relation to cancer is even more complicated, since there are separate sets of genes for each type of cancer. This enables one to understand why the role of heredity in cancer should be so hard to recognize when studied in communities of people (or animals) of mixed genetic con-
A word of warning is necessary here. The term "inbred strain" is used in the technical sense only. Such a strain is obtained by twenty to thirty consecutive brother-to-sister matings, and only by such means can one hope to approach identity in genetic constitution among all the members of the colony. The popular conception of inbreeding in man (that is, the mating of cousins) is, therefore, far removed from the geneticist's idea of inbreeding. Any fear that inter-marrying may accentuate the tendency for cancer among the offspring is remote, and can probably be dismissed.

A layman is likely to be unsatisfied with such an explanation, however, and re-state his question this way: Since the geneticist's results apply only to animals in controlled experiments, what possible bearing can this have on the human problem? It has this bearing on the human problem: the geneticist can formulate theories about the role of, say, hormones, in human cancer; and he can be reasonably sure of his results. It is true that such results may not lend themselves to a literal interpretation for man; but it is also true that, by breeding animals susceptible to cancer and animals not susceptible to cancer, the geneticist can knock one variable (the gene) out of his possible experimental error and more easily formulate broad concepts of the disease.

At least he understands the material he is dealing with and can assert, with some assurance, that, given this situation, such a result will be achieved; or given that situation, another result will be achieved.

By constantly refining his methods, he hopes to arrive at a completely controlled experiment where he can draw conclusions which might apply, quite dramatically, to the human problem. Such a level of excellence has not yet been reached, but the geneticist has given cancer workers some clews about the disease.
15. Genetics:

*Fish Melanoma and the Mouse Milk Factor*

The more a geneticist looks at cancer, the more convinced he becomes that there are many forces at work in the development of the disease, only one of which is, strictly speaking, the so-called genetic—or “susceptibility”—factor. The use of the word “genetic,” or in this case “susceptibility,” means simply something under the control of the gene but exactly what the gene controls in cancer, or how it controls it, is not clear.

A geneticist has bred certain animals, notably mice, a great percentage of which will, at the appropriate tumor age, come down spontaneously with certain types of cancer, for example, mammary cancer, lung cancer, liver cancer, and cancer of the blood-forming organs (leukemia). He can also breed mice which have a low incidence of the disease. Many of these lines were started years ago—dating from 1920—by Dr. L. C. Strong, now at Yale. There have been 103 gen-

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*Genetic factors in tumor development are illustrated by studies on fish. When an albino swordtail without black pigment (A) is mated with a black-spotted platyfish (B), their hybrid offspring develop pigmented tumors—melanomas.*
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erations of the A strain of mice started by Dr. Strong. This is an albino strain with a high incidence of breast and lung tumors.

Such breeding is done by brother and sister mating of “susceptible,” or “non-susceptible” lines, and in some cases the anticipated cancer at the expected age will run as high as 90 to 100 percent; that is, of 100 mice of a susceptible line, anywhere from 90 to all of them will come down spontaneously with the expected cancer.

Dr. Walter E. Heston and his colleagues at the National Cancer Institute have shown that four specific genes will influence susceptibility to lung cancer in mice: the flex-tail gene (that is, a gene which produces a flex-tail in certain mice), the so-called Shaker II gene (which is associated with a neuromuscular defect in mice), the hairless gene and the lethal yellow gene. What this means is that cancer susceptibility increases as these genes are present but why this should be so, no one knows.

There is another way to look at this question, and it involves—of all things—fish. The fish are swordtails and platyfish, two fairly well-known species (at least to fish-lovers they are well-known), and experiments with these fish have thrown a clew onto the researcher’s table.

A scientist at the New York Zoological Society has been able, by breeding experiments, to produce spontaneous cancer in fish along lines that suggest some similarities to the human problem.

The scientist, Dr. Myron Gordon, a geneticist, did the experiments in laboratories at New York’s American Museum of Natural History. Immediate significance of the work is that it helps to explain how animal cancer is linked to a gene, or, more likely, to a constellation of genes which produce a condition favoring the development of cancer.

The cancer—in this case a type known as a melanoma—is induced simply by the mating of a swordtail fish and a platy-
Genetics

fish. No chemicals are used—in fact, no artificial laboratory procedures of any kind are used. When platyfish mate, this type of cancer does not appear. When swordfish mate, it does not appear. Mix the species, and it does appear.

Briefly, here is the point:

Normally the platyfish has certain pigmented areas on its body, particularly on the dorsal fin. When platyfish breed, this pigmentation is perpetuated from generation to generation without harm to the host.

The swordtail does not have the black markings, but if a swordtail is mated to a platyfish, the black pigment cells overflow in the progeny, so to speak, developing into various stages of the type of cancer known as melanoma. For technical reasons, the experiments are so manipulated that half the progeny of a given mating will develop melanosis (an extreme form of blackening which can develop into a melanoma).

Although relatively rare, melanoma can be an especially vicious form of the disease in humans, particularly if it arises in pregnant women, as it does only infrequently. As nearly as pathologists can determine, the melanoma cells of the fish and the human are similar in appearance, if not identical.

In the series of experiments conducted by Dr. Gordon, the cancer was produced simply by cross-mating one species of fish with a closely related species. This gives the experiments a somewhat different slant than the classical mouse genetic experiments, where the animals are produced by brother-and-sister mating.

In a sense, the fish work may more closely approximate the actual situation as regards humans than the mouse work, for the scientists not only mated two closely related species, but actually mated various types within the same species and produced somewhat similar results.

The second experiment, completed more recently, turned on finding two populations of a single platyfish species which had been separated for ages, and reuniting them. They were
found in different Mexican streams, which, according to geologists, were cut by land upheavals 300,000 years ago at which time the fish, which probably had all been living together, were permanently separated in nature.

In this experiment with these fish of the same species, one type of the platyfish had the dorsal fin pigmentation and the other did not. The progeny developed melanosis of the dorsal fin which, in effect, repeated the result of the platyfish-swordtail experiment. All the fish were found in Mexico, Guatemala, and British Honduras and the original research dates from 1931.

As far as the geneticist is concerned, the experiments, in simple terms, show that the swordtail contributes several genes to the progeny which convert the normally quiescent pigmented cell into a rapidly proliferating one. In some way the normal growth regulators, whatever they may be, which hold the black cells of the platyfish under control, are loosened by the introduction of genes from the swordtail. Evidence indicates several genes are involved in this process.

Dr. Gordon calls the gene introduced into the progeny by the swordtail a “modifying factor.” By this he means that the swordtail gene or genes modify the genetic environment of the hybrid progeny in such a way as to convert the normally non-cancerous black cells into cancer cells. One of his objectives now is to refine his research to get closer to the actual genes involved, to find out how many modifying factors may be at work in this process.

Another possibility would be to try to find a chemical that would induce the same type of cancer produced by the mating experiment. Then one might be able to draw some guarded conclusions that if the chemical produces the same cancer as the mating experiment, and if the mating experiment can be interpreted in terms of a gene, then possibly here is a clue as to how genes produce these effects. This is not a completely
satisfactory concept, and probably oversimplifies the problem, Dr. Gordon concedes.

In any event, Dr. Gordon would like answers to these questions: What chemical and physical forces can change normal fish pigmented cells to the cancerous cells? What chemical and physical agents can reverse the process in changing the cancerous cells back to normal pigment cells?

With this and a mountain of similar experimental evidence, one might suppose that the geneticist could formulate, at least for certain types of animal cancer, a simple view of the origin of cancer to embrace a number of rather remarkable effects.

But the problem in the mouse is complicated by many factors, including the following: a genetic factor or factors which control susceptibility to a virus, control the ability to propagate a virus and control as well the hormonal activity of the animals; a milk factor, or influence; and a hormone factor, in addition to the one controlled genetically. In February, 1949, at the National Cancer Conference in Memphis, one of the factors was formulated this way: a factor concerned with or resulting from the pregnancy of the animal, hence, presumably, hormonal.

One might add here immediately, to ward off any misunderstanding, that the bearing of young increases the disease incidence in mice, but decreases it in man; women who have borne children have a statistically lower incidence of breast cancer than those who have not, with the possible exception of those with five or more pregnancies.

The milk factor was discovered a decade ago by Dr. John J. Bittner and his colleagues at Bar Harbor growing out of previous experiments indicating there was a maternal influence at work in mouse mammary cancer.

Dr. Bittner noticed that when the young of a high-cancer mouse were foster-nursed by a female of a low-cancer strain, the young failed to develop cancer at the appropriate age as would have been expected. He also did the reverse experi-
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ment: he took young from low-cancer strains and wet-nursed them to mice of high-cancer strains, discovering that many of these mice later developed mammary cancer.

This indicated that there was a factor in the milk inciting the cancer and this "factor" or "agent" seems to have many properties of a virus, although some exceedingly cautious workers do not absolutely identify it as a virus. The agent, or factor is of small size, it can be filtered the way a virus can be filtered, it appears to propagate in a living cell and it has certain antigenic properties, all of which link it, presumably, with a virus. But there is an exasperation here, for one is not able to produce antibodies against this virus, if it is a virus, directly in the mouse. One can inject rabbits with an extract from the mouse tumor, get antibodies against the agent which is injected, and then on injecting these antibodies back into mice, one can get immunity to the milk factor. It is possible that researches being carried out by Dr. Duran-Reynals at Yale, discussed under the section on the virus, may help to explain this phenomenon. But at the moment it is one of the roadblocks in progress toward understanding what kind of an entity the milk agent is.

The difficulty does not end here, however, for Dr. Bittner has told this writer that there are cases where a male and female from strains presumably free of the milk agent have been mated and produced progeny with the milk agent, and these progeny, moreover, will show spontaneous mammary cancer under certain circumstances.

If you aren't sufficiently baffled at this point, examine the experiment performed by Dr. H. B. Andervont at the National Cancer Institute: he took females of a strain of mice which shows less than 5 percent spontaneous mammary cancer, bred this animal to a male from a high mammary cancer strain (a strain with the agent), and the female progeny showed a 60 to 90 percent incidence of spontaneous mammary cancer, an utterly baffling result when viewed in the light of previous
experiments with offspring from high and low mammary tumor strains of mice.

To add to this nice riddle (or, if you prefer, mice riddle), one might point out that in these progeny (where spontaneous mammary cancer developed in 60 to 90 percent of the animals), only a very small percentage of the young show the milk factor, and these mice develop tumors at an early age. Thus far efforts to detect a milk factor in the mice that develop tumors at an older age, have given negative results.

It is possible, in the case cited by Dr. Bittner and in Dr. Andervont's experiment, that researchers are unwittingly contaminating the mice by passing the milk agent from their fingers. Or, since it known that the agent is in the blood of high tumor strain mice, it might be transmitted by a biting insect, thus adding an error to the experiment.

It is also possible, in Dr. Andervont's case, that the milk agent is not the real explanation for the high incidence of cancer, but that there are other factors at work. Or it is possible that the agent may be there and is masked, a term which would fit Dr. Duran-Reynals' theory, or it may be there and counterbalanced by an inhibitor, or it may lack some constituent x that keeps it from producing mammary tumors.

On the basis of Dr. Andervont's experiment, one might guess that a milk factor can be transmitted by both the male and female, which adds something new to the picture. But this immediately raises the question that if this is so, then why does it not show up, in these particular experiments, in the progeny in substantial measure? The question arises as to how the milk factor can be transmitted through the male, if it is. Dr. Andervont reports that the factor has been shown in the spermatic fluid of males known to contain the agent.

The mouse work of the geneticists has led pediatricians to wonder if the milk agent should be taken into account in advising mothers as to whether or not they should nurse their young. It is difficult to get an agreement on an answer.
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among scientists. For one thing, mouse mammary cancer is in many ways of different structure, when viewed under the microscope, from mammary cancer in humans. But this would not in itself throw out the mouse findings as far as human beings are concerned.

Experimenters have tried to find the milk factor in other animals and up to this point have met consistently with failure. Often a biological phenomenon found in one species is likely to be found in a whole series of species. But in this case, the positive animal evidence would indicate that the milk factor is strictly a mouse problem.

As far as the available statistics in human beings are concerned, one can argue the question either way. One geneticist can cite statistical evidence to show that the incidence of breast cancer is just as high on the paternal side as on the maternal side. A recent British report, however, showed that the incidence among mothers and sisters of women who develop breast cancer was two to three times higher than what one would expect in the general population, a finding which has impressed some investigators, leading them to wonder if there is, in man, a phenomenon similar to the milk factor of mice.

The best one can say is that conclusions applied to humans, on the basis of mouse mammary cancer, are dangerous; and as far as the statistical human picture is concerned, the evidence is equivocal.
16. Hormones:
The Treatment of Cancer

The word hormone derives from a Greek word meaning "to rouse or set in motion" and that's about the simplest way there is to explain what these remarkable chemical messengers do in the human body. They travel by way of the blood stream, linking several important glands. They affect growth, reproductive capacity and the body's elaborate and little understood mechanism for protecting itself against invasion by agents from the outside world.

The hormones originate in such organs as the pituitary, which is a small gland at the base of the brain; the thyroid, the pancreas (which secretes insulin, generally considered a hormone); the adrenal glands, which lie above the kidneys, and the reproductive organs. The reproductive organs produce estrogen and progestrone, the female sex hormones, and androgen, the male sex hormone.

The pituitary—the gland at the base of the brain—seems

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The location of the endocrines (ductless glands) is diagrammed. The hormones secreted by the endocrines promote and regulate normal growth, and their effect on the growth of certain tumors has been clearly shown.
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to run most of the endocrine show by producing hormones which act on other endocrine organs. And the pituitary in turn is acted on by secretions from these other organs. So the hormones are traveling along a two-lane highway, so to speak, influencing other hormones, or, to mix the metaphor, holding the network in control by a magnificently arranged system of checks and balances.

Geneticists have found some interesting facts about hormones and cancer and are finding new ones as the weeks go by. Much of this evidence provides the foundation stone for the modern treatment of some forms of cancer.

Other experimenters, working with strains of mice susceptible to breast cancer, castrated the males, transferred the ovaries from the sisters of the mice into the males and noticed that these male mice, with ovaries, came down with as high an incidence of breast cancer as the virgin females. Dr. La-cassagne, a Frenchman, did the same experiment, essentially, in a different way. Instead of transplanting ovaries (which produce estrogen, the female sex hormone), he injected the female hormone, estrogen, into the males. He also noticed the increase in breast cancer.

Dr. William Gardner, at Yale, and his colleagues, Drs. Carroll A. Pfeiffer and Charles W. Hooker, produced testicular and pituitary tumors in mice of certain strains with estrogen, the female sex hormone, and tumors of other types with various kinds of hormone administration. This led the workers to the general conclusion that several endocrine tumors arise, in experimental animals, under conditions of what might be described as "hormonal imbalances." What this means is that there is a certain normal relationship among the endocrine organs and if one or more of them is disturbed, tumors can result.

A beautiful experiment by Dr. George Woolley at Bar Harbor, threw added light on this problem. Mice of certain strains, castrated immediately after birth, will develop an
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adrenal tumor in 6 months. (The adrenal gland, as noted previously, is part of the endocrine system.) It is possible to arrest this process in the first 2 months of the mouse’s life by administering either female sex hormones (estrogens) or male sex hormones (androgens). Dr. Woolley, in other words, produced cancer on order, then found a way to stop it on order.

What is the explanation of such an experiment? It is this: castration upsets the balance between the pituitary (the gland in the brain which runs the endocrine show) and the gonads, which are the reproductive glands. There is a reciprocal relationship between the pituitary and the gonads, each acting on the other. With less check on its activity following castration (the gonads could no longer act back on the pituitary), the pituitary becomes stronger and overwhelms the adrenals. The adrenals, battered by pituitary activity for months, reach a point where presumably some chemical transformation takes place which converts normal adrenal cells into cancer cells. So when Dr. Woolley administers sex hormones, he helps to maintain the balance among the endocrine glands in castrated animals. By maintaining this balance, the problem of adrenal tumors is minimized.

One may ask why both the male and female sex hormones help to maintain this balance, in both male and female animals. The explanation of this seeming paradox is that both hormones will depress pituitary activity. The reciprocal effect on the pituitary, in other words, is not sex specific.

The literature on hormones has reached gigantic proportions, much of it in recent years due to the interest which cancer has stimulated in hormone studies, or perhaps vice versa—the interest which hormones have stimulated in cancer studies. Today some workers in this field will assert that much about cancer in man—possibly even the basic problem of certain forms of cancer—will be explained ultimately in terms of the activity of hormones.

A mass of experimental evidence from many types of ani-
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mals, and prominently from mice, has revealed a significant relationship between the hormones and cancer, and today the sex hormones are among the drugs used in the treatment of cancer.

Some scientists would argue that a sex hormone never cured a case of cancer and, in man's present state of knowledge of these substances, quite possibly never will. Others point out that this is much too dim a view and that in any event a few years ago there was no way to treat cancer, if not cure it, by simply giving a pill by mouth.

Although the pill—the hormone—may not cure cancer, it is beneficial in treatment of certain types of the disease, it is argued, causing the cancer to abate temporarily, on occasion, and offering a relief from pain, thus prolonging life and making the patient more comfortable.

Hormones are used in treatment of cancer of the breast in women and cancer of the prostate in men; also in treatment of male breast cancer.

Interest in the surgical aspects of the hormone problem dates from 1896 when an Englishman, Dr. G. W. Beatson, removed the ovaries of a patient with breast cancer and noticed that the cancer regressed. He wrote in "The Lancet" that "I feel there is ground for the belief that the etiology (causation) of cancer lies not in the parasitic view but in an ovarian or testicular stimulus, and that the whole subject requires careful working out."

In modern times interest has been stimulated in hormone treatment, particularly in recent years, by a number of developments, among them the surgery performed a few years ago by Dr. Charles Huggins, of Chicago.

In a bold move, based on evidence derived from his experiments on dogs, Dr. Huggins castrated men with cancer of the prostate gland. About 25 percent of the patients were cured—at least they were alive more than 5 years after the operation—with no signs of the disease.
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The treatment showed that cancer is associated with the production of the male sex hormone, androgen, and that castration, which cuts off this production, can palliate, and in some cases perhaps cure the disease. Therefore, something new was added to the cancer picture in man—the realization not only that hormones are implicated in the cancer problem but that it is possible to do something about it.

Here is the point: if one can antagonize cancer by shutting off, through surgery, the activity of the male sex hormone, then would it be possible to achieve the same result by some less drastic, say, a chemical, treatment? The next logical step would be to pursue known leads involving the female sex hormone, estrogen, to see if it would antagonize the male sex hormone. Dr. Huggins and his students tried it in human cancer and they found that estrogen does, indeed, cause a temporary remission of the disease in some cases.

Dr. Huggins, and some other scientists, made it clear, and subsequent findings have borne them out, that although estrogen has a palliative effect occasionally, it does not cure the disease. Hormones would seem to be able to abate the cancerous process, in some cases, but the evidence would indicate that they do not alter the end result.

Not only is this true in prostatic cancer but it seems to be true as well in breast cancer in woman where the treatment in some cases—notably older women—involves the use of estrogen, and in other cases—covering a more widespread range in age—includes the use of androgen.

In another direction, hormones may offer clews to the nature of the cancer process. Here is an example. There is associated with the onset of prostatic cancer a rise in the activity of a certain enzyme in the serum. The substance is known as acid phosphatase. The level of acid phosphatase in the blood serum is a delicate indicator, in prostatic cancer, of cancer activity. It is so delicate that as a doctor watches the enzyme's curve of activity, as it rises and falls, he can predict
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when the patient is going to feel badly and when he is going to feel well. As the enzyme rises, the cancer becomes worse. Under castration and hormone therapy it is lowered for the length of time that the treatment is effective.

It is probably too much to hope that the enzyme itself is the fundamental problem. But as an indicator of the course of the disease, it becomes an important tool for the investigator.

There is another vital point in connection with Dr. Huggins' work. Cancer traditionally has been looked upon as an autonomous growth, which in some way frees itself from controls the body exercises over normal tissue. Yet if hormones have the faculty of reversing this process—even though temporarily—then the theory of autonomous growth must be modified.

This, in a sense, adds a bright side to the picture. If one substance will reverse the cancer process—again, even though it is only a temporary reversal—then it is a fair guess that there must be others which will do the job even better.

As a matter of fact there are other hormonal agents which do have a marked but temporary effect on certain forms of cancer, and recent work at the Sloan-Kettering Institute and Memorial Hospital in New York, and at other research centers, has thrown open what virtually amounts to a whole new line of investigation into the endocrine aspects of cancer.

Scientists there report that two scarce hormones, which previously have received wide publicity for their palliative effects in a variety of conditions, including rheumatoid arthritis, have produced experimental results in cancer which justify further investigation. The hormones are known as ACTH and cortisone. ACTH is extracted from the brains of hogs. Cortisone, formerly known as Compound E, is made from the bile of butchered cattle.

Both are in such short supply that even if the substances should prove valuable in the management of certain types of cancer—a fact which is not yet established—there would
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hardly be enough for extensive therapeutic purposes. Scientists have gone so far as to assert that for years to come there will not be enough of the hormones for more than experimental work on a few patients.

The usable front half of each hog's pituitary is about the size of a pea. It takes 1,360 of them to make a pound, from which about 1½ grams (a third of a teaspoonful) of ACTH can be extracted in a solution and separated as a white powder. The Armour Laboratories in Chicago, the main source of ACTH, with the cooperation of other stockyards not under the direction of Armour, can get only about 125,000 hog pituitaries a week, enough to make 5 ounces of ACTH. All the hogs slaughtered in the United States would not yield much more than a pound a week. Cortisone is even scarcer. Merck & Co., which makes it in 37 steps from cattle bile, produces only about 1½ ounces a week. Only 1 pound of this ingredient can be obtained from 130 pounds of bile.

There are serious limitations to the use of these drugs, among them the possibility that in the doses required to achieve therapeutic effect in cancer the substances may cause such distressing side effects as severe nervous disorders and a host of symptoms associated with a condition known as Cushing's Syndrome. This latter condition is characterized by water retention, a moonlike face, buffalo neck, marked increases in blood pressure, growth of beards on women, and a rise in blood sugar.

Despite all these limitations, however, and even if the drugs do not provide a new, practical treatment for certain types of cancer, investigations with these two hormones, and other hormones, have stimulated an enormous amount of interest among researchers. The study of hormones seems to be putting into medical literature clew after clew concerning certain fundamental mechanisms in a wide range of diseases, and this is particularly true in the cases of ACTH and cortisone. On the basic structure that seems to be develop-
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ing may ultimately be built sound treatment of many conditions now beyond the control of laboratory chemistry.

The cases reported by the Memorial group included a patient with cancer of the prostate and another with cancer of the breast, neither of whom seemed to receive appreciable benefit from ACTH, and six cases of cancer involving the lymphatic organs, where the drugs caused progressive decrease in the size of enlarged lymph nodes and of enlarged spleens. Effect of the drug was apparent after 3 days of ACTH treatment and 6 days of administering cortisone.

In none of the patients studied has a complete clinical remission of the disease been obtained. Of the six patients, four showed a regrowth of abnormal masses within a period of 10 weeks of observation after ACTH was discontinued, two of them showing a second response to the administration of ACTH or cortisone. This indicates that tumor resistance has not yet developed to these agents. Of the six patients, two had shown no evidence of regrowth of abnormal masses within a period of 10 weeks of observation after ACTH was discontinued.

ACTH is chemical shorthand for a substance known as adrenocorticotropic hormone. It is secreted by the pituitary, the small gland at the base of the brain, and stimulates the production of hormones in the adrenal cortex. One of these adrenal hormones is cortisone. The adrenals, as noted earlier, are small organs which lie above the kidneys. The cortex is the outer portion of these organs.

There were a number of clews in the literature that led the Memorial workers into the experiment, among them evidence that increased adrenal cortical function in animals resulted in an involution (shrinkage) of normal lymphoid tissue, and evidence that administration of Compound E resulted in regression of a lymphoid tumor in mice.

At another level of the cancer problem, a Memorial Hospital team, which includes Drs. Konrad Dobriner and Sey-
Hormones

mour Lieberman, is working on an assumption that in cancer, or at least in certain forms of cancer, there is a disharmony in the endocrine system due to faulty regulation and production of the steroid hormones of which the sex hormone is a type.

They are studying the end products of these hormones in the urine of cancer patients and normal patients, trying to find significant differences. If these differences can be found, the chemist may be able, by deduction based on a knowledge of test-tube reactions and chemical reactions in animals, to figure out what the disharmony is in man. Then, perhaps, by chemical means he can reverse the process.

The Dobriner group has come up with some interesting findings but the work cannot yet be applied to any extent at the clinical level. It has been found that there is present in a significant number of cancer patients a compound which is significantly associated with cancer.

The compound has one of those chemical names which terrorizes a layman: \(11\)-hydroxyetiocholanone. It is a compound associated with certain functions of the adrenal cortex (one of the endocrine organs). It appears in the urine of cancer patients. The appearance may mean one or both of the following things: (1) faulty manufacture of hormones, in general, in the adrenal cortex; (2) a faulty turnover of this particular substance in the adrenal cortex.

It has taken years of research and \$500,000 to do the many kinds of work necessary to isolate this compound. In the view of the Memorial group it offers a sound lead in cancer. Work is proceeding in an effort to determine urinary excretion patterns before and during treatment in cancer; to find why one person shows one pattern, another person shows another pattern; to determine if nature, through the excretory processes, offers clews to an understanding of cancer.
Growth is a fundamental fact of life, but little is known about it. Cancer is an abnormal form of growth. Since little is known about normal growth, little can be known about abnormal growth.

Scattered through the scores of thousands of experiments aimed at uncovering the facts of growth are a few clews, some of them provided by study of the endocrine system. This is the system involving the internal secretions of various glands. These glands discharge substances known as hormones into the blood stream.

According to Dr. Roy Hertz, at the National Cancer Institute, the endocrine aspects have shown a number of things of importance in recent years, two of them of special interest:

1. Abnormal hormone relationships in the body can result in malignancy. In experiments with a certain strain of mice,

The profound effect of hormones on normal growth is one indication of their importance in cancer. The smaller rat has failed to grow because its pituitary gland, which secretes growth hormones, was removed. The larger rat is normal and the same age.
The Challenge of Cancer

the male does not get breast cancer, but incidence in the female is high. If female sex hormone is administered to the male, the male will get breast cancer. If the ovaries of the female are removed early in life, thus cutting off production of sex hormones, incidence of breast cancer is reduced.

2. The work of Dr. Charles Huggins, of Chicago (referred to in the previous chapter), shows that if one is dealing with a tissue such as the prostate, which depends upon the male sex hormone for its normal functioning, even when this tissue becomes malignant it still depends on this hormone. This has a practical application in treatment of the disease, as noted previously.

Dr. Hertz and others are attempting to unsnarl the knotted threads of this problem in a somewhat different way. Dr. Hertz is interested in the growth effects of hormones and how this growth relates to the action of certain vitamins, such as folic acid, also involved in growth.

Thus, perhaps, a link may be established between two types of chemicals normally used by the body. If the evidence should hold up and show that this line of reasoning is sound, then the growth picture will be brought into sharper focus. With it will come a better understanding of the body’s complicated chemical factory.

To show how this picture appears to be developing, let’s look at some of the evidence from a few of Dr. Hertz’s experiments.

Both estrogen, the female sex hormone, and androgen, the male sex hormone, produce tremendous amounts of growth in the genital tract. The chick female genital tract will rise from a weight of 20 to 800 milligrams in 6 days under estrogen stimulation.

But to get such growth, certain things are necessary in the diet. One thing which is quite critical is folic acid, a member of the vitamin B complex. Dr. Hertz found that if the experimenter omits folic acid, but administers the same hormone
Hormones
dose to the animal, the genital tract will rise in weight only
60 to 80 milligrams, or about only a tenth of what it would rise
to under the influence of both substances.

If one returns folic acid to the diet, there is an increase in
growth, proportional to the amount of the vitamin used. The
experiment holds good for both the chick and the monkey
and has been confirmed in other laboratories.

This work has implications for man. The implications
lie in the direction of finding, among other things, certain sub-
stances which antagonize the action of folic acid. Such sub-
stances would allow for the possibility of inhibiting tissue
growth, normally supported by hormones, through dietary
(vitamin) antagonists.

Such a procedure, could it be worked out, would give the
experimenter an additional weapon in the hormone problem.
He would be able not only to match hormone against hormone
(as he does now by using estrogen, the female sex hormone, to
counteract androgen, the male sex hormone) but he might
also be able to counteract hormones with antagonists of dietary
elements.

There are a number of folic acid antagonists, so-called,
available for experimental work, but what is more important
is the fact that it has been discovered that certain of these
antagonists have irregularly a marked but transient effect on
acute leukemia, especially in children. Acute leukemia is a
cancer-like condition of the blood characterized by an ab-
normally high number of white blood cells.

Perhaps the best known of these antagonists is Aminopterin,
but there are at least two others which are used in the treat-
ment of acute leukemia. These are known as A-Methopterin
and Amino-an-fol.

Dr. Sidney Farber, at Children’s Hospital, Boston, was one
of the early workers with the anti-folic acid compounds, re-
porting encouraging results with Aminopterin, although he
did not claim to cure leukemia, nor did any other scientist.
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He reported he was able to produce significant remissions in the disease, not achieved by conventional forms of therapy. The picture is not completely clear yet and at this point it is difficult to decide where the so-called folic acid antagonists stand in cancer therapy, although many workers argue that these drugs have added a new weapon against cancer to the meager few that existed before to combat the leukemic form of the disease.

Returning to the main theme—the question of growth factors—it would appear that the problem is broader than a mere relationship between hormones and vitamins and vitamin antagonists.

The nucleic acids, which were discussed previously, seem to be implicated in this problem, which would tie together along a still somewhat tenuous thread, hormones, vitamins, and nucleic acids, three substances currently under intense investigation in laboratories throughout the nation.

In the discussion of nucleic acids it was pointed out that some of the constituents of nucleic acids are known as purines and pyrimidines. Certain antagonists of these substances can interfere with the growth of certain bacteria which require folic acid for growth.

One of these antagonists is known as 2,6 Diaminopurine, which antagonizes a nucleic acid constituent known as adenine. Dr. Hertz has shown that 2,6 Diaminopurine stops 60 percent of the growth response in the female chick genital tract. Such an effect is reversed by adenine.

One of the groups interested in this substance, 2,6 Diaminopurine, is a Sloan-Kettering team headed by Drs. George Brown and Aaron Bendich. It had been shown by Dr. George Hitchings, at the Wellcome Laboratories in Tuckahoe, that the substance inhibits growth in certain organisms which require folic acid.

The Sloan-Kettering group synthesized the substance in such a way that a stable isotope could be incorporated into
Hormones

the 2,6 Diaminopurine molecule. This enabled them to study the pathway of the drug through the organism. The experiment illustrates the important use to which tracer substances can be put in attempting to understand normal and abnormal chemical patterns in the body.

In animal tests, the drug proved to inhibit leukemia and other types of cancer, but this does not necessarily prove that it will have a valuable, practical effect on human cancer. But it may be a lead.

Another possible lead grows out of the work of Dr. George W. Kidder and his colleagues at Amherst College. They, as all other chemists interested in cancer, are looking for a significant chemical difference between a cancer cell and a normal cell. The work suggests there may be such a difference in terms of one of the nucleic acid components. The component is guanine, which, it is surmised, is a dietary requirement of tumor cells. By antagonizing guanine with another substance—guanazolo—tumor growth in mice was retarded. There is no evidence at this point that the procedure is applicable to man, a question which only future experiments can answer.

This discussion covers a wide assortment of experimental facts drawn from many fields. It adds up, somewhat sketchily, to a picture of the growth problem, in terms of certain chemicals used by the body. An attempt is made—it is one which many scientists are making—to relate some of these chemical facts to each other.

The picture would indicate that there is a relationship, in terms of growth, among hormones, vitamins, and certain nucleic acid constituents. The relationship is somewhat vague at this point and the evidence does not admit many conclusions. But it is conceivable that if this picture can be completed, much will be known about normal growth. Therefore, much may also be learned about abnormal growth, of which cancer is a manifestation.
If man would keep himself fit instead of fat, the chances are that cancer would be less of a menace to the human race than it is.

There is evidence from animal experiments that caloric restriction reduces the incidence of several types of tumors; there is statistical evidence, from various insurance companies, that overweight persons have a distinctly greater tendency for developing cancer.

This does not mean that overweight persons are necessarily going to be prey to cancer. It means that if one is fit, instead of fat, one stands a better chance of avoiding the disease and, it is believed, many other degenerative diseases as well.

Much of the evidence for these conclusions has come from

*The size of the tumor may indicate the effect of a special diet on cancer growth. Certain diets retard the appearance of spontaneous tumors in animals, and others affect the growth of animal tumors already established.*
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the work of Dr. Albert Tannenbaum at the Medical Research Institute of the Michael Reese Hospital in Chicago.

Dr. Tannenbaum hit on the idea for some simple experiments in 1937 when he noticed that in a group of mice on normal diets unrestricted in amount, some of the mice weighed less than others and it appeared that fewer of the smaller animals developed tumors. This led him to wonder if and how the amount of food intake might affect the incidence of tumors.

He did the following experiment:

Two groups of animals were studied, a control group which was given a diet unrestricted in amount and an experimental group in which calories were restricted either by simple underfeeding or by cutting down carbohydrates only.

All groups were then given a standard treatment with a cancer-causing hydrocarbon: In a suitable period of time, the control and experimental groups were compared for tumor incidence. The group on the restricted diet showed a significantly lower incidence of cancer. This experiment has been repeated, with the same results, on many types of induced and spontaneous tumors.

This raised an important point: Does the caloric restriction affect the origin of tumors or the growth of tumors, or both? It clearly affects the origin of tumors, according to Dr. Tannenbaum. That is, an animal which is fit instead of fat is less likely to develop cancer. But having developed cancer, for whatever reason, does caloric restriction inhibit the growth of the cancer?

Dr. Tannenbaum’s evidence and that of others indicates that it does but the experimenter adds a very important qualification: Although the growth of tumors in mice can be inhibited by caloric restriction and protein-deficient or vitamin-deficient diets, these effects, in general, are not produced selectively because the host loses considerable weight.

It may be concluded, he asserts, that at present no nutritive
components are known which alone or combined with others have sufficient selectivity to affect the growth of a tumor in a practical, useful way. Therefore, it is not proposed, on the basis of the mouse results and clinical experience, that cancer can be cured by restricting the cancer patient's diet.

There is a possibility, however, that Dr. Tannenbaum's work can provide a preventive measure of some significance. For if the population will keep itself fit instead of fat—which is a good idea for reasons relating not only to cancer but to other diseases as well—it may be possible to reduce the general incidence of the disease in the population, or at least prolong the onset of the disease.

After Dr. Tannenbaum got his mouse findings, he searched insurance statistics to see if they could be correlated with experimental results in animals.

A typical study was that of Dr. Louis Dublin, who used approximately 192,000 records (1887–1921) of the Union Central Life Insurance Co. for an analysis of cancer mortality. In this study the policyholders, men who had bought insurance at 45 years of age and over, were classified according to weight at issue of policy. The analysis resulted in the following distribution of cancer mortality with regard to weight:

<table>
<thead>
<tr>
<th>Weight at issue of policy</th>
<th>Cancer Mortality per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 percent or more overweight</td>
<td>143</td>
</tr>
<tr>
<td>15 to 25 percent overweight</td>
<td>138</td>
</tr>
<tr>
<td>5 to 15 percent overweight</td>
<td>121</td>
</tr>
<tr>
<td>Normal weight</td>
<td>111</td>
</tr>
<tr>
<td>5 to 15 percent underweight</td>
<td>114</td>
</tr>
<tr>
<td>15 to 50 percent underweight</td>
<td>95</td>
</tr>
</tbody>
</table>
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Dr. Tannenbaum then brought together conclusions of various statistical analyses from several insurance companies, showing, in general, that overweight persons have a distinctly greater tendency toward developing cancer.

All this raises an important practical consideration for the layman, namely: what is the standard by which one measures being fit but not fat?

At the School of Public Health at Harvard University, Prof. Fredrick Stare teaches the following doctrine: throughout adulthood one should keep within one’s “ideal” weight, perhaps a few pounds less than “ideal” weight. Ideal weight is defined as average weight for height at age 25, for the given sex. Dr. Stare’s theories about this are based on findings of the Metropolitan Life Insurance Co.

Advice on “ideal weights” has nothing to do with a cancer cure. But, in Dr. Stare’s view, it is good preventive medicine, in so far as cancer, or any other disease, can be associated with excess weight.

Research in vitamins, particularly members of the B complex, which are growth factors, is playing an increasingly important role in the hunt for agents which will inhibit cancer.

A group of researchers at Memorial Hospital, and a team at the University of Wisconsin, showed that riboflavin, a B-complex vitamin, counteracts the effects of a cancer-causing azo dye in the production of liver tumors in rats. The animals were subjected to the azo dye and it was found that if the dosage was not too severe, they could be protected almost fully by generous administration of riboflavin.

The Memorial group added another dimension to this later, showing that in the detoxification (that is, knocking out the toxic effect) of cancer-causing materials, including hormones, the riboflavin intake is a significant factor.

In other words, the conclusion is reasonable that the animal uses riboflavin to protect itself against hormones apparently implicated in cancer. This finding would tend to tie together
two major elements in the cancer problem—the vitamins and hormones. But it would be dangerous, in view of the limited evidence, to arrive at hard and fast conclusions about this. The significance of the riboflavin findings for man are not yet clear.

The vitamin problem has still further ramifications of a practical nature, for at the National Cancer Conference in Memphis, it was reported that dietary deficiencies of proteins and B-complex vitamins are “an important predisposing cause of cancer of the mouth.”

These observations were in the nature of additional evidence for a nutritional doctrine that has won much favor in the last decade, a doctrine which, in general, is based on the following observation: Americans are overfed and undernourished.

And what can be done about this? In general—and the situation might vary with the individual—the diet can be arranged so that it is relatively high in protein (meat, eggs, milk, fish, cheese, and legumes), relatively low in carbohydrates and moderate in fats.

Evidence would indicate that for the average American this diet would probably be an improvement over the one he is following, although his doctor would know best about this, and such generalizations do not cover all cases.
19. Conclusions:

**Difficulty in Understanding Disease Does Not Mean Its Conquest Is Impossible**

The study of cancer is the study of the basic forces of life at a chemical or physical level. This is why cancer is so difficult to understand.

No scientist has ever been able to probe, with any real discernment, the crucial events which occur within the living cell. Nor has the scientist been able to measure, with any accuracy, the forces which enable a cell to assemble and reassemble chemicals for growth.

Basically, a cell can do two things. It can assimilate nutritive elements and convert them into living substances. This is known as anabolism, which derives from the Greek word meaning “a raising up.” The cell can also break down complex units of living matter into waste products of simpler

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One of the latest sources of X-radiation in the range of 20 to 70 million volts, the synchrotron (betatron) may prove more effective in treating certain types of cancer than the present X-ray machines, because the radiation produced by this machine gives a more favorable distribution of energy in the human body.
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construction. This is known as catabolism, which derives from a Greek word meaning “a casting down.” Anabolism and catabolism, collectively, are known as metabolism. Metabolism is a crude chemical definition of life.

Science has made some progress in understanding one aspect of metabolism—the catabolic side so to speak. Something—but not really very much—is known about the mechanism whereby the cell smashes up complex chemicals and disposes of them as simpler units. But practically nothing is known about the system the cell uses to build simple chemicals into complex chemicals for growth.

One might say that this, then, is the cancer problem from a scientific viewpoint. And it is a tough one, one of the toughest facing science today, perhaps the toughest.

Yet because the science of cancer, so to speak, is fraught with pitfalls and the basic problem is, from this distance, shielded by what appears to be an impenetrable curtain, this does not mean that the disease cannot be managed.

Successful treatment may precede complete understanding of the problem by years or centuries—in fact, probably will. Indeed, there is successful treatment now—surgery and irradiation—but it must be applied early for the best results. And this means that a good diagnostic test, one which is specific for cancer and will pick up cancer in the early stages, can, conceivably, eliminate the disease, or many aspects of it, as a major medical problem.

So the problem of cancer is really three problems: understanding it, treating it, diagnosing it. This booklet has been aimed mainly at the first problem: the attempt, in a general way, to understand some scientific problems of the disease and the objectives on the scientific horizon, objectives which cut deeply into basic biological problems.

In summary, one can say that cancer is a problem of growth, and there are many known elements which enter into the growth picture, probably many others still unknown. The
Conclusions

The chemist has an interest in this problem, and he works at it from many directions. He is absorbed in a study of the family of chemicals known as nucleic acids because cell division proceeds in the presence of some of these chemicals. It would appear to be a shrewd guess that the forces controlling cellular division also provide clues to the cancer problem.

The chemist is also interested in the ways in which a tumor acquires energy, for all living things need energy. This is a point that was touched on earlier. There seems to be a significant difference between the way cancer cells and normal cells use their carbohydrate foodstuffs. But investigation of this problem has not yet led to practical therapy.

Basically, the chemist is trying to find a significant chemical difference between a normal cell and a cancer cell in the hope that some special characteristic of the cancer cell will prove to be its Achilles heel. Such a difference has not been found, at least at a level which has produced consistently successful chemical therapy for the disease.

The chemist dreams that he will come upon such a finding, either by design or accident, and in that dream, and the thousands of experiments which will be necessary to realize it, lies one hope for the ultimate control of cancer.

The geneticist has provided some clues to cancer and many scientists think that the discovery of the milk factor—in mice—is one of the most significant cancer findings of the century. It is easy to extrapolate such findings to the human level, but the evidence for doing so is pretty thin.

Indication that the milk factor is a virus has contributed, with other evidence, to a renewed interest in viruses as possible causes of cancer. But a virus has not yet been identified with human cancer.

Viruses most certainly have been identified with chicken cancer and other animal cancers, and it is conceivable that ultimately viruses will be unmasked in human cancer. At this point the evidence from animal work permits only a guess,
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and many scientists think it is not a very good guess, but others think it is the best guess of all.

The study of nutrition has thrown some light on the cancer problem, as the preceding chapter indicated.

Dr. Tannenbaum's work, and the work of others, suggests that if the population will keep itself fit instead of fat, it may be possible to reduce the general incidence of the disease or at least delay onset of the disease.

In another direction, nutrition offers some tantalizing prospects, for example, in the work at Memorial Hospital and at the University of Wisconsin showing that a B-complex vitamin, riboflavin, counteracts the effect of a cancer-causing dye in the rat. The experiment appears not to have any immediate practical ramifications for man, but it represents a kind of thinking about the problem which has exciting possibilities. If a B-complex vitamin protects the rat against one type of cancer, is there a nutritional element which protects man against some types of cancer? This is a question which many scientists ask themselves, but experimental work has provided only a hint here and there, hints which many scientists think are worth exploring.

Planning research in cancer is one of the most difficult things in the world, for although the scientist knows his foe, he does not know how to get at him.

But, nevertheless, the search continues in one of the greatest of all mystery stories, a search not for the killer—the killer is the cancer cell and he was found more than 100 years ago—but for the weapon which the killer so adroitly conceals. It is an odd kind of a search, in many ways, trying to deal with an enemy who frequently can be watched rather closely but who hunches over in such a way that one cannot see how he is doing the job.

It is a search that has enlisted, directly or indirectly, the best scientific minds of the generation, a search that is costing millions of dollars, a search that proceeds with greater vigor as
Conclusions

the years go by, yet a search which still appears to be, in 1950, miles from the objective.

The fact that the objective seems so distant bothers the scientist, but in his working moments he is much more susceptible to the kind of observations of Dr. W. M. Walshe, professor of pathological anatomy in University College, England, who wrote in 1846 (in "The Nature and Treatment of Cancer"):

"There is no medicine known having claims to the character of a specific in cancerous diseases, nor even endowed with the special attribute of invariably modifying the course of the affection. But this is no reason that such a medicine may not be found. . . . The efforts of those, who are placed in a position fitted for the purpose, should be unceasing in the search after such a medicine; for nothing can be more unphilosophical than to conclude that it does not exist because it has not yet been found."

He observed that such a discovery can be expected "from him who, thoroughly versed in the diagnosis of disease, has enough of incredulity in his intellectual composition to doubt the evidence which is not repeated time after time in similar cases, who has a fund of patience which no labour can exhaust, and a conviction of grandeur of his task, which disappointment, be it repeated ever so often, can never succeed in shaking."

Prof. Alexander Haddow, of the Royal Cancer Hospital, observed, in quoting Professor Walshe, that it is to be feared that the problem is even more unpromising than even Walshe believed, but on his note of buoyancy—which will certainly be needed for a long time to come—we may end.
Source Materials

Bibliography

Material for “The Challenge of Cancer” was culled from approximately 200 sources, including books, pamphlets, and scientific papers, and from interviews with about 60 scientists throughout the United States. Some of the source material is listed for reference.


“Approaches to Tumor Chemotherapy” (Amer. Assn. for the Advancement of Science, 1947).


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"Concerning the Cancer Problem," Peyton Rous (Science in Progress, Yale University Press, 1947).


THE CHALLENGE OF CANCER

A RESEARCH STORY THAT INVOLVES
THE SECRET OF LIFE ITSELF