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Pathfinder—Dr. Charles B. Huggins, who developed the new serum test for incipient cancer, lectures at the University of Chicago.

What We Know About Cancer

An appraisal of medicine's most challenging mystery reveals increased but incomplete knowledge, and a wide area of hope.

By WALDEMAR KAEMPFFERT

CANCER is as old as life. Plants, animals and men have died of it for thousands of years. Yet experimental research in cancer, research that deserves to be called scientific, began only fifty years ago.

The knowledge acquired in those fifty years is enormous, gratifying and perplexing. It is gratifying because tumors can now be removed with safety from parts of the body that no surgeon would touch only twenty years ago and because we are now entering the chemotherapeutical or medical stage of treatment, so that injections or pills will accomplish as much as X-rays and radium, and sometimes more. And it is perplexing because so many contradictions, so many observations, manifestly related, await the magic touch that will make them click into significant patterns, like the colored bits of glass in a kaleidoscope.

THE perplexities are naturally the direct concern of science. Here are a few:

In a mixed population of an island in the Netherlands East Indies, Malays and Chinese eat the same food, but the Chinese are subject to cancer of the stomach, whereas the Malays are virtually free from it. Why?

Does cancer run in families? The authorities say that only a susceptibility is inherited. A Madame "Z" comes down in medical literature because out of twenty-six members of her family sixteen died of cancer. Out of 174 members of the "G" family of Michigan forty-one succumbed to cancer. There are striking cases of identical twins who developed tumors in the same period of life and occasionally in the same site. Some types of cancer appear generation after generation in families.

Malignant tumors have been known to shrivel and disappear spontaneously in a few cases. Why? Nobody knows.

Why should excessive doses of X-rays, radium and other agents incite cancers, but proper doses destroy them?

Cancers of the skin, mouth, esophagus and stomach are more frequent in the poorly paid than in the well-paid and well-to-do classes. A matter of nutrition, perhaps?

A diet lower in calories than is considered necessary for the maintenance of good health reduces the incidence of cancer in both animals and man. But why should restriction of calories have little if any effect when a malignant tumor is well started?

Why is cancer more prevalent in the temperate climate?

There is no pre-pneumonia stage, no pre-diphtheria stage, no indication in the body that a particular infectious disease is about to gain a hold. But there is a pre-cancerous stage. Why?

THERE are several hundred of these puzzles. Fifty years of research have not solved them, so that there is no cure for cancer—yet. Meanwhile, the scourge exacts an ever-increasing toll of life. In 1930 it killed 117,800 in the United States; this year it will kill well over 190,000; in 1980, unless some spectacularly successful treatment is discovered, statisticians estimate that of the 58,731,000 Americans who will be over 45, it will kill 288,500.

These statistics are not as gloomy as they look. Though cancer spares neither children nor octogenarians, its victims are chiefly those who have reached and passed middle age. Because of the advance in medical science, we live longer than did our grandparents. The dreadful increase in cancer mortality is, therefore, what statisticians expect.

Yet, if you ask experimenters and investigators where the treatment of cancer stands after fifty years of research, the answer is bright with hope. Even in the backward present, 65,000 of the 190,000 who are doomed to die of cancer this year can be saved, if they have the benefit of the best surgical and medical skill in time.

What is cancer? A disorderly, usually rapid, abnormal growth of tissue that destroys life if allowed to run its course.

Because there is as yet no cure for cancer in the medical sense, malignant tumors must be cut out, or destroyed—in a way not yet understood—by X-rays or by the rays given off by radium. So blunt a summary does scant justice to advances in surgery or radiology. No one would have dared to remove a cancerous lung twenty years ago. Now it is done. Sufferers from cancer have had three-fifths of the stomach, part of the colon and the whole spleen cut out and lived for years. As for the X-ray machines of today, they are marvels of power and ingenuity—precise in the dosages delivered. Besides, we have the radioactive isotopes which are now so plentiful that whatever place they may have in the treatment of cancer should soon be established.

BOTH surgery and powerful rays are of no avail if a malignant growth is detected too late or if malignant cells have been carried to distant vital organs, there to start secondary cancers. Hence for decades efforts have been made to find a chemical test for incipient cancer—not just early cancer, but the deep hidden cancer that is just starting and that escapes the best diagnostic skill. In other words, a chemical test as good as a Wassermann in syphilis is wanted. There are urine tests, ultra-violet-ray tests, tests with such dyes as methylene blue and cresyl blue, electrical tests and a score or so of blood tests. Some of these are about 80 per cent accurate, but they are complicated and they can be made only by trained technicians. Also they indicate too much. Nearly all are positive for diseases other than cancer and usually for pregnancy, *(Continued on Page 24)*

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sient beneficial effect in about 15 per cent of breast cancers.

Giving extracts of female sex hormones combats the male sex hormone that stimulates malignant growth in male prostates and so produces much the same result as castration. Later, it was found that breast cancers in women stop growing for months and even shrink when male sex hormones are given. Not only this, but the spreading of cancer to the bone is slowed down and damage to the bone is repaired. One-fifth of the first group of men who were treated for cancer of the prostate in accordance with Huggins' method were alive seven and a half years later. The record for cancer of the breast is not so striking. The hormone treatment of cancer of the prostate and of the breast is now officially approved, so that it stands on as firm a footing as treatment by X-rays and radium.

This is no high praise; for X-rays and radium have thus far disposed only of skin cancers. But the use of sex hormones to check some forms of cancer, if only for months or a few years, is a milestone in medical progress. For the first time it becomes possible to cause some tumors to shrivel merely by taking pills or receiving injections. Thus with Huggins begins the chemical and hence the medical treatment of cancer. Some credit must also be given to the late Dr. W. B. Coley who used a toxin made from bacterial products. He checked the development of bone cancers temporarily with his preparations.

THE CHEMICAL APPROACH

DURING the recent war it was discovered that a score of chemicals have striking temporary effects on various types of cancers. Nearly all these chemicals are deadly poisons—a handicap that may be overcome so that larger and probably more effective doses can be given without toxic results.

Most important are the nitrogen mustards, which are related to the mustard gas of evil military reputation and which are at least as effective as the X-rays in prolonging the life of sufferers from leukemia (in which white blood cells multiply so abundantly that they invade important organs). Then there are urethane, also a palliative in leukemia; the sugary chemicals produced by some germs; three antibiotics, the generic name of chemicals which, like penicillin and streptomycin, are extracted from mold-like organisms in the soil; aminopterin, an antagonist of folic acid, which is one of the B-complex of vitamins; podophyllin, obtained from mandrake root; colchicine, extracted from the autumn crocus and used for centuries as a remedy for gout; Fowler's solution or potassium arsenite.

What of the radioactive isotopes, now obtainable at low cost from Oak Ridge? As yet they have cured nothing. So far radioactive iodine is the only one that has a pronounced selective action; it goes straight to the thyroid gland in the neck, sometimes with remarkable temporary benefit. Radioactive arsenic shows promise in the treatment of leukemia, and radioactive phosphorus also does some temporary good in one type of leukemia. The radio-



Dr. John J. Bittner.

active isotopes are no better and no worse than the drugs that have been used.

THE STUDY OF GROWTH

ALL the work so far described does not touch fundamentals. Every cancer originates in a normal cell, which goes wild. What keeps a normal cell normal? This is the profoundest of all questions that research must answer. A tumor is a useless, shapeless mass that penetrates tissues and organs; an arm or a leg is a shapely and useful member. Normal cells multiply by self-division and grow into hearts, livers, lungs, skins, eyes in the right locations and stop growing when organs and tissues are of the right size.

Cancer cells do not specialize in this way. No longer subject to restraint they multiply with frightening rapidity and take possession of the tissue or organ where they grow. The end is death. Often a few of these unruly cells find their way into the bloodstream to lodge in distant parts of the body, there to start new malignant growths—a process technically called metastasis, "meta" meaning "later" and "stasis" meaning "place" or "stand."

It is plain enough that the problem of cancer is the problem of growth, normal and abnormal, and it is for this reason that the National Research Council has appointed a Committee on Growth which passes on all research projects submitted by the American Cancer Society.

The problem of growth has many aspects. So far only a few have been studied. Drs. Warburg and Meyerhoff have focused on enzymes, which are substances that bring about chemical reactions in the body yet themselves remain intact. Without enzymes, the fermentation of beer and wine would be impossible. Without the enzyme familiar to us as pepsin, we could not digest a piece of meat.

IT turns out that there is indeed a difference in the chemical mode of life of normal and cancer cells—a difference in enzymes. Both types of cells ferment and thus utilize sugar. With the aid of enzymes the normal cell breaks the sugar down into lactic acid, the substance that gives sour milk its taste. Then follows a second stage in which lactic acid is further broken down into carbon dioxide, the gas that bubbles in ginger ale and beer and that we exhale when we breathe. A normal cell needs oxygen to burn up sugar completely and leave only carbon dioxide. But the cancer cell keeps on breaking down sugar into lactic acid and never reaches the second stage in which oxygen is necessary. A tumor can grow just by splitting lactic acid into sugar without oxygen, but normal tissue dies if it is deprived of oxygen.

All this means that normal cells ferment much as beer does in the brewer's vat or hard cider in a farmer's barrel in the process of changing sugar into alcohol. Cancer cells also ferment, but not in the normal way.

Warburg found out that no fewer than eleven enzymes working in relays are required to ferment sugar into lactic acid, enzyme A preparing the way for enzyme B, B for C and so on. Suppose the chain were broken. If only one enzyme could be inactivated a tumor would stop feeding on sugar and die of starvation. Here we have what may well be the best of all clues to the conquest of cancer.

IT may be that somebody will stumble in the darkness of his ignorance on a discovery that will rob cancer of its terror, but it is more likely that such a success will be scored when the fundamental problem of growth is more systematically attacked than it has been and when groups of scientists representing different disciplines are organized for the attack. It was thus that we developed an atomic bomb and thus that scientists in industrial laboratories gave us metal-filament lamps, television, synthetic rubber. It is thus that planes that will fly faster than sound are being developed. Let no one answer that it is easier to produce inventions than to evolve and prove theories of growth. Theories are also inventions.

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which is not astonishing when it is remembered that an embryo and a tumor are both new growths.

LAST March Dr. Charles B. Huggins of the University of Chicago, one of the most distinguished of American scientists who have devoted their professional lives to the study of malignant growths, published a paper in which he described what may be the long-hoped-for, reasonably simple serum test, serum being the clear liquid that separates from clotting blood. It has been known for twenty years that normal serum and the serum of a sufferer from cancer differ in their albumin. Albumin, most familiar as white of egg, coagulates when heated. Huggins pulled together all that was known about the relation of albumin to cancer, added information that he and his colleagues had gathered at a cost of $160,000 and came forth with a synthesis which is a brilliant contribution of its kind to the early detection of cancer.

The serum albumin of a healthy person coagulates more readily than that of a sufferer from cancer. Positive results do not appear in pregnancy, but they do appear in tuberculosis and massive infections. Such false positives can be ruled out one by one, leaving only the dread, inescapable diagnosis of cancer. There is as yet no specific chemical test for cancer. All the tests so far devised are only indicators of abnormality.

All this being so, the impatient practical man reasons that every disease has its cause and that when this has been found a scientific treatment usually follows. Why not concentrate on the cause of cancer?

THE question is meaningless because there is no one cause of cancer, as there is of smallpox, infantile paralysis, typhoid, typhus or any infectious disease. Moreover, cancers differ. The ultraviolet rays of the sun, X-rays, irritations, hormones, arsenic, nickel carbonyl, chromium, cobalt, mesothorium, extracts of diseased tissues, asbestos, a few viruses, mineral oil, pitch, tar, soot, creosote, parasitic worms, smoking, heat — all these can incite cancers. So can any one of about 300 chemicals derived from coal-tar and oil, many of them synthetics with no counterpart in nature. How, then, can we talk of "the cause of cancer"?

Scientists are trying to find out what happens when a normal cell changes into a cancer cell and why the changed cell remains malignant. There are many ways in which the problem is approached in the laboratory, but these four have the strongest experimental evidence in their favor: (1) Cancer is a virus disease; (2) excessive stimulation by sex hormones starts cancers in the male prostate and the female breast; (3) some chemicals can temporarily arrest cancers; (4) normal and cancer cells differ in the way they utilize sugar.

THE VIRUS APPROACH

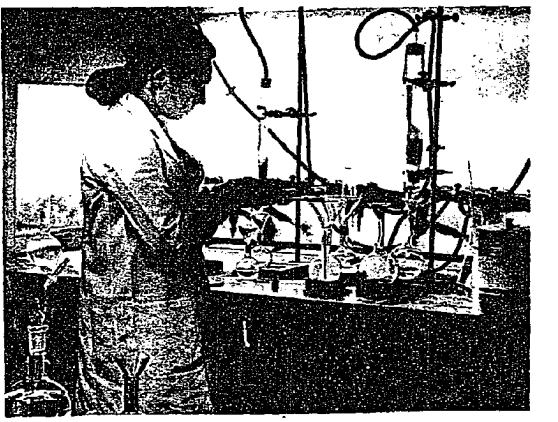
A FEW specialists in cancer research now maintain that it is right to talk about the cause of cancer and that the cause is a virus, just as the cause of influenza or measles is a virus.

Belief in the virus theory started in 1911 when Dr. Peyton Rous of the Rockefeller Institute for Medical Research passed the juice of mashed chicken tumors through a filter so fine that even a microscopic microbe was held back. He injected the filtrate into healthy chickens. Always a tumor grew where the needle had entered. Since then it has been established that warty growths on the ears of some wild rabbits are caused by a virus and that these growths turn into cancers when transplanted to domestic rabbits.

The discovery that did more than any other to strengthen the virus theory was one made in 1935 by Dr. J. J. Bittner, then on the staff of the Roscoe B. Jackson Me-

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A laboratory at the Sloan-Kettering Institute for Cancer Research.

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morial Laboratory, Bar Harbor, Me., and now of the University of Minnesota's faculty. He experimented with inbred mice, so that he knew exactly what physical defects and diseases were inherited and what diseases could be attributed to outside influence. Genealogically, his mice were aristocrats with lineages going back for a hundred mouse-generations and more.

In some of these inbred strains of mice cancer of the breast appeared spontaneously in 90 per cent and more of the females; in other equally pure inbred strains breast cancer appeared in only 1 or 2 per cent. Bittner transferred the young immediately after birth from the mother of a cancerous stock to foster mothers of a virtually cancer-free stock. The number of expected cases of breast cancers dropped to almost nothing.

NEXT Bittner transferred the newborn young of cancer-free mouse mothers to foster mothers that were bound to generate cancer of the breast. Many more than the expected number of breast cancers developed. If the mouse mother of cancerous stock suckled her young for only an hour or so, cancer of the breast appeared in nearly all when middle or old age was reached. On the other hand, a whole strain of mice could be saved by feeding it on pasteurized mouse-milk or transferring it at birth to cancer-free foster mothers. Evidently there was an agent in the milk of some strains of inbred mouse mothers that incited cancer of the breast.

What is this inciter? Because it has been seen in the electron microscope, because it has been inactivated by pasteurization, because it has been found in whole-blood, in the spleen, in the thymus gland, in the liver and in the brain, because it can be neutralized in the culture tube with an immune serum, and, above all, because it increased prodigiously in mice to which it has been transferred it is generally regarded as a virus.

Is cancer of the human breast caused by such a virus? There is no statistical reason to think so as yet. Nor is there any evidence that dairy milk, on which millions of babies have been fed, contains a virus.

Ask a geneticist—that is, a student of heredity—whether cancer runs in families, and he will deny it. What, then, is inherited? A susceptibility, he answers, a favorable soil. But what becomes of "susceptibility" when even the future generations of an inbred stock of mice in which cancer of the breast is transmitted "vertically," to use a term invented by Dr. Ludwik Gross, can be protected by the simple expedient of feeding them on virus-free milk? Whether the stock is inbred or not, a virus-laden milk will infect it.

Are all cancers caused by a virus, no matter of what type they may be? Are there as many cancer viruses as there are cancer types? The skeptics in cancer circles balk at this extension of the virus theory. Almost every virus goes to work as soon as it enters the animal or human organism. But not the milk virus, or other cancer viruses, if there are such. It must be assumed that all remain latent for thirty or forty years. It must also be assumed that all plants and animals, man included, are born with some kind of cancer virus in them, and that the virus springs into action when the right conditions are created.

THE HORMONE APPROACH

IT was long suspected that there was a relation between some cancers and sex organs. When the sex hormones were discovered and isolated it was possible to experiment. Sure enough, the relationship was there. Dr. Huggins followed up the clue with dramatic results. After careful experimenting with animals he found that when castration cut off the supply of male hormone, cancer of the prostate in men was checked and pain relieved, sometimes rapidly and miraculously, even though it had spread to other parts. Cancers even disappeared entirely for a time in a few fortunates. Spaying of females had a tran-

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