

MEDES AND REIMANN

**NORMAL
GROWTH
AND
CANCER**

NORMAL GROWTH and CANCER

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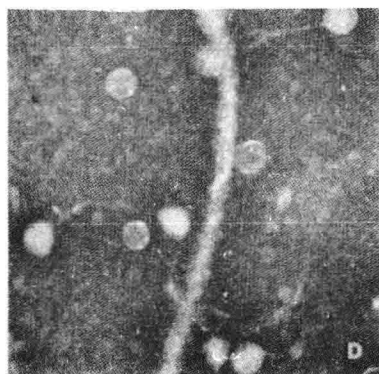
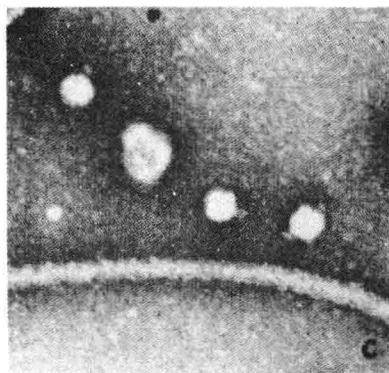
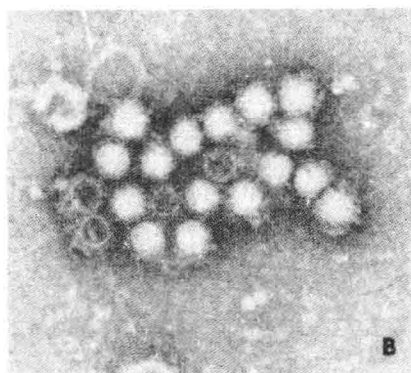
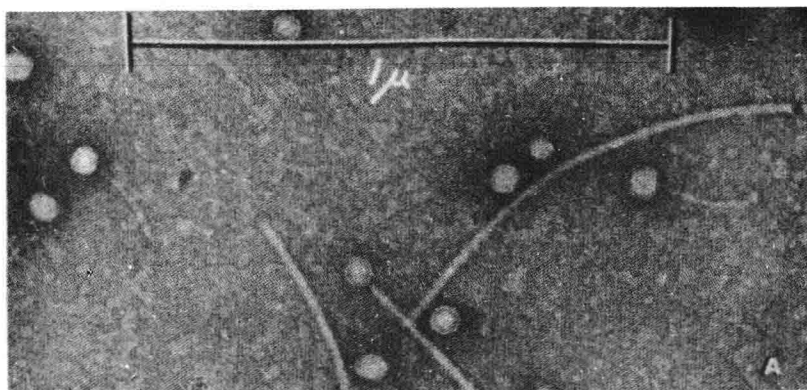
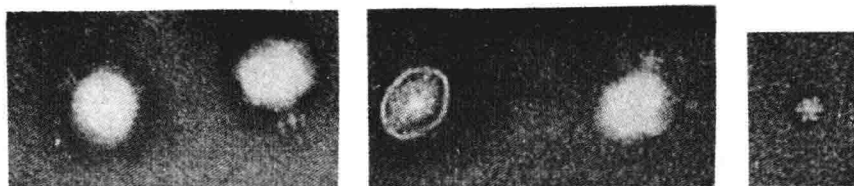
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Electronmicroscopic views of bacteriophages and of their reactions with antisera. See page 252 for details of each view. (Yamamoto, Nobuto, and Anderson, T. F.: Genomic masking and recombination between serologically unrelated phages P22 and P221, *Virology* 14: 431 and 433)

Preface

Few families in the world have not had to face at some time the problems of cancer. In one or another of its many forms it has forced itself on their attention, if not directly, then indirectly in friends, acquaintances and publicly known individuals. Inevitably, questions are asked. What causes cancer? Is its incidence increasing? Have methods of eradicating it improved? How is it detected, especially in its early stages? How can it be prevented? Is progress being made in understanding it? Many queries are more detailed than these. To answer them—and there are a large number of reasonable, if incomplete answers—volumes would be required.

In speaking of the “causes” of cancer, we are confronted with the question of how deeply we want to delve into the subject. Without pursuing the meaning of the meaning of causation, we might start by saying: We know much about the conditions under which cancer arises. Yet to many these conditions are not really the causes of cancer. Discussions of them and of cancer itself are couched for the most part in descriptive language, which has served a large group very well in the degree possible to descriptions. However, in the beginnings of other sciences, after description seemed adequate, it was followed by language at another level, namely, the more dynamic language of chemistry, physics and mathematics.

Cancer entered this stage only a few years ago, and this book records merely a small part of the progress in this endeavor. Those who consider description adequate will maintain that the cause or causes of cancer are adequately known; those who want to push explanations further will find that many paths are open for exploration. Approximations to the answers to all of our queries are coming ever closer to the base line, although we know they will never reach it. Nevertheless, each new announcement is received with interest, and many discoveries arouse excitement.

The important discovery following the invention and use of the

first great extension of our limited vision, the microscope, was that cancer is a growth of living cells. This discovery placed the emphasis on the study of general growth and development, with malignant growth and development and normal growth and development as reciprocal controls. To these studies more and more specialists in many branches of science began to contribute: chemists of various kinds, physicists, mathematicians, clinicians, botanists, pathologists, biologists of different genres, geneticists and many others. The materials for study were found to be innumerable. Wherever cancer was hunted, it was found—in mammals, amphibia, crustacea and, in fact, in all species, for they all grow and develop. It would seem as if the possibility of developing cancer were one of the penalties of living.

Yes, we know much of the conditions under which cancer develops in living things, but this knowledge is not enough. We have not contrived as yet a clear definition of "living." However, it is a sign of progress that we consider the known microscopic appearances only approximations, for subcellular particles, even fragments of compounds, like those of the nucleic acids, are coming under scrutiny as candidates for the office of the bearer of life.

Is the incidence of cancer in human beings rising? The authors remember the controversy of some 30 years ago, when statisticians of life insurance companies were arrayed in separate camps. Is the increase in incidence an actual increase or only a seeming increase? Today there is agreement in most places. There is an actual increase. Statistics from many sources could be quoted. Here are some in the U.S.A.: In 1900, cancer was the cause of 3.7 per cent of the deaths in the death-registering states; in 1958, 15.4 per cent of deaths were from cancer. Among the variables are increased longevity, decreased mortality from infectious diseases, and lengthened time of exposure to various carcinogens. Also complicating the question is an apparent increase due to the increased accuracy of diagnosis.

Diagnosis by microscope of a piece of suspicious tissue remains the final means of distinguishing cancer from the many conditions in which the microscope is used, such as infections, benign tumors and other conditions. In Chapter 2 are described some of the modifications that have been made in the microscope for obtaining clearer images of the structure or lack of structure of tissue on a microscopic slide.

For a number of years the American Society of Clinical Patholo-

gists has conducted seminars in tissue diagnosis for its members and others who are interested. Collections of slides have been accumulated for loan, notably through the Armed Forces Institute of Pathology and its predecessor in Washington, D.C. It is quite safe to say that the quality of microscopic diagnosis has increased noticeably, and that clinicians are well aware of its possibilities.

Have methods of eradicating cancer been improved? The answer to this is an emphatic "yes." Methods of control, whether by x-irradiation, cobalt-60 theratrons, radium, or radioactive cobalt in applicators have improved tremendously as more and more has been learned of the effects of irradiation in therapy as well as in cancer induction. Many malignant growths that were formerly resistant, such as the leukemias and the skin carcinomas, have been not necessarily cured but at least temporarily brought under control.

The methods of surgical treatment have been improved greatly, and its extent has increased. This may be the place to remark that many of the improvements in the practice of surgery depend on research done in many different fields. Surgery can be used as an excellent example of how seemingly *unbrauchbare gedanken*, i.e., knowledge or ideas not usable at the moment, have borne the fruit of application. As scattered examples we need mention only the applications of the knowledge of hormones in thyroid, breast and prostatic conditions; water and nitrogen balances in extensive resections of the sigmoid and the rectum; antibiotics; and dependable and safer anesthetics. In this book will be found condensations of knowledge from many sources, quite a few of which are still in the *unbrauchbare gedanken* stage, but all somehow bear on the problem of cancer.

As far as the prevention of cancer is concerned, the answer is concentrated in knowledge of how and what is the irreversible change that has occurred within division-capable cells, leading them to distort their differentiation and lose their ability to organize with normal cells. Therefore, it is in the realm of the causes of cancer or, as it is put, carcinogenesis.

The authors, one of whom is primarily a biochemist, and the other of whom is a clinical pathologist, have chatted informally for many years about cancer research. They decided finally to record some of their discussions, and this book is the result. It was quite obvious from the beginning that it is impossible to use a level of language specifically adapted to every person, and so a course has been adopted

whereby a certain minimal acquaintance with chemistry and biology was assumed without a highly specialized knowledge of these subjects or their branches. We planned the contents of the book from a consideration of the older, more restricted knowledge and compared it with what might be termed the luxuriant growth of information that during the last years has come from the many disciplines contributing to knowledge of the intricacies of growth, both normal and cancerous. Truly, these are interdisciplinary problems. In one sense, then, this book may be regarded as a history of progress.

The authors agreed that no excuses are necessary for accenting technics. All experience has shown that an increase in knowledge depends on the use of more and more accurate and reliable technics. On the other hand, while it is necessary to concentrate and specialize in mastering the technics of complicated procedures and apparatus, technics are not to be worshiped as such; they are only tools to be used for the greater knowledge that these technics can uncover. Therefore, in this book there will be found considerable accent on concepts and theories that have led workers to more experiments and to more comprehensive generalities.

The authors hope that the material and the methods of presentation in this book will be of help to the thoughtful practicing physician. Premedical students should find it of particular use, and students in other branches of science, as well as in such fields as sociology, will find it of interest. The general public will find it an affirmative answer to the often-asked question: "Is progress being made?"

The authors express great appreciation to the many friends and colleagues who over the years have helped them in their professional careers. They acknowledge their deep indebtedness to their teachers, who not only gave of their knowledge but, just as important, aroused curiosity and the desire to know. We might mention Dr. Clarence E. McClung, formerly Professor of Zoology, University of Kansas; Dr. David H. Tennant, Professor of Biology, Bryn Mawr College; Dr. Allen J. Smith, Professor of Pathology, University of Pennsylvania; Dr. John B. Deaver, Professor of Surgery, University of Pennsylvania, all of whom are now no longer with us, and Dr. Howard T. Karsner, formerly Professor of Pathology, Western Reserve University, now retired. These are only a few of the many whom we remember with the highest regard.

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GRACE MEDES
STANLEY P. REIMANN

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Cancer as Conceived Previous to the Microscope

CANCER IN FOSSIL ANIMALS

Many millions of years ago, before man had evolved as man, cancer is known to have occurred among the creatures of the Age of Reptiles. The records are written in such of their bones as have survived as fossils. Of course, the soft tissues were not preserved; hence, there are no records of what other types of cancer existed. The skeletons of dinosaurs, animals which are estimated to have lived 18 million years ago, have been found showing changes characteristic of bone hemangiomas (a tumor made up of lymph or blood vessels), and a few million years later monosaurs, aquatic reptiles some 50 feet in length, developed bone growths, called osteomas (bone tumors), which have been preserved as fossils. An osteosarcoma, by which we mean a highly destructive malignant growth in bone, was identified on the right pelvic bone of a she-bear from the Pleistocene age about 500,000 years ago. (A later pathologist believed that this growth was a callus-formation.)

CANCER AS RECORDED IN EGYPTIAN PAPYRI

The earliest records of cancer in man appear much later. One of the first collections of medical and surgical observations was assembled in Egypt in about 1550 B.C. and is known as the Ebers Papyrus, from the name of the famous Egyptologist, Ebers.

A slightly earlier papyrus, the Smith Papyrus, possibly only a fragment, is much shorter and is limited to diseases or injuries of the

head and the shoulders. Two still earlier fragments, the Kahun and the Gardner papyri, date approximately 2000 B.C. However, there is no evidence that the medical or surgical procedures described are older than those in the Ebers, since all of them represent collections accumulated during many centuries, and chance awaited the right man in each region of the world to record and reveal the accumulated knowledge. The actual time during which this process of accumulation had been going on is purely conjectural. There are no dates available. We can only accept the speculation of expert archeologists as to how long it would take a primitive people to evolve a culture such as medicine and surgery—language, writing, hieroglyphics or letters—a wide knowledge of useful plants, nonpoisonous, suitable for food and for healing, and finally a man of culture, who can understand it, organize it and present it to the world. The individual descriptions were said to have spanned a period of some 20, possibly 30 centuries. Among the diseases described are many tumors, demonstrating that even at the dawn of written history the subject of cancer was of paramount importance to man.

To an Egyptian of the Ebers period, a tumor meant the enlargement of any part of the body, a new structure, an overgrowth or even a simple swelling. A generalized swelling such as dropsy was considered a tumor of the entire body. Some of the tumors described were probably tuberculous, some leprous, some specific inflammations, but others were cancers as we would diagnose them today.

To understand the methods of ancient therapy we must remember some important facts. Medicine, as we know it, developed from ancient beliefs and practices, well described in a number of texts in the history of medicine and in many books not devoted exclusively to this subject but in which medicine had perforce to be mentioned. Sickness, disease and injuries played a large part in human history, and endeavors to alleviate sickness and to repair injuries necessarily are based on the knowledge and the beliefs of the day, which are in turn history. Such books as Frazer's *The Golden Bough* treat of beliefs of the times, and medicine was inextricably woven into those beliefs. It is true that throughout the ages accumulated knowledge has eliminated errors in beliefs and practices, but it is also a truism that knowledge throughout history continuously creates other magic which the next generation must exorcise. Another truism states that

when certain general principles are formulated over a period of one generation or many, deductions and practices are added from time to time which were not in the original general beliefs. Later, when the original general principles were found to be in error, the applications of the previous principles continue as traditions, the beliefs become highly cherished, and they are then difficult for mankind to relinquish. In fact, it often happens that not only are cherished traditions and beliefs retained, but also they lead to dissatisfaction with, and often active opposition to, new beliefs and practices which more recent knowledge indicates should be adopted.

At first the idea was general that all medical difficulties, that is, all sickness and disease, came from without and were due to the action of malignant spirits responding to a slight or an offense to particular spirits or gods. From this belief it was an easy step to the belief that one human being might wish on another human being the evil spirit which was to damage his health and welfare. Take an obvious case, such as that in which a warrior was hit on the head by the club of an enemy. It was often believed that while the club was the immediate cause of the injury, nevertheless, residing in the club and in the might of the individual wielding it was an evil spirit which guided the club and at the same time entered the injured person and rendered him susceptible to the club and less able to withstand its onslaught. Thus, much of medicine was devoted to getting rid of evil spirits or blocking them, often by calling on a more powerful benign spirit to render ineffectual any effort on the part of the evil spirit. Naturally, in any community there would be particular individuals who were regarded as capable of influencing evil spirits. There arose, then, priestly classes who placed curses on or removed curses from members of the communities in which they lived. Hence, medicine became a mixture of magic, dispensed as sacrifices, incantations or concoctions to exorcise evil spirits, and a beginning of scientific treatment, seen, for instance, in surgical procedures.

In Egypt treatment for the cancerous tumor was cautery, and the wound was covered with plasters. Since the knife was invented during this period, its use was also advised.

When thou findest a purulent swelling with the apex elevated, sharply defined and of a round form, then sayest thou, it is a purulent tumor which is growing in the flesh. . . . I must treat the disease with the knife.³