to many or all of these sources of inspiration and strength. The value and significance of the experience has not, however, been sufficiently appreciated. You will need to find beauty in humanity if you are to serve it well.

To those who are given the opportunity to observe repeatedly it soon becomes evident that not only the larger phases of nature contain these elements of beauty, but also that its detail is full of them. I shall never forget the experience of observing under the microscope for the first time the thin sections of the tissue of parts of tiny mosses which those of us who were students in a course in Botany had made. In the structure of these small plants there appeared, as if by

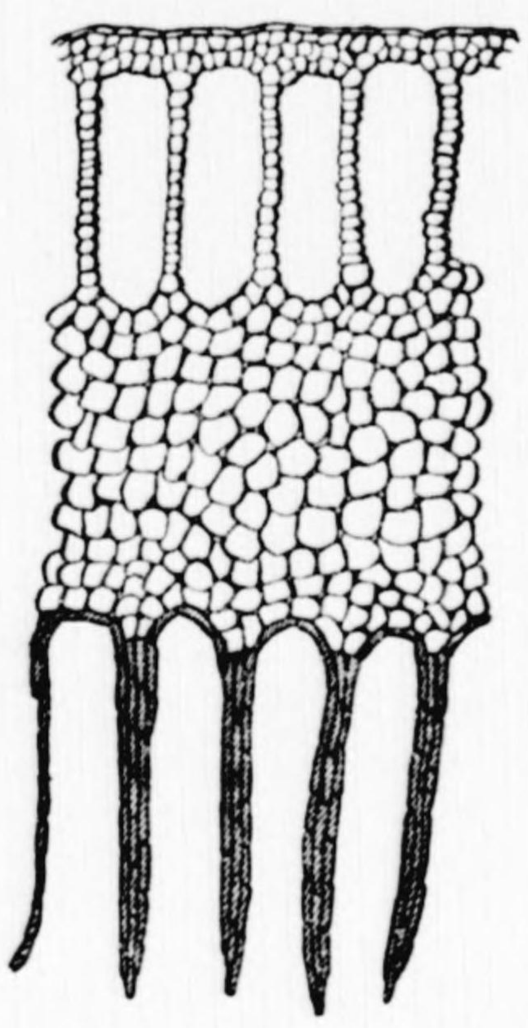


FIG. 3. An illustration of a thin section of lichen viewed through a microscope, showing the intricate structural forms found in even some of the lower forms of life.

magic, beautiful mosaics of structure which surpassed the finest inlaid work that man has ever performed. There were patterns and designs, some of them simple, some of them complex, but all of them symmetrical and beautiful. There were the elements of the structural arch as though carefully put in place by the straining bodies and tired hands of those who built the ancient cities of Assyria, Greece, Egypt or Rome.

There had been shouting and command, toil and sweat to produce the temples or cathedrals which men had made. They had pushed up above the level of the earth to inspire the eye and the spirit of those who observed them through centuries. Here, however, in these small, delicate mosses, without a sound, there had been accomplished the same task more permanently and in a form which could not be worn or destroyed by the passage of time. Here each generation of plants which followed one another had faithfully reproduced the beauty of that which had gone. Here the patterns which satisfied the inherent love of symmetry and order which man possesses and which life needs, had themselves become living so that they did not belong to any one people or city but to life itself and as such could face the future without fear of conquest or destruction.

10. REVERENCE

The third quality which is essential is that of reverence or awe in the presence of manifestations of forces and powers so far beyond our creative ability that those who see them in their true perspective cannot accept any finite or material explanation as the whole description of their true nature.

It is all very well to recognize that seasons follow one another as a physical and chemical consequence of proximity to or distance from the sun. That is a fact. But that mechanism is not the only type of event that life presents and which we must evaluate. Anyone who asks why and how there can exist in living plants and animals a definite pattern and detailed response to sun and wind and water and why this is handed on from generation to generation with faithful precision is faced with the need for something more than a mechanical theory to satisfy his full appreciation of what is going on in the world around him.

There exists, of course, a whole school of biologists and others who prefer to explain everything in a material way. So, too, there exist theories of government and of human behavior which hold that material values are all sufficient. No effort will be made to convert such persons. They have the right to believe as they wish. To those, however, who have added something above and beyond that limited perception and who have lost complacency but gained peace thereby, the change is priceless. It is the confession of what that change has meant and means to them that they must admit. They make it gladly realizing that it leaves them open to criticism and perhaps scorn, neither of which things, however, possess any longer the power to hurt them.

What, for example, records in birds the knowledge of direction, distance and locality necessary to bring back from thousands of miles to the same elm tree in a New England town the same pair of orioles year after year until death interrupts the expression of that power? What makes and breaks the flocks of migrating birds, the great north and south journeys in company with hordes of their own species and the subsequent breaking up into pairs or smaller colonies while the young are being raised? What has taught the mother partridge to feign a broken wing and a halting, stumbling, slow flight to lead an intruder away from her nest, and what in turn makes the newly hatched partridge chicks freeze into instant and absolute silence and immobility at a single note of alarm from their mother? Of course, there is some sort of physical basis for all of these things, but back of all those facts there must be a force which is so far beyond the power of our senses to grasp it that only deep awe and reverence remain to provide an adequate response on our part.

This is one of the most delicate and most difficult matters which one encounters in attempting to bring science home to the layman and in introducing a proper appreciation of a lay point of view into the deliberations of scientists. There are among the ranks of experimental scientists a great many individuals who are just as unimaginative and bigoted as the most partisan and prejudiced sadist in the service of any religious cult or sect. There are men who feel that if anyone who works in the laboratory admits that he does not know or will not find the total answer to all the problems of the universe within the realm of facts and processes encompassed by man's intellect, he is being disloyal or even dishonest in a strange sense. In other words, these persons worship fact and intellect as their god and to admit or even to suggest that fact and intellect are not all powerful is, in their opinion, some sort of basic weakness.

It is unwise to condemn these persons too fiercely for it must be admitted that a fact or process completely grasped or explained by the intellect possesses a degree of definiteness which is necessarily missing in the realm of extra-physical forces. It is helpful and soothing to the ego to be able to place a name on anything that we do not fully understand. Thus the student of heredity finds temporary comfort in naming the smallest unit of inherited organization a "gene" and the chemist or physicist has a reasonable sense of satisfaction in calling the smallest unit of organized matter an "electron."

There are definite counter-parts to these scientific bigots to be found in every religious denomination. In each such group there exists a number of people who feel that they have lost caste and made a damaging confession of inferiority if they allow anyone to question a single phase of the creed to which they adhere. We all of us know many examples of this sort and the better we know them, whether in the laboratory or in the field of religion, the more we are forced to admit that they do not notably contribute to the growth of man's spirit or to the broader appreciation of his unsolved problems.

The truth of the matter is that it is well enough to be interested in finite and concrete facts and processes just as it is a good idea to use the doctrine of religion as a place where the mind and spirit can *rest*. When, however, either the mind or the spirit wishes to *grow*, it must very certainly leave the realms of the definite and be willing to venture out into the vast field of human experience which is intangible, unpredictable and perhaps unanalyzable.

Infinitely small particles of dust suspended in the air are invisible under ordinary circumstances. When, however, at the beginning or close of day the sunlight passes through them at a certain angle on its way to us, the beautiful and varied colors of the sunrise and sunset are produced. Clouds which a few minutes before had been characterless and unnoted assume under the same stimulation of the passing light all sorts of beauties which they did not have before. The sun has in a very real sense moved in and utilized the suspended particles and cloud centers of condensed moisture to make a sunrise or sunset which was not there before and does not last. Yet in the time that it existed the sunset was quite as real as the physical material of which it was made. It has a right to recognition and in a way a closer claim to survival because it has had a beginning and an end and played its lasting part in the experience of those who observed it.

So many millions of people have experienced a contact with something outside and beyond themselves and have been left the awareness and memory of those contacts that uncertainty in their case has been replaced by very definite faith. Some people, strangely enough, consider this faith a weakness because so many others find comfort and strength in it. It is looked upon as an escape from reality, a figment of the imagination and an ephemeral and transitory thing. This attitude is, however, merely a confession of the fact that those who express it have not themselves experienced faith. For once faith has come it cannot be argued out of existence by even the keenest intellects or by physical persuasion.

Those also who have experienced faith know that with it there comes a very definite sense of reverence and awe. Such a feeling is quite apart from conscience for it is strangely impersonal although it may completely absorb and take up the individual. A paradoxical condition of that kind is in itself an indication of the immaterial nature of the force that one is experiencing. Only non-material things can become greater by spending them and more fresh and powerful by using them.

These considerations may seem far removed from the cancer problem, but you may rest assured that they require attention to fit us for a lifelong combat against a cruel and relentless enemy.

11. APPROACHING THE SUBJECT

It is natural for men to be interested in nature, and one may be sure that if an individual is not so interested either he has been left uninformed as to the type of the world in which he lives or else he has been given information without any spiritual interpretation or attempt to produce a sense of proportion in his appreciation of what he experiences. The fact that even the most learned men know only a small part of the explanation of the various things which they encounter should be more often emphasized and brought to the attention of less well-trained persons. Unless this is done the latter are apt to feel that they are inferior, that they are of little use in the scheme of advancing human knowledge and that they are looked down upon by those who have acquired more information.

Sometimes, of course, it is true that this is the case. Many well-informed persons, however, who look down upon those who are less well-informed are confessing, before the world, that they themselves have not learned the first thing about the relative importance or unimportance of their own knowledge. What is needed is the realization by all men and women that they have a vital part to play in making human progress possible. There need be no false democracy or stupid sentiment in such an assertion. The sum of the unknown remains so great that no one can afford to neglect or ignore the help in battling ignorance, which can be obtained from any human source.

This is especially true in the campaign against a disease like cancer. It is, of course, an often repeated truism that cancer is no respecter of persons and that rich and poor, educated and ignorant alike are subject to its attacks. The very fact of its basic nature provides it with a certain dignity which is lacking in those diseases or disorders which result from invasion of the body by outside bacteria or other micro-organisms. As long as man is physically of the type that he is (and there is not the slightest prospect of any radical change) he must pay the penalty which controlled growth of his body and its component parts imposes upon him. As we shall see later, this control of growth is part of an orderly and necessary division of labor between the tissues and the organization of them for specific duties and functions.

Much can be learned about these matters from an intensive study of man himself, but quite as much, if not more, can be learned from studying his closer and more distant physical relatives throughout the animal and, in fact, the plant kingdom. Everything that is alive has certain qualities in common. Some possess these qualities to a greater degree than others and some exhibit them far more extensively than do other types. If, however, we reduce higher animals and plants to the stage where they consist of a single cell and compare them with the animals and plants which throughout their lifetime remain a single cell, we shall find very insignificant differences and many points of striking similarity between the two groups.

For this reason it is customary in approaching the subject of biology to study first the animals and plants which remain as single cells throughout their life. This has some advantages, but it also has the disadvantage of leading the student at once to unfamiliar ground. We shall not follow that method, but shall instead first consider the life of individual cells in higher animals and plants. We shall have to remember that each of these organisms consists of thousands of millions of such cells and that the skin on the back of our hand contains perhaps 600,000,000 individual cells in an area one-half an inch square. We can also realize, however, that each one of us, and in fact every animal or plant, had its beginning from a single cell and it may be interesting to study first of all what these cells are like and how long their life normally is.

12. CELL COMMUNITIES

Every higher plant and animal consists of many different sorts of cells. They possess vast numbers of each type placed in certain localities where they can perform very definite duties and functions.

Each plant or animal is thus an organized community where the labor and function needed for the well-being of the whole is divided between the different tissues and organs that compose it.

The complexity of such a community is often very great. Not even the largest and most highly developed city approaches it. This is a somewhat surprising statement. We are so familiar with the vast crowds and obvious diversification of activities in a great city that it does not seem possible that our own body could quietly and steadily be carrying on the even more complicated and extraordinary processes of manufacture, storage, repair, communication, transportation, police, waste distribution, administration, food production, temperature control and other functions.

The complete story of any one of these major problems and of the way in which the body solves them would be in itself a fascinating topic. It is not possible to treat them in detail at this time. We can, however, mention each briefly to show what an ordinary mammal such as a mouse or a man does as a part of its every day activities to maintain proper balance and organization within its body and between that body and the outer environment with which it comes in contact.

There is no predetermined order in which the major functions of the body are best to be considered. We may, therefore, take them up as follows.

13. BODY FUNCTIONS

The utilization of food is one of the most basic and vital functions of the body. This capacity to manufacture living material by sorting out the necessary chemicals from vegetable and animal food is in itself superior to what man can do by machines on any extensive scale.

There was a great to-do in the scientific world when a substance known as *urea*, which occurs naturally in the urine, blood and body fluids of mammals, was made in the laboratory, outside of the body. Since that

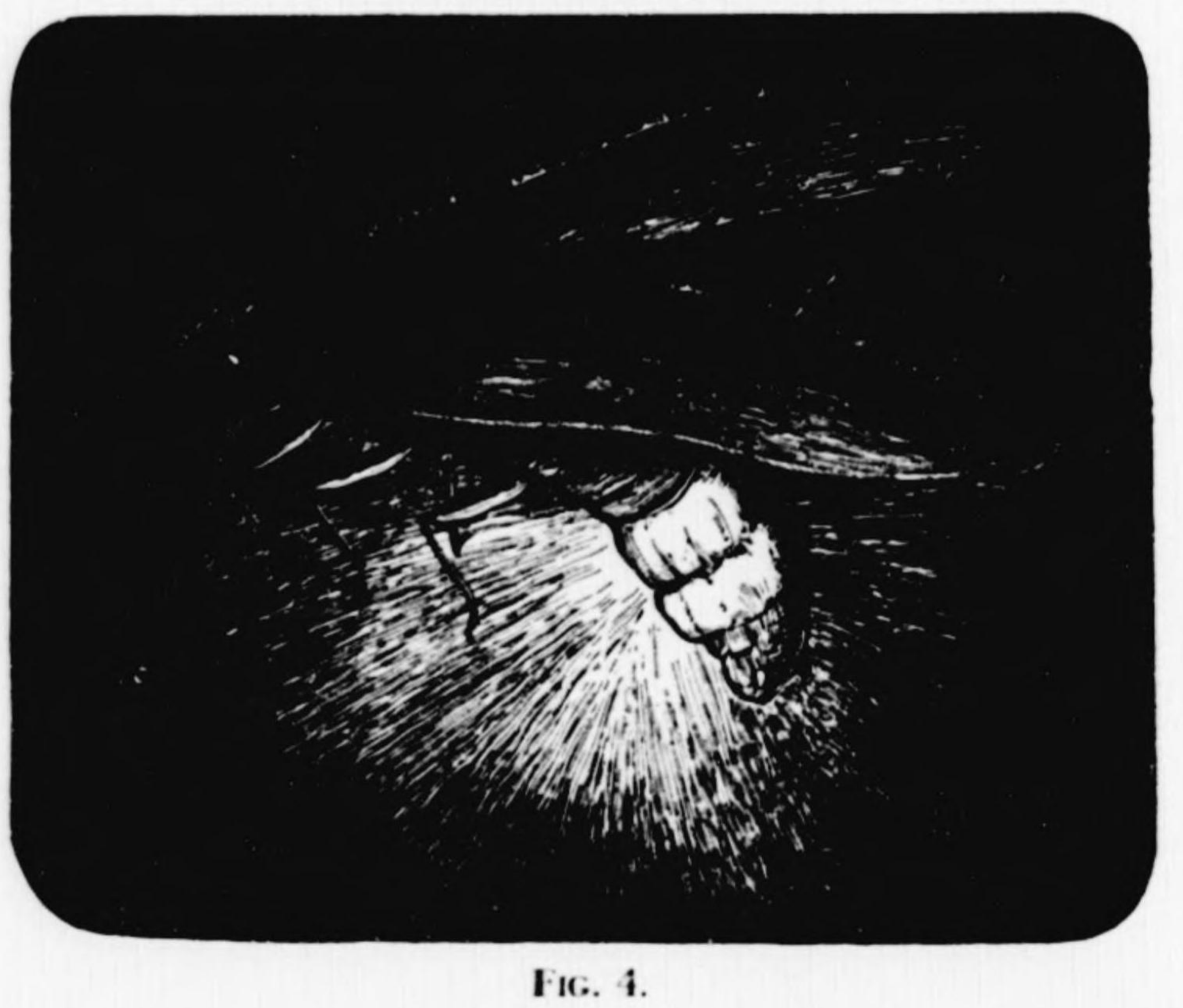


FIG. 4.

time a few other "natural" products have been built up in the laboratory. The body can, however, still make thousands of compounds which man cannot.

It can make them economically, accurately and at the proper and necessary intervals. It can prevent their contamination or deterioration under any circumstances that endanger the organism. This mechanical self-regulation of the needs of the body is, of course, far more effective than any invention which man has been able to devise.

One of the standard examples of the unequaled efficiency of animals as manufacturers is the production of light by the firefly. This light is far more economical and effective than are those produced by the combined mental efforts of all the greatest human inventors.

Storage of needed energy-producing material is also handled in an excellent manner by those human bodies whose owners will give them half a chance. To be sure there are millions of us who overload our bodies with so much fat that in spite of all efforts the natural distribution of that cargo becomes asymmetrical. Under ordinary circumstances, however, the fat is stored with great symmetry in distribution so that all the normal functions of the body are interfered with to the least possible degree.

Waste distribution is also well handled not only by the easily recognized main sewage disposal systems but by emergency structures which can be used if needed. The inelegant but highly successful function of vomiting can be unused for years but will be found to work according to schedule in the solution of a crisis if circumstances demand.

Sweat glands can help beyond their normal function and activity if other methods of drainage fail. Even such cavities as the sinus or the antrums can ordinarily find sufficient outlet for excess secretions if that is needed.

The temperature control of the body is beautifully and accurately carried out. Changes of fractions of degrees are recorded by the individual even though a clinical thermometer shows that various parts of the body register different levels as a normal condition. Thus the temperature taken by mouth is 98.6° while the normal rectal temperature is 99.6°. Similarly the areas of thin skin on the surface of the body are normally at a much lower temperature than that in internal regions.

A series of very interesting experiments brought out this point in a most striking manner as follows. It was noted that in newborn mammals the male sex glands or testicles are located *inside* the body cavity, but that before sexual maturity accompanied by the production of functional male sex cells or sperms occurs these organs descend from inside the body cavity and occupy a sac known as the scrotum.

When, by experimental procedure, the testicles are prevented from leaving the body cavity they are unable to function properly and the animal is sterile. It became clear, therefore, that the function of the scrotum was to provide an area of lower temperature in which the male sex glands could perfect the successful formation of sperm.

Carrying this study further the female sex glands or ovaries of mice were transplanted from their usual site within the body cavity to a position beneath the skin of the ear. In this location they would very evidently be subjected to a lower temperature than that which they normally experienced. Studies of the nature of the material secreted by the transplanted ovaries revealed that it contained *male* hormones when the temperature was kept low and *female* hormones when it was high.

This shows a great degree of versatility and adaptability on the part of the ovary which ordinarily would

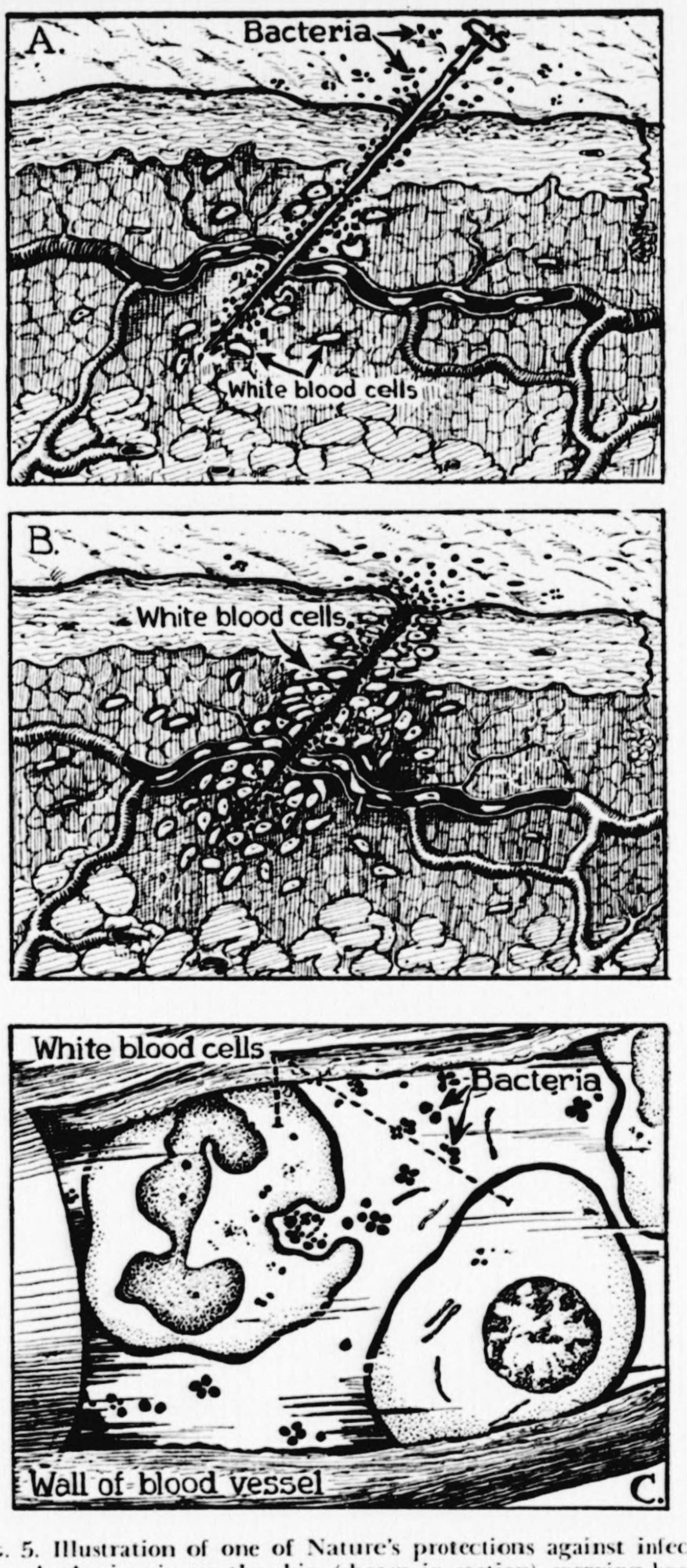


FIG. 5. Illustration of one of Nature's protections against infection. A. A pin pierces the skin (shown in section) carrying bacteria into the subcutaneous tissue. B. White cells found in the blood supply shown penetrating the walls of the blood vessels and surrounding bacteria. C. White blood cells shown engulfing and destroying the bacteria.

have given no evidence of its ability to secrete male hormones. It also indicates how delicate is the temperature balance maintained within the body by constant conditions.

The police function within the body is divided between those activities which protect from external dangers and those which must take care of any menace to the security of functions inside the body.

To the first group belong the wonderfully rapid protective reactions such as the closing of the eye as a visible foreign body approaches that organ. These reactions are free from conscious control and are called "reflex." They have an evident and direct protective value called for by an emergency.

Of quite a different sort are the much more complex and prolonged "police" problems caused by the invasion of the body by plant or animal parasites causing disease. Such invaders cause disease by multiplying in numbers with almost unbelievable rapidity and by giving off toxins into the blood and tissues of the invaded organism.

They are fought by the white blood cells, each of which then behaves as though it were an independent single celled organism. Under conditions requiring it the number of white blood cells may increase very rapidly and they may move in great concentration to any part or parts of the body where they are needed to fight the invaders. The efficiency of this quiet and largely self-regulating mechanism for policing the body makes our man-made system of law enforcement seem primitive and clumsy by comparison.

14. COORDINATION

One more system of marvelous effectiveness may be briefly mentioned. This has as its function the job of "communications." It consists chiefly of the nerves and nervous tissues. It must receive and transmit various messages. It must differentiate between those which can be answered locally and those which require control from the central headquarters.

All over our skin are scattered the open ends of the receiving system. A fly lighting on our hand stimulates nervous response which transmits his presence to our brain. This system is tireless. It works twenty-four hours a day. It keeps on the job even when the central control is off duty. Coming back to the muscles beneath our skin either from the central control or from secondary controls along the spine are the myriad nerve fibers which produce action in the proper muscles.

Some muscles are relatively independent of conscious nervous control from the brain because, being needed and used under any and all conditions, evolution has relieved the more complex nerve centers from the responsibility of caring for them. The normal function of digestion is an example of a vital process normally cared for with little or no interference with consciousness.

The brain itself has certain areas set aside for characteristic groups of general responses. It must, in addition, store the various nervous experiences of which memory is made. It must maintain order and balance in the functioning of the body. Even more wonderfully, it must combine emotion with reason and both with any and all other influences both tangible and intangible so that order can exist and chaos be prevented.

Man's interest in and understanding of his mind are increasing rapidly. He is coming to a much more intelligent evaluation of what contributes to its proper function. His definition of normal and abnormal is becoming less a matter of opinion and more a question of experimentation.

All of this trend is healthy. It must, however, be accompanied by a sense of values. It is easy to become lost in a maze of sophisticated semi-scientific social interpretations of man's nature. It is well to be healthy and free from insinuation in our analysis. It is well to remember that man experiences and utilizes phases of life in which idealism and beauty exist for their own sakes or for the sake of something even higher and finer than man himself.

15. SCIENTIFIC VIEWPOINT

We have seen that man and laboratory animals are really highly organized communities with very complicated but marvelously adjusted methods of internal regulation and control.

The building of each of these communities is evidently a matter which requires time and certain other material conditions which control temperature and spatial relationships.

We shall return to this question later, but in the meantime will point out another requirement which must be met.

This is the maintenance of a mechanical system by which variation can be kept within limits so that each succeeding generation will resemble its own species and more particularly the two parents and other direct ancestors from which the individual is derived.

In order to meet these conditions the formation of certain specialized cells has been perfected and is guarded jealously by those animals which represent, at any one time, the active and reproductive members of the species.

We are going to consider the formation and nature of these specialized sex cells which are produced by male and female individuals and we are going to compare them and their methods of reproduction with the animals and plants which remain single cells throughout their life.

In so doing we shall be approaching two very great and majestic fields in which life manifests itself.

The question of the formation of sex cells and their behavior lies at the basis of man's social behavior and is directly responsible for theories of philosophy, theology, sociology, economics and many of the problems which civilization has to face.

The nature and behavior of single celled plants and animals introduce us to the origin of life, to evolution, to the history and development of physical man. Here, too, we meet agents that cause plague and disease and questions of philosophical importance that bear on theology and sociology.

Since this is the case, and since emotions, prejudice and unreasoning impulses loom large in such fields it will be well to give you certain equipment with which you can approach the subject with as nearly a scientific point of view as possible. This will enable you to evaluate both the experiences of life itself and your own reaction to them.

The dignity of the material about which you will learn requires calm and fair treatment and a careful introduction. This introduction may be called the outline of a scientific point of view.

16. COMPONENTS

Probably your first reaction to the idea of a scientific point of view will be that it is a matter of extensive information, of profound and dull scientific terms and of long preparation. Such an opinion would be incorrect. As a matter of fact, wisdom and courage are much more essential to a scientific point of view than learning derived from books. It is a question of habit of thought, a problem in self-discipline.

As such it is one of the basic, perhaps actually the greatest, psychological need of Americans today. Because of its absence we have found ourselves in the midst of world wide chaos. Without it we can *never* build a true democracy or expect "freedom" and "peace" to be anything more than hollow words without power to survive or to create.

There are four simple components of a scientific point of view and you must learn to live by and with them if you are to be a worthy citizen of a real and lasting democracy. Briefly the four steps are: *Observe, record, analyze* and *interpret*. Let us discuss each of them in turn.

17. OBSERVATION

Observe—with eyes, ears and all other senses including intuition if you chance to have it. Wise intuition may be a very useful adjunct in cancer control as well as in everything else. You have to observe tirelessly, steadily and carefully. This is not as easy to do as you might think. People who wish to rush into war work observe that there is a need but often do not observe where a still greater need exists. It is very easy to see part of things as you go—parts of people or situations —easy to be careless and sloppy in your impressions based on lazy or careless observation. Steady observation is different from sporadic observation and is very essential because very often looking at a thing steadily for a long time changes your entire idea of what that thing is.

I am sure that enough of you have seen mirages and have looked at them steadily to a point where you were able to evaluate them, whereas if you looked at them intermittently your observation would not be accurate. In hunting, lack of steady observation often costs a deer its life. It is possible for the hunter to wait until the animals become careless and cease from watching you. You can then move up on them because they have not observed steadily and evaluated you as dangerous and capable of motion.

All of us give up too easily. William James once said that few individuals ever drive themselves beyond the threshold of what it was comfortable to do. As soon as things begin to go badly we are apt to quit, using some easy excuse. "Oh, I just can't do anything more. I am never going through *that* again. I am through." James showed that people can drive themselves through such a period of temporary fatigue without injuring themselves in the least. Among the students that he pushed past the threshold of fatigue none showed injury in any way. It is obvious, therefore, that freedom from slavery by fatigue is something that can be cultivated.

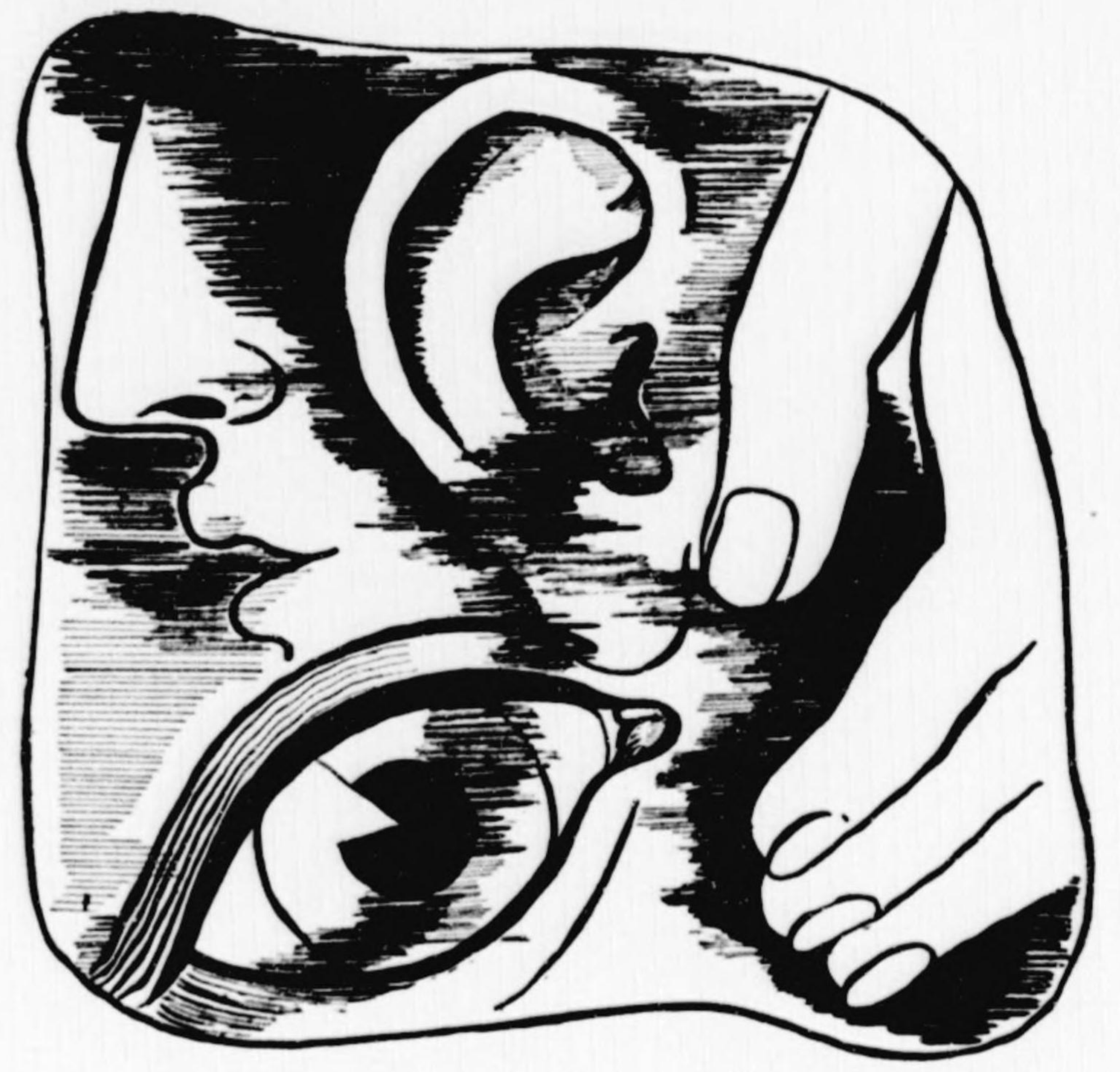


FIG. 6.

Continuous observation pays great dividends. It builds up experience and experience in turn creates and enriches wisdom. Tireless observation also often creates enthusiasm because one does not miss the variety and beauty in life even though it may appear disguised as disaster or discomfort. Enthusiasm in turn is one of the roads that leads to the retention of youth of mind and of spirit.

Even though observation is listed as the first of the four essential basic principles of a scientific point of view, it has a great and lasting value in its own right as a key to open wide the door to life.

18. RECORDS

Next comes the question of *recording* what you observed. You must record accurately, clearly and completely. That doesn't always mean putting things on paper. You have to sort out in your own mind your observations and prevent what you see from becoming a mince pie of unrelated observations. You have to learn how to record accurately in your mind what you have observed. This depends on memory, ability to pigeonhole certain things in your mind, not to let them become confused. Don't, for example, let *one* irritating experience influence you in the least when you meet another similar experience. In university work I have noticed that when there are 16 boys to be seen for having cut classes, that by the time numbers 14, 15 and 16 get into the Dean's office they often get "crucified" for the same thing for which numbers 1, 2 and 3 were merely warned. The Dean has not *observed* in the way that he should nor has he *recorded* accurately in his mind what he has observed in each boy. That is a very easy mistake to make. He has allowed irritation to warp his scientific attitude.

It requires an effort for most of us to pigeonhole a certain thing. There is no point in making written records unless we or somebody else can use them. If our experience is to be transferred in any way except by personal contact we must learn to put on paper what we have observed. Luther Burbank was a tragic example of this fact. He was a brilliant observer, but unfortunately did not enjoy or would not always practice clearness of keeping records. As a result, a large amount of what he did has not been transferrable to anyone else. Some of his methods are still, to some degree, hazy.

Complete records are necessary. Let us take an example. Suppose you as an officer of the Field Army are having a conversation with a series of your subordinates. If you do not record completely what you

FIG. 7.

have heard you are likely to forget that doubts were expressed by 5 out of 12 persons as to whether methods used by another group for raising funds could be handled adequately in relation to the Field Army enlistment drive. If you have not recorded completely what you have heard you may fail to note that these 5 who are doubtful about such methods are located in an area where the head of that group is a potential trouble maker. You may miss a source of increasing trouble that could be corrected. We cannot tell at once what is going to be significant and what is not. It, therefore, pays to keep records so that if we need to recall any phase of past experience it may be still readily available.

19. ANALYSIS

The next step is to *analyze* exhaustively, fearlessly and impartially. This is not at all easy. Inasmuch as this applies to your own self and your habits of self-evaluation you are going to find it extremely difficult. It is easy to *start* trying to analyze what you have seen and recorded and to stop with superficial results.

It is also extremely hard to face further analysis when you begin to find that you yourself are showing up poorly. Sometimes you will think that you have had a lot of trouble with certain of your officers and will suddenly find that careful analysis shows that it is because of something that you have done or failed to do. This is not a happy situation, but is one with which we are all constantly faced and one which never hurts any part of you except your pride. I know that oftentimes I have caught myself blaming a number of people who are my subordinates for the failure of some plan and then found, by a direct and fearless analysis, that I could trace the failure back to things which were errors on my part, either sins of commission or omission. It was possible, for instance, to find that in one case the deans in a university were, I thought, becoming noncooperative and unfriendly. I stopped and analyzed the situation carefully and found out that three of the eleven deans were personal friends of mine. I was seeing a great deal more of these three deans informally. When I looked back over what was happening in the deans' conferences, it was apparent that the others felt that favoritism was being shown.

As another example, I find again and again that I can keep with me followers and associates up to a certain point. I hold their loyalty to this point and then in many cases they have "fallen overboard." I had the habit of blaming them. Finally, it became so general and so often repeated that I suddenly came to realize that if people believe very strongly in things, as I do, if they lose themselves in what they believe and if they attempt to force their own strong belief on others there eventually comes a negative reaction. If you still, at that stage, keep on being loudly assertive and aggressive, your associates subconsciously feel that you do not need them. They say to themselves: "I will keep a few cards of affection, loyalty and sympathy 'up my sleeve' for somebody who really does need me." Most people when they get to following a leader feel: "This fellow seems to need me." If he keeps on indefinitely with his motor still running loudly from internal combustion and the exhaust still making considerable noise they say: "Well, after all, he isn't going to need *me* to help him drive this car. I will save my energy for someone who *does* need me." People want to be needed by those they admire.

It pays to analyze yourselves as leaders. To what extent can you become gracefully dependent? Are any of your subordinates following you up to a certain point and then you find that they fade out of the picture? Do you get them aroused and have them with you as long as you are on the scene, only to find that they later slow down? That is perhaps because you haven't informed the person in that position that you really need them and that their work is appreciated.

Fig. 8.

Impartial analysis is, therefore, essential. It is a hard thing not to play favorites, but impartial analysis is a much safer and happier method. You have to be impartial about things as well as people or else expect to find that you have created enemies who have a right to criticize and blame you.

20. INTERPRETATION

The fourth and final thing that you have to do is *interpret*, and here you must do so conservatively, temporarily and impersonally. The happiest and easiest of these three qualification is the "temporary" requirement because that is where one can find an alibi for poor judgment. I know that all of us have attempted to make final judgments and I assume that all of you who have been in this work for any length of time realize by experience that that is the stupidest thing that one can do. It is very much better to tie yourself to any interpretation by the type of mental knots that can be loosened by one "yank" of the string so that you can be free to make new analyses and interpretations. This is especially true in the case of science.

New experimental facts are constantly being discovered to change our evaluation of any situation.

Conservative interpretation means not to interpret beyond the observed facts. Speculation is lots of fun but should not be confused with an interpretation. Do not mix in your work what you can *stand* firmly on with what you can *skate* rapidly on. You can slide around and do some good figure skating on speculation or theory. Don't mistake this, however, for an interpretation.

The need for an impersonal type of interpretation must be emphasized. Don't try to interpret other people's motives. People have a right to their own motives. They belong to no one else. If you wish to speculate about another's motives well and good. Do not, however, try to raise your opinion of what you think a person is trying to do and why you think that he is doing it to the dignity of a scientific process. It is really a horrible and suicidal thing at times when sensitive people are involved. They can be bitterly and needlessly hurt by a wrong interpretation of motives.

There will be times when you meet people who do not know why they are doing things. If you decide to interpret why they are doing these things you may not only harm them, but make worthless all that they are trying to do. This is a hard thing to explain. The only way that one can ever be comfortable about other people's motives is to have a personal faith in that individual which raises you beyond the point of needing to know why they are doing things. That is something which you alone can build. It is a great spiritual victory once it is accomplished.

It is utterly impossible, for instance, for you to carry this faith like a material gift to other people. You can build it in them only as you live up to it yourselves. You cannot possibly *reason* it into them or they *reason* it into you. One cannot possibly build a lasting human institution without motives being open and taken on faith. It is clear that people are not in this work of cancer control without having met this problem in their own experience and of understanding why it is so strongly emphasized.

21. FACTS VS. DOGMA

This brief summary and discussion of the principles which determine and constitute a scientific point of view makes no claim to being adequate or complete. It may, however, serve as a foundation for an impersonal approach to the consideration of the information to be derived from a study of the sex cells and to other matters likely to become personal or controversial.

Men have long mixed their interpretation and evaluation of biological topics with religion. Various creeds and sects place different degrees of spiritual significance upon the various successive stages, in the formation and development of the individual. Similarly they accept or reject in different measure the concept of a common origin of man and other forms of life.

For the present purpose—namely, our study of cancer and its conquest—we must obtain information about some of these controversial stages in our development. We can and must do so, however, from a purely scientific point of view, agreeing not to confuse facts with dogma.

We must find our interest and inspiration in the wonderful and orderly job which is accomplished naturally and regularly by the animal body generation after generation through the centuries and eras during which life has been privileged to occupy the earth.

There is enough profound spiritual significance in the facts themselves to occupy our full and undivided interest and activity. We must remember that cancer does not spare mankind whether it be white, black, yellow, brown or red or whether it be Jew, Gentile, Christian, Buddhist, Hindu, Mohammedan or Atheist.

The qualities that mankind possesses in common have a survival value and a contribution to make to the creation of the world of the future. The nationalistic, denominational and group interests and monopolies which have ruled our thoughts and purposes for centuries have made a ghastly mess of the common "brotherhood of man."

Cancer is a great equalizer—an enemy that plays no favorites. It is perhaps of greater value to us because of this fact than we have realized. Although far from being either poetic or pleasant, cancer is certainly "one touch of nature" that "makes the whole world kin."

If we remember this constantly we shall derive a great deal of satisfaction from the fact that the conquest of this disease demands of us a very sincere determination to forget the destructive social distinctions which man has fostered.

22. SEX CELLS

With this introductory and general statement we may turn to the most important independent single cells in the bodies of higher animals and especially of

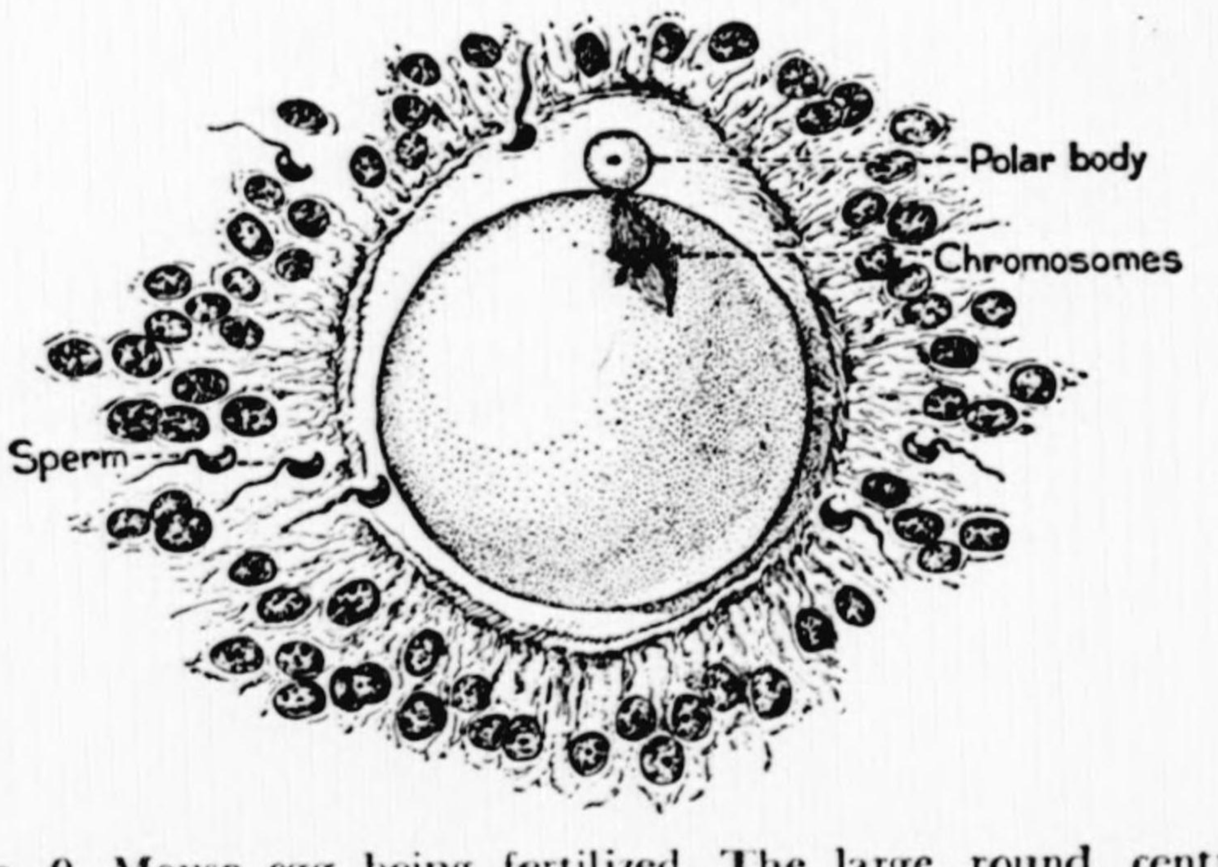


FIG. 9. Mouse egg being fertilized. The large, round, central mass is the egg. At its surface is a smaller sphere called a "polar body" which is being eliminated from the egg substance. Just inside the egg is a "spindle" of chromosomes which are the bodies that carry the chemical basis of hereditary characters. Around the egg and separated from it by a clear zone is a ring of cells through which are penetrating seven male sex cells or "sperm." Of the two at the lower left hand corner, one is about to reach and fertilize the egg.

mammals like ourselves. These cells are the sex or germ cells called the *egg* in females and the *sperm* in males.

The two mammalian sex cells are very different in appearance. The egg is spherical and is just on the border line of visibility with the naked eye. It is incapable of any locomotion on its own part. The sperm is only a tiny fraction of the size of the egg. Tens of thousands of sperm could find room on the head of an ordinary pin. The sperm is highly motile and consists of an inert, dark colored head-piece often elongated and oval or curved in shape and a very thin lash-like tail which vibrates rapidly from side to side and thus propels the head forward.

FIG. 10. The reproductive system of the female mouse. At the bottom right is an undissected uterus showing the paired ovaries, from which the eggs are liberated, and the oviducts which lie like coiled tubes. The enlarged drawing illustrates one ovary, oviduct and the upper part of one "horn" of the mouse uterus. A section has been removed from the ovary to show an egg being liberated from a follicle or "pocket" near its surface. The egg travelling the length of the oviduct eventually becomes lodged and implanted in one of the folds of the uterus or "womb." Here the embryo will continue its development until birth.

Eggs or ova are formed in two similar reproductive glands called ovaries. The number of primitive ova which will be used throughout the life cycle of a normal female mammal is determined and fixed at birth. At that time the ova are present in a primitive condition within the ovary and are performing no obvious physiological activity. As the female mammal matures sexually the ova grow and undergo certain basic changes. They begin to mature and ripen. Around each as it ripens is formed a fluid-filled space at the bottom of which the ovum is attached. Distention of this space by the fluid which it contains results in thinning the outer wall of the ovary until at a period known as ovulation the wall of the ovary ruptures and the mature egg is discharged. The egg is then ready for fertilization. It is deposited from the ovary in a long coiled tube which leads from the ovary at one end to the womb or uterus at the other. The latter organ is adapted for the lodging and growth of the embryo during development.

Sperm are formed in a pair of male sex glands known as *testes* or testicles. Sperm formation is practically a continuous process from the time that the male individual becomes sexually mature until reproductive activity ceases. Unlike the egg, there is no rupture of any part of the testicular material in the formation of sperm. This process is accomplished merely by the transformation of certain specialized resting cells into motile, mature sperm. The testes are connected with the outer genital opening in the male by coiled ducts through which the sperm are transferred to the exterior during the process of sex intercourse. When the sperm are deposited in the reproductive tract of the female they are kept in motion and are driven forward by the vibration of their lash-like tails. Within a period of hours or at most one or two days they thus reach the coiled tube lying between the ovary and the uterus where they come in contact with the mature eggs. Ordinarily the first sperm to encounter an egg attaches itself to the outer surface and by so doing creates almost instantly a chemical reaction on the surface of the egg which prevents the similar attachment of any other sperm. Subsequent to the attachment of the sperm, its head works its way through the outer surface of the egg leaving the tail behind. It thus deposits the head-piece composed of material called "*nuclear*" in the substance or *cytoplasm* of the egg. The head-piece so deposited becomes what is called the *male pronucleus*.

Several new terms have been used in the previous paragraph and it may be well to define or explain some of them.

Every cell has a core of rather dense substance usually spherical in shape. This is called the *nucleus*. In the origin of sperm the *nucleus* of each cell transformed into a sperm becomes the head-piece of that sperm.

Around the nucleus of every complete cell is located less dense and more foamy material which is called the cell-body or *cytoplasm*, this being the Greek equivalent of the English term. Latin and Greek are frequently used in science since these languages are a part of the basic training of scientists of many nationalities.

23. REPRODUCTION

The egg cell, like all functional, free cells, contains a nucleus of its own which, at fertilization, is called the *female pronucleus*. This unites with the male pronucleus to form what is called the *fertilization nucleus*.

There are certain remarkable facts in connection with the process of fertilization. It is, in fact, difficult to define exactly whether the penetration of the outer embryo of the egg or actual fusion of the male and female pronuclei constitutes that process.

As an example, some years ago a German zoologist named Hertwig tried experiments in fertilizing eggs of certain marine forms of life with sperm which had been given a very heavy dose of radium but which still retained their motility. It was possible for Hertwig to observe under the microscope the process of approach of these damaged sperm to the surface of the egg, their attachment to it and their subsequent penetration of the cytoplasm of the egg. At that point, however, they failed to function further. The male pronucleus was inactivated. The egg itself on the other hand began to show the physiological activities characteristic of a normally fertilized egg. Embryos resulted which were entirely like their mother. In other words, the male sex cell or sperm had started the process of development but took no part in it.

Even more extraordinary are the experiments of Loeb and of Battalion who independently activated mechanically the unfertilized eggs of frogs by pricking them with a very fine and sharp needle. Most of these eggs showed little or no response, but a number began to develop and actually formed embryo frogs which lived throughout the tadpole stage and eventually, in a few cases, changed into adult frogs.

Both of these experiments suggest that fertilization, if we consider that process the activation of the egg to development, can be started without participation of the male sex cell. Most biologists, however, prefer to define fertilization as the actual fusion of the two pronuclei and speak of a process such as that observed by Hertwig, Loeb and Battalion as *virgin birth* or parthenogenesis.

Parthenogenesis is another Greek equivalent of the English term virgin birth. It may be perhaps more easily remembered by recalling the fact that the Parthenon was the temple dedicated by the Greeks to the virgin goddess, Athena. It will be recalled that this goddess sprang fully armed from the head of Zeus. It is perhaps unfortunate that her origin, so purely masculine in nature, is associated even indirectly with a process entirely feminine.

Virgin birth, or parthenogenesis, although it seems extraordinary to the ordinary reader actually is the common form of reproduction in certain insects. Some of these types have several generations of parthenogenetic reproduction followed by one of sexual reproduction as their regular annual cycle. The interesting point about parthenogenesis is that it shows that the higher animals formed by fertilization are usually *double* structures. This will be referred to again when the structure of the germ cells is discussed in more detail.

Ordinarily, after fertilization, the egg develops into a single individual. In species like mice or rabbits a number of eggs are liberated at one time and each individual mouse or rabbit which is born represents the production of its own particular fertilized egg. In humans ordinarily one egg is liberated. Occasionally, however, two or more are liberated resulting in twins or triplets which are not similar to one another and which in their origin are just as much independent individuals as though they had been born at separate births.

There is, however, another extremely interesting form of behavior of a fertilized egg which is rare in laboratory animals and also unusual, but far from unknown, in man. In this case a single egg starts to develop and after having formed a number of cells by the process of division, the mass thus created splits into two equal halves, each of which forms a separate individual. These individuals are both contained in the same embryonic membranes and are called similar or "identical" twins. Each pair of such twins is always of the same sex and the physical resemblance of the two individuals forming the pair is so close as to make identification often a matter of great difficulty.

The formation of many individuals from a single fertilized egg is the established rule in one form of mammal which occurs in southwestern United States and Mexico. This animal is called the armadillo. It has somewhat scaly legs and feet, a long snout and a tough shell made of plates on its upper surface. Its tail is also armored in much the same way. In the armadillo a single fertilized egg regularly divides into four equal parts, producing identical quadruplets. It is extremely interesting that among the thousands of species of mammals this one type should have developed such an unusual form of reproduction. The reasons for it are not clear, but the existence of this unique type of behavior indicates once again how large numbers of progeny can be produced by many different methods.

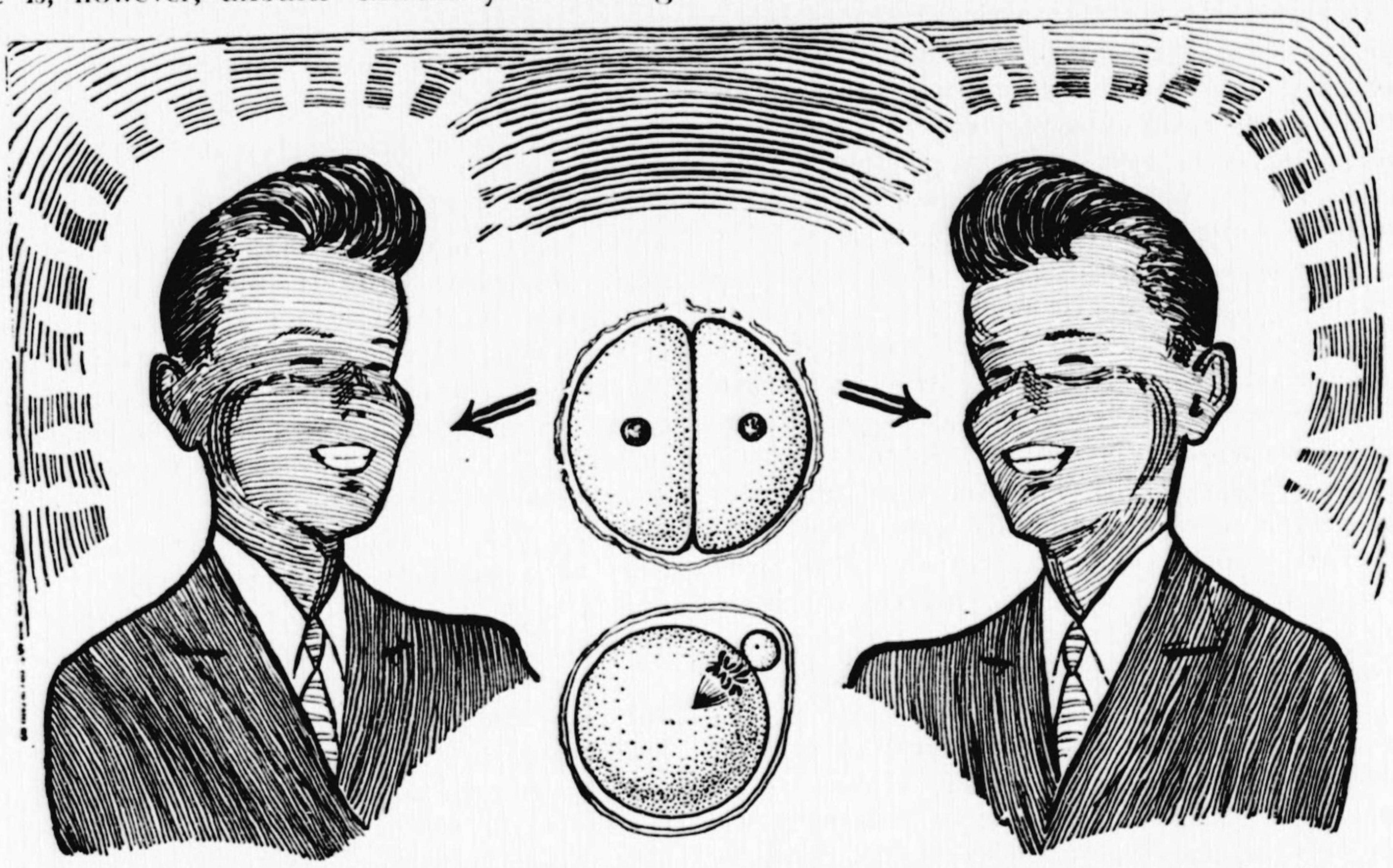


FIG. 11. So-called identical human twins formed as indicated by the equal division of an embryonic cell mass descended from a single fertilized egg. The egg is shown in the bottom central figure, the division of the cell mass in the top central figure.

24. STRUCTURE OF SEX CELLS

Considering now the structure of the sex cells, the important part in each case is the nucleus. This, it will be remembered, formed the great majority of the material of the head of the male sex cell or sperm and was present as a spherical body in each egg cell before fertilization.

Studies of this minute nuclear mass show that it ordinarily consists of long strands of material coiled in a complicated and probably irregular manner. This material when prepared for microscopic study absorbs and retains to a high degree certain of the chemical stains used to bring out the structure of cells and tissues. The material thus stained and existing in the nucleus in the complicated coil is called *chromatin* or "colored substance." It remains coiled and inactive as long as the cell of which it is a part is similarly inactive. When, however, the fusion of the male and female pronuclei takes place at fertilization certain activities are initiated within the nucleus. These reflect themselves in the behavior of the coiled chromatin material. At this stage the material breaks up into a certain number of rod-like bodies known as *chromo-*

somes. The number of these is constant for each species. The fertilized egg of man has forty-eight. The fertilized egg of the mouse has forty. The fertilized eggs in certain insects have as small a number as eight. Some of the amphibians and insects have hundreds, but in every case the number is constant and characteristic of the species involved.

Not only is the number constant, but it is possible to observe under the microscope that these chromosomes occur in pairs, one of each pair coming from each parent. The members of each pair of chromosomes have a characteristic shape which enables the skillful student to identify them individually under the microscope. The importance of these chromosomes in biology is extremely great. Careful studies have shown that they represent the physical basis for inherited characteristics. It is difficult to understand what this means, but the fact must be that within these tiny bodies there exists in an extremely concentrated form the chemical structures necessary to reproduce a given characteristic by the patient, complicated cooperation of cells with each other during the process of development. So extraordinary is this fact that it is not surprising that the older biologist gave to these tiny centers of directive force or nuclei located within the sex cell an almost mystical entity. Biologists like Darwin and his contemporaries believed that each part of the body had its particular representative in concentrated form located in the sex cells. They felt that influences acting on a part of the adult body were transferred by the blood or some other mechanism to the particular center that represented that part of the body in the sex cell. They thus envisioned a minute microscopic sized man within the sex cell of each human being.

This conception seems rather naïve to us at present for it very quickly reduces itself to an absurdity. If, for example, we followed this line of reasoning we would have to imagine that within this tiny counterpart of the human being there were even tinier sex cells and within each of these a still smaller individual until the theory defeats itself. Very evidently Darwin and his associates were on the wrong track. The situation is a good deal simpler chemically but much more complicated from the point of view of trying to explain how and why a sex cell in which minute quantities of concentrated chemicals are present can express itself in such a regular, symmetrical, orderly and accurate way in the adult animal.

25. ENZYMES, VIRUSES, GENES

We know that certain chemicals called enzymes exist and that only an infinitesimal amount of such an enzyme is necessary to start a series of reactions or developmental processes. We also know that by some strange quality enzymes are able to reproduce themselves so that given sufficient time they can produce remarkable results. It is interesting also to note that viruses, those strange substances on the border line of the living and the non-living, are able to do this same thing. This ability also must exist in the unit of inheritance or *gene* located in the chromosome.

As a result of common properties possessed by these three groups of material—enzymes, viruses and genes—there has been in recent years a great deal of intelligent and stimulating speculation as to whether all these three types of substances are in reality one basically. We have no definite information on this point, but it is interesting to mention it because it represents the sort of correlative thinking which modern biology is beginning to produce and which will increase undoubtedly in a great degree during the next few decades.

It will be well, at this point, to digress from a consideration of the sex cells of higher animals in order to discuss the plants and animals which remain as single cells throughout their life history.

26. ONE CELLED ORGANISMS

Single celled organisms whether they are plants or animals are thought by many to represent the lowest grade of organized life. It should, however, be pointed out that while this may be true of certain of the single-celled forms, there has been developed over a period of geologic time an immense number of highly specialized single-celled forms living independently and fulfilling the definition of a protozoan or bacterium as the case may be. One must be careful, therefore, when he picks an illustration from single celled organisms, with an idea of showing simplicity of structure and a primitive type of organization, to select his material with great care.

The common example of a simple, single celled animal is the *Amoeba proteus*. This animal which is found usually among the decaying leaves and vegetable matter of ponds or brooks is too small to be visible to the naked eye. When examined under the microscope the impression is given that it is a somewhat flat disc with an irregular and changing outline. It must be remembered, however, that this view is one which does not or cannot take into account the fact that the amoeba is three dimensional. It is really an irregularly shaped mass of living substance. Most of its substance consists of transparent or translucent, colorless material known as *protoplasm* in which there occur at irregular intervals small particles of dark material representing food about to be digested or the waste products on their way to the outside of the body. At intervals there appear around these particles spherical areas called vacuoles. These represent drops of liquid formed by the process of digestion. From time to time the vacuoles discharge their contents from the surface of the body and disappear, new ones being later formed as the amount of waste fluid accumulates. In the center of the amoeba's body, as in any cell is a spherical, dark structure—the nucleus. This appears to be important in maintaining orderly function of the cell and in providing a central, orienting structure when a new amoeba is about to be formed.

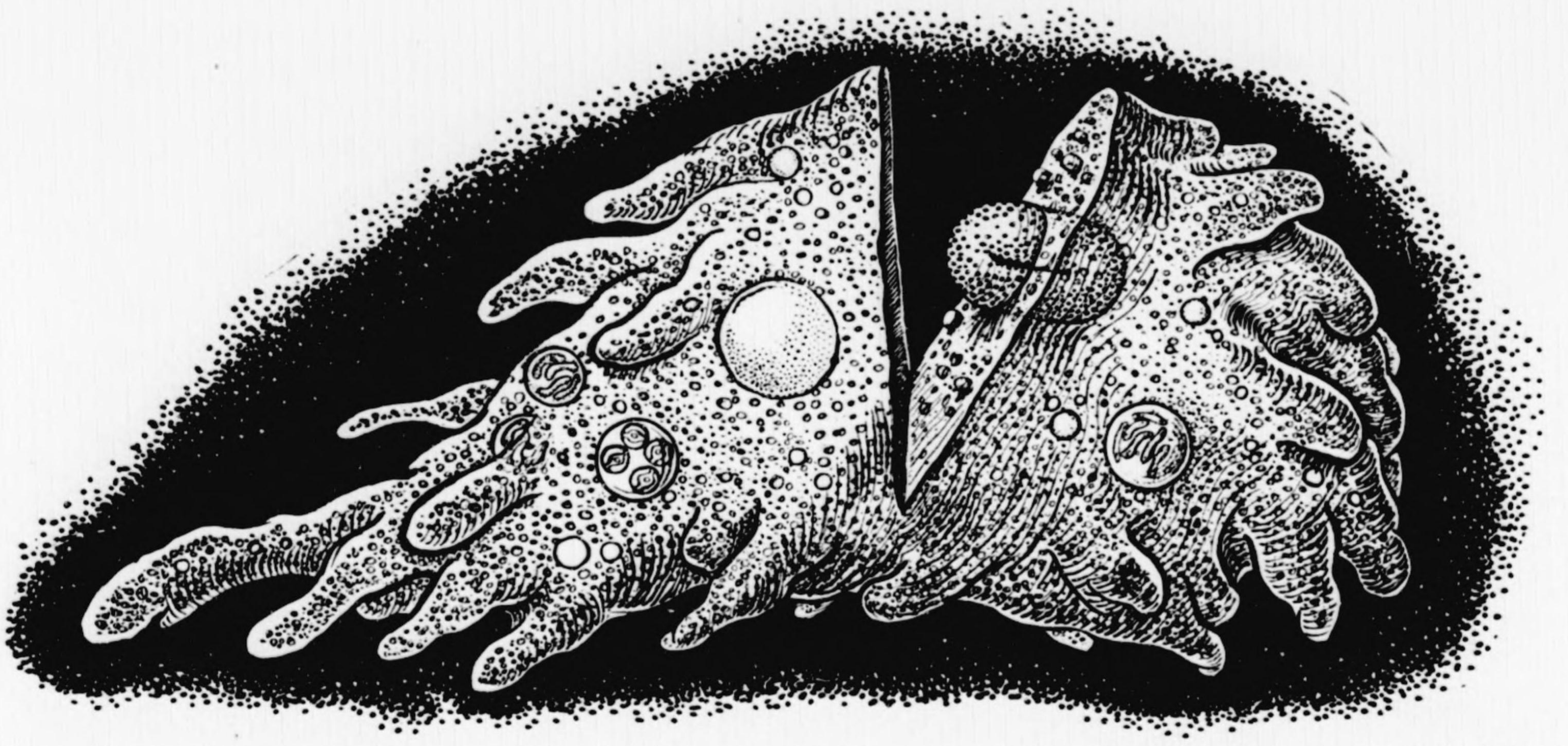


FIG. 12. An amoeba—one of the most primitive of all animals, consisting of only a single cell. Actually these animals are too small to be seen with the naked eye. This figure shows one artificially slit open to give an idea of its form and structure. The "nucleus" which protrudes from the cut surface is the central organizing and directive structure. The sphere containing rod-like or round bodies are "food vacuoles" and the bodies included are tiny single-celled plants which have been surrounded and taken in by the amoeba. The clear, round sphere is a "contractile vacuole" which fills with liquid excreted by the amoeba and then by contracting expels this liquid from the outer surface of its body. It then fills again and repeats the process. The irregular protuberances from the surface are "false feet" or pseudopods. They reach out from the surface in the direction in which the amoeba will move. Their tip then remains fixed in position while all the rest of the amoeba half flows, half rolls up to the point where the tip of the pseudopod is located.

The amoeba moves by a peculiar flowing process in which part of its own substance pushes out ahead of the main mass of material in a finger-like process known as a pseudopod (false foot). After this has

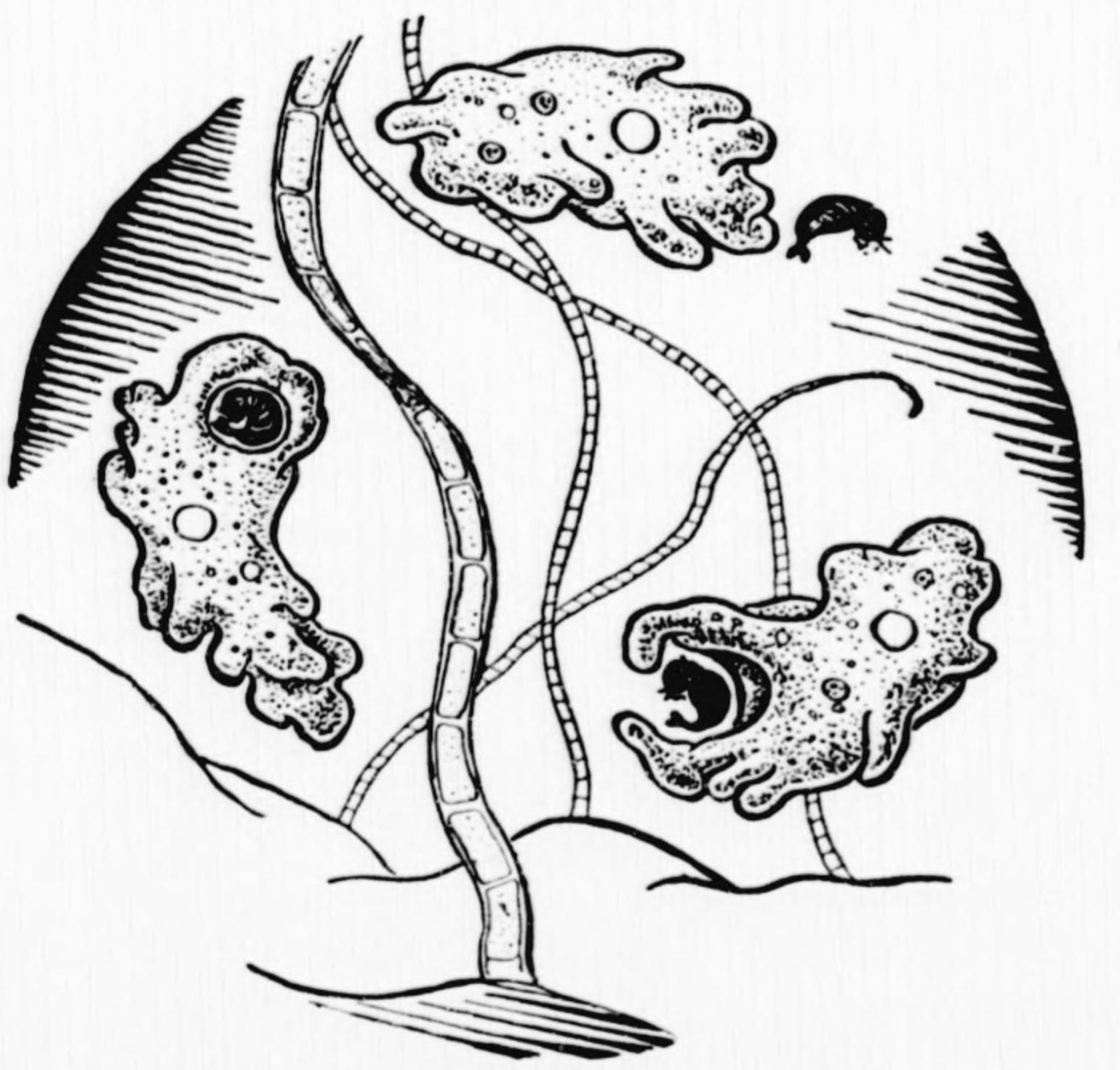


FIG. 13. An amoeba engulfing food.

reached a certain distance the tip of it appears to become fixed in position and the rest of the body flows up after it to that point. If one could view the animal from the side while this process was going on he would observe that the pseudopods extended from the upper part of the animal reaching forward and that the animal in moving up after them really shows a slow, rolling method of advance. These animals do not possess any central nervous system, any true circulatory system or any true digestive system, since the functioning of all of these systems as such requires many cells and tissues.

When an amoeba has grown to a certain size it often prepares to reproduce. This is done by the simpler of two forms of cell division. We can consider this function at present, leaving the discussion of the more complicated type of cell division until later.

The first sign of the fact that an amoeba is preparing to divide into daughter cells is the elongation of the nucleus and a similar elongation of the whole structure of the cell. Almost immediately after this lengthening has taken place the center of the elongated nuclei end of the substance of the animal starts to contract, producing roughly what is a dumbbell-shaped cell. The narrow, central portion shrinks still further and finally snaps apart leaving two daughter cells or amoebae approximately one-half the size of the mother individual which has just divided. Each of these then proceeds to carry out an independent existence repeating the behavior and function of the original mother cell. It is a somewhat awe-inspiring thought to realize that countless millions of these forms are being produced daily throughout the world and have been so produced each day since the first life appeared on the earth. It is unlikely that they have changed much in structure, for their needs are simple and their capacity of supplying them adequate. Conditions of water and food are general and widespread and must have been so since the earliest general extent of vegetable life. There appears to be no reason, therefore, why they should change or be eliminated. They survive by simplicity, adequacy, small size, invisibility and the wide extent of the environment in which they can live.

Cells which can simulate them very closely in appearance and behavior are the white-cells of the blood of mammals and certain cancer cells when grown in tissue cultures. These two sorts of cells can live independently as single individuals, they can divide by the same process as the amoeba, absorb food in the

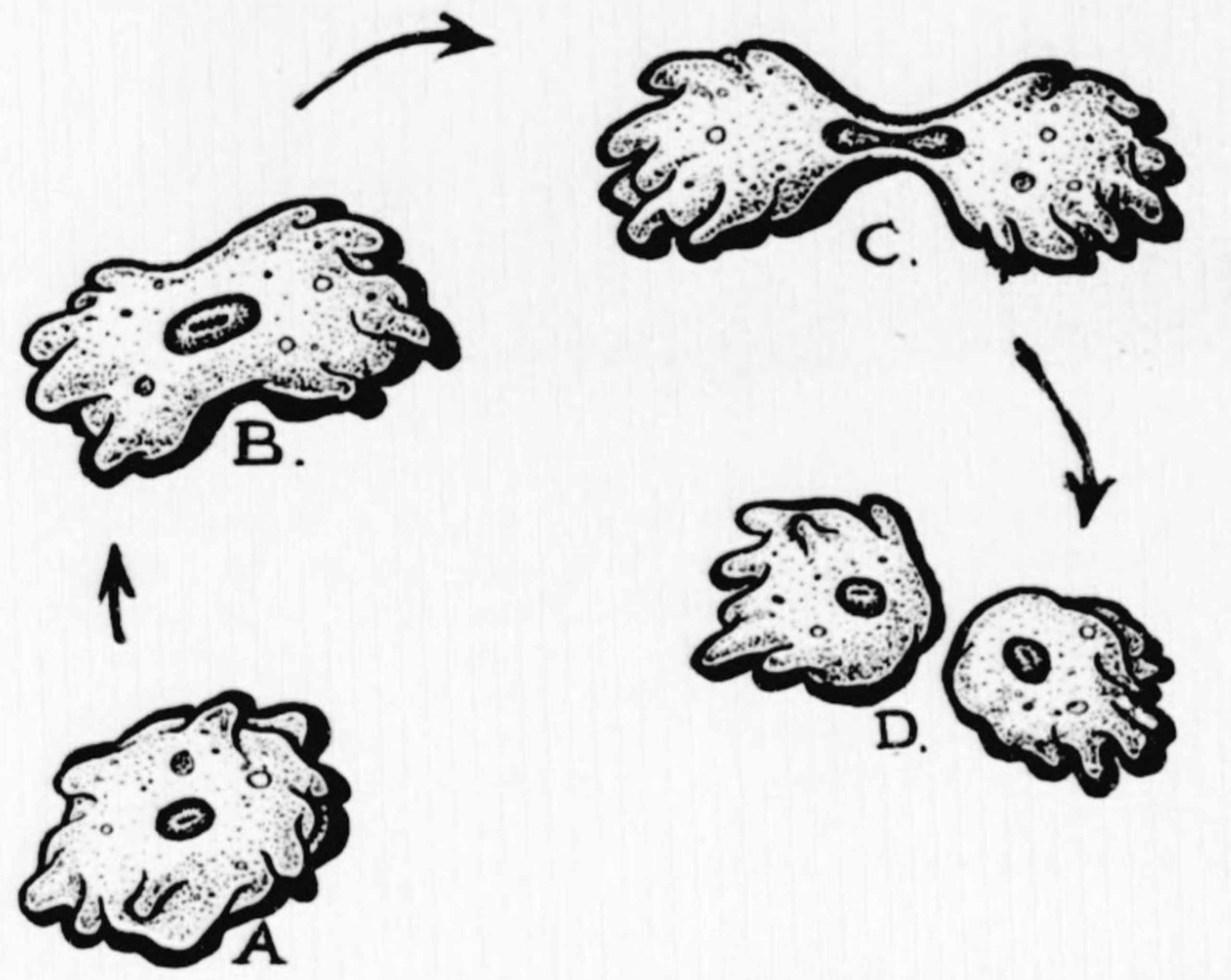


FIG. 14. The process of "division" by which one amoeba becomes two. Note that the darker "nucleus" is dividing as is the rest of the cell substance.

same way and move in the same manner from place to place within the body. Of course, the white blood cells are ordinarily carried by the circulation of the blood infinitely more rapidly and in greater numbers than their independent motion would allow. They can, however, under certain circumstances utilize the more primitive type of locomotion just as successfully as their simpler ancestral types.

27. ANIMAL RELATIONSHIPS

The discussion of amoeba leads us to certain general matters which we should consider at this time and which will be important in establishing a point of view toward other matters discussed in this book.

The first of these is that in all studies of groups of living animals one finds simpler forms like amoeba which have intimate connection with other types and which contribute to our knowledge of basic biological processes. There are also other forms which are highly specialized and which show the extent to which nature is able to produce diversified smaller groups of animals related to one another.

The degree of biological relationship of living things is the basis of all human attempts to classify them. There are two types of relationship. The first is based on resemblance and function and habits of life regardless of ancestral forms or of the factors of heredity extending throughout the centuries. The second type deals with hereditary resemblance and forms the basis for the theory of evolution. The concept of evolution is based on the general theory that existing resemblances between groups of animals may depend upon these groups having had common biological ancestry or origin. Both of these sorts of analysis are fruitful and helpful. Both have their very definite place in the scheme of man's knowledge of life.

It will be well to mention briefly some of the groups of living things which men have used in their attempts to map out relationships between different forms of living things. The groups are of different size and different order of importance.

28. COLD BLOODED ANIMALS

In the animal kingdom there are fourteen major groups, each one of which is characterized by some outstanding structure or function not possessed by any of the others. Certain examples of these may be helpful. The "lowest" of these groups and the one to which amoeba belongs is called *protozoa*. This means primitive or first animals and its membership is confined to those animals consisting of a single cell. Also one finds here the parasite that causes malaria and free-living forms, the countless shells of which form limestone. All single celled animals belong to this group and there is no form in the group that has more than one cell at any time during its life history.

At the "upper" end of these large groups is the one to which we belong. It consists of the vertebrate animals, animals with a backbone consisting of a number of segments arranged in a definite order. The backbone is the central axis of the supporting skeleton from which extend the skeleton of the various appendages such as the head, arms, legs, tail and ribs, all of which perform supporting or protective functions.

Another very large group of very great importance to man is that of the animals which have jointed legs known as the *arthropods*. Insects form the most numerous and striking sub-division of this large group to which also belong the spiders, scorpions and so-called crustacea (crabs, shrimps, lobsters, crayfish).

Still another of the larger groups is that of the *mollusks*. In this group are included the clams, oysters, snails and mussels. Certain of the larger groups have so few forms or such little known and seldom observed types that they are not of very great importance for our study. They may exhibit extremely interesting characteristics and be of considerable value to the professional student of biology, but from the point of view of the generally educated layman and in the study of cancer they have not as yet assumed sufficient importance to justify their extensive consideration. Within each major group exist certain other subdivisions and because the group with which we are most familiar in our general reading is the group to which we belong, we may consider some of the subdivisions of that group. Among the vertebrates the most primitive group is that of the fishes. These are given the Latin name, pisces, which of course is one of the signs of the Zodiac. Common conceptions of the word "fish" are in general all that is necessary to define the group. It involves cold blooded, scaled, water inhabiting vertebrates which have fins for their appendages in place of arms or legs. The only forms which are not fishes and are likely to be confused with them are the whales, porpoises and dolphins to

FIG. 15.

which we shall refer later. The only forms which are fishes but are likely to be thought of as something else are the eels, the so-called flying fishes and the lung fishes, a strange African form that can, under adverse conditions, exist for some time buried in the mud and breathe largely air instead of oxygen from the water. All true fishes have permanent gills which are a booklike arrangement of parallel structures serving instead of lungs and bringing the blood in close contact with the water over a complicated and extensive surface so that waste products may leave the blood and fresh oxygen be absorbed.

Above the fishes come those forms which can breathe both in the water and in the air. Some of these animals can do both of these things at one and the same time while others have different stages of life in one of which they are water living and in the other air breathing. This group is called the *amphibians,* meaning two forms of life. To it belong the salamanders, newts, frogs and toads. These animals are not scaly-skinned, but are cold blooded. They are almost always slimy or slippery on the surface although some of them, such as the toads, which spend a vast majority of their life away from water in our gardens and woods have developed dryer skins than the others. Fishes and amphibia are both egg laying and ordinarily develop their young outside of the body of the female. Interestingly enough, there are some exceptions to this condition.

It may be well to point out that there are in animals two broad types of reproductive behavior. First, that of fertilization and development of young outside of the mother's body, and second, that of fertilization and development inside of her body. These are fundamentally different. The first relies on tremendous numbers of eggs and young animals which are unprotected and can be easily preyed upon by other species from the moment of their formation. The second depends upon fewer eggs and the protective function of the mother's body which delivers the young in a relatively advanced stage where it can compete with or be protected from unfriendly forms of life and other adverse environmental factors.

Above the amphibia and at times resembling superficially the land inhabiting forms of the latter group come the reptiles in which are included the lizards, snakes, tortoises, turtles, crocodiles and alligators. These animals have dry, scaly skins and lay eggs on the land. The eggs, unlike those of fishes and amphibia, are protected by a dry shell. Ordinarily they are incubated by the heat of the sun.

29. WARM BLOODED ANIMALS

Somewhat closely related in its primitive forms to the reptiles there follows the large and well-known group of the birds. Here for the first time we find a protective mechanism that produces warm blood and maintains the body at a relatively constant level of temperature independently of the outer world. Fishes, amphibia and reptiles are directly and importantly influenced by external temperature. Birds can put up a good fight against great changes in temperature. Birds are, of course, egg laying and ordinarily incubate their own eggs. Most of them have the power of flight. They invade air, land and water with marked success in every case. They have developed a diversity of structure and function and form found in few other groups in the animal kingdom. They are characterized by a skin more or less completely covered with a new type of structure known as feathers. These are infinitely lighter and provide better insulation than any type of skin covering developed in the lower groups. There is also a remarkable difference in the development and function of the arms and legs of birds, the former becoming the wings while the latter retain the function of locomotion on the land or in the water.

The superficial and actual resemblance of the young of certain groups of birds to the physical conditions found in reptiles is somewhat striking. This is not evident in the newly hatched individuals among the scratching birds, such as partridge, quail, poultry and pheasants, but is particularly apparent in the young of pigeons, herons and other types which are born naked and are not covered with the thick down which exists in most of the sea birds and scratching birds.

The group to which we belong is known as the *mammalia* or mammals. It is characterized by the fact that the young in their early stages are fed on milk secreted by the mother. No other vertebrates have milk and no mammals lack it. Occasionally one finds an extraordinary and abnormal form like the Duck-billed Platypus which lays eggs and yet nurses the young hatched from those eggs. Another interesting group of mammals includes the kangaroos, wombats, opossums and other forms which give birth to their young and then with their mouths transfer these young to an abdominal pouch in which are located the teats on which the young nurse. The young usually become attached to these teats by a temporary secretion and remain there until they have developed to a point where they are able to leave the pouch for varying lengths of time and finally to obtain complete independence. Mammals are also ordinarily characterized by the possession of hair, although this is difficult to identify in the case of the whales, porpoises and dolphins which belong properly to this group.

In all of these groups one finds that the environment in which the animal lives makes certain demands upon its structure in order to allow survival. If mammals wish to live in the sea they have to pay the penalty by losing very largely their power of land locomotion. Whales and dolphins have lost all appendages that resemble arms or legs, so to a large extent have the seals, walruses and similar types. Yet inside of their flipper-like appendages are most of the bony structures which characterize the true arm or the leg.

30. POTENTIAL IMMORTALITY

To return to the protozoa or single celled animals, we may compare with amoeba which is a primitive and relatively simple type some of its relatives which have developed striking, specialized characteristics. Closely related to the amoeba which lives freely in the fresh water among decaying vegetable matter is one which lives as a parasite in the intestine of man. This causes the disease known as amoebic dysentery and is a form which in order to be able to be transferred from one human being to another passes through a "spore" stage in which it is relatively small and covered with a resistant outer layer. In this stage it passes from the body of one human being, is transferred to the drinking water of others and enters the intestine where it develops into the active stage.

Also closely related to the amoeba is a group which consistently forms around it a skeleton consisting largely of calcium. The amoeba that we considered was free living and without any protective shell. This other general type of protozoa is called "foramenifera" which means "bearing an opening." This in turn signifies that their shell has a hole in it through which the false feet or pseudopods can extend and the animal can obtain contact with food and develop the power of locomotion to some extent.

The degree to which these animals exist and multiply is one of the somewhat appalling facts of nature. They are largely marine in habitat and have from the beginning of recorded geographic time existed in such numbers that the vast deposits of limestone from which our temples and public buildings are built consist of the skeletons of these animals, any one of which is invisible to the naked eye. If one considers the literally countless numbers of skeletons formed by these tiny masses of living material and the vast stretch of time which it takes for them to be deposited in layers sometimes miles in thickness and adds to that the further time necessary to place these layers under sufficient pressure to consolidate them into rock he will, I think, realize that it is not necessary to move out into interstellar spaces in order to develop his appreciation of the almost limitless boundaries of activity in the universe.

It will be well to emphasize once more and to remember at all times this continuing power of growth of the single celled organisms. It is absolutely clear and undisputable evidence that the individual animal cell possesses potential immortality provided food and a proper environment is given to it. In other words, protozoa today are multiplying in the same way and just as fast as they did millions upon millions of years ago. There has been no slowing down of the rate of cell division. There has been no indication that it is likely to slow down as long as water, decaying vegetable matter and reasonable extremes of temperature continue to exist on earth.

31. SINGLE CELLS AND COLONIES

This brings us to a consideration of the same sort of simple form of life in the plant kingdom. Here we have two general groups, one free living and the other parasitic to the extent that it must invade the cells or tissues of other forms of life in order to multiply. The free living forms of single-celled plant life are called *algae*. Salt and fresh water are full of them. They form the chief food supply of the vast majority of higher forms of aquatic life. They differ from the single celled animals chiefly in the possession of green pigment called *chlorophyl*, literally meaning "green leaf." Some of them have the power of locomotion much as some of the single celled animals do although few if any travel by pseudopods as the amoeba does.

The parasitic forms of single celled plants are the bacteria, known to us chiefly by their bad reputation as the cause of many of the diseases of plants and animals. They are also at times beneficial. The bodies of higher plants and animals often contain millions upon millions of them which are in no way harmful and often aid in the performance of functions of the body. Both the algae and bacteria have demonstrated the same inexhaustible power of growth that the single celled animals have shown. The algae have in their composition all the elements necessary for a free living cell. They have a nucleus and surrounding cell substance or cytosplasm. The bacteria are for the most part almost, if not entirely, composed of nuclear material. For this reason it is necessary for them to use the cytoplasm of other animal or plant cells as the place in which to live and multiply.

Both single celled plants and animals have a way of adhering to one another and thus forming a colony. Many of these colonies are very large in size, some of them are permanent and some of them temporary. To a large extent they are merely mechanical groups without any signs of division of labor or organization. This is an important point to remember, for it is in this respect that these colonies chiefly differ from the groups of cells which unite to form multi-cellular or higher plants and animals. It is also interesting to remember that many of the single-celled plants and animals can under adverse circumstances or sometimes even in normal surroundings enter into a resting or spore stage in which they are able to resist extraordinary environmental conditions, such as absence of water and extremes of temperature not ordinarily encountered. The resistance of spores of bacteria to extreme heat or cold is well known and is the reason why sterilizing instruments have to be constructed so that they can create very high temperatures.

This type of colony of cells formed by adhesion of many units in a mass is very different, in most ways, from organizations built to form many-celled plants or animals.

32. MITOSIS

We have discussed briefly in an earlier section the type of cell division by which such animals as an amoeba commonly increase the number of individuals.

This type of simple cell division which results in two daughter cells of essentially equal size and which takes place by elongation and constriction of the nucleus as a whole is called amitosis (without thread). The meaning of this will become evident when we consider the other form of cell division common in the tissues of higher animals and in their development.

This second type of cell division is both more complex and more exact than amitosis. It is preceded by a reorganization and fractionation of the nucleus into an exact and constant number of chromosomes (see Section 24).

After the formation of the chromosomes and their arrangement in a plate extending across the center of the cell, one member of each pair of them moves to one end of the cell while its partner moves to the opposite end. This brings about an accurate division of all the chromatin and makes certain that each pair of chromosomes is represented in each daughter cell.

The course to be followed by the migrating chromosomes as they move towards the poles of the cell is marked by converging threads or fibers so that a spindle shaped figure is formed with its broadest dimension at the center of the cell and its tips at the poles. The presence of the "threads" gives to this type of cell division the name "mitosis" meaning "with threads."

Once more it is well to stop and consider the marvellous exactness with which this process of cell division goes on day after day, year after year, generation after generation down through the centuries, down through the geological eras. It proceeds a little faster at one point in the body, a little slower at another, maintaining balance and order, form and function, without requiring conscious planning or control. It is characteristic of both normal and cancer cells. It is a general attribute of life.

Cell division in point of fact is growth and growth in turn enables life to continue and to expand over time and space.

Here in cell division and growth we meet face to face for the first time the birthplace of cancer—for cancer is a center of cell division out of control, out of balance, out of its relationship to the growth rate of the rest of the tissues and organs of the body. That is all there is to it. It is as simple and as powerful as life itself.

That is why our understanding of cancer leads us along the road to humility, patience and a deep and lasting sense of the dignity and beauty of that life which we are trying to free from fear and ignorance.

33. CELL TO EMBRYO

Since we are now well on our way in our study of the nature of cancer it will be well to consider some of the ways in which growth behaves and how it proceeds to establish the controlled and orderly organization which characterizes the higher animals and plants.

The fertilized egg cell we recall was of a size to be on the border line of visibility to the naked eye. Starting as a single cell, it goes through several series of cell divisions producing first two, then four, then eight, sixteen and thirty-two cells as it proceeds down the coiled tube or oviduct which leads from the ovary to the uterus. (See Fig. 16.)

The cells of which it is composed adhere to one another forming a somewhat spherical mass not unlike a blackberry or raspberry in form. Eventually it reaches the uterus or womb, where it becomes mechanically lodged in one of the numerous tiny folds which are found in the wall of that organ.

After implantation in the wall of the uterus the growth of the developing embryo is very rapid. It obtains nourishment from the blood of the mother, but from the very start it is interesting and important to note that the mother's blood does not reach the embryo *directly*. It passes through a very interesting system of filters which are located in an organ known as the *placenta*. The placenta is familiar to us under the name of "afterbirth" since it commonly is expelled from the body of the mother after the child has been born.

As the embryo develops it becomes surrounded by a sac filled with fluid. This is at one and the same time a protection against blows or injuries from the outside and an effective means of sealing the embryo from infection or contacts which might prove harmful inside of the body itself.

34. REPRODUCTION RATES

The structure of the reproductive system in mammals is very well adapted for economy and protection.

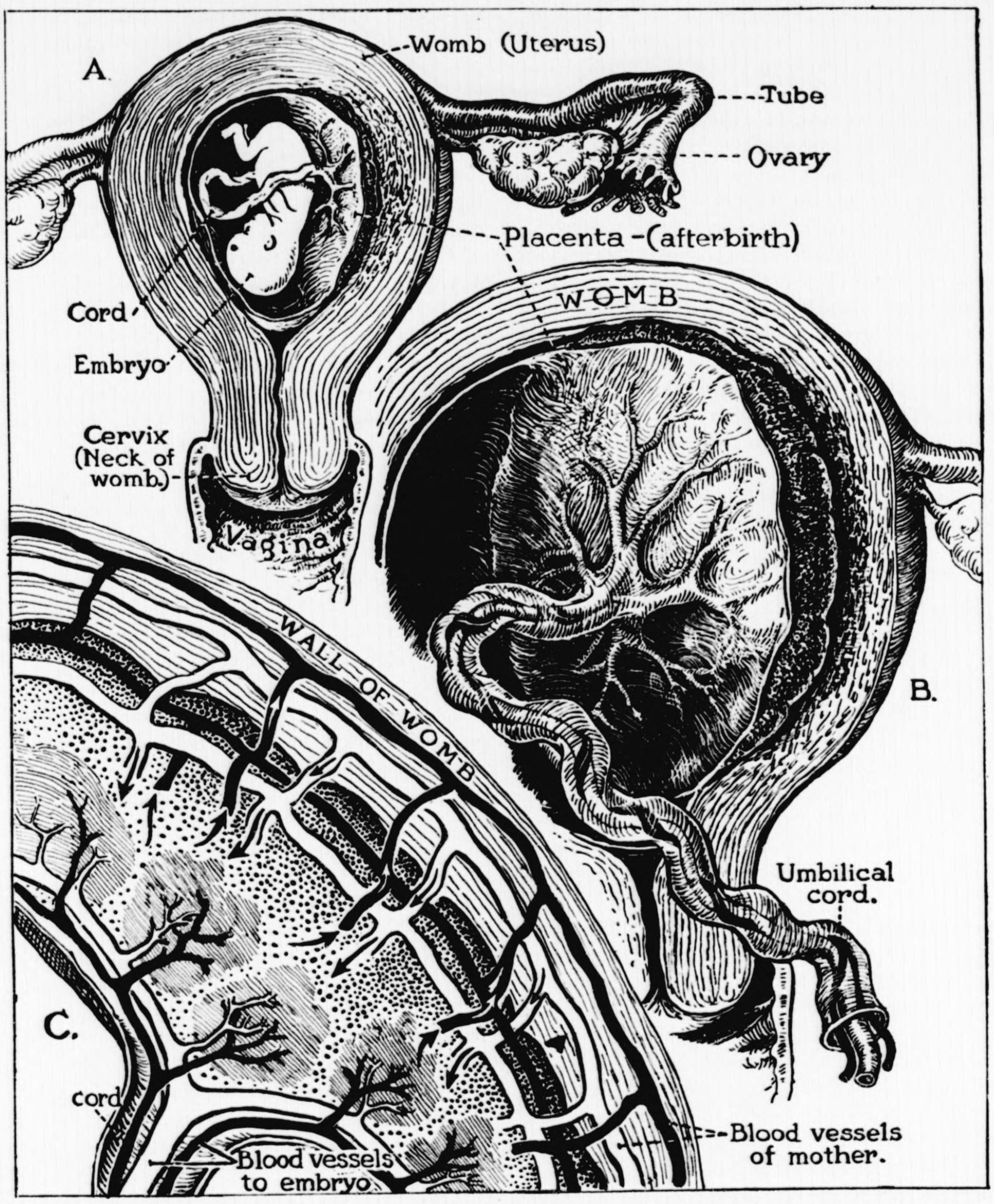


FIG. 16. The Placenta (After-birth). A. Its location in the womb and manner of attachment to the embryo. B. Enlarged drawing of the placenta in the womb showing the blood vessels contained within the umbilical cord. C. Diagrammatic illustration of the placenta and the wall of the womb showing the indirect connection of the maternal circulatory system (in the womb) and the circulatory system of the fetus coming through the umbilical cord into the placenta.

The lower forms do not differ very greatly from the higher. The uterus or womb of the mouse is shaped like a Y (see Fig. 10), the arms being long and the stem short. Embryos are located along the walls of both arms or horns of the uterus. Their number may vary greatly. Records show that from one to nineteen or twenty young can be born in a single litter. The average number is perhaps six or seven. The period during which the young develop inside of the body of the mother is normally from nineteen to twenty-one days. This means that the rate of reproduction of mice is very rapid compared with such forms as man, for example, in which the average number of embryos is a little over one and the period spent inside of the body from 270-275 days. Not only do mice produce large numbers of individuals rapidly, but these individuals themselves mature at an extraordinary rate of speed. It is usual for a mouse to be sexually mature at from five to seven weeks of age and one can thus obtain a generation in from sixty-five to eighty days. This, of course, means that four or five generations of mice can be produced and recorded in a year. This may be contrasted once more with the human situation where the normal interval between generations today is perhaps twenty or twenty-five years.

35. GROWTH CONTROL

We have mentioned the word "maturity" in connection with growth. It is an all important word. It represents the attainment of a stage of balance where increase in size due to growth ceases, and repair and replacement of tissues subject to wear and tear keeps pace with the needs of the organism.

This stage has been preceded by a period of growth which began soon after fertilization of the egg. During this period, growth took place most rapidly in the earlier stages of development and less rapidly in the later part.

This is a rule of very general application. It has great significance in our understanding of the nature of the organism and of cancer.

When the cells of the embryo are dividing most rapidly they are producing the highest rate of growth. This occurs at a time when division of labor and diversification of form among the cells of the embryo have not proceeded very far. In general the rate of growth becomes slower as such differentiation progresses.

It is as though the body was laboring under two conflicting tendencies. One expresses itself in growth by cell division, a process seen at its most efficient level in relatively primitive and unspecialized cells. The other is the process of formation of specialized cells developed for some particular function within the economy of the body as an organized community of cells.

There are as we stated before many types of cells in the various organs and tissues. They occupy orderly and fixed relationships within those structures and maintain a predictable and effective balance in relation to one another.

Departures from a perfectly balanced condition are frequent. Some conditions of unbalance occur at regular intervals in cycles as a part of the normal function of the animal. Others are induced by exceptional or abnormal conditions which are irregular and unpredictable.

In almost every case, however, the body is able, after a time, to correct the unbalance and to regain the condition which existed before it occurred.

In some circumstances, however, local, uncontrolled growth which produces or accompanies a condition of unbalance gets completely out of control and remains so. When this happens the center of local uncontrolled growth produces an increased mass of tissue which is out of place and useless in the orderly functioning of the body. This mass is a *neoplasm* or center of new growth.

We do not as yet understand all the conditions under which such centers of new growth arise. We have, however, observed many of them under very diverse and varied surroundings within the animal. We have discovered and listed over 400 chemicals which tend to increase the incidence of such centers and we have found that some of these chemical substances may occur naturally in the body. This is important and exciting, for many such centers of new growth, both natural and induced by experimental procedure, remain completely out of control and thus become malignant neoplasms or *cancer*.

36. GROWTH RATES

Not every individual reaches maturity at the same time or at the same rate. There are differences in this respect which appear to be inherent in the nature of the individual itself.

All of us are familiar with the varieties of vegetables which mature earlier than others. It is possible by using the knowledge which we have acquired concerning the time of maturity of different garden varieties to plan our production so that flowers come into bloom, seeds are set and the ripe produce obtained at various times throughout the growing season. Similar differences appear to exist in animals. Even within a single species there are to be found very definite differences. In rabbits, for example, there is a small breed of white rabbits known as Polish, while one of the largest known breeds of rabbits is called Flemish Giants. The largest Polish rabbits do not attain the size of the smallest grown Flemish rabbits. Both of these breeds of rabbits form egg cells which do not seem to be very different in size. It would be impossible under the microscope to tell whether one was looking at the fertilized egg of a Flemish rabbit or of a Polish rabbit. When, however, the fertilized eggs of the two breeds begin to divide and form daughter cells a difference at once becomes evident. The fertilized eggs of the Flemish breed divide much more frequently and rapidly than do those of the Polish breed. This, of course, results in a larger cell mass at any given stage of growth. The end result of the process is naturally that the Polish rabbit is smaller and the Flemish larger. We do not know what it is that determines the rate of cell division. Such differences exist among the descendants of different single celled animals or protozoa, so that it is possible to isolate fast growing and slow growing strains of these organisms.

Very evidently this fact as well as the difference in cell division rate of fertilized rabbit eggs indicates that glands of internal secretion, or endocrines, are not necessary to determine the rate of cell division.

This fact is mentioned because in higher animals and man it has been definitely shown that the endocrine glands *do* have a marked effect on the rate, type and extent of growth in later stages of the individual's development.

37. MATERIAL FOR STUDY

It will be well to remember that growth by division is the normal and natural function of every healthy cell and that even those which are forced to remain quiet and behave in an orderly manner within the body may possess a hidden and ordinarily unused capacity for growth.

We have seen that the incidence of a cancer depends upon the appearance within the body of one or more centers of rapid and uncontrolled cell division. Remembering how complex the body is and recalling the vast number of cells of which it is composed, it will be evident to anyone that to the research worker the procedure of waiting for the natural incidence of cancer in animals is painfully slow, uncertain and time-consuming. It is necessary, therefore, to devise methods of increasing the incidence of cancer under experimental conditions so that we may have as large an amount of cancerous tissue as we wish for study and investigation.

This apparent paradox of increasing the incidence of a disease in order to be able to understand it and eventually to control it is not as absurd as it sounds. The old saying that "familiarity breeds contempt" might be modified to the statement "familiarity offers the opportunity for complete understanding." In a condition of war, for example, the circumstances provide (unfortunately for the individuals affected) vast numbers of wounded and maimed individuals. From this material surgeons derive information and advance our knowledge within a short period of intense human suffering further than they could in ten or twenty times that period of the normal rate of incidence of similar injuries. In much the same way epidemics of infectious or contagious diseases which sweep through concentrations of troops and of civil populations herded together under the artificial conditions created by war, offer the medical man material for study in such abundance that he, like his surgical brother, drives ahead to new heights of control and understanding of his material. Let us see what has been done to create a supply of cancer in experimental animals under conditions which we can control.

38. INBREEDING AND IMPLANTATION

The first and most obvious method of increasing the amount of cancer is to transplant bits of an already established cancer into other individuals in the hope that it will grow in each case to a large mass, thus providing material for other transplants. If successful this process can be continued indefinitely.

For years investigators attempted such transplants in the ordinary run of laboratory animals which they could obtain. Under these conditions the proportion of inoculated animals which successfully grew the implanted bit of cancer varied from one experiment to another between 100% success and complete failure. There was no means of estimating what percentage of successful transplants would be obtained and results were incapable of repetition. In many cases failures far outnumbered successes and any and all transplanted cancers were in danger of being "lost" by the failure of any one experimental group of inoculated animals to grow them.

It was found by experimentation that if animals were inbred by matings of brother to sister or parent to offspring without interruption over a period of twelve or more generations, sufficient uniformity was produced so that all animals thereafter obtained from a single line of descent would grow cancer tissue which originated within an individual of that strain. This all important discovery has resulted in the establishment and maintenance of a number of transferable cancers which can now be obtained in more than 98% of the animals used for implantation. The contrast between this condition and the old method of hit or miss experiments is striking and significant. Under the present conditions if one observes careful precautions against infection of the transferred bits of cancer, the essential immortality of cancer is evident to all who work with it. This characteristic of cancer research forms the basis of much of our biological research.

In other words, it is possible 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 7 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 from two to four weeks each of these hundred animals will have a cancerous mass weighing seven grams. The original seven grams of cancer tissue will thus have become 700. Repeating the process, by the end of the next month the investigator would have 700 times 700 or 490,000 grams. This rate of increase could be continued if the men, animals, time and resources were available. It would thus be theoretically possible, within two or three years, to obtain tons of cancerous material, *all of which was directly descended by cell division from the tissue of the original cancer mass, and resembled it in every respect.*

This example has been chosen from long series of experiments with mice. The largest and fattest mouse recorded does not greatly exceed 100 grams in weight. The cancer, no matter how large its eventual total mass or how widely distributed it is among numerous mice, represents actually the expansion of the original tissue of the original mouse. We must, therefore, conclude that the mouse which weighed at the most 100 grams and which would have normally not exceeded that weight possessed the ability to form out of its own tissues what appears to be essentially an unlimited amount of living material which might be described as "unorganized mouse tissue." This it did when food and other environmental conditions were provided in sufficient quantity and under proper circumstances to avoid infection and to free the tissue from the physical limits imposed by restricted food supply and other mechanical surroundings of the individual mouse in which it originated.

It is perhaps interesting to note in passing that normal tissue also has this power of essential immortality. Many years ago investigators used another method of growing tissue which successfully attained that result.

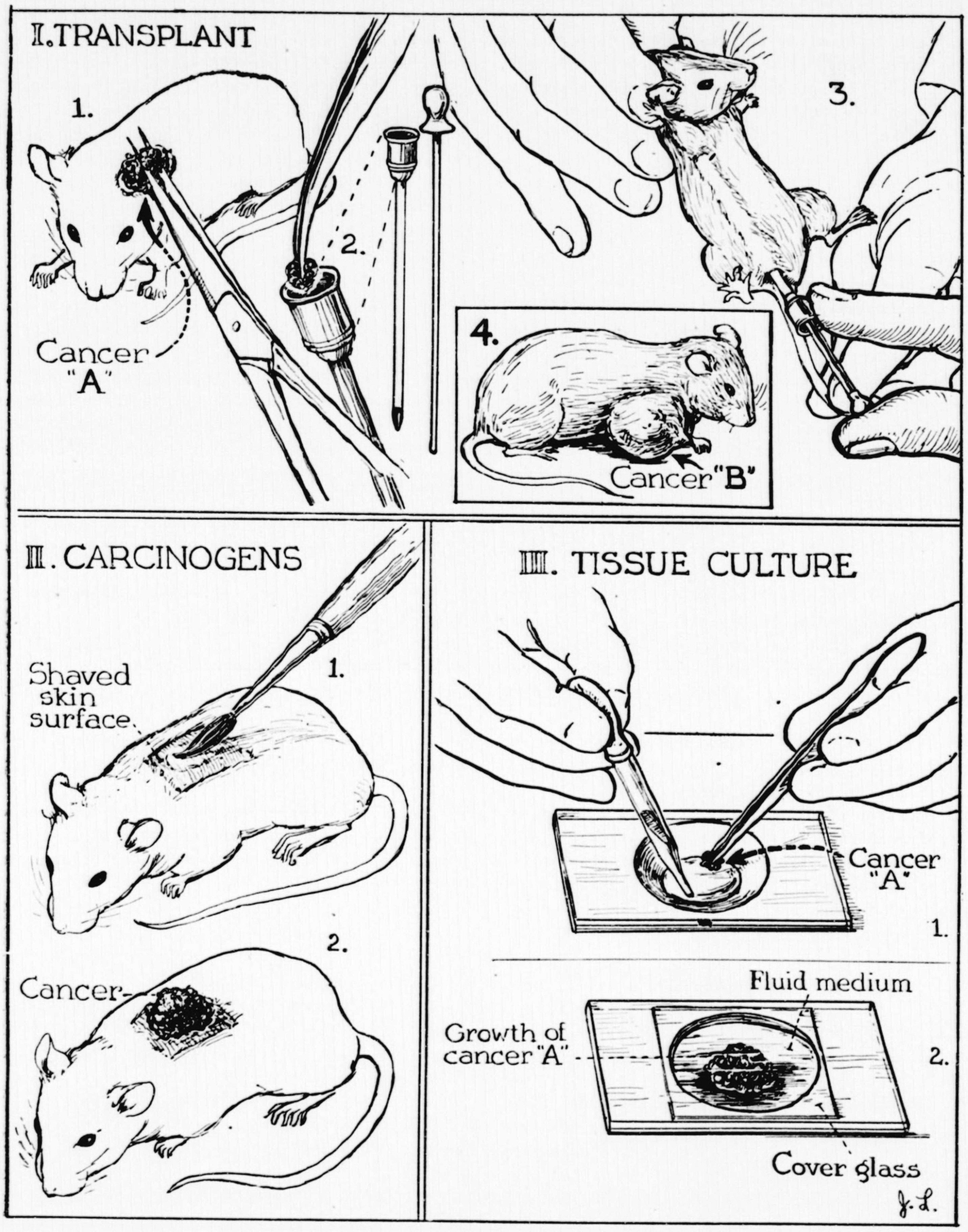


FIG. 17. Method of increasing the supply of cancer for study.

39.

This method is known as tissue culture. It is carried on outside of the living body, under aseptic technique which eliminates all possibilities of infection and under conditions which maintain the right temperature.

In this case frequent transplantations of very minute masses of living tissue are made into hanging drops or other small amounts of liquid containing food for the implanted tissue. Care is taken to establish means by which the waste products of the growing transplant of tissue can be drained off from the preparation. Under such conditions animal cancer and human cancer as well as normal cells of both have been successfully maintained for years. One can see that such cultures are readily available for study under the microscope.

Within relatively recent time they have been photographed and recorded in the form of motion pictures showing their growth and activity. Under such conditions cancer cells have been observed moving about, dividing and behaving for all the world just as the single celled amoeba would in its natural, free environment.

Some reference has already been made to the existence of more than 400 chemicals which can be used as the third method of increasing our supply of cancer for study. It was more than fifteen years ago that two Japanese investigators found that repeated painting of a highly refined derivative of coal tar on the ears of rabbits was followed by irritation, overgrowth and eventually cancer of the tissue of the rabbit's ears. Since then other animals have been successfully used as experimental material and a great number of additional substances identified as agents that may be followed by the appearance of cancer. The word "carcinogenic," cancer forming, has been given to these substances.

The opportunity given by the discovery of such chemicals is a very great one. Not only can the local effects of the chemical be studied and the investigator be ready and prepared to observe pre-cancerous changes and the initial phase of the disease itself, but he can also, by chemical analysis of the substances, begin to derive some sort of picture concerning the nature and relationships of substances which have this property in common.

As before stated, most of these chemicals occur outside of the living body, but a few of them have been identified as substances formed naturally by the normal function of the body itself. There remains a great deal of work to be done before the nature of the cause and effect relationship is clearly understood. In the meantime, however, the application of carcinogens has provided us with another valuable line of experimental attack on cancer.

40. INBRED STRAINS

The fourth, and in a way the most natural method of increasing the supply of cancer, is by selection of the descendants of naturally cancerous individuals and the inbreeding of these descendant animals. If this process is carried on patiently over a series of twenty or more generations, one establishes strains of animals which, without further experimental treatment whatever, form in some cases as high as 90% incidence of cancer of a certain type. All that is necessary is to maintain the inbred strain without crossing it with other strains or families of animals. This method has been successfully used so that there exist today strains of mice some of which give 90% breast cancer in females that live to be a year old or older, while other strains selected for low cancer incidence give less than ½ of 1%. It is an obvious advantage to the investigator to be able to study the appearance of cancer in these animals which are not interfered with by the addition of chemicals or by any inoculation or operation of any sort. Studies of this type are increasing in number and are being used not only for a future analysis of the origin and nature, but in various experiments which attempt to prevent the appearance of cancer in animals subject to it or to cure it once it appears. All of these techniques for increasing cancer need to be maintained and expanded. They cost money and require specially trained personnel. They are, however, invaluable from the point of view of further increase of knowledge and are essential if we are some day to control the disease either by prevention or by early cure.

One will naturally wonder what degree of importance should be given to the rôle of heredity in the case of cancer in humans. The influence of heredity in mice becomes clear only after there has been practiced a degree of inbreeding illegal in humans. In an ordinary mixed population of mice of similar biological variation to that met with in humans the practical importance of heredity to anyone individual would not ordinarily be great. One could not and cannot tell in advance what the degree of resemblance between parent and offspring as regards cancer incidence will be.

Inheritance of one or more tendencies to form cancer may be operating in the human race all around us. Yet, because of complexity of the biological nature of the human race and its mixed ancestry as regards all sorts of hereditary characters the importance of heredity as a force is scattered, unpredictable, and so uncertain that it must at present be given a rôle of minor importance as a practical matter in cancer control.

As research progresses we may suddenly unearth a method of observation or collecting data that changes our ideas. Until that happens, however, the statement given above holds good.

41. VALUE OF MICE

In the discussion of ways by which the supply of cancer for experimental purposes can be increased the use of mice has been frequently mentioned. It is interesting to discuss that matter a little further because few people realize the extent and nature of the service which those small animals are providing to mankind. There are definite reasons for using them as experimental material.

One must not confuse the laboratory mouse with the wild mice encountered in the kitchen or attic. There is as much difference between the two as there is between a tame, domesticated dog and a wolf. Mice, in fact, have been kept in captivity since many centuries before the beginning of the Christian era. There are actually more color varieties of mice than there are of any other domesticated mammal. Not only has the color of mice varied so that one can obtain pure white, piebald, yellow, cream, maltese, fawn, chocolate brown, black and many other varieties, but the amount, form and texture of the hair has varied so that there are mice with curly and wavy hair and some actually described as "caracul" because of their resemblance to the sheep of that variety. There are also hairless mice just as there are Mexican hairless dogs, as well as partially naked mice with strange, alternating areas of full length hair and bare skin giving them an extraordinary moth eaten appearance. These originated in Russia, but have been established successfully in many laboratories elsewhere.

The bodily form of the animals also changes. There are dwarf mice, mice with kinky, curled or greatly shortened tails, as well as those actually tailless. There are mice with extra toes, short ears, hanging or lopping ears and one strange strain that has actually an extra hind leg in some individuals. This leg juts out from the body and is not functional. All of these facts are mentioned to show that all mice are not alike and that it is a mistake to underestimate the degree to which they have been domesticated. They really rank with dogs and cats in that respect.

Mice mature with extraordinary rapidity and it is chiefly this factor which makes them ideal material for use in cancer research, or in the study of any other disease which occurs chiefly during middle or old age of the individual. A mouse a year old is as old as a man or woman of forty or forty-five and has reached the same relative physiological condition as a human individual of that age. A mouse two years old is comparable to a human being of seventy.

Similar shortening of the various age periods is found at the beginning of life. A mouse develops in the body of its mother for from 19 to 21 days as compared with a period of more than 270 days in man. A mouse ordinarily becomes sexually mature at from five to six weeks of age, thus enabling the investigator to obtain a large number of generations even within as short a period as a year. All but a very few human beings are relatively low in fertility. Nine or ten children is a large family, whereas a female mouse may produce in her lifetime eighty to one hundred young or even more. This again is an advantage when one wishes to study the inheritance of any tendency toward disease or the variation of any biologic characteristic within the descendants of a single pair of animals, or in a single strain. Mice are thus remarkable reproductive machines providing a shorthand version of the life process which is greatly dragged out and unduly prolonged in humans.

42. MICE AND MEN

One may reasonably ask how close is the comparison between mice and men. Are we justified in doing research work in mice and then transferring the results to man? The answer to this is very definite, but not a plain "yes" or "no." We may say that we have no right to draw detailed conclusions concerning man from the behavior of any laboratory animal including mice. In other words, it is not justifiable or safe to swallow whole the application of results obtained from animals to the field of human therapy.

On the other hand, it is actually true that mice and other laboratory animals possess bodily structures of sufficient similarity and distribution within the body to those found in man so that the general pattern is strikingly alike in the two cases. This means that mice can be used in great numbers and with great convenience to establish certain principles and results which can be in turn used as guides and indicators of the direction which our studies of humans should take. No great advance has been made in medicine without a strong foundation of animal experiments. All broad principles which apply to the care and treatment of humans can find their counterpart in work with animals. This is even true in some of the fields involving mental traits such as nervous instability and other phenomena which control the nervous balance of the individual. You may, of course, react to this statement by insisting that man has a spiritual side which is lacking in mice and that human beings can be benefited and perhaps even sometimes cured of their ills by non-physical means. There is no point in debating the pros and cons of that attitude at the present time. It is much better, I think, to agree that individuals have the right to hold that point of view and that if it is correct such treatment of humans and the beneficial results obtained are individual matters which do not follow a definite pattern and cannot be reduced to material terms for the purpose of transferring them to other individuals. In other words, all that we can know and record about *physical* man in finite terms will have a close and important relationship to studies with animals and for this reason the need for laboratory material such as mice is one which will continue indefinitely into the future.

43. OTHER LABORATORY ANIMALS

Several other types of laboratory animals besides mice are making worth while contributions to our knowledge of cancer. Among these may be listed rabbits, guinea pigs, rats and larger animals such as dogs or monkeys. Each has some particular advantage to offer as well as some drawbacks. Rabbits and guinea pigs are of convenient size for quantitative chemical studies but are much slower breeding than mice. Rats are good for nutritional studies but do not exist in nearly as many varieties or biological strains as do mice. Dogs and monkeys are both expensive and slow breeding.

A relative newcomer in the ranks of laboratory animals is the Syrian hamster. He is reddish brown—about six inches long, with a very short tail and large, shoe-button eyes. Rapid in reproduction, he possesses all advantages which guinea pigs possess and is easier to handle and to raise. He has not yet been extensively used in cancer research but will undoubtedly be important in the future.

We may expect that as chemical research broadens, more new forms of animals and plants will be found useful. It is difficult to predict what they will be but undoubtedly many not yet appreciated as good material will be found to be so and will do their share in increasing our knowledge.

Wherever growth can be observed and modified experimentally the opportunity for establishing some

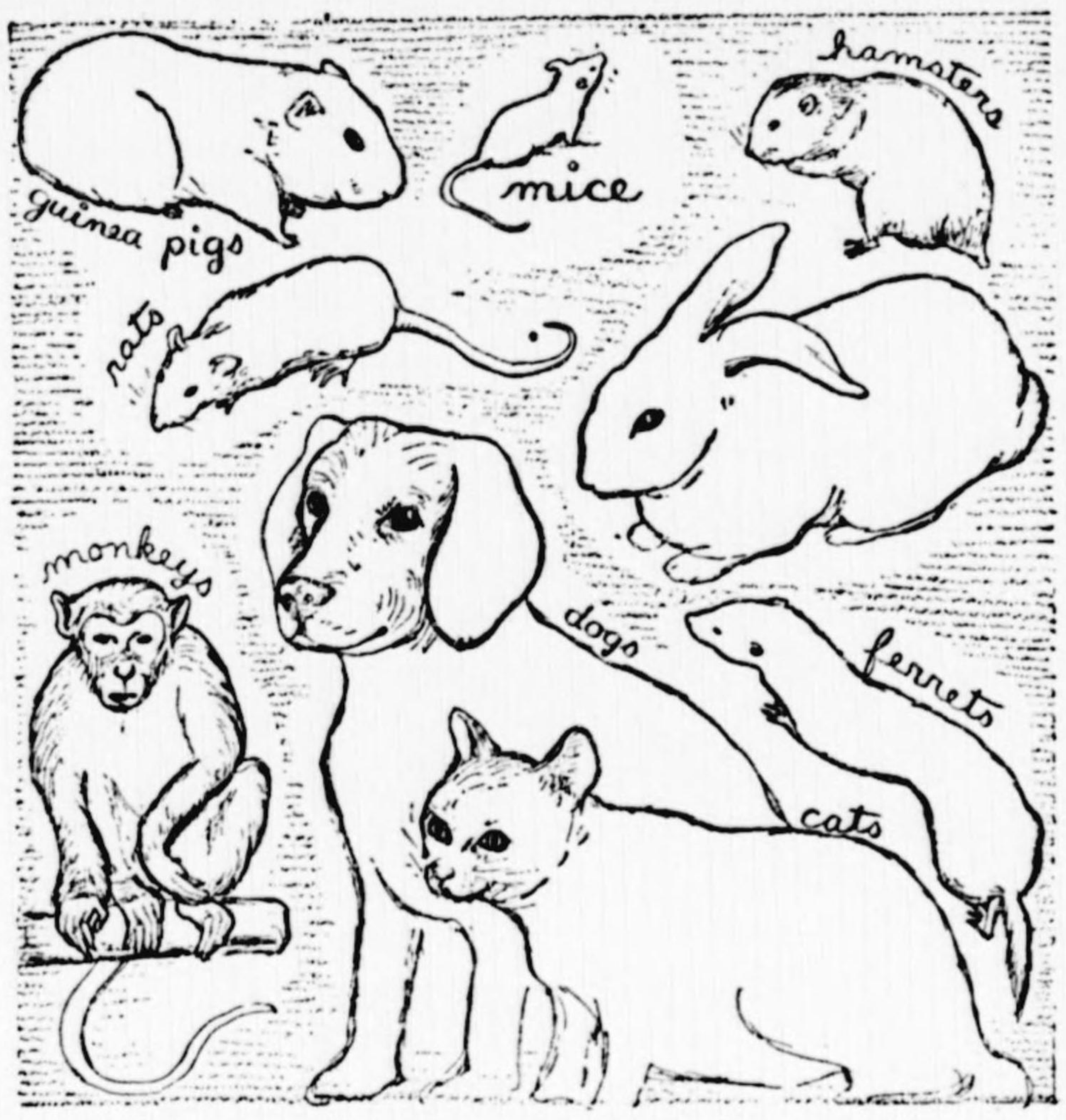


FIG. 18. Friends of suffering humanity. Animals used for experiment.

relation to the cancer problem exists and should be kept in mind.

44. HUMAN MATERIAL

Although human material is not subject to the same order of scientific control as species which can be bred and observed experimentally, it offers some very interesting and suggestive topics for investigation.

We must of course realize that there exists among human beings no degree of inbreeding as close as that found among laboratory animals. There are, nevertheless, groups of human individuals related more closely than by random matings. To a certain extent the broad groups of nationalities or skin colors fulfill this requirement. A study of these groups shows a definite biological difference in the degree of risk which the various organs present from a point of view of cancer incidence. If we contrast four main groups: negro males and females and white males and females, this point can be illustrated. Up to and including the period of adolescence all four of these groups are very similar. Cancers of the kidney and those of the long bones and brain are the commonest types. At that point the situation begins to change. Cancer of the testes becomes a serious risk to white males while being relatively infrequent among negroes. Ovarian tumors are found in both negroes and whites. In the height of the reproductive period and toward its cessation cancer of the uterus predominates in both negro and white women, while cancer of the breast is an important risk in the latter not observed as such in the former. Cancer of the stomach is a severe risk in all four groups but is overshadowed by the continuing menace of cancer of the uterus in negro women in a way not observed among whites. In the later age groups cancer of the skin becomes a relatively common disease in whites especially males and is relatively rare in negroes. Cancer of the prostate affects extensively both groups of males. Breast cancer remains a serious risk in white women.

There are sufficient other less important differences to encourage the belief that studies of cancer incidence according to site, age and sex as related to skin pigmentation would be important and interesting.

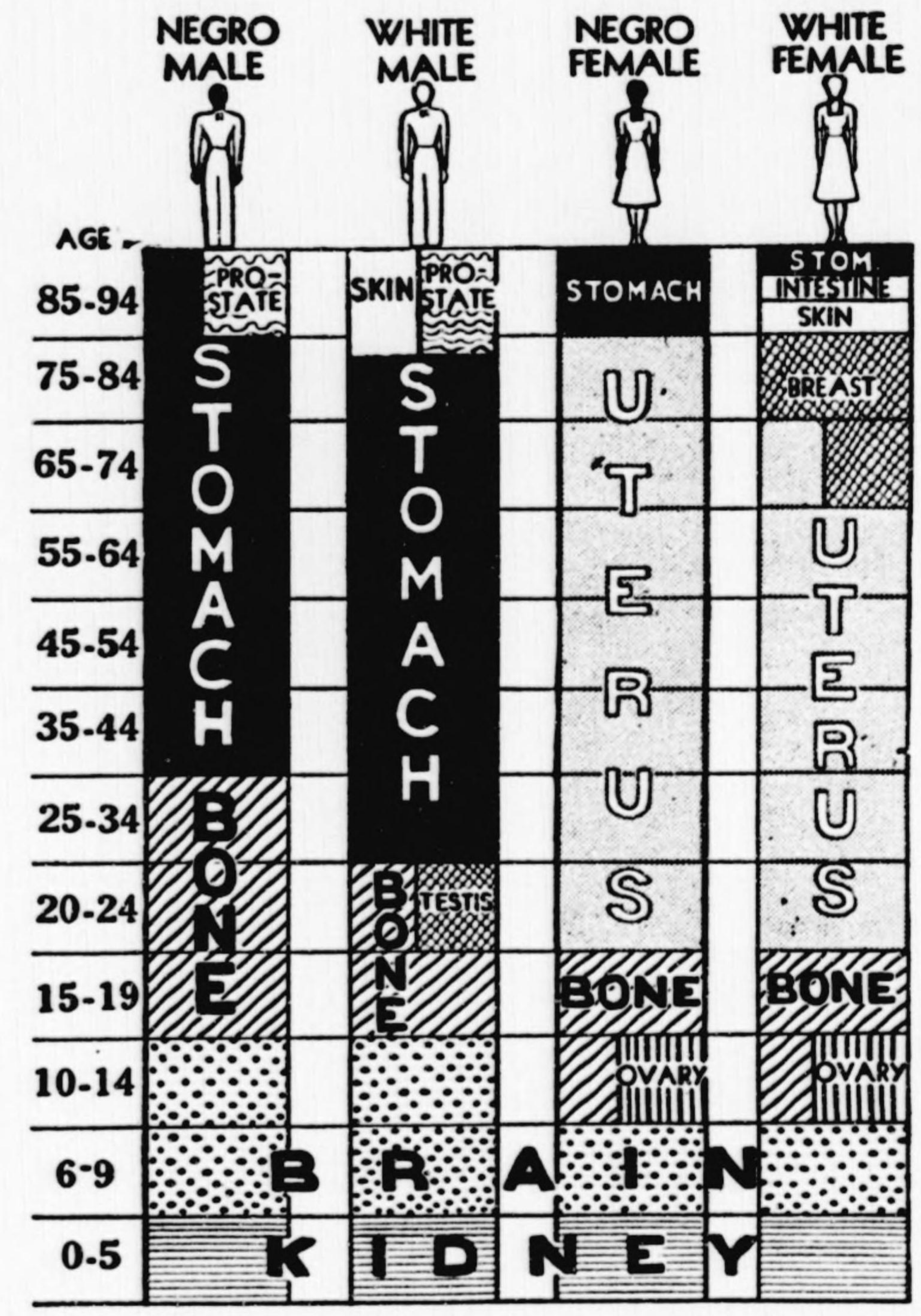


FIG. 19. The distribution of cancer varies by sex and color. Shown above is the dominant frequency of cancer in different sites.

Not only do groups divided according to color show important differences but occasionally one finds a social or religious classification that appears to be significant. It has been recognized for a long time that Jewish females have proportionately less cancer of the uterus than non-Jews. Various explanations have been advanced for this fact. The most probable seems to be that it is related to religious procedure in orthodox Jews as affecting the physiology of sex behavior.

45. DISTRIBUTION OF CANCER

Occupational and geographic studies on the distribution of cancer are also suggestive. Early workers in x-ray therapy and individuals who have been employed in plants using radium have shown more than the ordinary tendency to develop cancer after a prolonged exposure to these agents. This has resulted in greatly increased precautions for the protection of those so employed. Those who work with analin dyes have shown an increased incidence of cancer of the bladder while certain types of cancer among chimney sweeps have been known for a century. All of these cases have in common an experience of prolonged irritation which may well be the factor that leads to the eventual cancer change. The record in the case of skin cancer in relation to sunlight and exposure to prolonged attacks of wind and weather shows a similar sequence to prolonged irritation. Not only are farmers, sailors and others more exposed to the elements apt to develop an increased proportion of skin cancer but the incidence of this type of the disease is greater in the southern parts of the U. S. than in the central or northern. The effect of the ultra violet rays in sunlight may well be considered as being under severe suspicion. It is undoubtedly significant that these rays either from the sun or from a quartz mercury arc lamp will cause irritation often followed by cancerous growth on the ears and skin of rats and mice. Further studies of their carcinogenic potentiality in humans are definitely needed.

46. AMOUNT OF CANCER RESEARCH

The exact amount of research being done on cancer throughout the United States is very difficult to estimate. As our conception of cancer has broadened to include the fundamental sciences of physics, chemistry and biology, projects of research in those fields have developed some relationship to the investigation of cancer. Such pieces of research are not, however, primarily designed to advance our knowledge about cancer, but have as their main objective advance in the theory of one of the basic sciences itself. For example, the epoch making discovery of the cyclotron by which atoms are broken and the energy formerly contained within the atom is released is in effect a problem of pure physics. Since, however, the liberation of this energy involves the production of radiation of tremendous power and since radiation of that general sort is the basis of x-ray and radium therapy in cancer, it is evident that knowledge obtained concerning the neutron rays produced by the cyclotron will have an important bearing on our knowledge of radiation and cancer in general.

Until the discovery of the cyclotron only a few of the chemical elements that we knew were naturally radio-active as is the case in radium. By subjecting ordinary chemicals to the influence of the cyclotron it is possible to make them radio-active. This activity lasts for different periods according to the chemical element so modified. In some the duration of the radio-active phase is only a matter of minutes or hours, but in others it lasts for a very much longer time. Since any or all of these elements can be introduced in the human or animal body either as food or by direct methods, it is evident that it may be possible to follow their distribution and activity within the body as long as their radio-active properties remain present. This may give us important information concerning the functions of various organs and tissues.

One series of experiments, still in its relatively early stages, involves the feeding of radio-active phosphorus to patients suffering from leukemia. Leukemia is a type of uncontrolled multiplication in the growth of white blood cells. These are most frequently formed in the bone marrow and spleen. Phosphorus has a particular affinity for the regions of the body where active formation of such white blood cells is in progress. When phosphorus is taken as food, therefore, it tends to travel to those locations. If now we substitute radio-active phosphorus for the ordinary type, it is evident that on arrival at the location where white blood cells are being formed, the radio-activity shown by the phosphorus may perhaps affect the excess formation of white blood cells so that it becomes a less uncontrolled and dangerous process. As above mentioned, the work is still in its early stages, but the evidence as far as it goes is somewhat encouraging.

Quite naturally the locations at which research in the pure sciences overlap the field of cancer investigation are usually the universities and colleges where departments dealing with the pure sciences are maintained permanently. In almost every large university and in some of the colleges the importance of such research to the field of cancer is formally recognized. Funds are obtained either from the financial resources of the university or by grants in aid from foundations to follow up certain well-defined and formulated problems.

Reference has been made to foundations from which grants in aid may from time to time be obtained. It is desirable to list certain of the most important of these with the understanding that the list is not complete and is intended to be of general interest and to stimulate further study on your part rather than to be a final source of information. The examples given are listed alphabetically with no desire to attempt to compare individual importance.

(a) The Jane Coffin Childs Fund for Medical Research. This fund was established at New Haven, Connecticut, some years ago by the Childs family and is administered by a board representative of scientific and business interests. Its income is used primarily for the investigation of cancer, although its objective may be broadened if the Board sees fit. There is no limit placed on the geographic location of projects which may be supported by it.

(b) The Commonwealth Fund located in New York City has a broad and important history of support of all sorts of medical, scientific and sociological problems. It has recently included certain cancer research problems among its supported projects. It has an adequate and able staff of resident executives as well as a supervisory and administrative board of directors.

(c) The Anna Fuller Fund, also located at New Haven, Connecticut, is entirely devoted to cancer control and at times, supports projects outside of the field of pure research such as educational programs as well as those in the laboratory.

(d) The International Cancer Research Foundation, which is the oldest fund in the United States established chiefly for the support of cancer research, was established by Mr. William T. Donner of Philadelphia in memory of his son who died of cancer. This Fund is administered by a board of business directors and has a small scientific advisory committee to review and make recommendations concerning applications for grants in aid. The fund has supported projects abroad as well as at home and has a wide and intelligent conception of its opportunities.

(e) The National Cancer Institute is located at Bethesda, Maryland, under the United States Public Health Service and the National Institute of Health. It is supported by funds voted biennially by Congress and is established under the so-called National Cancer Act. This Act establishes a National Advisory Cancer Council made up of scientists selected on a nation wide basis. The Council is small, compact and effective. Its duties are to make recommendations concerning policies of the Government's own program of research and to recommend grants-in-aid for projects outside of the National Cancer Institute if it is considered that these are worthy of support.

47. RESEARCH UNDER-FINANCED

It sounds from the above list as though cancer research was well and adequately cared for, but this impression should be immediately corrected. It is probable that the amount from all sources spent for cancer research in the United States each year is less than a half of that which is raised from the American public alone for the control of infantile paralysis.

Cancer, however, is not a single problem. There is no one cause of the disease or one answer to its control. Research must be carried on in biology, chemistry, physics and all the borderlines of those subjects. Research must be conducted in the most highly advanced, theoretical phases of these sciences and also in the actual hospital or clinical problems of cancer patients. The extension of our knowledge in the cancer field is slow and painstaking. Long-time programs have to be instituted and maintained without the expectation of important results for a period of years. All of this consumes resources both in personnel and finances. Yet if we stop to compare the total amount spent on cancer research in the United States with the budget set aside for research by *one* great commercial corporation we find that that corporation spends annually from fifteen to twenty times as much money as the whole country spends in studying cancer. If, then, we make a further comparison between cancer and infantile paralysis with no attempt whatever to decrease interest or damage in any way the program of research being conducted against the latter disease, we find that infantile paralysis kills approximately 1% of the number of people killed by cancer each year. By either comparison cancer research work is vastly under-financed. The worst part of it all is that the problems are present for solution in the cancer field and are not being attacked because of lack of financial resources which prevent the training, hiring and direction of personnel. It is part of the duty of every citizen to recognize this situation and

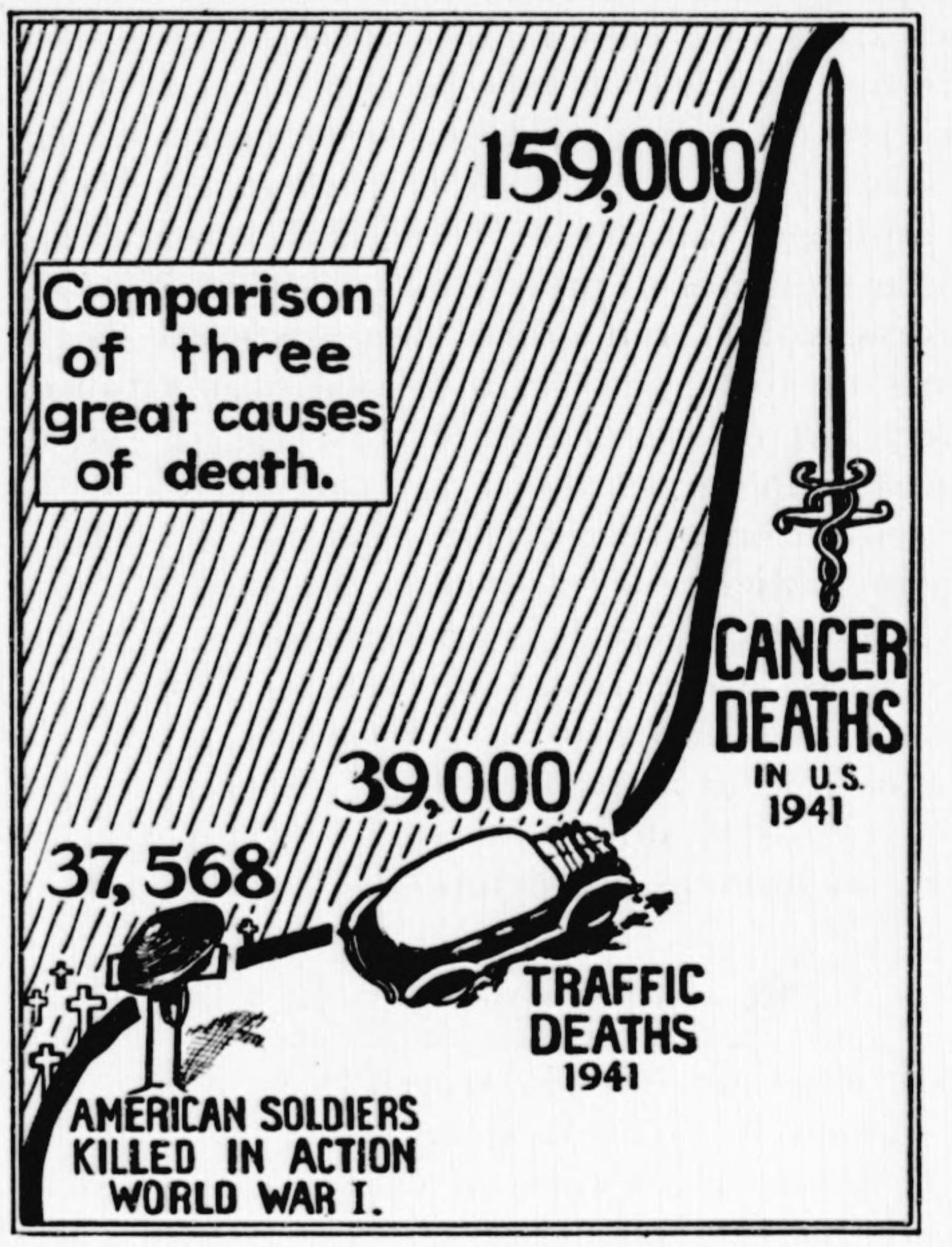


FIG. 20.

to do something to correct it. The interesting point is that no one individual need make any unfair sacrifices if the general public could be educated to make small contributions at frequent intervals.

48. REGENERATION

We shall, in due time, return to the work of the American Society for the Control of Cancer and other organizations cooperating in the program of cancer control. First, however, there are certain other matters which concern growth and its control and which need discussion.

The first of these is a process called "regeneration" —a word with which we are familiar. In common usage the term signifies a "rebirth"—a being born over again. Most of our structures do not have this power, but some of them do. If, for example, we lose a hand or a foot, an arm or a leg by amputation, we cannot form a new one. If, on the other hand, we break a bone, new bony tissue usually regenerates and "knits" the ends of the broken bone together. If we remove by an injury the outer layer of skin without damaging the underlying tissue, new skin regenerates and no scar is formed. A scar itself is not regeneration in that it does not possess the characteristics of the lost tissue which it replaces. While most higher animals have largely lost the power of producing regeneration, certain of the lower types possess it in a marked degree.

Perhaps the most striking example is to be found among the flat worms or Planarians. The ordinary person goes through life unaware of the existence of this type of animal. This is chiefly because of the fact that it is small, inconspicuous and unimportant economically. There are many sorts of flatworms all more are less related to one another. Those capable of living independently inhabit either fresh or salt water, living among the leaves and mud beneath logs and rocks, all of which does not make it any easier to be familiar with them or to find them.

They are for the most part, about a half an inch long, dark brown or deep brownish green in color with rounded heads, a flat unsegmented body and tapering hind end or "tail." They lack even the vestiges of limbs of any sort. Two cresent-shaped eyes usually help to give the head a grotesque sort of jack-o-lantern appearance. If one cuts one of these worms in two just back of the head both cut surfaces begin to regenerate new tissue.

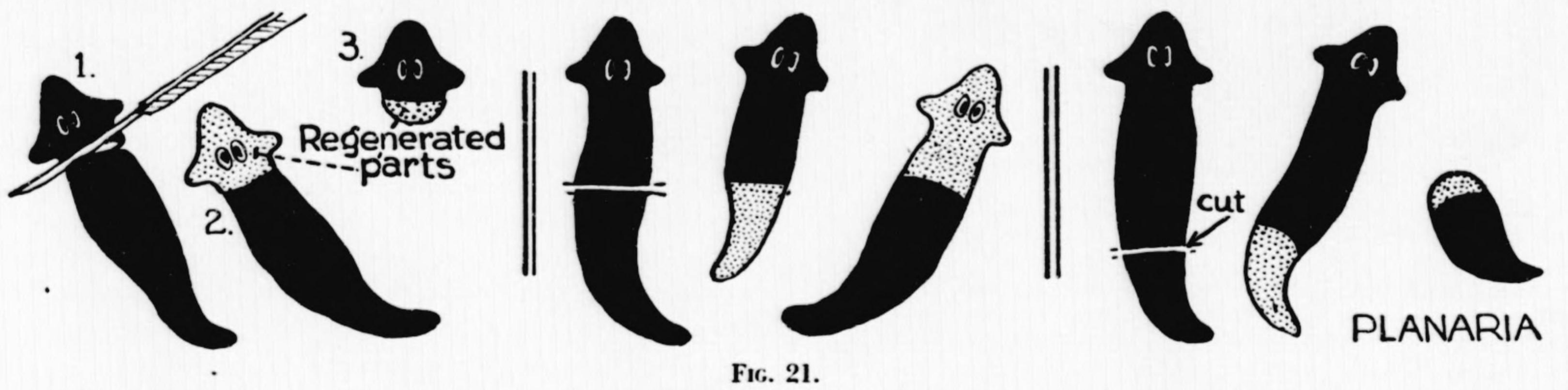


Fig. 21.

The body remnant also regenerates a complete and functional head which begins where the former incumbent 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, 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. So, also, may the small portion where the old tail remains.

Regeneration is not confined to worms. Animals as high in the scale as the salamanders—vertebrates like ourselves—can regenerate limbs or a new tail when these are removed.

All of these cases emphasize once more the impressive latent power of growth which certain tissues retain in a form where it can be utilized in emergency.

It is not surprising, therefore, to find that the cells and tissues even of animals from which the broad, general, orderly regenerative power seems to have been lost still may and do retain the power of starting up growth of a disorganized or cancerous nature under certain conditions.

49. REPRODUCTION

We have, in animals, come to look upon the power of reproduction of a new individual as being a particular function of the sex cells. This is far from being of universal application. Many plants can produce a completely new and well formed individual from cells of the stem or leaf. These cells ordinarily might never exercise that ability but would live and die as normal members of the tissue to which they belonged.

In certain begonias this is true of leaves which usually live and die on the plant. If, however, a leaf is removed from the plant and is placed on soil of the proper type a complete new begonia plant arises from the cells at its base.

Certain of the lower animals, such as sponges or forms closely related to sea anemones, reproduce regularly by forming buds which develop into new individuals and then drop off the parent animal to become independent. In these cases of different types of reproduction we see once again the amazing variety and adaptability of life. It does not "place all its eggs in one basket" relying on a single process to determine survival or death. It reaches somewhat similar results by more than one road so that if one method of progress towards the goal of a new generation is blocked or thwarted another may be tried and may succeed. Only in cases where circumstances demand particular specialized responses does life gamble with a single method. When this is necessary it evolves a highly efficient method of protecting the process of reproduction and of perfecting its details to an almost unbelievable degree.

Mice and men are two examples of a case of this sort. Reproduction in both is very similar and is designed to produce and maintain a type of organization which will enable them to cope with and at least partially control their environment and conditions in the world around them.

50. PROTECTION OF EMBRYO

In this process of reproduction both mice and men as well as all forms of life related to them take the greatest care to protect the sex cells and the developing individual in the early part of its life. The egg cell is formed inside the mother's body and is there kept under a most exact control of temperature and in a confined space. When the egg is liberated from the ovary where it is matured it is at once received into a tube which leads to the uterus (womb). In this tube fertilization takes place and the development of the new individual begins.

While in this tube the egg receives little or no food. If, in its early development, things go wrong it degenerates and dies in the vast majority of cases. It is as though the egg was given a test of its normalcy under none too favorable conditions before the body of the mother is obliged or expected to spend its substance and energy in feeding it further. If, however, the egg

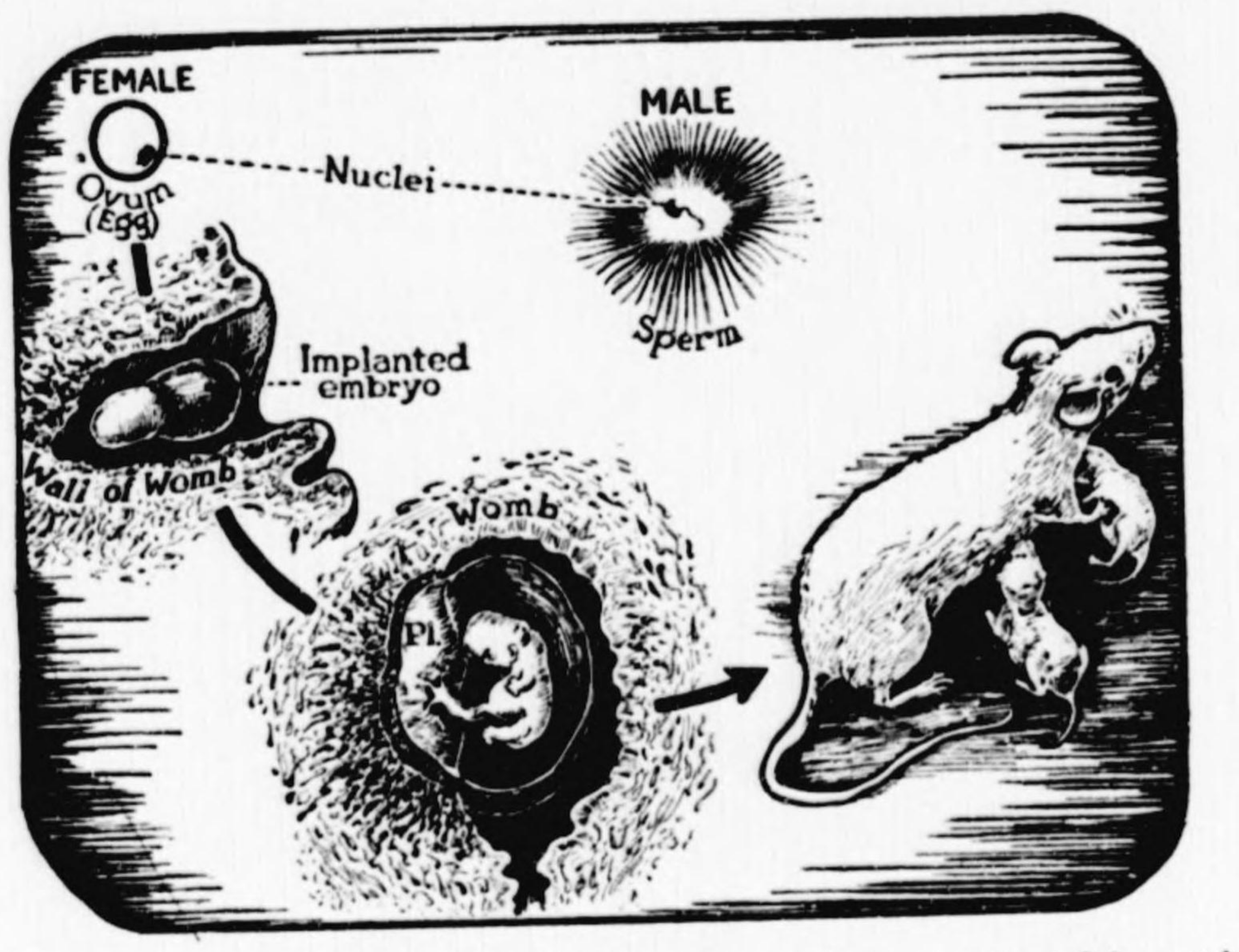


FIG. 22. Comparative contributions of and contacts with male and female parents during the development of the young. The top two figures show the large female and small male sex cells in which an *equal* contribution is made in nuclear material only. The next two figures show contact between mother and developing embryo. The final figure shows the process of nursing during which the mother supplies the total diet of the young.

reaches the uterus in a normal condition it finds a resting place in one of the minute folds or pockets in which the wall of the uterus abounds. Here it lodges and almost at once is met by a reaction on the part of the wall. The reaction results in the egg becoming imbedded in and fed by the maternal tissue. As development proceeds the embryo is enveloped in a sac filled with clear fluid. This sac is hermetically sealed so that no external influence can reach it. The fluid around the embryo provides equal pressure which encourages symmetrical development. It also protects the embryo from mechanical injury. After birth a considerable degree of control is still exercised over the young animal for the period while its food is restricted to milk, a product of its mother's body.

These facts are of great importance in our experimental attack on cancer.

51. UNIQUE STRAINS

Many of the more promising lines of research work on the biology of cancer hinge on our ability to invade experimentally these protected zones where animals carefully guard themselves and are not prepared for outside interference. Carefully developed techniques have made it possible to make such scientific invasions in a number of vitally important ways. As a result we have discovered and brought to light many interesting facts that have increased our knowledge of the origin and nature of cancer. We have, for example, found that various strains of mice derived from different ancestral backgrounds react in characteristic but distinct manner to the same experimental procedure.

As an example we may consider the behavior of three different inbred strains of mice to a surgical removal of the sex glands (ovary or testis) at a very early age. These three strains designated in the laboratory as C57, dba and ce respectively have been entirely unrelated to one another for more than a hundred generations. Among the individuals of each single strain, however, there is, as the result of close inbreeding, a high degree of biological uniformity. This is shown by similarity of behavior *within* the strain just as the difference *between* strains is shown by distinct reactions.

The mice are operated upon when only a day or two old. At that stage a mouse is not as large as the end of one's little finger. He is naked, blind, helpless and pink in color except where, if he is fortunate enough to have nursed, the milk in his stomach shows through the skin of his undersurface as a white circular area, readily recognized.

At first ether was used as an anesthetic. Since, however, it made the young mouse smell peculiarly and since the mother mouse considered him (smelling as an unwelcome stranger) an intruder when he was returned from the operating table, a change in technique was required. The new technique was one used successfully at the University of Iowa on very young rats. It consisted in leaving the prospective patient in an electric refrigerator for several minutes. By that time the cold had slowed down all his biological functions so that he was inactive, comatose and his blood was running very slowly under diminished heart beats and respirations. He was insensitive to operation and remained under the influence of cold for 20-30 minutes, long before which time he was well through the operation and back in his home nest. There being no unpleasant and foreign odor which could not easily be erased by previous rubbing in his home bedding, he was accepted back without question. Post operative mortality was thus reduced to a tiny fraction of what it had previously been.

Ordinarily when the sex glands are removed early in life one finds that the sex organs and breast tissue remain in a relatively undeveloped stage and fail to reach the size or complexity of structure observed in normal animals. This was what happened in the mice of the C57 strain. Even though they were kept under careful observation until they died at a ripe old age they exhibited on the whole the expected and classic results of sex gland removal.

On the other hand, the two strains, dba and ce, behaved differently. For some months there was no very striking mark of distinction between them or between their behavior and that of C57. Then, however, the dba mice showed increasing development of the mammary tissue. The uterus (womb) which up to that same time had remained in an underdeveloped condition began to increase in size and to take on a different and more normal appearance. These changes continued and extended. Eventually a number of the animals developed tumors of the mammary tissue just as do normal dba mice at advanced age. The ce mice, however, formed no such tumors. Instead, after an initial period of underdeveloped sex organs and breast tissue, they showed development somewhat similar to the dba animals leading eventually to active and malignant tumors of one or both adrenal glands. This is all the more interesting because the appearance of adrenal cancer in normal, unoperated animals is extremely rare. There was also evidence in operated male mice of the ce strain that, in later months, the prostate glands and other accessory male sex structures remaining after operation began to increase in size and to develop.

Study of the adrenal glands after the death of the animals gave the clew to what had happened. In the C57 mice the adrenals showed no characteristic changes and remained small as in normal, unoperated animals. In the dba mice, late in life, the adrenal had increased greatly in size both by enlargement of existing adrenal cells and by the formation of new adrenal tissue. There was clear evidence that the old adrenals of dba mice were secreting a substance or substances similar to that of a *female* sex gland. In the ce mice the adrenals showed marked growth of new tissue resulting in cancer. Interestingly enough this tissue secreted substances *not* like the female sex gland but like the *male*.

These experiments bring to our attention two very important matters. One of these is the group of substances called hormones which are secreted by the endocrine glands. The other is the hereditary or otherwise recurring biological characteristics by which these strains differed from one another. It will be well at this time to consider both of these topics; namely, the endocrines and heredity. We shall take them up in that order.

52. ENDOCRINE ACTIVITY

Variation in activity of the various endocrine glands is reflected in differences of structure and function of different parts and organs of the body. The relationship may be clear, specific and localized or it may express itself obscurely and in a more general way.

Much is already known about endocrine function but it is probable that the extent of our present knowledge is greatly limited compared to what the future will reveal.

As before mentioned, the endocrines act through characteristic chemical substances called hormones which are given off by the gland into the blood. The blood serves as a transportation system to move these substances throughout the body. The various tissues with which the blood comes in contact react to its hormone content in very different ways. As a result relative overdevelopment or underdevelopment of different parts of the body may result. This produces structures and functions which deviate from the normal condition found in balanced endocrine relationships.

At times, unbalance of endocrines is deliberately created in domestic animals in order to produce desired types more suitable for particular purposes. One of the commonest cases of this sort is the removal of the male sex glands (castration) in male calves to produce oxen for the farm and steers for the market. Another frequently encountered example is castration of young male chicks to produce capons. In each of these cases the castrated animal is fully as large or larger than the uncastrated male. It is also quite as strong. Its temperament, however, is much more docile and its meat for marketing far more tender and desirable.

The castrated male animal tends to retain the juvenile body form and proportions. Castration in both sexes is apt to be followed by an increased formation of adipose tissue. It seems likely, however, that this is a secondary effect of relative inactivity rather than a direct result of the operation. Since castration changes the relative rate of growth of various parts of the body it is a factor in determining the degree to which the body presents regions in which the risk of uncontrolled growth exists. It is thus, indirectly in all cases and apparently directly as in the case of the adrenals of ce strain mice, a possible factor in the origin of cancer or other types of new growth.

The fact that breast tissue of female animals is definitely influenced by secretions (hormones) of the sex gland (ovary) is shown by a number of facts. Among these may be mentioned the underdevelopment and absence of any cycles of activity in the breast tissue of female animals without ovaries. The opposite condition also is evidence which is of interest. In normal females, cycles of ovarian activity are accompanied by cycles of activity in the development and functioning of breast tissue.

Pregnancy is accompanied by the liberation of hormones into the blood. These in turn cause extensive development and enlargement of the ducts of the breast. The increase both in extent and in complexity by branching of ducts is tremendous. There is a vast degree of activity like a busy army camp preparing for the job of supply service. In the case of the breast the commodity to be supplied is milk and the whole energy of the organ is given over to preparation for and fulfillment of that task.

The limits of variation in the structure and function of breast tissue are much narrower in wild species than among domesticated animals or man. Domestication and civilization preserve the descendants of individuals with little or no mammary function or development by making available to the newborn young some source of food other than mother's milk. In the same way the artificial aids to birth preserve many individuals which would otherwise never survive. Since "like tends to beget like" the female offspring are likely to reproduce abnormalities of form or function similar to those produced by their mothers. In this way strains with defects become established. There is no doubt that such variations from the normal types offer opportunities of unusual degrees of hormonal unbalance and that this in turn may well influence the chance of abnormal or uncontrolled growth.

53. CANCER EXPERIMENTS

The breast then is an organ subjected to violent changes in the intensity of physiological activity. It must build at full capacity during pregnancy and regress after lactation. If, as frequently happens, the breast is not used for nursing after all its extensive preparation has been made it is faced with the critical task of rapid and extensive regression and absorption of the materials which it has built up. Careful studies of mouse breast tissue have shown that both in the process of building incidental to pregnancy and the process of regression following it, there occur small areas of cells that lag behind the response of the organ as a whole. These areas which refuse to follow the essential function of the surrounding tissue may and often do get out of control. When this happens they may begin to grow in an irregular and aimless manner. They refuse to take part in the creation of orderly and useful structures which contribute to the proper adjustment of the organ. They may, in fact, if they continue on their career of uncontrolled growth become cancer. How great a role pregnancy and lactation may play in the origin of breast cancer is shown by the following two experiments.

There are four different inbred strains of mice which we may designate as A, dba, C3H and C57 respectively. The percentage of female mice which breed, lactate and later form breast cancer in these strains is as follows: A—88%, dba—85%, C3H—92%, C57—0.5%. If females of these strains are kept as virgins the cancer incidence becomes: A—5%, dba—50%, C3H—90%, C57—0%. It will be noticed that strains C3H and C57 show little if any difference between the breeding and the virgin females. On the other hand, dba virgin females have 30% less breast cancer than do breeding females, and A virgins 80% less.

The second experiment deals with blockage of nipples and resulting need for absorption of milk. A series of dba females were used. Each female mouse has five nipples on each side—a total of ten. These particular females had the nipples of one side sealed by cautery when young. The nipples of the other side were left untouched. When the mice became mature they were bred and allowed to nurse their young. It will be remembered that normal breeding females of this dba strain give about 85% cancer incidence. This percentage held good. The interesting thing, however, was that of the *cancers formed about 75% were on the blocked nipples and 25% on the normal nipples.* It was also interesting that the cancers on the blocked nipples occurred much earlier.

54. HORMONE INFLUENCE

At times the hormones of the sex glands exert an interesting influence on color. This is especially true among birds.

Almost everyone is familiar with the ordinary barnyard varieties of duck in which the female is mottled dull brown and black with narrow and not very conspicuous dark blue wing bars. The male, on the other hand, has a light whitish gray breast, a brilliant iridescent green head and neck, a shining green black back and bright blue wing bars.

Experimental removal of the ovary from female ducks of this dull colored type is followed at their next moult by the assumption of the brilliant male plumage. This shows that the ovary secretes materials which holds in check or cover up that bright coloration.

In poultry, abnormalities of the ovary occurring perhaps in some middle aged hen have caused her spurs and comb to grow and have given her the resounding voice of the cock and a desire to use it.

There is no doubt that hormones do strange things as well as aiding mightily in making possible many essential activities. The sex hormones are perhaps the most studied at present. They may also prove to be among the most complex not only because of their own structure and multiplicity of effects but because of their inter-relations with other hormones as well.

Certain hormones such as those of the pituitary gland may markedly affect the whole form and degree of maturity of the individual. So may those of the thyroid. Hormones are thus very powerful influences in determining the extent and relative location of growth. As such they are of necessity a matter of vital interest to students of abnormal growth of which cancer is a type.

55. ENDOCRINE GLANDS

The endocrine glands of mice and of men are essentially similar in number and structure. They are located in different parts of the body and differ characteristically in form and structure. They may be briefly described as follows:

1. The *Thyroid Gland.* This is a paired structure with two elongated oval lobes, one on either side of the windpipe. In man there may be small, irregular bodies of similar structure scattered along the tube leading to the lungs and extending as far down as the heart. These scattered masses are called accessory thyroids. Removal of the thyroid in young individuals causes marked lessening and delaying of growth. Bone formation is defective. The thyroid hormone is called *thyroxin.* Over- and under-secretion of the thyroid cause definite recognized disorders. The latter produces goiter and the distorted and arrested physical and mental deficiency known as *cretinism.* Over-activity of the thyroid causes excess nervous irritability and protrusion of the eyeballs known as *exopthalmia.*

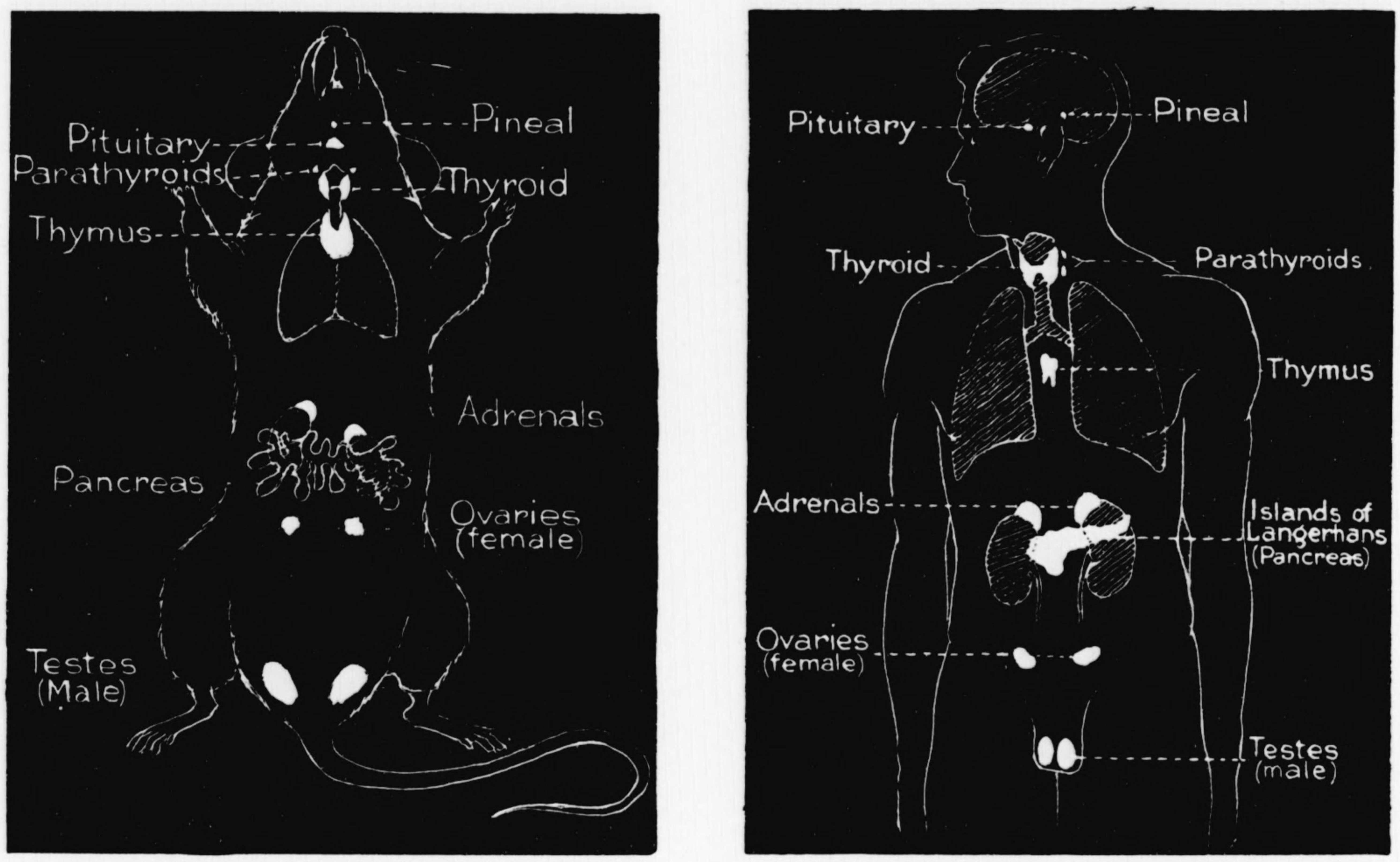
2. Close to the thyroid gland lie two pairs of small endocrine glands known as *parathyroids.* They are composed of compact masses of glandular cells. At first they were supposed to have the same function as the thyroid, but more recent investigations have shown more and more clearly that they have certain distinct and characteristic functions of their own. Complete removal of the parathyroids is usually followed by

marked toxic disturbances which develop rapidly and which may cause muscular spasms and tetany. It is believed by many that the parathyroids influence markedly the formation and use of calcium by the body. They also help to maintain within the body the balance between acidity and alkalinity. They may have other functions as well. It is interesting to note that no clearly identifiable hormone has as yet been isolated from them.

3. The *Thymus Gland* is located beneath the upper part of the sternum (breast bone). Its functions although of general importance are not as well understood as those of the thyroid. It is relatively large at birth and has almost or entirely disappeared by puberty. It is apparently importantly concerned in early growth. It may in fact be questioned by some whether the thymus is a true gland of internal secretion since its functions are imperfectly analyzed and its surgical removal is not followed by characteristic endocrine disturbances.

4. *Adrenal or suprarenal glands.* These are two in number, one being situated anterior to each kidney and close to it. Removal of adrenals is ordinarily followed by death. Evidence that any mammal can continue to live after their complete extirpation is not clear. Their secretion has a marked effect on the rate of the heart beat. The adrenal has an outer region or "cortex" and an inner region called the "medulla." There is evidence that these two regions do not have identical functions. The medulla secretes the heart regulating principle known as epinephrine. The cortex does not contain epinephrine but seems to be the area mostly concerned in the series of experiments on mice already mentioned.

5. *Pituitary Body* (Hypophysis). This gland consists of two lobes, an anterior and a posterior one, of entirely different origin during development. The gland is located in a depression occurring at the base of the brain and above the palate of the mouth. Extracts of the posterior lobe have several effects: (a) an increase in secretion of urine, (b) a slowing of the heart rate and raising of the blood pressure, (c) an increased flow of milk during lactation, (d) contraction of muscles, among them those of the uterus (womb). Extracts of the anterior lobe accelerate growth, while deficiency of its secretion may be followed by underdevelopment of the genital organs and the accumulation of excess fat. Overactivity may, in some cases, produce what is known as pituitary gigantism and the peculiar disproportionate heaviness of facial bones known as *acromegaly.* Reference to this fact will be made again when the parallelism between the effects of endocrine disturbances in men and in dogs is considered.



FIGS. 23a and 23b. Comparison of endocrine glands in mice and men. Note the close similarity in type and location. These glands secrete the vitally important substances known as hormones which, carried by the blood, affect growth and development.

5. *Sex Glands.* Considerable mention has already been made of these glands—the ovaries in female animals and the testes in male. Both are paired. The former lie in the body cavity, the latter in a sac known as the scrotum, exterior to the body cavity. Experiments have shown that a temperature as high as that inside the body produces sterility and prevents the

normal functioning of the testis. The testes secretes several hormones, the ovary at least two. These hormones affect directly the development of the sex organs and of other secondary sex characters.

6. *Pancreas.* This gland forms not only an external secretion, the pancreatic juice, but an important *internal* secretion which controls the sugar formation and use in the body. The hormone is known as *insulin.*

In addition, some investigators believe that the liver, by the formation of glyogen (sugar) really falls in the category of a glandular structure producing an internal secretion. This, however, is not of the same type as the hormones to which reference has been made.

This brief survey will provide an outline of the endocrines as at present identified. Taken together they form an extremely important group of organs concerning which those of us interested in cancer must be informed.

56. HEREDITY AND TRANSMISSION

The second basic question suggested by the different reaction of various inbred strains of mice is that of the part that heredity plays in determining the incidence of cancer. This question is one that interests not only the research worker who is concerned in investigating the origin and nature of cancer, but also the average man and woman who is primarily concerned with his or her individual well-being and health.

In order to obtain a satisfactory answer to the problem of heredity it is first necessary to define clearly how offspring receive from their parents influences which may affect the nature and type of the individual. Some of the ways in which the parent can affect their progeny are direct. There are three important levels at which this is possible. The first of these is the substance of the fertilized egg (cytoplasm) which is actually a part of the mother herself.

At times the cytoplasm of the egg actually can carry material which affects the development of the individual formed from it. An example of this process leading to harmful results is the transfer of the microscopic organism which causes syphilis from parent to child. This is not heredity in the true sense of that term. It is direct *transmission.* We shall see that true inheritance is a different process.

Another period at which the parent can directly affect the offspring is during the development of the latter in the uterus (womb) of its mother. We have as yet only a very little knowledge of the extent of this type of influence. It is probable that it will be found to be much more important than we had expected. Investigation of its full extent has only become possible with the development of technique which allows the fertilized eggs of one female to be transferred to the uterus of another, there to continue their development until birth. Preliminary experiments have already shown an entirely unexpected influence of the foster mother on the development of a certain characteristic of the skeleton in mice.

The third level at which the offspring may have its reaction to later developmental processes very markedly influenced is during the period of nursing when the mother naturally is intended to provide all the nutriment of the young. The most remarkable case of this sort was discovered by Bittner only a few years ago.

We have seen that certain inbred strains of mice produce naturally a high incidence (90%) of mammary cancer while others may form as low as one-half of one percent of the same sort of tumor. In 1935 the staff of the Jackson Memorial Laboratory reported that the female offspring produced by crosses between high and low breast tumor strains of mice gave strikingly different percentages of this sort of tumor according to the strain from which their mother was selected. A typical cross gave the following result:

High tumor females from a 90% tumor strain crossed with low tumor (0.5%) males gave female progeny that developed 90% of mammary tumors. Low tumor females from 0.5% strain crossed with high tumor (90%) males gave female progeny that developed less than 5% mammary tumors.

It was evident, therefore, that the mother exerted a commanding influence on the incidence of mammary tumors. The next problem was to find out how and when she did so. The clew to her most important type of influence was provided by transferring newborn young from their own parent to a foster mother of another type. When this was done startling results were obtained.

The hybrid young which should have formed 90% mammary tumors were transferred to low tumor (0.5%) foster mothers for nursing. The incidence of tumors in these transferred animals was less than 5 per cent. The opposite type of transfer was also made. Hybrids which should have formed 5% mammary tumors were nursed by high tumor (90%) foster mothers. They produced between 70 and 80% mammary tumors. Either the milk or contact during nursing was able to influence markedly the incidence of mammary tumors. Later work showed that the milk was the agent which transmitted the influence.

This does *not* mean that milk as such, produces cancer. Certainly cow's milk can be given a clear bill of health for there is evidence that cows are singularly free from cancer of the breast. If one asks the direct question concerning mother's milk in humans the answer is not so easy. It is true that it has not been shown whether the same principle that applies to mice also operates in humans. It is also true that steps should be taken to collect data by direct observation to determine this point. At best this will be time consuming. It should, therefore, be begun at once. This problem is typical of many important studies not yet undertaken because of lack of funds.

Having briefly considered transmission of influences from parent to offspring via the egg cytoplasm the uterine environment and the milk, we may next take up true inheritance.

57. MENDEL'S EXPERIMENTS

The process of true heredity must of necessity be somewhat indirect. We know, for example, that it is the ability to form or to produce a certain character which is inherited rather than the character itself. The ability to form blue eyes or brown eyes or some other character must exist and be inherited long before the character itself is formed. We know that this is the case as a result of the experiments of an Austrian monk named Gregor Mendel.

Mendel was a botanist and a mathematician who lived at the time of Charles Darwin and worked in a monastery garden at Brünn. Both of his scientific abilities aided him in his research and both contributed to the successful discovery of the law or laws of heredity which bear his name. He had a new point of view about the material with which he worked. He was interested in distinct characters of an organism rather than in the organism as a whole. Up to his time biologists had been more interested in a "type" or "variety" of plant or animal than in any simpler unit as represented by any single character of that organism.

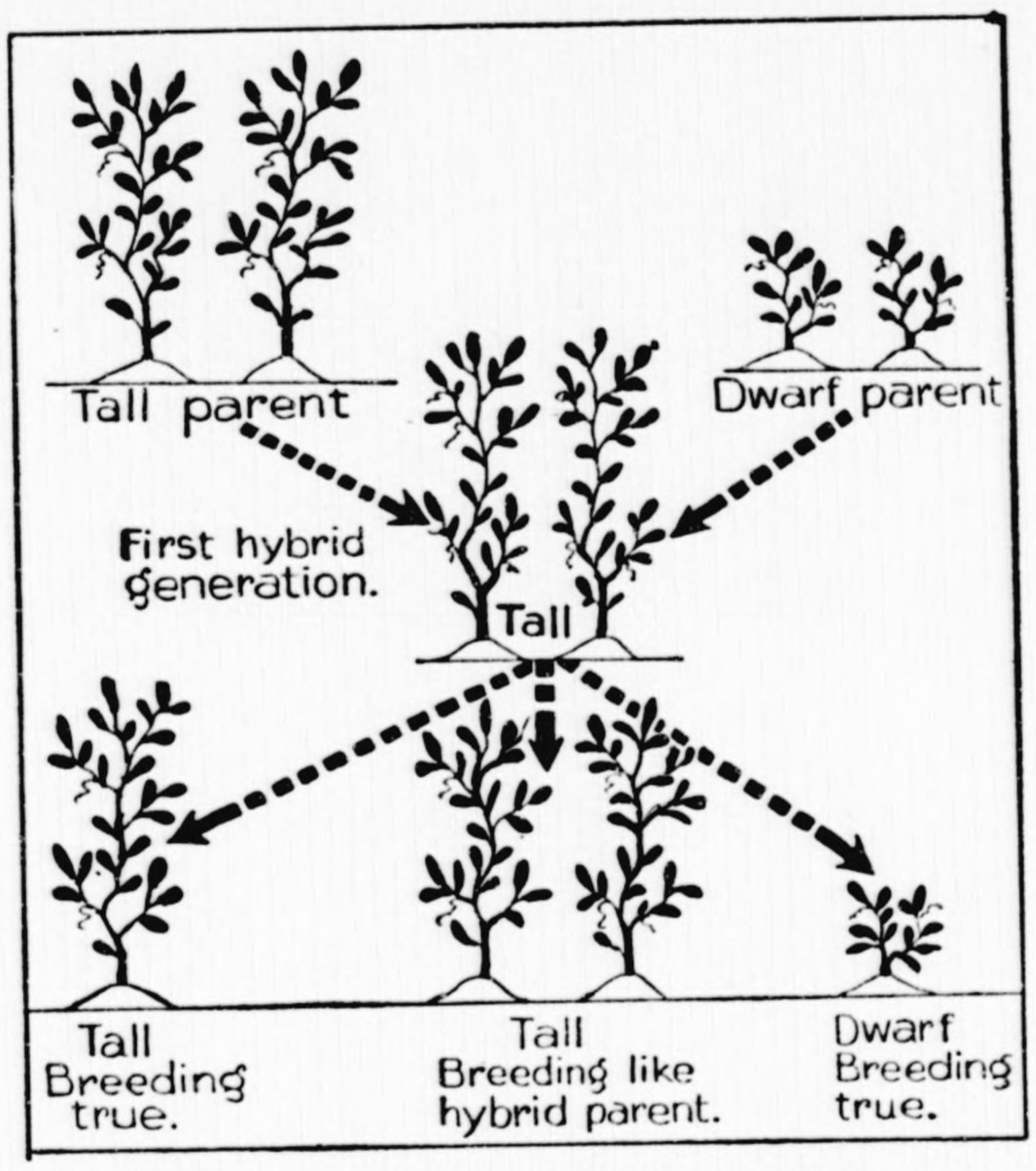


FIG. 24. Mendel's Law of Inheritance. One of the actual experiments performed by him with the common garden pea. Note that the habit of growth is either tall or dwarf and that the two characters do not blend but are alternative in inheritance.

Mendel, on the other hand, approached the matter from the latter angle. Using as his experimental material the ordinary garden pea he picked out varieties which differed in one or more of three contrasted pairs of characters. These were as follows: *green* seeds vs. *yellow* seeds, *round* seeds vs. *wrinkled* seeds and *tall* habit of growth vs. *dwarf* habit of growth.

He chose varieties which regularly bred true to these characters and then proceeded to cross them in order to find out how they behaved in inheritance. Let us see what some of his results were. For this purpose we may take as an example the cross of tall and dwarf peas. Both of the varieties with which he started his work were well established, horticultural types, each of which bred true to its own habit of growth. The tall variety produced only tall plants and the dwarf only dwarf plants generation after generation. Each, therefore, had a fixed hereditary type and extent of growth.

When he crossed the two varieties all the first generation hybrids resembled exactly the tall parent. All sign of the dwarf parent was absent from them. The "tall" character is called "dominant" because it dominated the form of the hybrid. The "dwarf" character is called "recessive" because it receded and disappeared in the hybrids.

His next step was to cross together the first generation hybrids and obtain a second hybrid generation. This generation consisted of "tall" and "dwarf" plants with the former far more frequent. He studied and recorded carefully the proportion of "talls" to "dwarfs" in a number of different populations of second generation hybrids and found that it approximated in each case 3 tall to 1 dwarf; that is to say, 75% of the former, 25% of the latter. In testing further the nature of the second hybrid generation plants he used the process of self-fertilization. Here the nature of his material aided greatly. The flower of the pea has both male and female sex organs. It can fertilize itself, thus simplifying experimental conditions.

Mendel found that *all* the second hybrid generation "dwarfs" bred true. They gave *no* tall progeny whatever. They were exactly like the original dwarf variety and showed no effect of having been derived from a first generation hybrid tall parent.

The second generation tall plants on the other hand were of two distinct types. Although they looked exactly alike some gave only tall progeny while others reproduced in their progeny the ratio of 3 talls to 1 dwarf as their hybrid parents had done. Approximately one-third of the second generation "talls" were true breeding, giving only tall plants while two-thirds produced the 3 tall to 1 dwarf ratio.

58. MENDELISM EXPLAINED

We may now consider the explanation of the observed results. It is here that Mendel brought order out of chaos and gave science its first exact and predictable laws of inheritance.

In this explanation we can call the tall character T and the dwarf character D. We should also remember that individual plants and animals are ordinarily double structures as far as heredity is concerned. They are formed by union of two sex cells, one from the male and the other from the female parent. The germ cells are *single* structures, the individuals *double*.

True breeding tall varieties would, therefore, consist of individuals which could be represented as TT. True breeding dwarf varieties would be DD. As long as talls, TT, were bred with other TT plants only T could enter the germ cell and no sign of D would be present. As long as dwarfs, DD, were bred to similar dwarfs, DD, only D could enter the germs cells and no sign of T would be present.

If now the cross of the two is considered the TT parent will form T germ cells and the DD parent only D germ cells. The first generation hybrid will be formed by the fusion of a T and a D germ cell and be TD in constitution. This plant *looked* just like a TT plant because T was dominant and concealed the presence of the recessive D character.

We now come to Mendel's first law which is that when the TD hybrid forms its germ cells, there is complete segregation or separation of T and D. One but not both enters each germ cell. As a result two sorts of pollen grains, T and D, are formed in approximately equal numbers. So, too, are two sorts of ovules or female sex cells, T and D.

Mendel's second law reveals itself in the formation of the second hybrid generation. This law states that the germ cells formed by two first generation hybrids recombine according to chance without selection or preference for one another. As a result we would have two sorts of pollen grains, T and D, with an equal chance of fertilizing two sorts of egg cells, T and D, in equal numbers. Let us see what this would produce.

If a T pollen grain meets a T ovule a TT or true breeding tall plant is formed. If a T pollen grain fertilizes a D ovule at TD hybrid tall individual is formed. A similar individual TD results if a D pollen grain meets a T ovule. If, however, a D pollen grain fertilizes a D ovule a DD dwarf is produced.

The second hybrid generation would, therefore, consist of one TT, two TD and one DD plant. This would give a ratio of 3 talls to 1 dwarf. It would also explain why all the dwarfs bred true and why one third of the talls were true breeding TT and two-thirds, being TD gave a 3 to 1 ratio.

Mendel found that green seeds and yellow seeds behaved in the same way, green being dominant and yellow recessive. Round seeds were dominant over wrinkled and the same law of segregation and chance recombination applied here also.

Later cases have been found where dominance of one character over another is not complete. These serve to clarify and establish the correctness of the principles of Mendelian inheritance. One of them may be cited as an example because of its importance in establishing a breed of fancy poultry known as "blue" andalusians.

59. INCOMPLETE DOMINANCE

Andalusian fowl are of the same general delicate and graceful type as leghorns so frequently used for white egg production. The variety most often exhibited at poultry shows is a pale slate gray called "blue" by the fancier. There are also two other varieties of andalusians, one a coal black, the other white or white with a few scattered black feathers. The blacks and whites are usually considered culls by the fancier and are not used for breeding.

It is, however, the *universal* experience that when any considerable number of chicks are hatched from a "blue" by "blue" mating, blacks and whites crop out as well as some of the more desirable "blues." The explanation came when blacks and whites were carefully bred and studied.

The first fact that was discovered was that black

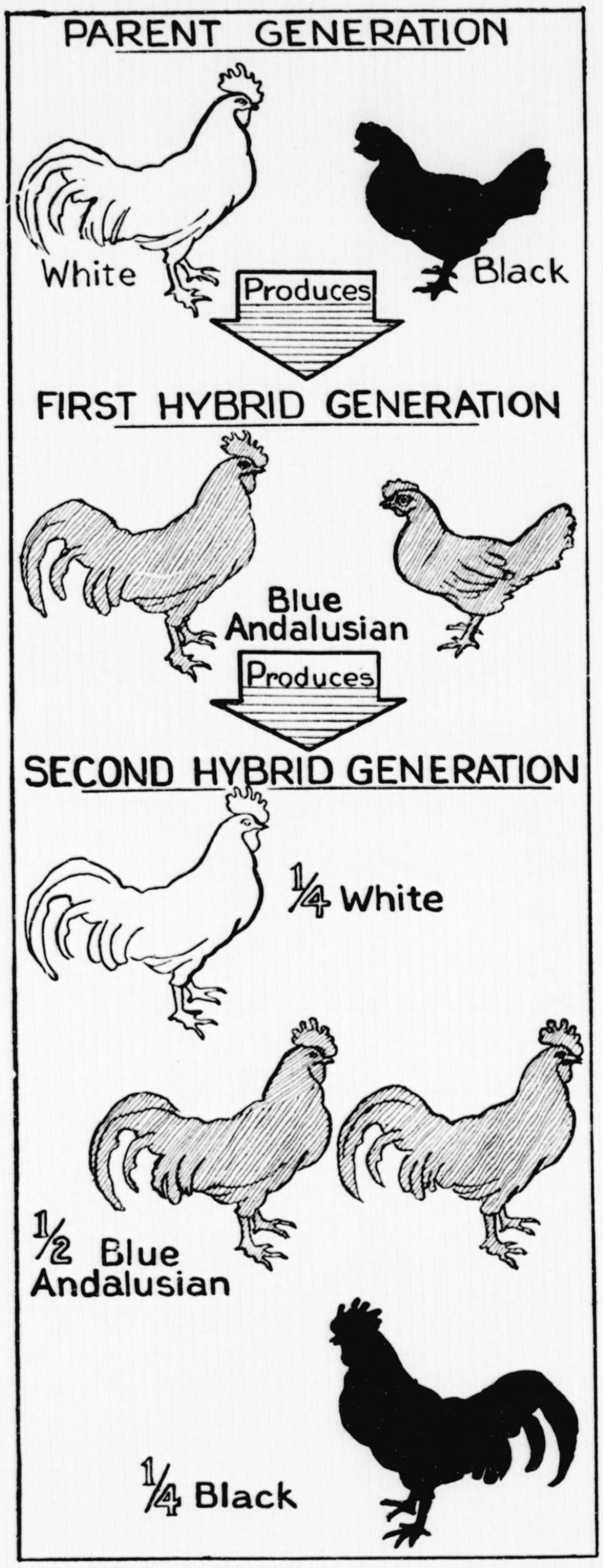


FIG. 25.

mated with black gave *only* black. Similarly white by white gave only whites. The amusing fact, however, was that when blacks were crossed with whites *only blues* resulted. All this could be explained if we suppose that blacks are BB, whites WW and blues BW in their hereditary make up. If this was the case blues should form two sorts of sex cells, B and W, in equal numbers. Two such birds crossed together would give among their progeny one BB black, two BW blues and one WW white, or 25% black, 50% blue and 25% white. This was found to be actually the case. "Blue" andalusians will never breed true to blue alone because they are a temporary combination of two contrasting plumage colors, black and white, and the hereditary basis for these colors segregate in the germ cells. In the long run the most that a fancier can expect from crossing two "blues" is fifty per cent of chicks of that color.

A similar case was described some years ago in the Journal of Heredity only this time it was a "blue" hog —then described by the somewhat alluring name of the "Sapphire" hog. Here, too, despite all efforts to "fix" the blue-gray coat color, unwelcome black pigs and white pigs kept appearing in even the most select pedigree combinations.

Mendel's law is fascinating not only because of its brilliant simplicity but because of the fact that it remained dormant for thirty-five years due to a remarkable set of circumstances. The first of these was its original publication in an obscure and little read local scientific journal at Brünn. The second was that in 1865 and for some years thereafter the scientific world was being rocked by the violent arguments incidental to the theory of evolution as advanced by Darwin. This left little room for the introduction of new thought on other lines in biology. The final and most remarkable element in a strange triangle of events was the independent and simultaneous rediscovery of Mendel's principles of segregation and recombination by three different botanists, deVries in Holland, Correns in Germany and von Tschermak in Austria. This occurred in 1900, the first year of the Twentieth Century, and marked the birth of experimental biology as a laboratory science destined to modify fundamentally our knowledge of nature and of ourselves.

60. CHROMOSOMES AND HEREDITY

The most remarkable thing about the process of Mendelian heredity is the orderly and exact way in which it operates. It is as mechanical and impersonal as anything could be. It very clearly provides for equal contribution from each parent. It separates pairs of alternative characters with exactitude and without preference. It recombines characters with no evidence of selection or of any factor except the law of chance. There must be some mechanism to make this possible, some physical basis for the location of the hereditary units that are so fixed and predictable in their behavior.

Students who have observed the structure of the nucleus of the cell have long known that the cells of plants and animals possess certain bodies or structures which fulfill the necessary requirements to serve as the vehicles in which the chemicals representing the hereditary units are located. These nuclear structures are called chromosomes—"color bodies"—because in the process of being prepared for microscopic study they absorb more readily than does the rest of the cell the chemical stains which are applied by the investigator to bring out detailed structure of the cell.

The number of chromosomes in all cells of every individual plant or animal is constant for each species. In the body cells of mice the number is 40, in man 48, in the fruit fly 8, in corn 12. In all species the number of chromosomes in the sex cell is one half that of the body cells. They are thus single structures in the sex cell and double or paired structures in the body cells. This as we saw was the way in which the hereditary characters themselves behaved.

This was the stage at which the knowledge of the physical basis of heredity rested when in 1912 Morgan described an unequal distribution of chromosomes that opened the door to further knowledge of a most fascinating type.

Detailed observation of the pairs of chromosomes in body cells showed that while the different pairs were of different sizes and shapes, the two members of a single pair were usually alike. There was a marked exception to this in the fruit fly, Drosophila, where the small number of chromosomes made them easy to count and identify. In this species three of the four pairs of chromosomes were composed of members similar to one another. The fourth pair had similar rod-like chromosomes in the female, but one rod-like and one hook shaped chromosome in the male. Calling the rod-like member X and the hooked member Y the two sexes were described as XX in the female and XY in the male. All egg cells contained an X chromosome, but the sperm cells were different. Approximately half contained an X chromosome and the other half a Y chromosome. When a sperm with an X chromosome fertilized an X egg, an XX individual (female), resulted, but when one with a Y chromosome functioned the individual was XY and a male.

On top of all this, certain hereditary characters were found which had their physical basis located on the X chromosome. Such characters could not be carried in the Y chromosome. They, therefore, showed a peculiar type of inheritance which was characteristic and important in its effects. For no particular reason it appears that mammals have the same general sort of sex linked inheritance and we may give two examples that indicate what sort of results are produced.

We may suppose that in cats, for example, females are XX and males XΘ. This may serve to explain the occurrence of a peculiar relation between coat colos and sex. In cats black males and females are common. So also are yellow males and females. The peculiar blotched black and yellow coat color known as tortoise shell is, however, confined to females except in a handful of rare and abnormal exceptions.

If we suppose that germ cells of cats may carry the hereditary base for yellow or black but not both and that this hereditary base is located in the X chromosome and not on the Θ we should have the following types: YXYX yellow female, YXΘ yellow male, BXBX black female, BXΘ black male.

If a yellow female, YXYX, is crossed with a black male, BXΘ, an equal number of BXYX females and YXΘ yellow males should be produced. The BXYX

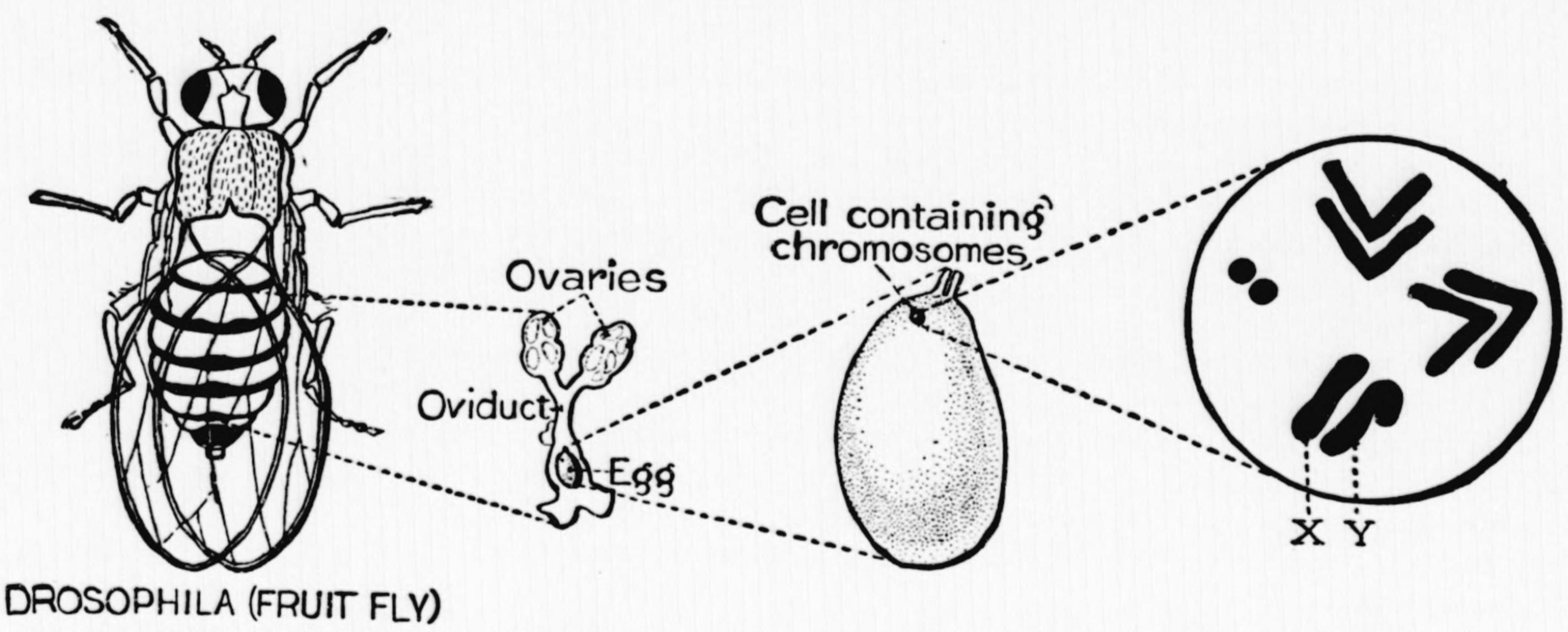


Fig. 26. In this series of drawings is shown first the adult Drosophila (fruit-fly). This is enlarged about 15 times. Next, enlarged 20 times is the female reproductive system removed from the body. Note the ovaries, oviducts and egg. The third drawing shows the egg enlarged 50 times. Most of its substance is composed of nutritive and supporting material. The chromosomes which bear the chemical basis of inheritable characters are only a small part as indicated. These, magnified 5,000 times are shown in the right hand figure. Note their individual characteristics as described in the text.

females are potentially the tortoise shell animals. It is only necessary to suppose that neither black nor yellow is completely dominant, but that they both appear in streaks or blotches. The opposite cross of BXBX black female by yellow male, YXΘ, produces equal numbers of BXYX or tortoise shell females and BXΘ black males. In each case the sons resemble the mothers which is called "criss-cross" inheritance. These results were actually obtained and recorded as early as 1912 at the time that Morgan was describing sex linked inheritance in Drosophila. Matings of tortoise shell females with black or yellow males give slightly more complicated but equally definite results as follows.

Tortoise shell females crossed with yellow males can give the four following types:

Tortoise shell female BXYX by YX yellow male

BXYX	tortoise shell female
YXYX	yellow female
BXΘ	black male
YXΘ	yellow male

Tortoise shell females crossed with black males also give four types:

Tortoise shell female BXYX by BX black male

BXYX	tortoise shell female
BXBX	black female
BXΘ	black male
YXΘ	yellow male

61. SEX-LINKAGE IN MAN

In man himself color blindness depends upon a recessive hereditary unit carried in the X chromosome. Normal type of vision depends upon a dominant hereditary unit similarly located. If N represents the normal unit, and n the color blind, the constitution of a normal female is NXNX and of a normal male NXΘ. A color blind woman would be nXnX and a color blind male nXΘ. There are six possible types of matings:

1. Normal female NXNX by normal male NXΘ gives NXNX normal females and NXΘ normal males.
2. Normal female NXNX by color blind male nXΘ gives NXnX normal females (carrying recessive color blindness) and NXΘ normal males.
3. Color blind female nXnX by normal male NXΘ gives NXnX normal females (carrying recessive color blindness) and nXΘ color blind males.
4. Color blind females nXnX by color blind male nXΘ gives nXnX color blind females and nXΘ color blind males.
5. NXnX normal females (carrying color blindness) by NXΘ normal males gives NXNX normal females, NXnX normal females (carrying recessive color blindness), NXΘ normal males, nXΘ color blind males.
6. NXnX normal females (carrying recessive color blindness) by nXΘ color blind males gives NXnX normal females (carrying recessive color blindness), nXnX color blind females, NXΘ normal males and nXΘ color blind males.

This type of inheritance accounts for the large number of color blind men compared with color blind women. The main point of emphasizing these cases is that they provide an important link in proving that the chromosomes are the bearers of the concentrated chemical entities which form the basis of hereditary characters.

62. LINKAGE AND CHROMOSOMES

We have spoken of chromosomes, the extremely small, deep staining bodies that occur in a definite and fixed number in each cell of the body. We have seen that they give definite evidence of being the vehicles which carry the chemical basis for each of the hereditary characters in the body.

It will be interesting for a short time to consider how very exact and convincing that evidence really is. In so doing it will probably be best to use as an example the most simple and extensively analyzed form—the fruit fly Drosophila. The sex cells of these flies contain only four chromosomes each and the body cells four pairs or a total of eight. Three of these four pairs have, as we have stated, members both of which are apparently identical chromosomes in both male and female. One pair has identical chromosomes in the female and dissimilar ones in the male. The relative size and shape of the four pairs are illustrated in Fig. 26.

If these chromosomes follow the Mendelian procedure of clear cut segregation from one another and of chance recombination pair by pair it is evident that there can be only four hereditary pairs of elements which are entirely independent of one another, one located in each chromosome. On the other hand, if more than one hereditary element is located in a chromosome those together in a chromosome should show some degree of association and some sort of grouping. Morgan and his co-workers found that this was actually the case.

There have been more than four hundred distinct hereditary elements identified in Drosophila. These are associated in inheritance in four groups. Each group is independent of the other three. Within the groups, however, the hereditary elements show various constant degrees of association with one another. This association is called "linkage." The degree of independence of two pairs of hereditary elements within a chromosome is called "crossing over" for when they break linkage it means that one of the two has crossed over to the other member of that particular chromosome pair. Naturally the orderly behavior of the hereditary elements and their definite and predictable relationship to each other led to the conclusion that they were very definitely located in the chromosome. The pattern of their arrangement was supposedly like beads in line on a string. The closeness of the beads to one another would be the measure of the closeness of association of elements in heredity or *vice versa* as one prefers.

The most extraordinary proof of the correctness of this theory was provided by the fact that the chromosomes in the cells which make up the salivary glands of the fruit fly are approximately one hundred times as large as the ordinary chromosome. This makes it possible to determine their structure by studies under the microscope. Photographs reveal actual structures arranged in a line and corresponding in relative position in the chromosome to where they should be located on the basis of association of hereditary elements. There is no chance that this structural arrangement and the order of hereditary behavior can be due solely to coincidence. The degree of correspondence is altogether too complete and too perfect for that. Morgan, undoubtedly, has established the fact that the chromosomes are the bearers of those hereditary elements which follow Mendel's law of heredity.

63. HEREDITY AND CANCER IN MAN

Let us now see whether and to what degree these facts and principles bear on the problem of cancer.

The first definite fact is that cancer is not a simple, single entity from a biological or hereditary point of view. There is no great general hereditary tendency to form cancer and there is no great general hereditary tendency that protects one against it. The types of physiological activity which are characteristic of certain individuals may and often do have a part of their origin in hereditary elements. These, however, may be numerous and also be only a small part of the combination of events which result in cancer. When, by long continued inbreeding, great biological uniformity is produced within a strain of mice the result is that the development of individuals in that strain is similar and that they repeat in each case a complex but definite series or chain of physiological steps which reproduce the same end result—cancer if the circumstances are so combined in one strain and no cancer under different conditions in another.

Very evidently human individuals are not and will not be produced by any such process of inbreeding. The individuals will not be of uniform types similar in hereditary elements and in their tendency to form cancer of one or another sort. They will vary and will require knowledge of both their ancestry, their collateral relations and finally of their progeny before we can classify them biologically with even a passable degree of accuracy in relation to the more simple inherited traits. To determine their individual potentiality to form or to resist the formation of cancer would be very nearly impossible by any experimental study of the application of the Mendelian principles of heredity.

This means that for the present at least and until further knowledge is obtained the individual whose parents died of cancer or in whose family the disease is frequent, should be alert, cautious and intelligent in detecting and reporting any sign or symptom of cancer in his own body. It does *not* mean that he should take a pessimistic or fatalistic attitude concerning his chances of having cancer. He is *not* doomed or condemned. He should understand that fact and impress it upon all others in a similar situation. Nothing is more cruel than the haunting fear that members of a "cancer family" are allowed to experience. Future experimentation may show that this fear is justifiable, but present knowledge does *not*.

64. HEREDITY AND ENVIRONMENT

This does not mean that studies of heredity in animals or that the use of biological methods of analysis are without value. On the contrary these methods both by themselves and in combination with chemical analysis are as promising a line of attack on cancer as now exists. For an indefinite period into the future this field should provide valuable information on the origin and nature of the cancer process. Without exact knowledge of the biological nature of the material being used we shall not be able to evaluate the relative importance of heredity and other factors in the production of cancer.

It is important also to remember that such structures as the endocrine glands to which we have given some consideration are themselves endowed with relative degrees of activity which to some extent depend upon an hereditary capacity for action. For this reason heredity must be viewed as a process, a point of view, a type of biological behavior – not an entity in itself. The tendency to place too great a degree of definiteness and concrete meaning on the term "heredity" is perhaps natural, but it is subject to overemphasis and abuse. Heredity remains a great and powerful means of perpetuating different forms of life but it requires cellular material on which to work and an environment from which the chemicals to create that material can be drawn.

There is no use to consider heredity and environment as opposed or antagonistic to one another. Neither would have much value without the other. Environment alone would produce unstable and variable forms of life which would be forced to change with every fluctuation of temperature, moisture, barometric pressure, light and food. There would have been no means of stabilizing variations in the pattern of living things. On the other hand, heredity alone would have resulted merely in concentrated helpless forms of living material like the bacteria which need and must have a favorable environment from which to derive the food needed for reproduction.

No biologist who overemphasizes heredity can or will be able to advance far in his understanding of growth as a process. No medical man or sociologist who ignores heredity and leans wholly upon environment can expect to understand the nature of the body of which cancer is a part.

65. CANCER IS PART OF BODY

This brief review of the biological principles involved in cancer research is, of course, very incomplete. It is hoped, however, that it will give you some idea of the way in which science has gradually accumulated methods and facts so that we are today better equipped than ever before in our fight against cancer. It will be important to remember that cancer is a part of a living animal. It is not a foreign body. It is not something added to the mouse or to the man as the case may be, but an actual part of the living tissue of that mouse or man. As such there is no reason why the animal should recognize cancer as a foreign body or take any steps to eliminate it. As long as the cancer remains young, active and healthy the animal supports its growth and feeds it just as it does any of its normal tissues. The type of growth which cancer shows does not differ fundamentally from the type of growth which normal tissue exhibits except in speed and in the fact that it cannot be controlled or stopped by any known mechanism within the body. All normal growth comes to a resting point where, because of the economy of the body as a whole, it is essential that growth be limited. Throughout the ages animals have developed internal mechanisms for regulation of growth. These mechanisms work with amazing accuracy in most instances. Cancer is the one great example of a condition in which regulatory mechanisms are not efficient. This places it in a unique position.

In many senses of the word it is not a disease at all. It is chiefly harmful because it occurs in a body where limitations of food and opportunities to support growth are not sufficient to take care of the cancer as it increases. It will be evident from the foregoing that our knowledge of the origin of cancer will be inseparably interwoven with our knowledge of the normal process of growth and its regulation within the body. All that can be learned about the way in which animals and plants develop and function will have its bearing on our eventual understanding of cancer. Without very extensive knowledge of normal growth and its control we can never expect to understand even the *principles* of cancer formation and growth.

That is why cancer research must always be allowed to invade any field of experimental science where its interest may lead it. That is why also cancer research as such will shift in emphasis from topic to topic and from method to method as time goes on. The investigator will need to be versatile and well-rounded and the American public will need to be well trained and completely appreciative of the magnitude of the task that lies ahead.

The leaders of the layman's fight on cancer cannot in the majority of cases be experts in cancer research. They can and should, however, develop sufficient knowledge of its problems so that they can help to support worthwhile research work and encourage others to do so. They must be the guardians of opportunity for the research worker just as an army fights to maintain the integrity of the nation to which it belongs. The enlightened layman must similarly fight to obtain the resources and opportunities essential to continued and progressive scientific advances against cancer.

66. HOW YOU CAN HELP

You will naturally want to know how you can go about assisting this program. There are two ways in which this can be done. One is local, the other is national. If you live in a state that has well organized and worthwhile cancer research it may be possible to establish, after consultation with those in charge of

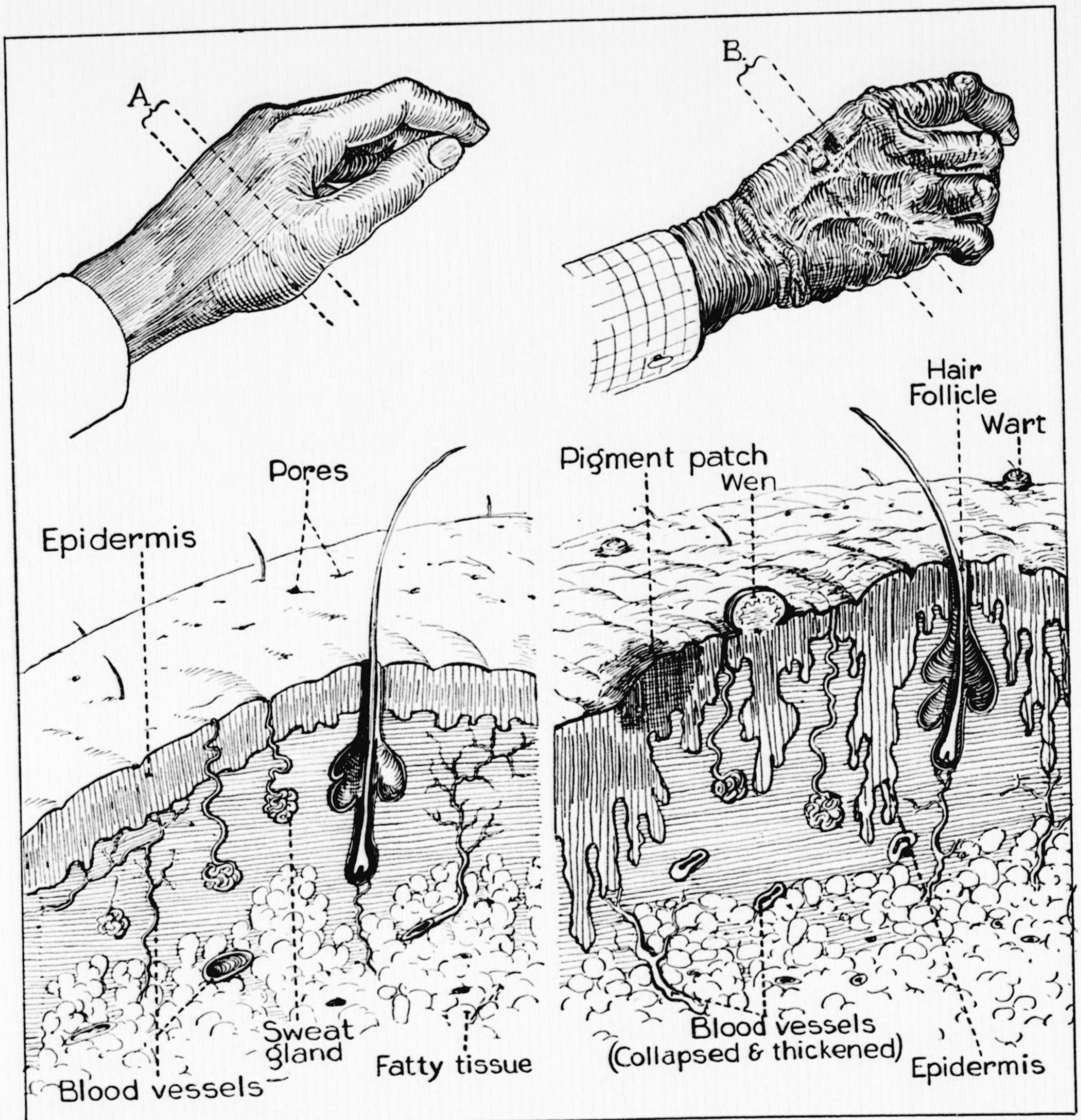


Fig. 27. The process of ageing is shown in the above figures. In A the skin of the hand of a young (20 year old) person is shown. Cross section of the skin reveals orderly, organized, well-defined and effectively functioning structures. In B the skin of the hand of an 80 year old individual is diagrammed. It is wrinkled, irregular, with disintegrating and disorganized structures. Note also the small benign tumors (wart and wen) representing new growth and useless tissue. The skin is one of the later structures to show the effects of age. **Its general behavior is however characteristic of the disintegrative changes that occur in all tissues.**

that research, a campaign of education of the people of your vicinity concerning the need for further finances. These could be obtained either by a direct appeal for a small amount of money from a large number of people, or by including that appeal in the general program of the American Cancer Society with the understanding that a certain percentage of the funds so raised would be given for certain specific research projects. In any case, the project or projects which appeal to you should be approved by the medical executive committee of your local unit. It should then be submitted to the state or larger division of the Society for its approval and eventually will be passed on by the American Cancer Society as a national body. The object of all of this caution is to avoid any possibility that ill-advised, non-scientific projects might be supported, or that well meaning individuals might be taken advantage of by charlatans and quacks.

It may be of interest to consider some of the laboratories at which considerable cancer research is being done. These again will be listed not necessarily in order of importance.

The National Cancer Institute at Bethesda, Maryland, is the largest research laboratory. This is housed in a building made possible by an appropriation from Congress and is, as above stated, supported by an annual budget from that same source. It deals with and investigates all phases of cancer research — the physical, chemical and biological. The Act which established it makes it possible for the Government to receive gifts from private sources if anyone cares to make such.

The largest center and program of cancer research at any American university is that conducted at Yale. Here, aided by proximity to the Jane Coffin Childs Fund and supported by university funds as well, an excellent program of a very comprehensive nature has been organized and is being followed up.

A third center of research is that at the Rockefeller Institute in New York City. Here cancer is considered by several of the divisions, but primarily and especially by the Division of Cancer Research which has done most of its work along the line of biology and chemistry. This work is supported by the general endowment of the Rockefeller Institute.

The Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine, investigates cancer from the point of view of biology and heredity and is not endowed. It derives its funds from grants-in-aid, from a limited number of private donors and from the sale of its surplus animals to other scientific laboratories throughout the country. There are a number of other laboratories or institutions such as the Biochemical Institute in Newark, Delaware; The Institutum Divi Thomae at Cincinnati, Ohio; and research programs at various universities such as Columbia, University of Pennsylvania, University of Chicago, University of Michigan, Harvard University and many others. There are research units at many hospitals such as the Barnard Hospital of St. Louis, the Memorial Hospital of New York and the Lankenau Hospital of Philadelphia. There are also scores of scattered investigators working on cancer or allied problems either under grants-in-aid or university budgets.

It may be asked whether coordination and correlation of this effort are not desirable. There have been some interesting discussions, debates and correspondence about this and in general the past few years have seen definite progress in this general direction. There is, for example, a very considerable degree of overlapping in personnel between the Board of Directors and Scientific Advisers of most of these institutions and funds. This, of course, is an informal type of coordination but it does a great deal to avoid duplication and waste. It is very doubtful whether any more formal and rigid type of supervision would be helpful or desirable. Where one is dealing with pioneer work against a dangerous enemy it is essential that a proper balance be established between individual initiative and exchange of ideas and information. This, it seems, has been approximated at present and can be further maintained and insured by the activities of such organizations as the American Cancer Society.

SECTION II

SERVICE
(Detection, Diagnosis and Treatment)

Introduction

In the first section of this book we have reviewed briefly certain of the lines of work that are contributing to advances in our knowledge of the origin and nature of cancer. This is one leg of the tripod upon which the program of cancer control properly rests.

We may now consider some of the more important facts bearing on its diagnosis and treatment. Quite properly these will be presented by medical men who are devoting their lives to the clinical aspects of the disease. No layman should attempt to diagnose cancer or to speak with authority on any of its medical aspects. On the other hand, every interested and intelligent layman should be familiar with the general discussion of the medical aspects of the problem.

With the exception of the papers by Florence R. Sabin, M.D., and C. C. Little, Sc.D., the following papers were presented informally by the staff of the Memorial Hospital in New York as a volunteer contribution to the first training school for officers of the Women's Field Army in 1942.

They represent very definitely a discussion intended for laymen and are couched in terms as free as possible of all technical complexities.

A similar set of papers could have been prepared in any one of a number of hospitals throughout the country. There has been, however, a fruitful and constructive contact between the staff of the Memorial Hospital and the governing boards of the American Cancer Society for many years. This fact and the geographic proximity of the hospital made the choice of personnel an obvious one.

The Society is grateful to the men who so kindly and generously prepared and delivered these papers.

The paper written by Dr. Florence R. Sabin, one of the Field Army's Honorary National Commanders, might well be studied before proceeding with the rest of this section.

It will also be advisable to read the statement on preparation of tissues for microscopic study and diagnosis. This is the work of the pathologist. It will be evident to the reader that the preparation of tissue and the work of a pathologist are highly specialized and require both specific training and technical equipment.

The Lymphatics

FLORENCE R. SABIN, M.D.

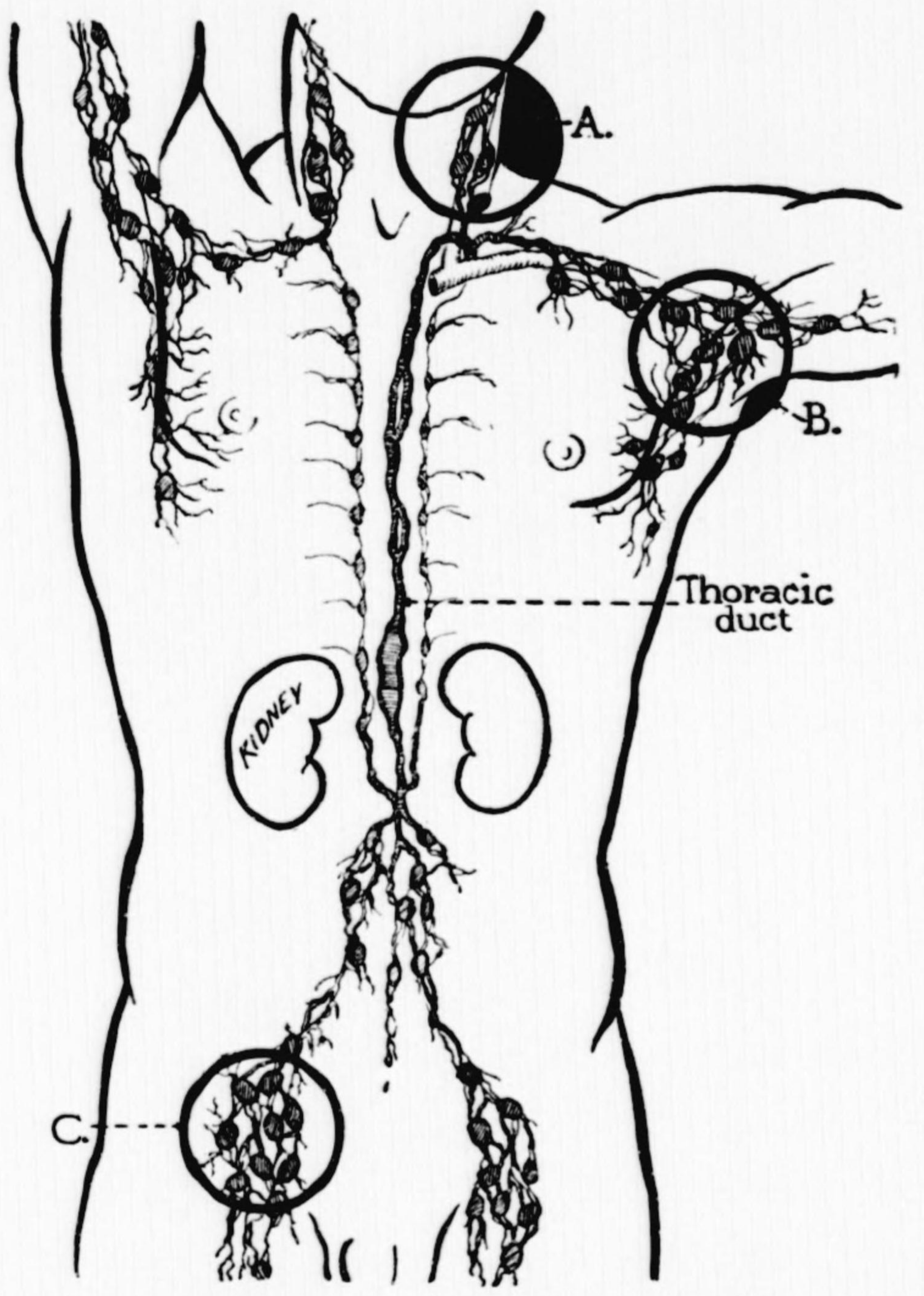


FIG. 28. The lymphatic system showing the common sites of secondary cancerous growth—the neck, armpit, and groin. Note the fine branched lymph channels which feed the larger concentrations of lymph forming the nodes.

THE lymphatic system is a part of the vascular system, specifically an appendage of the veins, sharing with the smallest veins their important function of bringing back into the circulation, fluid which has passed out from the smallest blood vessels known as capillaries to bathe and nourish the cells of the body. The lymphatics connect with the veins only at the root of the neck on either side.

The capillary bed is the functioning zone of the entire vascular system: heart, arteries, and veins exist to supply the capillaries with blood so that they may in turn maintain all the cells of the body. The walls of the capillaries are composed of a single layer of so-called endothelial cells. The cells of the body lie, as it were, between the blood capillaries and the lymphatic capillaries. Fluid containing many substances in solution comes to the cells from the blood capillaries. It is now known (Whipple, Drinker) that even the large molecules of the blood protein may leave the vessels, though in small amounts. Part of this protein may be used by the cells and the remainder returned to the circulation through the lymphatics. Some of the fluid goes back into the blood vessels at the place where the blood capillaries widen into veins, but the excessively thin, permeable endothelial cells of the lymphatic capillaries play their rôle in a nice balance of drainage of different materials back from tissues to vessels. Between the markedly serrated borders of the endothelial cells of lymphatic capillaries, whole cells, such as extravasated red corpuscles, or extraneous cells like those from cancers, can enter the lymphatics with ease.

The composition of lymph varies considerably in different regions, but the variation is confined essentially to the protein and fat content. From a fasting animal, the thoracic duct lymph is a transparent liquid, generally slightly yellowish. When obtained from an animal shortly after a meal, it is milky. The lymph from the thoracic duct has a protein concentration of about 3.2 per cent, but lymph collected from a limb during exercise may contain less than 0.5 per cent protein. Similarly, variations are found in the lymph from a single area; in the latter case the variations depend on the rapidity of lymph flow and on the conditions generating this flow. The lymph from all parts of the body contains fibrinogen; when shed it slowly clots. It also contains serum albumin and serum globulin. The colloid osmotic pressure of lymph depends on these proteins, and on the relation of the concentrations of the various proteins to one another. The concentration of salts and other diffusible substances appears to be close to those found in plasma; that of calcium is somewhat lower; that of chlorides and of non-electrolytes is somewhat higher. The thoracic duct lymph contains large numbers of white cells which are mainly lymphocytes similar to those of blood. The numbers observed vary greatly, from 500 to 72,000 per cu. mm.* Hence the lymph contains not only these cells (chiefly) but, as studied

* *Macleod's Physiology in Modern Medicine*, edited by Philip Bard.

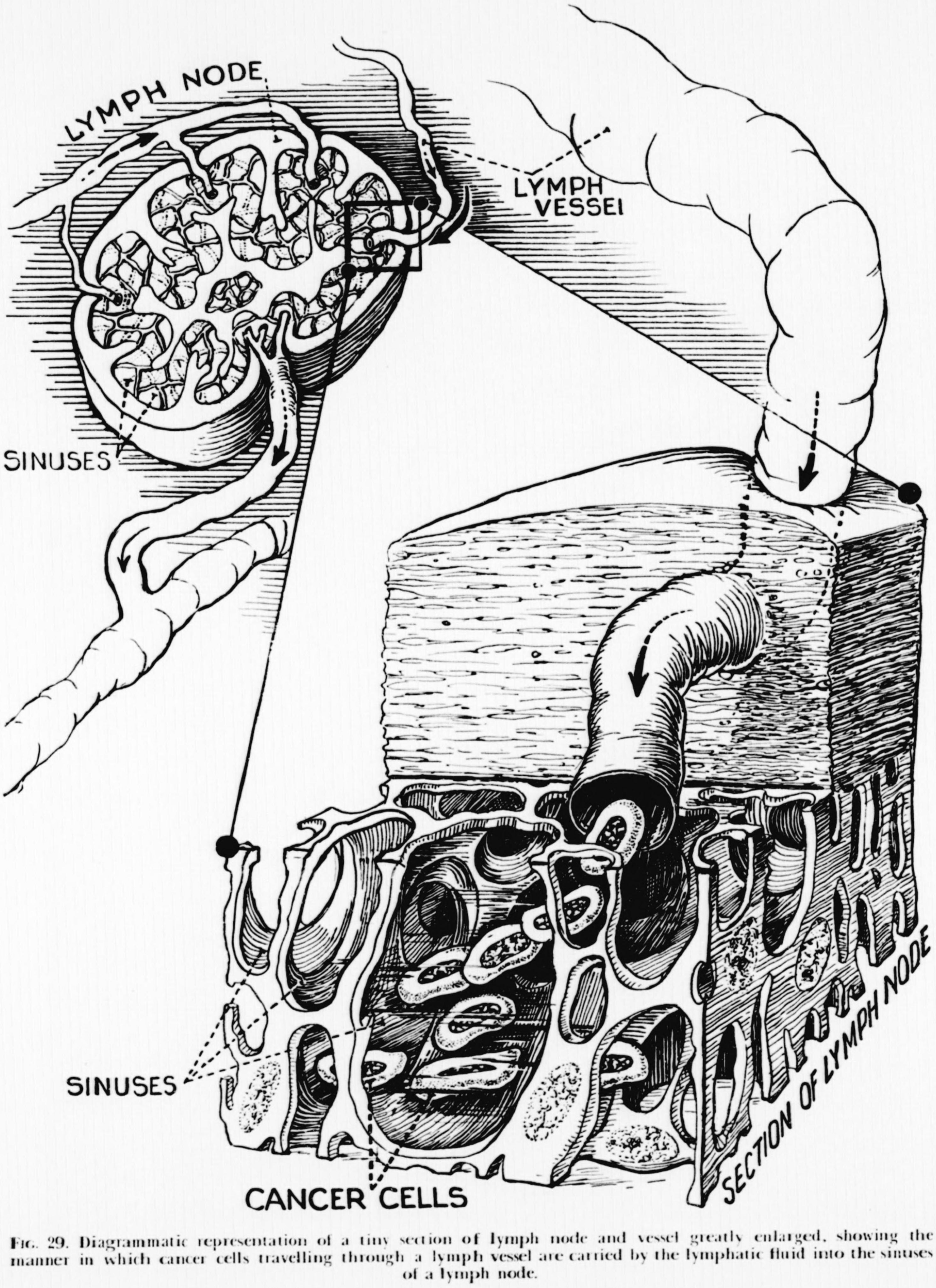


FIG. 29. Diagrammatic representation of a tiny section of lymph node and vessel greatly enlarged, showing the manner in which cancer cells travelling through a lymph vessel are carried by the lymphatic fluid into the sinuses of a lymph node.

by Drinker and Yoffey and expressed as the findings in normal dogs, the following chemical constituents in mgms. per 100 cc.: sugar, 115 to 273; non-protein nitrogen, 27 to 39; chlorides, 396 to 413; amino acids, 2.39; inorganic phosphorus, 2.8 to 3.6; calcium, 9.2 to 12.1, and potassium, 18.4. These readings are for lymph in the thoracic duct; anything changing the composition of blood would cause a corresponding change in the composition of the lymph. For example, liver lymph may contain more sugar if hepatic vein blood harbors more sugar than portal vein blood (Clark and Winter).

The superficial lymphatics drain the entire skin and the musculature of the body. The deep lymphatics drain the viscera. In the skin there are two capillary plexuses (networks) in the dermis, a superficial, finely meshed plexus almost devoid of valves, and in the subcutaneous tissue, a deeper, more coarsely meshed plexus. This deeper plexus is richly provided with valves that direct the flow of lymph to lymph nodes in the neck, the axillae (armpits) and the groin. The abundance of valves in these plexuses and in the lymph ducts that drain them means that there is no back flow of lymph as long as the valves are intact. The lymphatic plexuses are especially dense in the mucous membranes at the orifices of the body, at the finger tips, and in the foot pads. The vessels of lymphatic plexuses are extremely irregular in size—some being large and bulbous, and connected by tiny channels. There are frequently blind ones, with only one opening into the main plexus.

An abundant plexus of lymphatic capillaries in the muscle sheaths leads to lymphatic trunks along the veins; these trunks also drain into the regional lymph nodes mentioned above. Neither the plexuses nor the lymph trunks have any muscles in their walls to propel the fluid within these vessels. By placing a cannula in these peripheral lymph trunks, physiologists (Ludwig, Starling, Drinker) have shown that lymph is propelled in lymphatics only by extraneous influences, such as by muscle contraction during exercise, or by massage, and is entirely quiescent when the part is at rest.

The lymph nodes are small organs so constructed as to bring about a marked slowing of the flow of lymph. The lymph trunks are smooth-lined and the flow in them may be rapid but the channels for fluid in the nodes, called sinuses, are exceedingly complex and crossed by fibrous bridges covered with cells that have high phagocytic power, i.e., scavenger cells. It is as if a river flowed at certain places through a bog. This slowing of the flow of lymph in the nodes gives the phagocytic cells time to act. In these sinuses, extraneous cells that may be in the lymph stream, such as red cells, cancer cells, bacteria or debris, are filtered out and, besides, chemical changes in the lymph may be induced. These complex fluid channels surround masses of tissue formed by developing lymphocytes. Thus the lymph nodes have a double function—the formation of one type of white blood cell and an especial filtering of the lymph. All the fluid collected in lymphatic capillaries passes through one or more of these lymph nodes en route to the veins. When cancer cells are filtered out in the lymph nodes, they then multiply there and create new foci or reservoirs for their distribution in the body.

The lymphatic capillaries of the organs form very definite patterns, characteristic for each organ. Dr. Drinker has now cannulated the lymph trunks from the heart, the lungs, and the liver. Unlike the situation in the case of the superficial lymphatics, the fluid in these vessels is never quiescent. The flow of lymph from the liver is the most abundant and has the highest content of protein. The lymphatics from the small intestine are specialized absorbents for the fat taken in by the villi (folds in the intestinal wall). Thus the materials taken into the lymphatics of the viscera are more complex chemically than those in the superficial lymphatics. All of the lymph from the viscera likewise passes through lymph nodes, some of which lie within the organ itself and others in the chains of nodes along the blood vessels supplying the organ.

The central nervous system has a special mechanism for providing the abundant cerebrospinal fluid in which the brain floats, as it were. This system is not a part of the lymphatic system and its fluid drains into lymph vessels only indirectly through the mucous membrane of the nose.

The two terminal lymphatic trunks that connect with the veins, the right lymphatic duct and the thoracic duct, are asymmetrical. The duct on the right side drains only the head, arm, and chest, including the lungs (except the upper portion of the left) of that side, while the thoracic duct drains not only the corresponding parts on the left side but also the entire abdominal cavity and both lower limbs as well.

Preparation of Tissue for Microscopic Study

C. C. Little, Sc.D.

One of the most important steps in the diagnosis of cancer is the microscopic examination of a piece of the suspected tissue by a trained pathologist. The knowledge necessary to make such a diagnosis is technical and extensive.

The process of preparing the tissue for examination is, however, something about which officers of the Women's Field Army should be informed. You may be asked to help in the organization or support of a laboratory where such work is being carried on. You will be able to be more helpful if you understand the main objects of the preparation of tissue.

The first step in diagnosis is to procure a bit of tissue for examination. There are two times at which diagnosis may be required. One is *pre*-operative, the other is *post*-operative.

In the latter case a bit of the tumor mass is removed and is placed in a fluid known as a "fixative." Such fixatives are liquids able to penetrate the tissue rapidly and to prevent any decomposition or degeneration of its structure. There are many fluids used for this purpose. Each has its general value for all sorts of tissue and its peculiar value for certain types.

Since after being "fixed" in such fluids there is water present in the tissue, the next step is to drive this water out. This cannot be accomplished all at once. It is necessary to soak the tissue for a sufficient period in a series of alcohol solutions each progressively stronger.

When all the water is driven out the tissue is placed in a substance called Xylol. This is made from coal tar or methyl alcohol and is one of the benzenes. The function of this material is to permeate and "clear" the tissue, making it more translucent and susceptible to penetration. The tissue is then soaked in a melted paraffin which fills all the spaces in it. When thoroughly permeated with paraffin it is placed in a tiny box made of folded paper full of the same material and the paraffin is allowed to cool slowly. It solidifies into a block in the center of which is the bit of tissue. This part of the process is known as imbedding. When thus imbedded the tissue can be kept for years without change.

As the next step in preparing the tissue for study the solid block of paraffin containing it is trimmed with a knife until the outline and portion of the tissue is clearly defined and much of the superfluous surrounding paraffin has been removed. The base of the block is then cut smooth, warmed slightly and melted on to a flat metal disk which is attached to the end of a cylindrical steel bar.

This bar fits into a machine known as a microtome and holds the tissue in place by screwing it into position. When properly placed the block of paraffin has its outer edge just behind the blade of an extremely sharp razor edged knife. With one hand the microtome is then operated in such a way as to cause the part of the machine containing the block of paraffin to move forward 3 or 5 or 8 or more thousandths of an inch at a time. Each time it moves forward the tissue also moves up and down across the blade of the knife which thus cuts a slice of paraffin and of the imbedded tissue at the desired thickness. This is called "sectioning."

The thin transparent sections are then spread on a plate of thin glass known as a microscope slide. This will be their permanent resting place. They are fastened to it by a specially prepared substance.

Next the slice of paraffin in which the tissue was imbedded must be dissolved, a process accomplished by immersion in Xylol. Then the tissue must once more have the air and water driven from it by a series of baths in increasingly strong solutions of alcohol.

It is then ready for permanent staining. This is done by bathing it in different colored chemical dyes. Some of these stain all the tissue, others select different types of tissue or different parts of the cell or even different chemical constituents of the cell.

Staining makes it possible to see the structure of the tissue and of the individual cell under the microscope. It is a complicated and exact science which has been studied for years by scores and hundreds of skilled workers.

All of these steps consume a considerable period of time and have to be carried out very carefully and accurately.

When the tissue is stained as the investigator wants it to be, a drop or two of balsam is placed on it and a paper-thin cover glass is fitted to cover and seal it permanently. It is then labeled and so finally identified for study and filing.

This is the slower and more permanent of the two methods of preparing tissue. We may next consider a relatively recent method adapted for rapid diagnosis rather than for permanency.

In this method, which is often used while the patient is on the operating table under local anesthetic, a bit of the suspected tissue is removed and is placed on a metal disk which is held in firm position by a stem and clamps. Liquid carbon dioxide liberated as a gas from a metal tank where it is kept under high pressure freezes as it hits the tissue and also freezes the tissue itself. Thin slices of the frozen tissue are then cut with a razor edged knife and are at once stained for quick examination. It is possible in from three to five minutes after removal of the bit of tissue to bring to the operating room a reasonably accurate diagnosis of the suspected area.

The surgeon can then determine whether a localized or generalized excision of the tumor mass is required

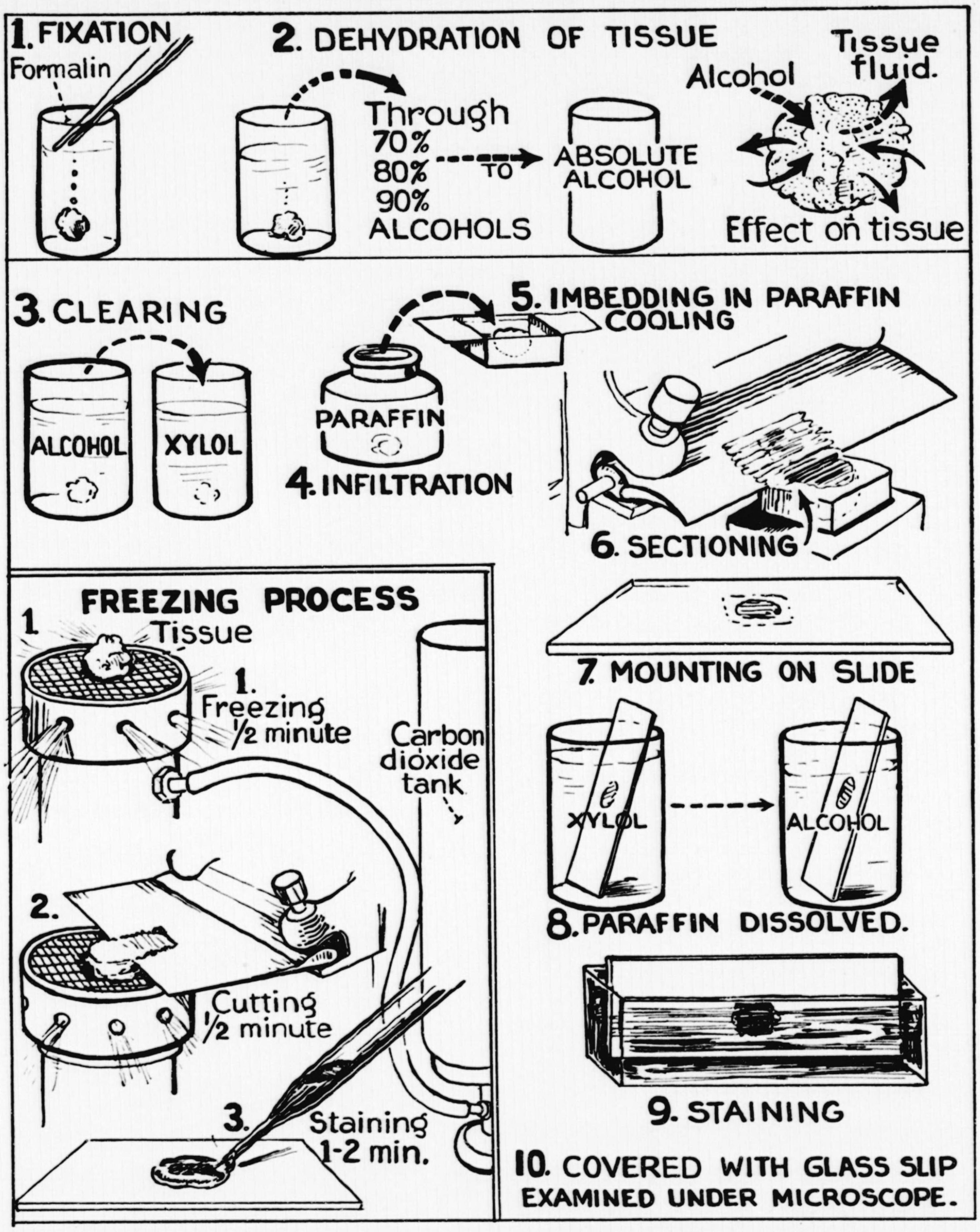


FIG. 30. The two methods of preparing tissue for microscopic study. A. Routine method, using paraffin. B. Freezing process—shorter method for obtaining quick diagnosis.

and can proceed with either type of operation, as indicated by the pathologists.

The availability of these two general methods of preparing tissue has been the foundation of the science of clinical pathology. The trained worker who can interpret microscopic conditions in terms of malignancy is an absolutely essential part of the accurate and effective diagnosis of cancer.

Conditions which superficially are very impressive and which sometimes seem to be certainly malignant from a layman's point of view are not *always* so when examined under the microscope. On the other hand, some nodules or sores that seem too small and insignificant to amount to anything may prove, on microscopic examination, to be early cancer in its removable stage.

This is why every intelligent layman should understand the principles of histology, the study of tissues, on which accurate diagnosis of cancer is based.

CANCER PREVENTION CLINICS

Within a relatively recent time there have been organized at least four clinics, the prime purpose of which is to detect cancer or signs and symptoms which may be considered as pre-cancerous. These clinics are an extremely interesting and important development in the field of cancer control. Their number will undoubtedly increase greatly in the near future. They will form an essential link in the chain of events necessary to reduce mortality from cancer.

The principle on which these clinics are organized is the physical examination of individuals who are entirely unaware that they have any symptoms or illness whatever. The idea is to encourage well individuals to report at fixed intervals for a physical checkup. Some of the existing clinics perform a complete physical examination and others limit their investigation to certain sites in the body where cancer is particularly likely to occur. It is not necessary to consider in detail the results obtained at these clinics, but certain general statements may be made and should be remembered.

1. A significant number of cases of early cancer have been found. In each case these have been discovered at a stage where treatment should be successful and eventual cure is almost certain.

2. A much larger number of cases have been discovered where conditions exist that can be relatively easily corrected, but which if ignored or untreated may very possibly lead to the formation of cancer at a later date.

3. A very large number of symptoms of diseases other than cancer have been found. These include early stages of diabetes, early tuberculosis and a number of other conditions. Here again the chance of eventual cure of the patient is greatly increased by the fact that the situation has been discovered before it gave evident symptoms.

4. The individuals coming to the clinic have been as free as possible from the handicap of fear and have been given a feeling of reassurance and confidence because the majority of them still show no conditions which need any treatment whatever.

5. The movement is directly in line with the best principles of preventive medicine and public health in that it arouses individual responsibility and increases the interest of the individual in maintaining his or her physical fitness at a high level.

6. Because the detection of conditions that need further diagnosis and possible treatment is a matter in which the general practitioner can participate, it seems probable that the extension of the prevention clinic idea will prove to be a natural and happy method of enlisting the interest and support of the general practitioner. His contact with the cancer problem up to the present time has been none too satisfactory. He has usually seen more or less advanced cases and since he cannot treat many of these himself he has developed a somewhat fatalistic and pessimistic attitude.

7. The support and development of cancer prevention clinics is a matter in which all intelligent lay people can cooperate and toward which they can make a real contribution. It requires no special knowledge to appreciate the validity of the principles involved. Lay individuals can and must continue to supply these clinics with the patients who are willing to adopt a progressive and modern attitude toward their own health.

The amount of good that can be done by a broad extension of this work is incalculable. The American Cancer Society has the matter under study and is developing, with the assistance of the American College of Surgeons and others, standards under which such clinics should be organized and operated. This will insure a proper level of work and will prevent the abuse of opportunity by unscrupulous or untrained individuals.

Why Do We Have Cancer Hospitals?

JAMES EWING, M.D.

The late Dr. James Ewing occupied a unique position in the field of cancer control. For years he was the active and tenacious advocate of the special cancer hospital as the best way of organizing the available knowledge in diagnosis and treatment of the disease.

Largely as a result of his efforts the Memorial Hospital, while situated in its old building at 105th Street and Central Park West, developed to a point where it convinced everyone of its fundamental value and significant potentialities. The new Memorial Hospital at 68th Street and York Avenue is a definite proof of this fact.

In the short talk which Dr. Ewing gave at the Women's Field Army School he discusses cancer hospitals in an interesting and stimulating way.

WHY do we have cancer clinics? The answer requires us to go back as far as 1802, when a wealthy Englishman financed a ward for cancer patients in the Middlesex Hospital, London. Even at that early date it was realized that special problems develop in the care of cancer patients. I think this was the first definite step taken to meet them. What the record of the early clinic in the Middlesex Hospital was I do not know. It didn't function very effectively, but the English profession have always been keen to the necessities of the cancer problem so that it is quite natural that many years later the London Cancer Hospital was built, for two main purposes: First, to meet the demand for special care of the cancer patient, which was uppermost in the minds of its founders, and second, they were very much thrilled over the possibility of finding the cause of cancer, which in those days was believed to be a parasite.

The first work of the London Cancer Hospital in this research field was directed toward the parasite of cancer, which we now know does not exist. However, they have always maintained a high level of an active service for the cancer patients, so it is a clinical institution. In recent years, I am happy to say, that the research staff of the London Cancer Hospital has contributed more than any other institution in the world to our fundamental knowledge of the origin of cancer. Dr. Cook and Dr. Kenaway discovered for the first time a specific substance, a coal tar product, which, when applied to animals, as you probably saw at Bar Harbor, produces cancer or sarcoma in almost every instance.

In the decade 1880-1890, there was a wave of activity in the foundation of special cancer institutes, the Memorial Hospital in 1884, the Buffalo Institute in 1886, the New York Skin and Cancer Hospital about the same time, about 1900 the Barnard Skin and Cancer Hospital in St. Louis. In Europe there was a special hospital developed at Heidelberg. All of these were distinctly service institutions, but I suspect that most of them, especially in this country, were stimulated with the idea of grand results in the discovery of the cause of cancer.

The later developments have come from different reasons. In 1900 began the era of experimental cancer research when it was discovered that cancer in animals is transferable.

You see to what size that field has grown in the laboratory at Bar Harbor. It became necessary to provide, on a large scale, laboratory facilities for the experimental study of cancer and that would best be done, we thought, in connection with a Cancer Hospital, so that all the institutions since 1900, as I have mentioned, provided considerable facilities for experimental study and always carried a large rat and mouse colony, as well as chickens, rabbits and guinea-pigs.

Another event of first importance in the history of cancer control occurred in 1899 and 1900, the discovery of radium and x-rays and when it was found they could influence the course of cancer favorably and in many cases cure it, it became necessary to provide extensive equipment in the form of radium and x-ray machines. I can acknowledge many a heartache in my experience in these last forty years in finding the money necessary to provide the radium and the x-ray machines, ever increasing in size, bulk, and cost. The last x-ray machine installed in this institution cost $50,000.

It was quite impossible for general hospitals to provide this expensive equipment in radium and x-rays and, in addition, they had to provide space. So the experimental study of cancer and the necessity of providing radiation therapy and research in radiation physics, combined to make it essential for our knowledge of cancer, to build special cancer hospitals.

One of the first of this newer type was the Radium Hemmet at Stockholm, a very distinguished institution. Then came the Radium Institute in Paris, all of which are doing fine work and stand high in the field of modern cancer experimentation and therapy.

Now, how did the medical profession take this development, because this movement meant that a large proportion of the cancer cases would be turned from general hospitals into these special hospitals. Therefore, the practice of surgery would be deprived of one of its largest fields of activity.

I have to admit, good naturedly, that the surgical profession was opposed to this innovation in almost every instance, although it was also necessary to say, and I say it with great satisfaction, that this new movement for cancer hospitals was sponsored very actively by some of our leading American surgeons, including Dr. Kelly of Baltimore, who has a cancer institution in Baltimore.

Dr. Clark of Philadelphia was one of the leaders and Dr. Abbe of this city. You will find in all cities where there are cancer hospitals the surgeons have been active in developing them but the general feeling of the surgical profession was that it wasn't necessary to have cancer hospitals. They didn't like cutting across established rules for the disposition of cases, and it was very inconvenient, and they didn't see why they couldn't do just as good work in a general hospital as in a cancer hospital. You will see how that comes out later.

However, in 1925, the American College of Surgeons appointed a committee to survey the situation for cancer service in this country, and as a result they approved of the establishment of large cancer hospitals in large cities, and the organization of special cancer clinics in all general hospitals. This had a very important effect upon the development and improvement of cancer service. These organized cancer clinics in general hospitals meant that all the free cases and voluntary private cases of cancer should be referred to a central committee that would pass upon the diagnosis and direct the treatment.

To carry out this program, it was necessary to have a well-organized staff of clerks, history taking, and standard methods of dealing with particular problems. An experienced tumor pathologist was required, and in order to bring about these arms of the service, it required a good deal of activity. This demand has been met with remarkable success, so that we have today about 400 special tumor clinics in the general hospitals of this country.

Another step of very great importance grew out of the development of the special cancer hospitals. The larger cancer hospitals, like Memorial and the Radium Hemmet at Stockholm, can exist only in large cities where there is a large population. What is to be done for the smaller communities? They can't all come to the big cities, it would be too expensive, and there aren't doctors enough in the special cancer hospitals to care for them all. This problem was solved again by the College of Surgeons, through the support of the several state governments, notably the State of New York, in undertaking to establish well-organized cancer clinics in all the moderate-sized cities and communities.

These cancer clinics were sponsored and subsidized by the State which furnished a salary for the director of the clinic. The director of the clinic was some young man who had experience and special training in a cancer hospital and was able to direct his associates in the proper methods of organization. He was to gather about him the various local surgeons and interest them in the modern problems of cancer diagnosis and treatment. It was necessary again to have the record system developed and to be sure that there was a good pathologist available for diagnosis. This required a considerable amount of energy on the part of the local profession, and in some communities it was not met with great enthusiasm, I will tell you what happened in one community.

About seven years ago they decided to establish a cancer clinic in Vassar Brothers Hospital in Poughkeepsie, and one of our graduates, Dr. Farrow, was sent up there by the State, at a salary of $1,000 a year, to organize a clinic. He found very little support. The hospital authorities said, "Well, we haven't any cancer patients here. We haven't any means of treating them." In talking to the pathologist, he said, "I know very little about cancer, and I see so little of it that I am not really interested in it."

The Board of Directors of the hospital said, "We can't afford any added expense." Nevertheless, they thought they would try it. Well, first he secured by contributions from the people of the city of Poughkeepsie enough money to buy an x-ray machine. He induced the pathologist to come here and spend two or three months in running over cancer material, and we assured him of our support in difficult diagnoses. We managed to secure the active support of one or two of the surgeons, most of whom at first thought the project would fall through.

At the end of the first year, they had dug up 75 cancer cases in the city of Poughkeepsie and surrounding territory, although the previous year they had only about a dozen. These cases were neglected, advanced cancer cases. In the second year their attendance doubled. In the third year, the reputation of the clinic was passed through surrounding counties and they began to draw cancer cases from three or four counties. The weekly clinics were attended by about thirty physicians. They developed excellent diagnostic skill, the records were fine, the people in the community were interested, the social service was organized, contributions came in in considerable quantity, and the general business of the hospital greatly increased. Today they are sending out nurses through surrounding counties, Dutchess County and others, who dig up early cancer cases, and there has been quite a transformation in the character of material in this seventh year from what it was in the second year when all cases were late.

So there is a complete transformation of the cancer situation in that group of counties that has been accomplished in that period by the simple development of an enthusiastic group, well organized as a local cancer clinic.

There are fourteen of these clinics in this State. The State Department of Health is attempting to establish them as rapidly as possible where local conditions will permit. This is an outgrowth of the special cancer hospital.

What are the reasons, the ultimate reasons for the existence of a special cancer hospital? Let us consider how it works. In the first place it provides a large material in the different forms of cancer so that it is possible for individual surgeons to specialize in different fields and not to attempt to be a universal cancer expert.

In this institution and in the others that I have mentioned, you will find six to ten different departments, staffed by three or four men who do nothing but the work of that department. There is the head and neck department, diseases above the shoulder. There is the breast department, the gastric, bone sarcoma, and so on all the way down. They are busy, because of the large amount of material they have to handle.

Some may say that the surgeon must find it very dreary to be doing nothing but stomach work or breast work or intestinal work. Well, it isn't dreary at all, because when you get material of that extent under proper circumstances, the opportunities for investigation and improvement are quite adequate to satisfy the intellectual ambitions of our most brilliant doctors.

As a matter of fact, this type of specialization is nothing new. For fifty years or more the leading men in the profession, especially surgery, have been specialists—brain surgery, stomach surgery, everywhere the record of eminent men includes, for the most part, those who specialize in special fields. This idea of specialization in cancer is nothing more than the adoption in our field of previous experience. Experience teaches as nothing else does.

What are some of the advantages of this specialization and concentration of cases? One of them is that you come to an entirely different conclusion about the best method of treating different diseases, and you become more skillful in those methods.

I like to recall the contributions made by a distinguished Philadelphia pathologist a few years ago reporting on tumors of the salivary gland, rather common tumors. He collected 360 cases of tumors of the parotid gland, and reached four definite conclusions regarding their treatment. Now, those four conclusions were all diametrically opposite to the conclusions reached by men in this institution and the Radium Hemmet at Stockholm and the Radium Institute in Paris, where all the cases of the salivary gland tumors are treated by one group of men. What was the reason? The reason was that the cases, 360, were gathered from 90 different operators, and over a period of twenty years. Ninety operators saw 360 cases in twenty years, four for each operator in a period of twenty years. How long will it take the ninety to learn how to operate on that particular tumor? I would say about a hundred years. That is the way it works in other fields, too.

Some years ago Salstein of Detroit found by accurate, careful observation that the operative mortality for rectal cancer in nineteen American cities of over a hundred thousand population was fifty per cent—every other patient who came to the hospital died on the table, or as a result of the operation. That was not very much inducement to make a diagnosis of rectal cancer. At that same time, the operative mortality for a few specialists in this field ran between fifteen and twenty per cent, sometimes as low as ten. To-day it is about 2 per cent. The reason was that they were more skillful in choosing their cases, preparing them for operation, and in technical skill.

The last hundred cases of rectal cancer operated on in this hospital have been carried through without a single death. Yet we may have a series of fatalities unexpectedly at any moment. So then as a result of specialization, training, experience, preparation of all sorts, the complete transformation and outlook for the patient with rectal cancer is good. In Cleveland, probably the leading American specialist in rectal cancer has another series of over a hundred cases operated without a single operative death. In other words, in order to give the cancer patient a square deal, it would seem that in the majority of cases, the outlook is very much better if they get in the hands of a man who has had experience. That is the service end of it.

Now, there is another, and even more important consideration. Unless the doctor knows just exactly what he is dealing with, how can he guide his method of treatment? If he has a diagnosis of one disease that isn't correct, of course all his efforts are misdirected. The accurate diagnosis of the case depends on the Department of Pathology, and the pathologist, and here is a field in which nothing but experience teaches. It is a matter of a lifetime of experience to be able to tell from gross examination of microscopic structure just what sort of disease the patient has, and this is the job of the pathologist. There are endless variations in structure which must be interpreted by the microscope, and can be interpreted only by an experienced pathologist. Where will he get his experience unless he picks it up? The average general pathologist in America is very well acquainted with tumors, but he has probably 15 per cent of cases which puzzle him and he doesn't know what to say, and there is another 10 per cent in which he is in error.

In a special cancer hospital where there is a vast amount of material, experience multiplies rapidly, and I think I may say, from my past experience of fifty years in this field, that the opportunities for accurate diagnosis are so far superior in a cancer hospital than in a general hospital that there is no comparison. Last year in this institution Dr. Stewart carried through over 10,000 special microscopic examinations. Many of them were difficult. He had consultations, but generally, after comparing with previous cases, looking over our records, we are able to locate the case and tell just about what it will do clinically, advise the surgeon whether it would respond to radium or whether he should make a very radical operation or only a limited operation.

We find that refined pathological diagnosis lies at the bottom of successful cancer therapy in every institution, and in my experience it is best attained in a large institution, and possibly only attainable in a large institution where the material is very large and varied.

The next point is education. How are we going to educate doctors—send them out to a general hospital where they do every possible type of work and see a cancer case only occasionally? That is the way it has been done up to date. The result is, the only men who are developed in cancer fields in general hospitals are men who have had very large experience and have eventually specialized in this field. Undergraduate students see very little about cancer in most institutions, and in most colleges. It is very much neglected, considering its importance, but with the vast material, in such an institution, as this and others, we get the fourth-year students from Cornell and we give them one month intensive training, in this hospital, 160 hours of solid work during the month. They are all enthusiastic; it is the most popular course in the fourth year, and in that time they see something of every department in the institution and know what is going on in the cancer hospital and acquire a correct attitude toward the subject. They realize its scope; they realize the methods by which the problems can be dealt with.

How about obtaining special men to go out in other communities? Through the generosity of Mr. Rockefeller, we have a substantial fund by which we maintain about twelve clinical fellows, who spend three years in this institution after having had a good surgical training in other institutions, who pass through all the different departments and become acquainted with what is going on in the different departments of the institution, in the different fields of cancer.

In addition to that, we have a very large visiting list. There are five or six pathologists here all the time. Sometimes the visitors are so numerous that the attending physician can hardly get at the patient. We are fortunate in having just now a very considerable influx of very able men from the South American countries, and we have their patients, too. We hope some time that the South Americans will be able to compete with us so that their wealthy patients will not come to New York and other institutions, but will be treated at home. That permits me to interject that the South American countries have accepted the idea of the special cancer hospital with great enthusiasm. They have built some magnificent institutions, although they are somewhat small in scale. The most beautiful of all that I know, a marble and granite structure, is in Lima, Peru. If you ever go there, by all means see the magnificent cancer hospital.

It is in the field of education, that many think that perhaps this institution and others like it are doing the best service. There are opportunities for education of students, practitioners, specialists, pathologists. I might say that the same advantages coming from large amounts of material apply to laboratory work. If our various laboratories in the x-ray department, physiological department, endocrine department, and many others, want human materials, as they should want and do want, they have plenty of it here in all the phases of cancer.

Right here I would interject another discordant note, and that is, it is my feeling that the most practically productive work in cancer research is generally connected with a cancer hospital. In addition to the very important fundamental work in which Dr. Little is such a distinguished leader, there is the other field of clinical research, a very large field, and it is largely through that field of clinical research, observation of cancer in the human being, that the improvement in the treatment of cancer has occurred, and in my opinion, I think history will repeat itself.

So then we have several different forces, all combining to render the existence and future of the special cancer hospital assured. I hope to be able to live to see half a dozen great cancer institutes planted in different large cities throughout the country. The movement is growing slowly; it has been retarded by war and economic conditions, but I think we shall see it in the next twenty-five years.

There is just one final problem, which is a practical one, for the women of the Field Army*. What are you going to do in your communities? You can't send all the patients to the Memorial Hospital, you don't want to; we have all we can handle. You can't send them to Boston. They are pretty full in Boston. The same with Chicago and all the large city institutions.

What are you going to do in smaller cities? The answer is the local cancer clinic. The hospital is ready, and most states are ready to lend support for the establishment of equipment in well-organized cancer clinics, managed by local medical men in most communities where they are needed. They are willing to put money into it, and all that is necessary, I think, is for the women of the Field Army to cautiously, not too aggressively, but cautiously, use influence in that direction. If you haven't such a clinic at present, what are you going to do with your cancer patients? If conditions are favorable, I advise that a cancer patient who requires a major operation be sent to some special institution in a large city. Most of the patients are sent in that way, in some manner or other, to the large city. If that isn't possible, then he can take his chances with the local surgeon. I don't depreciate the significance and skill and energy and devotion of the local surgeon, but I merely say it is quite impossible for any general surgeon to be equally competent in all the fields of this great disease.

This, then, would be a practical problem for the women of the Field Army*, and I trust that you will lend your influence to the provision of treatment facilities in your community as perhaps one of the most important immediate responsibilities that you will enjoy.

*The reference here to the members of the Field Army applies with equal propriety to any and all who desire to take an active part in the fight against cancer. Ed.

Some Facts About X-Rays and Radium

Edith Quimby, D.Sc.

Irradiation with x-rays or radium is one of the highly effective types of treatment of cancer. Formerly looked upon as a competitor of surgery, it is now recognized that the two treatments are allies and *not* opponents.

Dr. Quimby discusses the conditions under which irradiation therapy is employed and describes its general nature in a most interesting and valuable way.

Because irradiation has a powerful effect upon all living tissue many persons who distrust the medical profession or who are opposed to any type of medical therapy seize upon this fact to decry the use of x-rays and radium. Their point of view is illogical and dangerous. It is utterly unsound to emphasize the undesirable properties of any agent used in medicine when that agent under proper conditions is saving lives. To protect yourself, the workers with radioactive agents, and the health of the public, you should be informed of the facts. You should be not only acquainted but familiar with the subject matter of Dr. Quimby's paper.

I have been asked to tell you about a certain aspect of cancer therapy which perhaps may be novel to a good many of you. You all know, I am sure, that there are only two means at the present time of curing cancer. One is surgery and one is irradiation, either by x-rays or the rays from radioactive substances.

The method by which surgery accomplishes its purpose is obvious. It simply cuts out the offending cells, when that is possible. The method by which radiation accomplishes its purpose is not at all obvious; in fact, it is very little understood. We know the first step; we know the end results; what happens in between is at present a subject for a great deal of research. What I have to tell you, then, is in the nature of a sketchy introduction to the reason why radiation may cure cancer.

It seems to me that it should be a good idea to get a little bit of the background of the story of x-rays and radium before plunging into an idea of how they work. The whole subject of radiology is less than fifty years old as compared with hundreds of years of surgery, so that it is perhaps not surprising that radiology has not become as well established as surgery is in some respects.

It was a little less than fifty years ago that Roentgen, Professor of Physics in the University of Wurzberg, discovered x-rays. He was studying phenomena in vacuum tubes. Now, vacuum tubes are simply glass tubes into which two electric terminals are sealed and from which most of the air has been pumped. When a high electric voltage is put across the terminals, some sort of discharge takes place in the tube, its nature depending on the degree of vacuum. You are all familiar with them in the form of neon signs which used to be everywhere before we started to have dim-outs. A neon sign is a vacuum tube which has a little neon in it. If there were air, it would be pink instead of red; if there were something else, it would be green. If the tube is pumped out to a better vacuum, the light disappears, the glass walls of the tubes shine, and Roentgen got the idea that something might come out through those shining glass walls. Because of the light from the tube he could not see whether anything was coming out, so he wrapped his tube up in black paper. Then when he turned on the electricity with his tube thus enclosed, a screen treated with fluorescent material glowed in the dark. He knew some sort of radiation really was coming out of his tube. He put more black paper around it, and the glow persisted. He put a book between the tube and the screen, and it still glowed, although not so brightly. He put a piece of metal in and the light

Fig. 31. Wilhelm Conrad Roentgen discovered x-rays in 1895 while carrying out experiments in physics in his laboratory in Wurzburg.

disappeared; he put his hand in, and to his surprise, he saw his bones surrounded by flesh. That was the first fluorscopic examination.

Then he found very promptly that such records could be made permanent on a photographic plate. Thus Roentgen discovered and established the existence of x-rays.

His first papers are amazing examples of scientific research because in the first few weeks before he really published anything, he made preliminary observations on almost all of the things that we have spent the next forty years trying to work out in detail.

X-ray tubes, since Roentgen's day, have been improved enormously, naturally, but they remain the same in principle. Present day tubes are, of course, more powerful and more efficient. The higher the electric voltage across the tube, the more penetrating is the radiation. That is one reason why we continue to strive for higher voltages. The first x-ray tubes that were used for therapy were operated at less than 100,000 volts. The radiations from these would only go a very short distance into the tissues. Then we developed 200,000, then 400,000, and now you hear about 1,000,000-volt machines, and in the last few days the newspaper has reported something about a 3,000,000-volt machine. We don't know what the limit will be, but further increases are probable.

Roentgen published his observations in the fall of 1895, and immediately scientists all over the world started checking his results. In France at that time two scientists got a bright idea, which turned out to be a completely wrong idea, and yet which led to a very brilliant discovery.

I said a minute ago that when the vacuum in the vacuum tube got sufficiently high, the walls of the tube fluoresced, shone with a bright light. Poincaré and Becquerel, at the University of Paris, thought that possibly some of the substances which were known to fluoresce in nature under the action of sunlight might sumultaneously give off some of these same invisible radiations; they decided to investigate the matter.

What they did was to take some of these fluorescent minerals, put them on a tray with the photographic plate wrapped up in black paper, expose them to the sunshine, and after awhile develop the plate and see what they had. To their delight, they got some blackening of the plates, so they thought that these fluorescent minerals were giving off invisible rays, due to the fluorescence. Then one day, for some reason, after everything was all prepared, the sun didn't shine. The material was put in a drawer, and finally the plate was developed without the sun ever having shone upon it, and there was the picture just the same. It was obvious that the fluorescence had had nothing whatever to do with it.

I have here the sort of thing which was the record that Becquerel obtained. In this bottle is a little uranium ore, the type of material that he was experimenting with. I took these two pieces of yellowish rock out of the bottle, placed them on an x-ray film wrapped in black paper, and left them there for several hours. A print from the film shows the self-pictures of these little pieces of rock. This was just such a record as Becquerel found when he proved that certain minerals did give off these invisible rays, that they gave them off without fluorescing, and without any previous treatment. That was a discovery which, as I say, came because of a brilliant idea which was a bad one.

It was at this stage that Madame Curie came into the story. She was a student in Paris, and like all other physicists at the time, she was very much interested in these phenomena. She asked permission to go ahead and study other substances to see if they produced these radiations. In the next months, she studied every known element and compound. That was a big job, but not as big then as it would be now because we know about many more substances. She found that every compound of uranium and every compound of thorium, and no other substances possessed this property, which she called radioactivity. Furthermore, she found that some uranium ores from Austria were much more radio-active even than pure uranium. It appeared that this material must contain a hitherto unknown element. At this stage her husband got so interested in her work that he stopped what he was doing and joined her researches. They got a lot of this material and worked on it with all chemical processes, pulverizing, dissolving, precipitating, and they finally found out that they had not one, but two unknown elements which were very radio-active. They knew there were two, because one went with a certain series of chemical reactions and the other went with the other.

The first one Mme. Curie named polonium, in honor of her native country, and the second one she named radium, because it was so extremely radio-active.

Since then there has been a lot of talk about finding mines of pure radium, and every once in a while one reads a story based on somebody having found a radium mine. It is not possible ever to find radium in the pure state. We have not time to explain this, but we know that radium must always be mixed with at least three million times as much uranium.

Radium rays and the rays from an x-ray tube do all the same things, so that from the point of view of knowing how they work, we can study either radium rays or x-rays, and we will come out with the same answer. What we find about one, we can apply to the other. (See Figs. I, J, K on inside back cover.)

Now, I said in the beginning of my little talk that I was going to try to tell you a little bit about why or how these rays acted to cure cancer. The only way that anything can be made to happen in this universe is by the expenditure of energy, and, therefore, somehow or other the rays must transmit energy to the body cells. They do this by means of a process which we call ionization. In order to understand what we mean by ionization, we have got to know a little bit about the structure of the material that makes up the cells.

Many of you doubtless know that all matter is made up of compounds of the elements, of which there are 92; that the simplest, smallest particle of any element that we can get is an atom, that when atoms of different elements combine together in certain ways, we get compounds of different substances and that the smallest elementary particle of the compound is a molecule.

When the atomic theory was first accepted, atoms were believed to be just little, hard, golf balls or chunks of matter, small and indivisible. We know now that an atom is something much more complicated than that. An atom is really like a miniature solar system. It has a nucleus which contains most of the material of the atom and which has a positive electric charge. Then around the nucleus in orbits are systems of electrons, each electron being a negative electric charge, so that the normal atom is electrically neutral.

The amount of material in the nucleus and the number of electrons determine the chemical nature of the atom. When atoms come together in compounds, it appears that the nuclei occupy certain relative positions and that some of the outside orbital electrons appear to function somewhat in both of those atoms to hold them together.

The normal atoms or the normal molecules are electrically neutral. What happens when a beam of radiation passes through this matter is that some of the electrons are torn away from some of the atoms or some of the molecules. We could liken the process perhaps to a hail storm in an orchard. The hail storm comes into an orchard of cherries or plums, or something of that sort; some of the fruit is torn off the trees, and more of the fruit is torn off from the upper branches than from the lower ones because the hail stones have lost energy as they come down. Similarly, when a beam of radiation comes into matter, some of the electrons are torn out of the atoms and more molecules in the superficial layers of the tissue are damaged than in the deeper layers, because this hail storm of energy, these radiations, lose energy as they go down. Thus the nearer to the surface, the greater the damage which can be produced in the human body by the beam of radiation, and this damage is simply the tearing of electrons out of the atoms.

Now, while an atom or molecule is in this ionized condition, things can happen to it that don't happen to it normally. Complicated molecules can break down into simpler ones, and most of our body cells are made up of complicated molecules, such as protein molecules. These may break down this ionization, and it is because such reactions occur in the cells that changes take place.

Ionization is a very transient phenomenon. In this respect, ionization is different from the damage in our hypothetical cherry orchard, because once the cherries are off the trees, they don't go back, but when the electrons are torn out of the molecules, they do go back, not necessarily to the same atom they came out of, but they go back, and the normal neutral configuration is resumed; it is just during this transient period of ionization that things start to happen. However the reactions thus initiated may lead to profound changes.

In a beam of radiation traversing the body, at any given instant, billions and billions of molecules are in the ionized state. The more the x-rays, the more the molecules are ionized. If only a few billions of them are ionized, recombination may take place, and it may never be evident that anything happened in those cells, but if more are ionized, more changes may take place and a damage may occur to the cells, from which there may be recovery. If irradiation is pushed still further, the damage may be so great that there can be no recovery in one or a few cells, and if enough cells are damaged, there can be no recovery in a particular tissue.

The visible effects of radiation are that within the cell the protoplasm becomes more acid, the cell membranes become more permeable, so that things can go in and out through them, the protoplasm becomes granular, the chromosomes become fragmented, the cells stop dividing. At that stage recovery may ensue, a cell may stop dividing for a time and then recover and go on dividing, or it may die and just cease to exist. If only a few cells in a given tissue die, there may never be any evidence of it. If even a good many die, there may be gross recovery, just as when you cut yourself or scrape the skin off there is complete recovery. You don't miss those cells because the neighboring cells have proliferated and filled up the place. However, if enough cells in a given region are killed by this process of ionization and its subsequent results, then the tissue is damaged irreparably, and there will be just an empty place in the tissue left which will remain as a permanent defect, unless it is repaired surgically.

At the present time that is, in a general way, all we know about how radiation acts to cure cancer. Thus you can see we know the first step, we know what it leads to, and what we are trying to find out now is a little more of the detail about what happens in different cells. We do know this: Some cells are much more radio-sensitive than others, that is, it takes much less radiation to kill them.

If we had a tumor or a cancer in the surface of the skin which was more radio-sensitive than the skin itself, then we could irradiate the whole region to such a degree that the cancer would be killed and the skin would recover. If the cancer were situated underneath normal tissue, then it would have to be much more radio-sensitive than the skin, if it were to die and the skin and upper normal tissues were to recover. Sometimes we can avoid killing all the surrounding normal tissues by what we call cross-firing. For instance, if we have a cancer in the mouth; we can direct beams of x-rays from each side of the neck, and possibly also from the front or back, so that we go through several skin fields, centering all the beams on the tumor. You cannot focus x-rays like you can focus light, but you can center the different beams on the cancer and so build up a dose in the cancer itself which is greater than that on any one skin field.

It has also been found that if a given amount of radiation is delivered in small doses over a good many days, the body as a whole and all the individual tissues tolerate it better than if it is given all at once in one big dose, but it has also been found that in the case of some radio-resistant conditions, apparently the difference between the radio-resistance of the tumor and of the skin is greater in this divided or fractionated dosage, so sometimes therapy is better if it is given in a series of small doses than if it is given all at once. There is no rule to decide in which kinds of cancer this is the case. Every type has to be studied clinically to find out what is the best way to treat it. This we cannot do in the laboratory. Decision as to the best method of treatment must be the result of clinical trials of different methods.

There are a few facts about radiation therapy that everyone should know who has any possibility either of being irradiated or of having friends irradiated, or day after day, and pretty soon the skin where the radiation goes through begins to get sore. If the cancer is deep-seated and radio-resistant, he must be treated to the point where all those skin fields may actually become blistered, and painful. Now, this is a normal x-ray reaction, and it is too bad that so many people have talked about it as an x-ray burn. "These are burns and they are terrible," says some one who is untrained or unwise. They are normal reactions and they are not terrible. This notion has been fostered by doctors who don't appreciate what x-rays are. A good many people, both in and out of the medical profes-

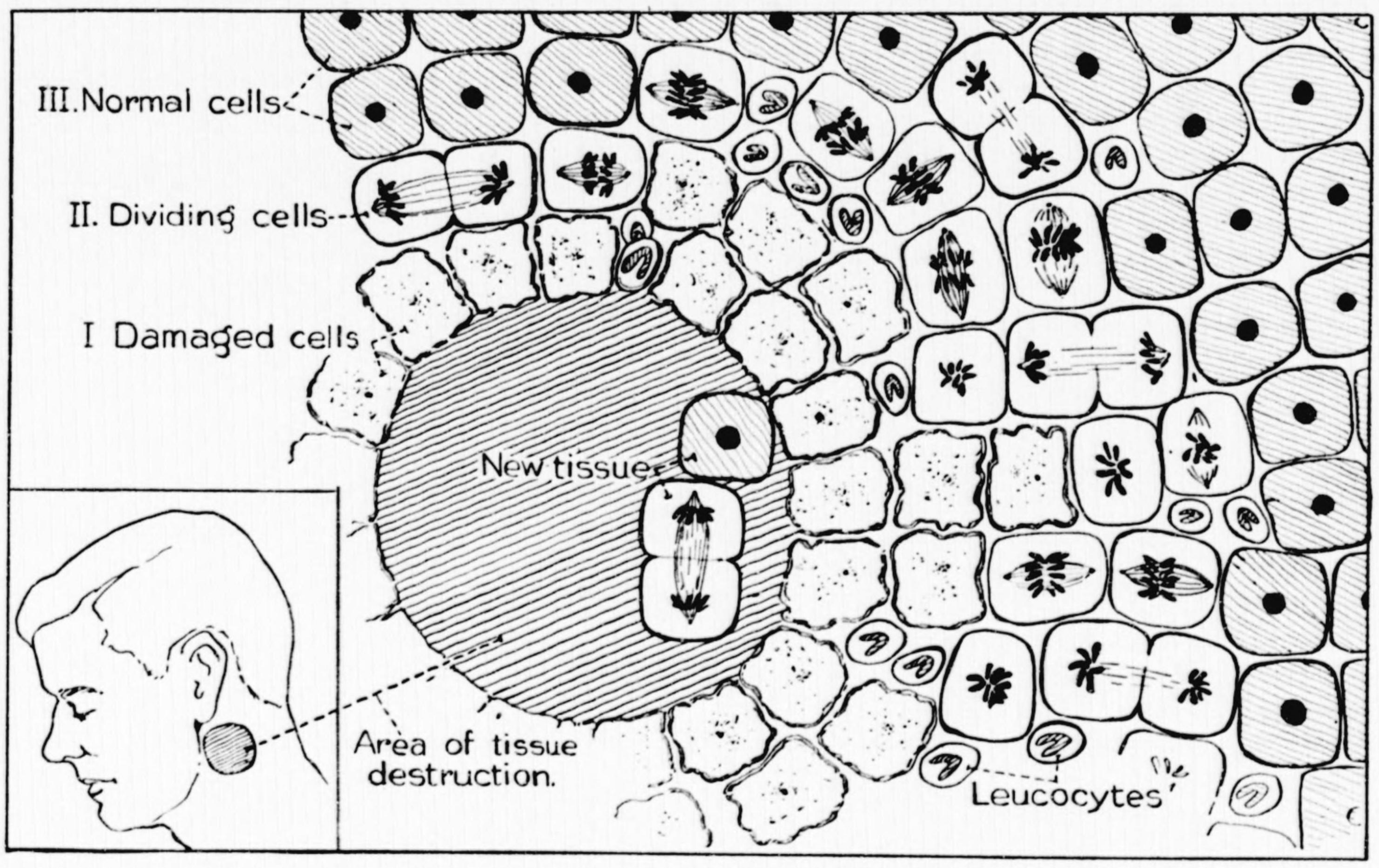


FIG. 32. In treating deep-seated cancers, for example cancer of the tonsil, the section of skin through which the x-rays penetrate sometimes blisters, as in a severe sunburn. As with sunburn the cells regenerate, forming a new layer of skin as shown in the diagram above.

having anything to do with it, because there is a lot of misunderstanding abroad about it. In the first place, during the actual irradiation, there is no sensation whatever. A lot of people have heard about x-ray burns until they think they are going to get under an x-ray tube and really be cooked. There is no sensation of heat. There is no sensation at all. With old-fashioned x-ray machinery there used to be a lot of noise and a lot of sparks, causing a smell of ozone and the equipment was big and rather terrifying. The patient was often rather distressed by some of these incidentals. Nowadays a patient undergoing x-ray treatment lies in a comfortable bed under an apparatus that doesn't look too formidable. He may not even know when the x-rays are turned on or off. However if he is being treated for cancer, he may have to have many treatments, treatments day after

sion, seem to think that x-rays are little magic things, that you can just sprinkle a few x-rays on a cancer and away it goes. This is typified by the sort of instructions that we used to get. We don't get them so much nowadays. A doctor would send a patient for x-ray treatment and say, "Please give this patient a good dose of x-rays but don't redden the skin." Now, what do you think a surgeon would say to a doctor who sent a patient to him and said, "Please cut out this tumor but don't cut into the skin in doing it"? There is just exactly as much sense to that remark as to the other. It is just as silly to say, "Give a good dose of x-rays and don't redden the skin," as it is to say, "Operate on this patient and don't cut the skin."

A patient expects to be sick and uncomfortable after major surgery; that is the normal thing. A patient must expect to be sick and uncomfortable after

..ajor irradiation. That is also the normal thing. Even ..o, in general, major irradiation doesn't mean the hospitalization or the difficulties that major surgery does, in a great many cases. So this is one thing that you can help to allay, the terror of x-ray burns. We aren't getting x-ray burns; we are producing normal reactions. They are uncomfortable, and they are a phenomenon in the skin which looks like a bad sunburn. Nobody thinks a sunburn is so very terrible. Recovery after these x-ray reactions is slower than recovery after a sunburn, but it is the same sort of thing.

To summarize the purpose of this informal discussion, I have simply wanted to give you a little bit of the background of what x-rays do in the treatment of cancer, and to try to pass on to you the idea that radiation is, in proper hands and properly used, a very powerful weapon against cancer, and in the wrong hands, it is just as dangerous as a knife in the wrong hands.

The Diagnosis and Treatment of Cancer

LLOYD E. CRAVER, M.D.

In those cancer clinics that have developed a well-rounded picture of what the diagnosis and treatment of this disease involves, the role of the internist is being increasingly recognized as of prime importance.

Not only are those of the profession who practice internal medicine in a key position for recognizing many of the significant signs and symptoms of cancer. They are also basically involved in the maintenance of the patients' health during and after many of the types of rigorous treatment which cancer requires.

Dr. Craver, in his work at the Memorial Hospital, is in a unique position to describe and analyze what the internist can and should do in the problems of cancer control.

His paper is a very human and very interesting description of a progressive and enlightened attitude towards this question.

FIG. 33.

I THINK perhaps I can best preface my remarks by narrating a story of a patient who came here just a few months ago. This man, referred to us from another hospital, had developed symptoms of obstruction of his small bowel. Because of those symptoms, the surgeons at the other hospital had found it necessary to operate upon him. They opened up his abdomen and found a tumor obstructing the small intestine, and removed it, performing at the same time the necessary repair of the intestine. The pathologist at this other hospital diagnosed the tumor as an adenocarcinoma. The man was all right then for a few months, but after that time again developed symptoms of intestinal obstruction, and was then referred here with a diagnosis of recurrent adenocarcinoma of the small intestine.

Upon examining this individual in the examining office here, we confirmed the history of symptoms of partial blocking of his small bowel, but also noticed that in the right armpit was a hard lymph node a little less than an inch in diameter, and he said that it had been there for two years. At first, there didn't seem to be any particular reason why there should be any connection between this hard "gland" or node in his right armpit, and the intestinal obstruction, which had recurred, but, nevertheless, the node in the right armpit felt hard enough to seem to us to have the characteristics of a malignant tumor, and we became curious. Our curiosity led to a search for the reason for this enlarged node in the right armpit. Upon looking over his arm, we found away down on the front of the forearm a small scar, almost imperceptible. We asked him how he had acquired that scar. "Why," he said, "About five years ago I had a little black mole there, and a skin specialist treated it by burning it off with an electric needle."

That led us to suspect that right there we had the clue to his intestinal tumor. So we sent to the hospital where his first intestinal tumor had been removed and diagnosed as adenocarcinoma of the small bowel, which would be a rather rare tumor, anyway, and obtained the slide and found, as we suspected we might find, that that tumor was a melanoma, that is, a tumor arising from the pigmented mole which he had had on his forearm five years before and which had been burned off by the dermatologist.

I think that story points out a few lessons to us. In the first place, the treatment of pigmented moles, when they undergo any change that attracts the patient's attention to them so that some treatment seems indicated, should not be by burning them out with an electric needle, but by complete, rather wide surgical removal. In the second place, it points out the value of careful history taking and really doing some detective work as far as you can on any patient suspected of having cancer, and certainly all of this story could just as well have been found out at the time of the first operation rather than five or six months later when he came here.

Perhaps another anecdote might not be out of order at this time. There is the case of a patient who last February was treated in a small town about 100 miles from here because he had some cough and shortness of breath and pain in his chest. An x-ray picture was taken, and was interpreted as showing a tumor of the lung. Without further investigation, he was then subjected to high voltage x-ray therapy over the tumor. He was not bronchoscoped; no aspiration biopsy was done. So he was treated really without a diagnosis. Now, he has in his lung a large mass, visible as a shadow on the x-ray film. He still has symptoms, and the problem now is to determine what he has and what he had. It is rather difficult, because the x-ray treatment has produced scarring in his lung.

Bronchoscopy now does not reveal anything definite, and aspiration biopsy of his lung has been tried once and has failed to yield tissue, because his lung is converted in that area into a dense, leathery mass, and our attempt three weeks ago to get an aspiration biopsy from it did not yield any definite information. I don't know whether at the present time we are going to be able to prove what this man has.

This story, I think, illustrates how important it is in the field of cancer to make the diagnosis, if possible, before subjecting the patient to radical treatment. We feel that in the lung field, for example, it is very unwise to subject a patient to high voltage x-ray therapy with its certain deleterious changes, unless one is justified in doing so by having proof of the existence of cancer.

In this cancer hospital devoted entirely to the treatment of cancer and neoplastic and allied diseases, we have had, during nearly three decades now, ever since the hospital has been organized on this basis, a system of examining all the new hospital patients in one central examining office. They now come through here at the rate of about 5,200 patients a year. That means that the fellowship men who spend usually six months working there as a first part of their three-year fellowship period of training, have an opportunity to see well over 2,500 cases either of cancer or of conditions which have to be differentiated from cancer. That is a most valuable experience, and we think that logically it comes as the first period of their introduction to training in cancer.

On the basis of the observation of that work which I have had the good fortune to be associated with for over two decades, I think we can come to certain conclusions as to what constitutes the lines of defense in this war against cancer. I feel that the first line of defense is the patient himself, together with all the educational agencies which are brought to bear on enlightening him as to what to look for and enlightening him as to the necessity for being on his guard against symptoms that may mean cancer.

The second line of defense is the general practitioner together with all the educational agencies brought to bear on him, his medical meetings and journals; and only as the third line of defense stands the specialist, the surgeon or radio-therapeutist, the tumor clinic in the general hospital, the special cancer hospital, or whatever agency has the job of actually treating the patient.

The great need today is for a coordination of all the educational agencies that have to deal with, first, the patient, second the general practitioner, and finally the institution or specialist that is to treat the patient.

The examination of the cancer patient may be a very simple matter, if his lesion is out on the surface somewhere, where it is easily visible, and can be easily inspected and felt, and where the symptoms of it have been very obvious to the patient; or the examination of the cancer patient can be a most complex, difficult matter, because there are so many of these serious diseases in the cancer field which begin in obscure locations, or in locations in which symptoms may at first not be produced.

It is very difficult, for example, to make an early diagnosis of cancer of the stomach because the symptoms may be very minor, until the disease has progressed to such a point that the diagnosis becomes relatively easy. Diagnosis is a most complex field, and no one within the limits of 20 or 30 minutes could attempt to discuss with you the diagnosis and treatment of the whole field of cancer.

As you know, there are many special procedures which may be gone through in certain cases in attempting to make a diagnosis of cancer. With modern facilities, we have now many means of gaining either direct or indirect access to these obscure locations, and in some instances, of actually portraying the obscure locations on x-ray films or by other means. For the lung, for example, we have the bronchoscope, an instrument which is passed through the mouth and throat, down the windpipe into the large bronchi, so that the examining surgeon can look directly through this instrument and find a cancer if it is in the larger bronchi.

We have instruments for direct visualization of the interior of the bladder. The interior of the kidney cannot be directly instrumented, but indirectly we can inject dye materials up through the ureter from the bladder and take x-ray pictures which show the outline of the interior of the kidney, and judge by deformities in that outline whether there is any disease there. That information put together with other data that we assemble, aids in making a presumptive diagnosis of cancer.

Even in the brain—a very special field which is left largely to such institutions as the Neurological Institute—they have methods of visualizing the interior of the brain for brain tumors, and the interior of the spinal canal for spinal cord tumors. Even the interior of blood vessels can now be demonstrated roentgenographically by certain dyestuffs which can be injected, with very careful teamwork and coordination, snapping x-ray pictures at exactly the right instant, determined by a previous test of what is known as the circulation time, that is, how long it takes the blood to get from a certain point of injection to the area in the chest or elsewhere which one is trying to portray. Thus one can show deformities in the blood vessels due to pressure upon them by tumors.

The diagnosis of cancer can never be regarded as certain on any purely clinical basis of history, physical examination, and x-ray films. It must depend on the identification of cancer cells under the microscope by the trained tumor pathologist.

That means that as far as possible, biopsies are necessary. In some way or other, if it is at all possible, a specimen from the tumor must be taken and the tissue identified by the tumor pathologist as showing cancer before you are safe in assuming that it is cancer.

In some situations, of course, that is not a practical or a feasible thing to do. There are many obscure locations in which one has to rest content with a presumptive diagnosis of cancer, a sufficiently strong presumptive diagnosis to justify an exploratory operation, the surgeon being prepared to go ahead with an operation for cancer if the findings at the time of operation confirm the previous presumption.

Also, in general, it is probably best for the biopsy to be taken not by the general practitioner but by the one who is going to be ready at the moment, or very soon afterward, to proceed with the necessary operation or treatment. For example, in breast cancer it is probably not good practice to have one doctor take a biopsy and then let five or six days elapse before the patient is referred to the surgeon who removes the breast. If the diagnosis is strongly presumptive of cancer, it is better practice to send the patient to the surgeon, let him take the biopsy and be prepared to go right ahead with the necessary treatment.

In the methods of biopsy, we have the usual regular surgical cutting method, often necessitating only a tiny incision. From superficial lesions, various little forcep appliances can easily pinch off a tiny bit of tissue, enough to enable the pathologist to make the diagnosis. In many locations such as the thyroid, where it is usually inadvisable to do a cutting biopsy, the needle aspiration biopsy can easily be done, and in a high proportion of cases will yield the information that you want.

The treatment of cancer is fully as complex a problem as the diagnosis and obviously cannot be discussed with any degree of thoroughness in the course of a short talk, but I am sure that you have already realized how complex the treatment of cancer is, even in these few fields that you have heard about so far.

I thought we might just take a typical example, in a field of cancer which until recently has been thought to be a rather uncommon variety, therefore not of so much importance, but which in the last decade or two we have come to realize is really a most important field because of the heretofore unsuspected frequency of the disease—and I am talking about cancer of the lung. In Dr. Ewing's 1928 edition of his book "Neoplastic Diseases," cancer of the lung was rated as comprising only one per cent of all malignant tumors, but we know now that actually cancer of the lung forms about 4 per cent of all the malignant tumors that there are.

Cancer of the lung is a disease almost entirely of men. They have it in proportion of eight, nine, or ten to one as compared with women. We don't know yet why this is. It may have something to do with the men's greater exposure to hazards of inhalation of various dusts from employment. There is somewhat greater liability to respiratory diseases, pneumonia, and so on. Whether or not it has anything directly to do with sex hormones, we don't know as yet, but at any rate the fact is there that cancer of the lung is a disease preponderantly of men, usually in about their sixth decade. It occurs with its highest peak of frequency at around the age of 53. It may occur in women. It may occur even in children. It does occur with some degree of frequency in people of 30, 35, and 40, but the peak of incidence of cancer of the lung is in males between 50 and 60.

The symptoms may be very obscure. It is a very common story that a man has had a chronic cough, thought to be a cigarette cough, for many years. Then he notices that his cough is getting a little more nagging and one day he sees a little fleck of blood in his sputum. Up to that time there has been no change in his general health; he weighs just as much, has a good appetite, has no pain. That is the time to think about cancer of the lung and to look for it. The trouble is you may not be able to find it. The bronchoscopists tend to preach that the early diagnosis of cancer of the lung should be possible in 80 or 90 per cent of the cases just by using the bronchoscope. Unfortunately, that isn't true. Nearly about half of the cases, even the later stages, can't be proved by the bronchoscope, because the tumor arises in the smaller bronchi, and the bronchoscope can't reach it, but at any rate, the effort should be made at that stage of the disease when a patient has an unexplained cough, and may or may not have spit up a little blood. That is the time to think about the possibility of cancer of the lung, especially in a man above 40.

The first step is, of course, a careful history, going over all the factors, the exact sequence of events, just how long he has had his cough, just to what degree does it annoy him, has he or has he not seen any blood in his sputum. Oftentimes a patient won't even mention the fact that he has had blood in the sputum unless you drag it out of him, like pulling teeth, because he tends to think that this little blood is something a little bit alarming, but he would rather not think about it the second time.

Then a very careful physical examination not only of the chest but of the entire body from top to bottom, because what seems to be primary cancer of the lung may be secondary to something else, perhaps even some obscure organ such as the pancreas. After the complete history and complete physical examination have been done and they indicate no suspicion directed towards any organ except the lung, the next step is a careful series of x-ray films which show this lung in all aspects, not just a straight, single front view of the chest, but side views and oblique views and preferably also fluoroscopic examinations so that you can watch the movement of the lungs and diaphragms and heart and great blood vessels.

The findings, then, up to this point may show perhaps a little shadow on one side of the chest that might or might not mean cancer of the lungs. Then the usual next step is bronchoscopic examination, because in about fifty per cent of the cases, that will succeed in visualizing the cancer directly since about fifty per cent or so of the cancers of the lung arise in the larger stem bronchi which are accessible to the bronchoscope.

Let us assume in this case that nothing particularly abnormal is seen. Perhaps there is a little bulge of one side of the bronchus, perhaps even the wall of the bronchus seems a little rigid. Those findings are accepted by some as presumptive evidence of tumor, but do not prove cancer.

The next step, then, might be to put in some lipiodol, an oily solution of iodine which will cast a shadow on an x-ray film. That is instilled into the bronchial tree, placing the patient in such a position, usually under the guidance of the fluoroscope so that you can see what you are doing, so that this iodized oil will run down the bronchial tree in and around the part where the suspected lesion is.

That may give you some very definite help; it may show a blocking off of certain branches of the bronchial tree and give you a much better idea of the true location of the lesion, because much of the shadow that you see on the ordinary films may not be due to the cancer itself; it may be due merely to its secondary effects. It blocks off certain bronchi, causes accumulation of secretion and mucus on the far side, and that is what causes most of the shadow that you see in cases of cancer of the lung. But up to now, we have had no proof of cancer. Then if the lesion is a suitable one for such a procedure, we may in this case perform an aspiration biopsy, and in some instances where bronchoscopy has not been able to prove the diagnosis of cancer, we have been able, with the use of the needle, again usually under fluoroscopic guidance, so that we know just where we are going, to obtain proof of cancer by dragging out a drop or two of this tissue, smearing it on a slide and showing that cancer cells exist there. You can easily see it might take a period of two weeks, or even three weeks, to go through all these various stages of proof of cancer of the lung, yet unless you do that, you are not justified in subjecting that patient to a total pneumonectomy, that is, removal of the entire lung on one side, on the one hand, or heavy voltage x-ray treatment which produces scarring in the lung, on the other hand. In other words, if a patient is going to be subjected to the radical treatment for cancer, we ought to know, if possible, that he has cancer and not take a chance on it.

I think with this general summary I have done about as well as I can without going into a lot of other details about specific organs in talking to you about the diagnosis and treatment of cancer.

Hormones and Cancer

Howard C. Taylor, Jr., M.D.

The field of hormones and cancer is a fascinating one. It has been briefly discussed in the section on research because evidence bearing upon our knowledge of this subject is being rapidly obtained in the laboratory. In many ways it would appear that studies on hormones in relation to cancer would form the most important bridge between experimental and clinical investigation. They may also prove to be the place where our knowledge of the whole process of the origin and nature of cancer advances most rapidly.

Cancers of the ovary, the uterus and the breast all need knowledge of hormones for correct evaluation and interpretation. So also do cancers of the testis and of the prostate.

Dr. Taylor has given us an interesting and stimulating paper on this subject which very evidently is one with which each of us should be familiar.

"Hormones and Cancer" is a difficult subject because it requires consideration not of simple things like anatomical specimens and symptoms that one can easily imagine, but of relatively difficult chemical and physiological conceptions. Nevertheless these hormones have become so important that they are a subject that ought to be the part of any moderately well educated person's general knowledge. On the other hand, the discovery of certain of these substances is relatively recent, and time has consequently not yet elapsed to have allowed them to penetrate everyone's fund of useful information.

Some hormones are undoubtedly very familiar to you. You know about insulin, which is given to patients with diabetes in order to help them to burn sugar, and you know about thyroid extract, which is taken to increase the expenditure of energy or to cause a loss of weight. In general, these, and other hormones are chemical substances which are produced in one organ of the body in order to affect a different organ or a different set of organs.

So far as cancer is concerned, we are not particularly interested either in insulin or thyroid extract. Particularly from the standpoint of gynecologic tumors we are concerned with two groups of substances. One set is produced by the pituitary, and is collectively termed "gonadatropic." "Tropic" implies stimulating, and the "gonads" are the sex organs. Hence the gonadatropic hormones are the hormones which stimulate the sex cells of the ovary and testis. (See Fig. 23b.)

The second set of hormones are those which, in general, are formed in the sex organs themselves. In gynecology we are concerned principally with the hormones produced in the ovary of which there are certainly at least two. The one that is most familiar is the so-called "ovarian hormone" which is also called estrogen. It has been given this name because in animals it produces heat or estrus. Estrogen may be familiar to some of you in the form of certain of the commercial preparations of it, which have been given various special names by the different pharmaceutical houses. This hormone which is commonly employed for the relief of various menopause symptoms is especially important in the theoretical consideration of the cancer problem.

There is a second hormone of the ovary which is called corpus luteum hormone. This is a hormone produced in a special part of the ovary. The term corpus luteum means "yellow body", and is used because the part of the ovary, which produces it, has a distinctive yellow color. The corpus luteum hormone is very important physiologically but seems at present to have less to do with the cancer problem.

There are also testicular hormones which are chemically, closely related to the ovarian hormones, and there are adrenal hormones which are related to both. The importance of these hormones cannot be realized unless you know something about their function. One must understand first that none of the cells of the reproductive system, that is to say, of the uterus, the cervix, the vagina or the breasts, can grow at all without the stimulation by some of these hormones. Similar relations exist between the hormones of the testis and the male reproductive tract. I am, however, going to take most of my examples from gynecology, because the understanding of the hormone relationships is further advanced in the female than in the male.

You probably know that if the ovaries are removed from a female child before puberty that there will be no further development of the breasts. The uterus will also remain very small and these organs will of course remain functionally inactive. Furthermore, if you remove the ovaries during mature life, let us say at 35, the breasts will grow smaller and the uterus will atrophy and become a simple vestigial organ in the pelvis. This is also what happens after the normal menopause and whenever the pelvic organs receive heavy doses of x-ray.

These facts are emphasized to show you that the normal growth of these organs is dependent upon these particular hormone substances. In a moment we shall progress to the next conception, that if these substances completely control the normal growth of these organs it is not surprising if pathological growth is to some extent conditioned by them also.

Another type of experiment tends to reinforce these ideas. Here instead of decreasing the hormone supply by removal of the ovaries, the effective amount is increased by injecting into an animal or into a human being large quantities of these materials. If you take a small laboratory animal soon after birth and begin treating it with an estrogen, the uterus will rapidly enlarge, and in a very few days, possibly in a few hours, it will approximate the size of an adult animal of that species.

This process is also known to occur to some extent when the ovarian hormone is given human beings. There is one disease for which the estrogens are given to girl children when eight or ten years of age. In the course of giving these injections, many observers have reported the enlargement of the breasts five or six years before the normal years of their expected development. Hence it is clear that these substances are

even the normal progress of pregnancy may be gravely interfered with.

The menstrual cycle is controlled by means of the chemical substances produced in the ovary.

After menstrual bleeding is complete the lining of the uterus regenerates and gradually becomes thicker under a stimulus from the ovary in preparation for another menstrual period. When the ovarian stimulus fails the uterine lining is lost and the process begins anew.

In the ovary, is the so-called follicle, containing the egg cell associated with a particular menstruation. This follicle develops up until about the 14th day of

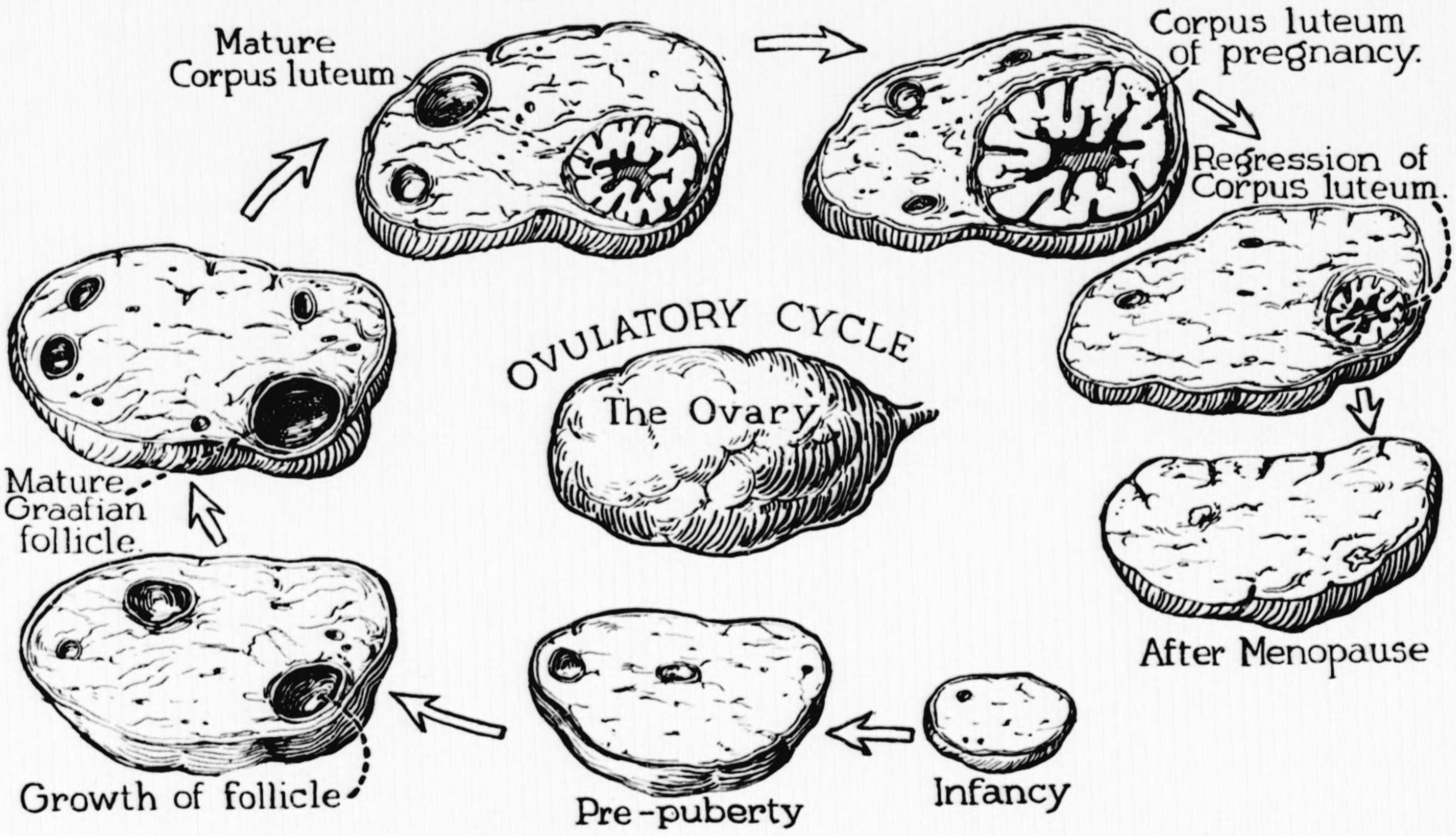


FIG. 34. The whole ovary illustrated diagrammatically in the center is shown sectioned in the other figures. The graafian follicles contain the female sex cells or eggs. The corpus luteum is such a follicle filled up with tissue after the egg has been liberated.

responsible not only for the normal development of these organs at a normal time of life, but may be responsible for the growth of these organs at times outside of the expected times for these organs to grow.

These substances are responsible for the function of the reproductive cycles, as well as for organ development. They control menstruation and produce much that is characteristic of the physiology of pregnancy. Why for example do the breasts develop early in pregnancy? How do the inactive milk glands know that a pregnancy to which they must respond is developing in a remote organ? The reaction of the breast is again the result of stimulation by these hormones which are produced in excessive quantities in the placenta and which, circulating through the blood, reach and affect susceptible organs throughout the body. If these substances are produced in the wrong quantities, or at the wrong time, or in the wrong relationships to each other, then the normal cycle of menstruation or

the month. During this time, the ovary is producing estrogen in great quantities, and as a result, as we have seen, the lining of the uterus recovers from the loss which has taken place at the time of menstruation. At about the 14th day after the first day of the previous menstruation, the follicle in the ovary is broken and the egg is let loose, perhaps to be fertilized.

The follicle is then rapidly transformed into a "yellow body," or corpus luteum. As this structure develops it elaborates a new chemical substance which is sent down through the blood stream to the lining of the uterus. As a result of its action on the uterus the glands become large and dilated. Then at about the 24th day of a menstrual cycle this corpus luteum degenerates and when its activity ceases the mucous membrane of the uterus no longer receives the chemical stimuli necessary to its growth, it also degenerates. This is menstruation.

This process takes place about 400 times in the life of every woman. If the mechanism in the ovary runs regularly, then the uterus will respond with perfect rhythm and you will have regular menstrual periods. Disturbance of this mechanism on the other hand resulting in a disorder of hormone formation will be followed by abnormal menstruation or irregular bleeding. Such abnormal bleeding is easily mistaken for a symptom of cancer.

The hormones have, therefore, two types of relationship to the cancer problem. (1) They are important in the first place because they are growth producing substances and an exaggeration of normal growth may eventually result in abnormal growth. (2) They are important secondly because a disorder of hormone relationships may result in functional disturbances which will give clinical symptoms that simulate cancer.

Although these are the substances which make tissues of the reproductive tract undergo normal growth, it is a long step further to say that they are actually the cause of cancerous growth. So far as animals are concerned, however, the evidence that these substances produce tumors is fairly good.

You are probably already familiar with the fact that there is a type of cancer developing in the breast of the mouse. This tumor is influenced by heredity and certain observations have been made about it which indicate that the ovary is an important factor in the development of the malignant tumor. If, for instance, you take female animals of a strain which frequently develop cancer of the breast and remove the ovaries at birth, these spayed animals will then rarely get cancer. Further, the males of these cancer strains ordinarily do not get breast cancer, but if you transplant ovaries into those males, or if you inject these males with estrogen, then they will develop cancer of the mammary gland as often as do their sisters.

The evidence for a hormone cause of any human cancer is not yet very good. This might be expected because we cannot set up controlled experiments on human beings. We cannot for example, take a prospective cancer victim at the age of ten and inject her with estrogen for twenty years in the hope of causing a breast cancer. We must on the contrary look backwards from a developed cancer case to find what signs of hormone disorder may have preceded its appearance. This by comparison is a clumsy and inaccurate approach. Hence the fact that we have not demonstrated a hormone cause for human tumors is no evidence that such a relationship does not exist. A few observations suggesting a hormone factor in human tumors are alone worth mentioning.

The so-called "fibroid" is a very common benign tumor which develops in the muscular walls of the uterus. Certain well known facts about this tumor show that it is in some sense dependent on the ovarian function. It never appears before puberty, and practically never grows after the change of life. In fact it tends to shrink as soon as the ovaries cease functioning. One method of treatment of this tumor utilizes the x-ray to destroy ovarian function and by thus producing an artificial menopause causes the tumor to get smaller. These observations cannot be interpreted as proving that a disorder of the ovary is the cause of fibroids, but we do know that you must have an ovary or you cannot have fibroids.

The fibroid is the best example of its kind, but there are other tumors which bear a similar relationship to the ovary. Among these are certain benign conditions of the breast which improve as soon as the menopause is established and chemical stimuli cease to be received from the ovaries. Other less common pelvic tumors also respond as do fibroids to the menopause. Finally, there are cases of breast cancer which seem to be a little benefited if the ovaries are removed or are destroyed by x-ray.

The five principal causes of abnormal uterine bleeding are as follows: cancer; benign tumors; inflammations; complications of pregnancy such as miscarriage, and finally hormone-produced functional disorders. The diagram based on an analysis of 4,000 cases illustrates the probability of cancer being the cause of this symptom at certain times of life. (a) During the 20's, twenty per cent of the cases examined were found to have no organic cause for the bleeding and must be claimed as examples of hormone disturbance. Forty per cent were due to miscarriage or extra-uterine gestation or some other complication of pregnancy. About 20 per cent were due to some type of inflammation in the pelvis. Ten per cent, even at this early age, were due to benign tumors and there were actually one or two patients with cancer. (b) In the next decade the functional causes are still important but the complications of pregnancy and pelvic inflammatory disease are disappearing. The benign tumors, particularly the fibroids, are becoming very important and the cancer cases represent a definite five per cent of all the patients admitted for abnormal vaginal bleeding. (c) In the forties, women are approaching the menopause. Functional bleeding in this decade is very frequent because, as you know, the change of life is often ushered in by disturbances in menstrual rhythm. Pregnancy and inflammatory disease are now uncommon. The great cause of bleeding during this epoch is the benign tumor, particularly fibroid, but again cancer can be seen creeping up in frequency and becoming a more definite factor than ever before. (d) The white line of the diagram represents the change of life. After the menopause the white area of the diagram, functional bleeding, tends to disappear, for the ovaries stop functioning altogether. There are a few minor inflammatory conditions in older women which occasionally cause bleeding and there are some benign tumors. Now, however, malignancy far surpasses all other causes of uterine bleeding. As soon as the menopause has occurred, the probability of cancer being the cause of bleeding is enormously increased.

A brief word finally might be said about possible dangers involved in the use of hormone preparations in the treatment of various human ailments. Their principal use in clinical therapy is to allay symptoms at the time of change of life, particularly the hot flushes, after the ovary has ceased to produce the hormones naturally. In treating the menopause the estrogens are used in large doses and sometimes for a long period of time. They are used at a time of life when they are perhaps not completely normal and they are not administered to give the cycle that the body seems to require for the normal physiology of reproductive activity. It must be admitted also that there have been a few cases reported in the medical literature, of cancer developing at the time of the menopause in women who were taking relatively large doses of an estrogen to cure hot flushes. The inference has been made by authors of some of these reports that it was the large dose of the hormones which produced the cancer. Actually, cancer is frequent at that age, and there are thousands of women taking these substances. The development of cancer in a woman taking an estrogen is probably simple coincidence. These preparations should, however, be taken with a certain amount of caution, and preferably for a relatively short period of time.

To sum up, one can make two points in regard to the relationship of the hormones to cancer. (1) So far as the production of cancer is concerned, these hormones are probably a definite factor for at least certain types, particularly for tumors of the reproductive tract. There is little direct evidence for these in the clinical study of women with cancer, but the evidence is good for some animal tumors. In addition it might be expected that substances, which have as a normal function the stimulation of the cells of the reproductive tract, should be one of the factors which make these cells grow abnormally.

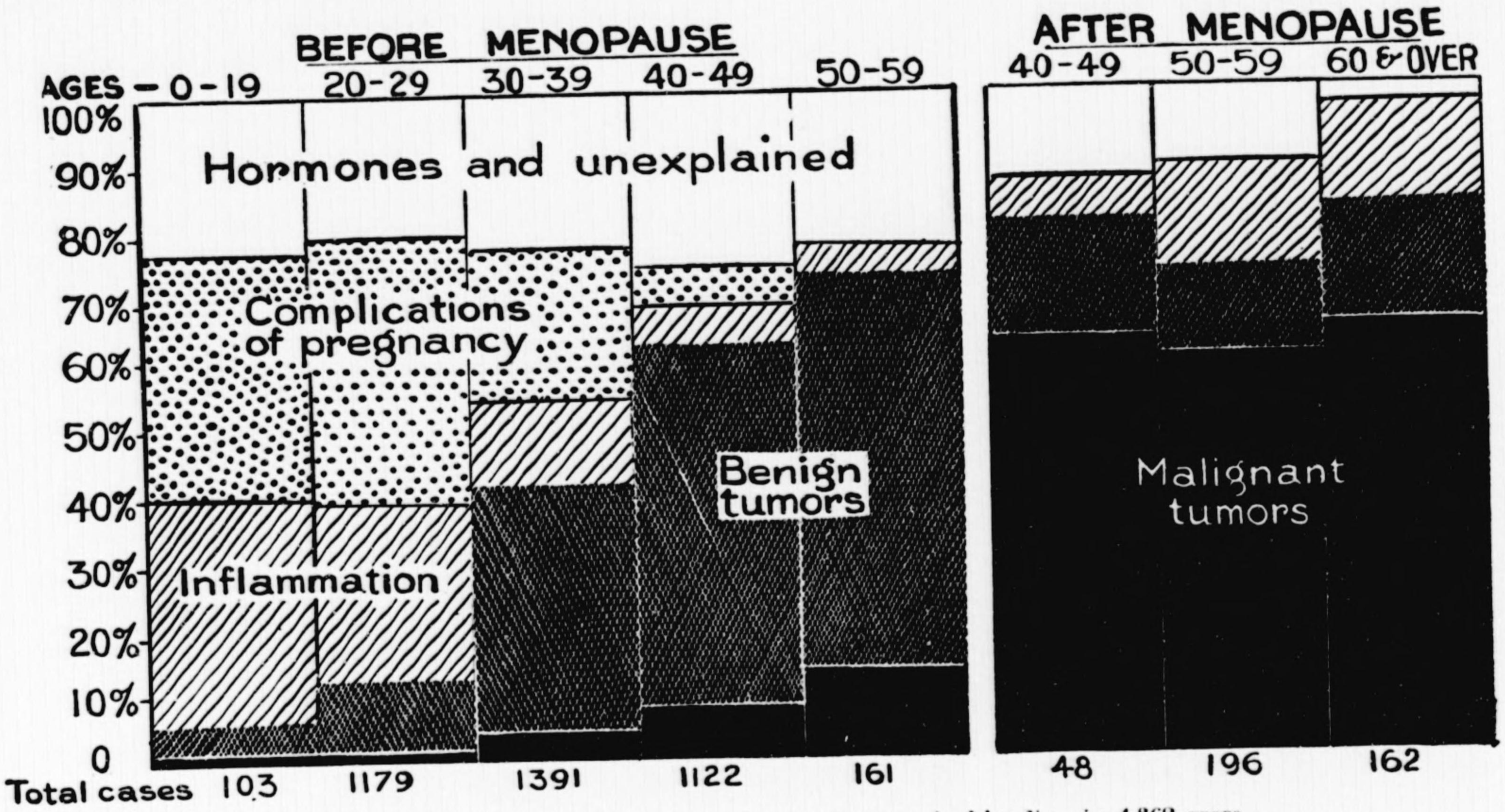


FIG. 35. Relative frequency of causes of typically female bleeding in 4,362 cases.

Secondly, the hormones are responsible for various functional disturbances which result in menstrual irregularities that can easily be mistaken by the woman herself for the beginning of cancer. This should tend to allay some of the fear felt by women at the appearance of abnormal bleeding, for the chances are great, at least before the menopause, that this symptom will, upon examination, prove to have a simple non-organic cause. However, any abnormal bleeding should receive an adequate explanation.

Cancer of the Skin, Lip and Tongue

HAYES MARTIN, M.D.

The figures accompanying this article by Dr. Hayes Martin will show how vascular and how completely supplied with lymph vessels is the region of the lips, mouth, tongue and neck.

For this reason it is imperative that signs and symptoms which may mean cancer in this area should be quickly recognized and promptly diagnosed and treated. It is easy for cancer to spread from these areas to other parts of the body and thus to become incurable.

Skin cancer can be and should be eliminated as a cause of death. Its location is favorable for treatment and for early and relatively easy diagnosis. The chances of its being localized in its early stages are good.

Some of the most successful and helpful results of education may be obtained in early treatment of cancer of the skin, lip and tongue.

Cancer of the Skin

There is probably not an adult in the world who has not seen a skin cancer. It is found most frequently on the exposed portions of skin, 75% or 80% of these cancers occurring on the face, particularly on prominent portions such as the bridge of the nose where sunburn and other chronic irritations occur, and on the neck. Because skin cancer is so common it is fortunate for the human race that the majority of skin cancers are not highly malignant. The type of skin cancer called "basal cell carcinoma," which is the most common form, tends to remain a local growth and lacks the characteristic ability of most cancers to spread from its point of origin to other sites. (See Fig. B inside front cover.)

The symptoms of skin cancer are characteristic of all cancers in that they are not alarming. A small pearly nodule or raised area may appear on the lower eyelid. A sore or small ulcer may develop on the bridge or the side of the nose. Except for their gradually increasing size, these undramatic tumors appear like many harmless blemishes which are so common on the skin. These tumors are usually painless, in fact the most malignant form of skin cancer, melanoma, "black tumor," may first show its presence in a mole or wart which will suddenly start to increase in size or to change in color.

A most encouraging fact, from the layman's point of view, is that under proper treatment 90 to 95% of all skin cancers can be cured. It is with skin cancer that many people will experiment with home remedies and commercial salves and ointments, not suspecting, the serious nature of their "sore," or, on the other hand, becoming concerned with their great danger are most susceptible to the advertisements of quack cancer cures, and it is for this reason that cancer control education should emphasize the point that sores that do not heal and continue to enlarge, and moles or warts that suddenly change in size should receive medical attention, and should not be rubbed or squeezed or cut into as such mistreatment may serve to speed tumor cells to other parts of the body, thereby greatly jeopardizing cure.

Cancer of the Lip

Cancer of the lip is a sort of half-way mark between skin and mouth cancers. Most lip cancers occur on the lower lip and at the junction where the skin meets the pink mucous membrane of the lip. It is a malignant form of skin cancer and will always be fatal if allowed to progress without treatment. A cancer of the lip is easily seen in the mirror and this "sore" is remarked upon by family and friends, so that most intelligent people see their doctor in the early stages of the disease, facilitating prompt diagnosis and treatment and a proportionally high cure rate. A cancer of the lip, if treated before it reaches a size of about ½ inch across, can be cured in approximately 97% of all cases, with a steadily decreasing percentage of cures as the cancer increases in size. A lip cancer which has reached a size of 1 inch across has a cure rate of about 80% only because of the chance of the growth spreading to other parts of the body. Cancer of the lip is largely a disease of men. (See Fig. D inside front cover.)

Cancer of the Mouth

Cancer of the mouth is more dangerous than lip cancer and also occurs in men in 80 to 90% of all cases. A recognized relationship has been demonstrated between chronic irritation, such as leukoplakia or "Smoker's Patch," and it is often a forerunner of cancer. Irritation from a plug of tobacco held habitually in the same side of the mouth may result in a leukoplakia which may then become the site of cancer if the individual has a susceptibility to cancer. It has also been shown that an abrasion on the cheek or tongue caused by a jagged tooth may eventually become cancer and it is not uncommon to find cancer of the gum or tongue around an infected tooth. (See Fig. G inside back cover.)

Cancer may arise in any part of the mouth—on the tongue, the gums, under the tongue, on the floor or roof of the mouth, on the tonsils or on the inner surface of the cheek that in early stages can be felt as a roughened area with the tongue rather than seen, as with cancers of the skin or lip. In other cases mouth cancers are discovered because they become infected and tender. Because in these locations a cancer can be felt, or, sometimes, seen in the mirror, the chances of early diagnosis and treatment and consequent cure are high. It sometimes happens, however, that a growth in the mouth will perhaps be so far back that it will escape the attention of the patient, so that the cancer will spread to the neck before the patient is aware of its existence. But here again a definite symptom, a lump in the neck, should bring the patient to the doctor for prompt diagnosis and treatment before the disease is hopelessly spread throughout the body. People should be made aware that any lump in the neck that appears suddenly, grows larger slowly, that is not tender or painful, should be examined by a doctor. These lumps felt in the neck are usually caused by steadily

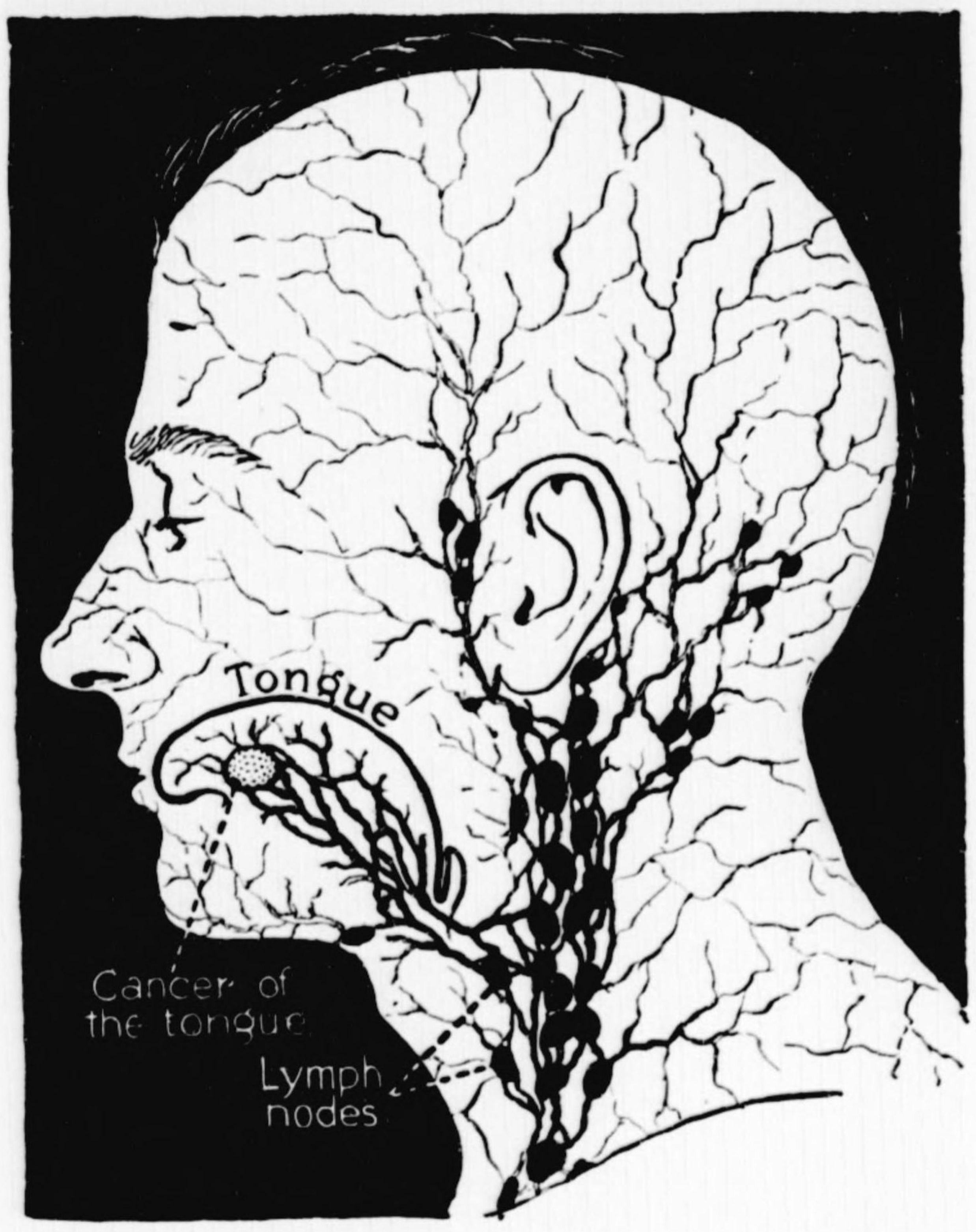


FIG. 36. Diagram of lymph vessels of the head and neck. Observe how easy it is for cancer cells to move from the tongue to the cervical (neck) lymph nodes.

enlarging lymph nodes, which may contain a spreading cancer.

If a cancer of the mouth is allowed to grow to a fairly large size before medical advice is sought, it may spread by way of the lymphatic system (see Fig. 36) to the lymph nodes of the neck. These nodes act as fairly efficient strainers in which are caught the cancer cells that have broken loose from the point of origin. If the cancer is discovered at this time—when the nodes first enlarge and if these enlarged nodes or lumps are brought to the attention of the doctor it can still be attacked surgically or by radiation with the possibility of cure. But if the danger signal of the enlarged nodes is ignored and the cancer finally overwhelms the barriers of the lymph nodes of the neck and spread to surrounding tissues or down the lymphatic chain to other organs below the clavicle or "collar bone," it will become inoperable and incurable. A large proportion of mouth cancers can be cured if the growth remains local and treatment is given in its early stages.

As with cancer in most parts of the body, the early symptoms of mouth cancer are not particularly distressing in themselves. This is an important point for most persons to realize—that in cancer, the seriousness of the disease is all out of proportion to the severity of the symptoms. Patients will come to the doctor with a condition in their mouths which they will describe as a "sore," "raw spot," "wart," "canker sore," "rough spot" or a "tickling," which has persisted for weeks or months. This is a particularly good example of what an early cancer seems like to the average person. He usually attributes his condition to some minor accident such as biting his cheek or drinking something too hot, so that there is apparently no one symptom startling enough to enable the average person to determine for himself whether the condition in his mouth is worthy of medical attention. One of the characteristics of cancer can be best demonstrated here, namely, that until the disease is advanced and complicated, it is not painful.

Cancer of the skin, lip and mouth is one of the best object lessons which can be used in cancer control education. Early cancers are not dramatic or painful and do not appear to be serious. They look to the untrained eye, very much like completely harmless conditions with which we are all familiar. Because these skin and mouth cancers appear as annoying "sores" or "blemishes," they are given medical attention in their early stages by most people and the cure rate is encouragingly high. They can be used effectively to emphasize the very important point to both the medical and lay public, that the possibility of these mouth and skin conditions being cancer should be ruled out before treatment is given for the relatively harmless lesions they may well be. If every apparently benign, harmless condition is thought of, discussed and treated before the possibility of cancer is investigated, valuable time may be lost. The great hope of success in the treatment of the skin and mouth cancer as in all cancers lies in early diagnosis and proper care.

Cancer of the Breast

Frank E. Adair, M.D.

Cancer of the breast is definitely curable in a high percentage of cases when diagnosed and treated in its early stages.

It presents certain interesting educational problems. Among these is the training of women to perform self-examination of the breasts at frequent intervals. No one except the individual herself can detect suspicious signs that may mean breast cancer in its very earliest condition. Since it is at that stage that chances of its cure are greatest and the correction or removal of pre-cancerous conditions most easily accomplished, the necessity of this training is evident.

Education is also needed to convince women that it is wise to report suspicious signs even if a radical operation is necessary. A great deal of unreasoning and ill-advised fear exists concerning this part of the problem.

Dr. Adair is recognized as one of our outstanding authorities in this field. He is also deeply interested in the progress and development of the Field Army and in all phases of cancer control. All that he writes is worth reading and remembering and the present article is a good example of that fact.

Cancer of the female breast is one of the greatest problems of women who are past 35 years of age. Professor Wilson of Harvard tells us that the greatest cause of death in women between the ages of 35 and 55, the time of such great importance in the life of every woman, is cancer. The types of cancer from which women suffer most are cancer of the breast and cancer of the uterus.

If one is to study the mortality tables one finds that during the year there are about 16,000 women who die from cancer of the uterus, and about 15,000 women die each year from cancer of the breast. Although these figures come somewhere near the truth, they give a totally erroneous viewpoint of its incidence because I feel sure that more women have cancer of the breast during a year than have cancer of the uterus. Furthermore, there is a higher percentage of cures in cancer of the breast than in cancer of the uterus. In *early* cancer of the breast the five-year salvage, or so-called cure, is approximately 77 per cent, while in the operable cases of cancer of the breast who are not early cases, those in which the disease has spread to the armpit, the cure rate is 42 per cent. This cure rate is one of the most interesting and encouraging figures that we have in all of cancerology because 30 years ago we were only curing about 20 per cent of this group of operable cases having involvement of the axilla, or armpit. Today with greater refinement in surgery, the improvement of the x-ray machines, greater skill in the application of the x-ray treatments together with the fact that women are now educated to report their lumps in the breast to the doctor at an early period, all are responsible for this great increase in the cure rates in the cases having axillary disease.

There is another item of great importance in this particular field; namely in 1920 when the Breast Department of Memorial Hospital was begun, our over-all cure rate, which signifies that every single case of cancer of the breast was recorded whether it was the hopeless case, the recurrent case, the early case, or the fairly early case, all together only had 8 per cent cures. Today our over-all cures have jumped up to 30 per cent. As I view the problem of breast cancer there is something new each year which gives me cause for encouragement in this field.

The responsibility of the Field Army and of all women is enormous, particularly in the field of breast tumors. The first thing which every women must learn and take as a personal message is the following: Every breast tumor must be removed and examined under the microscope. Do not let any doctor remove a breast tumor or lump in his office. Further, the patient should know that any doctor who removes a breast lump should be competent to go ahead and perform a complete radical operation if such is indicated by the microscopic study of the tissue removed. Too many doctors remove a breast lump without having the training or experience to perform the big operation indicated if the tumor proves to be cancer.

The probability is that any lump occurring in a woman's breast past the menopause will be a cancer. Cancer occurs in women's breasts at almost all ages, but more particularly after the menopause.

The removal of a lump from a woman's breast is a matter of very simple surgery, and here at Memorial if the lump proves to be a benign process, the patient is permitted to go home the next day; while if it proves to be a malignant process, cancer, the average case goes home on the ninth day following the radical operation.

There are certain signs of cancer which every woman should learn. Unfortunately, however, these signs do not represent early cancer, but occasionally early cancer will be picked up by heeding the warning of one or more of these signs:

First: Bleeding from the nipple. This is a sign which may or may not represent cancer of the breast. About 15 years ago 46 per cent of our cases having this sign of bloody discharge from the nipple proved to have tumors which were cancerous. Women are coming so early today because they have had this sign taught to them so thoroughly. I believe not over 10 or 12 per cent of those having this sign today have cancer in the breast. As a matter of fact bleeding from the nipple is a warning to you that the little benign tumor called a papilloma, or papillary cystadenoma, will eventually become a cancer if not removed.

Second: Deformity. There are many types of deformity, some of which are important and some unimportant. If you have had an operation or the opening of an abscess, any lack of perfect contour will be insignificant. On the other hand, if there is a spontaneous process gradually taking place resulting in loss of smooth contour, normal to the breast, one should consider the probability that a disease process is taking place, and should immediately present this problem to your doctor.

Third: Skin attachment. One of the very earliest signs which may mean cancer of the breast is a slight pulling-in of the skin overlying the lump, producing a slight depression. Do not neglect this sign.

Fourth: Retraction of the Nipple. There are several causes for retraction of the nipple, but one of the commonest causes is due to an underlying cancer which pulls in the nipple.

Fifth: Breast Elevation. Frequently the breast which is affected will be slightly higher than the opposite breast.

Sixth: Orange peel appearance. In the more advanced stages of breast cancer it is common to have the skin of the lower portion of the breast take on the appearance of orange peel. This is sometimes called pig-skinning, and is due to a mild blockage of the return of the lymphatic juice of the breast. In medical terms, called edema.

Seventh: Ulceration. Ulceration of a lump in the breast usually means a rather advanced stage of cancer.

Women come to the doctor today before many of the above signs have had an opportunity to develop. In our hospitals, clinics, and private practice, the doctor today finds that he is presented with the problem of making a diagnosis on a lump alone, and this is something that no doctor, no matter how expert, is able to do by inspection. The only safe rule for a doctor is to remove any lump which occurs in the breast. If he does not, the responsibility and the burden of proof for its being a benign process must rest on his shoulders. One of the safest rules for the protection of every woman is for her periodically to look at herself in front of a mirror and see if there is any deformity, any nipple retraction, any dimpling, or any of the other signs which indicate the possible presence of a serious tumor. Every woman should make this a rule.

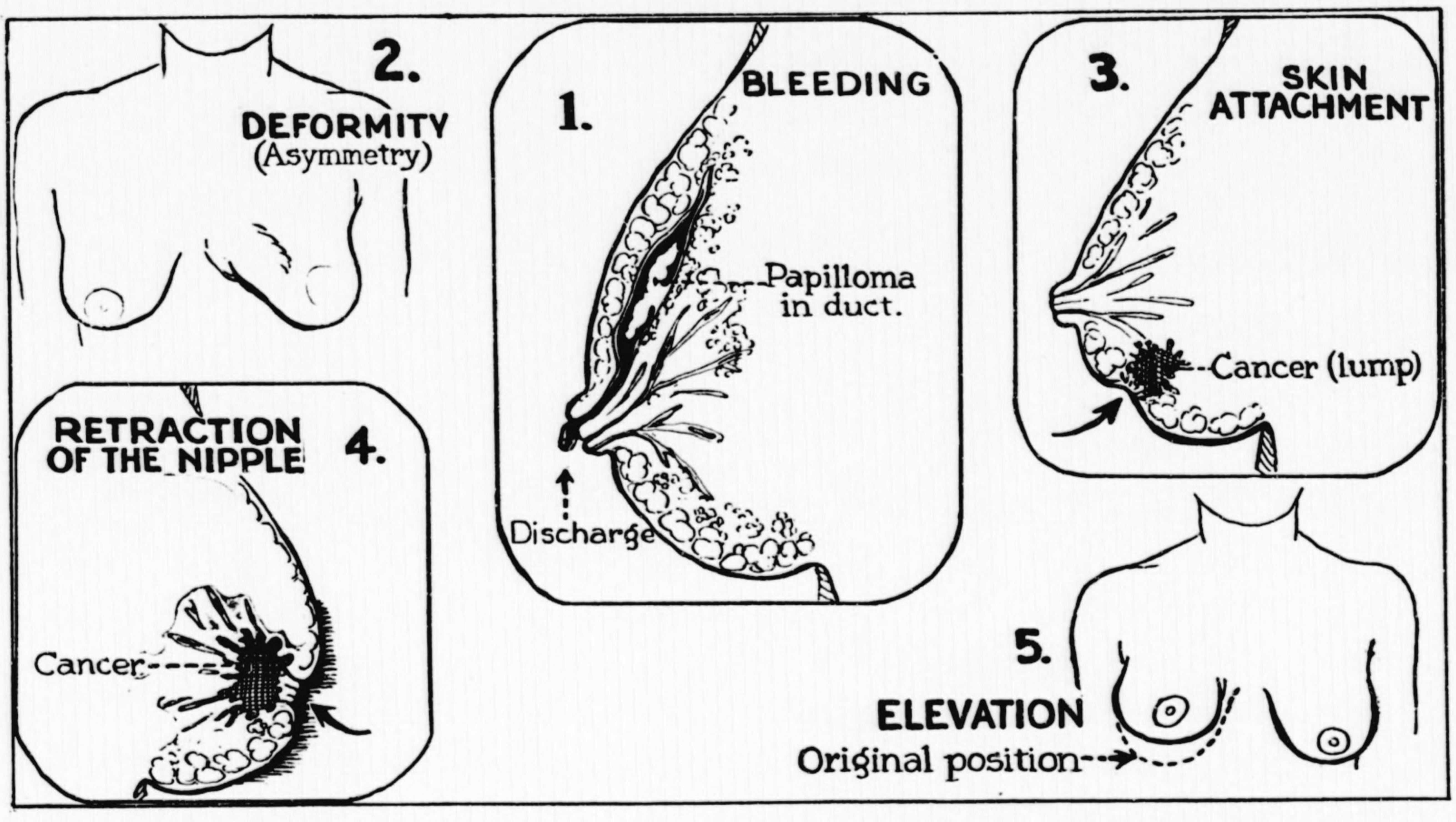


Fig. 37.

In a way it is a great tragedy for a woman to have her breast removed for cancer. On the other hand, she has no choice. Cancer is a disease which gives you no choice. Cancer if untreated will eventually kill, so that your only choice lies in the proper and intelligent selection of the doctor who will perform the operation. I, personally, have very little sympathy with the doctors who without making an exact microscopic diagnosis, first removes the breast. That doctor is unmindful of the psychology of womanhood. He probably has not stopped to consider the embarrassments and the difficulty in dressing of that patient who had the breast needlessly removed. The rule for the surgeon should be, remove the lump first, and have it microscopically examined. If it is benign, the surgery already done is sufficient, but if the lump proves to be malignant then he has no choice other than to resort to radical surgery.

Following the removal of the breast the average woman needs some moral support as she has psychologically taken a blow. In my practice I try to be very sympathetic and understanding of her problem. My secretary knows where to have an artificial breast made which exactly fits and is exactly like the opposite breast. In their embarrassment at this stage the help of an understanding secretary or nurse is of great value. Any surgeon who disregards this particular problem has little experience, or little understanding.

Cancer of the Uterus

HOWARD C. TAYLOR, JR., M.D.

Cancer of the uterus is one of the great killers which can and should be checked. Dr. Howard Taylor, Jr., in his paper will discuss many of its technical and medical aspects. There are, however, certain general facts concerning this disease which should be understood as background material for its control. These may be listed as follows.

1. *Periodic examination.* The best way of detecting conditions of the uterus which may precede cancer or which may even be that disease in its earliest stages is by a periodic examination. For women of over thirty this is recommended at least annually and, if possible, semi-annually. Obviously some more intelligent women will attend to this under their own initiative. Hundreds of thousands of others, however, will *not* do so unless they are made to act by pressure of events or by those of you who have assumed the function of acting as guides and advisers of your less well informed sisters. 2. *Maternal Health Clinics* should be encouraged to perform, as a routine matter, the necessary uterine examinations to detect lesions in need of diagnosis and treatment. 3. *Cancer Prevention Clinics,* where healthy normal women form the habit of periodic examination, should be established and maintained wherever possible at hospitals approved by the American College of Surgeons. The impetus to establish, and the encouragement of supporting such clinics under proper auspices are also part of your duty. 4. *Correction of uterine injuries.* After the birth of each child the mother should promptly receive and follow medical advice concerning repair of any uterine injuries received. There is definite evidence that neglected injuries of the uterus often provide a situation favorable to the eventual development of cancer.

THIS disease is important to you first of all because of its great frequency. It has been stated that cancer of the uterus is the commonest of the cancers occurring in women. Certainly it ranks as one of the first three.

If you are to understand the diagnostic and therapeutic problems associated with cancer of the uterus, it is first necessary to know where this disease begins and what its relationship is to other parts of the body. A complicating factor at once appears when one rec-

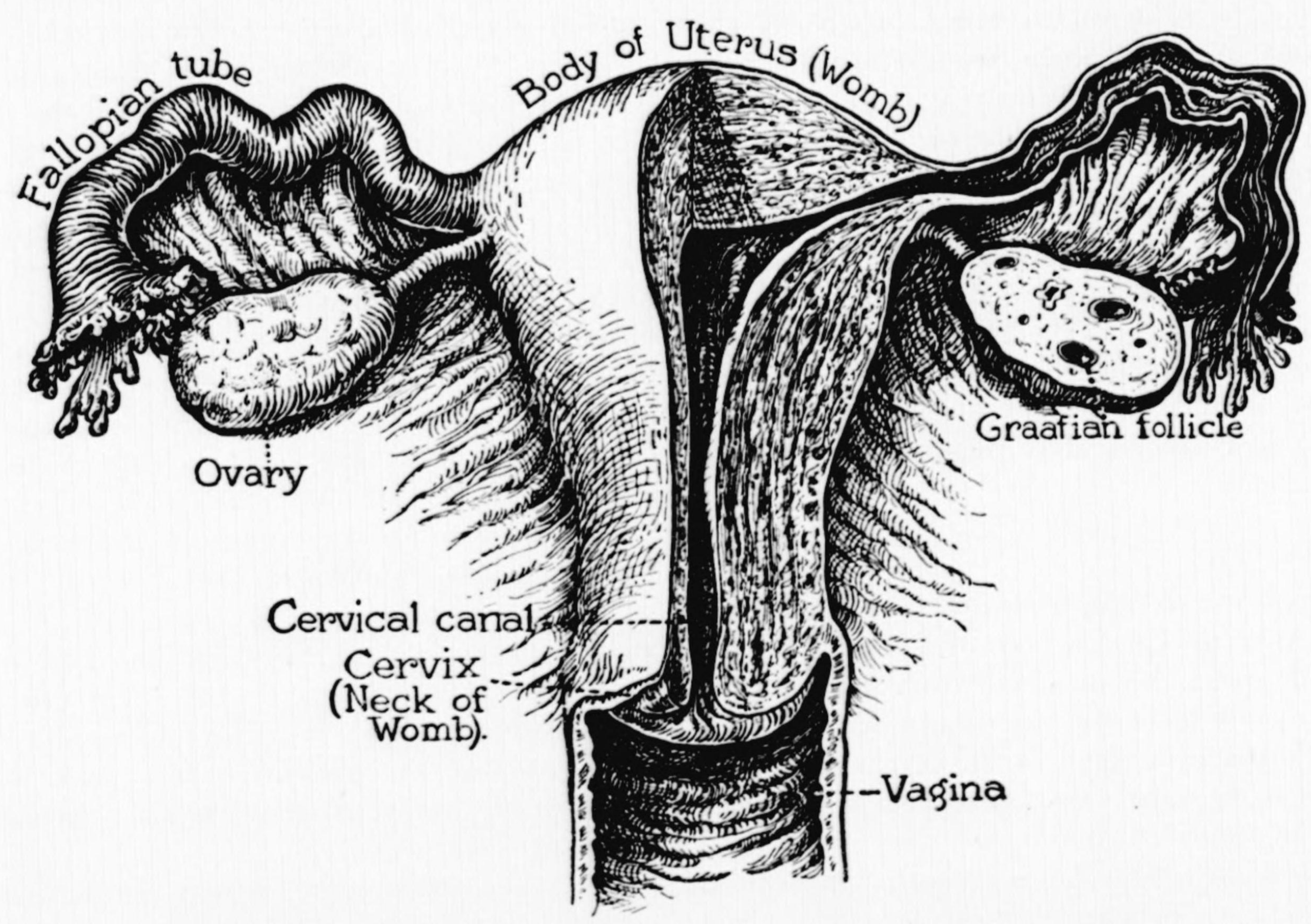


FIG. 38. Anatomical drawing of the structure of the normal human uterus.

Cancer of the uterus is of further special interest because it is one of the types of cancer for which an educational program may be expected to be most successful. This is because the disease gives, as a rule, readily recognizable symptoms and is accessible to a simple examination. Consequently, opportunities for control are especially favorable.

ognizes that there are really two types of cancer of the uterus. The distinction between these two types depends upon the exact point at which the cancer arises within the uterus. (See Fig. 38.) This distinction is not without analogy elsewhere. When you speak of cancer of the gastro-intestinal tract, for example, you mean something entirely different, depending upon whether you are referring to the stomach or the colon. Similarly cancer of the cervix or "neck" of the uterus is entirely distinct from cancer of the corpus or "body" of the uterus. The more common is that which arises in the cervix. The cervix of the uterus is not a particularly important part of the organ from a physiologic standpoint. The cervix is in fact simply a canal about one and a half inches in length through which the menstrual blood passes. It is the passive portion of the uterus which must dilate when a baby is being born. Cancer of the cervix arises usually from the lower outer part of the cervix as it projects into the vagina, but it sometimes starts within the canal itself. Altogether from five to ten times as many cancers arise here as in the deeper portions of the uterus.

Cancer of the body of the uterus on the other hand arises from the lining, the mucous membrane, of the interior of the uterus, which is that part of the womb from which menstruation comes. This type of uterine cancer, occurring less frequently and as a rule at a more advanced age, is much the less important of the two diseases. It differs from cancer of the cervix, not only as regards age of onset, but in relation to method of treatment and the outlook for a cure. Do not therefore think of cancer of the uterus as one disease, because of the existence of these two varieties which differ in many respects.

It is also important to have a general idea of where this disease starts in relation to other organs of the body. The female pelvis is shown in sagittal section in Fig. 39. You will note that the uterus is situated about in the middle of the pelvis. In front of the uterus lies the bladder and behind it the rectum. Yet in one sense, cancer of the uterus, particularly of the cervical portion, is an external type of cancer, because it is situated at the apex of the vagina where it can be seen in the office with the aid of relatively simple instruments. On the other hand, it does not arise on the surface of the body, such as cancer of the skin or face or a tumor of the soft tissues that produces a definite lump.

Cancer of the Cervix

Since cancer of the cervix is much the more important of the uterine carcinomas, this will be considered first and given the most consideration. From now on and for some time the discussion will be limited to it. A patient with cancer of the cervix, like one with any type of malignant tumor, presents a different clinical picture depending on the duration of the disease and the extent to which it has spread. The course of cervical cancer can be traced through several definite stages.

In the early case of cancer of the cervix, there may be only a small shallow area of ulceration or perhaps a little growth, red and granular or wart-like, projecting slightly from the surface of the cervix. The patient at this stage has perhaps noted a little unusual vaginal bleeding, but has experienced no other symptoms. She will have had no pain, because this organ, the cervix, is rather insensitive. Perhaps she has had a little leucorrhea, or vaginal discharge, but this symptom has caused no concern because of its commonness. It is in this stage that the disease should be diagnosed, for now the outlook is very hopeful. From two-thirds to three-quarters of the patients who are seen and recognized by the doctor when the condition is "early" will be permanently cured.

In the second stage the disease has progressed a little. The ulceration or growth on the cervix is larger. It has also begun to extend beyond the uterus itself, either along the walls of the upper vaginal canal or else by infiltration into the soft tissues beside the cervix. The patient with such a growth has probably noticed the bleeding for a longer time and perhaps the amount is increasing. The leucorrheal discharge is more obvious and perhaps there is now a little discomfort in the pelvis, although that is not a very prominent feature. The invasion of structures well supplied with sensory nerves has not begun. There is no interference with any vital function, such as respiration or digestion, and the patient remains well nourished and retains her strength. The bleeding may be intermittent and a few months of freedom from it may give a measure of reassurance which allows the loss of precious time.

Yet the disease continues to progress. It eventually erodes away the whole lower part of the uterus, producing an immense ulcer, lined by gray devitalized and degenerating tissue. The advancing margins of the cancer have spread down the vaginal canal and reached out to the bony walls of the pelvic cavity. Essential organs, such as the ureter, bladder and rectum are now encroached upon by the growing tumor. The patient develops various pelvic complaints, and her general health is now suffering from the anemia of repeated bleeding and the effects of the chronic infection accompanying the ulceration of the disease.

Unfortunately, the greater portion of all cases of cercival cancer are already in this, the third, stage when they first come to the clinic or the doctor and now only one case in ten is cured. The low cure rate in the treatment of patients in this stage must be regarded not so much a technical failure but the result of economic and social causes. Practically every patient who comes at this stage has had her symptoms for some time. Either she has been too unintelligent to consider coming to a doctor, or she has been too afraid to face the possibility of cancer, or else she has been to an uninstructed physician who has overlooked the diagnosis entirely.

There is a last stage, which we fortunately do not now encounter very frequently among new patients. In this group the disease has actually extended beyond the pelvis and has involved neighboring organs. It has grown forward to involve the bladder and the patient is having urinary symptoms or perhaps backward to infiltrate the wall of the rectum and produce obstruction. The patient now presents the typical picture of what one commonly regards as an advanced cancer case. Practically none of these cases in this stage are curable.

In summary, it is necessary to review the significance of the three principal symptoms, discharge, bleeding, and pain. Only one of these is of great practical importance in making an early diagnosis. The discharge is apt to be slight, and a small amount of leucorrhea is so frequent in all women who have had children that the patient with early cancer is apt to overlook it. The pain is also unimportant in the early recognition of the disease, because it does not appear until the late stages. For these reasons, it is the simple symptom of abnormal bleeding from the uterus which in the great majority of cases must bring the patient to the doctor.

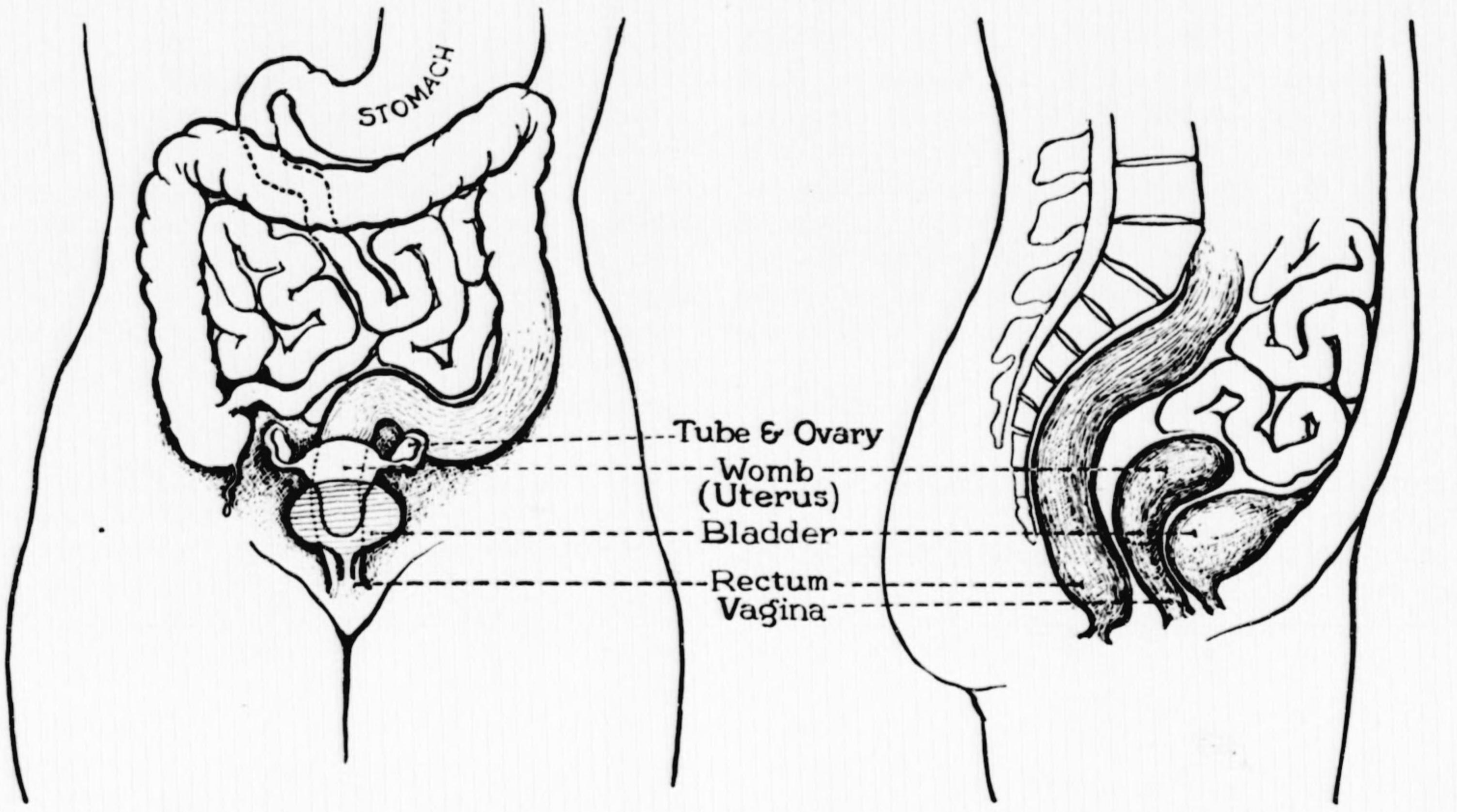


Fig. 39. The structure and anatomical relation of the uterus to the other organs in the pelvis.

The final diagnosis of cancer of the cervix is usually readily made by a simple examination in the doctor's office. Any physician who has seen a few of these cases can thereafter recognize all except the very earliest stages. On the other hand, the practicing physician who devotes most of his time to the care of general illnesses and who sees conditions of the cervix relatively rarely cannot make the diagnosis by clinical judgment alone. Under those circumstances he must exercise special caution by taking a small fragment of the tissue from the cervix, with a special instrument, called a biopsy forceps, and have this tissue examined in the laboratory. If he follows this procedure his diagnosis is just about as valid as that of the man who has specialized in the handling of this disease for a long time.

One very common but benign lesion of the cervix is not infrequently mistaken for cancer. This is the so-called "erosion," which appears as a red, faintly granular zone, about the external opening of the cervix. An erosion results as a rule from some minor infection of the cervix and is especially apt to be associated with the small lacerations of the cervix resulting from child birth.

When the patient first comes to the physician who is not a specialist in the subject, he will correctly consider the possibility that such an erosion is actually a carcinoma. Occasionally he will be convinced that he is dealing with cancer. A doctor recently brought his sister to the clinic with the diagnosis of cancer of the cervix, which he was afraid was even relatively advanced. Actually, she had only a simple erosion which was readily cured by a few treatments. This case needs to be stressed, because the great majority of cases in which symptoms are present that might be due to cancer of the cervix are actually suffering only from a simple and entirely harmless condition such as this erosion. A physician in general practice may even mistake this erosion for a cancer and give the patient a bad prognosis. Such an error, however, is of insignificant importance compared to the opposite error of seeing an early cancer of the cervix and calling it an erosion and sending the patient home.

A word must be said about treatment, because on this subject there exists a good deal of confusion. For many years a very radical operation for the removal of the uterus for cancer of the cervix was the accepted method of treatment and it yielded a fair percentage of cures. Unfortunately this procedure was accompanied by a very high mortality rate, for about one woman in ten who had this operation died immediately as a result. Consequently, when radium became available, it rather rapidly supplanted surgery for cancer of the cervix. A great variety of techniques combining x-ray with radium have been devised and detailed studies have been made to try to determine which was the most effective of several contrasted methods. Most techniques utilize the principle of applying radium and x-ray from several sources with the beams so directed that they converge upon the cervix and the adjacent tissues that are most liable to be affected by the spreading cancer.

The cure rate attainable by radiation therapy has tended to improve gradually with the perfection of techniques. If one takes all cases of cancer of the cervix as they present themselves for the first visit, one can now predict that about one-quarter will be alive at the end of five years. Of those that live five years, almost all will live to die of some other cause than cervix cancer.

The outlook for the individual patient depends particularly upon the stage of the disease at which she first presents herself. If she comes to the clinic with her cancer in the first stage, she has a three to one chance of a five year cure. If she comes in the third stage, the odds are reversed and the chances are considerably against her. In the fourth stage, the outlook is nearly hopeless, although a few cases are cured and quite a number are temporarily benefited by the radium or x-ray treatment.

Cancer of the Corpus

Cancer of the corpus, the second variety of uterine cancer, offers many points of contrast to what has been said about cervical carcinoma. It arises, as has been pointed out, from the mucous membrane lining of the interior of the uterus itself.

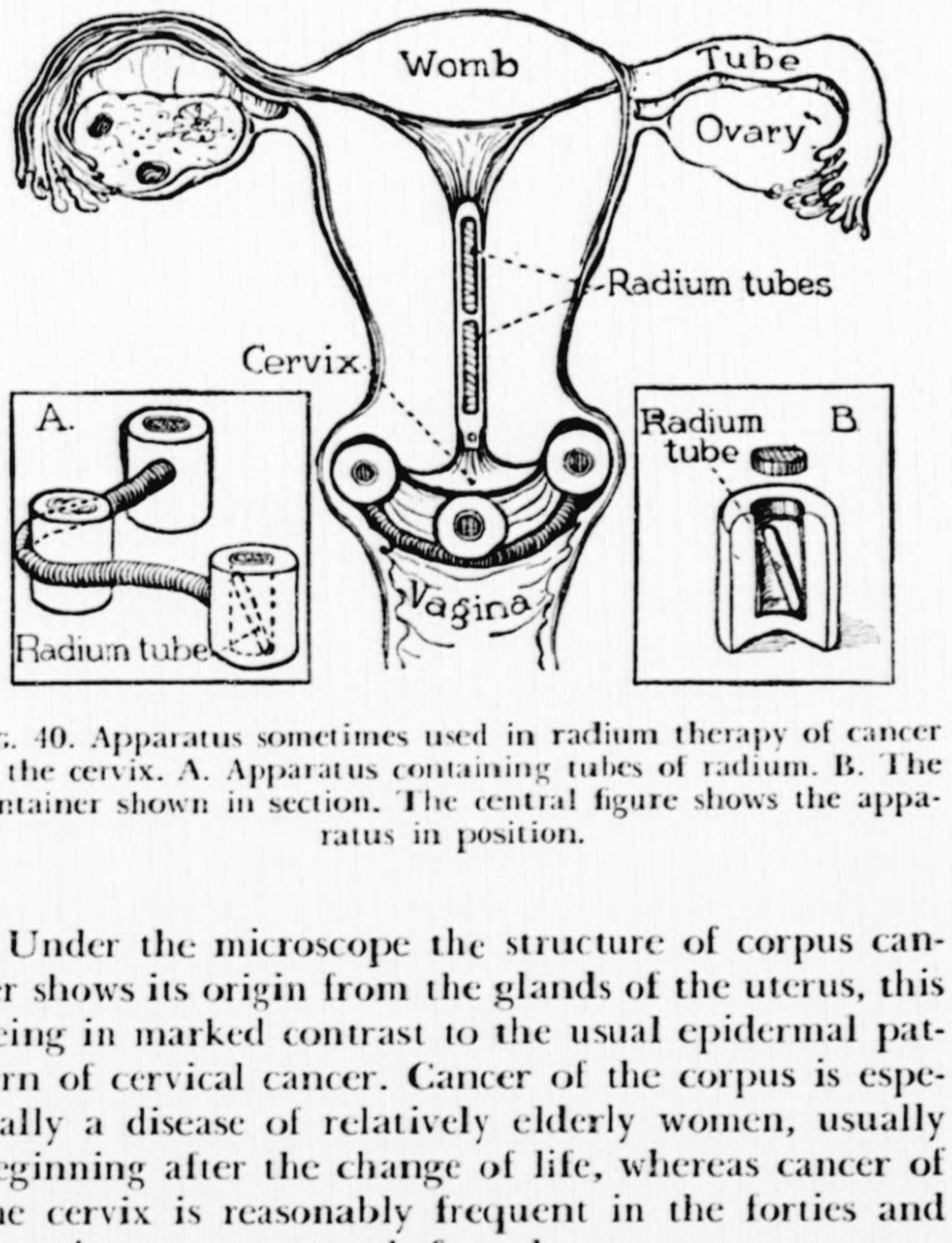


FIG. 40. Apparatus sometimes used in radium therapy of cancer of the cervix. A. Apparatus containing tubes of radium. B. The container shown in section. The central figure shows the apparatus in position.

Under the microscope the structure of corpus cancer shows its origin from the glands of the uterus, this being in marked contrast to the usual epidermal pattern of cervical cancer. Cancer of the corpus is especially a disease of relatively elderly women, usually beginning after the change of life, whereas cancer of the cervix is reasonably frequent in the forties and sometimes occurs even before that.

Finally, it is of some interest that corpus cancer tends to occur in women who have not had children. This does not mean that women who have had children cannot have this type of cancer, but it does mean that if you take a series of cases with this disease, it will be found that there are more women who have not had children than there are women with children in the general population living at the same age. This fact again reverses the conditions which are found for cancer of the cervix, which has an evident tendency to occur in women who have had children. From this contrast, it has been inferred that cancer of the cervix is predisposed to by the injuries associated with childbirth, while the disease of the body of the uterus is perhaps in some way dependent upon the endocrine constitution of women who have been sterile.

Cancer of the corpus uteri is not often observed in its earliest stages, because it is hidden within the uterine cavity. It begins as a small papillary structure which projects from the mucous membrane. Extension takes place slowly, the growth gradually spreading out over the interior of the uterus and slowly infiltrating the muscular wall. Eventually it may perforate into the peritoneal cavity where it then spreads rapidly to other abdominal organs.

The characteristic symptom of this type of uterine cancer is a small amount of vaginal bleeding, sometimes only a spot or two, developing in a woman who thinks she is through with her menstrual periods and past her change of life. Since such bleeding appears to be abnormal to almost all women, patients with this disease are apt to consult a physician rather promptly.

On the other hand there are certain difficulties in reaching a final diagnosis of corpus cancer not met in cancer of the cervix. The gynecologist cannot see the inside of the uterus directly or with the aid of any commonly employed instrument. The only way in which this diagnosis can be made is for the doctor to insert a little instrument through the canal of the cervix, which is very narrow, and grasp a little of this tissue for examination by the pathological laboratory. This is called a curettage and to be thorough requires a hospital admission and an anesthetic. This is the reason why, when a woman has abnormal bleeding from within the uterus itself it is usually necessary for her to enter the hospital and submit to this very minor operation of dilation of the cervix and curettage of the uterine cavity.

There are other causes of bleeding after the menopause, so that after the curettage the patient may be told she is perfectly well and can go home after two days, secure in her own mind that no cancer is present. On the other hand, the curettage may yield cancer tissue and then she will have to be treated more radically.

For various technical reasons cancer of the body of the uterus is, except in the very elderly or infirm, best treated by surgical removal of the uterus. This disease is more often cured than cancer of the cervix, which is perhaps unfortunate because it is a much rarer disease. About fifty per cent of all patients with corpus

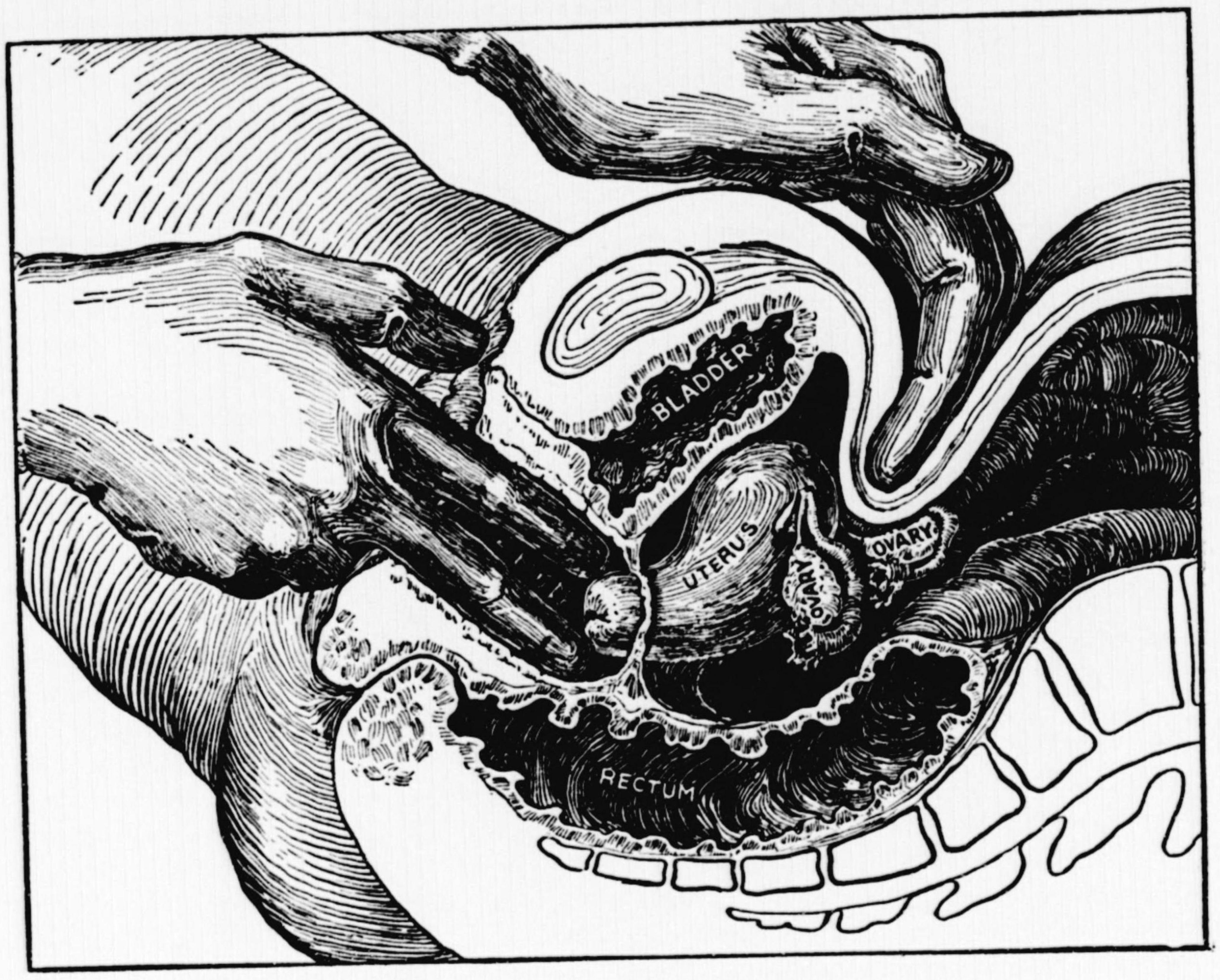


Fig. 41. Bimanual examination of the uterus.

carcinoma remain well. Few varieties of cancer anywhere in the body yield such favorable results.

In closing, let me emphasize again the importance of uterine cancer for a group interested in prevention by education. It is a disease which has a characteristic symptom, which should be significant to any informed woman. The tumor is usually accessible for both diagnosis and treatment. It is a cancer which with little risk can usually be cured when the patient seeks advice immediately after the initial symptom.

Cancer of the Stomach

GEORGE T. PACK, M.D.

Cancer of the stomach kills more people each year than any other single type of the disease.

This is partly because its early symptoms are often disarmingly vague. It is also partly due to the fact that its diagnosis requires a relatively great degree of expert technique.

Dr. Pack is recognized as one of the outstanding men in the field of gastro-intestinal cancer. He has prepared an interesting and readable article which should convince the intelligent reader that the situation is far from hopeless.

A conference held not long ago under the auspices of the National Advisory Cancer Council also emphasized that fact. Improved diagnosis and an increasingly high average of operative skill are combining to greatly improve the chance of cure.

This is a field where education, followed by close personal attention will bear fruit.

WHEN eight of every 100 men and eleven of every 100 women who reach the age of 35 years are destined to acquire cancer and when the yearly American toll of cancer dead is equal to the total mortal casualties of America in World War I, then it is time for the public as well as for the medical profession to awaken to the greatest disease menace the human race has ever known. From the Revolutionary War until the attack on Pearl Harbor, the United States has engaged in six major wars which have consumed fifteen years of our national existence. During these fifteen years of battle, only 244,000 soldiers were actually killed in combat. During the past fifteen years, deaths from traffic accidents totaled more than 400,000 persons, while during the same fifteen year interval almost 600,000 Americans died from cancer of the stomach. Of the various cancers which bring about death through failure of early diagnosis or failure of treatment, cancer of the stomach ranks first, causing 40,000 deaths yearly in our country or 30% of all cancer mortality.

Geographical and Racial Distribution. A study of the incidence of gastric cancer in the various states of the Union has led to the surprising discovery, that it is much more frequent in the relative sense in the upper central states bordering on the Dominion and in the Empire State of New York. Perhaps this may be attributed to the large proportion of Scandinavian and Jewish Americans living respectively in these locations, as both groups seem to be commonly afflicted with cancer of the stomach. The explanation of this preponderance remains a mystery. No people are more exacting and fastidious in the preparation of food than the Orthodox Jews; perhaps the only tangible difference in food selection is their preference for salty foods of high protein character. Cancer of the stomach is said to be relatively infrequent in Mohammedans, who boil their food and drink. The reputed rarity of the disease among primitive peoples is not substantiated when proper investigations are conducted among those who live long enough to enter the so-called cancer age. For example, the Eskimos of Labrador and Alaska, who subsist chiefly on meat and fish, are said to acquire cancer of the stomach occasionally among the older individuals. Statistics from Japan indicate that gastric cancer is two or three times as frequent there as it is in America; the explanation of this difference is not obvious, but it is probably approved in both civil and military circles at this time. In an island of the Netherlands East Indian group, in which the population is equally distributed between Chinese and Malays, reported necropsy figures show cancer of the stomach to be a common cause of death among the Chinese and yet it was encountered only with great rarity in the Malays; these people enjoy the same environment and have dietary habits which are not dissimilar. The American Negro apparently has the same incidence of cancer of the stomach as his white countryman.

The factors of Age and Sex. Cancer of the stomach is twice as frequent in males as in females. It is a disease which commonly develops in middle age or later life, the average age in our series being 59 years. It may occur in young people; e.g., we have collected a series of 500 cases in individuals under 30 years of age.

Heredity. Cancer of the stomach is not a directly inherited disease such as glioma of the eye and hemophilia. It is the susceptibility which is transmitted through generations and this is quite a different thing from the disease itself. The child inherits the physical make-up of the parents and by constant association acquires their habits and environmental influences, some of which are cancer hazards. The type of stomach in which cancer develops is perhaps a recessive rather than a dominant characteristic, nevertheless, the tendency occasionally manifests itself by the occurrence of several cases of the disease in the one family. I have removed gastric cancers in brothers within a two weeks interval, their ages being within the same quinquennial period. Several instances have been reported in medical literature of cancers of the stomach occurring simultaneously in single-ovum or identical twins. In addition to this fundamental, latent or inherited susceptibility, there must be an external influence, a provoking stimulus or irritation of diverse types which combines under proper conditions to induce the development of cancer in the stomach. There are two types of habitus or physical configuration which seem to predispose to the origin of this disease. In one, the individual is the short, hypersthenic, broad-shouldered, hairy type, a gastric athlete who digs his grave with his teeth and never suffers from indigestion in spite of a gargantuan appetite. He may develop cancer late in life. The other type is the anemic, beardless, asthenic, long-waisted person, who resembles Shakespeare's description of Cassius. He suffers dyspepsia from childhood and may develop cancer of the stomach in early life.

Experimental Production of Cancer in Animals. There is no satisfactory explanation for the extreme rarity of cancer of the stomach in lower animals. Tumors of all types, both benign and malignant develop spontaneously in animals of all species, but cancers of the stomach seldom occur except occasionally in hogs and chickens. In considering the eight or more essential differences which exist between human beings and the lower animals, such as (1) the substitution of tradition based on the written record or spoken word, for natural instinct, (2) the employment of fire for manifold purposes including the preparation of food, (3) the preservation of the unfit, (4) the adoption of clothes, (5) the cultivation of moral or spiritual values, (6) barter and exchange, (7) the thwarting of natural desires and (8) worrying about the future, perhaps the first two haven't any significant bearing on the problem. Cancer producing habits are as yet unrecognized in relation to cancer of the stomach. Domestic and wild animals and infants too young to come under parental influence and habits will not touch water or food that is too hot to be comfortably tolerated in the mouth. The experimental production of cancer in the stomach of animals is entirely possible, so the susceptibility must be present though latent. For example, the application of methylcholanthrene to the lining of the stomach results in the occurrence of adenocarcinomas, which are the same kind of cancers that originate in humans. One of the classical experiments on record was reported by Johannes Fibiger of Copenhagen, who found that rats fed on cockroaches infested by a tiny worm, would develop cancer of the stomach. He attributed the onset of the disease to the irritating action of the worm which could often be demonstrated as imbedded in the tumor on microscopical sections. Now we know that Fibiger fed his rats on white bread and water, a diet deficient in vitamin A; certain laboratory animals fed on a diet deficient in vitamin A may grow tumors in their forestomachs which closely resemble their human counterparts.

Factors which predispose to the occurrence of cancer of the stomach. We always think kindly of the stomach because we derive so much pleasure through its use. The ancients attributed many non-existent virtues and functions to it. It was considered to be the center of the emotions, and for a person who is hungry, it probably still is. This large dilated sac situated at the end of the gullet and at the beginning of the intestinal tract proper, serves as a temporary reservoir for food and initiates the process of digestion. Another function has to do with the production of blood not in the organ itself but through the medium of certain factors which it secretes into the blood stream and together with other substances originating in the all provident liver influences the bone marrow in the formation of blood.

The stomach is subjected to all sorts of abuse by everyone, who pays scant attention to what and how he eats. The stomach is equipped with a lining, which although not of cast iron, has the ability to tolerate

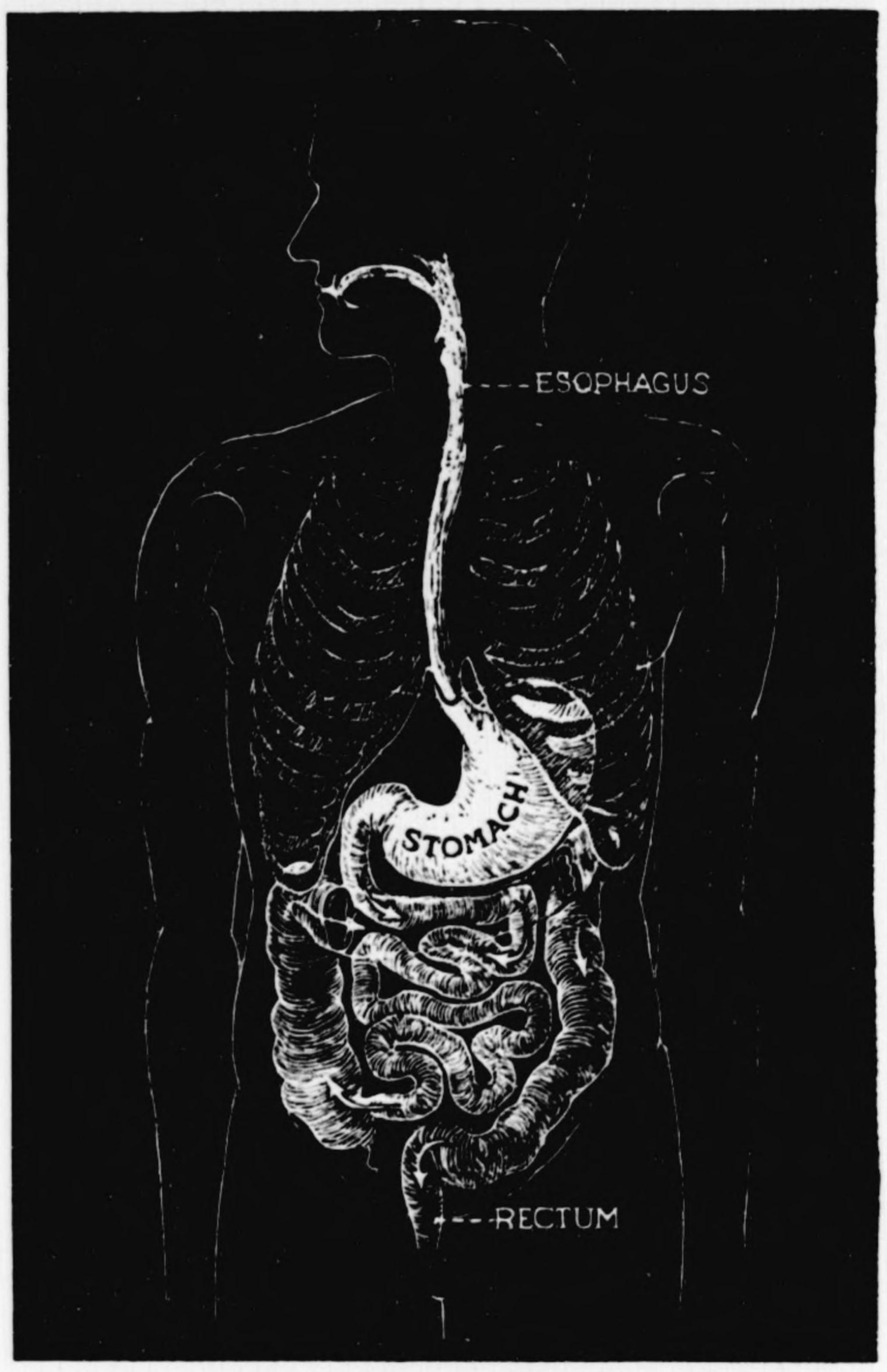


FIG. 42. The digestive system.

remarkably well the various insults that are heaped into it. We are dictated to by our appetites in the selection of food, rather than upon the ease with which it could be digested or the needs which the body has for certain food ingredients. Fortunately for us, because of the good dental care in this country, our mouths are better equipped to masticate food than in many other countries of the world. It does seem that certain factors of chronic irritation or of abuse play a part, although not the only role, in causing cancer in this particular organ. Many patients with gastric cancer will relate a preceding history of bad teeth, or perhaps had their teeth extracted and remained edentulous for one or more years during which time they learned faulty habits of eating, particularly the bolting of food without proper mastication. Bad or infected teeth may exert a role because of the constant presence of infection, which contaminates the food before entering the stomach. Some individuals will swallow food and liquids which are too hot, either by heat or spices, to be held comfortably in the mouth. The stomach, whose lining is rather insensitive, of course, does not cause much immediate objection as far as symptoms are concerned, but the irritation is sustained just the same.

Cancer is more common than ulcer in the stomach. The majority of so-called "stomach ulcers" are really in the duodenum, the first part of the small intestine, immediately where the stomach terminates. Duodenal ulcers never become malignant, that is to say, undergo cancerous transformation. Considerable argument is evoked over the moot point about the danger of true ulcers in the stomach serving as a nidus or starting point for cancers. From the practical point of view, it is most important to ascertain whether any ulcer in the stomach is simply an inflammatory ulcer or an ulcero-cancer. This conclusion cannot always be reached in spite of such determining aids as the history related by the patient, x-ray studies and examination of the interior of the stomach through a gastroscope. If an ulcer in the stomach proper, does not completely disappear on subsequent x-ray films made four to six weeks after the instigation of conservative or medical treatment, surgical removal is indicated for fear that it may be malignant.

Diagnosis. The Signs and Symptoms of Cancer of the Stomach. Inasmuch as most members of the laity feel perfectly competent in diagnosing and treating all diseases of the stomach, it may be presumptuous on the part of the author to contribute the following

Fig. 43.

words of advice. This inherent wisdom which springs from folklore and old wives' tales is rightly supplemented by the suggestions constantly emanating from numerous radio orators and through the medium of magazine and newspaper advertisements for proprietary concerns. These oracles without hesitation will advise you to take this or that alkaline powder, effervescent mixture, drops or tablets, to relieve gastric pain or indigestion. By their uncontrolled and nonprofessional medical advice, they have unquestionably increased the mortality rate from cancer of the stomach through undue delay in diagnosis. A woman who would seek immediate consultation at the first indication of a lump in the breast will take a proprietary

Fig. 44. Indigestion.

medicine to treat indigestion of unknown cause until her loss of weight or anemia is so great as to compel professional attention. There is no more dangerous thing to do, if you are 35 years of age or older and entering the cancer age, than to treat yourself for chronic indigestion.,

Indigestion which appears for the first time in life in a person 35 years of age or older and which cannot be readily explained by a recent dietary indiscretion or over-indulgence in alcoholic spirits and which persists for an unaccountably long time is a cause for worry, even for alarm. The majority of cancers in the stomach cannot be felt through the abdomen until the disease is so advanced that it cannot be cured. Of course, not all indigestion is of gastric origin, in fact the stomach is the biggest liar in the abdomen. It responds by causing loss of appetite, discomfort after eating or dyspepsia, to diseases that are located in other organs such as the appendix, gallbladder, pancreas, liver, small intestine, colon, rectum and pelvic organs. It is not for the patient to arrive at this differential diagnosis, however, much less a radio announcer hundreds of miles away, when even the most expert medical diagnostician often requires x-ray studies before a conclusive opinion can be reached.

The culpability for failure to establish an early diagnosis and for failure to institute early and curative treatment lies not with the patient alone, but unfortunately with the general practitioner of medicine. I hesitate to condemn my colleagues in the profession for their laxity in this situation, but when my associate Dr. Gallo and I analyzed a thousand case records in which we knew there was an unnecessary delay in the beginning of proper treatment from the time of onset of symptoms, we found to our dismay that in two thirds of the instances the blame for the delay originated with the patient, but in the remaining third the physician first consulted was at fault.

There is no one specific sign or symptom which infallably denotes or heralds the presence of a cancer in the stomach. Among the various complaints listed by patients with this disease are: a progressive loss of appetite, an aversion to particular articles of food such as red meat, rapid satiation at meal times or the inability to eat a normal quantity of food, displeasure instead of pleasure after eating, a discomfort in the upper abdomen or "stomach consciousness," a gnawing distress that is not relieved by alkaline powders or the intake of food, a sense of weight or heaviness as if the stomach were not emptying properly, relief of such distress by self-induced vomiting, chronic and repeated nausea, regurgitation of sour liquids and undigested food, difficulty in swallowing, an increasing tendency to substitute liquid for solid foods, vomiting of blood fresh or partly digested, the passage of black, tarry stools (in the absence of iron or bismuth medication) and finally an unexplained loss of weight or anemia. Every one of these complaints may be induced by one or another non-cancerous abdominal disease, but cancer must always be excluded first as the possible cause because of its greater importance.

FIG. 45. Unexplained loss of weight.

X-ray Diagnosis. The use of x-rays or the Roentgen apparatus is a most necessary aid in the diagnosis of cancer of stomach, if its recognition is to be made sufficiently early to permit a cure to be attempted. If the patient waits until the diagnosis becomes clinically obvious, then even the most radical attempts at surgical removal may end in failure. The X or Roentgen-rays make all parts of the stomach readily visible so that a growth, i.e., a benign or malignant tumor or an inflammatory ulcer can be recognized by a trained eye. Gastric cancers even when small may cause a change in the contour of the stomach or interfere with the flexibility of part of the stomach wall or may intrude their unwelcome bulk into the inlet or outlet of the organ and handicap respectively the entrance and the exit of food. X-ray pictures and fluoroscopic study of the stomach after swallowing an opaque meal enables the physician, within limitations, to appreciate the exact location of the cancer in the stomach and the extent of this involvement. Such information is an invaluable aid to the surgeon, who is planning his method of attack on the particular cancer. The cost to the patient of having a thorough x-ray study is one of the greatest obstacles to the early diagnosis of cancer of the stomach. It is to be hoped that this problem will be solved so that patients regardless of their finances can have the cause of their complaints discovered by x-ray studies if such be necessary.

Gastroscopic Diagnosis. As a supplementary measure to x-ray examination, the gastroscope is a valuable adjunct. It should not be used as a substitute for x-ray study and should only be employed after the complete x-ray investigation has been made. The usual instrument is a long flexible hollow tube containing a system of lenses and a system of magnification. The tip of the instrument is brightly illuminated. The tube is quickly passed into the stomach under local anesthesia, the stomach inflated with air, the eye of the examiner is quickly applied to the ocular end or eyepiece and the interior of the stomach is visualized and inspected. The method is harmless, painless, accurate, quick and does not require hospitalization. It is surprising how readily one can see and diagnose the various abnormalities in the interior of the stomach by means of this ingenious instrument.

The Treatment of Cancer of the Stomach. Cancer of the stomach is treated by surgical removal. Such operations are inevitably of major character because they entail the excision of a part or even all of the stomach. The stomach or the remainder of it, after the operation, remains in daily use; it cannot be placed at absolute rest, as a fractured bone, until it heals. The reparative suturing by which the stomach is reconnected with the small intestine, after the cancerous segment has been removed, must be done with extreme care and perfection, as it needs to be watertight. The operative mortality for gastric resection, that is to say the frequency with which death occurs following such operations for cancer is becoming lower and lower, due to several factors. In the first place, there has been a very great improvement in surgical technique. In the second place, many more surgeons have been trained to execute the fine operative precision necessary in the removal of these cancers. Finally, better knowledge exists concerning the methods of preparing a patient for the operation and taking care of him during the important post-operative period.

One can sacrifice a portion (two-thirds or threefourths) of the stomach without influencing one's subsequent digestive life. After convalescing from these operations, the patient is able to eat practically normal diets; within a period of two months the remaining stomach will expand and take care of normal meals, enabling the patient to regain weight and become a normal individual in every respect.

Unfortunately many cancers of the stomach are incurable by the time the patient is seen by the surgeon. Once the disease has extended in a wide-spread fashion far beyond the confines of the stomach, it is beyond the scope of the most skillful surgeon to remove it in its entirety. In the present age, it is the incurable extent of the disease rather than technical difficulties in removal, which blocks the efforts of the surgeon; for example, it is possible to resect cancers of the stomach together with parts of adjacent organs to which they may have become immovably attached, such as the entire spleen, a segment of the transverse colon, a portion of the capsule and substance of the liver, a part of the pancreas.

FIG. 46. Examination of the stomach through a gastroscope. Insert A shows a gastroscopic view of normal stomach lining. B, early cancer of the stomach.

In occasional instances, it has been necessary to remove the entire stomach because of the degree of involvement. The operation is completed by anastomosing or connecting the esophagus (gullet) directly to the small intestines. In other words, the stomach is not an organ that is necessary for life. These people who are lacking a stomach do not appear any different from the average citizen. It is true that they remain thin and cannot gain weight but they are not emaciated. They should be examined occasionally because of their tendency to develop anemia. One would logically assume that without the use of this stomach reservoir to hold the food, these people would be compelled to eat small meals many times a day. This is true for the first two or three months of their postoperative existence, but after that the intestines dilate to accommodate the meal without distress.

One reason for the high death rate from cancer of the stomach in the past was that many cancers situated in the upper end of the stomach were deemed inoperable and incurable because of the surgical difficulties encountered. Many people do not realize that two-thirds of the stomach is situated above the margin of the ribs and is under the left lobe of the liver and closely approximated to the diaphragm. This region is not easily accessible, therefore it is difficult for the surgeon to operate in this part of the abdomen. Eight to ten percent of cancers of the stomach are located in this upper end, called the cardia, and prior to the past decade, these patients were condemned by the very location of this cancer. Now it is possible to remove these cancers surgically, not through the abdomen, but through the chest. The cavity of the chest is opened through a long incision between the ribs, the diaphragm which is a muscular partition between the abdominal and chest cavities, is split and the upper segment of the stomach is freed and drawn into the chest. With such an excellent exposure, it now becomes readily feasible to remove the upper end of the stomach and the lower part of the gullet after which a new connection is established within the chest, the diaphragm is repaired and the operation completed. This operation is rapidly finding favor and marks another milestone in the forward march against cancer of the stomach.

Conclusions.

1. Cancer of the stomach is a curable disease.
2. The rate of cure depends on the diagnosis being made at an early stage in the development of the cancer.
3. The public should be more alert and concerned about the cause and character of indigestion occurring in adult life.
4. The individual who treats himself for chronic or progressive dyspepsia has selected a poor physician.
5. X-ray examination supplemented by gastroscopy is the most reliable method of detecting cancers of the stomach when they are in a curable stage.
6. The surgical removal of a cancerous segment

of the stomach, although a major operative procedure, is now relatively safe because of many technical improvements.

7. In advanced cases, it has even been possible to remove the entire stomach with restoration of health and preservation of life.

8. The removal of cancer of the extreme upper segment of the stomach through the chest has now become feasible and heralds the beginning salvage of eight to ten percent of gastric cancers which were formerly classified as inoperable.

Cancer of the Rectum

GEORGE E. BINKLEY, M.D.

Cancer of the rectum is one of the series of gastro-intestinal cancers that offers an excellent opportunity for early diagnosis and cure.

Dr. Binkley's paper deals not only with the problems of diagnosis and treatment, but with post-operative adjustment on the part of the patient. This has been in the past a serious and, at times, a difficult matter. Now, however, it can be accomplished with a minimum of disturbance and with no unpleasant features.

Cancer of the rectum is also interesting because its proper evaluation and consideration involves intelligent understanding of proper and regular bowel habits and of the proper treatment of hemorrhoids so commonly ignored or neglected.

It is, therefore, a type of cancer where both preventive and corrective phases of the educational process are involved and as such offers the layman an excellent field for developing sound educational methods and technique.

THERE are a few facts which I think the general public should know about rectal cancer. One can safely say that the status of treatment today is better than it has ever been. This does not mean that it is perfect; in fact, there is a great deal of room for improvement. That improvement can be brought about largely by the patients themselves who must seek medical advice early. In order to do so, it is necessary that they have some idea of the symptoms of this disease.

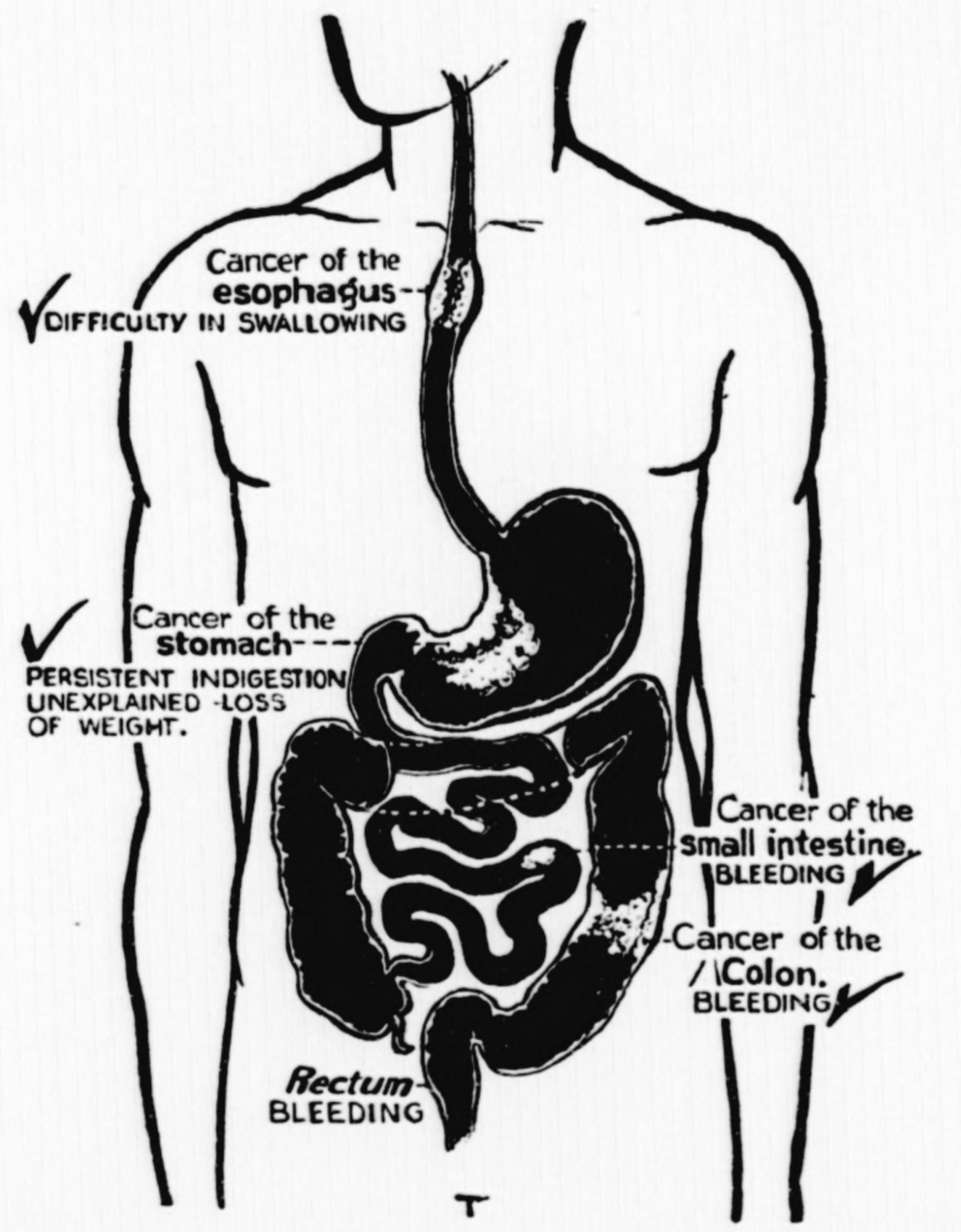


FIG. 47. Illustration of symptoms and possible locations of cancerous growths in the digestive system.

In checking the records of this hospital covering 1,000 patients with cancer of the rectum, it is interesting to note that this disease is not entirely a disease of old age. There were very few patients below the age of 20, but there were quite a number between 20 and 30, in fact 4.4 per cent of the total number of cases. The maximum number of cases were found in the age group 50 to 60. It is in the younger age groups, perhaps, that the greatest mistakes are made. Many people think that no one between the ages of 20 and 30 ever has cancer, hence they are not alert to discover the disease. In this series of cases, the males are dominant, except in the age group 20 to 30 where there are almost as many females.

Another factor which should be mentioned is the fact that there seems to be a tendency for more cases of cancer of the rectum to occur in certain families than in others. Whether you can say that it is heredity, whether there is a "weakness" or whatever we may decide to call it, it is not unusual to find that the fathers or mothers had this type of cancer, and usually in the same location. I have one mother and daughter, the mother was 48, the daughter about 22. They were operated upon, and they both are alive and fine today, and that was about four or five years ago. We have had a number of sisters, and frequently we get a history of a near relative who had cancer of the rectum in the same location.

There are a few symptoms of early rectal cancer that everyone should know. These are symptoms that occur in inflammatory as well as in malignant disease, but their presence *may* mean early cancer:

1. Sudden change of bowel habit
2. Bleeding from the rectum
3. Mucus
4. Pelvic pressure

Constipation. This is a term for which nearly everyone has his own definition, but let us think of it as a sluggishness of the bowels. If a person has always been constipated, in early cancer he usually becomes more so. If he has never been constipated, he will notice that he needs a little cathartic or something to move the bowels. I think you will find that symptom in possibly fifty per cent of very early cases. Constipation is a common complaint to which people pay very little attention, but, nevertheless, a sudden onset of constipation, or a complete change of bowel habit, is a symptom that is worthy of investigation: it may mean early cancer.

If there is ulceration of a tumor there may be a lessening of the constipation. In other words, the very constipated person, who has never had a normal bowel movement since childhood, finds he is having three or four daily movements without a cathartic. This is just as dangerous as constipation; he has an increased amount of mucus, and his constipation has been displaced by a tendency to liquid stools or increased amount of mucus, whereby he will pass three to five stools a day.

Carry that a step further and we have what is popularly known as diarrhea, that is, frequent stools, and this condition may alternate with constipation or be present with it. Finally we may have a situation where a person, after numerous stools, has a tendency to want to go to the toilet and pass slime or mucus, a condition we might term tenesmus.

With these three symptoms alone, very frequently a diagnosis of colitis is made without any examination, and the patient is treated for several months by various drugs and all kinds of diets, until he has reached an inoperable stage of cancer. There should never be any diagnosis of colitis without a thorough examination in a way I shall describe later.

As the disease progresses one finds gas in the abdomen, also passage of gas, and as soon as there is sloughing from a tumor in the lower intestine the gas usually has a very foul odor.

Bleeding. The next important symptom is blood. We are all aware of how common is the occurrence of hemorrhoids. They are so common that many people disregard them. People carry all kinds of suppositories and ointments around with them, never think anything about it, and will not go to be examined. Perhaps 75 per cent of the patients who have cancer decide for themselves that they have hemorrhoids and do not seek medical advice until the condition gets quite bad. No one should tolerate bleeding from the rectum without an immediate investigation to see whether it is caused by cancer. It is only by getting these cases early that we are going to get good results and cures. When we *do* get them early, the results are excellent.

Blood does not necessarily mean either cancer or hemorrhoids; it may mean many other conditions of the rectum or colon, but people should bear in mind that bleeding may be a symptom of cancer. If they are examined and there is no cancer, and they want to tolerate their bleeding, all right, but have them be sure that they are not harboring a cancer which is growing to the inoperable stage.

Mucus is another symptom which is not so distressing to the patient. As time goes on, people with this symptom become more or less anemic; there is a certain loss of appetite and a loss of weight; an increased nervousness; a sensation of pressure in the pelvis; and a feeling of general debility. Oftentimes it cannot be explained. I have had patients tell me that for months they thought they were just a little nervous or jittery because they had been working hard. A great many people will tell the doctor that they have had some trouble in the family and haven't felt well for several months. They found an explanation in their own minds, put it down to that sort of thing instead of investigating the trouble and finding the real cause.

Pressure in the pelvis is a symptom. Pain, however, is not an early symptom; it is a late symptom, but you can have nervous types of mild pain in the upper part of the pelvis. Pain in the lower part of the pelvis very frequently means cancer in the upper rectum. This pain is in the nature of a distress, hard to describe, throughout the back and the pelvis. This is often an early symptom; when the disease gets very extensive there is a great deal of pain.

A diagnosis cannot be made from symptoms alone. There must be an examination. That examination is not difficult; neither is it painful. It can be carried on in the office by any doctor who has the right equipment, within ten or fifteen minutes, provided the rectum is clean. The inside of the rectum can be seen with the help of an instrument known as a protoscope. This is simply a tube with a light on the end. With it the doctor can see for a distance of twenty-five to thirty-five centimeters just as plainly as he can see the palm of his hand. The protoscope is passed through the rectum and with it one can see the mucosa from the anal canal into the lower sigmoid. The examination can be carried out with the patient lying on his side, or in the knee-chest position. (See Fig. 48.)

A good many of these tumors can be palpated, or felt with the examining finger. In fact, I should say that sixty per cent of the early lesions within the rectum can be palpated. Far more than sixty per cent of the late lesions can be palpated as they grow farther down.

Cancer of the rectum is a surgical disease in which we use x-ray and radium as part of our surgical kit. The rectum is removed by surgical resection and an artificial anus is made in the abdomen. This operation has perhaps the widest field of usefulness of any of our present-day methods of treatment. The procedure is usually carried out in one operation, sometimes in two, and the mortality is comparatively low. We will run along sometimes with from 20 to 60 patients without a death, but the mortality rate should range somewhere between five and ten per cent if you are going to include some patients that you are not absolutely sure are going to stand the operation. After all, we are treating cancer and we are treating the patient as well; you can't carry out major surgery without some operative mortality.

An alternate method is to resect the rectum with a perineal artificial anus, that is, with an artificial anus in about the same location as the normal. This method restricts your dissection somewhat, and I do not think it is as good as the first method. I have tried it out in a number of cases, and I have discontinued using it except perhaps now and then in some patients who absolutely refuse to have the other.

There can be a perineal resection without an artificial anus. That would be the ideal thing if we could do it routinely, but we can't and get the same results that we do otherwise. In that type of operation, your dissection has to be restricted. As most of you know, cancer spreads to the lymphatics and sometimes gets a little ahead of the palpable tumor. If there are a few lymph nodes missed in the operation there will be an early recurrence. Therefore, this is a very restricted method.

Rectal cancer is sometimes treated with x-ray and radium treatment. We have nearly 50 cases who have gone five or more years after this form of treatment, without a recurrence. Here again we have to get our patients early for this method of treatment to be effective. If we could get all of these patients when the tumors are the size of your little finger, or even the end of your thumb, then we would be able to treat very successfully with x-ray and radium alone and no operation whatsoever.

Next we have treatment with x-ray, radium and surgical operation. This treatment is used rather extensively in this hospital because we try to include a lot of advanced cases in the group we consider operable and offer them a cure, if possible, or a good deal of palliation. For that reason we use a good deal of x-ray before the operation, then operate on them and use some x-ray afterwards. Many of these cases we feel certain are not going to be cured, but we can prolong their lives for a number of years and they are pretty happy and satisfied.

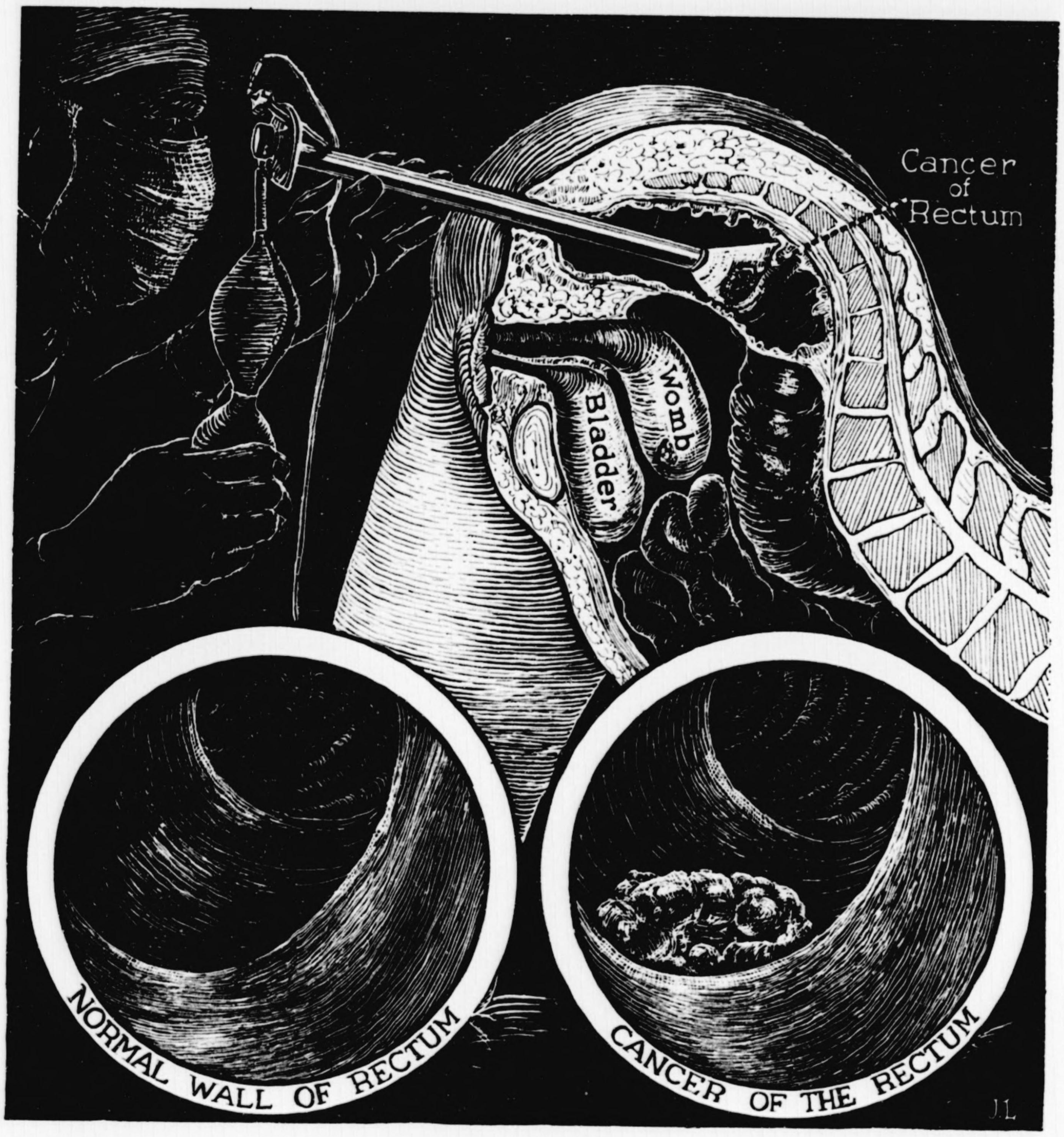


FIG. 48. Examination of the rectum with the aid of the proctoscope. Inserts show normal rectum and a cancer of the rectum as seen through the proctoscope.

In the majority of cases, as I said before, the ideal treatment is surgical resection with abdominal artificial anus, meaning an artificial anus on the side of the abdomen. The prospect of this treatment is one reason for causing patients to delay. As a matter of fact, an artificial anus is not anyways near as bad as it is believed by the public or the profession. Some doctors, who have not had sufficient experience with it, think that it is terrible. I know one doctor who tells me every time he sends me a patient, "You would never do a colostomy on me." But he keeps sending patients to me and his patients get well. He is an elderly man, and you will never change him, but his patients are well and they get along with an artificial opening, so it doesn't make any difference.

The care of an artificial anus no longer requires the use of the unpleasant rubber bag. There are different substitutes for this older method. Only yesterday I saw a fellow who came in to find out how to take care of his colostomy, and he had two sheets of paper all written out on what he should eat. Well, as far as I could see, it didn't make very much difference what he ate, because he had both sides, one to eat and one not to eat. He had things on one that were constipating, and he had things on the other that were loosening, so I told him I thought he could use his diet list or throw it away and he would be just as far ahead.

That doesn't mean that diet doesn't affect these people; it does. Each patient has to find out for himself what he can't eat. One fellow told me that if he took a glass of tomato juice it went through him like a dose of salts. Another will tell you something else that will act the same way. Usually inside of three months the patient knows one or two things that give him diarrhea and, with these exceptions, he goes along and eats everything.

How does he control his bowels? He hasn't control in the sense of muscle control, but he has control in that he can make his bowels move at a time he wants, and he does that with an enema or irrigation. He takes an irrigation either every night or every morning, or every other night or every other morning, some of them will go three days, and they go along from interval to interval without any soil. They may have an accident once in three months or once in six months or once in a year, but some of them never have an accident.

Don't forget: 70 per cent of these patients, I am safe in saying, will volunteer the information within three months to a year that they feel better than they have felt in the last five or ten years. That is due, I think, to being absolutely relieved of what we term intestinal intoxication. They have a different outlook on life. They trade a mean, lowdown feeling, as you might say, for a real good feeling and cheerfully accept their colostomy. After they have had that for three months or six months, you won't get one out of twenty, or maybe one out of fifty, who does not entirely accept the colostomy and go along and enjoy life. Of course we are all different; we all have characteristic nervous tendencies; so there is always the one fellow who can never accept it. I have one man like that at the present time. I sent him to a neurologist to find out why. He is a man about 45; he never was married, but thought that if he might want to get married this would interfere with it. He hadn't anybody that he wanted to marry; it was just one of those things.

As a matter of fact, they do get married. I have a doctor and a nurse. The nurse got married within the last year, and the doctor divorced one wife and got another one seven or eight years ago. So they get married and carry on ordinary life just the same as if they didn't have it. It is only the occasional patient who is not able to adjust himself to the new conditions.

For the most part these people take their irrigations, then they wear a good abdominal support and carry on in their ordinary way, whatever that life may be. I have doctors, lawyers, school teachers, laborers, preachers—they are all carrying on.

So if there is anything we can do to get earlier diagnosis and lessen the fear of operation and of this artificial anus, we have accomplished something. I can assure you that the artificial anus is only about one twentieth as troublesome as the average person would imagine. The operation itself, although extensive, is accompanied by a very low operative mortality and a very good convalescence, because pain is practically nil.

Cancer of the Bladder and Prostate

Benjamin Barringer, M.D.

Men are notoriously careless in caring for indefinite or ill-defined symptoms affecting their health. It is unfortunately true that early signs that might mean cancer of the prostate or cancer of the bladder are constantly ignored or neglected until they become acute.

Dr. Barringer's article is a happy combination of sound, important advice and of humor. He is a wise and experienced clinician who understands and appreciates that the patient is almost as large a factor in cancer control as is the disease itself.

His article is, therefore, valuable not only in itself but as an example of a sound and intelligent approach to the problem of cancer education in this particular field.

People seem to think that the treatment of cancer is a terrific job for a physician. They say, "How can you stand seeing these patients that are dying of cancer? You see them day after day and week after week, and if you are lucky, possibly year after year. How can you stand it?"

The reason we can stand it is that we are improving not only in the diagnosis and the treatment, but also in the number of cures of cancer. Let me instance one cancer, cancer of the bladder. Many years ago, in the Old Memorial Hospital auditorium, I asked the physicians present whether they had ever seen a cancer of the bladder cured. One of them said that there was a distinguished surgeon in this town who had had a cancer of the bladder and he was cured. We knew he was going around and he was apparently well. That intrigued me, and I looked into the history of this case and found that it was not cancer at all, but a papilloma, or benign tumor.

So we started in the old hospital, so to speak, from scratch. We knew that there were no cancers of the bladder being cured by any method, by surgery, radiation, or any other thing, so we had a clear, open field. To me it is much more fascinating to work in a field of that sort, where you really can do something, than to take out perhaps three or four thousand appendices, one after another, in much the same method, year after year. That, I think, would bore me to death.

I think the fact that you can make progress in a disease; see, over the course of years, what that progress has been; see real cures and have patients come back to you that are cured; shows we have achieved something which is of vital interest. Of course, you do have the people who are in trouble and pain, but I will come back to that in just a moment when I discuss the statistics of cures in cancer of the bladder and cancer of the prostate.

Cancer of the breast is an external cancer. The patient can see it, can feel it, can worry about it. Because of this worry she can go to the physician early, and she can get appropriate treatment if she and the physician act together in an intelligent way.

Cancer of the bladder and cancer of the prostate are what might be called semi-internal cancers. They are not on the outside, and they are not wholly on the inside. If a physician be really intelligent and hard-working, he can examine a prostate and feel its consistency, its size. If cancer is present, he can feel it. It is semi-internal. It is not on the surface, but it is half way inside. (See Fig. 49.) Cancer of the bladder is also, so to speak, semi-internal. It can be seen by means of an instrument called a cystoscope, which is introduced into the bladder and permits the bladder interior to be viewed. (See Fig. 53.) If a cancer is present, that cancer can be seen, and a piece of the cancer can be obtained for analysis. Thus, cancers of the prostate and of the bladder are semi-internal.

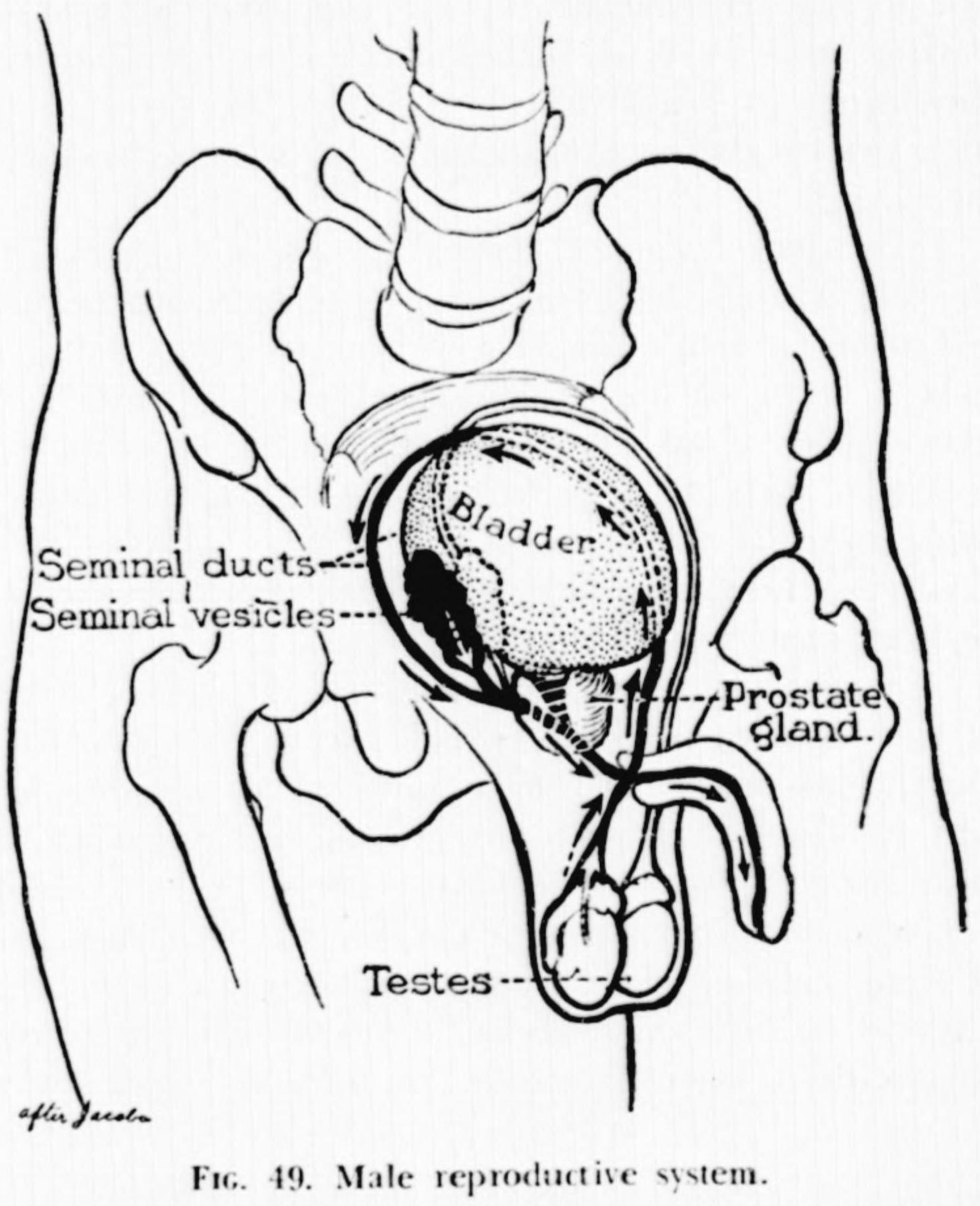


Fig. 49. Male reproductive system.

Cancer of the prostate generally occurs in men over the age of 60. It may occur earlier, but that is the age at which you would ordinarily look for it. For instance, the doctor will see a patient in whom cancer of the prostate might be suspected. If the patient is around 25, one can be pretty sure that he does not have cancer of the prostate.

The symptoms of cancer of the prostate are very vague and are associated with some change in the evacuation of urine. The urine may be evacuated more often than normally, there may be pain in evacuation, there may be the sight of blood. Cancer of the prostate is mixed up with some change in urination

There are other symptoms which are somewhat remote; sometimes they may be attributed to other diseases. A patient may have various pains in the bones of the legs, side-ache pains, but these patients

FIG. 50.

are very vague. I will come to that in just a moment in a little more explanatory way.

Because these symptoms are very vague the patient with cancer of the prostate, obviously, comes to the physician pretty late in the course of the disease, generally one, two, or three years after we have reason to believe the disease has started. Because the symptoms are vague and because this is a semi-internal cancer, the physician is often vague in finding the cancer. Hence, the treatment of the patient is generally deferred until the time when the cancer is beyond where it can be treated very successfully. That was true up to a couple of years ago when our treatment of this disease changed radically as I shall explain later.

Let us now turn to cancer of the bladder. I always like to discuss these two cancers at the same time because they are so totally different from each other. The reaction is different, the symptoms are different; they are very near together, almost on top of each other, but they are as different as the east is from the west in symptoms, time to go to the physician, and curability.

The one thing I should like to emphasize to you is that cancer of the bladder gives one symptom which should bring the patient to the physician early. I presume that 95 per cent of all patients with cancer of the bladder have blood in the urine at an early stage of the development of the cancer. It is obvious how this blood comes. All cancers have poorly developed blood vessels. They bleed rather easily. Remember, cancer of the bladder is in an organ which is eternally on the move. It is either opening up with the accumulation of urine in it, or it is closing to evacuate the urine. It is always on the move. Therefore it is always more or less injuring the cancer which is in it; it is stretching it one way and then squeezing it down the other way. The bleeding which results is seen in the urine.

To men, blood in the urine is a serious symptom. They recognize it, and it gets them to the physician early. In women, it may be confused with menstrual bleeding. Therefore, women with cancer of the bladder come to the physician at a later period than men.

Cancer of the bladder is liable to occur at an earlier age than cancer of the prostate, say from 50 on, and of course it occurs in both men and women. The diagnosis, treatment and cure depend upon three factors: the patient, the family doctor, and the specialist. A coordination between these three is necessary to really get at the trouble. You have got to get the patient to go to the physician, and the physician, if he isn't a specialist or if he isn't equipped to make an examination, should be intelligent enough to send the patient to the specialist and really get the diagnosis made or confirmed.

It is interesting that the patient with bladder cancer, as I have told you before, seeks the doctor generally within a week of the time he sees the first symptom. He is scared. A man with blood in the urine realizes that that is an important symptom, and he wants to know what causes it. He has learned in the past, for instance, that spitting up blood is an important and grave symptom. It may mean tuberculosis. So if he has blood in the urine, he is scared and will seek the family physician.

FIG. 51.

With this one symptom you can do a great deal of useful work. Patients with hematuria should be encouraged to see if they have any trouble in their urinary system. Now: every patient with blood in the urine does not have cancer of the bladder, or any other cancer. He may have stones, tuberculosis, or any one of a number of diseases. But every worker in the Women's Field Army must remember that a patient with blood in the urine has a symptom which is of grave importance; it must be looked after and the cause of the blood in the urine must be diagnosed.

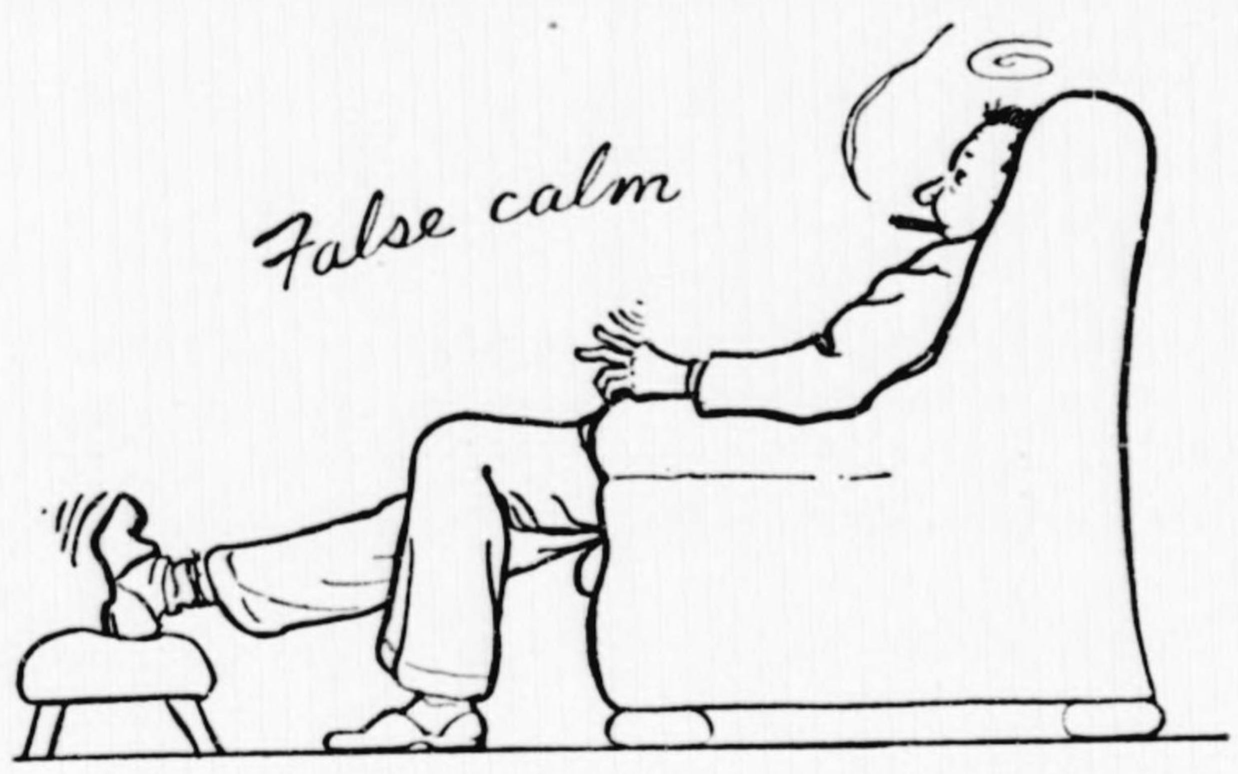


Fig. 52.

It is sometimes the uneducated family doctor and not the patient that delays the diagnosis. It is being emphasized more and more that it is not wise for the physician to play along with the patient and calm his fear. It is all right to calm his fear if he has nothing the matter with him, but if he has blood in his urine, he may have something very gravely the matter with him. According to our statistics, the usual delay in coming to the specialist, or to whomever is competent to make the diagnosis, amounts to one and one quarter years.

In that time, a year and a quarter, he delayed only about a week going to the physician after he discovered the blood in the urine, but he has been delayed a year and a quarter in seeing the specialist. This is bad coordination between the family physician and the specialist. Because of that bad coordination the patient is not diagnosed correctly until a year and a quarter later, when his tumor may be totally beyond successful treatment, and he may die because of this delay.

Of course, it is simple for the specialist to make a diagnosis when a patient is sent to him with a suspicion of some disease. All he has to do is put the patient through a routine which sometimes takes a a correct diagnosis. By means of the cystoscope the interior of the bladder can be seen, a small piece of the tumor can be taken for diagnosis, and the condition of the other organs determined. This process takes but a short time.

The diagnostic possibilities of x-ray are very great in bladder cancer. The bladder is filled with a substance opaque to x-ray, and a tumor shows up very readily.

With cancer of the prostate the patient is generally beyond the age of 60, and his symptoms are very vague. Remember, some change in urination may be important. However, not every patient with cancer of the prostate has had a change in normal urination; not every patient has had more frequent urination week, and more often only a day or two, to really get than normal; not every patient that gets up at night necessarily has a cancer of the prostate; but changes in normal urination should be studied. A visit to the family doctor may be delayed a long time, months or even years, because of the vagueness of the symptoms.

The family doctor's chief function is to realize that any change in urinary frequency or painful urination, or anything of that sort, calls for a rectal examination in the male, or a vaginal examination in the female. Those should be done by the family doctor, and I think more and more the family doctor is training himself to be competent in this simple procedure. It is not a difficult thing. I think more and more the family doctor is coming to know when these examinations are necessary.

As for the diagnosis of prostatic cancer, specimens of these cancers can be obtained; from them we can get an idea of the kind of cancer, and decide if it is confined to the prostate or has spread to other locations.

Cancer of the bladder may be treated by surgery or radiation. I like to emphasize that there are a certain

Fig. 53. Examination of the bladder by cystoscope showing the normal bladder wall and an early cancer of the bladder.

number of patients we can control very nicely without operation, by means of radon implanted in various ways with the help of the cystoscope. This is very important, particularly in elderly people who wouldn't stand an operation.

The other method of dealing with these tumors is through a suprapubic opening. An incision is made suprapubically, that is, above the bladder. The bladder is opened and the tumor is implanted with radon seeds. This is an operation of mild mortality;. if a more serious operation was performed there would be a higher mortality.

With cancer of the prostate, the whole treatment has changed within the last two years and also the possibility of cure. In the past we were able to control about five per cent for five years by any method, either by surgery or radiation. The mortality, therefore, was 95 per cent in all cases of cancer of the prostate. This cancer is frequently seen, and that shows how many patients over the world die of cancer of the prostate.

About two years ago, Huggins, of Chicago, did some work in removing the testicles of patients with cancer of the prostate, with quite extraordinary results. The implications of his results and the far-reaching ideas he has expressed will probably mean that we will cure a good many more of these cases than we have before.

The statistics are not yet available, but it is possible to make a rough estimate that from five per cent cures in a five year period, we have probably reached fifteen per cent or possibly twenty per cent of five year cures in totally hopeless cases. This is certainly evidence of progress.

The Thyroid Gland: Its Functions and Diseases

WILLIAM L. WATSON, M.D.

In many parts of the United States diseases of the thyroid gland are of great medical, social and economic importance. Among the diseases affecting this paired endocrine gland is cancer, which, as Dr. Watson says, occurs more than twice as frequently in women as in men.

The relationship of cancer of the thyroid to pre-existing goitre makes its diagnosis relatively easy and its cure in the early stages of its development entirely possible. Of all the endocrine glands the thyroid is perhaps the best understood. Correction for its overactivity or underdevelopment has long been practiced with considerable success.

Knowledge of it is an essential part of the equipment of all intelligent women. This follows because they are in a position to be of great practical assistance to their less fortunate and less well informed sisters.

Dr. Watson's paper is an exceedingly clear and interesting presentation of the essential facts.

In looking over a recent book on the thyroid gland, one of the best books on the subject, I was interested to note that there were 1229 pages in that textbook dealing exclusively with the thyroid gland. I am sure that you will realize I can't cover that amount of territory in anything but a very haphazard fashion. However, I will attempt to discuss briefly the functions and the pathological conditions of the thyroid gland which have a bearing on the broader subject of cancer.

The most important disease of the thyroid gland, namely, cancer, occurs more than twice as frequently in women as it does in men, a point that should have a particular interest to all women. Cancer of the thyroid, 96 times out of 100, develops in a pre-existing nodular goitre, a condition which can be seen and felt by the average person. It does not require medical treatment to observe this condition. Therefore, education here will undoubtedly bear fruit. It will bring in for surgery the people with lumps in their thyroid at a stage in their disease when they can be cured.

We may now tell you definitely that cancer of the thyroid can be cured. We have at least 13 such cases. We would like to have a good many more, but there are various reasons why we haven't, the main reason being that we haven't histological proof of the cases treated earlier than 1925 and 1926, and we, as accurate clinicians, do not include any case in the "cured" list which we can't prove from all angles.

In order to understand the thyroid gland, we might look at the development of the gland. When the human embryo, that is, the fertilized ovum, has reached a size of 5 millimeters (roughly one-fifth of an inch), the thyroid gland makes its first appearance. It arises from what we call a tuberculum impar, which is a portion of the floor of the pharynx, and gradually, as the embryo increases in size, it elongates and finally stretches down the neck and comes to rest as a bi-lobed gland situated in front of the trachea in the lower third of the neck. The development of that gland is important because cancer can occur at any point along that tract from the base of the tongue down to the base of the neck.

To give the function of the thyroid gland: It is one of the most important glands in the body, and a great deal has been written about it. You know something of its internal secretion; you know something of its external secretion, you know something of how it determines your life from birth to old age. After reading

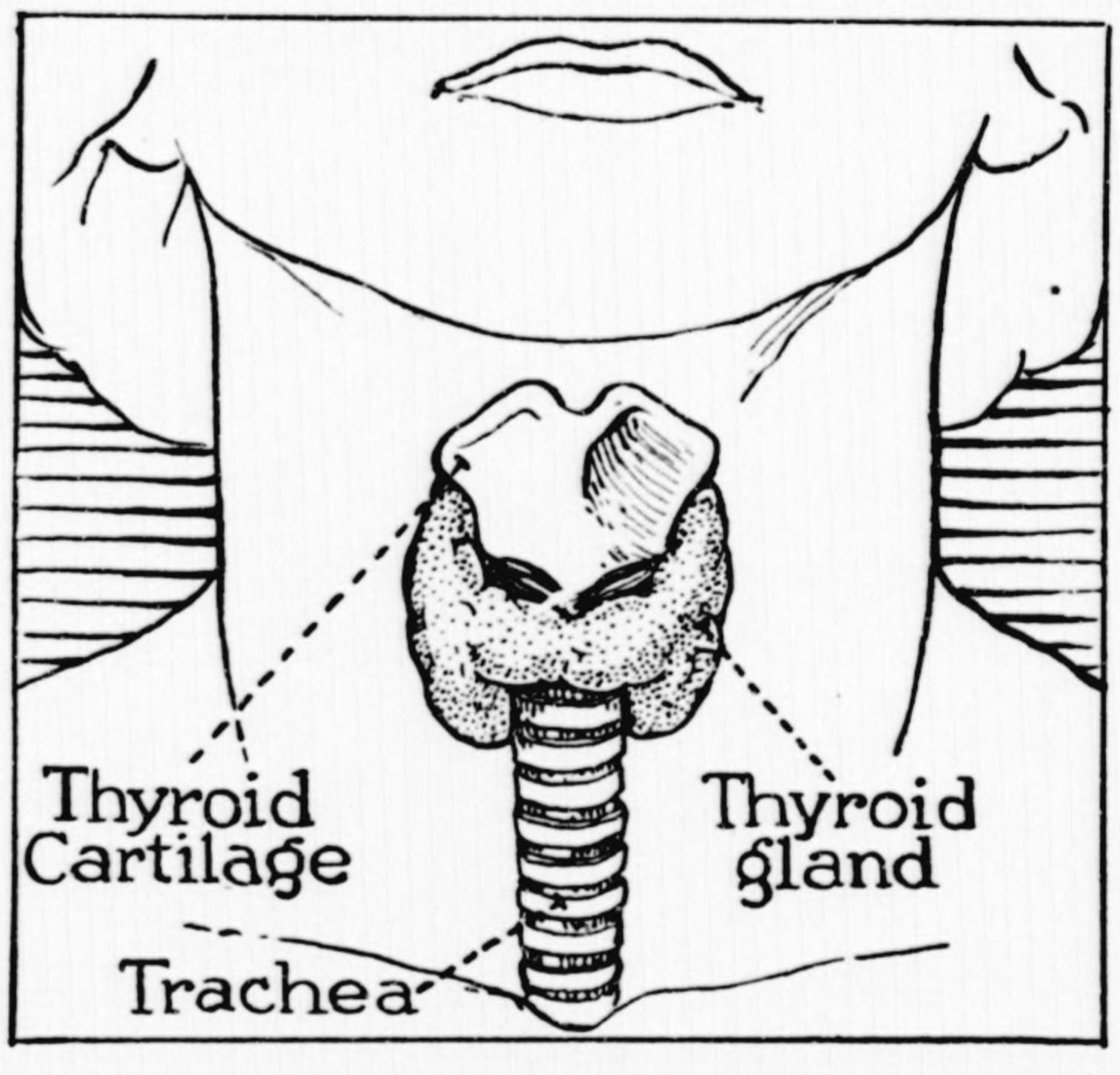


FIG. 54.

the opinions of various men, I came across a generalization which, like all generalizations, is not true, but which brings home the point. After studying the condition fully, the doctor I quote summed up the function of the thyroid gland by saying that it was the "governor" of the human body. I think that is a clear way of putting it. It really runs your life from the time you are born until you die. As an example of that, I can tell you of the children who are born with a deficiency of the thyroid. They develop quite spectacularly into what is known as a cretin. Those babies have bones which do not ossify. The skin is dry and hairless, the reproductive organs are undeveloped, and there is a marked lack of intelligence. In other words, they present a complete picture of arrested development.

In the adult, on the other hand, a thyroid insufficiency leads to a condition which we call, medically, myxedema, and this again is quite striking. The skin is thick, hairless and dry, and there is an increased deposition of fat and a lowered basal metabolic rate. The feeding of thyroid extract, will cure those conditions. The point I want to make here is that as surgeons we can safely remove all the thyroid tissue in the body and maintain the patient in a normal state of health afterwards.

There are several benign conditions (conditions which are not cancerous) that occur in the thyroid gland and which simulate cancer. The most frequent of these conditions is the common inflammation of the thyroid gland known as thyroiditis, just as appendicitis is an inflammation of the appendix. Thyroiditis is an inflammation in a previously normal thyroid. It doesn't occur very often; neither do we see tuberculosis or syphilis or any of the common metastatic diseases in the thyroid gland. It is rarely that we see any of those conditions, and we have a personal opinion that that condition is not an accidental one, but that relative immunity of the thyroid gland is due to its well-known functions and well-known content of iodine. Iodine prevents, we think, some of these infections, metastases from tumors or from infection, carbuncles, and so forth.

There is a different type of thyroiditis known as woody thyroiditis, which was described by Riedel in 1896. He called it "Eisenhart" strumitis. As I translate it, that means an iron, hard strumitis, an iron, hard thyroiditis, and, as you know, cancer is hard. Here we have an inflammatory condition which is hard, and it is hard for the surgeon to differentiate between the two.

In the interest of completeness, the exophthalmic goitre, with which you are all familiar, should be in this category. The person with exophthalmic goitre is the tall, skinny, nervous individual with the pop-eyes, fine tremor in both hands, the voracious appetite which doesn't put on any weight for the patient. This is a disease of the thyroid gland, and it is a common one, but it has absolutely no relation to cancer, because as far as we know, cancer does not develop in that type of thyroid. In other words, here we have some function of the thyroid gland which exercises a cancer control over at least that one organ.

I studied 167 cases of cancer of the thyroid and tried to find out some statistical facts about them. In that group, we had admitted to this hospital 53 cases who had been operated on before they arrived. Over one-third of our patients had had previous incomplete surgery. That was the first point that we discovered, and it led us on to the point where we decided to do a more radical operation than is usually done by the general surgeon in the treatment of cancer of the thyroid.

You would be interested in the first symptoms, because you can make a diagnosis or a presumptive diagnosis of cancer of the thyroid yourself without any medical training. Of our 167 cases, the first symptom in a hundred cases was a lump in the neck, a lump *in* the thyroid, and in another 38 cases, the first symptom was a lump in the neck, a lump *outside* the thyroid.

Cancer of the thyroid may occur at any age up to 80. We have one patient 91 years of age. It may occur in childhood from the age of 2 to the age of 10. It is most common in the decade between 50 and 60, and it is most common in women, twice as common as in men.

As I told you the thyroid gland starts its development from the base of the tongue, and cancer can occur anywhere along that tract down through the middle and lower third of the neck. We have an interesting case of a lady who was 86 years of age when she came here because she couldn't swallow and she couldn't talk. She was having trouble eating. She had a large tumor at the base of her tongue. That was thyroid cancer. Fortunately we were able to remove it and we put gold filtered radon seeds into the base. At the age of 86, she went back north and was perfectly well for five years. Then at the age of 91, she came back here with a metastasis in her neck, and we did a modified radical neck dissection. She went on and lived a very comfortable life for about three more years, and then died of old age.

In New York we have a large Negro and Oriental population, but we had only four Negroes and one Oriental in our entire series. Those people seem to be relatively immune to thyroid cancer. It seems to be most common among the white races, especially among the high-strung white races.

In order to make a preoperative diagnosis, as for the diagnosis and treatment of cancer of the thyroid: here at Memorial Hospital we do what is known as an aspiration biopsy. I suppose you have been told of that. We stick a needle into the thyroid gland and we suck out some of the tissue, put it on a slide and study it microscopically. That allows us to make a diagnosis, very often. In 83 per cent of our cases, we can thus make a preoperative histological diagnosis.

For treatment we recommend surgery. We do all our operations under local anesthesia. This is a long, tedious, dangerous operation, and they are done under local anesthesia because we feel it is safer for the patient. It is harder on the patient sometimes, much harder on the doctor, always, but the patients do not die. We have some 40, now, of these radical operations without a death. The operations take anywhere from three to four and a half hours.

Some men still believe in treating thyroid cancer by radiation. We have studied that method and we feel that radiation has something to offer as far as postoperative care is concerned, but so far we have no definite evidence that it cures people of their thyroid cancer.

When cancer of the thyroid breaks loose and gets into the internal jugular vein, it can spread to any part of the body. The favorite sites for metastases are the cervical lymph nodes, in 93 cases; heart, 2 cases; mediastinum, 31 cases. Ribs, liver, kidney, all the organs of the body, can be secondarily invaded.

The most common location for secondary deposits of thyroid cancer, of course, is the osseous, or bony system. We have recently seen, about half a dozen patients who have been to chiropractors, been to osteopaths, even been to orthopedic surgeons, complaining of pain in the bone. They have been treated by massage, manipulation, rubbing, what-not, the worst thing in the world for cancer. In these half dozen cases, we have found that the primary cancer was in the thyroid, and the bones were invaded by secondary diseases.

I should like to point out a little happier fact. Fifty-three of our cases are alive. Four of them are ten years or more free of disease. Nine of them are free of disease for from five to ten years, and twenty-six of them are alive less than five years.

In summary: First, cancer of the thyroid gland usually occurs in an abnormal gland. It does not occur in a normal gland. In other words, the nodular goitre and the adenoma of the thyroid are rightly considered to be pre-cancerous conditions. If it is true that a woman with a lump in her breast should see her doctor, it is equally true that a woman with a lump in her thyroid should have a surgical removal of the growth for prophylactic as well as for curative reasons.

The incidence of cancer in 26,974 goitres that come to surgery is roughly 0.93 per cent. Malignancy does not develop in a normal thyroid gland. That is, in 91 per cent of the malignant thyroid cancers, this malignancy develops in a pre-existing goitre. Consequently, a nodular goitre must be regarded as a pre-cancerous condition.

Another fact is that cancer does not develop in the so-called Graves' disease, the skinny person with a tremor and bulging eyes. The usual age incidence is between 40 and 60 years.

Incidence of thyroid cancer is almost 2 to 1 in favor of the female. We believe that it is 2 to 1 in favor of the female because the female is more definitely affected by the thyroid secretion throughout her genital life than is the male. At puberty, young girls' thyroids swell; at menstruation they swell. During pregnancy, the thyroid swells, and during the menopause, it goes through congestive changes. Thus the female is more susceptible to changes in the thyroid gland and changes in the thyroid gland make it susceptible to cancer.

Lastly, any hard nodule in the thyroid should be viewed with suspicion in regard to cancer. In fact, any nodule in the thyroid must be regarded as a pre-cancerous condition. If it is so regarded, we will have a substantial number of cured patients.

Trauma and Cancer

JAMES EWING, M.D.

One of the questions most frequently asked by the layman is the relation of trauma (injury) to cancer incidence.

In the natural course of human experience injuries occur by the millions or even billions. Cancer occurs also with very high frequency. It is quite natural, therefore, that those cases in which cancer appears after some single striking injury and affects some tissue at or near the site of that injury are considered by some to be a "cause and effect" relationship.

Dr. Ewing discusses this whole problem not only from the point of view of one familiar with all types of cancer, but as a technical expert who has given evidence in court in scores of cases where a claimed relationship between injury and cancer was involved.

Everyone should be sufficiently familiar with his ideas on this question to avoid unwise and non-scientific opinions and commitments which might easily produce antagonism on the part of the medical profession. A layman who is uninformed in this matter can carelessly become involved in legal situations which are most unpleasant.

Dr. Ewing's paper provides a sound and sane background for establishing a rational attitude which will help not only the reader but those influenced by his opinions and advice.

THE subject of trauma in relation to tumors is of the very first scientific and economic importance. As a matter of fact, the idea that malignant tumors can be produced by a single mechanical blow is the oldest rational theory regarding the origin of cancer. van Helmont, of Leyden, Holland, born in 1544, said about the end of the 15th century that bruises and contusions of the breast cause stagnation of secretions which become irritating and lead to inflammation and cancer. It is now 300 years since that statement was made, and it contains about all that we know about the origin of mammary cancer, and states definitely what I believe to be the chief cause of mammary cancer, namely, stagnation of secretions. However, one cannot today agree with van Helmont, that bruises and blows on the breast produce the stagnation, although such a thing is possible.

It is quite remarkable that this early historical record of any rational theory of tumors states clearly about all that we know about one major disease today. For many decades, in fact, for two and a half centuries, in the absence of any other rational notion about the nature of malignant tumors, the traumatic theory held sway, and it became a byword that most malignant tumors were caused by blows. Let me here define what is meant by trauma. A single bruising, mechanical injury to the tissue which causes structural changes and which, of course, must be followed by a healing process which it is easy to assume under certain circumstances may be atypical and neoplastic.

That is the definition of trauma. It must be distinguished from repeated irritations, chronic irritations which are mild in degree but prolonged in time over a long period. Everybody admits that under certain circumstances, chronic irritation, especially of peculiar types, can produce atypical regeneration and malignant tumors, but that is not the trauma I am talking about. It is a single mechanical force which causes alteration in structure of tissue and atypical conditions.

For two and a half centuries the traumatic theory was the only one which received any great consideration, and it became so popular that critical observers, beginning about 1800, began to doubt the validity of these clinical observations. All the doctors knew was that a man had a tumor, and by questioning him, they were able to elicit the story that at one time or another he had a trauma of one type or another, and that is all there was to the theory. In the early part of the 19th century, the literature shows increasing numbers of criticisms, some quite contemptuous, of the traumatic theory.

About the middle of the 19th century, 1850 and from there on up to 1900, the parasitic theory came into prominence, and that was a great help to the minds of those who were speculating about the nature of tumors. The human mind is a very simple, logical organ. It wants a cause for everything. Those of you who are Bible students will recall the saying, "They shall look for a sign and no sign shall be given." I don't know whether any of you know where that quotation comes from. I don't remember myself whether it is Isaiah or one of the other Prophets. "They shall look for a sign and no sign shall be given to them." That is what we are doing in the field of cancer.

People who had a malignant tumor and a serious prognosis wanted, for mental peace, some easy explanation which, being an easy, simple matter, could only be the cause of a simple and not very serious disease, and that is the popular tendency we find today with malignant tumors. They want an easy explanation.

When the parasitic theory came in, there was a race for at least fifty years between the popularity of the parasitic theory and the traumatic theory, so we find toward the end of the last century that medical literature is about equally divided. But the criticism of the traumatic theory was much more severe. Dr. Phelps, a New York doctor, in 1895 collected 500 recent reports on the traumatic theory of cancer and found about as many competent surgeons in favor of the theory as against it. However, when the microscope began to be used, then we were able to trace the beginnings of cancer, and this was the first set of observations which might serve as a reasonable basis for the formulation of any theory, because up to that time no one knew how cancer began. The microscope showed in one large group of cases that most malignant tumors did not begin from normal tissue, but from misplaced islands of tissue, supernumerary organs, vestigial organs, portions of organs that should have atrophied from the embryo but which persisted during adult life. This was Cohnheim's theory. Cohnheim established the doctrine that many malignant tumors are derived from congenital abnormalities in the structure of the tissue and not from normal tissue.

That cut out, from the basis of the traumatic theory, a great deal of its support, and for twenty-five years or more, and even up to the present time, the Cohnheim theory explains a great many malignant tumors.

Now, many replied, "Well, here are these abnormal organs, and all that, but a trauma may start them to grow." That is a conceivable possibility at the present time, but I may say now that there is very little evidence that a mechanical trauma has any special effect in starting the growth of the Cohnheim remnants.

So then by the beginning of this century, the traumatic theory had lost much of its force and acquired a great many opponents. Then came the era of experimental transplantation of tumors, and a study, especially in recent decades, of the development of tumors by specific cancerogenic chemicals; also a study of heredity. Those three sources furnished information which, in my opinion, deprived the traumatic theory of most of its support. All this time, too, there had been innumerable efforts to produce cancer or malignant tumors by trauma without any success.

There are numerous surgical operations going on all the time all over the world, none of which has ever been known to be followed by a malignant tumor. There are also on record, and a great many more not on record, efforts to experimentally produce tumors in animals by all sorts of trauma. Great ingenuity was used to imitate the possible effects of a mechanical blow without any definite report of the production of a malignant tumor. Then, it was found that by inoculation with one of these coal tar derivatives it was possible to produce a malignant tumor readily at the point of application or through the blood stream in different organs, and that these tumors would develop every time under proper circumstances.

Then we began to feel that if an extraneous agent could produce tumors, it must have some specific tendency in that direction, and that tendency was entirely lacking in a simple injury. This was, I think, a most severe blow to the followers of the traumatic theory, the discovery of cancerogenic chemicals.

In the last two decades, especially in the last one, it has been found possible to produce cancer of the sex organs by hormones (extracts of sex organs). For instance, Murray, about fifteen years ago, inoculated male mice with portions of the ovaries of their sisters. The male breast, which is ordinarily quiescent, became hypertrophied, and a high proportion of cases developed mammary cancer. This was a sensational contribution. From that time on it has been shown that growth of the breast, its function, and especially its atypical manifestations in chronic mastitis, cysts, benign tumors, and malignant tumors, is largely under the control of ovarian secretions.

To make it clear just exactly what is the situation in that field, I would say that in all probability the influence of the hormones of the sex organs, especially the ovary, adrenals, and to some extent the thyroid, form the basis for the development of carcinoma of the breast, but the old idea of van Helmont of stagnating secretions becoming irritating still holds, and the two factors combine in most instances to produce a tumor.

Where does trauma come in, then? As a matter of fact, it has very little to do with the development of mammary cancer, and I have traced the development of our evidence to prove the validity of that conclusion. So then with all the recent contributions on the actual causes of cancer, it became more and more difficult to accept the traumatic origin of any tumor.

Pathologists as a rule for the last fifty years have been almost unanimously opposed, generally often actively opposed, to the admission that a single blow can produce a tumor. Clinicians, however, are very greatly impressed by clinical facts. It is a fact that in a high proportion of cases of certain types of tumors, especially of the exposed organs, the patient will give a definite history of injury, and the tumor follows within a reasonable time, and you cannot convince the surgeon who sees these things so often that there is not some relation. It then becomes necessary to discover whether there is an indirect relation between trauma and malignant tumor. We may say today without any hesitation that a mechanical blow to normal tissues never produces cancer, but if the injury produces a sore which doesn't heal, or a fracture which heals slowly, or introduces irritating chemicals, perhaps some of these carcenogenic chemicals, or induces infection and the wound doesn't heal for weeks, and weeks, new factors may come in that would render the trauma an essential part of the set of factors which produce the tumor, because tumors are not caused; they are conditioned, and conditions are very numerous, and it may very well be that a mechanical blow under certain circumstances may be one of the essential conditions for the development of a malignant tumor. This is the present position of the traumatic theory, never the direct cause; possibly often an indirect and essential cause.

I have omitted to refer to the importance of the study of heredity in this history. Heredity studies have gone on now for forty years. You saw a great deal of it at the Bar Harbor Laboratory. We know now that in the lower animals, at least, none of these methods of producing cancer experimentally works unless the heredity of the strain of animals is favorable. If they have a strong hereditary tendency to develop the tumor, they will have many tumors from very slight applications of the irritants. If you take a resistant strain of mice, you can't produce them. How far does heredity affect human tumors? Well, that is a question which I would hardly undertake to answer. However, about two years ago I prepared a statement on hereditary tumors, hoping that it might be published in the bulletin of the Society, and I submitted it to Dr. Little. It was not the point of view of a geneticist. It represented the point of view of old-fashioned pathologists like myself, and it didn't pass muster. However, Dr. Little this summer for some reason or other, relented and wrote me while I was on vacation and said, "Have you still got that article on heredity?"

I said, "I have a copy perhaps."

"Well, send it up to me; perhaps we can fix it up so that our conflicting views may be unified and it may possibly be suitable to publish in the Bulletin."

I very much hope it will, because it represents in a brief way what we really know from the general standpoint of the influence of heredity. Heredity is a very important factor in cancer, and I can't pass it over without emphasizing that fact.

Let me give you one interesting story. A German medico-legal expert was called by the court to determine the relation of injury in the case of a bone sarcoma. This young man 28 years of age had suffered from youth from fragility of the bones. He would break a bone without any reason whatever. He had five or six fractures of that sort and all healed. After one of these fractures which resulted from a very mild injury, he developed a malignant sarcoma from which he died, and his widow applied for compensation. The doctor was asked to decide the relation of the trauma to the disease. He looked into it and said, "This is a very curious case. This boy has had all these fractures for many years. He must have some constitutional disease of the bone."

He looked into the family history and found his father had the same history, died at the age of 24 after multiple fractures which healed until one of them killed him with a malignant sarcoma. Also, he had two uncles who had the same story of multiple fractures which healed but eventually, produced a malignant sarcoma, which killed them. So there were four members of one family, all having exactly the same history, all dying from malignant tumors from minor injuries.

So the referee rendered to the court this conclusion: That the responsibility for the disease was equally divided between the hereditary tendency and the trauma. I think it was a merciful verdict, because there is no doubt this man would certainly have died of osteogenic sarcoma, without trauma, just as his forbears had done. However, he got an equally divided verdict, and that is about the best he could do. That shows how important heredity may be in bone sarcoma.

Now, we can report numerous instances in the experience of our surgeons in hospitals where patients who have a malignant tumor say, "My brother died of the same thing." Once we had two brothers come in with carcinoma of the stomach.

I must go on now and pursue further this question of the relation of trauma to malignant tumor. Today, while I am criticized by some as being too lenient on the question of trauma, I am also criticized by others as being too rigid, so I suppose I occupy a middle position. My feeling is, and that is shared by the majority of medico-legal experts in Europe, that while trauma alone never produces a tumor, occasionally it may be an essential indirect factor. Therefore, it becomes necessary to determine in each instance just how far the trauma acted and how it acted, and if it were really important, and on this account in all properly conducted medico-legal inquiries we establish certain criteria which must be met before one can assume that a trauma is related to a tumor. These criteria are quite famous. First, there must be evidence of the previous integrity of the wounded part. That is, there must be evidence that there was no disease before the trauma. Sometimes it is very difficult to get this evidence, but in a great many instances an examination of the patient clinically or radiologically will reveal evidence that the tumor supposed to result from the trauma antedated the trauma.

As to the authenticity of the trauma, it must be proved that the facts stated by the patient are genuine. This is the most difficult of all, because you would be surprised to see how unreliable the statements of people are. Some of them are out-and-out malingerers, imposters, but not many. A great majority undertake to establish a history which will prove to them a very mild cause of this disease, so they fix up stories to satisfy their own minds, and then they come to court with these statements as fact. In a few instances, there is a great deal of ingenious cooperation between the lawyer, the doctor, and the patient, where the lawyer's and doctor's fees are dependent upon the successful contest for compensation, sometimes amounting to ten, fifteen, or twenty thousand dollars. So that we run into that very unsavory field of human psychology.

In other words, this matter of establishing the authenticity of trauma is one of the worst phases of human psychology. I believe today compensation laws, undertaken for a good purpose, to compensate workers for injuries inherent in industry, are one of the most demoralizing influences in modern society. I should like to see it all abolished and replaced by life insurance.

A young woman some years ago came with a story that she had a disease in the palm of her hand that had been operated upon in another hospital. She had been told she had a bad sarcoma, and she must lose the hand, and she was very much distressed. She said in August—and this was November—she was summering up in the Berkshires with her family and sister and her husband pushed her out of a swing and she fell and struck her hand on a gravel bed, injuring the palm of her hand. It was a little peculiar, because people don't injure the palm of their hand when they fall; they injure their wrist. She should have had a Colles' fracture of the wrist.

She was asked, "Was the hand all right before?"

"Yes, because I was earning my living as a typist."

"Well, here," I said, "is a real case of traumatic neurosarcoma. I have just been looking for that." So I said, "We will verify these statements."

There was no compensation in this instance at all. She was a perfectly intelligent young woman. So I undertook to interview her in detail to get her to repeat her story. Finally I asked her to allow me to verify her statements, to let me talk to her husband. Then she was embarrassed. She had just been divorced from her husband. I said, "That doesn't make any difference; I will go and see him." After a short time, she said, "I don't think you can, because he is camping in Canada"—in November. So I gave up that line.

I said, "How about the previous story? You say you were earning your living typing?"

"Yes."

"For whom did you work?"

Well, she was embarrassed. She admitted then she hadn't used the typewriter for three years. So on careful questioning, this particular story fell to the ground completely. How did she develop that story? Piece by piece, repeating it to herself and to her physicians again and again until she came actually to believe in the existence of facts which had no reality whatever. That is not an unusual psychological deception.

Next, the adequacy of the trauma. The trauma must be sufficiently severe to cause some change in the tissues. The French and German courts, especially the French, are very insistent that they will not consider all manner of mild bruises and impacts of the external and the internal organs and subsequent tumors. Trauma must be sufficiently severe to cause severe pain, make the patient stop work, consult a doctor, and be followed by some signs of disability or disorder. It is a difficult matter to estimate the adequacy of the trauma. Then the trauma and the tumor must arise at the same site. Many people come in with a story that they hit their knee and they have sarcoma of the hip, or the head, or sarcoma in the spine. Unless the tumor arises at the point of injury, one could exclude traumatic relation as a rule, but not always, because this matter introduces a number of interesting and complicated factors, transmitted violence, for instance. What happens when a man falls from a distance and lands on his feet? The whole body is shaken up. Unless there are some signs of injury of a particular organ following a severe general shaking of the body, one may not attribute a subsequent tumor in any organ to the trauma. If, however, a boy is run over on the street and has bloody urine immediately afterwards, you can assume his kidneys or bladder are injured. If, however, his urine is clear, you can't assume such relation.

Now, the time factor. This is the great criterion and most important criterion of all. If a woman states she had a blow on the breast and a black spot on January 1st, and by February 1st she had a lump in the breast as big as a hen's egg, and by March 1st, when the operation was performed, she had a 3 cm. tumor with axillary lymph nodes, we know that the tumor could never grow that fast. We exclude that entirely and say the tumor antedated the accident. We don't know much about the chronology of most tumors. The time factor is the chief criterion which I find the various alleged traumatic tumors fail to meet. So with the use of these criteria, one may say that the number of traumatic malignant tumors now proved before the courts is very small. The number of traumatic cancers would be extremely small. The number of true traumatic tumors of soft parts, like bone, is considerable, and should be considered as a definite matter of fact.

There is one other factor which must be considered —coincidence. Granted that the patient has the injury and he has a tumor, the two may be entirely disconnected but happen together at the same time. The National Safety Council reports for 1941 over nine million disabling accidents in industry in this country, and a great many more of the minor type which are so often not counted. With all these injuries occurring, everybody has blows of one sort or another, and since the tumor may be referred to a trauma occurring four, five, even ten years before, you can see it is almost impossible to find any malignant tumor that hasn't had an injury. Coincidence is a very important consideration.

Another principle which I have emphasized is "traumatic determinism." This is a long term, but very simple. The presence of a tumor in any part of the body tends to bring about injuries to the site of the tumor, and to exaggerate the symptoms thereof. For instance, a young girl going down the subway steps trips and falls. She can't walk. She is sent to the hospital. An x-ray is taken of the bone and we find she has had for months a destructive giant cell tumor at the lower end of the femur which has interfered with the normal movements of the knee, and she wouldn't have fallen if she had a perfectly normal knee joint, but the knee joint being hard to move and just a little painful, made her fall, and she hit the knee. That is a very common occurrence, and it relates to all the different forms of tumors—traumatic determinism. These are some of the facts, then, which must be considered in estimating the existence of traumatic tumor.

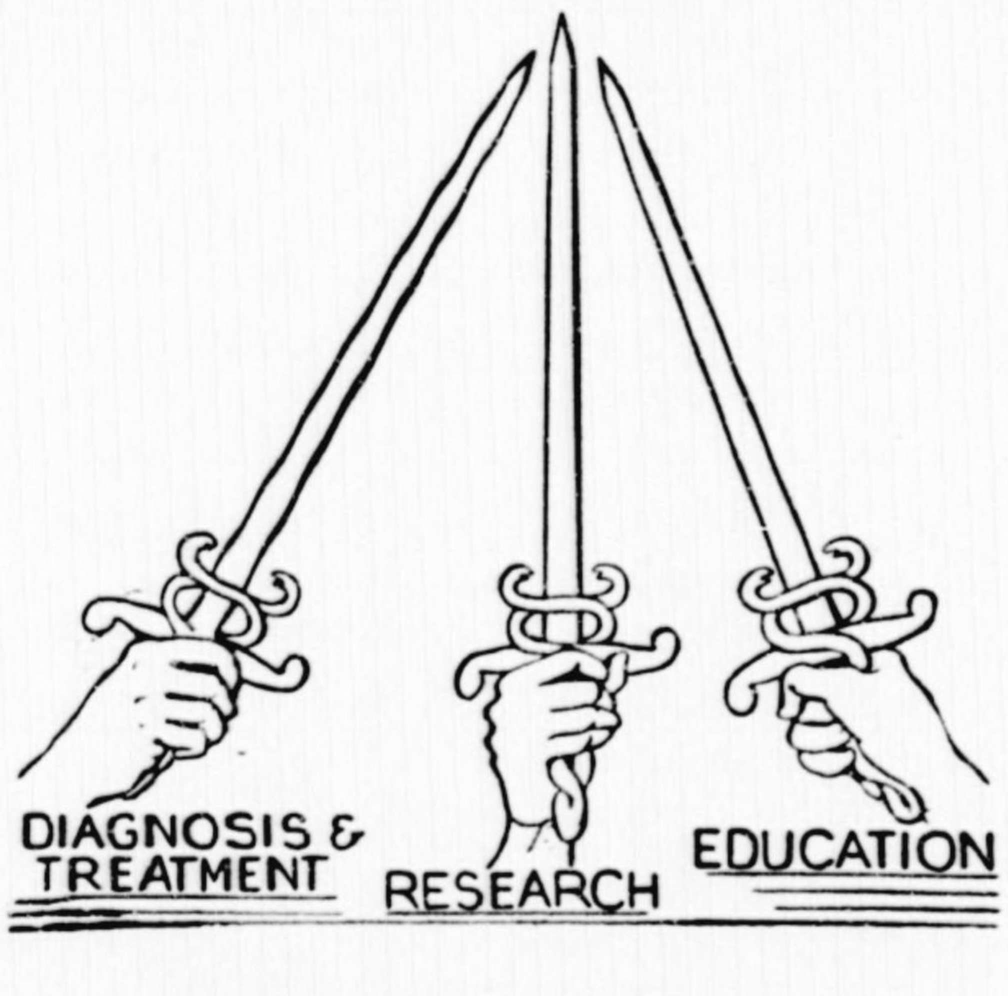
I think the women of this group ought to know the economic scope of the traumatic theory. In the year 1938 the State of New York spent seventy-two million dollars administering the compensation laws. This same situation exists in all the states of the Union and in all countries, so that the financial significance of the compensation law based on traumatic tumors is enormous. Incidentally, of the seventy-two million dollars spent by the State in the administration of the law, only about thirty million went to the injured parties; all the rest was wasted in legal fees, insurance fees, doctors' fees, and so forth, and I think a law which gives over forty per cent of its cost to its main object is not a very good piece of legislation.

What is the future of this subject, and what are we to do about it? Well, I think there is more need of actual, first-hand observation in this field than in any other department of medicine. Legal medicine in the field of traumatic cancer today is a medical dreamland where the doctor will go into court and express his opinion based solely on his own notions. Almost none of them is able to state any facts of observation on which they base their opinion. No one knows today what happens to the breast when it is injured.

In the last two months I have been over the world medical literature, and I don't find any reference whatever to observations on the effects of trauma in the female breast except records of fat necrosis, a matter which was brought to light first some years ago by Dr. Lee and Dr. Adair in this hospital. I do not know what happens to the breast after trauma, but I have been collecting data, and during this past winter I made six observations of what happens in the female breast after a definite trauma. All I can say so far is that very little happens. We need more facts of observation which are now almost entirely lacking.

I think that it requires the establishment of an institution of legal medicine supported by the state, where investigations of this sort may be gathered. It is an unpopular field. It is tedious, hard to get the material, but no one knows just what happens as a result of trauma in the great majority of cases, and until we know that and can trace the effects of trauma to the tumor and can devise methods of getting data before the courts, traumatic cancer will still remain a dreamland of medicine.

SECTION III



Education

Introduction

The Educational Section contains general principles and policies which have been found helpful in guiding the work of lay leaders in cancer education.

Most of them have been suggested by the excellent work accomplished by various officers of the Field Army.

Educational material can be obtained from the National Office of the American Cancer Society, in New York City, where the National Office of the Field Army is also located.

The individual worker must realize that the national organization exists to strengthen and supplement his or her efforts. Cancer control is a challenge not only because of the nature of the disease itself but because many particular qualifications need to be recognized and the ability to satisfy them must be developed.

Education

C. C. Little, Sc.D.

It is well from the start to have in mind the objects of the cancer educational campaign. These objects are many and varied, and affect different groups of people Some of them apply to the individual women interested in the program of the Field Army while others influence and extend to groups of individuals outside of that organization. A thorough understanding of the objects of cancer education is absolutely essential in order that the individual may carry conviction to those with whom she comes in contact. The first step is naturally her own preparation and the objects of this preparation may be listed as follows.

1. *To overcome fear.* No disease is so feared as cancer and none has been so widely discussed and so little understood. Because of the fact that the early stages of cancer are not accompanied by pain and other obvious symptoms all the cases of cancer that reached the physician's attention were formerly advanced. Many of them were beyond a stage at which anything could be done to cure the patient or even to offer any prolonged alleviation of the tragic and painful last stages of the disease. It is small wonder then that what amounted to a profound psychosis developed about the disease and that individuals attempted to hide its presence and were actually superstitious and irrational concerning it. There did not seem to be any help available from any source and as a result what almost amounted to panic was caused in the minds of the general public. All sorts of strange ideas about cancer were prevalent. It was given what amounted to almost a human entity in its malignancy. People spoke of male and female cancer and of its grasping and destroying normal tissue. It acquired almost satanic attributes which were whispered from one person to another without ever being brought to the level of investigation or analysis by rational and balanced minds.

Then, too, the fact that syphilis at times caused lip or mouth sores that superficially resembled early cancerous lesions in those localities led to an association in the minds of some people between cancer and social disease. This association was extended illogically and inaccurately to include all cancer with the result that people thought some sort of stigma was attached to its incidence. This, of course, added to the secrecy and the fear already prevalent. The first duty of a Field Army worker is to face cancer unafraid and to maintain an attitude of intelligent rational judgment concerning it.

2. *To overcome ignorance.* No one knows everything that there is to know about cancer. Even the greatest scientists today cannot be expected to acquire and retain all the detailed information concerning the biology, chemistry and physics of the cancer process and its relationship to normal growth. It may be thought that this fact is discouraging. On the other hand, it seems that it might be taken by lay workers and members of the Field Army to indicate definitely that even the so-called experts in the field of cancer are still learning things about the disease, and that this fact makes these men more nearly and directly partners of the lay individuals who were trying to learn the main facts concerning it. There is sufficient knowledge about cancer available in readable and easily understandable form so that any intelligent, lay person can acquire information concerning its basic nature. One needs to remember first, that cancer is a form of growth of the tissues of the individual itself. Second, that its growth is uncontrolled and up to the present cannot be stopped except by killing the cancer tissue or by removing it. Third, the occurrence of cancer is a natural event, always potentially possible in animals which depend for their health upon orderly balance of orderly function. Human beings and all higher animals fall in this category.

From these basic facts concerning cancer much other information can be derived. For example, we know that the chance of curing or removing cancer increases directly with the promptness with which it is brought to the attention of the medical profession for diagnosis and treatment. The earlier this is done the greater the chance for cure. This applies to all types of cancer in all ages and sorts of people. We also know that certain of the signs and symptoms which may mean cancer in different parts of the body may be listed as follows:

1. Any persistent lump or thickening, especially in the breast.
2. Any irregular bleeding or discharge from any of the body openings.
3. Any sore that does not heal, particularly about the tongue, mouth or lips.
4. Persistent indigestion, or changes in bowel habits.
5. Sudden changes in the form or rate of growth of a mole or wart.
6. Persistent hoarseness or cough unexplained by a cold.

We also know, as a result of this, that certain things can be done which help to decrease the chance of cancer. Among these may be listed the following:

1. Careful oral hygiene involving care of the teeth, repair of cavities, removal of decayed teeth, correction of ill-fitting dentures and other similar measures. Careful washing and cleansing of the teeth and mouth cavity at frequent intervals. Avoidance of undue irritation to the mouth or tongue by excessive use of

tobacco or other substances that cause local irritation.

2. Care of the skin to see that it is kept clean and is not abused by too prolonged or intense exposure to the direct rays of the sun or to violent changes in temperature or to the irritation of the weather. Naturally there are many occasions where these risks cannot be avoided. All that can be said is that the individual should be on the alert for signs of abnormal growth of any sort on any part of the surface of the body.

3. Avoid tight or chafing confinement of the breasts. In event of childbirth follow medical advice concerning whether the baby should or should not be nursed.

4. Repair all injuries to the uterus received during childbirth. Avoid the use of metal or other hard pessaries, avoid the extended use of any type of irritating douches.

5. Eat and drink material that agrees with you. Avoid things that cause distress or indigestion. Do not abuse the stomach or digestive tract and expect it to remain unresponsive to that abuse.

6. Establish and maintain regular bowel habits to avoid the irritating effects of constipation and the resulting sluggishness of various related bodily functions.

7. Although no definite evidence exists concerning the relation between the use of tobacco and the incidence of lung cancer, it would seem unwise to fill the lungs repeatedly with a suspension of fine particles of tobacco product of which smoke consists. It is difficult to see how such particles can be prevented from becoming lodged in the walls of the lungs and when so located how they can avoid producing a certain amount of irritation. One might also question the ultimate results of continued inhalation of the type of atmosphere which characterizes the lower levels of city streets. Experimental work with animals involving these matters is still inconclusive but it seems probable that the lung as an organ is not immune to the effects of chronic irritation and that it will in this respect resemble the other organs of the body. Such being the case, wisdom in avoiding unnecessary lung irritation seems to be established.

It will be noted that all of these matters involve on the part of the laymen the creation and maintenance of *personal responsibility*. This is the most important matter of all. The layman *must* appreciate that he has undertaken more than an ordinary share of individual responsibility in the fight against cancer. He should welcome this responsibility and become adjusted to it in a happy and natural way. It must not be allowed to worry or disturb him. If it does so it defeats its own purpose. There is so much to be done and such a great need of doing it that the troublesome and disturbing effects of added responsibility should be forgotten in the realization of the opportunity which the lay worker possesses. There is no time to think of one's own shortcomings and lack of knowledge. There is work to be done and the lay worker is the person to do it.

The first duty is, therefore, to "put one's own house in order" and to adopt an attitude in one's own hygiene and life which is consistent with what one is preaching to others. This involves periodic health examinations, close attention to one's own body, immediate reporting of any danger signals, avoidance of unnecessary cancer risks and a keen interest in learning more about the disease which one is fighting. All of these things can be accomplished with surprisingly little expense and with a minimum of disturbance in the daily routine of one's existence. They can really become a point of view, an attitude which is self-perpetuating and which is transferable to others. The quicker the lay worker reaches that stage, the sooner he has become a trained and integrated unit in the fight against cancer. We may next consider his duties toward other groups of persons.

1. *Medical Profession.* Strangely enough, one of the duties of the public is to arouse and encourage the doctor's interest in the cancer problem. The reason for this is that ordinarily, general practitioners do not see many cases of actual cancer per year and in the past have seen chiefly those that were incurable or inoperable. As a result the doctor, especially if he is isolated from contact with a modern and up-to-date cancer clinic, is inclined to be pessimistic and to take a fatalist attitude that nothing can be done about cancer. Doubtless as time goes on and prevention clinics are formed and more people come to the doctor's attention through these clinics as well as in the form of private patients coming to his office as a result of the cancer educational campaign, he will modify his attitude. This change may, however, be hastened by deliberate efforts on the part of the public. They must be optimistic and they must realize that it is a difficult problem to modify a professional man's attitude. They cannot afford to claim extensive knowledge of cancer as a disease, but they can if they will persist, influence the doctor, indirectly at least, by their own attitudes. In other words, if they themselves give the impression of sincerity, energy and intelligent action and if they continue to make that impression in spite of discouragements or handicaps, the doctor is bound to react. Many doctors will be afraid that laymen are trying to assume more important positions as cancer educators than their training or background justifies. Care should be taken to disabuse their minds on this matter and to do this repeatedly since doctors are apt to forget that it has been pointed out to them.

Increase also the doctor's confidence in the general curability of cancer. You will be surprised to find out how many doctors are not familiar with statistics showing the curability of different types of cancer. Many of these figures, reasonably up-to-date, are contained in this book. You should make use of these figures. If the doctor doubts them do not argue with him but merely say that you assume that they would not be published if the Society was not ready to back them with actual references. It might be well even to take an attitude that if the doctor doubts them both you and he would profit by his contacting the American Society at its central New York office and finding out how the figures were arrived at. This might result in his coming into closer contact with the program as a whole. It will be well to remember that some doctors are not able to make as good records in curing cancer as are others, and that if you by chance run into one who is not able to do as well as those with greater advantages he may resent the fact that the others are surpassing him. You should try to put yourself in his place and be tactful and careful when such a situation is encountered. It may help to take for granted that he knows that cancer is curable in a large number of cases when it occurs in accessible sites and when it is diagnosed and treated without delay. This will give him a chance to conceal the fact that he does not know this if he desires to do so and will incidentally lead to his obtaining further information quietly by himself.

It will also be well to increase his confidence in the value of lay support. This can be done by emphasizing the fact that the Field Army organization is one of the greatest guarantees that has as yet been devised for maintaining the influence of the general practitioner and for protecting his interests. Point out to him the fact that in every case we urge the patient to contact his or her physician and that we cooperate with medical societies in setting up machinery by which that physician, if he recommends patients to a clinic or hospital, retains his contact with them and does not lose them. In many states you will find that the mere mention of aiding indigent patients by transportation and other means will arouse suspicion and antagonism. It should be pointed out that all of this aid is provided under conditions approved and regulated by the state and local medical societies. This obviously gives them a means of helping the indigent patient in a manner that they approve. By so doing it builds a counterfire to the tendency toward unwise types of state medicine and to the efforts to remove authority from the general practitioner.

It will be well to remember the fact that the program of the Field Army includes aid to clinics, laboratories and hospitals under conditions and restrictions approved by the local medical groups and by the National Society. Be careful also to remember the fact that the Field Army and the American Cancer Society are prevented by their Articles of Incorporation from *owning* or *operating* laboratories, clinics or hospitals. Some doctors will be afraid that we are going to enter the field of cancer diagnosis, treatment or research and will need to be assured repeatedly that this is not the case. If they understand that it is against our articles of incorporation for us to do so it should increase their interest in and support of the efforts that we are making to aid laboratories, clinics and hospitals administered and conducted by others. It will be well also to point out the fact that we do not sanction the support or aid of any clinics or hospitals that are not first approved by the American College of Surgeons. In other words, we rely upon a purely professional group to establish standards which we accept and we count on these same groups to continue the inspection of approved institutions to make sure that these standards are maintained.

2. *Sociological Groups.* The lay worker or member of the Field Army should make clear to all groups and individuals interested in sociological problems that the Field Army may include in its program provisions and organizations for aiding indigent patients in three very direct ways.

First, by providing the actual transportation by which these patients are taken to approved hospitals for diagnosis or treatment.

Second, by making from old linen surgical dressings for indigent cancer patients in approved hospitals.

Third, by encouraging legislation or actually including in their own budget funds which support the transportation or treatment of indigent patients under conditions approved by local medical groups. This sort of work is practical and of immediate and personal value to the individual cancer patient. It should be emphasized that the opportunity to do this is in many ways unique and that the need is very great.

The Field Army also offers an opportunity for interested and available individuals to learn how to become nurse's aids under the conditions established at hospitals throughout the country. During the period of the emergency there is real need for relief of the nursing profession. This applies especially to diseases such as cancer where nurse's aids can be of great value during prolonged treatment.

The Society is also working on a program for medical aids. This would in general include opportunity for interested women to help doctors either in their office or clinical work and so relieve the scarcity of available, trained, secretarial personnel which is being felt acutely in various parts of the country. Needless to say, this sort of work offers an opportunity for women who undertake it to receive a great deal of valuable information concerning cancer control and thereby to fit them more completely for future leadership in the cancer control program.

One of the most important types of work that members of the Field Army and other lay individuals can undertake is that of social service work to follow up cancer patients who have left the hospital and to help in the collection of statistical data while the patients are still under treatment. It is an amazing fact that very little is known concerning end results of different specific types of treatment because our machinery for following up the cancer patients and collecting final data on the outcome of the treatment is entirely inadequate. Whenever efforts have been made to compare data collected in different institutions it has been found that there is no consistent method of collecting these data which enables one to evaluate