APPLIED BIOPHYSICS

Survey of Physical Methods Used in Medicine

A Symposium

Edited by
DR. N. HOWARD-JONES
Editor, *British Medical Bulletin*

1949
CHEMICAL PUBLISHING CO., INC.
BROOKLYN, N. Y.

CHEMICAL PUBLISHING CO., INC.
BROOKLYN N. Y.

PRINTED IN THE U. S. A.

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FOREWORD

MANY diagnostic and therapeutic procedures in medicine and surgery are based upon the elementary principles of physics. We have become so accustomed to accepting and utilizing these procedures in the everyday pursuit of our vocations that we have oftentimes neglected to pause and give thought to their origin. The present volume admirably emphasizes our obligation to fundamental science.

The radiologist, the radiation biologist, and the physiologist have of necessity been more closely associated with the physicist than have many of their colleagues. This association in conjunction with the biochemist has resulted in the development of the specialty known as biophysics which has been a major contribution to the advancement of the medical and biological sciences. This specialty is rapidly expanding in influence and usefulness. The biophysicist is frequently a catalytic agent, facilitating the successful progress of a coordinated research program.

The pile production of large quantities of radioactive isotopes and their distribution to competent investigators by the Atomic Energy Commission have stimulated research groups to redouble their efforts toward the solution of many complex biological problems. There is a notable tendency to coordinate the talents of many investigators, each specialized in his particular field, toward the solution of a specific problem. In such cooperative work it is particularly important that each worker's specialty be intelligibly presented for the illumination of his fellow workers as is done by the present volume.

The biological effects of penetrating radiations have been of the utmost interest to many investigators and clinicians since the discovery of X-rays by Roentgen in 1895; yet our knowledge concerning the actual mechanisms of the biological actions re-

sulting from exposure to these radiations is very meager and little understood. These radiations may be used as a tool for investigative purposes or in certain instances as a therapeutic agent. In either case a better understanding of their physical nature and their biological effects is needed.

The authors of *Applied Biophysics* are to be congratulated upon their excellent presentation of a very difficult and complex subject. The diversity of problems serves to emphasize the importance of the field and its implications in the broad aspects of medical science.

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TABLE OF CONTENTS

*PHYSICS IN MEDICINE

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Introduction

DURING the last fifty years discoveries and developments in physics have intruded so far into medicine that physical methods of treatment and diagnosis have become indispensable, yet physics still hovers a little uncertainly on the fringes of medical research, education, and organization. This is not surprising when one considers that physics is the most highly developed and abstract of the fundamental sciences, and the practice of medicine the most highly developed of the social arts. Numerical precision, mathematical analysis, and consequent extreme generality and abstraction are the distinguishing marks or, at least, implied ideals of physics, while in medicine the individual patient and his often incomprehensible complexities fill the picture, sometimes to the exclusion of general principles and more abstract erudition. Yet it is recognized more and more clearly that physics has now an important part to play in medical research and even in the daily treatment of the patient. Correspondingly, physics itself might benefit immensely from closer contact with the medical and biological problems awaiting solution.

Some Applications of Physics in Medicine

The most striking and perhaps best known of the recent applications of physics in medicine lie in the sphere of medical radi-

* This book is based on a collection of articles in the British Medical Bulletin.

ology, that is, particularly in the applications of radiations to the problems of medicine. This year marks the fiftieth anniversary of the discovery of X-rays by Röntgen, an event of outstanding significance both for pure science and medicine, for it provided the physicist with a most powerful weapon of research into the structure of matter, and the doctor with almost a new sense, and diagnostic possibilities of the highest order. Later, the rays were recognized as a lethal agent, whose proper power and scope against malignant disease are only now being unfolded. The year 1896 saw the discovery of radioactivity, which again has furnished, besides the most profound studies of the structure of matter, a powerful if still largely mysterious agent in the treatment of malignancy. Recently, artificial radioactivity has provided the experimental physiologist with a means of studying metabolic processes, while modern nuclear physics seems destined to influence medicine profoundly as our mastery of atomic techniques develops.

It would be easy to show how the classical lines of development of physical inquiry have been followed in medical radiology, the sequence first of qualitative observation, then of attempts at quantitative measurement, disagreement, and final agreement on units of measurement, subsequent discussion of the significance of such units, and the gradual development of mathematical generalization and detailed solution of practical problems. We are here concerned, however, rather with the need for an expanding horizon and the insistence that physics has a wider scope and role in medical thought, research, treatment, and education than so far usually accorded to it.

This scope of physics in medicine may, for example, be gaged from an encyclopedia of medical physics recently published in the United States. Merely to list the headlines would require many pages, and every branch of medicine and surgery is represented.

We think, for example, of the many applications of optical principles in medicine and surgery, ranging from the embodiment of laws of geometrical optics in spectacle lenses to laryngoscopes, bronchoscopes, cystoscopes, sometimes of real beauty in design

and adaptation. Coupled with the motion-picture camera, the bronchoscope enables a film to be made during the removal of an obstruction in a bronchus, and the observer is given a veritable conducted tour around the lung. Body cavities have become "accessible" in a new sense. The influence of the rather more subtle laws of physical optics may be found in instruments for measuring the average diameters of blood cells by the haloes they cause around a source of light, instruments descended directly from the "eriometer," invented by Thomas Young for measuring the diameters of fine hairs, at the time when this physician-physicist was laying the foundations of the experimental proofs of the wave theory of light. We might recall the rather obvious fact that the optical microscope is a physical weapon, studied and sharpened to a point where this same wave nature of light is itself the chief and impassible barrier to seeing the still invisible, and recognize in the substitution of streams of electric charges for the beam of light in the new electron microscope the next, and perhaps supremely important, contribution physics has to make to the science of microscopy.

We might similarly range through all the branches of physics and quote examples of the fundamental nature of the physicist's contributions, either in technique or in generalizations of wide and abstract character, which transform the nature of the problem. The use of specific electronic devices like the cathode-ray oscillograph with its attendant amplifiers occurs to us immediately. The science of electronics and electron optics has contributed and will contribute to many of the problems of neurophysiology. It may be noted in passing that "magnetism" seems a slightly disreputable word in medicine, which is unfortunate as it appears that a study of the magnetic properties, magnetic susceptibility, for example, of body fluids or tissues, might well yield both useful and interesting information. The study of sound and of modern radio-frequency techniques has resulted in great advances in the applications of acoustics, a subject once more intimately associated with Thomas Young. We think, too, of the possible applications of high-frequency radio science, now making available, both directly and indirectly, power of a hitherto undreamed of

amount at wave lengths of a few centimeters, and applicable to the heating of the human body.

No physicist turning over the pages of an anatomy textbook can fail to see before him fascinating problems in mechanics and the strengths of materials, yet how little we know of the mechanics of fractures or of the instantaneous stresses and strains when the human frame suffers some sudden impact or gradually changing pressure.

It would be, however, tedious and little to the point to attempt to enumerate the various direct or indirect effects which physical techniques have had on medicine, for no list can be complete and the influence is sufficiently obvious.

History of Medical Physics

It would be a fascinating task to trace the history of the connection between physics and medicine. The interaction might perhaps be seen as twofold, the two eternal aspects of scientific progress; on the one hand the gradual development of specific techniques and on the other the grasping of great generalizations, which transform the picture of the world and so, of man's supposed place in it and the significance of his needs.

Most frequently, the repercussions of physical discoveries are incidental and not at all in the mind of the discoverer. Röntgen may have been gratified at the medical utility of X-rays, but certainly no such application was in his mind. This consideration should be kept continually in view in the development of medical research programs, where the widest possible latitude is necessary. The point is rather the importance of the closest correlation between pure science and medical practice, and the necessity for organization to secure the most rapid and efficient development of scientific discoveries of medical importance.

If it appears that medicine has a debt to physics, there must be at least some corresponding recognition of the contributions made to the fundamental sciences of those whose primary education has been medical. Certainly we cannot claim that the physicist interested in medical problems is a new phenomenon or that

medical men have not shown the greatest interest in the use of physical techniques. The significant development of the present day is rather the emergence of a group of physicists employed solely in the study and control of physical agents in their applications to medicine, and in the recognition that the physicist is now an indispensable member of any team of specialists using X-rays or radium in the treatment of malignant diseases, and generally in the therapeutic use of ionizing radiations. In this development Britain has played a notable part, and it is probably true to say that the importance of the physical aspects of medical radiology are as well recognized here as anywhere in the world.

It is to be hoped that similar development of physical medicine may occur in the near future, for the crying need in this branch of medicine is for quantitative information, a great deal of which can be obtained only by exact physical experiment. It is a curious thing that the use of heat, one of the oldest medicaments, is from the physical point of view almost entirely unscientific, and that only recently have measurements in absolute units been linked to clinical practice.

It is natural that we find the medical man, a member of one of the few educated sections of the community, among the first to make a contribution to "pure" physics. As late as 1600 we have Gilbert of Colchester, physician to Queen Elizabeth, becoming the father of electrical science, or Borelli seeing in the movements of man and animals applications of the laws of levers. Even in the beginnings of the modern epoch we find many physicians and surgeons contributing vitally to pure physics.

Thomas Young perhaps stands out as the physician who, in the early years of the nineteenth century, did most to transform physics into its present shape. Mayer, the tragic German physician, so stoutly championed by Tyndall as one of the discoverers of the great generalization of Conservation of Energy, on the basis, be it noted, of observations of the blood of the Javanese, is a notable medical contributor to physics. Tyndall himself, through his researches in the domain of radiant energy, as well as his intervention in the controversies around spontaneous generation and the bacterial origin of disease, is one of the greatest

"medical physicists" of the nineteenth century. Again, physics in medicine certainly found one of its most able exponents in Helmholtz, whose mathematical and experimental ability transformed the science of acoustics, while earlier in the century, a German physicist, Ritter, seems to have been the discoverer of ultraviolet radiation, although hotly followed by Wollaston, another medical physicist.

So from the medical student, Galileo, interested in the swinging of a lamp as a time-keeper to his pulse, to Lawrence and his giant cyclotron on the hilltop in California, technical advances in medicine have been linked with physics.

As we have already indicated, physics may influence medicine very profoundly by its general conceptions of the Universe, as well as by its detailed techniques. The "recent advances" of science are bound to excite the more progressive and impatient medical men of each generation. Again, any adequate account of these relationships is a task for the medical historian, but it is tempting to stray a little and recall the influence of the Newtonian philosophy on the medical practitioner of the early eighteenth century. Newton contributed directly to, and indeed in one sense founded, the science of radiology with his studies of the visible solar spectrum. In radiation physics his influence is obvious, and no one reading, for example, Herschel's description of the experiments following his discovery of infrared radiation in the year 1800, could fail to note the similarity of the train of thought and experiments with those in Newton's *Opticks,* published about a hundred years earlier. Newton, however, influenced medical thought very profoundly in many other ways, as for example, by his "mechanical" explanation of the Universe, which gripped the imagination of his contemporaries. It is interesting to recall that in 1702, one of the most remarkable physicians of the early eighteenth century, Richard Mead, published *A Mechanical Account of Poisons,* complaining a little that "to unravel the Springs of the several Motions upon which such Appearances do depend, and Trace up all the Symptoms to first Causes, requires some Art as well as Labour." Let Mead speak for himself in his preface:

"My Design in thinking of these Matters was, to try how far I could carry Mechanical Consideration in Accounting for those surprising Changes which Poisons make in an Animal Body; concluding (as I think fairly) that if so abstruse Phaenomena as these did come under the known Laws of Motion, it might very well be taken for granted, that the more obvious Appearances in the same Fabrick are owing to such Causes as are within the Reach of Geometrical Reasoning."

Again,

"It is very evident, that all other Methods of improving Medicine have been found Ineffectual, by the Stand It has been at these Three or Four Thousand Years; and that since of late Mathematicians have set Themselves to the Study of It, Men do already begin to Talk so Intelligibly and Comprehensibly, even about abstruse Matters, that it may be hoped in a short Time, if Those who are Designed for this Profession, are early, while their Minds and Bodies are Patient of Labour and Toil, Initiated in the Knowledge of Numbers and Geometry, that Mathematical Learning will be the Distinguishing Mark of a Physician from a Quack; and that He who wants this necessary Qualification will be as Ridiculous as One without Greek or Latin."

So much for those who feel that even if Philosophy and Physics can agree, Mathematics and Physics cannot. It seems that mathematics had already invaded medicine, although we might even now be a little shy at claiming such prerogatives for it.

It will doubtless be equally interesting to look back in the year 2200 A.D. and see the influence that the electrical theory of matter, developed during the first few years of the twentieth century, had upon medicine.

Physics in Radiotherapy

Advancing techniques in physics applied to medicine bring problems of organization and human relationships, and it is perhaps interesting to illustrate some of these problems of daily

collaboration of physicist and doctor from the field of medical radiology, the only one in which the writer could claim firsthand knowledge. In radiation therapy the closest collaboration between radiologist and physicist is now recognized to be essential, yet even to most nonmedical physicists the problems appear strange and bewildering, and it is scarcely surprising that medical radiologists find increasing difficulty in following the detailed mathematical and physical studies of their techniques.

We may take the view that the medical man has so many problems of his own that it is quite impossible and undesirable for him to attempt to follow these details, and similarly the physicist may find incomprehensible what is to the radiologist the most elementary anatomy and pathology. Unless the medical radiologist understands something at least of the power and limitation of the physical methods, he will certainly not be able to make the best use of his physical colleagues, who in their turn will be unable to make relevant suggestions of alteration in technique, or criticisms of present procedures, unless at least superfically acquainted with the medical radiologist's mode of speech.

One of the most efficient ways of bringing together these two groups of people with such different training and, therefore, outlook, lies in the regular attendance of the physicist at radiological clinics, where he may see the difference between a neat diagram of radiation fields and cancer in its anatomical and most "unmathematical" forms. The radiologist on his part will find regular visits to an experimental laboratory stimulating and chastening experiences. A good deal might be done to relieve the situation by a more systematic training of the hospital physicist. Frequently even a change in mathematical approach to a problem will make collaboration much easier. It will be found, for example, in studying radiation distributions showing the dose at various points in the tissues, that the medical radiologist will visualize results much more clearly if the physicist avoids formal mathematical analysis and substitutes geometrical methods. A formula is anathema, but the shape of an "isodose surface" is almost anatomy. The physicist is apt to think his

job is done when he states, let us say, "that for a length of 2.7 centimeters the dose in a certain plane does not fall below 90 per cent." Such a statement means little to most medical radiologists, but expressed in the form that "the 90 per cent isodose surface stretches anteriorly from the lower border of the hyoid bone to the upper border of the cricoid cartilage" instantly brings a look of relief and gratitude. This method of approach implies that the hospital physicist should be instructed in elementary anatomy, so as to be able to take a more intelligent interest in the parts of the body he helps to treat, as well as to be able to transmit his hard-won information in a more acceptable form to his medical colleagues. The anatomy taught to him should of necessity be of rather a special variety, which we might describe as "geometrical anatomy." Size, shape, and position are of more importance to him than structure or function, which clearly lie outside his province.

It has usually been thought that too close a reliance on physical methods leads to rigid techniques and standardized dosage, that the individuality of the patient is lost, and that all is subordinated to an inflexible régime. This is a grave error, and the reverse is more nearly true. There can be no doubt that variation of size, condition, and sensitivity from patient to patient is of the utmost importance, but standardization of technique becomes increasingly indefensible as the detailed physical studies provide the necessary information to enable adjustment of technique from patient to patient to be made on a rational basis. Physical studies of sufficient range tend towards flexibility rather than standardization. This is an important lesson for both medical man and physicist to learn, and they are more likely to learn together than separately.

Only the closest personal collaboration of radiologist and physicist, only the daily discussion of common problems, and the realization that the medical man has the final responsibility but the physicist an indispensable interest, can solve the problem of one of the most important applications of science in medicine. The physicist must realize that however fascinating and important his more academic problems, his primary responsibility

in this respect is to be useful, while on the part of the medical radiologist we ask for a more enlightened understanding of the importance of the physicist, not only in solving the technical day-to-day problems, but also as a spearhead of the attack on the fundamental biophysical problems of the structure of living material and its interaction with radiation. As new fields of medical physics develop, doubtless similar problems of cooperation will arise, but the principles of cooperative study and education are universal.

Developing Influence of Physics in Biology and Medicine

It is certain that the materials of the living organism are much more complex than any hitherto subjected to physical inquiry, but that advances in knowledge of the structure of these living materials, both normal and pathological, might bring about revolutionary changes in medicine no one could deny. The use of modern physical weapons like the X-ray spectrograph, the electron microscope with its possibilities of electron diffraction, or the radioactive tracers, offers nothing less. A great deal of the knowledge may not at first be new, but both physics and biology seem to have reached a stage where the techniques and perhaps the "ideology" of physics are becoming vital to biological progress. The cyclotron producing its wealth of artificial radioactive products, and the electron microscope lowering the limits of visible size over a critical region covering the viruses and colloidal particles, make possible an attack on the wealth of organization lying between the small molecule and the visible speck of living matter. These and other weapons hold out promise of rich rewards in a field in which hitherto physics has hardly dared to venture. Whether there will develop a reasonably well-defined science of biophysics analogous to biochemistry it is difficult to foretell. Physics is such a vigorous parent that its lusty children tend to early maturity and independence.

It will not be easy to combine the distinctive features of physics and biology. The conceptions of physics tend towards

the static and universal; those of biology towards the dynamic and individual. The physicist learns to deal with effects accomplished and finished with fairly clear comprehension of the chain of events between. The study of living organisms necessitates intrusion into a delicately-poised working mechanism which may react in unsuspected and disconcerting ways. There is apt to be a great gap of ignorance between the original stimulus and the resulting effect, with a consequent belief that the mechanism is much simpler and more amenable to mathematical analysis than is in fact the case. The physicist is prepared to admit variability, but has a feeling that proper statistical methods will lead to unerring conclusions. The biological experimenter (and good clinician) has to make many inspired guesses on most insufficient evidence, and sometimes needs a good deal of convincing as to its inadequacy.

Again the only solution seems to be the closest possible collaboration between experimental biologists, cytologists, biochemists, and many others with the physicist, each knowing enough of the other aspects to visualize the outline of the picture even if the sketch is a little misty.

These considerations inevitably raise the question of education. It is an unfortunate fact that most physicists learn extremely little or no biology and conversely, that the biologist is usually quite innocent of physics and has an alleged dislike of mathematics. It is most important that opportunities be available for members of both groups to be educated in the two fields. The medical undergraduate, again, presents special problems in this respect, for physics will not be applied in medical practice and so make its proper contribution to medicine unless the doctor of tomorrow has at least some grasp of its scope and potentialities. This is not easy, for the truth is that the fundamentals of physics are often most clearly exemplified with simple nonmedical examples, while the branches of physics which are of most direct application in medicine are complex, difficult, and often regarded as "unsuitable for children."

Moreover, those teaching physics in the ordinary way have little if any contact with the medical profession and courses

are better adapted to the needs of engineers. There can be no doubt that a medical school in the closest possible contact with a large general hospital is the best training ground in medical physics, for even at the most elementary stage it is very doubtful if the teaching of physics in medicine can be adequately dealt with away from the hospital and patient. Certainly, here will occur the best opportunity of making physics a real part of medical education, particularly if the courses are constructed so as to bring vividly and continuously before the mind of the student examples of the applications of physical principles and instruments in daily practice. Without such education it seems improbable that the applications of physics to medicine will be made as rapidly or as completely as is desirable.

To sum up then, physics seems destined to assume an increasing importance in medicine, by the introduction both of specific techniques and of general ideas. Its influence has already a fascinating historical background, but the interest at the moment lies rather in the organization and training of physicists devoted solely to discovery and application in medicine. There arise many questions of education and cooperation for both medical man and physicist, and these problems can best be solved by the development of mutual understanding while working together. It seems that we must provide education in both the biological and physical sciences to the hospital physicist of the future, for the developments of biophysics are likely to play an increasing part in medical practice.

BIOPHYSICAL FACTORS IN DRUG ACTION

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Introduction

THE rapid advances which have been made within the past few years in our knowledge of tissue ultrastructure and cell chemistry have introduced new perspectives into the possibilities of a better understanding of the various modes of drug action, by closer collaboration between the biologist and the chemist. Perhaps one of our chief difficulties in seeking a rational explanation of the biological activities of drugs in terms of simple physicochemical or biophysical factors is the apparent simplicity of the relationships which may readily be deduced by analogy with artificial model systems. The justification for the use of such models has frequently been based on the assumption that the living system is so complex that the gross properties of a particular structure are often embodied in a simplified reconstructed system.

But the physiologist is now inclined to enquire a little further into the intermediary factors which influence the production of a biological response to a drug. The morphologist is becoming increasingly interested in the dynamic significance of the structures he examines, and he is better acquainted with the uses of the ultraviolet and electron microscopes in detecting structures which cannot be resolved with the ordinary light microscope. Moreover he is able to interpret the molecular arrangements in these structures with the polarization microscope and the methods of X-ray diffraction analysis.

The Analytical Approach to the Study of Drug Action

The aim of the biochemist has primarily been the isolation and analysis of the purified components of the living cell, and considerable information is now available concerning the structural components, which are essentially lipids and proteins, and the vital enzyme systems which are intimately associated with these components. In this connection, the physical chemist has been able to offer valuable cooperation, for the organization of living matter frequently takes the form of discrete cellular fabrics or membranes, and, apart from the permeability of such membranes, the uptake of a drug is also influenced by the asymmetrical forces resident at their surfaces of separation. Schulman and Rideal [35] have shown how it is possible to study the nature of the interactions of drugs with the biological components of membranes by means of the Adam-Langmuir trough. Lipids and proteins can be spread on suitable substrates as two-dimensional films, or monolayers consisting of a single layer of molecules. The changes in the physical state, surface pressure, and surface potential of the monolayers gives an accurate measure of the associating forces between the biological components and the drugs which are introduced into the underlying substrates.

The "Receptor Theory"

Yet despite these ordered advances in what we might term the analytical approach to the nature of drug action, the bulk of existing pharmacological data can be interpreted only by assuming that drugs combine with hypothetical "receptors" in the living organism to produce similar or antagonistic responses. When this occurs it is supposed that the drugs compete for the same receptors in the surface or tissue which is the site of drug action. For example, the bacteriostatic action of sulphonamide drugs is neutralized by the presence of *p*-aminobenzoic acid, an essential metabolite which is utilized by the bacteria. Woods [42] has advanced the view that the antisulphonamide activity of

p-aminobenzoic acid is due to the similarity in structure between the drugs and the metabolite, and that owing to this similarity there is a displacement of metabolite from the bacterial enzyme receptors by the competitive action of the drug. This reduction in available substrate results in an inhibition of bacterial growth.

The "Lipoid Theory" of Narcotic Action

It is less easy to apply the structural relationships of the receptor theory to the mode of action of depressants or narcotics, where activity appears to depend mainly on the physical properties of the drug molecules rather than on special molecular configurations. Here the drugs have a characteristic reversible action. The numerous relationships between the intensity of a depressant action and the changes in the physical properties of narcotics in homologous series of drugs suggest that there is a physical equilibrium between the drug and some component of the living cell which is narcotic sensitive. If we assume that narcotic action depends on the uptake of the drug by the cell lipids, we can collect a great deal of experimental evidence which supports the coincidence between narcotic action and simple drug distribution in model systems containing a mixture of oil and water. This relationship forms the basis of the well-known "lipoid theory" of narcosis which was advanced towards the close of the last century by Overton [27, 28, 29, 30] and Meyer.[24] A later generalization by Traube [37, 38, 39] seeks to correlate narcotic action with the adsorption of drugs at cell surfaces or interfaces. This "adsorption theory" depends on the parallelism between narcotic activity and the surface activity of drugs, and it is supposed that the cell lipids are not necessarily the dominant biological substrates or receptors involved in drug uptake.

The literature abounds with numerous discussions and criticisms of the Overton-Meyer and Traube concepts. These principles have the outstanding merit of simplicity, and their attraction rests in the abundant evidence that has since accumulated and which lends added support to either theory. An adequate survey of the extensions and modifications of these early gen-

eralizations is beyond the scope of the present article, and many comprehensive reviews on the subject are already in existence. But the central problem is to elucidate the mechanism by means of which we can relate narcosis with the depression of the oxidative events of the living cell and also with the association of the drugs with the structural fabric of the cell. We can demonstrate the inhibition of enzymic activity in isolated enzyme systems. We can also detect changes in the molecular orientations of the structural fabrics which form the natural environment of these enzyme systems, but we have been quite unable so far to link these changes in the living system.

Reconciliation of "Rival" Theories

In view of the uncertainty which exists as to the nature of the drug receptors, it may be more constructive at this stage to assume that the "rival" theories which have been proposed from time to time are not necessarily divergent, but are rather expressions of experimentally observed regularities in the relationships of drugs with particular systems. The justification for this assumption will become apparent when we search for common physicochemical factors in some of the diverse structural arrangements in membrane organization which are consistent with pharmacological action, and it will be of interest to notice that the anomalous systems often provide more information than those which show more regular coincidence with simple model systems.

The early work of Overton stressed the importance of the lipids in cell organization and membrane permeability, and the parallelism between the uptake of substances by cells and differential oil-water solubility indicated the preponderance of fatty material in the cell membrane. More recently Osterhout and coworkers [26] have studied the permeability of homogeneous artificial membranes consisting of organic solvents, such as guaiacol, and have related the passage of substances through such oil films with the permeability of the protoplasmic surfaces of large multinucleate plant cells, such as Valonia, Halicystis, and Nitella. In these systems the cell membrane appears to behave as an

oily liquid of low dielectric constant. Collander [8, 9] was in general agreement with the view that the penetration of nonelectrolytes through the plasma membrane takes place through the membrane lipids, but he found that small molecules penetrate into the cells of the alga *Chara fragilis* more rapidly than would be expected from considerations of oil solubility alone. He concluded that the cell membrane acts as a molecular sieve in which the specialized channels become a dominant factor in drug access when the molecular size of the penetrating molecules decreases to a critical value. Nathansohn [25] was similarly led to conclude that the cell membrane is heterogeneous, but his concept differed from that of Collander in assuming that the specially differentiated patches are much larger than molecular sieves, and that the penetration of substances depends on their chemical properties rather than on their molecular size. If we accept the view that the cell membrane is heterogeneous and consists of a mosaic arrangement of relatively hydrated patches distributed in a lipophilic framework, we must also suppose that interfaces exist in the membrane structure, which may, however, approximate to a homogeneous lipid layer in certain types of cells. In this way, some measure of agreement is found which relates the Overton-Meyer and Traube principles in terms of structural membrane relationships, rather than the relationships which exist in model systems.

Investigations on the Erythrocyte Envelope

The erythrocyte has been the favored object of much investigation. Despite the convergent attack which has been made on the nature of the structural organization of the erythrocyte envelope, a considerable degree of uncertainty still exists as to its precise structure. Here, also, the biological complexities in the system are so marked that many new concepts of cell structure have been based on analogy with simple models. For example, by means of the analytical leptoscope, Waugh and Schmitt [41] have estimated that the total thickness of the erythrocyte envelope is about 200 Å. of which up to 100 Å. may consist

of lipid. This instrument has only recently been developed, and the essential principle involved consists in the comparison of the relative intensities of light reflected from the cells and built-up step films of barium stearate of known thickness deposited on a similar substrate to that used for the erythrocytes, which are examined in the form of the dried hemolyzed "ghosts."

Gorter and Grendel [15] reported that the fat-soluble lipid is sufficient to form a bimolecular layer, 50 Å. in thickness, covering the surface of the envelope. Danielli and Davson [11] and Danielli and Harvey [12] have proposed a more stable form of membrane which consists of a lipid layer several molecules in thickness stabilized by the adsorption of protein on the internal and external surfaces which are in contact with the more aqueous environment. It cannot be denied that this "paucimolecular theory," [11] which is a modification of Overton's concept of a homogeneous lipid layer, serves to rationalize a large body of existing permeability data.

Rather critical evidence has been presented recently by Parpart and Dziemian [31] which suggests that a considerable proportion of the lipids in the erythrocyte envelope is firmly bound to the structural fabric of the ghost in the form of fat-insoluble lipo-protein "complexes." The molecular ratio of the fat-soluble fractions, comprising the phospholipids, cephalin and lecithin, and the sterol, cholesterol, is more related to permeability than the total lipid contents of the erythrocytes in different mammals. The cephalin fraction is relatively uniform in the different cells, but there is a much greater divergence between the molecular ratios of lecithin and cholesterol. These results have some bearing on the structural features of the envelope, for the permeability to fat-soluble substances shows little variation in the species examined, but a higher proportion of lecithin and cholesterol is present in the cells which are more permeable to lipid-insoluble substances. It would appear that the cephalin has a structural role in the organization of the erythrocyte membrane, while lecithin and cholesterol are involved in the more labile diffusion processes. In support of this, we may cite the evidence offered by Chargaff and coworkers,[4, 5, 6, 7] who

found that cephalin forms a salt-like lipo-protein with salmine, which is a basic protein, over a *p*H range of 2–11 ; lecithin forms an analogous complex only at *p*H 10–11. The complex formed between cephalin and salmine has rubberlike physical properties. The dried precipitates swell in water and organic solvents, and they may be recrystallized from ethyl alcohol. Other basic proteins, such as histone, also form complexes.

X-ray Diffraction Analysis

From X-ray diffraction analysis of such complexes, Schmitt and Palmer,[34] in collaboration with Chargaff, assumed the existence of a single layer of protein between each bimolecular double layer of cephalin. According to Schmitt and Palmer, the positive polar groups of the extended protein molecules are attached to the negative polar groups of the cephalin molecules on both sides of the protein, and this association results in a decrease in the solvation or hydration of the system. Analogous bimolecular lipid leaflets were detected in emulsions prepared from mixed brain lipids, but the diffraction spacings between the leaflets were much larger than those which occur in the dried lipoprotein complexes. This shows that even in highly solvated systems, the lipid molecules retain their relative orientation to the interlayer aqueous phase. The spacing between the lipid layers in the mixed lipid emulsions is greatly reduced by the presence of divalent cations such as calcium, and this may be related to the conduction of the nerve impulse, for Scott [36] has reported that the bulk of the calcium in a nerve fiber is located in the myelin sheath.

Boehm [3] and Handovsky [16] have described the results of X-ray diffraction analysis on surviving nerves. The association of narcotics with the lipids results in a dispersant action on the packing or orientation of the layers, which become wider and more diffuse. Using similar methods, supplemented by birefringence studies in polarized light, Reynolds, Corrigan, and Hayden [32] were led to believe that orientated lipid associations occur in the human brain, but the degree of orientation varies

and is apparently more marked in nerve trunks than in white matter.

The Pattern of Lipid-Protein-Enzyme Relationship

These diverse observations stress the close relationship between the lipids and proteins in organized tissues. We may imagine that the lipids exert a protective action on the protein structural components of membranes. Baker, Harrison, Miller, and Wexler [1] have found that the action of synthetic detergents on bacteria is inhibited by the presence of phospholipids, and it is supposed that the denaturation of the proteins of the bacterial membrane is prevented by the lipids. Perhaps a similar protective action may account for the resistance of the cell membrane or ghost to the digestive action of pepsin and trypsin, but Ballentine and Parpart [2] point out that this may depend on the resistant nature of the protein itself, and have suggested that the structural proteins of the erythrocytes are scleroproteins, possibly of the albuminoid type.

It is permissible to conclude from these examples that, although we have not yet obtained a coherent pattern of the way in which lipids, proteins, and enzymes are organized in living systems, the shape of this pattern is gradually being resolved. The biologist holds the initiative in this respect, for, as he extends the range of his biological systems and his technical resources for examining these systems, he can select model systems to assist in the elucidations of the complexities of membrane structure, instead of selecting his biological systems to elucidate complexities in model systems which are of uncertain biological significance. What may we profitably look for when we encounter a natural membrane which we have not examined? We can visualize a structural framework or fabric composed of a relatively resistant lipo-protein complex in which the components swell in fat solvents or water but are not readily dissolved in these media. Incorporated functionally in this framework are labile lipids and proteins or lipo-proteins, and possibly enzymes which can be more readily displaced or removed from

the membrane lattice. The membrane is heterogeneous or mosaic in structure, but the preponderance of lipids may confer upon the membrane the properties of a homogeneous oil layer. Moreover, the membrane may have a lamellar structure, which possesses peculiar significance according to the particular physiological function of the membrane.

Insect Cuticle as Test Material

The author [18, 19, 20] has found that the study of the uptake of drugs by insects is facilitated by the fact that the cuticle can be readily removed from the insect and studied as a separate physicochemical system. The insect cuticle consists of an outer lipoidal layer which covers a much thicker inner more hydrophilic layer. The outer layer, which is only a few μ in thickness, contains lipids incorporated in a lipo-protein framework. A proportion of the lipids can be removed by the action of fat solvents. This outer layer, or epicuticle, confers on the cuticle framework its physiological function as a water-impermeable membrane. The inner layer, or endocuticle, may be more than 100 μ in thickness, and consists of hydrated protein closely associated with chitin,[14] together with a smaller proportion of lipids. This layer serves a mechanical supporting or exoskeletal function in relation to the internal tissues and body fluids. The cuticle has a pronounced lamellar structure, and the positive form birefringence indicates the presence of orientated lipids in the lamellae, while the extension of the molecules of protein parallel to the cuticle surface is supported by the X-ray diffraction studies of Fraenkel and Rudall,[14] and by the fact that the cuticle can be mechanically separated into component layers.

Effects of Mixed Drug Systems on Insect Cuticle

The soft cuticles of blowfly larvae, or "maggots," are very suitable for experimental manipulation, and they can be attached to small tubes in the form of osmometers. Some very interesting results have been obtained from the study of mixed drug sys-

tems. Owing to the high resistance of the cuticle, drugs may be applied to the insect at concentrations which would be rapidly toxic to less resistant organisms. When an aqueous solution (10%) of ethyl alcohol is injected into the blood of the blowfly larva, *Calliphora erythrocephala*, the insect is rapidly paralyzed, but will remain active in pure alcohol for more than an hour when this is applied externally. It is clear that the alcohol cannot penetrate through the cuticle into the tissues of the insect. If the alcohol is now diluted (1:1) with a fat solvent, such as kerosene, which is by itself nontoxic, the insect is killed in less than a minute, starts to swell owing to the rapid penetration of alcohol into the tissues, and bursts explosively in about 4 minutes, during which time the body weight has increased by some 50% (figure 1*a*). If the insect is transferred from the alcohol-kerosene mixture to pure alcohol when the body weight

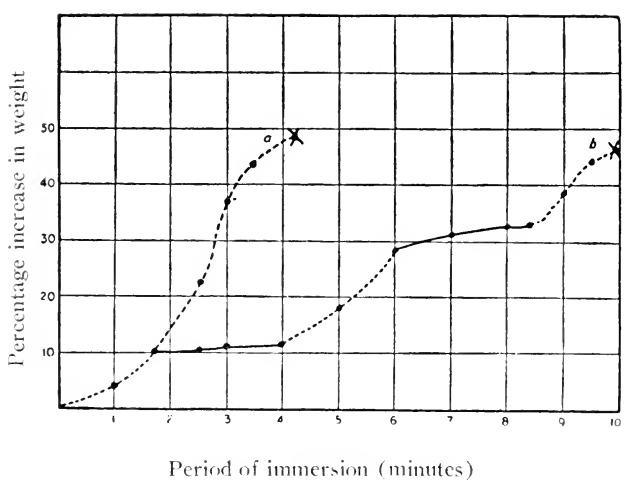


FIG. 1. Uptake of Ethyl Alcohol by Blowfly Larvae (*Calliphora erythrocephala*).

a Continuous immersion in alcohol + kerosene mixture.

b Alternate immersion in alcohol + kerosene mixture and pure alcohol.

× Bursting point of insects.

····· = alcohol + kerosene.

—— = alcohol.

has increased by 10%, the rate of swelling slows down and stops, but increases again rapidly when the insect is returned to the mixture (figure 1*b*). These effects can be repeated in smaller increments, and are not dependent on vital transfer processes, for they can be reproduced with the isolated cuticle attached to a small osmometer filled with water.

The penetration of the alcohol through the cuticle is clearly dependent on the presence of kerosene in the cuticle framework. This must be a very labile association, as the kerosene is readily eluted from the cuticle when the insect is transferred from the mixture into the pure alcohol. The penetration of alcohol which is induced by kerosene is accompanied by a simultaneous increase in the exosmosis of water from the cuticle. This can be observed in the cloudy swirling zone near the surface of the cuticle indicating that kerosene is thrown out of solution in this region. The insect is not dehydrated when immersed in pure alcohol.

Similar results can be obtained with methyl or propyl alcohol, and with fat solvents such as ether, benzene, or chloroform instead of kerosene. The synergistic action is also shown in mixtures which contain structurally related components, such as ethyl and octyl alcohol. Here, apart from its own toxicity, the octyl alcohol increases the permeability of the cuticle to ethyl alcohol, resulting in a progressive swelling of the insect which does not occur in octyl alcohol alone.

The problem which arises is to decide how fat solvents, which are only slightly soluble in water, increase the permeability of the cuticle to water-soluble fat solvents and also to water. Experiments with isolated layers of the cuticles attached to osmometers show that the site of the increase in cuticle permeability is in the outer lipophylic epicuticle. The inner thicker endocuticle layer is very permeable to water, and exosmosis of water takes place very rapidly when this layer is in contact with ethyl alcohol or with alcohol-kerosene mixtures. We are led to consider the possibility that the uptake of kerosene by the epicuticle lipids does not involve only a simple swelling or disorientation of this phase *in situ,* but also a displacement of lipid from the more hydrated protein or lipo-protein components.

But the effects of induced penetration of alcohol also occurs when the fat-soluble lipid has been removed from the cuticle, so we must study the structural organization of the cuticle for a further clue to the nature of the spatial relationships of the lipids and proteins in the epicuticle. For this purpose, the epicuticle is stained red with acid fuchsin and the underlying endocuticle is counter-stained with iron hematoxylin.

Structure of Insect Cuticle

In a transverse section, through the cuticle of the blowfly larva, *Sarcophaga falculata,* the heavily-stained epicuticle is apparently homogeneous, but in a tangential section, the heterogeneous or mosaic structure of this layer can be clearly seen (figures 2*a*, 2*b*). There is a closely packed network of

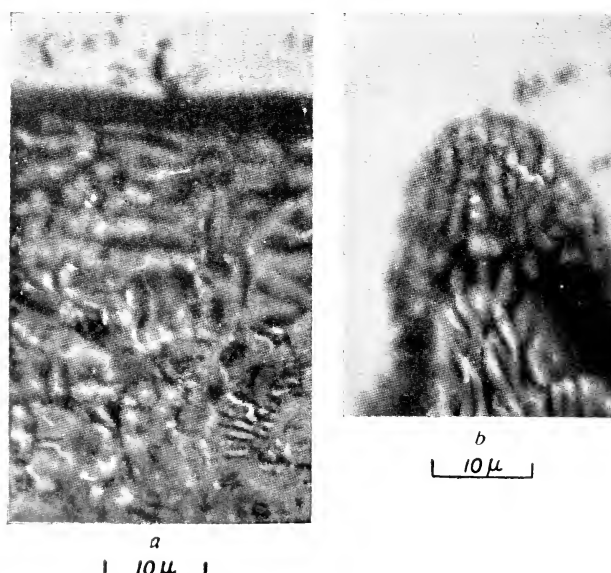


FIG. 2. *a* Transverse section through cuticle of blowfly larva, *Sarcophaga falculata,* showing densely stained outer epicuticle and portion of inner lamellar endocuticle.

b Tangential section through epicuticle, showing mosaic lipophilic network (dark strands), and transitional zone between epicuticle and endocuticle.

lipophilic aggregates which have a somewhat fibrous appearance and are generally radially disposed across the epicuticle framework. The network is interlaced with more hydrated processes from the underlying endocuticle. Lamellation cannot be seen in the epicuticle although it is marked in the endocuticle. This may be due to the more heavily staining outer layer, and as both layers are secreted by the same layer of epidermal cells, it is probable that a lamellar fabric exists also in the epicuticle. The spacing between the layers is relatively wide in the endocuticle and it is possible that a more minute form of structure may be revealed by X-ray diffraction analysis. If we assume the existence of a microscopic lamellar fabric in the epicuticle, and suppose that the visible mosaic network is incorporated in the membrane, the gross relationships of the structural components become more apparent (figure 4*a*).

Effect of Permeability on "Tanning"

We can explain the action of fat solvents in increasing the permeability of the cuticle to other fat solvents such as ethyl alcohol, by assuming that the solvents swell the more lipophilic radially disposed strands of the mosaic network which extends across the epicuticle. But we still have to account for the associated increase in the permeability to water, and this makes it necessary to depart somewhat from the usual classical concepts in which the heterogeneity in a membrane is supposed to consist of pores or channels. Any increase in the permeability of the cuticle to water will probably involve the displacement of protective lipid from the more hydrated protein or lipoprotein structures. But if we "tan" the cuticle by means of a protein reagent such as *p*-benzoquinone, the protected protein zones will tan more slowly than those in which access of *p*-benzoquinone is restricted by the competitive action of the lipid for the amino groups of the protein.

As with ethyl alcohol, the access of *p*-benzoquinone through the cuticle takes place more rapidly in kerosene than in alcohol or water, and this can be measured by the darkening of the

cuticle and by the lethal symptoms which are coincident with the first visible signs of a reddish-brown tinge in the cuticle. The tanning action of the quinone monomer is also accompanied by the deposition of the colored polymerized oxidation products, and these can be observed in optical sections of the cuticle outer layers. The mosaic structure of the epicuticle in the housefly larva, *Musca domestica,* is now shown up clearly by the differentiation of the tanned zones from the untanned zones where the lipid is more strongly attached to the protein. The extension of the dimensions of the tanned regions which takes place under the progressive action of chloroform sensitization or kerosene sensitization results in a reduction in the more lipophilic zones, corresponding to the mosaic shown in figure 2*b*. We may conclude that the lipid between the discrete aggregates of the mosaic is also more readily displaced from the apparent network in which the lipophilic mosaic is embedded (figures 3*a*, 3*b*, 3*c*).

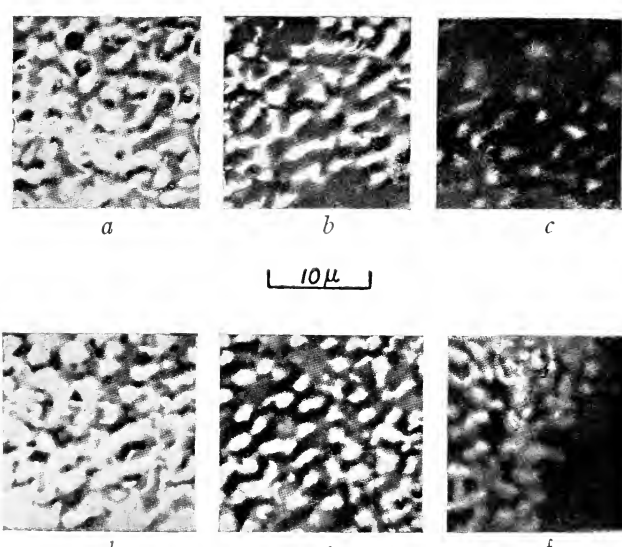


FIG. 3. Artificial Tanning and Hardening of Insect Cuticle (*Musca domestica*).

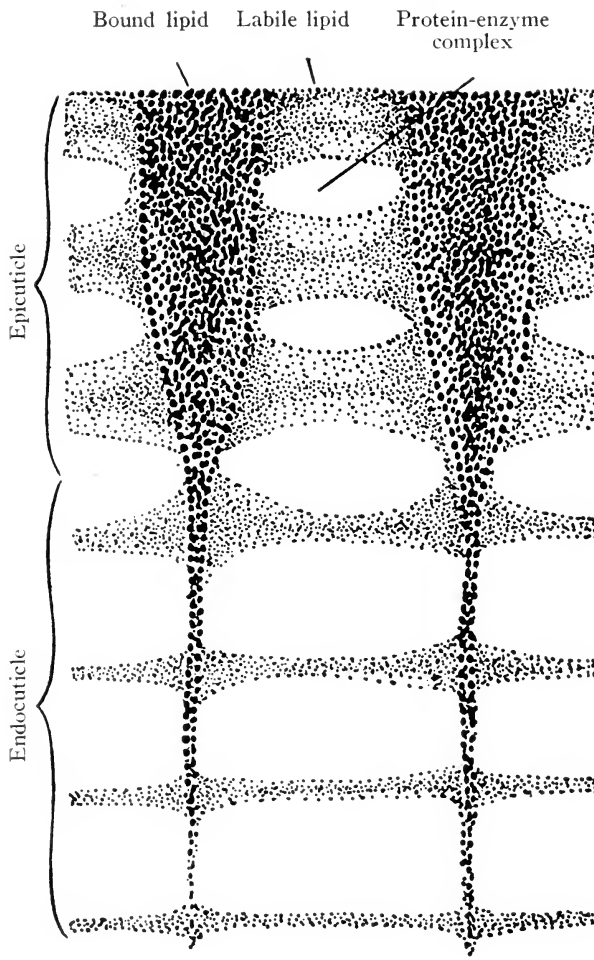
a, b, c Optical section of epicuticle layer, showing progressive tanning by *p*-benzoquinone in mosaic network where lipid is displaced by fat-solvent action (dark regions) (NONENZYMIC).

d, e, f Similar progressive tanning by catechol (ENZYMIC).

The fact that the whole cuticle becomes eventually deeply tanned and hardened by prolonged treatment with *p*-benzoquinone indicates the general lipo-protein character of the cuticle structure. We may conclude that the spatial changes produced by a fat solvent or narcotic in the mosaic organization are as shown in figures 4*a*, 4*b*. There is a general swelling and increase in phase volume of the lipophilic radially arranged aggregates, resulting in an increase in the permeability of this phase to fat solvents which have less lipid-dispersant properties, such as ethyl alcohol. At the same time there is a disorientation and displacement of lipid, probably from the general lamellar fabric of the epicuticle, and this results in an increase in the hydration of the lipid and the protein from which the displacement occurs. In this way, the permeability of the cuticle to water and *p*-benzoquinone is increased.

Permeability and Enzyme Activity

Finally, we can now consider the interesting question of the relation of these changes in membrane permeability to the activity of enzymes which are protected by the environmental influence of the membrane framework. A lipid-free gelatin membrane immersed in a *p*-benzoquinone substrate becomes rapidly tanned, but if we now substitute a catechol substrate for the *p*-benzoquinone, tanning of the membrane does not occur. Wagreich and Nelson [40] have shown that the enzymic oxidation of catechol results in the production of an intermediary *o*-quinone. This quinone has tanning properties similar to those of *p*-benzoquinone, and it is readily produced by the action of an enzyme known as peroxidase which can be extracted from horseradish roots.[21] Catechol is very rapidly oxidized in an aqueous substrate containing peroxidase and hydrogen peroxide, and gelatin membranes in this substrate become rapidly tanned by the diffusible *o*-quinone. Similarly, we can prepare gelatin membranes which contain peroxidase. These also become tanned when in contact with catechol and hydrogen peroxide, but here the reactive *o*-quinone is formed within the membrane framework. Insect cuticle behaves as a membrane of this type, for it



a

FIG. 4A. MECHANISM OF SENSITIZING ACTION OF FAT SOLVENTS ON INSECT CUTICLE. Mosaic arrangement of bound and labile lipid in lipo-protein framework of cuticle of blowfly larvae. A lamellar distribution of labile lipid is shown in the epicuticle and endocuticle.

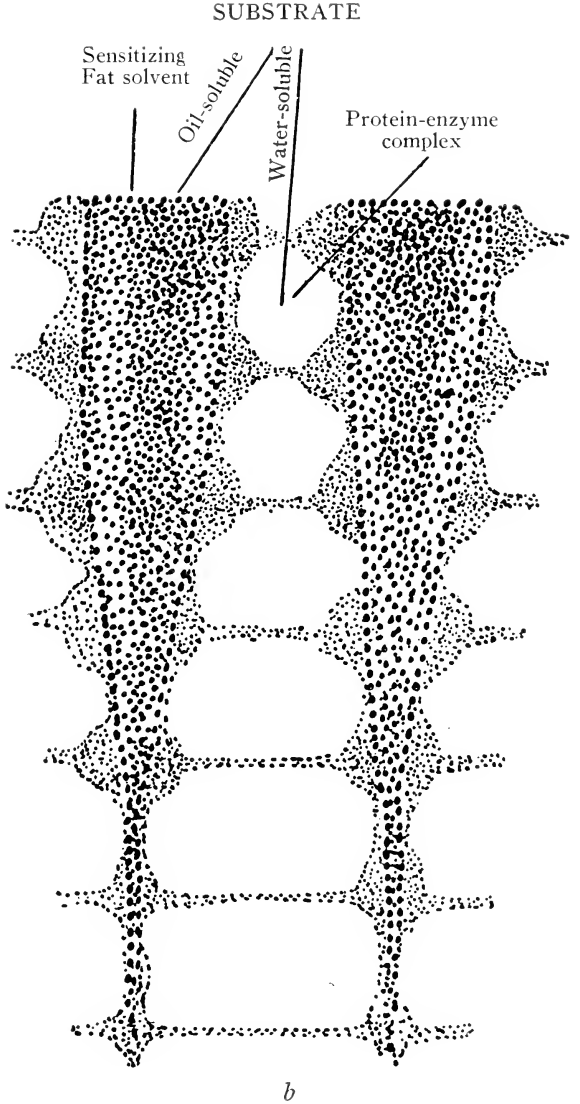


FIG. 4B. Mechanism of Sensitizing Action of Fat Solvents on Insect Cuticle. The uptake of a fat solvent, such as chloroform, results in a swelling of the bound-lipid mosaic network. There is a simultaneous displacement of labile lipid, resulting in an increase in cuticle permeability to fat-soluble and water-soluble substances.

contains an enzyme system which oxidizes catechol very rapidly in the presence of hydrogen peroxide. This enzyme system is involved in the natural hardening of insect cuticle. Both the enzyme and natural polyphenol substrate are secreted into the cuticle by specialized epidermal cells. The rate of natural tanning is increased by abrading the outer layer of the cuticle and impregnating the abraded layer with a concentrated aqueous horseradish-peroxidase extract. Alternatively, the penetration of catechol into the cuticle is increased by treating the cuticle with a fat solvent and then immersing the insect in an aqueous catechol substrate containing hydrogen peroxide. The catechol is oxidized to the *o*-quinone inside the cuticle framework, but the diffusion of the quinone within the membrane framework does not take place uniformly owing to the mosaic structure, and in this respect the insect cuticle differs from the simpler homogeneous gelatin membrane.

However, when we examine the pattern of enzymic tanning which has been induced in the cuticle (figures 3*d*, 3*e*, 3*f*), we see that it is similar to that induced by the nonenzymic tanning with *p*-benzoquinone (figures 3*a*, 3*b*, 3*c*). We note further, that there is a general parallelism between the degree of induced enzymic cuticle tanning produced by sensitizing the cuticle with fat solvents such as hexane, heptane, benzene, ether, or chloroform, and the degree of nonenzymic tanning by *p*-benzoquinone induced by the action of these fat solvents on the protective lipids in the cuticle framework. We conclude that access of catechol to the cuticle enzyme receptors is similarly influenced by a permeability factor or by competitive action of protective lipid on the structural protein-enzyme complex.

Analogy between Insect Cuticle and Cell Membrane

It may well be argued that the insect cuticle is a highly specialized membrane which has little in common with the more complex and submicroscopic cell membrane. But when intact isolated insect tissues are treated with a fat solvent such as chloroform, there is a large increase in tissue-peroxidase activity, suggesting a similar sensitization of the bounding mem-

branes of the component cells. Using appropriate substrates, analogous results can be demonstrated with the phenoloxidase systems, catechol oxidase and tyrosinase, which are also present in the cuticle and internal tissues.

These results can be most logically explained by postulating a lipoprotein mosaic structure in the cell membranes of the tissues, in which the availabilities of the enzymes are influenced by the labile lipids present in the structural frameworks. Similar increases in the availability of these enzymes can be induced in the intact insect by two different kinds of physical stimuli: (1) heat, which increases cuticle permeability and phenoloxidase activity in the internal tissues, and (2) mechanical damage of the cuticle and tissues which exposes the available enzymes. If the posterior segments of an insect such as mealworm larvae, *Tenebrio molitor*, are subjected to the action of (*a*) chloroform, (*b*) heat (40–45° C), and (*c*) mechanical damage by squeezing, the insects first become paralyzed, and this stage is followed by a similar local blackening in the posterior segments owing to an increase in the availability of tissue tyrosinase in these regions, a change which is associated with an increase in oxygen uptake.

These results are in accord with Henderson's suggestion that narcosis and oxidative processes are separable phenomena.[17] Although fat-solvent narcotics appear to exert a physical action on the cell lipids, the secondary changes which cause a disturbance in oxidative metabolism may be much more complex. In insects, the increase in tissue-phenoloxidase activity results in the accumulation of reactive *o*-quinones in the blood and tissues. Richter [33] has shown that these oxidation products act as powerful inhibitors of catechol-oxidase activity; it is likely that they would exert a general toxic action on the vital processes within the insect.

Conclusions

It is doubtful whether this selective environmental influence of the structural tissue components on enzymic activity can be simulated specifically in reconstructed enzyme systems, where

we study the nature of the reactions, but not their dynamic aspects in relation to the living system. The so-called "law of homologous series," which expresses the regularity with which pharmacological activity increases with the length of hydrocarbon chain, is possibly due to the close association of the lipids and enzyme receptors at the site of drug action. The primary role of the structural lipids may be the storage and presentation of drug to the active groups in the enzyme system.

The characteristic rise and fall in activity as a series of homologous drugs is ascended, for example, with the maximum pressor activity in the aliphatic primary amines; antiseptic activity of the alkyl phenols,[10] resorcinols [23]; and bactericidal and fungicidal activities of alkyl derivatives of *o*- and *p*-chlorphenols investigated by Klarman, Shternov, and Gates,[22] may simply be due to some optimal association of the drugs with the structural lipids or lipoproteins, which is consistent with maximum access or presentation of the drugs to the associated enzyme complex. This concept would also explain how the maximum activity in a homologous series of drugs may vary in different tissues and organisms.

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A SURVEY OF THE APPLICATIONS OF ELECTRONICS IN MEDICINE

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Introduction

ELECTRONICS in medicine covers such a large field that, in this article, only some of the more important and interesting aspects of the subject can be dealt with. There is hardly a branch of medicine which cannot benefit from the application of electronics.

The phenomena with which a physician has to deal—sound, pressure, heat, etc.—can easily be transformed into electrical equivalents which can be amplified by thermionic-valve amplifiers, and graphically recorded. Bioelectric quantities, such as the electrical variations of the heart, lend themselves readily to valve-amplifier technique and registration. The extent of amplification of the signal is governed by the amplification given by the valves in the various stages, and is modified by the attenuation which occurs as a result of the relationship of signal frequency to the resistance-capacity values used for coupling. This relationship is the frequency response characteristic of the amplifier.

The amount of useful amplification really depends on the "resolving power" of the amplifier, i.e., the smallest potential change that can be detected, and this in turn is mainly dependent on the working of the first stage of the amplifier. At present we can detect an input change of one microvolt in a circuit of high resistance, like a small nerve trunk, but it is difficult to deal with anything less than this because of fluctuations introduced by the resistors, valves, etc.

Nerve Action Potentials

Nerve fiber is a tissue in which some of the properties of living matter, especially conductivity and excitability, have become developed to an exceptional extent. The electrical stimulus is the common one employed experimentally, but chemical or mechanical stimuli are also effective. A nerve impulse travelling along a nerve fiber is accompanied by a characteristic electrical change, which is a diphasic potential wave. Once the impulse has been initiated in a nerve, it is "all or none." If a nerve fiber is stimulated electrically, the rate of travel and magnitude are independent of the strength of the stimulus, and depend only on the state of the nerve at the point under consideration. In any particular fiber, stronger stimulation causes only an increase in the frequency of the potential waves. A nerve trunk may contain thousands of fibers of varying types and sizes, and records may show a complex series of transients. In the human body, the waves have a peak potential of about 1.0 millivolt (which is only a fraction of that developed by the nerve owing to the shunting effect of the inactive adjacent fibers in the nerve trunk), and last about 1.0 milliseconds.

The early work on nerve action potentials was handicapped by the fact that the majority of recording instruments which were sensitive enough for the purpose, for instance, the capillary electrometer and the string galvanometer, required appreciable power to work them, besides suffering from inertia. Pioneer work was done by Adrian,[1] using a capillary electrometer, and Forbes and Thacher [20] with a string galvanometer. Gasser and Erlanger [21] used the cathode-ray oscillograph as the recording device. Adrian [2] in his monograph on *The Mechanism of Nervous Action,* gives a review of the work done in this field to that date.

Wever and Bray [53] had the courage to connect the auditory nerve with an amplifier and telephone. They found that any sound reaching the ear was reproduced in the telephone; speech could be understood, and the speaker identified by his voice.

These nerve action potentials can be demonstrated visually by means of the cathode-ray oscillograph.

A suitable amplifier for the demonstration of the electrical changes in sensory nerves consists of a four-stage resistance-capacity coupled amplifier employing MH_4 thermionic triode valves. The plate of the first valve is fed through a resistance of 50,000 ohms, 20,000 ohms of which is used for decoupling through a 4 mfd condenser. The second valve is fed through a similar resistance, 10,000 ohms of which is used for decoupling through a 4 mfd condenser. The third valve is fed through a similar resistance, and the decoupling is the same as in the preceding valve. The output valve is fed through a 11,000 ohms resistance, 1,000 ohms of which is employed for decoupling through a 4 mfd condenser. The anode of this stage is fed via a 2 mfd condenser, and the earth line to the Y plates of a cathode-ray oscillograph. The intercoupling condenser of each stage is 1 mfd, and the grid-bias resistor is 0.25 meg ohms, giving for each stage a time constant of 0.25 seconds.

Various specialized amplifiers and general purpose biological amplifiers have been developed for this type of work. Other recording devices besides the cathode-ray oscillograph, such as the mirror oscillograph, have been used.

Muscle Action Potentials

The action potentials of muscle fibers are similar in shape to those of nerve fibers, but are larger and slower.

Wedensky [52] used the telephone as an indicator to study the rate of electrical changes in voluntary muscular contraction. Piper [37] used the string galvanometer in recording the electromyogram. Adrian and Bronk [3] demonstrated that the action potentials from voluntary muscle can be recorded by means of a concentric needle electrode. Denny-Brown and Pennybacker [10] showed that the recording of action potentials from voluntary muscle in certain pathological conditions gave useful information concerning the nature and position of the underlying pathological process. Weddell, Feinstein, and Pattle [50] point out that

the activity of normally contracting motor units and of fibrillation can be easily distinguished, and it is consequently possible to decide whether a muscle is innervated normally, partially, or not at all. For the exploration of the whole muscle, about six punctures of the needle electrode may be required, but this is rarely necessary and gives only trifling discomfort. Elliott [17] made electromyographic studies of tender muscles in sciatica. He demonstrated that the tender spots in the muscles are, as a rule, the seat of a localized increase of irritability and a continuous discharge of action potentials, which lasts as long as the needle remains in the muscle.

A technique commonly employed in electromyography is to insert a concentric electrode, made of fine wire running through the center of a fine-gage hypodermic needle, into the belly of the muscle. The needle's barrel acts as an earthed shield, and the minute wire electrode picks up the electrical activity of units within a radius of 1 millimeter. The electrical potentials are amplified by a standard amplifier, and records can be observed and photographed on a cathode-ray tube. Weddell, Feinstein, and Pattle [51] employ a special all-mains-operated amplifier. Cathode-ray oscilloscope tracings are used for permanent records, for practical purposes, however, only the sounds emitted from an output loudspeaker are noted; the detection of small differences in duration and frequency are more easily assessed by auditory than by visual methods.

Chronaxie Meters and Electronic Stimulators

The effectiveness of a stimulus depends not only on its strength, but also on the time during which it is allowed to flow through the tissues. Chronaxie is defined as the time during which a current, twice as great as the rheobase, must flow through a tissue to set up activity. It is a measure of the excitability of a tissue.

Brian Denny [9] developed, from the original circuits of Bauwens, an apparatus which aims at providing the means of determining, accurately, the response to electrical stimulation of

muscle and nerve and of applying electrical treatment of known character and dosage.

Ritchie [42] has described a simple variable "square-wave" stimulator for biological work. The instrument uses two standard triode valves to produce impulses independently variable in intensity, duration, and frequency over the wide ranges used in the excitation of nerve and muscle.

Electrocardiography

The electrical variations produced by the heart during contraction are distributed through the body, and can be led off from the moist skin surface of such areas as the arms and legs, and recorded.

Kölliker and Müller [29] showed, by physiological experiments, that an electrical change accompanies the beat of the isolated frog's heart. Waller [46] demonstrated similar changes occurring in the human heart, when electrodes are applied to the limbs. He used Lippman's capillary electrometer, and his experiments remained of academic interest only. Einthoven [16] introduced the string galvanometer which made electrocardiography, in its modern form, a clinical science. Some of the disadvantages of the string-galvanometer type of electrocardiograph are: the fragility of the string, the necessity of skin-current compensation, and the use of nonpolarizable electrodes.

Because of the extremely low voltage generated by the action of the heart, instruments for its measurement in the past have necessarily been extremely sensitive, and the recorders of these have, therefore, been very delicate. The introduction of thermionic-valve amplifiers, and the substitution of robust oscillagraphs changed all this. The usual form of recorder employed with thermionic-valve amplifiers was the mirror galvanometer of comparatively low sensitivity. Examples of such instruments are the Victor electrocardiograph and the Matthews electrocardiograph.

The Both electrocardiograph works on the thermionic-valve amplifier principle, but feeds a small cutting stylus which indents

a specially prepared surface. The resultant electrocardiogram is $\frac{1}{50}$ of standard size, and must be viewed through a microscope for direct visual observation. If a permanent standard-record-size electrocardiogram is desired, the original record must be sent to the agents for enlarging.

The ink-writing electrocardiograph uses a valve amplifier and an ink-writing oscillograph. The record is made on inexpensive paper tape. It is immediately visible, and requires no process of developing or fixing. The upper-frequency response of the instrument is limited, due mainly to the friction between the writing pen and the recording paper.

For exact reproduction of the wave shape of the electrocardiogram, it is essential to use an oscillographic recording element which will respond to the highest-frequency components. Such a device is the cathode-ray oscillograph. The cathode-ray tube is essentially an oscillographic indicator characterized by two striking and valuable properties: first, the almost complete absence of inertia in the recorder, and, secondly, the two-dimensional recording field. The tube, itself, is essentially a complicated thermionic valve. It contains, at one end, an electrode structure, called the "electron gun," and, at the other end, the fluorescent screen. The "electron gun" possesses a filament, a cathode, a grid, and an anode. The electrons emitted by the heated cathode are accelerated by the high positive potential of the anode, and are caused to pass down the length of the tube in the form of a narrow beam. These high-velocity electrons impinge on a fluorescent screen, and there give rise to a spot of light. The direction of motion of the electrons, forming the electron beam, is affected by electric or magnetic fields. At any point between the accelerating system (or "electron gun") and the screen, the beam may be deflected by the electric or magnetic field; the resulting displacement of the spot is a measure of the strength of that field. In the most usual arrangement, the cathode-ray tube is fitted with two pairs of deflecting plates mutually at right angles, and the deflection of the spot along an axis is closely proportional to the voltage difference between

opposite plates. In the gas-focused type of tube, the combined action of a small amount of gas within the tube, and of the negative grid potential, causes the beam to be focused to a fine spot. A modern high-vacuum type incorporates several refinements. Instead of a simple plate for the anode, two or more cylinders are used; focusing is brought about by electrical optical means. The pair of deflecting plates in the vertical plane are called the Y plates, and those in the horizontal plane are called the X plates. The deflectional sensitivity of the cathode-ray tube is insufficient to produce a record when the heart potentials are applied directly to it. A high-gain amplifier is therefore necessary to magnify these potentials sufficiently to give a trace on the screen of the tube. The output of this amplifier is connected to the pair of Y plates, and thus gives a vertical trace. If required, the vertical movements can be photographically recorded on moving film. If it is desired to view the wave form of the electrical variations of the heart on the screen of the cathode-ray tube, it is necessary for the beam to move slowly across the whole of the screen of the cathode-ray oscilloscope in the horizontal, or X axis, from left to right. This movement is given by a time-base circuit. For the direct visual observation of the electrocardiogram, the fluorescent-screen material used in the tube is chosen to have a very long afterglow, so that the trace of the spot, when seen in a darkened enclosure, is visible for several seconds after the spot has gone by.

Rijlant,[41] Schmitz [44] and Matthews [33] were among the first who adapted the cathode-ray tube to electrocardiography. They used the cathode-ray tube merely as a recording device, and not as an oscilloscope. Robertson [43] introduced a new electrocardiograph employing the cathode-ray tube as an oscilloscope and fitted with a screen having a long afterglow, which permitted direct visual observation of the electrocardiogram. Brokes-Smith [8] devised a similar apparatus, but without any device to obviate origin distortion. Asher and Hoecker [4] mention in their paper that Wilson has adapted the afterglow cathode-ray oscilloscope to electrocardiography.

The cathode-ray tube has been adapted to vectorcardiography

by Hollmann and Hollmann,[26] Wilson and Johnston,[54] and others.

Hoff, Kramer, DuBois and Patten[25] have employed valve-amplifier technique for recording the electrocardiogram of the embryonic heart of the developing chick. Mann and Bernstein,[32] Ward and Kennedy[49] and others have used electroencephalographic technique for the registration of the electrical variations of the human foetal heart.

The Phonoelectrocardioscope

The phonoelectrocardioscope[11, 12, 13, 15] incorporates a double-beam cathode-ray oscilloscope fitted with a long afterglow screen, which permits the simultaneous and constant viewing of a pair of phenomena such as the phonocardiogram and electrocardiogram at the patient's bedside, while the heart sounds can be heard at the same time through an electrical amplifying stethoscope or a loud-speaker. The double-beam cathode-ray oscilloscope has also many uses in biology and medicine.[14]

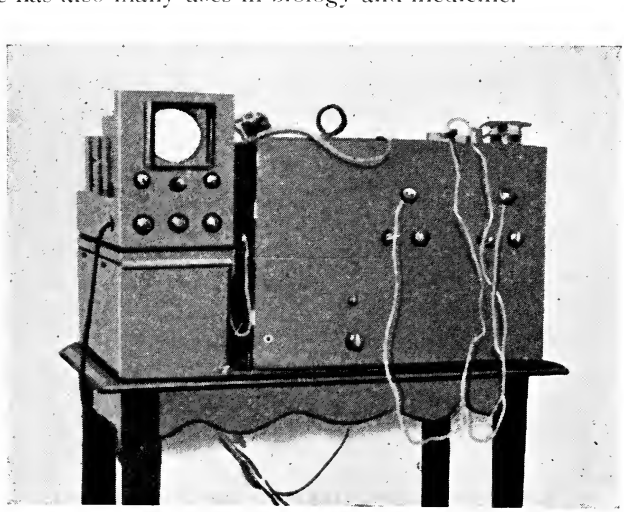

FIG. 1. The Phonoelectrocardioscope.

Figure 1 shows a photograph of the apparatus, and figure 2 a schematic diagram. The heart sounds are picked up by a piezoelectric microphone, which converts them into electrical pulsations. These are amplified by a thermionic-valve amplifier which has special variable electrical frequency controls incorporated in it. An electrical stethoscope reconverts the amplified electrical pulsations into sound waves. The phonocardiogram can be directly observed on the long afterglow screen of the double-beam cathode-ray oscilloscope. The electrical variations of the heart can be simultaneously amplified by the second channel, and directly observed as the second trace on the screen.

The following are some of the uses of the phonoelectrocardioscope in cardiology:

1. Simultaneous direct visual observation of the phonocardiogram and electrocardiogram, plus amplified auscultation.
2. Simultaneous direct visual observation of the phonocardiogram and sphygmogram, plus amplified auscultation.
3. Simultaneous direct visual observation of the electrocardiogram and pneumocardiogram, plus amplified auscultation.
4. Simultaneous direct visual observation of a logarithmic phonocardiogram, and stethoscopic phonocardiogram, or any one of the foregoing with a linear phonocardiogram, plus amplified auscultation.
5. Simultaneous direct visual observation of the phonocardiogram of one area with that of another, plus amplified auscultation.
6. Simultaneous direct visual observation of any pair of electrocardiogram leads, such as leads I and III.
7. Photographic registration.
8. Murmurs or desired sounds can be accentuated and undesirable ones muted by filter controls.

Figure 3 shows a peculiarity of the double-beam cathode-ray tube. It will be noted that the bottom logarithmic phonocardiogram is apparently 180 degrees out of phase compared with the similar trace on the top. This can be rectified by

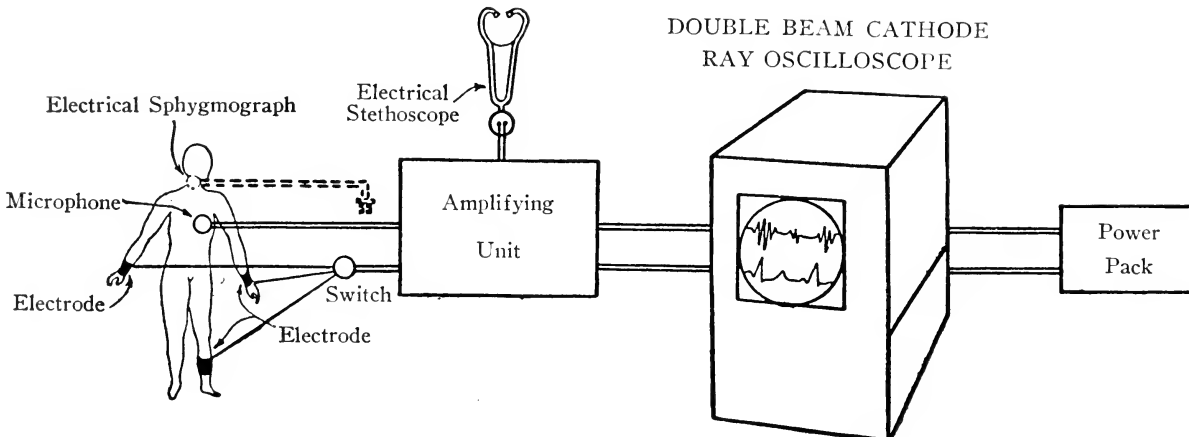

FIG. 2. SCHEMATIC DIAGRAM OF THE PHONOELECTROCARDIOSCOPE.

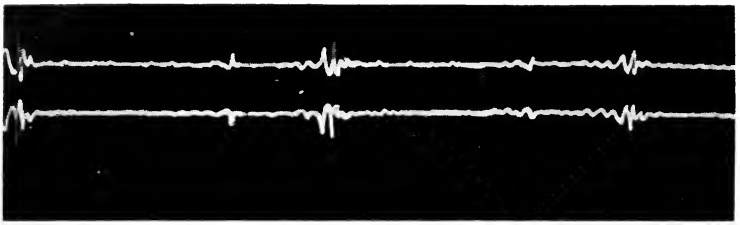

FIG. 3. The same apical phonocardiogram has been recorded by both beams on moving film. It will be noted that they are apparently 180° out of phase, and that there is no "fogging." Illustrative tracing taken with the author's phonoelectrocardioscope.

reversing the input leads for the bottom trace. The pair of traces have been recorded on moving film, and, despite the long afterglow screen, there is no trace of "fogging." Figure 4 shows a logarithmic phonocardiogram and electrocardiogram,

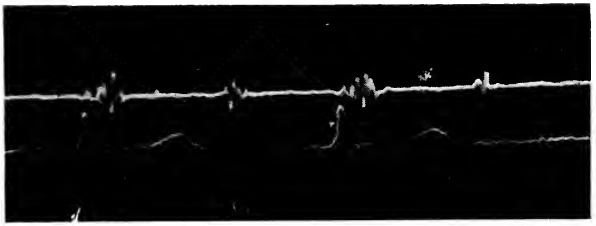

FIG. 4. Logarithmic apical phonocardiogram. Electrocardiogram, lead II. Recorded on moving film. Illustrative tracing taken with the author's phonoelectrocardioscope.

lead II, recorded on moving film. The precaution mentioned above has been adopted, and the electrocardiogram shows the right way up.

Figure 5 shows how a pair of traces look on the screen when viewed directly. The top trace is electrocardiogram, lead II, and the bottom trace is the jugular-pulse sphygmogram. They have been photographed by focusing a camera on the fluorescent screen of the double-beam cathode-ray oscilloscope, and taking one traverse of the pair of spots as they appear for visual ob-

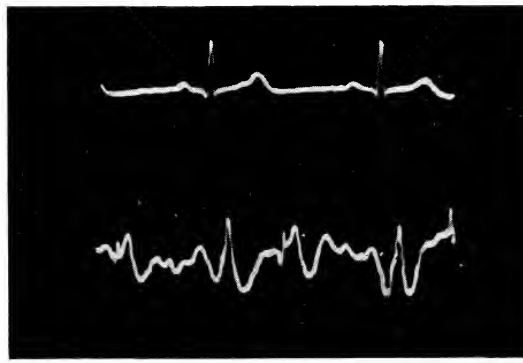

FIG. 5. Electrocardiogram, lead II. Electrical jugular pulse tracing. The traverse of the pair of spots was photographed as they appeared for visual observation—opening the shutter at the beginning and closing it at the end of the traverse of the spots. Illustrative tracing taken with the author's phonoelectrocardioscope.

servation—opening the camera shutter at the beginning, and closing it at the end of the traverse of the spots. Figure 6 is similar to Figure 5, but shows electrocardiogram, lead II, and a stethoscopic phonocardiogram, taken over the mitral area of a case of rheumatic endocarditis.

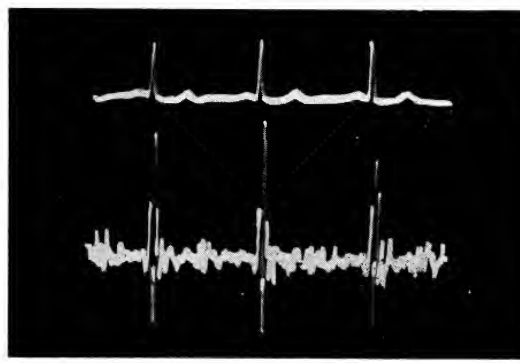

FIG. 6. Electrocardiogram, lead II. Apical phonocardiogram of a case of rheumatic mitral endocarditis. The traverse of the pair of spots was photographed as they appeared for visual observation—opening the shutter at the beginning and closing it at the end of the traverse of the spots. Illustrative tracing taken with the author's phonoelectrocardioscope.

The loudness of the heart sounds as heard in the amplifying stethoscope is governed by a tone-compensated gain control, which helps to correct certain deficiencies in the human ear in which the auditory sensation produced by complex sounds may be decidedly different in character as well as intensity when the stimulating level is increased or decreased. Such a device permits greater latitude in varying the intensity levels at which the heart sounds are heard.

It is easy to pick up the jugular sphygmogram by shunting the microphone with a 1 mfd condenser. The shunted-condenser microphone method is also used for recording the pneumocardiogram. It is an obvious advantage to have an all-electric method of recording these traces.

The phonoelectrocardioscope is of value in teaching, research and clinical medicine.

Electroencephalography

The technique of electroencephalography is analogous to that of electrocardiography, viz., amplification and registration of the electrical potentials from the brain as picked up from the surface of the body. The upper limit of size of the brain potentials as led off from the scalp approaches that of the electrocardiogram, i.e., about 1 millivolt. Potentials even greater than this are obtained when leads are placed directly on the exposed cortex. Discharges of this magnitude are rare, and only found in abnormal conditions.

The electrical variations generated by the brain fall into certain patterns. The alpha waves, normally present in most people, have frequencies in the neighborhood of 10 cycles per second and amplitude of 10–50 microvolts. The beta waves have a frequency of 30–40 cycles per second, but are of lower voltage. Low-frequency waves, below 3 cycles per second, are called delta waves, and are often of larger amplitude than either the alpha or beta waves. The patterns are frequently superimposed. Walter and Dovey [48] suggest that rhythms at about 6 cycles per second should be termed "theta" rhythms, and that such

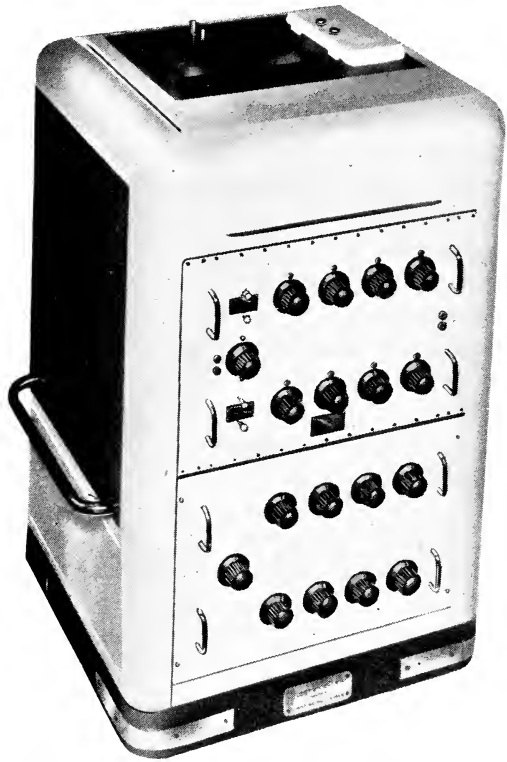

FIG. 7. The Marconi encephalograph. (Courtesy of Marconi Instruments, Ltd.)

rhythms are characteristic of the resting, immature, or isolated parietotemporal cortex. Single rounded waves, alternate with sharp spikes, are found during epileptic seizures, sometimes not perceptible through other symptoms. Williams has dealt with the clinical application of electroencephalography in a recent number of the *British Medical Bulletin.*

The cathode-ray tube suggests itself as the most convenient form of recording apparatus in electroencephalography, but its use in this field is by no means universal. It is being replaced, for routine work, by the ink-writing recorder. The mirror oscillograph is still used by some workers.

Parr and Walter [36] describe the technical methods, and give circuit diagrams of amplifiers suitable for electroencephalographic recording. Traugott [45] discusses electroencephalograph design and publishes the circuit of his amplifier. The Technical Subcommittee of the Electroencephalographic Society has drawn up recommendations for recording apparatus.

The Marconi four-channel electroencephalograph (see figure 7), particulars of which, as far as the author is aware, have not yet been published, consists of two double-channel amplifiers, and a four-pen ink-recorder, with a variable-speed paper drive. Each pen is actuated by a moving iron armature, the signal winding being stationary (a permanent magnet field system is used). Provision is made for the attachment of auxiliary equipment, such as a cathode-ray oscilloscope, or a frequency analyzer. Power supply units for operation from alternating current supply mains are incorporated. The final smoothing of the high-tension supplies is accomplished electronically and, where necessary, electronic regulation is also employed to take care of mains voltage fluctuations. Each amplifier channel has a differential input and uses a common-cathode push-pull circuit throughout. The time constant is controllable in four steps between 1 second and 0.01 second, and the limit of high-frequency response is variable between 15 cycles per second and 4,000 cycles per second. The upper limit of response with ink-recording is 75 cycles per second. The overall sensitivity is such that, at maximum gain, a 20 microvolt peak-peak input produces a 20 millimeter peak-peak deflection of the recorder. Inputs up to 100 millivolts peak-peak are accommodated. The amplifier noise with the input short circuited and earthed does not exceed 2 microvolts root mean square.

Beevers and Furth [5, 6] devised the encephalophone which converts the electrical-potential changes into sound waves. Basically, this apparatus is a form of heterodyne oscillator, where the brain rhythm varies the frequency of the heterodyne beat note. The "alpha" and "beta" rhythms give characteristic trills, while "delta" waves produce slow sweeps of tone.

Various ways of supplementing primary inspection of the

electoencephalogram have been devised, such as that by Grass and Gibbs.[22] Walter [47] introduced a device to overcome the difficulties of the foregoing method. Briefly, Walter's method is as follows: A series of tuned reeds are energized by the output of the electroencephalograph. These reeds act as frequency splitters, since each is tuned to a frequency in the band to be studied. Each reed is provided with a fine steel contact wire, which dips in and out of a mercury cup when the reed vibrates, but is just out of the mercury when the reed is at rest. A high resistance, a source of electromotive force, and a condenser are in series with this mercury reed-contact. The condenser is charged up to a potential which is a function of the total duration of the contact time, and, therefore, of the amount of energy at the reed frequency during the specified time. An amplifier is connected to each condenser in turn by a motor-driven rotary switch, and this amplifier works a wide-arc recording-pen across the recording paper on which the original electroencephalogram is at the same time being traced. The summation epoch is chosen to be 10 seconds, so that each 10-second stretch of record has traced over it a histogram of its spectrum. The analysis is performed automatically every 10 seconds. The details of design are fairly intricate and the adjustment is critical.

Electroencephalographic amplifiers can be modified for use in electromyography, cardiography, and as general purpose biological amplifiers.

Sound

An audiometer is an apparatus for the measurement of hearing loss. Many of these devices have been introduced. A popular model of such an instrument comprises a tone source (a thermionic-valve oscillator working on the heterodyne principle) which has a frequency range of 100–10,000 cycles per second continuously variable. The output of the tone source is fed to a high-fidelity moving-coil ear piece via an attenuator calibrated to read in hearing loss or gain. An auxiliary control automatically corrects the reading for the variation of the threshold

of hearing with frequency. A piezoelectric microphone may be switched into circuit to facilitate speaking to a partially deaf person undergoing test. They are valuable in the diagnosis of deafness and the accurate prescription of hearing aids. Many a physician who prides himself on his skill with his stethoscope would be surprised at his audiogram if he were tested with an audiometer.

Hearing aids employing modern small piezoelectric microphones, miniature valves and batteries, and compensating tone circuits, can be of great value to the deaf. Tone-compensated and automatic volume controls have increased the usefulness of these instruments. Lately there has been a tendency for wireless specialists to "fit" deaf persons with hearing aids; this is a dangerous practice. One must remember that many deaf persons will not benefit at all by the use of these aids.

There are many types of amplifying stethoscopes working on the thermionic-valve amplifier principle. Instruments have been introduced for the graphic registration of the heart sounds, which incorporate such devices. Olson [35] introduced a new acoustic stethoscope which transmits all frequencies over the range from 40–4,000 cycles per second without discrimination or appreciable attentuation, whereas an ordinary stethoscope has an effective range of only 200–1,500 cycles per second. There is a marked falling off in the frequency response of an orthodox acoustic stethoscope below 200 cycles per second. A filter control is incorporated in the instrument described by Olson. The arrangement used for comparing the response characteristics of this stethoscope with others is as follows: Sound vibrations were developed in the human body by means of a subaqueous loudspeaker fed by an audioamplifier and audiosignal generator. An artificial ear was first held directly against the opposite side of the body to secure a reference characteristic, and different stethoscopes in turn were then introduced between the artificial ear and the body.

The recording and reproduction of sound is of interest to the physician. Such records are of value for teaching and research purposes. Henriques [23] described an apparatus for record-

ing the heart sounds on gramophone records. Sound can be recorded on discs, steel wire, and photographic film. It may also be recorded by embossing a track with a needle on film or plain cellophane strip.

Reynolds [40] has experimented on the problem of synchronizing the electrocardiogram, as recorded by a cathode-ray type electrocardiograph, with a cinematographic film of the heart cycle. The writer suggests that, theoretically, it should be possible to develop this technique so that a cinematographic film of the cardiac cycle could be produced, which has a sound track of the heart sounds. If necessary, a simultaneous jugular sphygmogram, phonocardiogram, etc., could also be shown on the film.

Synthetic sound is a term applied to sound produced by methods like those devised by Rudolf Pfenniger who painted by hand the desired wave forms, afterwards photographing them onto a sound track for conversion into sound.

Electronic *p*H Meters

The estimation of the hydrogen-ion concentration of fluids such as the blood in clinical practice is, in the main, confined to the tintometer method. A number of pathological departments and bacteriological research institutions are now using *p*H meters employing thermionic-valve circuits. The results obtained with these devices are more accurate than those obtained with other methods. Serum electrodes have been devised which are capable of dealing with very small quantities of fluid—0.2–0.3 milliliters. In clinical bacteriology, the growth of cultures can be retarded, advanced, or even the manner of growth can be directed by proper *p*H control.

Thermostromuhr Apparatus

Rein [39] introduced the thermostromuhr method for measuring blood flow through a blood vessel. A small insulator clip is placed around the blood vessel. Two small plates which pass a radio-frequency current through the blood stream are fixed in

the central portion of the clip on opposite sides of the vessel. At each end of the clip, there is a thermocouple differentially connected. These make contact with the vessel wall. The passage of the radio-frequency current through the blood stream warms it slightly. The temperature difference, which varies inversely with the blood flow rate, is read electrically with a sensitive galvanometer. Calibration of the instrument is done by measuring the radio-frequency current used and adjusting a comparison resistance to take the same current, thus permitting the dissipated wattage to be estimated. The constants of the blood vessel clips are readily fixed by the application of a simple formula. A graph is obtained which permits this nondestructive instrument to be used almost as easily as a direct-reading mechanical flow meter. This method has been improved upon by Essex, Herrick, Baldes, and Mann [18] and applied even to the coronary circulation.

Photocells

Light-sensitive devices have been responsible for some of the more recent developments of control engineering, as well as of sound reproduction and optical determination. There are three main types of photocell, the photoconductive, the photoelectric and the photovoltaic.

Photoelectric colorimeters are being used in many laboratories. They can be applied to practically every colorimetric problem, from the simple evaluation of intrinsic color at selected portions of the visible spectrum, to the more complex requirements of the analytical chemist.

A fall in hemoglobin level is one readily detected sign of incipient malnutrition. Another use for a rapid hemoglobinometer would be in assessing minor degrees of anemia among blood donors. The photoelectric hemoglobinometer is more accurate than the visual method. In these, as green light is absorbed by a red solution (of oxyhemoglobin), a constant source of light is used together with an appropriate green filter

to pass a green light through the oxyhemoglobin solution; the amount of light able to pass is measured by a photoelectric cell. The amount of light absorbed is proportional to the concentration of oxyhemoglobin, and thus it is possible to construct a scale from which the percentage of hemoglobin can be rapidly and accurately determined. Bell and Guthmann,[7] among others, have devised a simple photoelectric hemoglobinometer.

Photoelectric colorimeters can be used for turbidimetric determinations just as readily as for colorimetric procedures. The basis for the calibration of these methods, which depend on the development of a uniform turbidity rather than a color, is a solution of standard turbidity. Readings and results are obtained just as with colored solutions. There are many applications of photoelectric turbidimetric methods, but only their use in penicillin assay will be mentioned here. Joslyn[27] and McMahan,[31] among others, used such methods. Rantz and Kirby[38] studied the action of penicillin on staphylococci by such a device.

Nygaard[34] studied the kinetics and phases of blood coagulation by means of a photoelectric device. His method depends on recording the amount of light transmitted through clotting blood to a photoelectric cell. A continuous photographic record of the diminution of the transmitted light can be taken.

Photoelectric Plethysmography

The basic principle of Leibel's method[30] of measuring peripheral blood flow is that the light intensity passing through a finger or toe on which a beam of light is directed will vary with the blood volume within the part, and will thus be an index of the circulation through it. The emergent beam falls on a photoelectric cell which changes any variation in the intensity of the light into a corresponding variation in an electric circuit. These electrical changes are amplified and then recorded with an electrocardiograph. Two practical applications of this method are the measurement of the pulse velocity by superimposing the electrocardiogram on the tissue-circulation record, and the other

is the demonstration in senile gangrene of increased blood flow in the affected toe for some hours after the application of a Parvex glass boot.

Hertzman and Dillon [24] have applied photoelectric plethysmography to the vascular reactions, such as Raynaud's disease, or in evaluating the completeness of sympathetic denervation of the skin, etc.

Radio-frequency Oscillators

The main uses of these devices in medicine are diathermy and short wave therapy. These are so well known that it is not necessary to deal with them here.

Radio-frequency probe. Farmer and Osborn [19] describe an apparatus for indicating the approximate position of metallic substances. Theoretically, the instrument should be of value in conjunction with X-ray examination. The principle is as follows: A radio-frequency oscillator works on a frequency of the order of 10^6 or 10^7 cycles per second and the whole of the turning inductance of this oscillator is in the form of a search coil capable of being moved about near the patient. If the search coil approaches a metallic substance—such as a splinter in the operation area—the inductance of the coil will change, and hence, the frequency of the oscillator. The change of frequency can be made audible by heterodyning these oscillations with those of a second oscillator working on a slightly different frequency. A beat note can be detected which can be heard through a loudspeaker or headphones.

The Electron Microscope

The resolving power of a microscope is limited by the wave length of light used. Moving electrons act as if they were associated with a wave length. By using electron waves, 10^{-6} of the wave length of visible light, much greater resolution can be got than with the optical microscope.

The electron microscope is classified as follows: the magnetic

electron microscope, the electrostatic electron microscope, the scanning microscope, and the shadow electron microscope.

The electron microscope is of value in the study of viruses, bacteriophages, the combination of antibodies with flagellar and somatic antigens, the structure of bacteria, organic chemistry, etc.

The Cyclotron and Betatron

Rutherford, twenty-six years ago, performed the first mutation of one element into another, viz., nitrogen into oxygen, and directed attention to the means of energizing particles to such a degree as would enable them to penetrate the nuclear barrier of the atom. J. H. Lawrence experimented with lower voltages tuned to give the particles a series of pushes. Thus, the cyclotron was brought into being—an instrument in which the particle is kept moving in a circular path by a magnetic field, and intermittently accelerated by an electrical field. These particles move inside two hollow semicircular electrodes placed between the poles of an electromagnet, and are accelerated by an oscillating potential applied to the electrodes every time they cross the central gap between them. The angular velocity of the particle caused by the magnetic field is constant, but the successive acceleration of its linear velocity, caused by the electrical field, makes it move in an ever widening flat spiral. The ultimate energy of the particle is limited only by the diameter of the hollow electrodes. Experimenters in nuclear physics, in the last ten years, had energies extending up to 16 million electron volts available in the form of high-speed positive ions from the cyclotron.

The three major fields of biological study developed about the cyclotron are: the use of a radioactive element to trace the absorption, utilization, and excretion of its stable isotope by the body in both health and disease; the therapeutic effect of the radiations emitted by radioactive substances internally administered; and beams of both fast and slow neutrons are being used in the treatment of cancer in a manner similar to X-rays and γ-rays in external therapy.

The cyclotron did not provide high-energy electrons as well as positive ions, because the lightweight electron behaves relativistically when its kinetic energy is still very small. Kerst [28] gives details of the construction of an improved induction accelerator which gives electrons 20 million electron-volts energy. The accelerator has a 19-inch [about 58 centimeters] diameter pole face and weighs approximately 3½ tons [about 3,050 kilograms]. The X-ray output, as measured in a thick-wall ionization chamber, is 16 revolutions per minute at one meter. The most important improvement incorporated in this accelerator is the electromagnetic expansion of the equilibrium orbit, which can be timed to send the electrons against the target at any desired energy up to 20 million electron-volts.

The high-energy X-rays and electrons which are made available by the betatron can be employed for both physical experiments and practical purposes. It is probable that all the elements in the periodic table can be disrupted with the 20 million electron-volts now available by a photonuclear process. The energy of the X-rays or γ-rays is used, generally, in ejecting a neutron from the parent nucleus. The electrons of 20 million volts energy are capable of penetrating at least 10 centimeters into the human body. It has been suggested that they could be used therapeutically instead of X-rays, and that they would have the advantage that the ionization produced by them would stop rather abruptly at about the middle of the body, and do no damage beyond. The betatron produces X-rays which have intensities comparable with those produced by commercial machines. The maximum ionization caused by these X-rays occurs at about 4 centimeters beneath the surface, which makes it possible to administer a large dose to the interior of the body without harming the surface.

In conclusion, I wish to thank Mr. C. Horne, of Marconi Instruments; Metropolitan Vickers of England; Mr. G. Parr, editor of *Electronic Engineering;* Mr. T. J. Shields, librarian of the British Medical Association; and Mr. G. F. Home, librarian of the Royal Society of Medicine.

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THE CLINICAL APPLICATION OF HEAT

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Introduction

IN VIEW of the fundamentally important part which heat energy plays in the life of the human being, and the prominence of the physiological processes regulating the body temperature, it is remarkable that so very little is known about the *quantitative* administration of heat in clinical practice. In most cases, the recommendation of heat treatment goes no further than the ancient prescription "Keep the patient warm." Coupled with our ignorance of quantitative administration, there is also a remarkable lack of information about the exact therapeutic effects produced by heat. While it is generally true that by the application of heat energy the production of heat by the body can be supplemented to the advantage of the patient, we have to face the fact that, for instance, the application of a hot-water bottle produces an increase in body heat greater than the amount actually transmitted from the bottle. Clinicians are also aware of therapeutic effects produced by radiant heat at depths in the tissues quite out of the reach of the radiation employed.

Physical Basis of Heat Therapy

However, before all these questions can be discussed, we must first establish a basis for the dosage of heat treatment and, since the methods of administration of heat are governed by the laws of physics, our first concern must be to establish a sound *physical* basis for clinical heat treatment. Normally the body disposes of about 100 kilogram calories of heat per hour, and it is therefore

likely that therapeutic effects will be obtained only if the amount of heat administered to the body, or to part of it, approaches the total metabolic heat, or the proportion of this normally allocated to the part of the body in question. It is thus clear that, in contrast to X-ray or ultraviolet therapy which relies on a selective action of the radiation, in the case of heat application therapeutic effects will require the application of considerable energy. As in every other kind of therapy, the chief danger to be guarded against is overdosage. From what has been said, two different kinds of overdosage can be foreseen. In the first place the tolerable concentration of heat input over a restricted area may be exceeded. When heat is applied to one square centimeter of the skin its temperature is raised, and the degree to which this happens depends on the strength of the energy flow provided by the heat source, and on the capacity of the tissues to remove the local heating. With increasing heat flow, removal processes are stimulated, but they will break down eventually and a serious local over-heating of the tissues will be the result; in other words a burn will be produced. The limiting temperature above which the skin tissues must not be heated has been determined by Mendelssohn and Rossiter,[6] and has been found to be 45–50° C.

The other danger lies in the general application of heat. If the amount of heat applied becomes of the same order as the total metabolic heat, and especially if, in addition, normal methods of heat excretion (radiation and perspiration) are restricted, then the total heat balance of the body may be upset, and the patient may develop heatstroke.

Methods of Heat Transfer

The physical distinction between methods of heat transfer is usually made as between convection, conduction, and radiation. However, in the methods employed by the clinician, this clear distinction can rarely be drawn, for usually several modes of heat transfer are operative simultaneously. Pure convection is met with, for example, only in the case of a hot-air cabinet,

and even here it may be necessary to consider also conduction through the air, and radiation from the heated walls of the cabinet. Methods relying mainly on conduction are met with more frequently, examples being hot baths, electric blankets, and hot-water bottles. All these methods of conveying heat to the patient are admittedly convenient, but they present considerable difficulties from the point of view of quantitative control of administration. It is extremely difficult to discover how much heat the patient actually receives, for example, from a hot bath. The increase in body temperature produced can serve only as a very rough indication of the amount of heat received, for it must be remembered that as soon as heat is administered, the processes of heat removal are also speeded up. In addition, the ability to excrete heat may differ very considerably from patient to patient, and even in one and the same patient there may be changes according to the state of health.

A further difficulty in the application of electric blankets and heating pads arises from the time factor. As has been pointed out by Brown and Mendelssohn,[2] it takes more than an hour for an electric blanket to deliver heat at full strength.

Heat Transfer by Radiation

The administration of heat by radiation has proved to lend itself better than either convection or conduction to accurate measurement and quantitative dosage. It is for this reason that attention has been turned to this method of clinical heat application.

X-rays, ultraviolet rays, visible light, and infrared rays are all of a similar nature, and can all be classified under the heading of electromagnetic radiation. All represent a transport of energy, and when any of these rays is absorbed in a perfectly absorbing or "black" body, this energy appears as heat. The difference between these various types of radiation is solely that of difference in wave length: the wave length of X-rays is from several thousand to several hundred times shorter than that of visible yellow light; ultraviolet rays are intermediate in wave length

between X-rays and visible light. Deep-blue light with a wave length of 0.45μ represents the shortest wave length visible to the eye, while red light with a wave length of from 0.63μ to 0.70μ represents the longest visible wave length. Infrared radiation describes wave lengths from 0.70μ to 20μ or more, and these merge imperceptibly into the short electric or radio waves. The wave lengths used in radiant heat treatment are from the visible red up to, say, 20μ.

In addition to the generalized heating produced when electromagnetic radiation is absorbed, specific effects may be produced, and these have been explained by the quantum theory. This theory states that radiation is not to be considered as a continuous flow of energy but as a shower of minute energy parcels or *quanta*, each representing an energy contribution of a definite amount. Emission and absorption of radiation can only take place in whole or multiple quanta, never in fractions of a quantum. The energy contribution of each quantum in radiation of a given wave length is inversely proportional to the wave length, i.e., the energy parcels of X-rays are larger than those of ultraviolet rays, and these in turn are larger than those of visible light or infrared radiation. The production of certain intramolecular changes, for example, those leading to the production of vitamin D in the tissues, requires the action of quanta of a certain minimum size peculiar to this particular change, that is, this change can be produced only by light of a wave length sufficiently short to give quanta of the necessary size. The application of radiation of longer wave length will not produce the same effect, even if large amounts of energy are supplied, simply because this longer wave radiation contains no quantum of the necessary size. The efficacy of X-ray and ultraviolet therapy depends on this fact. They are administered in small doses—only 10 gram calories or less at a treatment—and produce specific chemical changes in the tissues. They also, of course, produce heating of the tissues, but this is so slight as to be masked completely by the specific changes, even though the latter are caused by only a small proportion of the total incident energy.

The visible range of electromagnetic waves represents roughly the size of quanta below which no specific action is produced in the body tissues. In other words, the action of infrared radiation is distinguished by the fact that it produces no specific reactions at all, and its absorption merely causes a rise of temperature in the tissues. The short wave radiations, such as X-rays or ultraviolet rays, are limited in their application by the harmful effects which are produced by an excess of the specific changes for which they are responsible. Infrared radiation, on the other hand, can be applied at a strength which is limited only by the capacity of the tissues to withstand heating. It is for this reason that infrared radiation has become known under the name of "radiant heat" for, in contrast to the shorter wave length radiations, it offers a safe method of pumping heat energy into the body.

To produce any sensible effect with infrared, large doses, in some cases as much as 200,000 gram calories at a treatment, are used, but this infrared radiation must not be accompanied by more than a minute proportion of ultraviolet radiation, which, in this case, would produce unwanted specific effects, and would severely limit the total energy which could be pumped into the patient without injury.

When a body is heated it emits electromagnetic radiation, and the total quantity of energy emitted from one square centimeter of its surface, as well as the wave lengths in which this energy is emitted, depend on the temperature of the body. A body at 2000° K * emits 256 times as much energy from each square centimeter of its surface as a similar body at 500° K. For the first, the greatest intensity of radiation is in a wave length of about 2μ; for the second, the wave length of maximum intensity is four times as great. Even a body at 4000° K, which is sixteen times as efficient an emitter of radiation as one of 2000° K, emits the greater part of its energy in the infrared, but now there

* It is convenient to give temperatures in degrees Kelvin or *"absolute,"* which means the centigrade temperature *plus* 273°. The total energy radiated from a black surface is proportional to the fourth power of the absolute temperature, and other characteristics of the radiation are all most simply expressed in this temperature scale.

is an appreciable contamination with ultraviolet radiation.

In practice, the hot bodies used as sources of radiation are all at fairly low temperatures, and so provide radiation which is all in the infrared with a little visible red light. An exceptional case is provided by the arc lamp, where the hottest part of the carbon rods may be at a temperature as high as 3500° C (3730° K) and gives a considerable proportion of ultraviolet radiation, even though the greatest part of the energy emitted is in the infrared. Even an ordinary incandescent filament lamp actually emits a small proportion of ultraviolet radiation, but this is all absorbed in the glass of the lamp bulb.

At all temperatures, therefore, which may be acquired by the dull emitter heating elements, or the metal shields and reflectors of radiant heat apparatus, the radiation emitted is in the infrared, and, because of absorption by glass, the actual radiation which reaches the patient from an incandescent filament lamp is also infrared, accompanied by a small proportion of energy in the visible region.

On the other hand, low-temperature sources are relatively inefficient, and thus, if we wish to secure a large total emission of radiation from the source, we must use extended sources, such as heated metal sheets, or groups of point sources. To illustrate this point, the example of a heated metal sheet radiating to surroundings at room temperature may be quoted. At a temperature of 100° C this emits only one calorie per minute from each square centimeter of surface.

Calculation of Dosage

The X-ray worker always has to deal with a point source of radiation, so that the radiation comes to his patient as a beam. For him it is a comparatively simple matter to calculate the dosage received by the patient from the strength of the source, the distance of the patient, the area irradiated, and similar data. In radiant-heat therapy with extended sources, such as, for example, radiant-heat cradles, there is no single beam of radiation, and each part of the patient's skin receives

energy from all directions. It is possible to calculate the energy received on the skin from the strengths, temperatures, and positions of the various parts of the source,[3] but it is a somewhat severe mathematical problem, and is clearly an impossible method for ordinary clinical use. Reliance must be placed on direct measurement, and what is needed is some simple method of measuring the energy actually received on the patient's skin.

In X-ray work, with beam therapy, a suitable standard of measurement would be the energy falling in one minute on a surface of one square centimeter placed normal to the beam. That was suggested by Mayneord and Tulley [5] as suitable also for infrared work, but, in fact, a slight amplification of their definition is necessary. A more suitable specification would be the total energy coming from all directions which impinges in one minute on a surface of one square centimeter placed in the position to be occupied by the skin of the patient. For a unit incident energy flux of one gram calorie per minute, we have suggested the name *pyron*.[3]

This unit specifies the total incident energy without regard to wave length (color, quality), but as the effect of all wave lengths of infrared radiation is simply to heat the tissues, the consideration of the range of wave lengths used in any given circumstance is of an importance secondary to the consideration of the total energy received in all wave lengths. There are, of course, problems connected with the difference in penetrating power of different wave lengths, but the first task is to provide convenient methods of determining the total flux.

Special Problems of Measurement

Before discussing practical methods of measurement we must first consider a theoretical point. As explained above, all hot bodies radiate energy, and cease to do so only if cooled to the absolute zero of temperature (zero on the absolute scale, see footnote, page 63. Thus, all our surroundings continually radiate energy, and energy is being continually radiated from our skins to our surroundings. What we must measure, there-

fore, as being of clinical importance, is not the absolute amount of radiation energy received from a clinical source, but the excess of radiant energy received on the skin, over that which would normally arrive from the surroundings. That is, we must compare the incident flux with that from surroundings at normal room temperature.

The fundamental physical method of measuring radiation flux is to absorb all the incident radiation on the blackened surface of known area of, say, a block of metal, and to determine the energy received from the rise in temperature of the receiver. Corrections must be applied for the cooling of the receiver which will lose heat by radiation and by conduction to the surrounding air. To eliminate the latter and to secure a rapid reading, the receiver is made of small heat capacity, is placed inside an evacuated glass envelope, and its temperature is measured by thermoelectric methods. Estimates of intensity of infrared radiation made with a vacuum thermopile are, however, liable to be very misleading in clinical practice, because the glass envelope absorbs all radiation beyond about 3.5μ, and we have found,[3] that in certain clinically important cases, two-thirds of the incident flux may be beyond this limit.

The Thermoradiometer

We have developed an instrument for the clinical measurement of radiation flux (thermoradiometer) which dispenses with such an envelope. It consists of two receiver plates which are blackened and carry a pair of thermojunctions on their reverse faces. The upper one receives the radiation flux to be measured, while the lower one receives radiation from a surface maintained by water cooling at room temperature, and which, therefore emits the radiation characteristic of our normal temperature surroundings. The two receiver plates are screened from one another by a small metal block, which has the effect of smoothing out random fluctuations of temperature. On the other hand, the two plates are very close together, and, therefore, the air temperature for each of them

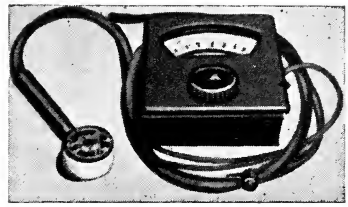

FIG. 1. The complete thermoradiometer, consisting of receiver unit (to be placed in the position of the skin area to be irradiated) and millivoltmeter calibrated in pyrons (gram-calories per minute passing through a square centimeter). In addition to the current leads, tubes for water-cooling are attached.

is likely to be very nearly the same, so that the losses of heat by air conduction are practically the same for the two discs. Since the quantity which is actually measured in this arrangement is the fairly small temperature difference between the two discs, all temperature effects due to air conduction are cancelled. The lower, or reference, disc is screened from stray radiation which would falsify the readings, but a small air gap is left between the screen and the main part of the instrument through which a slow convection of air takes place. Without this air gap, layers of hot air might be trapped in the concavity of the water jacket and would falsify the readings. We find that such an instrument registers a final reading in 30–40 seconds, and that it is accurate, certainly within 5%. It should be pointed out

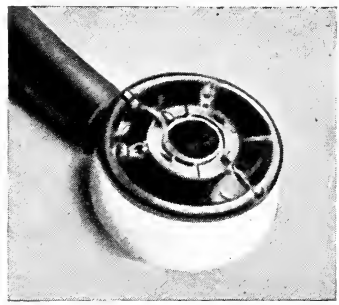

FIG. 2. Close view of the receiver unit. The circular plate in the center is the actual receiver plate which, like a similar plate facing the water-cooled background, is suspended on the screening block.

here that this accuracy is probably better than is needed in clinical work. What is needed is an instrument which, under varied conditions of use, will always indicate within a few per cent the total incident radiation. A vacuum thermocouple is more accurate in the sense that it measures a certain quantity very precisely, but as we shall see, under certain not unusual clinical conditions, the quantity which it does measure is very different from the quantity which the clinician needs for controlling his treatment. Our instrument must, of course, be calibrated against known radiation sources, or by other methods, but when this is done it is found to have a linear response, and the millivoltmeter or other instrument used to measure the thermoelectric current may then be calibrated with a linear scale of pyrons. Typical examples of determinations of total flux under various clinical radiation sources are shown in the figures on pages 69 and 70.

When this instrument is used to measure the incident flux under various types of clinical radiation source, it is usually found that the flux increases with time. This is due to the fact that the glass envelopes of the electric lamps, metal reflectors, and other parts of the source, become heated in course of time, and these in their turn become sources of radiant energy. The temperatures attained by these parts of the source are low, but in many cases they are of considerable area, so that they may eventually come to provide the major part of the flux received by the patient. On the other hand, the radiation which they do provide is all low-temperature, long-wave radiation which is absorbed by glass. Therefore, a glass-enclosed instrument will show little or no increase even under circumstances when, in the course of an hour, this instrument will show a three-fold increase of flux. We have pointed this out in a discussion of radiant-heat cradles,[3] where we found that the flux at the center of the cradle increased from 0.4 pyrons to 1.2 pyrons in an hour. The patient, of course, will respond to this change in ways which may be unpleasant, but for the reasons given, a glass-enclosed thermocouple will not respond to it. This time factor is thus of peculiar importance in estimating radiant-

heat dosage; its effects cannot be detected with a glass-enclosed instrument, but, if it is neglected, serious overdosage and injury to the patient may ensue.

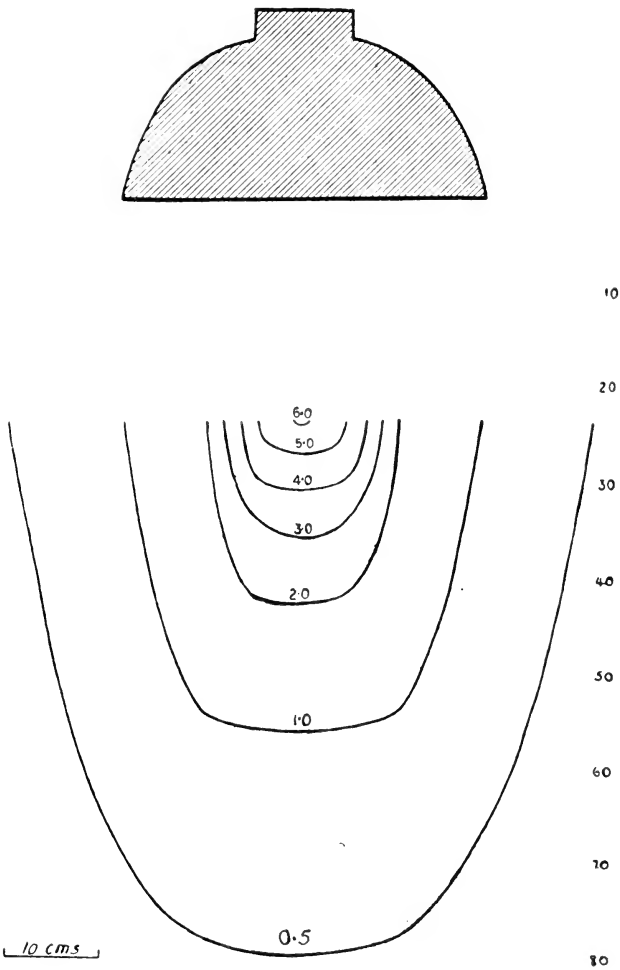

FIG. 3A. Isophotes (curves of equal radiation flux) from a bright-emitter treatment lamp of 1000 watts determined with the thermoradiometer (receiver plate normal to the axis of the lamp).

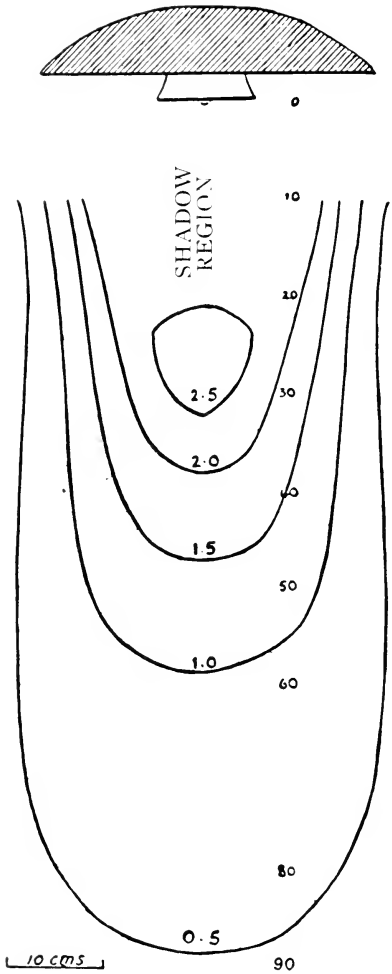

FIG. 3B. Isophotes (curves of equal radiation flux) from a dull-emitter treatment lamp determined with the thermoradiometer (receiver plate normal to the axis of the lamp).

Quality of Radiation: Transmission by Textiles

The study of the quality, or dominant wave length, of infrared radiation under conditions of clinical treatment is a difficult one, and little progress has been made. Some advance can be made by comparing different types of source, such as, for

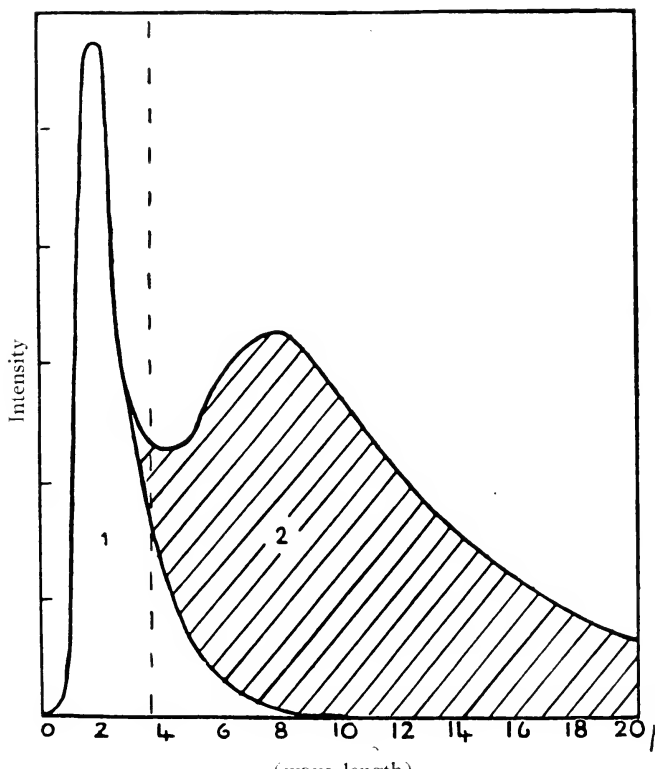

FIG. 4. Wave length distribution of radiant energy from a heat cradle. The area (1) represents the energy from the bulbs, which is all the energy emitted in the first minutes of treatment. The area (2) is radiation from the cradle background after one hour of use; the total energy emitted after one hour from switching on the cradle is represented by the sum of (1) and (2). The figure shows not only that the energy transmitted to the patient increases greatly with time, but also that the additional radiation from the background will escape detection if a glass-enclosed thermocouple is used. The wave length beyond which glass will cut off all radiation is marked by the dotted line.

example, an electric lamp (giving a radiation maximum at $\sim$ 1.5μ) with an electric fire (giving a radiation maximum at $\sim$ 3μ). Mayneord and Tulley [5] have approached this problem by studying the absorption of radiation of different temperatures in various thicknesses of celluloid. However, as they point out, care must be taken in the interpretation of the results because of the scatter of radiation in this medium. This difficulty is, of course, aggravated in the case of infrared radiation which is not administered in a beam. Secondary radiation from the filter may also cause falsification of results.

We have made preliminary experiments on the transmission by various types of textile materials (blankets, towels, cotton and linen sheets, lint, etc.) and find that, in general, materials transmit 20–30% of the long-wave incident radiation, and 30–40% of the short-wave. However, if a patient is covered by a blanket, it must not be assumed that he will only receive, say 25%, of the energy incident on the upper surface of the blanket. In addition, the blanket will gradually warm up to a temperature depending on the particular circumstances, and will transmit energy, not only by secondary radiation, but also by conduction, both by direct contact and across air pockets trapped between the blanket and the skin.

What is of importance is the total heat supplied to the patient by all mechanisms, and we have been able to evaluate the different contributions in one case. Before an open electric fire we found that a layer of lint transmitted 27.5% of the incident radiation, and that conduction was responsible for transmitting an amount of heat equal to 32% of the incident radiation. In this case the covering was not enclosed, and so the lint did not acquire a high temperature, and did not in consequence provide any appreciable amount of reradiation. The total energy received on a calorimeter placed behind the lint was, in this case, 60% of the incident radiation.

Conclusion

Thus, although some progress has been made during the past few years in the assessment of the physical factors governing the clinical application of radiant heat, and in its quantitative measurement, very much remains to be done. In particular, the physical details and clinical significance of the absorption processes of various wave lengths in the tissues needs careful study. However, the most important problem of the clinical application of heat in general is the determination of limits of tolerance, together with the study of the relative therapeutic value of heat dosages of different magnitude. It is likely that, in this field of quantitative dosage, radiant heat will be found to be the method of administration for which quantitative control can most easily be achieved.

The work described in this paper on the physical factors governing the clinical application of heat constitutes a part of a general investigation of methods of administration, and of the effects of heat treatment carried out in the Nuffield department of clinical medicine, Oxford University, and it is a pleasant duty to thank the director of this department, Professor L. J. Witts, for his interest and help at all stages of the work.

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THE MECHANICS OF BRAIN INJURIES

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Introduction

THERE is some truth in almost all the theories of the mechanisms of brain injuries due to violence,[1, 10, 13] but in the writer's view[7, 8] only skull bending, fracture, and rotation[5] of the head are important. The physicist would attribute the comparative failure of most of the theorists to their wrong method of approaching the problem, in that they began by fastening their attention on a particular mechanism (e.g., coup and contrecoup, or production of cerebral anemia). The physicist's initial assumption is that damage to the brain is a consequence, direct or indirect, of the movements, forces, and deformations at each point in the brain. The movements, forces, and deformations are not independent; so that it is sufficient to express everything in terms of deformations. These are worked out with strict adherence to Newton's laws of motion, but with approximations to the constitution and shape of skull and brain. Hence further advances can come only from making better approximations.

The Forces to be Considered

As a consequence of the principle of superposition, it is reasonably correct to assume, in this particular problem, that each cause produces its own independent injury. These causes may be regarded as (a) forces on the brain resulting from bending of the skull, (b) forces resulting from fracture of the skull

or separation of sutures, (c) forces resulting from movement of the head as a whole and which would exist even if the skull were undeformable. (c) may be subdivided into (c_1) linear acceleration forces, (c_2) rotational acceleration forces, (c_3) centrifugal forces, (c_4) Coriolis forces. Of these (c_3) and (c_4) are clearly negligible.

Now it is allowable to analyze the deformations of each infinitesimal element due to (a, b, c_1, c_2) into two and only two types (α) change of shape, or distortion, without change of volume (this is analyzed by physicists into a set of shear strains) and (β) a change in volume without distortion. (α) is extremely liable to injure animate [9] or inanimate objects. (β) is of two kinds (β_1) decrease in volume due to increase of hydrostatic pressure and (β_2) increase in volume due to decrease in hydrostatic pressure. Common sense suggests that (β_1) is harmless provided it does not cause prolonged occlusion of blood vessels. Its harmlessness has been verified for peripheral nerves.[6] (β_2) is also harmless unless the decrease in pressure is sufficient to cause cavitation, i.e., liberation of bubbles of vapor or dissolved gases.

Changes in Volume

Unfortunately the terms "increase in volume" and especially "decrease in volume" are imprecise. Decrease in volume of a particular region might be brought about by a true hydrostatic pressure acting equally in solid tissues, blood, and tissue fluids, and not allowing anything to pass out of the given region. Under such conditions the ratio of the volume decrease of a cubic centimeter of brain to the pressure increase is the true compressibility, and is the same as that of water, 5×10^{-11} dyne^{-1} square centimeter. Alternatively, the pressure causing the decrease in volume might act only on the solid tissue and might allow blood, or blood and certain tissue fluids, to escape from the region considered. Under such conditions one would obtain a pseudocompressibility, whose value would depend on many things. A value of 2×10^{-6} dyne^{-1} square centimeter was found

by Flexner, Clark, and Weed.[4] It can be shown, however, that in any ordinary sort of accident very little blood or other fluid is forced out of the brain, and most of it will return when the blow is over. Therefore, exsanguination is not the cause of immediate loss of consciousness, and the brain during an accident may be assumed to be nearly as incompressible as water. The medical man may, perhaps, be more easily convinced of the unimportance of immediate exsanguination by the observation that it is clearly not responsible for such things as massive hemorrhages into the temporal lobes, and that in slow crushing injuries, where exsanguination is greatest, there is no concussion.[3] Of course, long after the blow is over, anemia may occur owing to various pathological processes; but this is outside the scope of the present article.

Comparative Effects of the Forces: Linear and Rotational Acceleration

To recapitulate, therefore, the forces (a, b, c_1, c_2) are important only in so far as they give rise to (α), distortion (or shear strain) or (β_2) decrease in pressure sufficient to cause cavitation.

On these assumptions, bending of the skull (a) produces, owing to distortion, superficial bruising of the brain near the spot hit, combined with injury (usually negligible) where tissue is squeezed out of a foramen or defect; (c) causes distortion injury to brain and blood vessels near the fracture; (c_1) can be neglected because, as the brain is nearly uniform macrascopically in density, it causes almost entirely increases of (β_1) or decreases of (β_2) in pressure at every point. (β_1), as explained, is harmless. (β_2) would be injurious only if the pressure fell by, say, 5×10^8 dyne per square centimeter. Now, in the average accident, the pressure fall due to linear acceleration is accompanied by a shear stress in the brain due to rotational acceleration of about equal order of magnitude when expressed in dyne per square centimeter. But 5×10^8 dyne per square centimeter of shear stress would cause utter destruction of brain. Therefore,

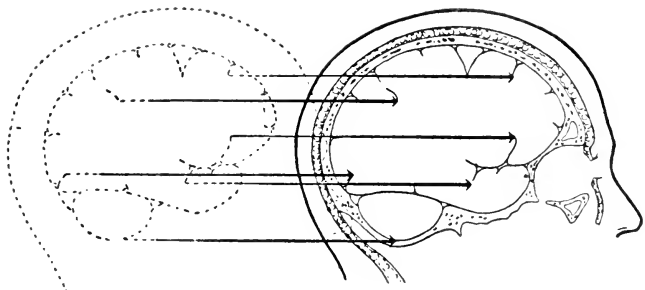

FIG. 1. Absolute movement in space of the skull and brain when the skull experiences a linear acceleration. Arrows mark the actual paths in space of particles of skull and brain. The brain participates completely in the motion, each bit being pushed forward the requisite amount to keep step with the skull owing to the brain's extreme incompressibility. No part of the brain moves appreciably relative to the skull. Thus, the brain suffers no distortion and therefore no injury.

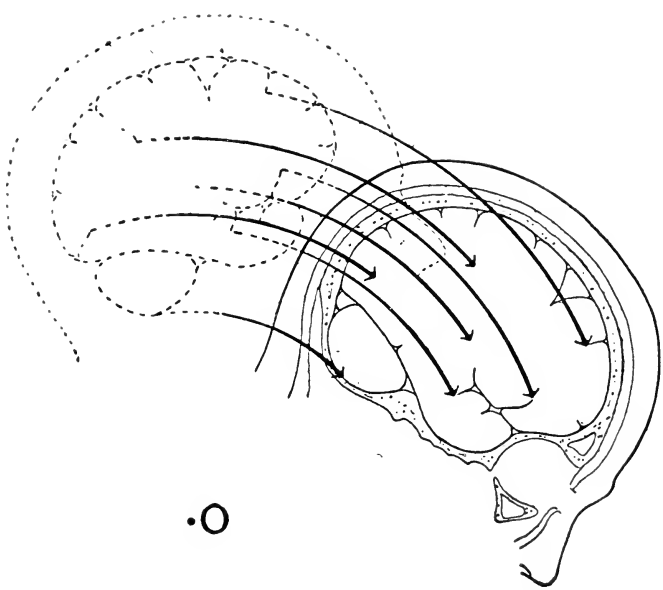

FIG. 2. Absolute movement in space of a skull and hypothetical brain, supposed completely incompressible and completely rigid, when the skull is rotated about o. Arrows mark actual paths in space. The skull and brain move as a single rigid unit and the brain is not distorted.

in almost every accident, the linear acceleration, (c_1), can be neglected in comparison with the rotational acceleration, (c_2). There is an essential difference between linear and rotational movement. When the skull is moved in a straight line, it is the brain's *incompressibility* which prevents it from being left behind. This being very high, none of it lags behind, so that it moves as a whole, and there is no appreciable distortion (figure 1). On the other hand, when the skull is rotated, the brain has to depend on its *rigidity* to avoid being left behind. But its rigidity is small, so that parts of it do get left behind to a considerable degree. It is therefore distorted (figures 3 and 4).

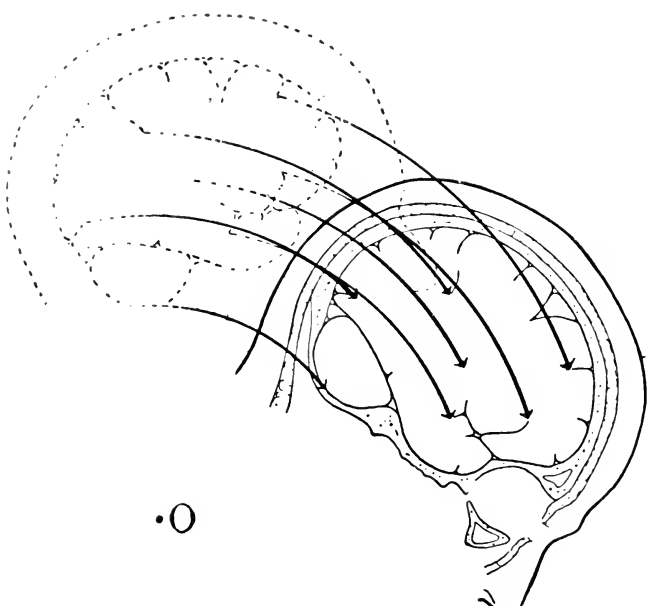

FIG. 3. Absolute movement in space of a skull and real brain of small rigidity when the skull is rotated about o. Arrows as in figures 1 and 2. Skull and brain do not rotate together as a single rigid unit. The brain moves relative to the skull and is therefore distorted and injured.

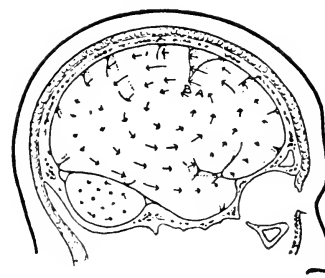

FIG. 4. Relative movement of the brain with respect to the skull when the skull is rotated as in figure 3. In other words, this is a diagram of the lag of the brain behind the skull. The tail end of an arrow marks the starting position of a particle of brain relative to the skull and the point the final position, e.g., a sulcus moves in relation to the skull from the dotted position A to the full line position B. It is seen that the brain makes the only lagging movement open to an incompressible substance in an enclosed space, viz., a whirling movement. The amount of the rotation and rotational acceleration is completely independent of the position of the point o in figure 3. Neither this figure nor figure 3 are quantitatively accurate.

Distribution of Damage from Rotation

As rotation is theoretically so important, it is of interest to find the distribution of damage produced by it. This is done easily, though approximately, by making a model of a section of the brain out of gelatin, and giving it a rotational jerk in a circular polariscope which renders the shear strains in the gelatin visible. Figure 5 shows a system of shear strains obtained in this way. The good agreement with the findings at necropsy is to some extent fortuitous, as the following approximations have been made. There are no fissures or sulci in the model. The elasticity of the gelatin is uniform throughout the model, whereas white matter, for example, is stiffer than gray matter. This nonuniformity would tend to cause specially large strains near the junction between white and gray matter.[9] There is a two-dimensional strain system in the model, but a three-dimensional strain system in the brain. The brain has different rheological properties from gelatin, which nearly obeys Hook's law. On the other hand, differences in stiffness between gelatin and brain do not matter; in fact exactly the same strain diagram would

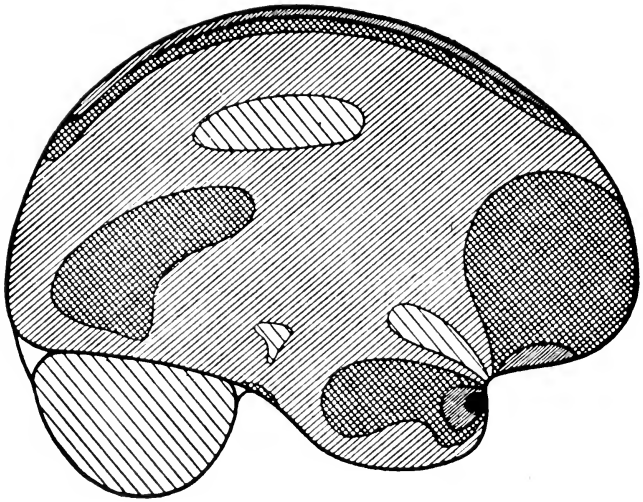

FIG. 5. The shear strains (= distortion) which arise when a gelatin model is rotated as in figure 3, or in the reverse direction. The darker the shading the greater the distortion. Note the comparative absence of distortion in the lateral cerebellar lobe and high distortion at tip of the temporal lobe.

hold for glass or metal. Figure 5 refers only to blows of long duration.

Rotation causes the so-called contrecoup injuries, and presumably (as the effects of fracture and skull bending are purely local) concussion. It follows that if the head can only rotate slowly, e.g., in the case of crushing between railway buffers, or is fixed, there is no concussion. The latter result agrees with that of Denny-Brown and Russell,[3] but not with that of Scott.[11] From a well-known theorem in kinematics, it makes absolutely no difference to the rotational component of injury whether the rotation is one about an axis through the "center" of the brain, or is an equal one about a parallel axis through the atlas or through Timbuktoo. But since the last case would involve a linear acceleration up to millions of miles per hour, the rotational component of injury would be comparatively unimportant. The rotational injury is approximately the same whether the head rotates forward from a blow on the occiput, or backward from

a blow on the forehead. In both of these cases, the damage is clearly symmetrical with respect to the midplane; but it is also approximately symmetrical with respect to the midplane whenever the head is hit at any point whatsoever by a blow whose direction is exactly perpendicular to the midplane. Such a blow causes a rotation about an axis lying in the midplane or parallel to it.

If the distribution in any region is sufficiently great, everything in that region that can be injured will be injured—blood vessels will be torn, axons torn, synapses disrupted, etc. The injury due to lesser amounts of distortion will depend on the degree of distortion, on the nature of the distorted region, and on the directions of the shear strains relative to fiber directions. But, in general, it must take less distortion to produce a quickly reversible effect in a cell body or axon than it takes to produce an actual tear in them or in a blood vessel. The small distortions in a peripheral nerve produced by a falling drop of mercury or a jet of air are known to excite it without causing injury.[2] It is reasonable to suppose that there is some similar sort of effect in the brain, and thus, that blows so small that they produce no anatomical injury nevertheless momentarily upset the existing activity in the brain. Possibly momentary amnesia or the splash of light which often accompanies a blow are due to this effect. The shear strains which arise as a result of squeezing a peripheral nerve can cause it to fail to conduct impulses, and if the strains have not been too severe the nerve will recover spontaneously after some minutes, even in the absence of a blood supply. Once again, one would expect a similar effect in the brain. Amnesia lasting only a few minutes might be the result of such a mechanism.

Although the whole brain is distorted by rotation, some parts are much more distorted than others. Thus, so far as the physics of the problem is concerned, loss of consciousness might be due to a diffuse neuronal injury, or to injury to a particular region, or both, or sometimes one, sometimes the other.

Conclusion

To sum up the position as it appears to a physicist: in the vast majority of accidents to human beings, only skull bending, fracture, and rotation are of any importance; but, with sufficient experimental ingenuity, it would obviously be possible to produce injuries by other mechanisms: some of the experimenters who report results due to the other mechanisms may have had this ingenuity; others may be misinterpreting their experiments.

The treatment given here needs modification in the case of injury by high velocity missiles.

Postscript. After this article had gone to press, a film showing the surface of the brain as seen through a transparent window[12] was exhibited in England. It shows that in the case of a nonpenetrating blow, the surface of the brain slides several millimeters along the under-surface of the skull, no gap appearing between the two. Hence the brain is executing a swirling movement like that in figure 4. Of course, there is no proof that all the damage is due to the swirling, but no reasonable person who has seen the film can doubt its importance.

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THE BIOLOGICAL EFFECTS OF PENETRATING RADIATIONS

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Introduction

WHILE Planck was putting forward his theory of energy quanta, Becquerel, by accident, and Curie and Aschkinass, by design, made experiments upon themselves and, with others, demonstrated the destructive action of radium and X-rays on living tissues. As a consequence, the biological effects of penetrating radiations became widely studied, in part to satisfy a natural curiosity, but also to determine how the rays might be usefully employed in medicine. The fiftieth anniversary of the discovery (in November 1895) of X-rays seems a fitting time to review the trends and some of the achievements in this now vast field of experimental radiobiology, which was born so soon after Röntgen's momentous announcement.

For roughly 25 years, biological observations were mainly qualitative and were concerned with the changes, seen in a great variety of biological material, after exposure to arbitrarily chosen and crudely measured doses of radiation. By this seemingly haphazard method, however, many facts of fundamental importance were learned. For example, the selective action of radiation was recognized in the discovery that the cells of some tissues were more affected by a given dose of radiation than the cells of other tissues exposed to the same dose under identical conditions. It was also found that the same dose produced a different result according to whether it was given at a high intensity for a short time or a low intensity for a longer time. It

was noted that proliferating tissues showed a more marked reaction to radiation than those without dividing cells and that a latent period, which varied for different types of response, elapsed between exposure and the appearance of radiation effects.

From about 1920, biological response was, in the laboratory at least, much more frequently measured quantitatively, though all tissues were not equally convenient for experiments of this kind. Some observers chose what was already familiar to them, and others what was most conveniently available. Meanwhile, work on the physical measurement of dose made progress, culminating in the international unit of measurement for X-rays, now applicable to gamma radiation as well.

Experimental radiobiology has thus grown to a science in which physical dose and biological response can be measured with reasonable accuracy. Its development has been greatly influenced by its relation to medicine and, while attempts are sometimes made to distinguish those investigations which have obvious application to medical practice ("applied radiology") from those which have not ("pure research"), opinion would often be divided as to which category any particular investigation should be assigned. At least one major effort has been made to review the literature not immediately concerned with practical radiotherapy.[30] The vast mass of literature which has accumulated on the other side has been the subject of many reviews.[23, 24, 25, 30, 41, 102, 103, 121] The purpose of this paper will, however, best be served by ignoring this somewhat arbitrary division and giving a brief summary of each of the main branches into which the subject has, through circumstance or convenience, become divided.

Background Theory

The most conspicuous advances in experimental radiobiology have been made when physicist and biologist have worked in harmonious collaboration, an achievement which in practice is too seldom realized. This is mainly due, perhaps, to a difference in training and outlook which needs to be remedied by reeducation on both sides.[88]

The effects produced by radiations in their passage through living matter may be studied in two ways. The investigation may be concerned with the mechanism of the action of radiation by means of specially designed experiments on selected materials, usually of the simplest kind. This is often referred to as "fundamental research," and is a long-term program of research in which much detailed information is gradually collected for a particular material, but it does not necessarily follow that what is observed for one tissue applies to other kinds of tissue after similar doses of irradiation. The other, or short-term method, involves a study not of the exact mechanism of the biological action of radiations, but of their histological effects under given physical conditions. Much of this work forms the background of medical radiotherapy, and its results are no less fundamental than those obtained by the other approach; they are sometimes of great practical use.

It was natural, perhaps, that the physicists should be attracted to problems concerned with the mechanism of action of radiation on living cells, while the biologists, in the main, devoted their energies to recording changes in behavior of irradiated tissues under a variety of experimental conditions. This division of labor has, however, had an unfortunate tendency to sharpen the difference between the physical and biological approach to radiological problems. The result has been the elaboration of theories of action of radiation with, at best, only a limited scope, which have generated a great deal of controversy, not always to the advancement of the science. Theories of action start from the law of Grotthus and Draper that only absorbed radiation is effective. The physical unit for absorption is the atom. The biological unit is the cell, made up of some 10^{10} molecules in active motion, within which effective radiation energy must be absorbed. Absorption of X-rays in matter produces secondary electrons, and it was suggested by Dessauer[27] that these electronic energies are nonspecifically degraded on colliding with protein molecules, and that the energy is transformed into the basic process of heat at isolated points.

According to Holthusen,[62, 65] on the other hand, the energy required for the radiation effects originates from the state of

excitation (Bohr) of protein molecules, following the absorption of quanta of radiation, making the molecules capable of new reactions. For example, an increase in intracellular osmotic pressure may result from the formation of substances with smaller molecular weights than the original substance. If the surrounding fluids are not changed to the same extent, this would cause swelling of cells. An increase in cell size after irradiation is known to occur in certain instances,[51, 80, 113, 114] but is by no means common to all cells affected by radiation. A suggestion that radiation caused a rearrangement of colloid charges,[12] which was at first regarded as an alternative mechanism of action, can now be fitted into Holthusen's photochemical theory by regarding the change of charge as a photochemical process.

Ionization rather than excitation became generally regarded as the link between energy absorption and biological response, and a hypothesis which has attracted a great deal of attention was put forward,[14, 17, 43, 66, 72] according to which there exists in the cell a specially sensitive volume within which ionizations are biologically effective, and these account for the changes subsequently observed. More than one ionization may be required to produce a biological effect, but any ionization which occurs within the cell, but outside the sensitive volume, is ineffective. This view of the mode of action of radiation has come to be known as the target or "quantum hit" theory, and among its supporters are many physicists. Differences in sensitivity to radiation are explained by the chance distribution of ionizations in the vital volume of the cell. Those who oppose the idea have, perhaps, less well-defined views on radiation action, and are united mainly in their opposition to the theory. As an alternative hypothesis they suggest that a chemical or metabolic change is produced in the cell by irradiation, and they argue that the biological results of physical as well as chemical agents can be explained on the assumption that individual cells differ in their reactions to the changes produced: the weakest succumb first, then the less weak, and the strongest last of all. A great deal of time and effort has been spent in attempts to prove and disprove one or other theory, and most lively controversies have

taken place between the contending parties.[121] The idea of a compromise has come late, but the results of at least one investigation [152] were shown by the author to be equally well explained either by the quantum hit theory or by that of variation in individual sensitivity.

That the target theory holds for particular cases now seems indisputable. It is true in certain instances where the criterion of effect is a lethal action, or a type of injury is produced from which there is no recovery.[79, 80] But it cannot be made to fit all types of biological response to radiation, since by definition it makes no allowance for adaptability in living organisms to changes of environment, including those brought about by radiation. The cell is not inert until it is dead, and so long as it is alive it is capable of a change of behavior, and with that change, an alteration in its susceptibility to radiation, which cannot be predicted. The types of response must be learned from observation under different biological conditions. For example, the same cell differs in its susceptibility to radiation, among other things, according to its state of dryness, its metabolic activity, its stage of growth, and its age.[37, 53, 54, 105, 120] There is a danger in attempting too much simplification by physical explanations when dealing with such complex biological material.

Physical Dose and Biological Response

The need for a quantitative measure for radiations was apparent as soon as their biological effects had been recognized, and one equally suited to experimental and clinical use was desirable. The question of a biological or a physical basis for radiation dosimetry has been debated for many years. As early as 1918 it was suggested by Russ [117] that the amount of radiation necessary to kill mouse cancer cells might be used as a standard for which he suggested the name "rad." Since then, many similar methods of dosage have been devised and will be considered under Biological Indicators.

The most practical and useful method of dosimetry, however, is that based upon the ionization produced in air by radiation,

originally suggested in 1908, and now developed into the international röntgen (r) of X- and gamma-ray measurement.[4a] Much research has been done to discover under what conditions the ionization in air may be taken as a measure of the dose in living tissues.[87, 146]

Assuming that ionization in the tissue is responsible for the biological changes produced, the röntgen should be a useful unit for linking physical dose with biological response, since an accurate measure of any well-recognized biological response in terms of the röntgen would enable the experimental conditions to be repeated anywhere by any competent person. The first and most obvious biological response to be recognized was the erythema produced in human skin, and since the tolerance of the skin to radiation is a limiting factor in many radiotherapeutic procedures, the determination of the "skin erythema dose" (SED) in röntgens has been the subject of much careful investigation.[105, 109] The difficulties of such an apparently simple procedure are, however, considerable. The dose received by the skin is due not only to the incident radiation, but also to scattered radiation which may constitute half the total dose, and which varies with the quality of radiation, the size of the irradiated area, and the particular part of the body (depending on the relative amount of bone, muscle and fluid) being irradiated.[35, 67, 111, 138, 149] On the biological side, the accuracy of the determination is vitiated, partly owing to individual variation in the response to irradiation, and partly to difference of opinion of various observers as to what constitutes the proper erythema reaction. Taking the results obtained from the majority of observations made, it is possible to compile tables of the approximate value of the SED for different quality radiations falling on a field of given area [111, 149] or volume of given size.[107] In any one series of observations made under constant conditions by the same observer, the doses are likely to be comparable with each other, but where different series of experiments are considered a comparison of doses must be made with caution.

The determination of the SED for different quality radiations has shown a rise in the skin tolerance as the wave length

of the radiation shortens. Large doses of highly penetrating radiations can now be given to a deep-seated tumor with comparative safety to the skin. But with this decrease in absorption of radiation on the skin, there is an increase in the energy absorbed in the deeper parts of the body, and this, in turn, indirectly affects the "treated area" by the production of adverse constitutional disturbances. This question of body dose was raised in 1938, when the constitutional effects of teleradium therapy were under consideration at the Radium Beam Therapy Research, London.[150] It has been systematically developed by Mayneord in a series of publications. For measuring this radiation he suggests a unit to be called the "gram-röntgen," which may be defined as the energy absorbed in 1 gram of tissue irradiated with one röntgen.[87]

TABLE I

ILLUSTRATING BIOLOGICAL RESPONSE TO A VARIETY OF RADIATION DOSES

No.	Dose in r	Biological Response
1	10^{-5}	"Safety" limit of exposure for radiographers, etc., per second [5]
2	0.175	Dose received per day by attendants using a 4-gram radium unit [6]
3	0.25	"Safety" limit of exposure per day (7-hour day) [5]
4	0.5–1.0	Front of fluorescent screen during examination of patient [82]
5	1.0	Palpating hand of operator using fluorescent screen every 10 min.[82]
6	1.25	"Safety" limit of exposure per day (5-day week) [5]
7	8.0	Threshold for mitotic effect in grasshopper [7]
8	9–70	Received by diagnostician making complete radiographic study of gastro-intestinal tract (see No. 13) [68]
9	15	To either gamete produces developmental abnormalities in 5% of individuals (frog) (see No. 18) [57]
10	34	Threshold for mitotic effect in chick fibroblasts (*cf.* No. 7) [129]
11	40	Alteration in ultraviolet absorption in cell-cytoplasm

No.	Dose in r	Biological Response
12	50	30% inactivation of enzyme in dilute solution (*cf.* No. 28)[21]
13	50–100	Tube-side of fluorescent screen during examination of patient (see No. 8)[82]
14	170	Temporary sterilization of ovary in women[148]
15	290	Cessation of ovulation[86]
16	350	Increases by 1% sex-linked lethal mutation in *Drosophila* (maximum yield 15% with 5,150 r, above which dose sperm degenerates)[135]
17	400	Initial injury to ovarian follicles and germinal epithelium of domestic fowl[34]
18	500	Developmental abnormalities nearly 100% in frog (see No. 9)[57]
19	800	Follicular disintegration in domestic fowl[34]
20	1,000	Mean lethal dose for *Ascaris* eggs[63]
21	1,039	Average skin-erythema dose for gamma rays[108]
22	1,200	Total destruction of male gonads of domestic fowl[34]
23	2,000	Total destruction of female gonads of domestic fowl[34]
24	7,000	Prevents "take" when inoculating benzpyrene-induced sarcoma in rat[50]
25	9,000–20,000	Inhibits regeneration in worm-segments[132, 140]
26	30,000	Delays cleavage in sea-urchin egg[56]
27	40,000	Causes complete inactivation of frog-sperm[57]
28	100,000	30% inactivation of enzyme in concentrated solution ($\times$ 345 that of No. 12)[21]
29	117,000	Immediate death of chick-fibroblast cultures[123]
30	200,000	Mean lethal dose *B. mesentericus* spores[78]
31	330,000	Mean lethal dose *Colpidium colpoda*[14, 15]
32	1,000,000	Inactivation of plant viruses[81]

These considerations illustrate some of the complexities of the irradiation problem where organized body tissues are concerned. Great technical advances have been made on the physical side in delivering a given dose to a selected volume of tissue, but a stage has been reached when it is easier to deliver a given dose of radiation than to know precisely what biological changes that irradiation produces in the tissue irradiated. It is time now for corresponding advances on the biological side.

Radiochemistry

In studying the effects of radiation on biological material useful information may be obtained from experiments on nonliving matter. A recent survey by Allsopp [2] of the chemical action of radiations has shown how developments in the field of radiochemistry can be related to the study of the biological effects of radiation. Until quite recently, enormous doses of radiation were required to produce measurable chemical changes *in vitro,* and it was suggested that chemical processes could not be involved in therapeutic radiation at any rate, since recognizable changes could be obtained only with doses far above the maximum human tolerance dose.[17]

Recent work by Dale,[19, 20, 21] however, has shown the fallacy of the conclusion. Dale arranged his experimental procedure so that the chemical changes produced by irradiating purified enzymes in aqueous solution were magnified many times by the accompanying changes in biological activity. Dale's results show quite clearly that a constant amount of solute is inactiviated for a given amount of radiation energy absorbed in the whole solution, irrespective of the concentration of the solution. The simplest explanation of these results is that the initial process consists in "activation" of solvent molecules by absorption of radiation, followed by the transfer of energy to the solute by inelastic collision, without the term "activation" being precisely defined.[40, 112]

It may be recalled here, however, that in the initiation of radiochemical reactions in gaseous systems, excitation of molecules is apparently more important than ionization, since radiochemical reactions in the gas phase in general follow the same course as the corresponding photochemical reactions.[36, 61, 122] There is no reason to suppose that radiochemical reactions in aqueous solutions are not similarly initiated by energy-carrying solvent molecules.[2] The experimental evidence is consistent with the hypothesis that the energy carrier is a free hydroxyl radical.[144]

Since the number of solute molecules decomposed by a given

radiation dose depends on the concentration of activated solvent produced (not on the concentration of the solute) and will, therefore, be relatively small, the concentrations of solute employed must be the smallest consistent with chemical analysis, in order that changes in them may be relatively large. It was the widespread failure to recognize this which led to the supposition that significant chemical changes could not be produced *in vitro* by doses within the therapeutic range. For the simplest case, i.e., only one substance in solution, the activation theory would seem a reasonable interpretation of observed facts.

Dale has recently described some striking experiments in which an apparent loss of radiosensitivity occurs when enzymes are irradiated in the presence of varios protein and other substrates which share the available energy between them and thus "screen" the original solute.[22] This work on the protection of one solute by another is a valuable contribution to the interpretation of the chemical effects of radiation *in vivo*. If the indirect-action theory is applicable under these conditions, then a new light may be thrown on the mechanism of action of radiations. From the point of view of a solute, e.g., an enzyme, its inactivation by energy carriers derived from molecules of aqueous solvent could be regarded as the target theory in reverse! The possibility of this mechanism operating *in vivo*, if only under certain conditions of dilution, is a further caution against making any generalization prematurely.

Whether "activated water" is also connected with such physicochemical effects as the precipitation of positively charged colloids, viscosity changes, and change of electrokinetic potentials remains to be seen.[16] It seems more likely that the physicochemical effects are produced by simple ions.[2]

Biological Indicators

From time to time, investigators have sought for a simpler biological material with a more definite and convenient reaction than the skin erythema to serve as a biological dose unit. When the irradiated tissue is very small, such as the egg of an insect,

and is suspended in air so that scattered radiation reaching it is at a minimum, the absorption of energy is uniform throughout the object irradiated and is directly proportional to the intensity of the radiation beam. For example, if a large number of *Drosophila* eggs is exposed to an X-ray beam of unknown intensity for 10 minutes and if, as a result, half the individuals fail to hatch, then 180 röntgen units have been delivered at the rate of 18 r/min.[98] The constancy with which such quantitative experiments yield the same result is perhaps one of the most striking features of this type of investigation. With *Drosophila* eggs the error is not more than 3%,[100, 102] and this order of accuracy is obtained with other types of biological material under laboratory conditions.

A great variety of organisms has now been used as biological indicators of radiation action by many observers, and each material has its advantages and its limitations. The most important consideration is that the experimenter shall be familiar with the material chosen for experiment, and be able to distinguish with certainty the changes produced by radiation and those unconnected with it.

These indicators are of particular use where the biological effects of two different types of radiation, with no physical unit of measurement in common, are being compared; for example, a comparison of the biological effects of X-rays and neutrons.[47, 125] If the biological response can be matched, then a useful comparison of the physical conditions of irradiation is obtained. Biological indicators are also useful to establish the relationship between injury produced by radiation and other types of injury, e.g., to determine whether the effects of two agents are additive, equal, unrelated, or whether one is capable of potentiating the other.[119] The indicators should be small in size, easily available in large numbers at all times, they must show only a small and definite amount of normal variation, and the reaction to radiation must be sharp and easily measured.[64] Some investigations may be simplified by using a response which is independent of the time factor. Since radiosensitivity varies enormously with stage of development, it is essential that the greatest care is taken

to insure constancy in age and temperature of the biological indicator selected.[121]

Among the materials used in this way, the following may be mentioned, although not all conform to Holthusen's specification for the ideal test-object: Eggs of the sea-urchin, *Ascaris, Drosophila,* silkworm, grasshopper, frog and axolotl, viruses, bacteria, yeast, pollen grains, protozoa, vegetable root-tips, and tissue cultures.[58, 97, 99, 104] Germ cells and somatic cells of higher animals, blood cells, skin, and even whole animals have also served as indicators in special cases.[32]

Such material has been used for demonstrating the wide difference in sensitivity which exists among biological objects. This is illustrated, for the lethal effect, in Table II, taken from data given by Packard [101] and by Crowther.[15] The reason for these great differences is quite unknown.

TABLE II

Dose in Röntgens Necessary to Kill 50% of the Samples of Organisms Irradiated or to Reduce Their Growth to Half That of Controls

Organism	Dose in r
Eggs of *Calliphora*	40
Eggs of Axolotl	50
Eggs of *Drosophila*	190
Eggs of *Ascaris*	1,000
Larva of *Drosophila*	1,300
Escherichia coli	5,100
Mesotaenium	9,000
Saccharomyces	42,000
Imago of *Drosophila*	95,000
B. mesentericus	200,000
Colpidium colpoda	330,000

Biological indicators have also been extensively used in studies of the effect of wave length on biological response, in genetics, and in testing the validity of various theories of action of radiation and the significance of alterations in the physical conditions of irradiation.

The results, although usually consistent for a given material,

are often at variance when the response of one material is compared with that of another. Each result has to be considered by itself. The contrast is most marked when the results of irradiating independent biological units, such as bacteria or insect eggs, are compared with those of an organized colony of cells which make up a body tissue. This is hardly surprising, since in the one case radiation acts on single units without any biological spread of effect to adjacent units, and in the other it acts upon cells capable of being further influenced by changes brought about in adjacent cells. However nearly the radiosensitivity of the indicator approaches that of the body cells (one of Holthusen's stipulations for the ideal test object) it is unlikely to give the *same* information as would be obtained from direct observations on the body cell. This is the limitation which restricts the usefulness of most of the indicators listed above. Tissue cultures constitute a special case, since the technique enables samples to be taken from the body (before or after radiation), and observations or experiments to be made under the relatively simple conditions of growth *in vitro* for direct comparison with changes seen in similar tissue *in vivo* after similar irradiation treatment.[124] An intermediate step is thus provided between the simplicity which is the essence of laboratory experiment, and the complexity of irradiation of organized tissues *in vivo,* which is a very useful guide in comparative investigations.

Genetic Effects of Radiation

The demonstration by Muller [91, 92] and shortly after by Stadler [131] that X-rays could produce gene mutations in *Drosophila* and barley excited geneticists throughout the world to take the keenest interest in this property of radiation; X-rays immediately became their most important tool for producing mutations. An extensive literature bears witness to the enthusiasm aroused by this discovery, which has opened up a new and large field of research.[8, 13, 38, 74] The sterilizing effects of X-rays were discovered nearly a generation earlier,[1] and much fundamental work on the results of irradiating genetical material was completed

before any observations on mutation production by radiation diverted attention in this direction. These early observations were somewhat restricted and rarely extended to the offspring of irradiated organisms. The effects of radiation were judged by abnormalities in development after irradiating sperm or ova, or by alterations in the chromosome configuration of dividing cells. It was later found that radiation may cause an abnormal distribution of hereditary material without change in its composition. Then, as cytological technique advanced, it was realized that the alterations in the chromosomes themselves were of at least two kinds: (1) changes in the linear arrangement of the chromosome threads, resulting from single or double breakage and recombination in new alignments, with or without loss of chromosome fragments; and (2) changes in the composition of the unit hereditary particles or genes, without disturbance of their position on the chromosome thread (gene mutation).

Chromosome abnormality offers a very convenient method for making a quantitative measure of radiation effect. The scoring of abnormalities is tedious, but can be made with fair accuracy. Some breaks in the chromosome thread rejoin immediately, but for the rest, the injury, once made, is permanent, so that the result is not complicated by gradual recovery processes. A great variety of structural change is seen after suitable radiation dosage, and this may be classified according to whether one or more chromosomes have been involved and how the broken ends have reconnected.[75, 76] The material is almost ideal for statistical purposes, because the chromosomes act as targets which mark the hits by breaks in continuity of the thread which can be seen and counted. The tangle in which the broken threads in some cases become involved may cause the breaking up of the cell, or the production of nonviable daughter cells owing to the unequal distribution of the hereditary material. In this respect, chromosome abnormalities are more detrimental than gene mutations (which may not exert their effects for several generations) since they cause marked infertility in the first-generation offspring.

Structural changes in chromosomes are most easily investi-

gated in insects and plant cells which have a small number of chromosomes of large size, and they are most easily recognized in the metaphase and anaphase of division, at whatever point in the life cycle of the cell the irradiation is given. The practice of scoring abnormal anaphases as a measure of radiation effect [83, 84] has the limitation, however, that cells irradiated in premitotic or early mitotic stages may break down altogether in late prophase or early metaphase. Such cells are, therefore, missed in the anaphase count.

The total number of breaks produced is proportional to the dose and independent of intensity, but neutrons are more efficient in producing breaks than are X-rays.[42, 75, 137] These observations can be explained on the hypothesis that a chromosome is broken by the passage through it of a single ionizing *particle,* but that it is necessary for the ionizing particle to be sufficiently densely ionizing for several *ionizations* to be produced within (or very near) the chromosome. A proton (from neutron irradiation) is sufficient; only the "tail" of a fast electron track gives a sufficient number of ionizations in the given volume. On this hypothesis, X-rays of long wave length should be more effective than those of short wave length, and this has been found to be the case with an optimum at 4Å.[7] Longer wave length X-rays produce too short an electron track to span a chromosome, and so their efficiency is diminished.

Changes in the composition of hereditary particles which lead to gene mutations occur in germ cells of all types, but have been studied most extensively in the case of the fruit-fly, *Drosophila.*[10, 75, 76, 93] A dose of 3,000r of X-rays produces a mutation rate of about 12%. This is about one hundred times the natural mutation rate, but qualitatively is indistinguishable from spontaneously-occurring mutations. The yield of radiation-produced mutations is proportional to dose, independent of intensity, and diminishes for equal doses of different radiations in the order: X-rays, neutrons, alpha rays. It is considered that a mutation in *Drosophila* is the result of a single ionization.

All cells are not equally susceptible to the mutational effects of radiation, and other factors, e.g., temperature, anesthesia,

state of nutrition, and degree of germination, affect the mutation rate.[51] Most gene mutations are recessive, i.e., able to produce their characteristic effect only when paired with another mutated gene of the same kind. Only a minority produce any conspicuous morphological abnormality. Occasionally a change in the gene occurs which initiates new developmental processes.[94] A mutation caused by one irradiation may be reversed by a subsequent exposure.[139] This is exceptional, however, and in nearly every case the mutation effect is exactly proportional to the amount of energy received, and exactly cumulative over an indefinitely long period even in successive generations. It is unknown to what extent these observations are applicable to man.

Thus, radiation can be regarded as a useful tool in purely genetic investigations on such problems as the properties of genes and chromosomes, the size and number of genes and their mutational potentialities. Investigations on the genetic effects of radiations provide valuable data on *one* of the ways in which biological material responds to radiation, but, as rightly emphasized by one of the foremost genetical investigators, "Not all the effects of radiation in killing organisms or disturbing their development are referable to changes either of the class of gene-mutations or chromosome re-arrangements." [95]

Injurious and Lethal Effects of Radiation

In previous sections some account has been given of the injuries caused to small organisms (biological indicators) and to particular organs within cells (chromosome effects) by penetrating radiations. There still remains to be considered the largest field of inquiry within the domain of experimental radiology, namely, studies of the effects of radiation upon complex tissues both in health and disease and after experimental injury.

Innumerable observations have been made of the effects of radiation, under the greatest variety of physical conditions, upon embryological development, the various systems of the body at different stages of growth, individual organs and on the body

as a whole. Such studies on the response of normal tissues to radiation are not only of interest and importance in themselves, but also because of the information they give concerning the amount of radiation that the healthy body or organ can tolerate. Unless healthy tissue were able to tolerate a greater quantity of radiation energy than diseased tissue, penetrating rays would be of little use in radiotherapy.

In general, biological indicators show a response which is independent of the wave length of radiation but dependent on the intensity, while the mutation effect, though dependent on the wave length, is independent of the intensity. The biological effects now to be considered vary with alteration in both the intensity and the wave length of the irradiation to which they are exposed.

Radiation affects any given cell of a complex tissue in at least two ways, first by a direct action on the cell, and secondly by injuring neighboring tissues upon the health functioning of which the cell depends.

The term "indirect effect of radiation" conveniently describes all the effects of radiation except its direct action on the cell, but it has by custom come to be restricted to those effects produced as a result of injury to the blood supply. This quite arbitrary and rather unfortunate limitation of a useful term requires another to describe the consequences of the action of radiation upon remote tissues and body fluids. For this the term "constitutional effects of radiation" is now reserved.

When blood supply is restricted or inhibited by radiation the results are so conspicuous [52] that it is not surprising, perhaps, that they should at one time have practically monopolized attention. It has even been suggested that all the radiation effects on a complex tissue are the results of the action on the circulation. This view is easily refuted, however, by reducing the radiation dose below the level which affects the blood supply, when the direct effects of the radiation can be seen, unmasked by injuries caused from lack of blood. Alternatively, the role of the blood supply can be demonstrated by irradiating embryos *in ova* before and after the establishment of the circulation and comparing

the results.[147] So long as the circulation is intact, recovery from the direct effects of exposure is hastened; when the blood supply is compromised, the injurious results are additive.

The indirect effect of radiation upon embryonic tissue has been strikingly demonstrated by means of tissue-culture experiments[135] in which it was shown that the cells of a six-day embryo, irradiated *in ova* and explanted shortly afterwards, could be cultivated *in vitro* in an apparently healthy condition for days. If the embryos were incubated *in ova* for 21 to 25 hours after irradiation, however, they showed no trace of growth when explanted *in vitro*. The cause of cell death was shown to be due to the absence of gaseous exchange in the tissues of the chick when incubated in the shell, resulting from the arrest of the blood circulation shortly after irradiation.

The level to which the dose must be raised to affect the circulation is considerably above that which causes a direct effect upon tissue cells. For the chick the doses differ by a factor of about 10.

Of the various body systems, the blood vessels and blood-forming tissue were among the first in which the direct effects of radiation were observed.[23, 31, 115] These studies have recently been greatly extended by the use of radioactive substances, introduced into the body and selectively absorbed in the blood-forming tissues, in place of external radiation by gamma or X-rays. The range of sensitivity of these tissues is remarkable; less than 10 r of X-radiation is required to affect the leucocytes of the blood, while a dose of 100,000 r has no demonstrable effect on the isolated (frog's) heart.[121, 126]

Alteration in the blood count in man is an early and convenient warning of injurious exposure to radiation, but there is no agreed opinion as to where the danger line can be precisely marked.[118] The lymphocytes show the more marked change in patients who have been irradiated, while the polymorphonuclear cells may be the first to show any change in blood counts of the therapeutic staff. Small doses of gamma rays spread over a long time may lead to a specific aplastic anemia which is not seen after X-radiation.

Exposure to X-rays or gamma rays has pronounced effects on the embryological development of all species of animals which have been investigated. In general, sensitivity during development decreases as the age of an individual increases. This, so far as the direct effect of radiation is concerned, is probably associated with, although not wholly explained by, cell multiplication and growth rate. A determination of all the factors involved is one of the central problems of radiation.[54, 59, 60, 98]

Some light is thrown on the problem by studying the inhibitory effect of radiations upon regeneration, which has demonstrated a differing susceptibility of different types of cells. Or to put it another way—the potencies of specific types of cells play a significant part in determining the result of any given irradiation. There is evidence that, under certain conditions of irradiation, the process of differentiation among embryological cells is promoted,[46, 136] although sensitivity to radiation is lost as differentiation proceeds.[18, 143]

The response of the skin and its appendages to radiation has perhaps been more extensively studied than in any other system.[85, 89, 90, 109] In these investigations the ultimate aim is often to discover ways and means of protecting the skin from injury, while permitting effective irradiation to reach the underlying tissues.[48, 69]

Observations upon the direct effects of irradiation on the generative system of the male rat led to one of the earliest generalizations on the biological effects of radiations,[4] which emphasized the relative radiosensitvity of proliferating cells and the relative radioresistance of differentiated cells. Subsequent observations have shown that this applies to all species of animals investigated, though the dose level at which mitotic activity is affected differs for different species.

While such comparative studies of radiation effects on different biological material have a considerable interest, perhaps more useful information is obtained by comparing the effects of gradually increased doses of radiation on the same type of tissue. This is perhaps most easily seen when the data are arranged in tabular form (see table III). A definite gradation

in the results immediately becomes apparent, especially if the issue is uncomplicated by the intervention of any indirect effects.

TABLE III

CHANGE IN BIOLOGICAL RESPONSE OF AVIAN FIBROBLASTS GROWN IN VITRO AND EXPOSED TO INCREASING DOSES OF RADIATION *

Ray	Intensity in r per min.	Duration in hours	Dose in r	Effect
γ	81.5	24	117,000	"Immediate" death of all cultures
γ	81.5	18	108,000	Death within 2 days of all cultures
γ	81.5	12	58,600	Death within 4 days of all cultures
γ	81.5	9	54,000	Death within 8 days of all cultures
γ	33	24	48,000	Death within 8 days of all cultures
γ	81.5	6	29,000	Death within 10 days of all cultures
γ	81.5	4½	22,000	Death within 13 days of all cultures
γ	81.5	3	14,600	Death within 18 days; some cultures recovered
γ	33	9	18,000	Death within 18 days; some cultures recovered
X	100	1⅔	10,000	75% degeneration; peak at 3 hours
X	100	..	5,000	60% degeneration; peak at 3 hours
X	100	..	2,500	50% degeneration; peak at 3 hours
X	100	..	1,000	7% degeneration at 3 hours, count rising
X	100	..	500	7% degeneration at 3 hours, count rising
X	100	..	100	2% degeneration at 3 hours, count rising
γ	33	..	33	Reduction in mitosis, no degeneration, ultimate recovery

* The X-ray data are taken from Lasnitzki.[73]

The table shows that there is no single type of response which can with any justification be called *the* biological effect of radiation, but that at various dose levels *a* change in behavior occurs in the irradiated cells. At the highest dose level the result is "immediate" death, presumably caused by a breakdown of the physicochemical structure of cell protoplasm; at lower dose levels, however, death of cells results from different kinds of initial injury; at the threshold dose for any observable change, complete recovery of the cell from the effect of radiation occurs. These dose levels are altered if the physical conditions of irradiation are changed. Thus, there is a minimum amount of radiation energy required to produce any given type of biological response in organic tissue, which can only be determined by the method of trial and error.

Summary of Effects on Normal Tissue

The biological effects of radiation upon normal tissue may be summed up as follows:

Radiations are always injurious to the cells which absorb them; the changes produced may be transitory (reversible effects) or permanent (irreversible effects), with an intermediate class of effect where the radiation changes disappear completely but leave the tissue in a state of lowered resistance to further radiation (conditioned reversible effect). There is a latent period between irradiation and the recognition of the biological effect it produces.[33]

There is a tenthousandfold difference between the extremes of sensitivity among different types of living cells when measured by the lethal effect.[121]

Radiation has a marked effect in interfering with cell proliferation, and the dose which produces the first recognizable changes in cell proliferation is always small relative to the direct lethal dose for the same tissue.

During development, radiosensitivity decreases as the age of the individual increases, but the decrease is not necessarily progressive throughout development. Sensitivity to radiation is

Scheme (After Glucksmann) Illustrating the Relationship Between Cell Division and Cell Differentiation in Different Types of Normal Tissue

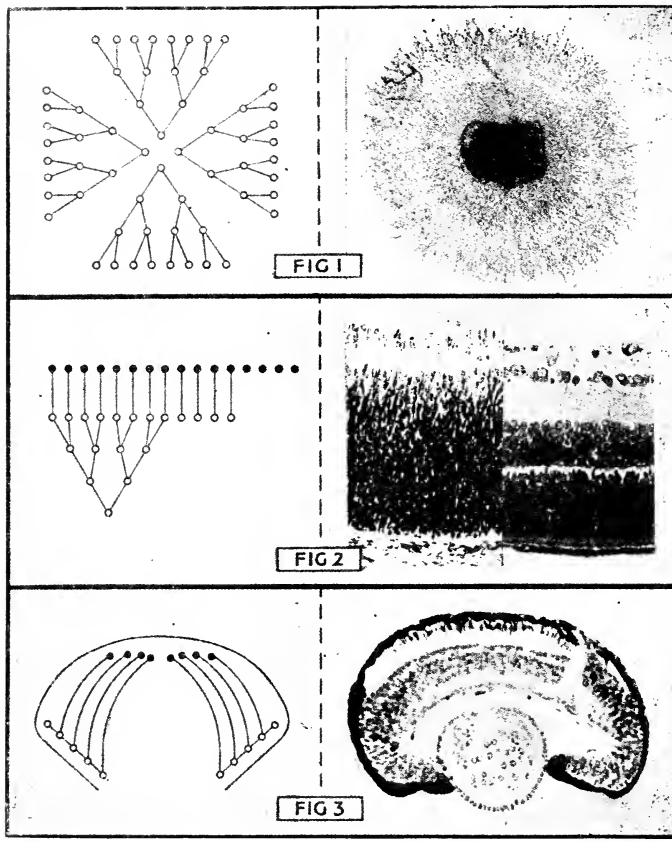
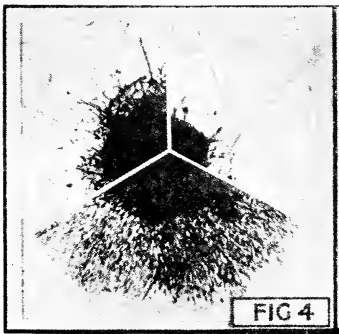
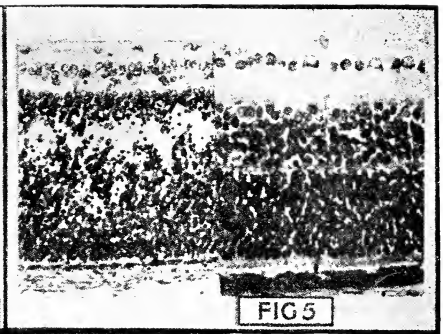


FIG. 1 represents the relatively simple conditions in a hanging-drop preparation of chick fibroblasts *in vitro*. The culture presents a form of growth consisting only of proliferating or of potentially proliferating ("resting") cells (magnification × 10).

FIG. 2 represents condition in the rat embryo where the processes of proliferation and differentiation are separated in time. Photomicrographs show section through eye of 2-day (left) and 10-day (right) postnatal rat (magnification × 210).

FIG. 3 represents condition in the eye of the frog tadpole where differentiation and proliferative activity are separated in space, the central parts being fully differentiated and functioning while proliferation still continues in the peripheral region (× 360). (Figure reproduced from *Proc. Roy. Soc. Med.* 1942, **35**, 597.)





DIVIDING CELL
● DIFFERENTIATING CELL

FIG. 4. Irradiated tissue culture showing generalized destruction.

FIG. 5. Eye of 2-day rat (left) showing degeneration only in the undifferentiated layers of the retina; eye of 10-day rat (right) showing differentiated retina and absence of degeneration after exposure to radiation.

FIG. 6. Part of the eye of the frog tadpole showing degenerate cells restricted to the germinative zone.

Genetic Effects of Radiation

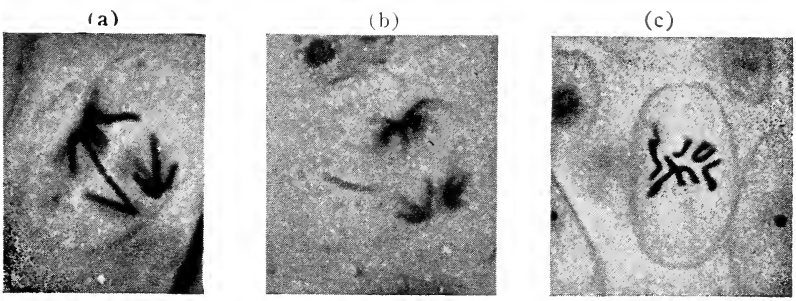


FIG. 7. Photomicrographs of chromosomes in *Tradescantia* pollen-grains that have been X-rayed. (*a*) A dicentric chromosome, arisen by sister chromatid-union in a chromosome-break, forms a bridge at anaphase joining the two polar groups of chromosomes. (*b*) An acentric fragment-chromosome lags at the equator of the spindle at anaphase. (*c*) Asymmetrical chromatid-interchange and a chromosome-break at metaphase.

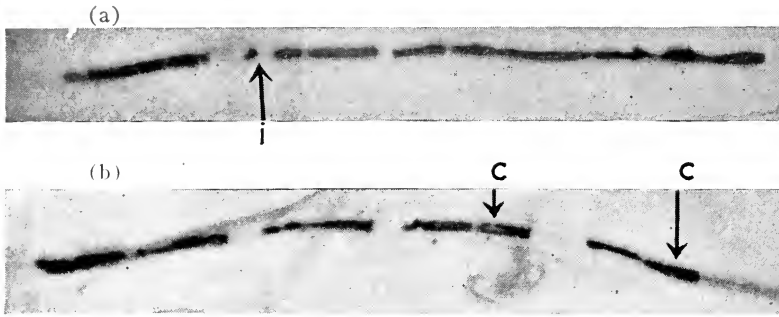


FIG. 8. Photomicrographs of chromosomes at metaphase blocked by colchicine in pollen tubes of *Tradescantia*. (*a*) Chromosome-break (i) with sister chromatid-unions in both the centric and acentric fragments. (*b*) Chromatid-breaks, *C*.

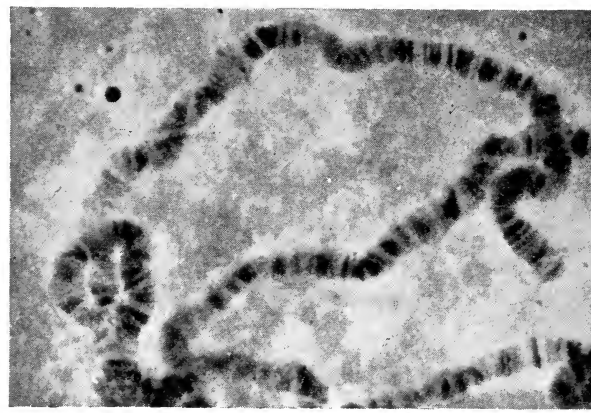


FIG. 9. Photomicrograph of part of the nucleus of a salivary-gland cell of *Drosophila*, showing an inversion-loop (lower left). The loop is produced by the intimate pairing of the parts of the inversion-chromosome with the homologous parts of the normal chromosome.

lost as differentiation proceeds; in certain circumstances radiation may promote the process of differentiation. Apart from a direct lethal effect, cells may be so injured by radiation as to be incapable of successful division, and thus either perish on attempting mitosis or produce nonviable daughter cells. The degeneration which is linked with interference with mitosis can be distinguished from that resulting from the breakdown of the so-called resting cells.[127]

Radiation and Malignancy

Much of the experimental work on the biological effects of radiations has some relation to the radiotherapy of malignant disease. The demonstration that radiation can cure a cancerous tumor raises the question of how this effect is brought about. There is a tendency for the results of experiments in any one of the fields of experimental radiology which we have considered to be applied too exclusively to the cancer problem. For example, the effect of radiation up on a proliferating tissue is so striking that it has been suggested that malignant cells die mainly by degenerative mitosis.[73, 96] Although this has been disputed,[11, 29] the idea has been revived by recent genetical work which has attributed the death of the cancer cell to the effects of radiations on chromosomes.

There can be no doubt that very many irradiated cells die when mitosis is attempted after irradiation. That this action of radiation is frequently due to direct hits on chromosomes seems also beyond dispute. In the light of Dale's work, however, there is now the further possibility that radiation may act also on dissolved enzymes *via* the solvent molecules, and where dosage is high enough to affect blood supply, the destructive effect on malignant cells of damage to the circulation is obviously another important factor. Objections can be raised against accepting any *one* of these explanations as the principal means by which radiotherapy achieves its success. Thus, as regards the mitotic effect, the low percentage of dividing cells present at the time of any one irradiation leaves the majority of cancer cells in a tumor unaccounted for, and a high proportion of mitotic cells in a tumor is not in itself an indication of marked radiosensitivity. A direct lethal action upon all tumor cells seems to be excluded (except where radiation is used as a cautery) in view of the high dosage required to produce such an effect under experimental conditions, while the suggestion that all therapeutic effects are the result of an indirect effect of radiation on the blood circulation is against clear experimental evidence [26] and has never received any substantial support.

The problem can be approached from another angle. Instead of attributing the destruction of a tumor to a single radiation effect, irradiated malignant tissue may be examined to see how many types of action can be recognized, and an attempt can be made to assess the relative importance of each in the eradication of the growth. If serial biopsies are taken from tumors during and after radiation treatment, it is possible to follow histologically the changes in cellular activity in a quantitative manner for each type of cell present.[44, 45] Radiosensitivity measured by rapidity of disappearance of the tumor soon after irradiation is by no means synonymous with radiocurability, i.e., permanence of radiation effect.[6] Thus, while much emphasis is often placed on the marked changes produced in anaplastic tumors by radiation, several observers have pointed out that the differentiating tumors, which seem clinically to respond to radiation more slowly, give on the whole a more satisfactory ultimate response.[3, 28, 106, 110] These clinical results may be explained in the following way. It is obvious that, if sterilization of all potential dividing tumor cells could be achieved, their total destruction by radiation would be unnecessary, since the altered cells would gradually disappear in the normal course of events. In a differentiating tumor, many of the daughter cells resulting from cell division become sterile because they differentiate, although abnormally. In this connection, the fact that radiation can promote differentiation as well as injuring proliferating cells is of some significance,[39, 41, 128] since, with suitable types of malignant tumors, radiation may exert a curative action both by mitotic inhibition and by sterilization. In the undifferentiated or anaplastic tumor, on the other hand, even a marked destruction of cells following a heavy dosage may lead to a recrudescence of the tumor from residual cells, incapable of sterilization by differentiation, which have survived the radiation.

It must be recognized, however, that a tumor, capable of responding to radiation by an increase of differentiation, may be adversely affected by excessive exposures which interfere with, instead of promoting, this process. Over-irradiated normal tissues show an increase in cell division and a decrease in cell

differentiation which has sometimes resulted in radiation carcinomata.[49, 70, 116] Such growths can, however, be treated by further radiation, if it is so delivered that proliferative tendencies of potential dividing cells are checked and the differentiation processes promoted.[145]

The conditions under which the inhibiting action of radiation on cell division is best achieved are beginning to be understood, and it remains to determine the best physical conditions for sterilizing cells by promoting differentiation.

In this connection the combination of radiation with chemotherapy would seem a profitable field for future research, as well as the effect of combining two or more different types of radiation in the treatment of a single tumor. The problem needs to be attacked from many aspects—hormonal, genetical, chemical (including organizer substances), physical, and nutritional—and upon its solution, in all probability, depends the next substantial advance in the treatment of malignancy.

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COMPARATIVE STUDIES OF THE BIOLOGICAL EFFECTS OF X-RAYS, NEUTRONS, AND OTHER IONIZING RADIATIONS

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Introduction

THE immense literature dealing with the biological effects of ionizing radiations is dominated by experiments in which the radiation employed has been therapeutic X-radiation, that is, radiation from tubes operated at voltages of between 80 and 200 kilovolts. This is not surprising, since the majority of the investigations have been undertaken with the object of obtaining information immediately applicable to therapeutic practice. Of the remainder, the approach has more frequently been that of the biologist seeking to explore the effects of radiation on different organisms and on different aspects of cellular activity, than of the physicist attempting to trace one particular lesion—such as a mutation, the breaking of a chromosome, or the inhibition of mitosis—to the interaction of the radiation with a particular set of atoms within the cell.

For the former purpose, the type of radiation employed appeared to be of little consequence, and either the gamma rays from radium or therapeutic X-radiation were generally employed as most convenient. For the latter, we need to employ a diversity of radiations, so that we may study the effects of changing in a known manner the distribution of the ions produced throughout the cell. Within fairly recent times, comparative studies with different ionizing radiations, such as gamma rays, X-rays, neutrons, and alpha particles, have led to the establishment of important and often remarkable facts, such as that the death

of a cell may result from the generation within a certain small region of an amount of energy which, if spread over the whole cell, would not raise its temperature by more than one hundred-millionth of a degree Centigrade. With the advent of the high-voltage X-ray tube, the betatron, and the cyclotron, the study of the influence of radiation type or quality upon biological response has assumed a practical importance, for with the help of these machines, it is possible to generate almost any type of ionizing radiation under conditions which are suitable for the treatment of a deep-seated tumor.

Linear Ion Density, the Distinguishing Feature of an Ionizing Radiation, from the Biological Standpoint

The discovery of radium followed quickly upon the discovery of X-rays, and some of the earliest biological experiments with ionizing radiations were carried out with "naked" and "screened" radium. As the screens used were of just sufficient thickness to absorb all the beta rays, the experiments were, in effect, comparative studies of the effects of the beta and alpha rays as they are generated by a small quantity of radium. Striking differences were at once noticed.[15, 38] Hardy [14] observed that an alkaline solution of serum globulin, i.e., on the negative side of the isoelectric point, was coagulated, and that an acid solution became clearer when exposed to naked radium. When screens were introduced to absorb all the alpha rays, so that the drop of solution was exposed only to the beta rays, no effect was observed even after twenty times the exposure. Chambers and Russ [4] observed that erythrocytes were hemolyzed when exposed to both alpha and beta rays, but not when the alpha rays were eliminated. Colwell and Russ [5] found that, when emulsions of bacteria were exposed to both alpha and beta rays, marked agglutination occurred before the lethal point was reached. When the alpha rays were eliminated, there was no agglutination, although a lethal condition was reached.

A consideration of the physical differences which obtained in these experiments will serve to illustrate important points in

the intercomparison of ionizing radiations in general. The beta rays are electrons, i.e., particles having $\frac{1}{1850}$ of the mass of a hydrogen atom and carrying unit negative charge, while the alpha particles are helium nuclei having 4 times the mass of the hydrogen atom and carrying two positive charges. Since it was the negatively-charged globulin molecules which were discharged in Hardy's experiments, the effect was at first attributed to the neutralizing action of the positive charge caused by the alpha particles. This now appears in the highest degree improbable.* All the chemical and biological effects so far studied are referable to the excitation and ionization of the molecules in the path of the ionizing particle, and it would be impossible to say of any individual excited or ionized molecule whether it had been produced by an electron or an alpha particle.

The essential difference between the two rays lies in the number and distribution in space of the ions and excited molecules which they produce. In the second place, it is important to notice that while the beta and alpha particles emitted by naked radium are comparable in numbers, the beta rays have initially an average energy of about a million volts, which is gradually transformed into ionization and excitation throughout a total path of several millimeters of water or tissue, whereas the 6 million volts initial energy of an alpha particle is dissipated in less than $\frac{1}{20}$ millimeter. Within the $\frac{1}{20}$ millimeter immediately surrounding the radium, the total number of ions formed by the alpha rays may therefore be several hundred times as great as that produced by the beta rays, and it is not surprising on this ground alone that the alpha rays appeared very much more effective.

We shall discuss in detail only experiments in which the total number of ions formed by the radiation per unit volume

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* In somewhat analogous experiments with colloidal graphite, Gray, Read and Liebmann [11] observed that similar changes in the charged condition of the particles were produced by negatively-charged electrons and positively-charged protons. The two radiations differed only in their numerical efficiency.

of tissue has been estimated with reasonable accuracy. From such experiments, we learn that biological effect is not in general uniquely determined by the total number of ions, but that it is also conditioned by the spatial distribution of these ions; the effect of a small number of particles, each producing a large number of ions, is not necessarily the same as that of a large number of particles, each producing few ions.

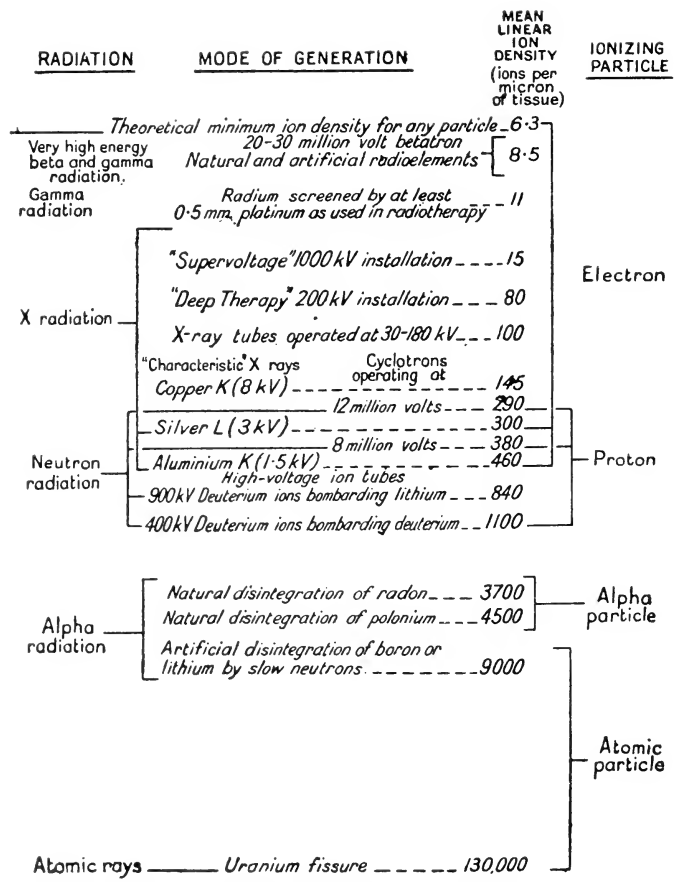
To take a concrete example, consider the effect of equal doses (25 röntgen) of beta radiation and alpha radiation on the meristematic cells in the root tip of the broad bean, *Vicia faba*. The total ionization produced in a nucleus 10μ in diameter is, in each case, 23,400 ions. In the first case, the total is made up of the contribution from 500 beta particles, each producing on an average 7 ions per micron of path. In the second case, the whole ionization is produced by the transit of a single alpha particle producing ions at the rate of 3,500 per micron. The beta radiation will produce an appreciable diminution in mitotic activity 3 hours after irradiation, but the effect on the subsequent growth of the root will be scarcely detectable. The alpha radiation has no detectable immediate effect on mitosis, but six days later the average growth rate of the roots will be less than a third of its normal value, and a small proportion of the roots will cease to grow altogether.

The contrast between the effects of beta and alpha rays is sometimes striking, as in the example just given, because these two radiations lie almost at the opposite extremes of the known radiations in regard to the density of the ionization along the tracks of the particles. Even in this case, however, the differences are quantitative and not qualitative. A sufficiently large dose of alpha radiation has an immediate effect on mitosis, and a sufficiently large dose of beta radiation will kill the roots. Radiations intermediate between beta rays and alpha rays are not always intermediate in the effectiveness of a given amount of ionization, since there may be an optimum linear ion density for any given biological effect which is not at either extreme, but in the cases so far studied it has almost always * been found

* An exception is noted on p. 129.

TABLE I

Ion Density Produced by Different Ionizing Particles



As an ionizing particle slows down, it produces ions at an ever-increasing rate until it has been brought nearly to rest. The ion density, therefore, increases along the length of the track of any ionizing particle. The figures quoted in the table are average values for all the particles generated by a given type of radiation. It will be seen that this average value increases with decreasing voltage for each type of particle. Thus very high voltage X-rays give rise to the particles of lowest ion density, and high-energy neutron radiation is less densely ionizing than low.

that there is a smooth and progressive variation of effectiveness with the density of the ionization along the track of the ionizing particle irrespective of whether the particle is an electron, a proton, or an alpha particle.

The subject, therefore, admits of a great simplification, for in general it is not necessary to contrast the numerous types of radiation, but only to discuss the influence of the "linear ion density" on the total amount of ionization required to bring about a given biological effect. Experimentally, also, this involves a simplification, since there are sometimes alternative ways of generating particles of a given ion density, as shown in table I.

Certain points of therapeutic interest emerge from a consideration of the data contained in this table. It will be observed that strongly-filtered radium gamma rays, the beta rays from radium, and both the beta rays and the X-rays from a betatron operated at voltages up to 30 million volts, are all bracketed at the level of 6 to 8 ions per micron. Theoretically no charged particle can produce less than 6 ions per micron; moreover, the minimum is a flat one, rising particularly slowly on the high-voltage side, as has been checked experimentally by the study of cosmic-ray particles. While, therefore, the betatron offers attractive possibilities from the standpoint of radiological technique, there are no *a priori* grounds for expecting a marked difference in biological effectiveness between, say, 30 million volt X-rays and heavily-filtered radium gamma rays.

A second point in the table, at which large changes in the conditions of generation result in little or no change in the ion density of the radiation produced, occurs in the range of X-rays commonly used in radiotherapy. From the biological standpoint, the quality of an X-ray beam may be specified by stating the average ion density of the secondary electrons to which it gives rise in the irradiated tissue. Some of these electrons (photoelectrons) have the full energy of the X-ray quantum; others (recoil electrons) have only a fraction of this energy. As the kilovoltage of the X-ray tube is increased, the energy of both types of electrons increases, but those having only a small fraction of the

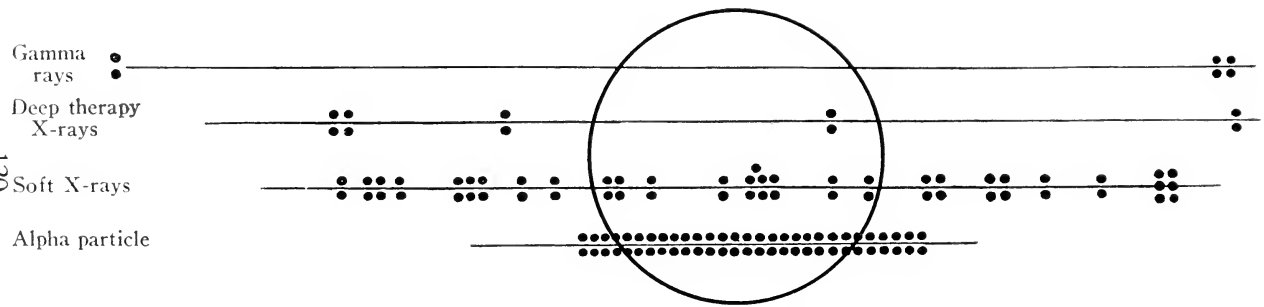


FIG. 1. Separation of Ion Clusters in Relation to the Size of a Virus Particle 27 mμ in Diameter

quantum energy become relatively more numerous, with the result that the mean energy of all the electrons of both types changes only very slowly. Detailed calculation [20] shows that the average energy, and, therefore, the average ion density of the secondary electrons, is almost constant for all X-ray-quantum energies between 15 and 90 kilovolts—i.e., roughly for the radiations from X-ray tubes operated at all voltages between 30 and 180 kilovolts. In consequence, it is not to be expected that a change in X-ray quality within this range will be accompanied by any appreciable change in the biological effect of a given total amount of ionization per unit volume of tissue.* The number of experimental investigations dealing with this point is legion, because the range of X-ray qualities in question happens to be at the same time the most accessible and the most interesting in current radiotherapy As might be expected, these investigations do not all lead to the same conclusion. It may be said, however, that there are no solid grounds for doubting the accuracy of the inference from ion-density considerations, and it would be possible to point to a number of very careful investigations, outstanding among which are probably those of Packard,[27, 29] who studied the percentage mortality among irradiated *Drosophila* eggs, which show particular biological effects to be independent of X-ray quality over this range to a high degree of accuracy. It appears, indeed, almost in the light of a freakish prank of Nature that she should have tempted so many to investigate a region destined to bear so little fruit.

The Influence of Ion Density on Radiochemical Yield

Many substances are decomposed when exposed to any of the ionizing radiations. When the decomposition takes place in the gaseous phase, the number of molecules decomposed is usually of the same order as the number of ions found by the

* This does not necessarily imply, of course, that the biological effect of a given dose, measured in röntgens, will be independent of X-ray quality. It is just in this region that the ratio of the ionization produced in tissue to the dose in röntgens may show a marked dependence on X-ray quality.

radiation, and is roughly the same for beta rays ($\Delta = 10$) and alpha rays ($\Delta = 3{,}500$).† This is true of the decomposition of ammonia, nitrous oxide, and hydrogen iodide. The decomposition of water vapor, however, appears to be exceptional in that the yield is very low with X-rays. Equality of yield with beta and alpha radiation has also been observed in the case of the synthesis of ammonia, hydrogen bromide, and ozone, and though there are no published data of this sort for neutrons or other radiations of intermediate ion density, it may be presumed that the yield will be completely independent of ion density in those cases in which it is the same for beta and alpha rays.

Chemical reactions in solution, and particularly in dilute aqueous solution, are of much greater interest from the biological standpoint. The decomposition of water itself is notoriously controversial, even in regard to the experimental facts, and it is not possible to say with certainty whether the much higher yield generally found with alpha radiation [6, 18, 26] than with X-rays [7, 13, 30] is to be referred to differences in ion density or to extraneous circumstances, such as the presence or absence of dissolved oxygen.

The position, as far as the published findings are concerned, is hardly less satisfactory with regard to dilute solutions, since there appears to be no reaction which has been studied at two different ion densities by the same author, and the difficulties associated with these experiments are such that small differences in the yield obtained by different authors cannot be relied upon. The evidence in the case of the decomposition of hydrogen bromide and hydrogen iodide, and the reduction of potassium permanganate, points to the absence of any dependence on ion density. It seems fairly clear, on the other hand, that the difference between Stenstrom and Lohmann's estimated yield ($\frac{M}{N} = 0.1$) for the decomposition of tyrosine by X-rays and Nurnberger's figure ($\frac{M}{N} = 0.003$) [26] for alpha rays is evidence of

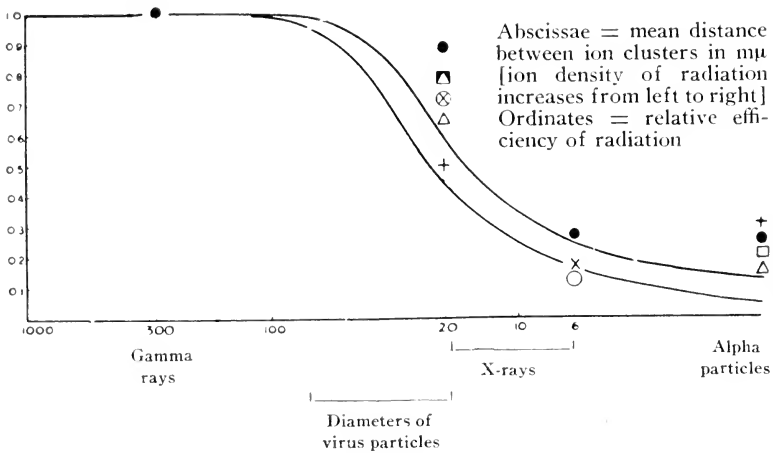
† The symbol Δ will be used throughout for the linear ion density, i.e., the average number of ions formed per micron in water.

a sharp fall in the proportion of molecules decomposed to ions formed by the radiation as the ion density increases from 50 to 3,500 ions per micron. Dale and Meredith, in collaboration with the writer, have recently examined carefully the inactivation of dilute solutions of the enzyme carboxypeptidase by X-rays and alpha rays. The alpha-yield was found to be only about one-twentieth of the X-ray yield, indicating a sharp fall in efficiency of the radiation with increasing ion density. It would appear that, in the case of the densely-ionizing alpha particles, a high proportion of the products resulting from the ionization of the water becomes ineffective before they reach the enzyme molecules awaiting inactivation. More experiments of this kind are urgently needed to throw light on the mechanism by which such inactivations are brought about in dilute aqueous solutions, particularly in view of their relevance to the biological studies. The influence of ion density on the inactivation of enzyme systems under *in vivo* conditions also awaits investigation.

Ion Density in Relation to the Inactivation of Elementary Biological Units

Perhaps the best understood examples of ion-density dependence are in connection with the direct inactivation of elementary biological units, such as viruses and genes, by the ionization of their constituent atoms. As separate articles of this series are devoted to viruses and genes, a brief reference will suffice.

The distinctive feature of the effects under consideration is that they are produced whenever an ionizing particle leaves two or three ion-pairs anywhere within the unit. It is possible that a single ion-pair suffices, but ion-pairs are, in fact, formed in clusters of 1, 2 or more pairs, the average number being 3 pairs, and rather accurate experiments would be necessary to be certain that the effect is invariably produced by a single ion-pair. Whether this is so or not, it is clear that since each cluster contains an average of 3 ion-pairs, the distance apart of the



●	Tobacco Mosaic Virus	(non-spherical)
○	Tobacco Necrosis Virus	Diam. 25 mμ
×	Tomato Bushy Stunt	Diam. 29 mμ
△	Dysentery Phage S.13	Diam. 16 mμ
+	Coli Phage C.36	Diam. 42 mμ
□	Staph. Phage K	Diam. 64 mμ
Calculated Curves	I for diam. 15 mμ II for diam. 50 mμ	

The experimental points and the calculated curves are based on inactivation doses given by D. E. Lea in *Actions of Radiations on Living Cells* (in press).

FIG. 2. Relative Efficiency of Ionizing Radiations for the Inactivation of Viruses

clusters will be given by $\frac{3}{\Delta}$ micra where Δ is the ion density of the radiation. For gamma rays, $\frac{3}{\Delta}$ is about 300 mμ, for hard X-rays 60 mμ, for soft X-rays 20 mμ, and for alpha rays 0.85 mμ.*

The diameters of the smaller viruses range from 15 to 50 mμ. The relation between the size of the virus and the spacing of the ions is thus roughly that shown in figure 1 for the four radiations mentioned. Even allowing for unevenness in the spacing of the ion clusters, it is evident that only rarely will a single ionizing particle give rise to more than one ion cluster within a virus particle irradiated by gamma rays. As long as this obtains, the chance that a cluster is formed within any given virus particle is just equal to the total number of clusters formed per unit volume of the medium multiplied by the volume of the virus, and, therefore, the inactivation dose should be independent of ion density.

On the other hand, an alpha particle will produce many ion clusters within even the smallest virus particle or gene, so that, if one cluster suffices for inactivation, this radiation must necessarily be inefficient, and a large dose will be needed to produce a given degree of inactivation.

In figure 2, the experimentally determined efficiencies of a number of radiations in inactivating virus preparations are plotted against the mean distance between ion clusters for six virus particles, ranging in size from 16 to 64 mμ.** The theoretical variations for spheres of 15 and 50 mμ diameter are drawn in full. It will be seen that, in accordance with expectation, the experimental values of the efficiency begin to show a dependence on ion density just at the point where the distance between clusters is comparable with the size of the particle.

The relation between inactivation dose and ion density thus

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* The millimicron (mμ) = 1/1,000 micron = 10^{-6} millimeter.

** The term "efficiency of a radiation" will be used throughout this article to mean a quantity inversely proportional to the total amount of ionization per unit volume of tissue required to produce a given biological effect.

provides a very useful approximate estimate of the size of the biological unit in cases where this unit may be inactivated by a single ion cluster. It is interesting to note that, on the basis of such studies, Lea and Salaman [21] put forward the view, before an internal structure was demonstrated by electron micrographs, that vaccinia virus should be regarded as a single-celled organism containing a considerable number of discrete structural units analogous to genes.

The Structural Changes Induced in Chromosomes by Different Types of Ionizing Radiation

The nature of the chromosome structural changes induced by radiation is discussed in detail in another article. Many of these structural changes are known to be injurious and some to be lethal to the daughter cells, and they are produced by relatively low doses of radiation—in the materials studied, the doses employed have rarely exceeded 500 röntgens of X-radiation, or a tenth of this dose of alpha radiation. There can be little doubt, therefore, that they play an important part in the response of many types of cell to radiation, including probably the response of normal and malignant tissue to X-radiation in certain types of radiotherapeutic techniques.[16]

Before considering the influence of the type of radiation on the response of cells, organisms, and tissues, it will be convenient to summarize the information regarding the chromosome structural changes. The production of a chromosome break requires that a particle shall pass through (or in the immediate vicinity of) the chromosome, leaving an adequate number of ions within the chromosome. The exact number of ions required probably varies from one type of cell to another, and may well vary with the stage of development of any one cell. Experimentally, it is found that high ion-density radiations are more effective than low ones in breaking the pollen grain chromosomes of the plant *Tradescantia* at prophase (figure 3), and in fact, it appears that only radiation which produces at least 200 ions per micron of track has a high break-producing

efficiency. Since the diameter of the chromated thread at prophase is about 0.1μ, it is inferred that a break is only likely to follow when at least 20 ions are formed at one locus within the thread. No other material has been analyzed for chromosome structural changes in such detail as *Tradescantia*, but a restricted analysis [22, 23, 24] of the changes produced by X-rays and neutrons in root tips of the broad-bean, the pea, the tomato, three mouse tumors—sarcoma 180, a mammary carcinoma, and a lymphosarcoma—and a carcinoma and lymphosarcoma of the rat, showed

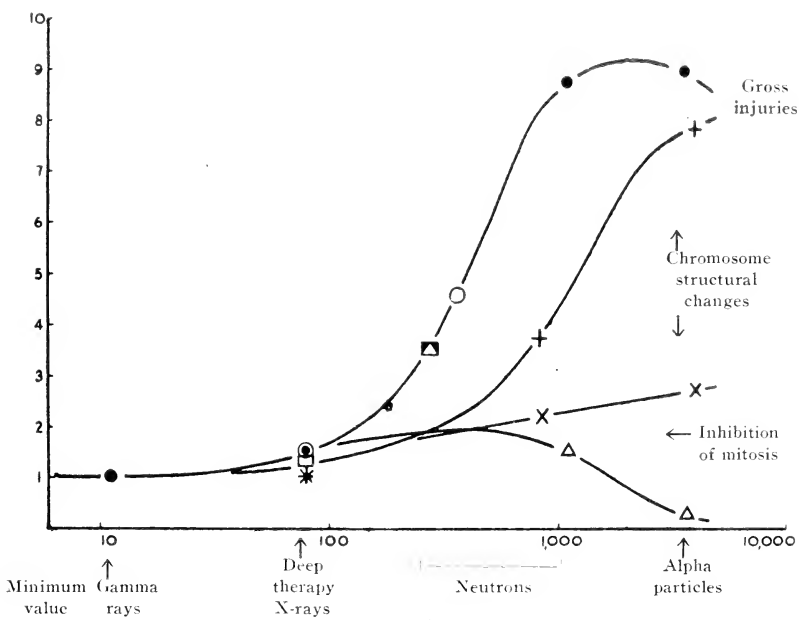

FIG. 3. Relative Efficiencies of Ionizing Radiations

× Chromatid-breaks } Produced in *Tradescantia* pollen-grains by
\+ Isochromatid-breaks } irradiation at prophase.
○ Inhibition of growth of wheat-seedlings.
□ Mouse tumors rendered inviable by irradiation *in vitro*.
● Cessation of growth } *Vicia faba* roots.
△ Temporary inhibition of mitosis }

Abscissae = linear ion density in ions per μ
Ordinates = relative efficiency of radiation

that for all these materials, more structural changes were produced by neutrons than by an equal dose of X-rays, from which we may infer that in all these cases the conditions for break production are of the same general types as those in *Tradescantia*. There is some evidence, on the other hand, that in *Drosophila* sperm, a single ion cluster may suffice.

Since the ion density along an electron track exceeds 200 ions per micron only when its energy is less than 3.5 kilovolts, not only is much of the ionization produced by the more energetic electrons generated by, say 200 kilovolt X-rays, wasted as regards chromosome-break production in *Tradescantia* and similar materials, but any one particle is unlikely to break two chromosomes separated by a distance greater than the range of a 3.5 kilovolt electron, i.e., greater than 0.4 micron.

For this reason, structural changes arising from the interchange of partners between two broken chromosomes almost always involve the action of two separate electrons. It follows that, when the dose is delivered in a short time, the number of such configurations produced will increase as the square of the dose. Furthermore, as the duration over which the total dose is spread is increased, fewer abnormal configurations will be produced because each individual break may reform the original chromosome, and the chance of this happening in preference to an interchange formation increases with the interval between the production of the two breaks. The same restriction does not apply to the recoil protons generated by neutrons or to alpha particles which maintain the required ion density over distances much greater than the diameter of the whole cell. It thus comes about that in *Tradescantia:*

a. Simple breaks produced at any time in the cell cycle, and certain structural changes (the so-called "isochromatid breaks"), arising from the breaking of two sister chromatids lying almost in contact at prophase, increase in proportion to dose, and are independent of the duration of exposure for all radiations. The number produced by a given dose increases with ion density.

b. Structural changes involving two chromosomes, other than the isochromatid breaks referred to in *a*, increase in proportion

to the square of the dose when the exposure time is constant, and decrease with increasing duration of exposure for all types of X-radiation; they increase in proportion to the dose and are independent of the duration of exposure (except in so far as this affects the state of development of the cells irradiated) for neutrons and alpha particles. The more densely ionizing radiations produce more structural changes of this type per unit dose than X-rays when the dose is small, and fewer when it is large.

It is interesting to note that we have here an exception to the general rule that, from the biological standpoint, a radiation may be characterized by its ion density. Very soft X-rays, on account of the limited range of the secondary electrons, do not exactly parallel neutrons, even when the ionizing particles generated by these two radiations have the same average ion density as was demonstrated experimentally by Catcheside and Lea.[3]

c. The ratio of the number of certain types of structural change produced by X-rays to the number produced by an equal dose of neutrons varies with the stage of development of the cell at the time of irradiation.

Comparative Studies with Other Biological Material

Lethal Effect on Drosophila Eggs

Many experiments have been made to determine the proportion of fertilized eggs which hatch after receiving varying doses of radiation. The eggs are usually irradiated about 2 hours after laying, when about 8 mitotic cycles have been completed and the egg contains above a hundred nuclei. The careful observation of Packard[27] showed that a given dose produced the same degree of mortality whatever the quality of the radiation within the X-ray therapeutic range, but this, as we have seen, throws little light on the question of a possible dependence of the efficiency of the radiation on ion density. Packard,[27] Henshaw and Francis,[15] and others, extended the investigations to supervoltage X-rays and gamma rays. It appeared at first that

a rather large dose of radiation was needed to produce a given mortality, but the measurements were carried out at a time when some uncertainty on the physical side was attached to measurements of gamma-ray dose.[25] Packard (1932) extended the measurements in the other direction down to 8 kilovolt X-rays, and concludes that between 8 kilovolts and 1,000 kilovolts, the mortality is independent of X-ray quality. The corresponding range of ion densities is from 150 ions per μ to 15 ions per μ.

The effects of 200 kilovolt X-rays and neutrons ($\Delta = 400$ ions per μ) were compared by Zirkle and Lampe.[39] The mortality curve, as a function of dose, for neutrons had the same shape as that for X-rays, so that the relative effects of the two radiations could be expressed by a single figure which was 0.8 for eggs $1\frac{1}{2}$ hours old, 1.2 for eggs $4\frac{1}{2}$ hours old, and 1.1 for eggs 6 hours old. It is doubtful whether the variation with age is significant, and we conclude that neutrons and X-rays are roughly equally efficient, i.e., that the effect is independent of ion density up to 400 ions per μ.

As was mentioned earlier, there is evidence that, under the conditions prevailing in the sperm, the chromosomes of *Drosophila* may be broken by an ionizing particle which leaves only one or two ion clusters within the chromosome thread. If the same is true of the chromosomes in the egg, then the fact that the mortality does not depend on ion density over the range investigated would out exclude chromosome structural changes as a possible origin of the lethal effect of the radiation. It would be of great interest to investigate the effect of a further tenfold increase in ion density by the use of alpha radiation.

Lethal and Sublethal Effects on Root Tips, Particularly of Vicia faba

The meristematic cells in the shoot and root tips of organisms are very sensitive to radiation, and the damage caused by 200 to 1,000 röntgens of X-radiation will lead to the death of a variety of roots. In passing from gamma radiation ($\Delta = 11$ ions

per μ) to X-radiation ($\Delta = 80$ ions per μ), the efficiency of the radiation has generally been found to increase by about 50%.

Zirkle and Lampe[39] compared the inhibition of growth of both the shoot and root of wheat seedlings, when irradiated by neutrons, for which $\Delta = 400$ ions per μ, with that produced by X-rays ($\Delta = 80$ ions per μ). The neutron radiation was about 3 times as efficient as the X-radiation, making a total increase in efficiency of 4.5 as the ion density is raised from 11 to 400 ions per μ. Very similar results were obtained by Gray, Read and Mottram,[12] who investigated the lethal effect of gamma rays, X-rays, neutrons, and alpha particles on the roots of *Vicia faba*. Their results are shown in figure 3. The wheat seedling results fall almost on the same curve.

The primary injury is evidently very sensitive to changes in ion density over the range 100 to 1,000 ions per micron. This is just the region of ion density in which, as we have already seen, there is a rapid increase in the efficiency of ionizing particles in breaking the chromosomes of a variety of materials including *Vicia faba*. Experimental data for two types of chromosome break observed in *Tradescantia* pollen are also shown in figure 3, since corresponding data for *Vicia faba* are not yet available. The trend of one of the curves is similar, suggesting that the inhibition of growth may arise from chromosome structural changes produced in the meristematic cells.

This hypothesis has been tested in a variety of ways, one of which is of special interest from the point of view of ion-density studies (Gray and Scholes, unpublished). It will be recalled that, whereas some types of structural change require the joint action of two ionizing particles when produced by X-rays, and, therefore, increase as the square of the dose and decrease with duration of exposure, all types produced by alpha particles increase in direct proportion to the dose and are independent of duration of exposure. Methods have been evolved of estimating the proportion of cells in the root tip which are injured by exposure to lethal and sublethal doses of radiation, and it has been found that this proportion does, in fact, increase linearly with dose in the case of alpha radiation, and is not

diminished by prolonging the exposure time even up to 24 hours, while with X-rays the proportion increases more rapidly than the first power of the dose, and in the case of the larger doses falls markedly as the exposure time is increased from a few minutes to 4 hours. This interrelation between the influence of ion density and duration of exposure is likely to be found also when the effects of neutrons and X-rays are compared. It is interesting to note that the curve for the temporary inhibition of mitosis in *Vicia faba* follows an entirely different course, showing that in this material, certain disturbances in the mitotic function must be traced to a different primary injury from that which leads ultimately to the death of the root.

Animal Embryonic Tissue and Tumor Tissue

The immediate effects of a variety of radiations, from heavily filtered gamma rays to neutrons, on the mitotic activity of chick-embryo fibroblasts cultured *in vitro* have been the subject of many investigations, starting with those of Strangeways, and continued mainly by Spear and his collaborators.[2, 9, 19] Spear and Grimmett [33] found a marked influence of the hardness of the gamma rays employed which, if real, would indicate an unusually rapid increase of efficiency with ion density in the region of 10 ions per micron, since the extreme variation of ion density in their experiments could only have been about 30%. The efficiency continues to increase with ion density, but more slowly until the X-ray region is reached ($\Delta = 80$ ions per micron), after which there is little if any further increase up to 1,000 ions per micron.

In its general features, the course of the curve, therefore, closely resembles that for the inhibition of mitosis in root tips, but no data are available to show whether the curve falls at ion densities above 1,000 ions per μ, as is the case with *Vicia faba*.

Many experiments by the Strangeways Laboratory team have shown that the effect of radiation on mitosis is essentially the same under *in vivo* as under *in vitro* conditions. In particular, Spear and Tansley [34] found that, as in the tissue-culture experi-

ments with chick-embryo fibroblasts, the immediate effect of neutrons on the mitotic activity of the developing rat retina was approximately the same as that of an equal dose of X-radiation. There are certain differences in the subsequent return of mitotic activity, but these may be bound up with the markedly greater efficiency of neutrons in causing cell degeneration.

Not only was much more cell degeneration produced in the rat retina by neutrons than by an equal dose of gamma radiation, but the degenerate cells appeared much earlier. This may indicate that cell degeneration follows a different course according to the radiation which causes the primary injury.

The effects of various radiations have been compared in regard to their ability to injure tumor tissue by irradiation *in vitro* in such a way that it does not "take" when inoculated into test animals. It appears to be established, particularly by the careful experiments of Sugiura (1939), working with mouse tumors, that X-radiation is about 50% more effective than gamma radiation. The experiments were extended [1] to neutron radiation of ion density about 300 ions per μ. The relative efficiencies of neutrons and X-rays, as tested on a lymphosarcoma, a lymphoma, and a carcinoma of the mouse, were 3, 2.3, and 2.4 respectively. When these data are taken in conjunction with Sugiura's, we find that the ion density curve (figure 3) follows closely the course of the curve for the lethal effect on root tips. Experiments at higher ion density are much needed.

Gray, Mottram, and Read (unpublished) carried out *in vivo* irradiations of inoculated mouse tumors, using neutron and gamma radiation. The neutron radiation appeared to be some 15 times as efficient as gamma radiation. In comparing this result with the *in vitro* studies already mentioned, we have to note first that the neutron ion densities were much higher in the *in vivo* experiments ($\Delta = 1{,}100$ ions per μ), and, secondly, that the influence of ion density and duration of exposure may be interconnected. The gamma ray and neutron exposures were of equal duration (3 hours), but the time may have been such that the effect of the gamma radiation, but not of the neutron radia-

tion, was thereby diminished compared with a very short exposure.

Mouse tumor tissue has also been irradiated by the very densely ionizing particles resulting from the disintegration of boron or lithium by slow neutrons. Very great technical difficulties were encountered in obtaining quantitative results in the *in vivo* experiments. An effect of the disintegration particles was clearly demonstrated in the *in vitro* experiments,[17] though it was not possible to estimate their efficiency relative to other ionizing radiations.

Neutron Therapy

In 1942, Stone and Larkin [36] reported upon 92 patients suffering from malignant disease who had been treated by neutrons. With regard to the clinical results, it is best to quote Stone's [35] views:

"It is difficult, in discussion of effects of a method of treatment tried almost entirely on patients with far advanced cancer, to convey any adequate idea of what actually takes place during the course of treatment. While the survival statistics presented and the autopsy findings reported appear discouraging, the general impression of one watching the patients being treated is that marked tumor regressions are being produced even when they were not expected. In many instances, large metastatic nodal involvements disappeared, showing a remarkable effect of the neutron rays on the tumors. The patients as a whole did not react so well, either because the tumor had spread beyond the treated regions and was not controllable for that reason, or because a debilitating ulcer remained at the site of the primary node. In many instances, biopsies from the edges of persisting ulcers did not show evidence of cancer, but because of either the extensive destruction caused by the cancer or the irreparable damage caused by the neutron rays, normal tissues would not react in such a way as to bring about the healing of the ulcer."

Skin reactions to neutron radiation followed the same general course as after X-radiation. Considerably smaller doses of

neutron radiation were needed to produce a given degree of skin reaction, and one may say roughly that the efficiency of neutrons in this respect appears about 2.5 times as great as X-rays. It is important to emphasize, however, that, as in X-ray therapy, the total dose was delivered in a large number of fractions spread over about 3 weeks, and until the influence of fractionation on the effects of both types of radiation has been fully investigated, a figure representing their apparent relative effectiveness gives little guide as to the nature of the processes involved.[8] It is at least clear, however, that both skin response and tumor response belong to the class of reactions in which, proceeding from gamma rays to neutrons, the effectiveness increases with increasing ion density. It has been pointed out [10] that, insofar as more favorable tumor response has been obtained with neutrons than with X-rays, this may be taken to indicate that the curve (figure 3) for tumor response is rising more rapidly than that for skin-damage. A further improvement might therefore be expected by the use of less energetic (greater ion density) neutrons, and advantage might be taken of the fall in the average energy of a neutron beam on passing into the body to increase the damage to the tumor relative to that to the skin.

Such an advantage, however, falls into the same class as the technical improvement offered by the increased depth-dose obtained with high-voltage X-ray tubes and betatrons. At best, they enable the therapist to deliver any desired dose of radiation to a mass of tissue which completely envelops all the malignant cells. There remains the problem of discriminating between two adjacent cells in such a manner as to destroy either the malignant character of the tumor cell or the cell itself, without destroying all its healthy neighbors. Such discriminations must be based ultimately on a biological difference between the two cells. Differences in matabolism, chromosome structure, and rate of development, are known to exist, and these differences, as we have seen, profoundly affect the manner in which the various functions of a cell are influenced by radiations of differing ion density. It would seem that a fuller investigation of

these differences may reveal improved methods of obtaining the desired discrimination.

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GENETIC EFFECTS OF RADIATIONS

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Introduction

GENETICS is concerned with the mechanism of heredity, with the reasons why offspring resemble their parents and in some cases differ from them. The characters of the human body, or of any other organism, are controlled by genes present in every cell. The genes are passed from parent to offspring in the gametes. They are situated in and largely, if not wholly, constitute the chromosomes, of which there is a fixed number in a given kind of organism. The gametes contain a haploid set (n), the zygote and body cells a diploid set (2n) of chromosomes. Thus each chromosome or homologue is represented once in the gamete and twice in a body cell.

Each gene occupies a fixed position (locus) in its particular chromosome of the haploid set. The gene present at a given locus may not always be exactly the same one, but may be replaced by a slightly different one, called an allelomorph (or allel). Thus, at a particular genetic locus in two homologous chromosomes, a given body cell may possess the same allelomorphic gene and be homozygous, or may possess two different allelomorphs and be heterozygous. The number of allelomorphs of a given gene is not limited. Thus 4 allelomorphs controlling the AB blood group series are recognized in man, about 20 allelomorphs of the *w* (white eye) series in the fruit-fly *Drosophila melanogaster*, and between 40 and 50 allelomorphs of the gene concerned with incompatibility reactions of pollen grains to style in certain self-sterile flowering

plants. However, in a normal diploid organism no more than 2 allelomorphs of a gene may be present together in the same individual. Moreover, each of the gametes produced by a given individual will contain only one allelomorph and, where the individual is heterozygous, half its gametes will possess one allelomorph and half the other. For example, the rare nervous disease Huntington's chorea is transmitted, on the average, to half the affected person's children. The particular genes of the affected persons may be symbolized as *H* for the abnormal gene responsible for the manifestation of the disease and *h* for its normal allelomorph. The affected person would be *Hh* and his (or her) gametes half *H* and half *h*. Since the disease is so rare, the spouse would normally be *hh* and the children therefore, on an average, half *Hh* (capable of developing the disease) and the other half *hh* (normal).

The gene, *H*, for Huntington's chorea is usually spoken of as being dominant to the normal gene *h* which is recessive. In fact, the term dominant implies that there is no difference in the appearance (phenotype) of *HH* and *Hh* individuals. In man this particular information is lacking, so the use of the term "dominant" in this connection is convenient rather than correct. Probably a majority of genes producing abnormalities in man are strictly recessive, the homozygous and heterozygous normals being alike, or else intermediate in their dominance, the heterzygous being more like the homozygous normals than the homozygous abnormals, which may be very extreme in their character.

Gene segregation is orderly and dependent upon the regular pairing together and separation of the chromosomes at meiosis. This precedes gamete formation and is constituted by two special nuclear divisions, in the course of which the number of chromosomes contributed to the daughter nuclei becomes half that in the parent nucleus. The orderliness is such that each daughter nucleus receives one each of the n different homologous chromosomes. Moreover, in any particular gamete, a given homologue may be compounded of complementary parts of the two homologues present in the parent. Thus, a parent which in one of a

pair of homologous chromosomes has the genes A B c d e F g H and in the other the genes a b C d E f g h, may produce gametes which possess for example A B c d E f g h or a b C d E F g H as well as chromosomes like one or other parental homologue. This orderly rearrangement comes about by crossing over during meiosis, the relative frequency of rearrangement occurring between two particular genes being a measure, technically known as the linkage value, of their distance apart on the chromosome. All the genes or loci present in one chromosome together constitute one linkage group, the number of possible groups in an organism being equal to the haploid number of chromosomes. For a further account of genetics particularly in relation to man the reader is referred to Ford.[9]

Stability of Chromosomes and Genes

Apart from the process of crossing over, whereby the chromosomes may recombine their differences, the chromosomes are highly stable structures. However, changes do occur very rarely, resulting in alterations in the linear order of the genes within one chromosome or linkage group, or exchange of blocks of genes between two non-homologous chromosomes or linkage groups. The frequency of these structural changes, spontaneously very rare, is greatly increased by various radiations. Similarly the genes themselves also possess a high degree of stability. They have a capacity of self-reproduction which is one of the most important characteristics of living matter. All the evidence indicates that they reproduce exactly, and that, if any change occurs within one of them, the gene reproduces in its changed form.

Changes in genes do occur spontaneously, but usually the frequency of such mutations is very small. The normal frequency is of the order of one change per million genes per nuclear division cycle, and may be smaller even than this for a great many genes. A few genes are highly mutable, with a rate of about one per thousand or ten thousand genes per nuclear cycle.[5] There is, however, no indication that they are fundamentally

different from the stable genes, and probably there is no discontinuous range in mutation frequency.

The stability is very little affected by ordinary environmental fluctuations, temperature being the most potent of such influences. A 10° C. rise in temperature will increase the rate of mutation about five times.[39] Thus the principal hereditary material, the chromosomes and genes of which they are constituted, is distinguished by a remarkable stability of minute structure, both as regards the constituent particles, the genes, and the way in which these are ordered and bound togeher to form chromosomes.

The significant genetic effects of radiations are that gene mutations and chromosome structural changes become much more frequent under their influence. The order of increase over spontaneous changes is a hundredfold for quite moderate doses of X-rays. The chief biological interest lies in the possibilities of studying the nature of the mutation process and, by extension, of the gene itself, and also of the manner in which the genes are tied together to form chromosomes. With the help of radiations, experiments can be carried out which, if dependent on spontaneous mutation alone, would be almost impossible.

Medically, the importance lies firstly in the fact that most mutations are recessive and deleterious and, therefore, that deep radiotherapy may run the risk of producing mutations in the gonads. The mutations may be transmitted to the treated person's children and spread undetected in the population in which, generations later, homozygous defective individuals may arise. The genetic change is immediate but the physiological consequences are delayed. Secondly, many kinds of induced chromosome structural change are lethal to all cells in which they are produced, and it is this property, among others, of radiations that renders them effective in killing unwanted tissues such as cancers.

Apart from radiations, only a few agents have been found capable of greatly enhancing mutation rates. The most effective are certain synthetic chemicals, the naturally-occurring mustard oil, allyl isothiocyanate,[1] and antibodies.[8]

Most researches on the genetic effects of radiations have been confined to a few organisms that are technically favorable from the point of view of ease in handling the large numbers of individuals needed in controlled experiments. The principal ones are the fly *Drosophila melanogaster*, maize, and some fungi such as *Neurospora*, together with the flowering plant, *Tradescantia*, for chromosome studies.

Radiation-induced Mutation in Drosophila

When adult male flies are exposed to radiations and subsequently mated to untreated virgin females, a proportion of the eggs laid fail to hatch although they have been fertilized. The premature death of the individual is ascribed to the induction of a dominant lethal mutation in the sperm. The existence of such mutations was first proved by Muller,[20] who showed that their "number was so great that thorough egg counts and effects on the sex-ratio evidence could be obtained from them *en masse*." At moderate doses,[3, 7] the graph relating the logarithm of the percentage of eggs reaching the larval or adult stages to the dose is a linear one. Above 4,000 r the gradient becomes steeper, suggesting that a mixture of "single-hit" and "multiple-hit" effects contributes to the total yield of dominant lethals. The predominant contribution, particularly in the lower dose-range, is single-hit, and dominant lethals involving more than one hit, and so increasing more rapidly than the first power of the dose, become important only at higher doses (figure 1, A).

The occurrence of dominant lethals is expressed also in the sex ratio, i.e., the proportion of females relative to males hatching from a batch of eggs. As the X-ray dose increases, the sex ratio declines (figure 1, B), owing to the extra probability of a dominant lethal being induced in an X-chromosome-bearing sperm as compared with a Y-chromosome-bearing sperm exposed to the same dose. The female-producing X-chromosome is a little larger than the male-producing Y-chromosome, and so presents a larger target in which the dominant lethals may be induced.

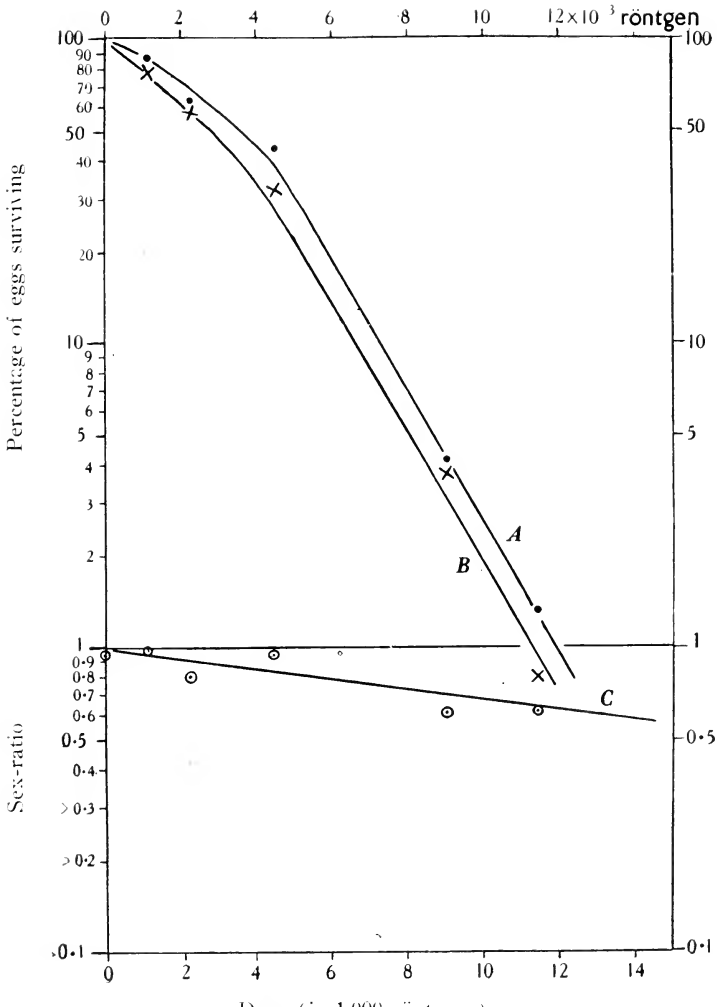

FIG. 1. Relation of frequency of dominant lethals produced in sperm to dose of X-rays employed. A = percentage of eggs hatching; B = percentage of eggs producing adult flies; C = sex ratio. In each case the logarithm of the frequency is plotted against dose; points experimental. Reproduced from Catcheside & Lea [3] by kind permission of the Editor of the *Journal of Genetics*.

Discussion of the nature of the dominant lethals is deferred, except to indicate that the change in the heredity material does not produce an immediate effect. Eggs which fail to hatch are found to have undergone a number of nuclear divisions before breakdown occurs.[30]

Among the viable offspring of treated male flies, a number carry mutations. The great majority of these are recessive, and so do not produce any visible effect immediately, since they are heterozygous. Special measures have to be taken to obtain individuals homozygous for such mutations. The simplest are those for detection of mutations in the X-chromosome, a sex chromosome that is present twice in the female flies and once only in the males. It crosses and recrosses in heredity in a regular fashion from father to daughter and mother to son. Thus, males will be hemi-zygous for genes in the X-chromosome, and so will manifest them.

Treated male parents are mated to *C l B* females,[21] one of whose X-chromosomes carries a cross-over suppressor (*C*, actually an inversion), a recessive lethal (*l*), and a dominant marker-gene (*B*, Bar-eye, which is narrower than the normal round eye). Among the offspring, females with a Bar-eye are chosen and mated individually with any suitable males, preferably with their X-chromsomes suitably marked with recessive genes. Any one of these F_1 females will have a treated X-chromosome from her father and a *C l B* chromosome from her mother. The *C l B* chromosome will be lethal to male offspring carrying it, so all male offspring of F_1 females will carry only treated X-chromosomes from their grandfathers. Inspection of these males will disclose genes having a visible effect, though their detection will depend on the skill and experience of the observer. On the other hand, if a recessive mutation is lethal, the culture containing it will be marked by a complete lack of male offspring. Such sex-linked lethals are produced by radiations about ten times as frequently as visible mutations. They provide an objective criterion for quantitative work, and have been widely used in experimental studies on mutation-rates. The recessive lethals, of course, represent mutations at a large number of different loci,

and the grouping together of such a heterogeneous group is justified mainly by the convenience of their frequency.

When viable recessive mutations are to be studied, the attached-X method may be adopted. In this case, the treated male is mated to an attached-X female, whose two X-chromosomes are joined together and so are segregated together at gamete formation. Her eggs will be of two kinds, one with two X-chromosomes, and therefore female-producing, and the other without any X-chromosomes. The latter, with an X-bearing sperm from the irradiated father, will produce a male in which any visible mutation in the treated X-chromosome could be detected.

These techniques, and others like them, are simple but enormously laborious, since the mutation-rates involved are small even for fairly large doses of X-rays. Nevertheless, many facts about the mutation process are well established. In the first place, the mutations induced by radiations do not differ qualitatively from those occurring spontaneously. In both cases, too, the mutation rate differs from one locus to another, and from one allelomorph to another at the same locus.[36, 37] It can be concluded that the genes differ among themselves in stability, the less stable ones undergoing the more frequent mutation. An important point to note is that the radiation cannot determine what particular mutation is produced. Which gene is activated and what allelomorph is finally formed is a matter of chance. The former depends upon the chance of the target, the gene, being hit, and the latter upon the innate characteristics of the individual locus; in particular, apparently, upon the relative stabilities of the different allelomorphs.[28]

Further, a given gene *A* may be changed to the allelomorph *a*, and the latter on being irradiated changed back to *A*. Such back-mutations, demonstrated first by Timoféeff-Ressovsky,[34, 35] are important in showing that whatever change is involved in the conversion of *A* to *a* cannot be a loss that may not be restored with relative ease.

The quantitative relationship between the mutation rate and the radiation dosage, intensity, wave length, etc., has been

determined satisfactorily only for the group of recessive sex-linked lethals, though sufficient has been done with visible recessive mutations and with mutation in other organisms to suggest that the results are characteristic. First of all, however, it should be mentioned that the natural mutation rate in *Drosophila melanogaster* (measured by sex-linked lethals) increases with the age of the tissue tested and with the temperature at which it is kept. Further, it differs from stock to stock and in a few cases may be relatively high. Thus, Demerec [6] found that the Florida stock gave about 1% of sex-linked lethals, the average of all other stocks being about 0.1%. This he found to be due to a recessive gene, located on the second chromosome, which raised the general mutation rate of all the genes in the organism. This behavior is to be contrasted with the case found by Rhoades [23] in maize, where the gene *Dt* increases the mutation rate only of the gene a_1.

The mutation rate induced by X-rays is found to be linearly proportional to the dosage. The frequency of sex-linked lethals induced in *Drosophila* sperm is about 3% per 1,000 r.[28] This rate is independent of the wave length of the radiation throughout the gamma ray and X-ray range up to a wave length of 2.6 Å. It is independent of the time occupied by the irradiation, i.e., is independent of intensity down to the lowest tested (0.07 r per minute) and of whether the dose is fractionated or given in one exposure. Lastly, it is unaffected by temperature and is probably independent of the natural mutation rate of the particular stock employed. Timoféeff-Ressovsky [38] should be consulted for full details.

These facts indicate that the induced mutations must be due in quite a direct manner to a single ionization excited in a sensitive volume which may be the gene itself or include the gene or some part of it.[39] The ionization adds considerable energy to the affected gene, and the excited molecule, rendered temporarily unstable, is enabled to slip from one relatively stable chemical state to another. What the precise change may be is unknown, but any change in the gene molecule may be expected to alter the properties of the whole gene and so to be disclosed

as a mutation. A simple account of the physical principles involved is given by Schrödinger.[27] Probably not all changes provisionally classed as gene mutations are intramolecular, but the further consideration of this matter must be left until the grosser effects of radiations on the chromosomes have been described.

Estimates of the sizes and of the number of genes may be derived from mutation data. The best estimates are probably those derived [13, 16, 17] from a comparison of the mutation rates induced by X-rays and neutrons. These two radiations differ considerably in their relative efficiency in producing sex-linked lethals, the ratio being about 1.6:1 for X-rays: neutrons for a given dose measured in terms of ionizations.[40] This leads to an estimated volume of a single gene of about 2.8×10^{-20} cubic centimeters, containing about 1,000 atoms, and to there being about 1,860 genes in the X-chromosomes of *Drosophila,* each capable of giving X-linked recessive lethals.

Induced Chromosome Aberrations

The chromosomes in a body cell pass through a cycle of division, mitosis, whereby two nuclei, each an exact reproduction of the parent nucleus, are produced. Before prophase, i.e., in the resting stage, each chromosome divides lengthwise into two chromatids, except at the centromere, and during prophase each assumes a condensed spiral form and becomes coated with nucleic acid. At metaphase, each chromosome moves on the spindle so that the centromeres come to lie in the equatorial plane. At anaphase, each centromere divides, the two halves each with their attached chromatid then moving to opposite poles of the spindle. A new nucleus is then organized at telophase from each of the two groups of daughter chromosomes.

Radiations affect the different stages in various ways. A lengthening of the nuclear-division cycle may be caused, especially by heavier doses. A further physiological effect, shown by adhesion or clumping of the chromosomes, occurs in cells already in division at the time of irradiation.[12, 19] With large doses, excessive clumping may prevent the completion of mitosis.

Nuclei at resting, or early prophase, stages at the time of irradiation, although delayed in division, recover and show no adhesive tendency when they reach metaphase. Instead, they may show structural changes. These are due to the production of breaks in the chromosomes, which may be followed by the formation of structural rearrangements resulting from the recombination of the breakage ends in various ways. This subject has recently been reviewed [2] and space permits the description of only some of the manifold changes. The descriptions refer to the appearance of the affected chromosomes at the metaphase of the division cycle in which the changes are induced.

Structural changes are of two kinds: *chromosome,* where both the chromatids are similarly affected and *chromatid,* where only one of the two chromatids is affected at a given place. The former are normally produced by irradiation during the resting stage, at which time the chromosomes are simple undivided threads. The latter are produced by treatment at the early prophase, when the chromosomes are divided into two chromatids. In flowering plants, the pollen grains in a given anther and bud develop approximately synchronously. In *Tradescantia,* for example, at 20° C the division cycle, including a prolonged resting stage, occupies about 10 days, all the grains in one anther reaching metaphase within a period of less than 24 hours. The material is thus convenient for radiation work in providing a group of cells all approximately at the same stage of mitosis. Chromosome division occurs about 30 hours before metaphase. A change from chromatid to chromosome structural changes is shown by metaphases observed respectively less than, and more than, 30 hours after exposure of pollen grains to radiations.

Other convenient material is provided by germinating pollen grains on an artificial medium, and using the nuclear division that takes place in the very thin pollen tube, 7μ in diameter. This is especially valuable where soft, weakly penetrating radiations must be studied.

Radiations produce breaks in the chromosomes, and the breaks suffer various fates (figure 2). A large proportion, estimated at 90%, undergo restitution, the two fragment chromosomes

rejoining in the original way so that no permanent effect can be seen.[15, 24] This restitution is a matter of inference from intensity experiments to be mentioned later. A further proportion of breaks undergo reunion in new ways. Thus, two breaks, one each in two different chromosomes in the same nucleus, would produce four fragments A_1, A_0, B_1, B_0. Two of them (A_1 and B_1) have centromeres and two (A_0 and B_0) are without these bodies. Reunion in a new way to produce interchanges could be symmetrical, producing two new viable chromosomes A_1-B_0 and B_1-A_0, each with one centromere; or could be asymmetrical, producing two defective chromosomes, one (A_1-B_1) having two centromeres and the other (A_0-B_0) having none. Similarly, two breaks within one chromosome could produce symmetrical changes (inversions, cf. figure 5)* or defective (ring or deficient rod) asymmetrical changes. The defective chromosomes are not permanently functional, since a chromosome without a centromere is inert on the spindle (figure 3*b*),* while in one with two centromeres there is a complete lack of coordination of the two kinetic bodies. The inertness leads to loss of parts of chromosomes from the daughter nuclei and, if this entails the loss of vital genes, the nuclei die. The noncoordination of two centromeres leads to chromosome bridges at anaphase, and ultimately to breakdown and death of the cells. Causes of this type are responsible for those dominant lethals, referred to earlier, that are dependent upon two or more hits.

A final proportion of the original breaks neither restitute nor undergo reunion in new ways, but instead remain open as chromosome breaks, the chromosome being present as two fragments, one centric and the other acentric. In some cases the pairs of sister chromatid ends may undergo sister union (figure 4*a*),* and in other cases not. Where sister union occurs in the centric fragment, a bridge would be formed at anaphase (figure 3*a*), leading ultimately to cell death. Single chromosome breaks, exhibiting sister union, account for the major proportion of dominant lethals, namely for those proportional in frequency to the first power of the radiation dose.[16, 17, 22]

* Figs. 3 to 5 are on p. 104 and 105.

Chromatid breaks produce a series of analogous chromatid structural changes (simple chromatid breaks are shown in figure 4*b*,* and a chromatid interchange in figure 3*c*),* some of which are defective, leading to death, and others of which are fully functional and viable. In general, a functional nucleus must have a full complement of genes, and each chromosome must be rod shaped and have just one centromere. This is not strictly true, since very small deficiencies (absences of one or a few genes) may be viable. Thus, a proportion of the recessive lethals induced in *Drosophila* sperm are actually small deficiencies, as is disclosed by examination of the giant salivary-gland chromosomes.[29]

The yield of persistent chromosome breaks and chromatid breaks is linearly proportional to dose in the case of X-rays,[25, 26, 33] e.g., neutrons,[10, 33] and alpha rays (Kotval and Gray, unpublished). The yield is also independent of the radiation intensity.[4, 25] Therefore, simple breaks are products of single radiation hits.

The yields of interchanges and other two-break aberrations produced by X-rays diminish with increase of the time over which the irradiation is spread, i.e., with decreasing intensity. These two-break aberrations also increase more rapidly than the first power of the dose. With high intensities, the yields are practically proportional to the square of the dose; at lower intensities, the power of the dose is lowered.[26] A square law is also found if the dose is varied by varying the intensity at a constant exposure time. These facts are readily explicable if the two breaks are produced by separate ionizing particles. However, the effects may be distorted by restitution of breaks, unless the irradiation is completed in a short time or the irradiation extends over the same time at all doses. The data also may be employed to show [15] that the mean life of an original break in a *Tradescantia* chromosome is about 4 minutes at 20° C. At lower temperatures, its life is probably longer.

With neutrons, the yield of interchanges is independent of the time over which a given dose is spread, i.e., of the intensity, suggesting that a single ionizing particle usually causes both the breaks in the neutron-induced interchanges.[11] In agreement

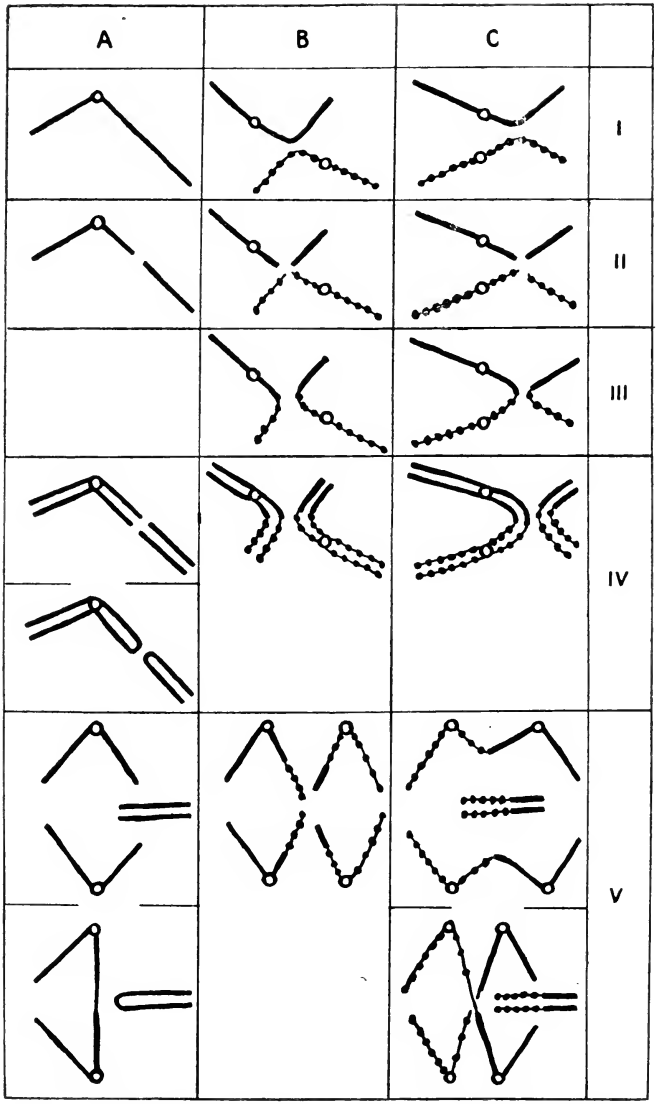

FIG. 2. Diagrams of the Mode of Production of Some Chromosome Structural Changes

A: Chromosome break B: Symmetrical interchange C: Asymmetrical interchange
I: Unbroken; II: Broken; III: Reunion;
IV: Metaphase configuration; V: Anaphase configuration.

with this inference is the fact that the yield of neutron-induced interchanges increases in linear proportion to dose.[10, 11, 33]

X-rays ionize by means of electrons, the ionizations in a path being in clusters spaced apart, except very near the end of the path where the electron has lost most of its energy. Neutrons ionize by means of protons, the ionizations in the path forming a dense column. For a given dose, depending upon the X-ray wave length and the neutron energy respectively, about ten to twenty times as many electrons as protons would traverse a nucleus. It is for this reason that, at the low dosages normally employed, neutron-induced interchanges are predominantly one-hit, while X-ray-induced interchanges are predominantly two-hit.

Providing that X-ray doses are measured in röntgen units and neutron doses in *r*-units, units which represent approximately equal energy dissipations in tissue, the ratio of the yields of chromosome aberrations for equal doses of the two radiations may be taken to be the ratio of the efficiency per ionization of the densely ionizing particles (protons) in neutron experiments to that of the less densely ionizing particles (electrons) in X-ray experiments. This ratio is about 2 to 4 for chromatid breaks and chromosome breaks in *Tradescantia* pollen grains.

The X-ray and neutron data taken together may be used to derive an estimate of the distance apart, at the moment of breakage, of breaks which exchange. The order of magnitude is 1μ,[15] and this estimate agrees with those based on other data.[2, 14]

It has already been seen that a *Tradescantia* chromosome can be broken by a single ionizing particle. If a single ionization were the causative agent, the efficiency per unit dose should be less for neutrons than for X-rays, since those ionizations in excess of the minimum needed to break the chromosome would be wasted. But neutrons are more efficient and this indicates that several ionizations are usually needed to break a chromosome. The probability of a chromosome being broken when a proton traverses it is fairly high, most likely between 0.5 and unity. On the other hand, the probability of breakage by an electron is rather low for all of its path except the last densely

ionized quarter-micron.[15] It has been estimated that 15 to 20 ionizations represent the minimum amount of energy which, dissipated in a chromosome, is sufficient for the probability of breakage to approach unity. It should be emphasized that these numerical values refer to *Tradescantia* chromosomes, and that quite different values may characterize the chromosomes of other organisms.

From a genetical point of view, the use for therapeutic purposes of neutrons and similar radiations with densely ionized paths instead of gamma rays and X-rays, is to be favored, for the following reasons. For a given dose, neutrons are more efficient in the production of chromosome structural changes that will lead to the death of the cells and tissues, while they are less efficient in the production of gene mutations which, produced in gonads, could be harmful to future generations.

Finally, reference should be made to ultraviolet radiations. These can cause excitation but not ionization, i.e., they can introduce into genes or chromosomes at one time only a small amount of energy compared with that which may be introduced by X-rays. Ultraviolet radiations produce the usual range of gene mutations,[18, 31] the rate being directly proportional to the dose. The shorter wave lengths, notably those between 2,500 and 3,000 Å approximately, are considerably more effective than slightly longer wave lengths. The ultraviolet is also able to produce chromosome breaks, although with a remarkably low efficiency;[32] however, there is no certain evidence that interchanges or other two-break aberrations can be produced. From a genetic point of view, the ultraviolet can be extremely useful in providing mutations free from chromosome structural changes, always provided of course that the objects to be treated are small enough to be capable of penetration by the rays.

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THE ACTION OF RADIATIONS ON VIRUSES AND BACTERIA

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Introduction

THE viruses are parasites of bacteria, plants, or animals, characterized by their small size and their inability to multiply except in or on the living cells of the appropriate host. The larger viruses, such as vaccinia, are probably correctly regarded as single-celled organisms. The smallest viruses are nucleoproteins, capable of being concentrated and purified by the methods of protein chemistry, and in some cases obtainable in a crystalline form. It is evidently not correct to regard these small viruses as cells. From a biological standpoint, they may be thought of as naked genes.[15] From a chemical standpoint, they are to be thought of as large molecules *(macromolecules)* of molecular weight 1 to 100 millions.

Thus, one may expect to find analogies between the mechanism of action of radiations on viruses (at any rate in the case of the smallest viruses), and chemical effects of radiation, and we shall therefore recall the outstanding conclusions of the study of the chemical effects of radiation.[1, 7]

Chemical Effects of Radiation

If a chemical substance is irradiated in the pure state by X-rays or alpha rays, the typical result is that approximately one molecule is decomposed for each ionization produced. It appears that the ionization of an atom usually leads to the decomposition of the molecule of which it is a part, a result

which is not unexpected in view of the fact that the energy involved in ionization exceeds the binding energy of an atom in a molecule. This (approximate) result has been established for substances in the solid, liquid, and gaseous states, and for substances ranging in molecular weight from about 20 to about 20,000. There are some notable exceptions, but these are probably to be explained on the basis, on the one hand, of recombination of the products of decomposition giving low yields, or, on the other hand, of chain reactions giving enhanced yields.

Many substances undergo chemical change when irradiated in dilute aqueous solution. Among inorganic solutes, reducing agents are oxidized, and oxidizing agents are reduced, while organic solutes are usually eventually converted to CO_2 and hydrogen. These reactions in dilute aqueous solution take place with doses of radiation much smaller than would be necessary to produce the same percentage chemical change in the solute if irradiated dry, and the number of solute molecules reacting greatly exceeds the number of solute molecules directly ionized by the radiation. Evidently, the ionization of the water is able to lead to chemical change in the solute, and it is believed [16] that the explanation lies in the production of free H atoms and OH radicals following the ionization of the water.

Inactivation of Viruses

Both the direct action of radiation, i.e., chemical change due to ionization in the molecule concerned, and the indirect action, i.e., chemical change in the solute molecules due to ionization in the solvent, have been demonstrated in studies of the inactivation of viruses by X-rays. Thus, in figure 1,[13] it is shown that in sufficiently concentrated solution, the dose required to inactivate a given percentage of a virus is independent of the concentration of the solution, indicating that in such solutions the direct action is predominant, but that in sufficiently dilute solutions, the dose required to inactivate a given percentage of virus diminishes, showing that in dilute solution, the indirect action predominates.

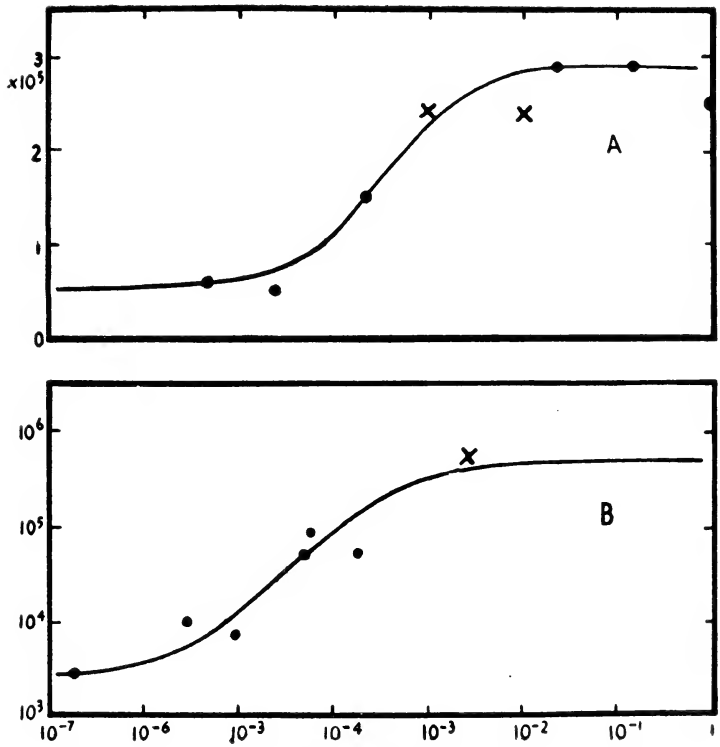

FIG 1. Inactivation of Viruses in Aqueous Suspension by X-rays

Abscissae = concentration of solution in grams per milliliter.
Ordinates = inactivation doses in röntgens.
A. Tobacco mosaic virus.[13]
B. Shope rabbit papilloma virus.[4]

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Macromolecular Viruses

The study of the direct inactivation of viruses has so far yielded results of greater interest than the study of the indirect action, and we, therefore, confine our subsequent discussion to the direct action. If, on the basis of the results of chemical experiments already mentioned, we are prepared to accept that, in the cases

of the macromolecular viruses, every virus particle ionized is inactivated, we are able to use radiation experiments to estimate the size of the virus particle.

Suppose that D röntgens is the dose which produces an average of one ionization per virus particle. Since 1 röntgen corresponds to the production of approximately 2×10^{12} ionizations per gram, D röntgens corresponds to the production of 1 ionization per $\frac{1}{2 \times 10^{12} D}$ grams. This, then, is the mass of the virus particle.

This calculation, while satisfactorily illustrating the principle, is somewhat simplified. The ionizations produced in an irradiated material are not distributed spatially at random, as the above calculation has tacitly assumed, but are localized along the paths of ionizing particles, as described by Gray. If an ionizing particle passes through a virus particle, usually more than one ionization will be produced in it, the actual number depending on the diameter of the virus and the *ion-density*, i.e., the number of ionizations produced per micron path, of the ionizing particle. The ion-density is greater in alpha-ray experiments than in X-ray experiments, and is greater with X-rays than with gamma rays. We shall, therefore, expect that the inactivation doses will increase in the order gamma rays, X-rays, alpha rays, since a radiation which produces several ionizations in one virus particle, when one would suffice to inactivate it, is inefficient.

Table I shows that the experimental results [11] confirm this expectation for a bacteriophage. Similar results with plant viruses have been obtained by Lea and Smith.[12]

TABLE I.

Inactivation of Phage S-13

(Phage diameter 16 mμ)

	Gamma rays	X-rays	Alpha rays
Inactivation dose in millions of röntgens	0.58	0.99	3.5
Inferred "target" diameter in mμ.....	15.5	15.9	16.0

From the experimental inactivation doses, one can calculate the "target" diameter, i.e., an estimate of the diameter of the virus based on the hypothesis that an ionization anywhere in the virus particle will inactivate it. The agreement between the three estimates of target diameter and their close approximation to the size of the virus as determined by other methods (centrifugation and filtration) satisfactorily confirms this hypothesis, and, incidentally, establishes that this bacteriophage is one of the macromolecular viruses.

Organism-type Viruses

If we attempt to apply the same type of reasoning to a large virus, we find that the estimates of the target size deduced from experiments with the three radiations do not agree, and are all much smaller than the true size of the virus, as shown in Table II.[10] It is evident that the hypothesis that an ionization

TABLE II.

Inactivation of Vaccinia Virus

(Virus diameter 200 mμ)

	Gamma rays	X-rays	Alpha rays
Inactivation dose in millions of röntgens	0.080	0.104	0.211
Inferred "target" diameter in mμ.....	31	41	70

anywhere in the virus particle leads to inactivation is incorrect. It is believed that a single atom ionized can inactivate the virus, but it must be an atom, not anywhere in the virus, but in certain radiosensitive constituents of the virus, these constituents comprising only a small fraction of the total bulk of the virus particle. This differentiation between radiosensitive and radioinsensitive constituents suggests a cell rather than a macromolecule, and it is probable that the radiosensitive material is to be identified with the genes. The fuller analysis of the radiation data enables an estimate of the number of genes to be made.[10]

We are thus led to regard vaccinia not as a naked gene, as

was appropriate for phage S-13, and the plant viruses, but as a single-celled organism with many genes.

Shortly after this suggestion was made, electron micrographs were published,[5] showing internal structures in the particles of vaccinia virus, and making it difficult to doubt that the particle of vaccinia is a single-celled organism rather than a macromolecule.

It appears from these examples that radiation experiments may be of value in elucidating the nature of viruses. Some recent experiments [11] on bacteriophages somewhat larger than S-13 suggest that these are very primitive organisms with only 10 or 20 genes.

Lethal Mutation in Bacteria

Effects of radiation upon bacteria which have been investigated are, the production of mutations, i.e., permanent changes in form or color of colony, the reduction of motility, a temporary inhibition of division, and the lethal action, the great majority of investigations being concerned with the last mentioned effect.

What is described as a lethal action in these investigations is the inability of a bacterium after irradiation to give rise to a colony visible to the naked eye when inoculated on a nutrient medium. There are, however, distinct differences between the "killing" of a bacterium by radiation, and killing by other agents, e.g., heat or chemical disinfectants. Thus, after irradiation, the bacterium which is rendered incapable of giving rise to a colony may still be motile,[3] may still be capable of respiration,[2] and may, when cultured and examined microscopically, show some growth.[14] In view of these facts, it is probable that one is dealing with lethal mutation.

The internal evidence of the radiation experiments supports this interpretation. It appears [6, 8] that a single ionization is able to "kill" a bacterium, but that, as with the large viruses, it does not suffice for it to be produced anywhere in the bacterium. It must be produced in a radiosensitive part which constitutes only

a small fraction of the total bulk of the bacterium, and which is, on our interpretation, to be identified with the genes.

Inhibition of Division of Bacteria

Ionization produced in a bacterium but not in the genetical material is not without effect. The most striking effect is a temporary inhibition of division. Bacteria grown in a nutrient medium in the presence of a suitable intensity of radiation continue to grow, in the sense of increasing in volume, but fail to divide. In consequence, rod-shaped bacteria grow into long filaments.[9]

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QUANTITATIVE HISTOLOGICAL ANALYSIS OF RADIATION EFFECTS IN HUMAN CARCINOMATA

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Introduction

TUMORS of apparently similar histological type and clinical extent in different parts of the body, or even at the same site, vary considerably in their local response to radiotherapy. Thus, good results are obtained in cases of carcinoma colli uteri, while almost complete failure attends the treatment of carcinoma of the esophagus. In carcinoma colli uteri, clinical stage 2,* 60% of the cases are cured for at least 5 years, while 40% of the cases fail to respond satisfactorily.

Attempts to discriminate between the radiocurable and the radioresistant cases by means of histological grading have led to widely divergent results.[4, 15, 19] The most anaplastic types of tumor tissue,[2, 13] as well as the most differentiated types,[1, 6, 9, 20] have been found to give the best radiotherapeutic results—a finding paralleled by the clinical observation that the highly differentiated keratinizing epitheliomata of the skin and lip usually respond favorably to radiation treatment, and that lymphosarcomata and other growths composed mainly of undifferentiated cells react dramatically to radiotherapy, at least locally.

* The clinical stages in carcinoma colli uteri are defined as follows:[14] Stage 1: The carcinoma is strictly confined to the cervix. Stage 2: The carcinoma infiltrates the parametrium on one or both sides, but does not extend to the pelvic wall. Stage 3: The carcinomatous infiltration of the parametrium extends to the pelvic wall on one or both sides. Stage 4: The carcinoma involves the parametrium up to the pelvic wall and the bladder.

These examples, as well as the rather vague and general statements composing the "radiosensitivity tables" of tumors,[5, 17, 18, 25] illustrate the difficulties encountered in an analysis of the factors determining the radiosensitivity of individual growths or groups of tumors, and of the likely response to any particular type and dose of radiation. Although some general principles have been elucidated by radiobiological research, their application to the practice of radiotherapy is handicapped by the hetergeneous collection of nosological entities lumped under the term "cancer,"[8] and also by the essential differences in biological characters and reactions of much of the biological material chosen for experimentation and of maligant cells and tissues.

The study of the local response of various types of neoplastic diseases to radiation can be undertaken only by investigating the actual response of individual tumors to treatment, i.e., by examining serial biopsies taken before, during, and after treatment, and by correlating the histological with the subsequent clinical and pathological findings. It is useless, however, to compare biopsies taken at random with one another, since owing to their localization in the tumor, i.e., whether near the necrotic center or the well-vascularized growing edge, the specimens from the same tumor may vary as to the proportion of old and young foci included. To obtain comparable results in serial biopsies of an individual case, sections should be taken from the growing edge of the tumor, and in such specimens only the young areas should be chosen for a detailed examination of the reaction of the tumor tissue to treatment. Young foci alone contribute to the further expansion of the tumor; they possess the greatest developmental potentialities in any given malignant growth, and are best able to react to, and to recover from, the effects of treatment.

If these precautions are taken, reliable and comparable "samples" of young foci in the tumor can be obtained. In a series of about 20 surgical and pathological specimens of various carcinomata, a number of small pieces of tissue equivalent to biopsy sections were taken from the growing edge, comparable

young areas were selected in each piece, and their cell population was classified and counted. The average coefficient of variation from the mean in the various pieces for any given tumor was of the order of 10%.[11] Similar observations have been recorded for the histological grading of various biopsies taken from the same tumor.[3, 16, 21]

The cellular population of tumors varies with tumor type. In most epithelial growths, 4 classes of cells can be distinguished according to their viability. There are 2 classes of viable cells:

A: The *resting* cells, which are the intermitotic "stock" cells capable both of division and differentiation (depending on the tumor type). They are relatively small, with a large, often hyperchromatic, nucleus and with little and basophilic cytoplasm.

B: The mitotic cells, i.e., stock cells actually in division.

There are also two classes of nonviable cells:

C: The *differentiating* cells, which are cells rendered permanently incapable of division by the differentiation of their cytoplasmic structures. Most of these cells are large, with a great amount of differentiating cytoplasm and a relatively small vesicular nucleus.

D: The *degenerating* cells, which are the cells in the process of disintegration. Their structure changes according to the form of degeneration (fatty, mucoid, parakeratotic, etc.), and to the cell type from which they are derived.

Very immature growths lack the differentiating cells. Figure 1 depicts diagrammatically the main characteristics of these four cell categories and their relationship with each other, as indicated by the arrows. The cellular composition of the foci is influenced by the tumor bed, i.e., the vessels, stroma, and cells surrounding the tumor strands, which promotes or inhibits mitosis, differentiation, and degeneration.

Young foci are formed by finger-like projections from tumor strands, and are characterized by the presence of many mitotic cells, the preponderance of resting cells, and the dissolution of the basement membrane at the growing tip of the projection. The comparison of young foci in serial biopsies is best made

quantitatively by classifying and counting all the cells in carefully selected young areas. The cell counts are plotted as percentages against time after beginning treatment, and thus a chart is obtained of the response of a given tumor to a given type of treatment.[10]

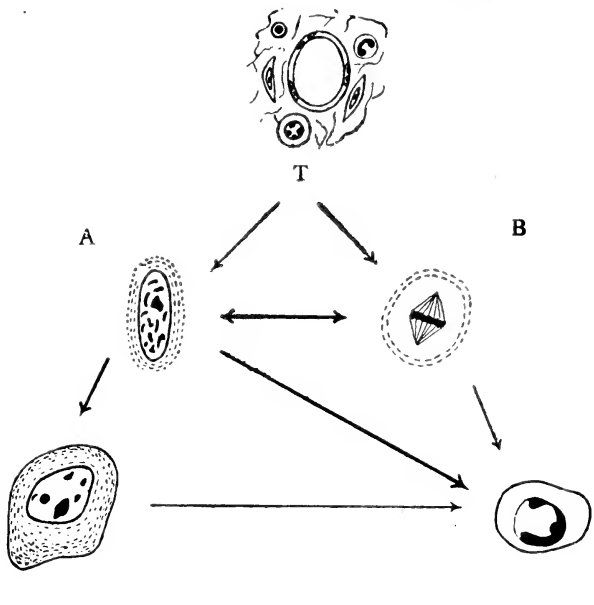

FIG. 1. Diagrammatic Representation of the Four Cell Categories Found in Most Epithelial Tumors

A: Resting cell } viable cells.
B: Mitotic cell }
C: Differentiating cell } nonviable cells.
D: Degenerating cell }
T: Symbolizes the tumor bed, i.e., the vessels, stroma, and cells surrounding the tumor strands.

Changes in the cell population of young tumor foci are the result of direct and of indirect effects of radiation. The direct effects concern mainly resting and dividing cells. After a transient mitotic inhibition, resting cells may break down on attempting division, they may differentiate according to their type and

potentialities, or they may disintegrate immediately after exposure. Enlargement of resting cells often follows an irradiation.

After a period of mitotic inhibition, cell divison may be resumed with varying degrees of abnormality. A sufficiently high dose of radiation delivered at a high intensity may cause the immediate disintegration of mitotic cells. The direct effects of radiation thus cause a diminution in number of resting and dividing cells and promote the "aging" of cells and foci. Apart from some increase in cell size, the effect of radiations on cells in the early stages of differentiation has not yet been precisely determined.

The indirect effects of radiation are due to the interference with the vascular and connective-tissue system of the tumor, and to the induction or exacerbation of inflammatory reactions. Insufficient blood supply affects the process and the incidence of cell division, and may cause the disintegration of cells. The inflammatory reaction leads to the infiltration and the breaking up of tumor strands by round cells, followed by the formation of fibrotic scars.

The aim of radiotherapy in malignant disease is to convert viable into nonviable cells, i.e., to induce the breakdown of dividing cells and to prevent cell division, to cause the immediate disintegration of resting cells, or their permanent sterilization by differentiation. The observed radiation changes in malignant growths vary according to the tumor type and the dose, dose rate, and time interval between a given dose and the biopsy excision. Some types of reaction of young foci to radiotherapy are illustrated in figures 2 to 5.

Figure 2 represents the reaction chart of a basal-celled carcinoma of the temple treated by a dose of 3,200 r of X-rays given in 13 days. Cell counts made in selected young foci of serial biopsies show a diminution and finally a disappearance of mitotic cells and an initially slow and later rapid disintegration of resting cells. Clinically, the lesion responded well to treatment and remains healed. This case illustrates the response of undifferentiated tumor cells to radiotherapy by mitotic inhibition,

degeneration of mitotic cells, and the disintegration of the "aged" resting cells. A few of the resting cells were apparently killed directly by the radiation.

The charts in figures 3 to 5 refer to cases of epithelioma (carcinoma) colli uteri, clinical stage 2, treated by radium insertions on days 0, 7 and 21 by a modified Stockholm technique.

Figures 2 to 5 show cell counts in young foci of serial biopsies taken from the growing edge of tumors before and during radiation treatment. In these figures:

Abscissae = time in days.
Ordinates = cell counts %.
Viable cells:
resting cells.
M mitotic cells.
Nonviable cells:
differentiating cells.
degenerating cells.

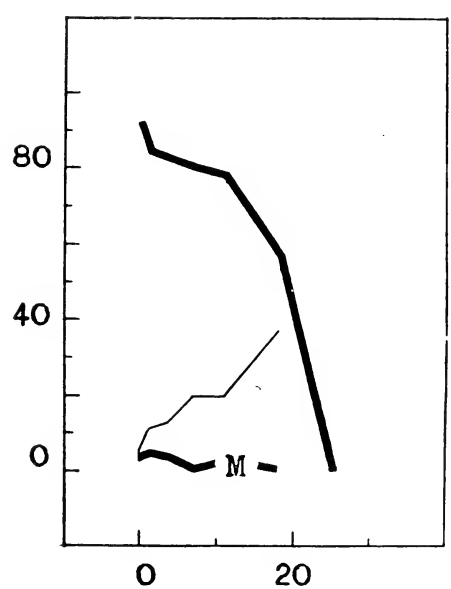

FIG. 2. Reaction Chart of Basal-Celled Carcinoma

Figure 3 shows the reaction chart of a favorably-responding tumor which was an epithelioma with keratinized foci, Broders grade 2.* The malignant tissue reacts rapidly to treatment, with a marked increase in number of differentiating

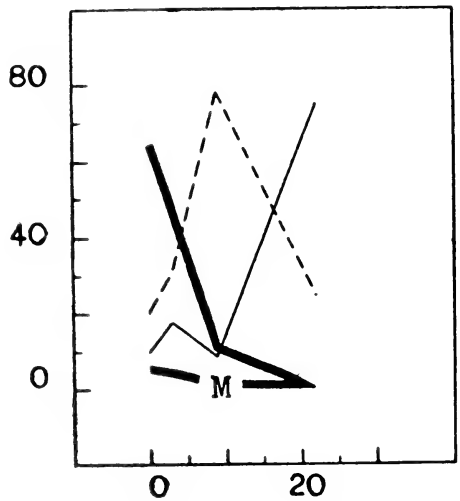

FIG. 3. Reaction Chart of Epithelioma

cells which subsequently disintegrate. The mitotic and resting cells decrease in number and disappear. Clinically, healing of the lesion was noted after 3 months and the patient has remained well and symptom-free for 5 years.

Figure 4 represents the reaction to treatment of another epithelioma of the cervix uteri, clinical stage 2, Broders grade 3. The effect of 3 radium insertions in this case is approximately equal to that of a single insertion in the case of figure 3, i.e., there is some reduction in the percentage of viable cells and a corresponding increase in the percentage of nonviable cells. This change does not, however, lead to the complete disappearance of viable cells, and the tumor tissue is thus able to recover from

* Broders's histological grading of malignancy is based on the degree and extent of cell dedifferentiation. The least malignant, i.e., the most differentiated form, constitutes grade 1 and consists of 0% to 25% of dedifferentiated cells. Grade 2 contains 25% to 50%; grade 3, 50% to 75%; and grade 4, 75% to 100% of dedifferentiated cells.

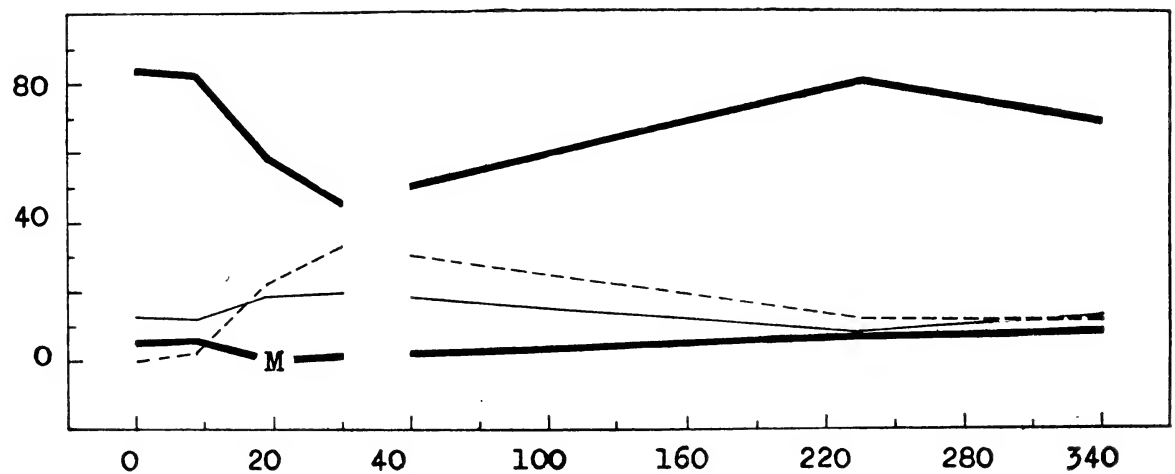

FIG. 4. Reaction Chart of Epithelioma

the radiation effects. This chart indicates a merely temporary inhibition of growth of the tumor tissue. Clinically, the lesion appeared to heal and there was no evidence of growth 6 months after treatment. The tumor reappeared later in the treated area and caused the death of the patient 16 months after the beginning of treatment.

Figure 5 illustrates the reaction to treatment of another epithelioma of the cervix uteri, clinical stage 2, Broders grade 3. There are only minor fluctuations in the cell counts, and the chart indicates the persistence of tumor activity almost unchanged by the type of radiation treatment given. Clinically, however, the lesion appeared to be healed after 3 months. Three months later a "recurrence" of the tumor in the treated area was diagnosed, and the patient died 6 months later with growth in the treated area and with extensions.

In these 3 illustrative cases of carcinoma colli uteri (figures 3 to 5), the lesion appeared to be healed 3 to 6 months after treatment, although in 2 of the cases the histological-reaction chart (figures 4 and 5) indicated the persistence of active tumor growth. In both these cases, the tumor recurred subsequently. In a series of 150 cases of carcinoma colli uteri, 26 cases reported clinically satisfactory during the first 4 months after treatment developed a "recurrence" during the succeeding 8 months; in each case the reaction chart, obtained within 3 weeks of beginning treatment, indicated the persistence of tumor activity.[12]

The histological findings based on a quantitative analysis of the cell population of young foci in serial biopsies seem to give a reliable and early indication of the likely outcome of radiotherapy in individual cases, whereas clinical healing is useful as criterion in the evaluation of therapeutic results only if it persists for the conventional period of 5 years. Practically all tumors shrink to some extent under treatment—presumably owing mainly to the damage inflicted on parts of the vascular system supplying the growth and to its sequelae—and this shrinkage allows of the restoration of the normal anatomical configurations in spite of the persistence of active, microscopic tumor foci. Decrease in tumor volume of itself is no real measure of the

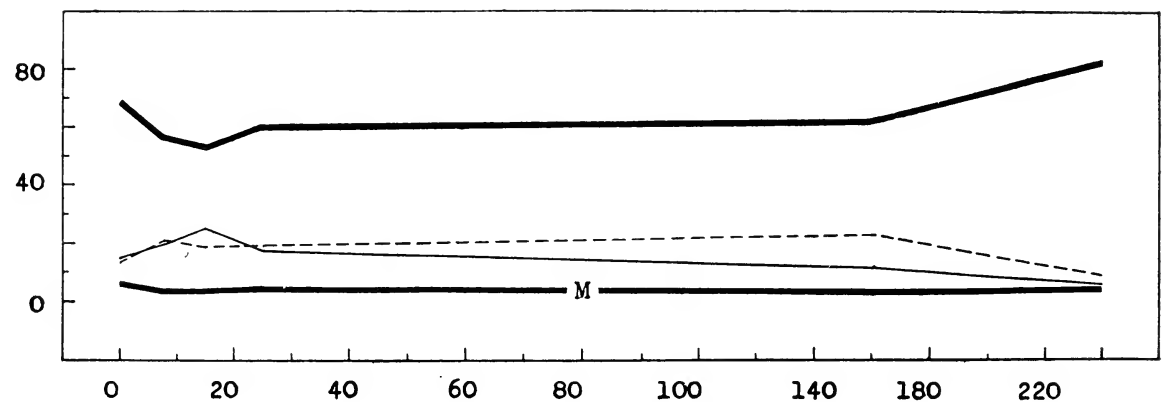

FIG. 5. Reaction Chart of Epithelioma

efficiency of therapy. As with surgery, radiation treatment of cancers aims at the complete elimination or sterilization of viable tumor cells, and a 90% success of therapy is ultimately a failure. The histological-reaction charts (figures 2 to 5) are measures of tumor activity, and bear no relation to the actual size of the tumor at the time of the biopsy excision.

The persistence of active microscopic tumor foci in apparently restored sites is the reason why, shortly after treatment, the histological findings may be at variance with the results of clinical examinations. Agreement becomes, however, closer with the lapse of time. For example, in the series of 150 cases referred to,[12] there was agreement between histological and clinical findings in only 50% of the cases after 4 months and in 80% of the cases 2 years after treatment.

Apart from showing within 3 weeks of beginning treatment whether or not the aim of therapy is being realized, the histological analysis gives some useful information about the way in which the therapeutic results are obtained. In cases like that of figure 2, the successful treatment is due in particular to the "mitotic" effect of radiation, i.e., the mitotic inhibition and to disintegration of dividing cells; this prevents the further formation of resting cells which consequently age and, having reached the limits of their short span of life, die. Some resting cells are also killed immediately by the radiation and others fall victims to unfavorable conditions in the tumor bed induced by radiation.

In epitheliomata like that of figure 3, the mitotic and vascular effect of radiation is supplemented by the "differentiation" effect, i.e., resting cells are forced (either directly or secondarily to mitotic inhibition) into differentiation, and are thus sterilized. This observation suggests that the capacity for differentiation in resting malignant cells and its stimulation by radiation may be one of the factors in the "radiosensitivity" of tumor tissue.

An indication of the capacity for differentiation of the tumor tissue—though not of its reaction to radiation—may be gained from the presence or absence of differentiated foci in the preradiation biopsy of the tumor. Histological classification as to

degree of differentiation of such specimens shows that, clinical conditions and treatment methods being equal, the results of radiotherapy tend to be more satisfactory in the cases with more differentiated tumor tissue.[12] The physical factors of radiation, such as time, dose, dose rate, and type of ray, which are most likely to elicit differentiation in cells with such potencies, are as yet little known and understood. It appears feasible that favorable results may be obtained with changes in technique in those groups of tumors which so far have proved refractory to treatment.

There are various limitations in the application of the quantitative histological method of analysis of radiation effects in individual cases of malignant disease. Thus, conclusions about a favorable response to treatment must be limited to the reaction of the growth in the treated area, presupposing that the radiation energy was fairly uniformly distributed in this area. In spite of cures in the treated area, the clinical issue may, of course, be compromised by the presence of untreated metastases, or even by fatal hemorrhages due to radiation damage inflicted on the vascular apparatus. Certain types of cancer are systemic diseases with local manifestations, and obviously the cure of one of these manifestations cannot prevent the formation of new ones which may even arise in neighboring precancerous lesions.

Conclusions

To summarize: the quantitative histological examination of serial biopsies of human tumors provides a useful guide in the evaluation of the therapeutic result in individual cases. As a research method, it facilitates the analysis of the "radiosensitivity" of an individual growth, makes possible the study of the factors influencing the response of a given tumor to a given type of treatment, and provides a basis for the understanding of radiation effects on tumor tissue of different types and for the better knowledge of the natural history of malignant diseases. The combination of such knowledge with relevant data contributed from radiobiological research is the necessary require-

ment for progress in the radiotherapy of neoplastic diseases. Ewing [7] has pointed out that "there is little significance in discussing the curability of cancer as a whole. The discussion has real meaning only when the different types of cancer are considered separately as nosological entities."

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THE MEASUREMENT OF RADIATION

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Introduction

A COMPREHENSIVE discussion of the whole of the vast field which might be implied in the above title is clearly out of the question here, so the present remarks will be arbitrarily confined to the subject of ionizing radiation, around which most interest is centered in the present context, leaving aside entirely the question of ultraviolet, infrared, and "short wave" radiations, which are of no less importance in biology and therapy.

By "ionizing radiations," we mean those types of radiation which in their interaction with matter are able, by virtue of their high intrinsic energy, actually to disrupt the individual atoms or molecules by the splitting-off of an electron. The electron thus set free quickly attaches itself to some other molecule, and so, dispersed among the normal electrically neutral molecules, there appear positively and negatively charged molecules or clusters known as ions, which may exist independently in the medium for considerable lengths of time, and endow it with the property of electrical conductivity.

If left to themselves, the ions will gradually neutralize each other, but the exact status quo may not be restored, for obviously the chance that various types of atomic and molecular rearrangement, i.e., chemical change, will occur is considerable. It is believed that such changes caused by ionization are the more immediate causes of the biological effects produced. On the other hand, by the application of sufficiently large electric field, it

may be possible, in a gas at any rate, continuously to remove the ions to the two electrodes almost as fast as they are produced by the ionizing radiation, before any appreciable recombination can take place. The electric current in such circumstances is called the "saturation current" and, in most cases arising in practice, it is very minute.

Examples of ionizing radiations are the electromagnetic type as in X-rays, and the gamma rays from radioactive substances, the swift electrons in cathode rays and the beta rays from radioactive substances, protons, alpha particles, etc., the neutrons, all of which have a similar ultimate mode of action in biology.

The necessity for some system of measurement of radiation in biological and therapeutic studies need hardly be emphasized, but in practice it has proved an exacting pursuit, aptly illustrating Kelvin's historical remark that no phenomenon can be understood till it can be measured and expressed in numerical terms. The difficulties lie in deciding on, and realizing practically, a suitable measure of "amount" of radiation, and arise partly from that common feature of the radiations which is most obvious, namely, their power of penetrating matter, and partly from the very small amounts of energy involved. For example, the total amount of energy communicated to the tissues in a typical complete therapeutic treatment would suffice only to augment the temperature of the mass by about one hundredth of a degree Centigrade.

To keep our discussion to a reasonable length, it will be necessary to confine ourselves to what is by far the most important method in this branch of radiation measurement, the ionization method, and to concentrate on the principles involved, omitting detailed descriptions of techniques. In an adequate historical account, considerable interest would attach to the photographic method of measurement,* but here, we merely remark in passing that it has been developed as a precision technique only in certain rather restricted fields, though it

* Some of the earliest dosimetry was done by finding the time required to photograph a hand!

remains a very useful and often simpler alternative to the ionization method when high accuracy is unnecessary—for example, in the recording of stray radiation in questions of staff protection. Other methods, such as chemical methods, change of color or fluorescence of salts, selenium cells, etc., proved unsatisfactory and are of historical interest only.

Again, comparative studies have been made by using some standard biological test material, for example, *Drosophila* eggs, but it is clear that far greater importance attaches to the more fundamental problem of relating biological effects to the radiation producing them, evaluated in precise physical terms. The radiations hitherto most commonly met with are X-rays and the gamma rays of radium, and they will, of necessity, occupy most of our attention.

X- and Gamma Radiation

Quantum Character and Interaction with Matter

These radiations are different examples of essentially the same type of radiation, and it may not be out of place to state briefly some of the most important facts relating to their interaction with matter. The radiation is electromagnetic in character, propagated with the speed of light. For our purpose, it is best to concentrate on the quantum character of the radiation, i.e., the energy of the beam of radiation is concentrated in discrete units rather like a hail of bullets, the amount per unit being given by Einstein's equation

$$E = h\nu$$

where h is Planck's universal constant, and $\nu = \frac{c}{\lambda}$, where ν, λ and c are the frequency, wave length and velocity of the radiation, the latter also being a universal constant. These quanta, or photons, interact with matter in several different ways:

1. *"Unmodified," or Thomson scattering.* A quantum is merely deflected from its course without loss of energy by an

individual electron, so that a unidirectional beam becomes diffuse. Unmodified scattering is not of great importance in our present considerations.

2. *"Modified," or Compton scattering.* A quantum "collides" with an individual electron, projecting it in one direction while itself rebounding in another (and related) direction, with a reduced energy (and, therefore, longer wave length) depending on the direction taken. The detailed theory of the fractions of the energy of an incident beam of quanta imparted to the recoiling electrons and scattered quanta and their angular distribution has been given by Klein and Nishina, and is in very good agreement with experiment. The phenomenon is only slightly affected by the atomic number of the substance.

3. *Photoelectric absorption.* A quantum is absorbed completely by the atom as a whole. Nearly all the energy (a very small fraction is expended in atomic recoil) is expended in extracting an electron from the atom and endowing it with kinetic energy. The phenomenon is practically completely described by theoretical and empirical relations. The fraction of energy of the incident beam converted, reckoned per electron, is approximately proportional to the cube of the atomic number, i.e., the effect is much more pronounced in "heavy" than in "light" elements. Apart from certain well-understood discontinuities, the energy conversion varies roughly as the cube of the wave length of the radiation, i.e., it becomes less important for higher quantum energies.

4. *Various nuclear effects.* Production of electron and positron pairs and nuclear disintegrations becomes of importance only for quanta of high energy. These effects are practically negligible even for radium gamma rays. They vary with the atomic number of the nucleus.

These processes all contribute to a removal of quanta from a beam; the fraction of the energy removed is termed an absorption coefficient, and may be reckoned per electron, per unit mass, or per unit volume of the material.* Some of the energy is

* The absorption coefficients of any one atomic type are practically independent of its state of chemical combination.

imparted to fast electrons, the so-called "corpuscular emission." It is these swift secondary electrons which actually ionize and excite the atoms and molecules of the medium.

The Concept of Quality

The "quality" of a beam of radiation refers to its intrinsic characteristics such as wave length, or quantum energy. It may be investigated exactly by spectrographic methods (crystal diffraction) or by measurements of the energy of the secondary electrons produced in matter. A quick practical method, particularly useful for approximate results with heterogeneous beams, is to measure the absorption or attenuation of the radiation in some suitable standard substance, from which an average or effective wave length of the radiation may be estimated. Thus, it is usual to quote the half-value layer (HVL) of a given beam of X-rays in aluminum, or copper, i.e., the thickness of material required to reduce the "intensity" (dose rate, see below) to one half.

By suitable developments of these principles, it is possible in some cases to form an estimate of the effective wave length of the diffuse radiation produced during the passage of a beam through matter. Thus, the measurement of "quality" is achieved by the application of familiar physical ideas and need not be dealt with here in detail. It may be mentioned in passing, that the particular aspect of quality of greatest biological significance is the spacing of the ions along the tracks of the ionizing particles, the "ion density." As the energy of the ionizing particle becomes less, the shorter the interval between successive ions.

The Concept of Quantity or Dose

When we come to the question of "quantity," it is necessary to break new ground. Normally, "amount" of radiation is expressed in terms of intensity, defined as quantity of energy flowing through unit area of the beam per unit time, but any arbitrary measure of "amount" related to this, however in-

directly, would serve. Obviously, it is desirable to choose as a measure that physical quantity which stands in the closest relationship to the biological effects produced by the radiation. By making a shrewd choice in this matter, the interrelation of physical cause and biological effect will not be obscured by a long chain of essentially irrelevant intermediate processes.

There is general agreement that the key quantity is the ionization produced in the biological substance. With a few exceptions, however, it has for technical reasons proved quite impracticable to measure the actual ionization in a solid or liquid, but a quantity which is almost as acceptable as ionization, as a measure of the radiation, is the energy communicated to the medium. The reason for this is that the proportion of this energy which goes to the production of ionization is probably independent of the quality of the radiation—this is certainly almost exactly true for air, where about half the energy goes to the production of ionization, the rest being expended in excitation, and thus the ionization is known apart from a constant of proportionality characteristic of the medium. In one of the very few investigations of a liquid, in this case carbon disulphide, Taylor has shown that the proportion of energy expended in ionization is not greatly different from that expended for air. In actual fact, however, the direct measurement of the energy communicated to the medium is also well-nigh impossible because of the minute amount required even for the most extreme biological effects. We shall see later how it is possible to derive this energy from other measurements.

The Röntgen

With these general ideas in mind, it is easy to see why, in actual historical fact, the ionization produced in air came to be adopted as a measure of radiation, partly as a matter of expediency on account of the relatively simple technical problems, and partly because it was realized that, on account of the general similarity of the atomic types in air and tissue, the energy conversion of X- and gamma radiation in these two

media would be roughly parallel for all qualities. If the average atomic numbers of two media are fairly close, then the relative importance of any one type of energy-conversion process (Compton, photoelectric, etc.) will be similar in the two media, and so the variation of the gross energy conversion with quality will be similar for the two media.

Thus Villard in 1908 first suggested a unit based on air ionization: that quantity of radiation which, by ionization, liberates one electrostatic unit of electricity per cubic centimeter of air under normal conditions of temperature and pressure. Much work remained to be done, however, before a satisfactory realization of the idea underlying this proposal was possible. Much of the difficulty lay in the phenomenon of the "wall effect" of the ionization chamber. The radiation causes the emission of secondary electrons from the walls of the chamber, so that the observed ionization in the air of the chamber, instead of depending uniquely on the radiation itself, is determined by a complex set of factors such as the nature of the walls and the size of the chamber. The surmounting of these difficulties and the development of the theory of the ionization chamber will be referred to later.

The necessity for general agreement on a satisfactory unit became ever more pressing, and in 1923, the first steps were taken by the British Röntgen and Physical Societies. Discussions followed with the first international congress of radiology in 1925, and finally matured at the second international congress in 1928. The unit of X-ray quantity, or dose, called the "röntgen" (symbol, r) was defined as "the quantity of X-radiation which, when the secondary electrons are fully utilized, and the wall effect of the chamber is avoided, produces in 1 cubic centimeter of atmospheric air at 0° C and 760 millimeters mercury pressure, such a degree of conductivity that one electrostatic unit of charge is measured at saturation current."

The "Free-air" Chamber

In order to make measurements in accordance with this definition, a rather special technique is necessary, namely, the

use of the "free-air" chamber. A narrow beam of radiation, accurately defined by a diaphragm, is passed through a large chamber of air and out through a hole in the far end, completely avoiding the walls. A uniform electric field between two parallel plates on either side of the beam collects the ions as fast as they are formed. A measurement is made of the current to a small, separately insulated section near the middle of one plate. The length of this section and the cross-sectional area of the beam define an effective "ionized volume" of air, so the ionization current per cubic centimeter of air may be deduced—that is, the dose rate in röntgens per second.*

The details of such a measurement call for very careful attention, but an intercomparison of the various national standards in 1931 showed that there was agreement to within $\frac{1}{2}\%$.

The "Thimble" Chamber

Parallel with these developments was the gradual emergence of the small ionization chamber, the so-called "thimble" chamber, the theory of which will be referred to below. The "free-air" chamber is clearly a special laboratory instrument and, further, is inapplicable to the measurement of the diffuse radiation produced when a beam enters matter. It was realized that the difficulty of the wall-effect of a "thimble" chamber would not arise if the material of the walls themselves behaved like air in its interaction with the radiation. It was hoped that a chamber with walls, the effective atomic number of which, in relation to the photoelectric process, was the same as that of air, would give readings exactly paralleling those of the "free-air" chamber for any quality, i.e., that it would be "wave length independent." Unfortunately this is not strictly borne out in practice, the precise reasons for the discrepancy still not being fully understood.

However, by suitable choice of such factors as the materials

* If the cross section of the beam at the defining diaphragm is used in the calculation of the ionized volume, then the dose rate so deduced refers to the strength of the beam at the diaphragm.

of the wall and the central electrode, the wall thickness and chamber size, it has proved possible to produce empirically chambers having a sufficiently close response to that of the "free-air" chamber, and the chambers can be calibrated to read directly in röntgens. The precise quality of the very heterogeneous radiation within a given medium is not in general calculable, or even easily measurable, and so it is of great practical importance that the "thimble" chamber to be used should not require an appreciable quality correction. It is clearly also of importance that the chamber should be as small as possible in order to define closely the precise location of the measurement, and that it should be sufficiently transparent to the radiation not to produce an appreciable "shadow."

Dosemeters

"Thimble" chamber dosemeters may be used in the direct measurement of dose rate or of dose. In the first case, the actual ionization current is determined by measuring the voltage drop across a high resistance. In the second case, the ionization current is allowed to charge a condenser, the final voltage of which is a measure of the total dose. In either case, a sensitive voltmeter of the electrometer type is likely to be required. All insulations must be of very high standards, for the currents dealt with are very small, for example, the relatively high dose rate of 1 röntgen per second produces in a chamber of 1 cubic centimeter volume a current of only one three-thousandth of a microampère. In some instruments, the ionization chamber, electrometer system, and recording mechanism are permanently connected, often with long cables, so that readings may be taken at relatively long distances from the point of measurement.

In the condenser-dosemeter, the ionization chamber is entirely separate from the electrometer and measuring devices during exposure to the radiation. The ionization current serves partially to discharge the originally fully charged capacity formed by the chamber itself, and any added condenser. The charge lost is thus a measure of the dose, This type of chamber is particu-

larly suitable for direct use in body cavities during therapeutic treatment. Very compact units have been developed, with small ionized volume and large electrical capacity, so that large doses can be measured. Chambers are now being used inside needle-like sheaths which can actually be inserted into the tissues, during treatment. Condenser chambers have the advantage that several may be used simultaneously, so that an extended field of radiation may be rapidly surveyed. Another particularly suitable application is the so-called "protection chamber" for recording the dose received by workers owing to small amounts of stray radiation.

The Measurement of Gamma Rays in Röntgens

To turn again to the more theoretical side of radiation measurement, the desire to measure gamma radiation in röntgens has resulted in great advances in the understanding of the ionization chamber and of the energy exchange between radiation and matter generally. Special interest attached to the problem of the gamma radiation from radium, in particular the dose rate produced by 1 milligram of radium at 1 cubic centimeter, when filtered by 0.5 millimeter of platinum (to cut out the primary beta radiation)—the so-called specific gamma-ray dose rate of radium.

As early as 1931, Mayneord [17] estimated this quantity from the known energy output of the radium gamma radiation (obtained by calorimetric measurements by Ellis and Wooster), and from the known absorption coefficient of air, to be 8.7 r per hour, and a measurement with a "thimble" chamber calibrated by comparison with an X-ray dosemeter gave 9.2 r per hour, in reasonable agreement. Mayneord, in 1933,[18] further estimated this quantity from Eve's constant (the number of ion pairs per second per unit volume produced in air at 1 cubic centimeter from the quantity of radium C in equilibrium with 1 gram of radium) as 8.9 r per hour. But at the same time, attempts to measure the specific gamma-ray dose rate directly with "free-air" chambers led to values of only about one-third

of the above, so that there was considerable fear that the expression of gamma-ray quantity in röntgens was without meaning.

This disharmony was resolved by Kaye and Binks in 1937,[16] who showed conclusively that on account of the large range in air of the secondary electrons produced by the gamma radiation, the dimensions of the "free-air" chamber need to be very much greater than in the case of X-radiation, for the equilibrium intensity of the secondary electrons to be reached, and for their energy to be fully utilized in producing ionization. The current obtained from the "free-air" chamber with gamma radiation no longer originates in the simple "ionized volume" as in the case of X-rays but, provided the dimensions are large enough, a geometrical argument shows that full compensation exists and the same simple calculation is valid. Kaye and Binks [16] found a value of approximately 8.0 r per hour for the specific gamma-ray dose rate of radium.

Friedrich provided further confirmation in 1938 [7] by measuring the ionization in a small thin-walled chamber suspended in air in the center of a large hall, so that it was influenced solely by the secondary electrons (in equilibrium) produced in the air. In this way, a value of 7.8 r per hour was found for the constant. Lastly, Taylor and Singer in 1940 [29] made very precise measurements with a "free-air" chamber operated at ten atmospheres' pressure, in order to reduce the size, and obtained the figure 8.16 r per hour. All doubts as to the legitimacy of measuring gamma rays in röntgens have thus been finally dispelled.

True Energy Absorption and the Theory of the "Thimble" Chamber

Of greater fundamental physical importance, however, was the work on the "thimble" chamber method of measurement, referred to several times above. The essence of this idea was provided in 1911 by Bragg,[1] rediscovered by Fricke and Glasser in 1925,[6] and again independently by Gray in 1929. Innumerable other workers have made contributions of various kinds, but

it was only after Gray's detailed treatment that an adequate insight into the problem was attained, and the idea of radiation-dose advanced a stage further than the röntgen unit.

It must be borne in mind that the röntgen is solely a measure of exposure to radiation—it merely describes what the beam of radiation will do in air, and not what it will do in any other medium, although it gives a good approximate guide to the latter in the case of light elements, such as occur, for example, in tissue. Furthermore, the energy absorption in a medium other than air cannot in general be calculated from the röntgen dose by correcting with the ratio of the absorption ("energy conversion") coefficients of the medium and air, because normally the quality of the radiation, on which these coefficients depend, is unknown.

Gray's theory removes this element of vagueness, for it enables the *actual energy* communicated to any medium to be deduced from *measurements* of the ionization produced in a small gas-filled cavity in that medium. If E is the energy communicated to the medium per unit volume, J the ionization per unit volume of the gas-filled cavity, and ϱ the ratio of the rates at which a secondary particle loses energy in the medium and in the gas of the cavity, and W is the average energy expended by the secondary particles in producing an ion pair in the gas of the cavity, then

$$E = \varrho W J$$

The detailed derivation and exposition of this relationship, called by Gray the "principle of equivalence" must be sought in the original publication. There are certain restrictions: (1) the fraction of their energy lost by the secondary particles in crossing the cavity must be negligible;* (2) the cavity must be surrounded on all sides by a thickness of the medium at least equal to the maximum range of the secondary particles; (3) the

* Restriction (1) is unnecessary if the gas in the cavity is of the same constitution as the walls.

strength of the beam of radiation must be sensibly uniform over the cavity.*

In some cases, particularly in the ordinary X-ray region, the behavior of small "thimble" chambers appears to deviate from the foregoing analysis. On general grounds, it may be presumed that the conditions attaching to the principle of equivalence have not been fulfilled in these cases. Although the deviations are not usually large, and the use of such chambers can be avoided in practice, yet the effects are of considerable intrinsic interest and have received much attention.

The Redefinition of the Röntgen and the Extrapolation Chamber

With the development of the work on the measurement of gamma radiation, the need was increasingly felt for a rewording of the definition of the röntgen. One reason was the desirability of admitting the "thimble" chamber, previously excluded by the clause about avoiding wall effect, as a valid device for measuring in röntgens, but more important was the practical necessity to disentangle the fundamental dose unit from the complexities surrounding the actual ionization in air in certain conditions.

For example, because of the relatively long range of the secondary electrons produced by gamma radiation, the ionization at any point may not bear any simple relation to the strength of the radiation beam there, i.e., the energy actually communicated to the medium at a given point may not come from energy conversion of the radiation at this point, but from various points, depending on the geometry of the environment. Normally, a complete compensation exists, and the energy converted is equal to the energy communicated to the medium at the same place,

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* Strictly, it must be sensibly uniform throughout all that part of the medium from which secondary particles can reach the cavity. One particular application of the theory is to determine the specific gamma-ray dose rate of radium by measurements with a "thimble" chamber. For a chamber wall of light elements, for example, graphite, the energy conversion of this quality of radiation is the same (per electron) as for air. Thus, by correcting the observed ionization in the chamber, according to the quantity ϱ (which is known), the ionization in a true "air wall" chamber is deduced. The specific gamma-ray dose rate of radium determined in this way is very close to 8.4 r per hour.

but this will not strictly obtain (1) if the strength of the radiation varies appreciably over a distance comparable to the maximum range of secondary particles reaching the point, or (2) in the region of a boundary between two different media. The question in such cases, therefore, is whether "energy conversion" or "energy communication" is to be adopted as the measure of dose. From the point of view of biological effect, the latter quantity is the important one, while the former is, logically speaking, irrelevant, but far simpler to deal with in practice, and it was adopted at the fifth international congress of radiology in 1937.

"The röntgen shall be the quantity of X- or gamma radiation such that the associated corpuscular emission per 0.001293 gram of air (the mass of 1 cubic centimeter of air at 0° C and 760 millimeters of mercury pressure) produces, in air, ions carrying 1 electrostatic unit of quantity of electricity of either sign."

This is effectively the same as the 1928 definition with certain ambiguities removed.

In a detailed consideration of the biological effects of radiation in the borderline cases referred to above, it is necessary to bridge the gap between a knowledge of the energy conversion in air and the energy actually communicated to the medium. For this purpose a very thin-walled chamber is used, the ionization in which gives an indication of the secondary particles (the "corpuscular emission") *effective* at the point.* The "extrapolation" chamber introduced by Failla [4] is of this type. The procedure is to take observations with a gradually decreased spacing between the walls of the chamber, and extrapolate the results to obtain the value for a chamber of negligible width. With the very high-energy X-rays that can now be produced by the betatron, studies of this kind, particularly for surface effects, i.e., at the skin of the patient, will become increasingly important.

* Note that such a chamber gives an indication of the effect of the secondary particles *on air* (which is normally used in the chamber) and not *on the medium*. To investigate the latter, it would be necessary to fill the chamber with a gas whose effective atomic number was the same as that of the medium, and to know the energy required to produce a pair of ions in the gas. Alternatively, the energy absorption in the medium could be fairly closely calculated from that in air if the composition of the former is known.

Neutrons

The consideration of the measurement of neutron radiation follows on naturally from that of X- and gamma radiation, for neutron radiation also produces ionization by an indirect means, namely, through the agency of secondary particles.

A neutron is a material particle of mass approximately unity on the atomic scale, that is, its mass is very similar to the mass of the nucleus of the hydrogen atom, the proton. But, whereas the proton has a positive unit elementary charge, the neutron has no charge at all, and so, unlike radiations consisting of charged particles, it is unable to drag electrons out of the atoms near which it passes. Thus it loses practically no energy by ionization, and will penetrate very much greater thicknesses of matter than, say, a proton of similar energy.

The interaction of the neutron is almost entirely with the nuclei of the atoms, and the commonest process is a simple collision which deflects the neutron with a reduced energy, and causes the nucleus to recoil with the balance of the original energy. The average energy transfer in a collision is greatest when the neutron and the nucleus have equal masses, and becomes progressively less as the mass of the recoiling nucleus increases. The energy transfer is greatest in hydrogen, when the neutron energy is on the average reduced to about 37% at each collision.

In addition to these scattering collisions, a neutron may be captured by a nucleus and provoke nuclear disintegrations of various kinds, sometimes resulting in the production of "artificial radioactivity." The relative probability of such processes is generally small, however, until the neutron has been made very slow by repeated collisions. In the case of biological material, these nuclear disintegrations may usually be ignored in considering the energy communicated to the medium by a beam of neutrons. It may be mentioned in passing, that the induced radioactivity produced in suitable substances is of help in making

relative measurements of the "strength" of a neutron beam, and in discriminating between neutrons of different energy.

An immediate extension of the definition of the röntgen to include neutron radiation would not be very suitable for use in biology and therapy because, as pointed out above, the energy conversion of the neutrons varies rapidly with the atomic type, even for "light" elements, in contrast to the energy conversion of X- or gamma radiation. In other words, air is no longer a satisfactory approximation to tissue (which contains so much hydrogen in the form of water and various organic compounds). For example, Gray and Read [12] have calculated that when soft tissues are irradiated by fast neutrons, about 92% of the energy converted goes to the recoil protons, 5% to the recoil oxygen nuclei, 2% to the recoil carbon nuclei, and 1% to other effects, and that 1 gram of average tissue would absorb seven times as much energy as 1 gram of air for neutrons of particular energy about 3 million electron volts.

For reasons such as these, Gray and Read [12] have proposed that energy absorption in water should replace that in air for the purpose of neutron dosimetry. The unit dose is then that quantity of neutron radiation which communicates to unit volume of water the same energy that is communicated by one röntgen of gamma radiation, i.e., about 94 ergs. This unit may be thought of as an "equivalent röntgen."

For the actual measurement of energy absorption in a given medium, use may be made of Gray's Principle of Equivalence. In a hydrogenous material, the "corpuscular emission" is predominantly composed of recoil protons. The application of the method has been treated in detail by Gray. A relative measure of exposure that has been widely used in practice is the ionization produced by the neutron beam in the Victoreen type of X-ray "thimble" chamber dosemeter. This arbitrary unit is known as the "n" unit.

Charged-Particle Radiations

All charged-particle radiations may be considered together, for they have this in common, that by virtue of their charge

they ionize directly, and in a qualitatively similar manner. Such radiations include electrons (beta particles), and the whole range of swiftly moving atomic nuclei, best-known of which are the helium nuclei or alpha particles, emitted by natural radioactive substances. Of these, electrons are practically the only kind of radiation used as an external beam, and even these not widely. But with the development of the betatron for producing very intense beams of high-energy electrons, the therapeutic applications may well be extended.

Since X- and gamma radiations produce their effects via the intermediary or secondary electrons, it is clear that the röntgen unit may legitimately be used for expressing dose in the case of a primary beam of electrons. A measurement of the ionization per unit volume of air gives the dose directly in röntgens.* This concept is also satisfactory for any other directly-ionizing radiation. The ionization in a "thimble" chamber is now independent of the nature of the walls, provided the primary radiation is not appreciably attenuated or reflected by them. Thus the dose rate of the primary beta radiation from "unscreened" radium plaques has been measured in röntgens.

In some cases, the radioactive substances are dispersed throughout the biological material. For example, radioactive prosphorus is used therapeutically for leukemia, and biological specimens have been immersed in an aqueous solution of radon. For such cases, slightly different concepts are appropriate, for the radiation is usually absorbed completely within the medium. Thus, knowing the total quantity of radioactive substance introduced, and the total energy emitted by each disintegrating atom, the quantity of energy communicated to the medium is known, i.e., the fundamental biological quantity is known at the outset. It merely remains to compare this true energy absorption (determined solely by the radioactive substance and entirely independent of the medium in which the substance finds itself) with that which is produced by other radiations in order to express it in "equivalent röntgens." This involves the adoption of some convention.

* The true energy absorption for a medium of specified atomic make-up could be calculated from this röntgen dose.

The actual energy liberated in 1 gram of the medium may be compared with the energy communicated by one röntgen of X- or gamma radiation to 1 gram of air, which is a definite quantity equal to about 85 ergs; or it may be compared with the energy communicated by one röntgen of X- or gamma radiation to 1 gram of the medium in question, which is not a definite quantity, but depends on the quality of the radiation and the nature of the medium. In view of the heterogeneous nature of "tissue," it is perhaps as well to base the comparison on energy absorption in air.* Thus, to arrive at the dose in equivalent röntgens, it is merely necessary to know the total amount of the radioactive material, the energy emission per distegrating atom, and the total mass through which the material is dispersed, from which is deduced the energy liberated per unit mass of the medium, which is divided by 85.

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* The energy absorption in water (for hard gamma radiation), i.e., Gray's energy unit, is in many cases a better basis for comparisons. This "equivalent röntgen" corresponds to about 94 ergs per gram.

** A comprehensive bibliography of this subject would be out of place here. The selection of references is arbitrary and in no way representative. It merely includes work referred to explicitly in the text and a few random papers which may serve as a possible entry point into the literature.

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TOTAL ENERGY ABSORPTION IN RADIOTHERAPY

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Introduction

THE dose of radiation absorbed at a point affecting individual structures, such as chromosomes, determines the local effect on these structures, and is the effect which is desired by the radiotherapist in the neighborhood of the malignant tumor. To enhance this effect by variations in quality, dose, dosage rate, fractionation, and total time is one of the chief aims of the radiotherapist. At the same time, however, general effects are produced by the radiation and manifest themselves in organs which have not been irradiated. These effects are troublesome and difficult to avoid and, in attempting to correlate them with dose, I perceived the necessity for estimates of the total energy absorption by the body. I, therefore, asked Dr. Happey to investigate the problem so as to provide an estimate of the volume dose in "röntgen cubic centimeters" (r cm.^{3}). Mayneord, however, was also engaged in a similar investigation on different lines, and had coined the terms "integral dose" and "megagram-röntgen." The latter is a more convenient unit and a more euphonious term, and so is to be preferred to the term "röntgen cubic centimeter." It is intended in this short paper to discuss briefly the physical approaches, attempts at correlation with biological effects, and then the practical value of the conception of volume dose.

Physical Estimates

Happey [9, 10] points out that the energy absorbed in the axial pencil of a very large field is maximal because the proportion

of scatter is maximal. If all the radiation scattered outside the geometrical beam were confined to it then, for any size of field, the energy absorbed at any point of the beam would be the same, at the same depth, as for the saturated pencil. Thus, assuming that all the scattered radiation is absorbed and that none escapes from the body, the volume dose is estimated by the product of the area of the field on the skin, the dosage in röntgens (corrected to allow for the "unsaturation" of the field) and a graph reading. The graph (figure 1) is obtained by integrating the area under the depth-dose curve for the saturated axial pencil of a very large field. The correction for unsaturation is the ratio of the dosage rate with maximum scatter to the measured axial skin dose of the field concerned.

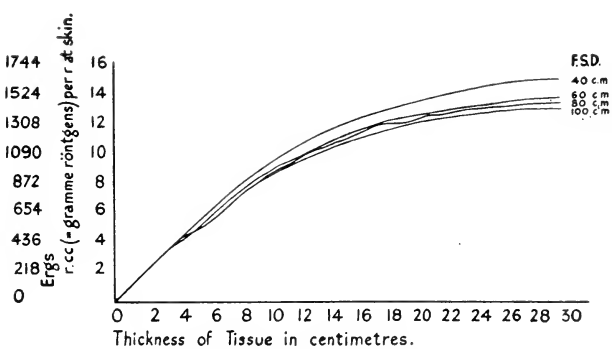

FIG. 1. Graph Relating Volume Dose per Röntgen at Skin Surface to Thickness of Tissue through Which the Beam Passes. (From Ellis.[4])

Thus, comparing a field of 400 square centimeters and one of 50 square centimeters, we have the following factors (200 kilovolts, constant potential 1 millimeter Cu 1 millimeter Al 40 centimeters FSD *):

Field size (cm^2)	Dose rate (r/min)	Tissue thickness (cm)	Graph reading	Volume dose per röntgen at skin
400	92	20	13	$13 \times 400 \times \frac{92}{92}$
50	76	20	13	$13 \times 50 \times \frac{76}{92}$

* FSD = Focus-skin distance.

Mayneord approached the problem on different lines, and has done a great deal of work alone, and with his collaborators, on the theoretical and practical aspects of the problem. His original paper [12] described a method of integrating the dose by measuring the volume of rotation between the isodose surfaces of a beam by practical measurement of the moment of the area, and gives values for volume doses of different types of radiation which throw into sharp contrast their differences in this respect. (See table I.)

He discusses [13] the mathematical theory of volume dose and derives the following interesting generalizations. For a beam in which the dose contours in a given plane-section are straight lines perpendicular to the axis of the beam, and the dose falls linearly with depth, the integral dose is given by the product of the mass of the body concerned and the dose at its center of gravity. From investigations made in collaboration with Clarkson, [15] on a wax model of a man, tables were constructed giving the "average" dose throughout a patient of a given thickness and a given quality of beam. (A body of mass M receives an average or mean dose $\overline{D}$ when the Integral or Volume Dose $\Sigma := \overline{D}.M.$) This "average dose," corrected for focus-skin distance and multiplied by the mass of the patient gives the "integral dose."

Mayneord further [14] discusses the mathematical theory of integral dose in radium therapy. It appears that, for concentric shells about a radium source, the volume dose of each shell is proportional to its thickness and the number of milligram-hours (mgh) at the center. Moreover, there is a reciprocal relationship between the source emitting radiation and the volume receiving it. "The integral dose throughout any volume whatever, due to a finite source, uniformly filled with radioactive material, is equal to the integral dose throughout the original source if the 'receiver' be filled with radiating material of the same uniform density." A graph is given from which the integral dose per mgh for point sources near the center of an absorbing mass, may be read (figure 2). For a sphere of radius

TABLE I

Number of radiation	Type of radiation	Type of technique	Potential (kv)	Filter	Mean wave length Å	Focal distance (cm.)	Diameter of field (cm.)	Gram-röntgens to 10% contour	Ergs/cm.²/r
1	X-rays	Röntgen cautery	45	Unfiltered Tube only	0.90	2.0	1	71.5	36
2	X-rays	Contact therapy	60	Tube only 0.2 mm. Ni equiv.	0.33	5.0	4	4,200	730
3	X-rays	Deep therapy	200	1 mm. Cu	0.12	50.0	10	96,560	3,200
4	X-rays	Super voltage	400 (peak)	4 mm. Cu	0.069	50.0	10	110,000	3,100
5	γ-rays	1-gram unit	—	1 mm. Pt equiv.	0.014	5.0	5	14,594	3,020
6	γ-rays	5-gram unit	—	1.4 mm. Pt equiv.	0.013	8.2	8	51,587	3,060

(From Mayneord [12])

a, the volume dose throughout the sphere was calculated by Mayneord to be

$$\Sigma = 8.3 \times 4\pi a \times \mathrm{F} \text{ per mgh}$$

where $$\mathrm{F} = 2a + \frac{a^2 - c^2}{c} \log_e \frac{a + c}{a - c}$$

c being the distance of the point source of radium from the center of the sphere, and the relationship of F to c/a is given in figure 3, taken from Mayneord. Examples of volume doses are given for certain situations and techniques met with in practical radium therapy.

For example:

1. In treating a carcinoma of the maxillary antrum with a dose of 3,000 mgh, the volume dose is assumed to be that for a sphere of radius 9.8 centimeters and of mass approximately 4 kilograms with the radium relatively centrally placed:

   $$\Sigma = 3{,}000 \times 0.89 = 2.7 \text{ megagram-röntgens,}$$

   0.89 being the graph reading (see figure 2).

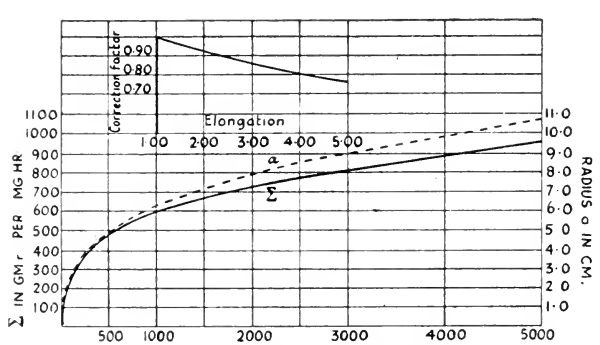

FIG. 2. Integral dose per mgh for point sources near the center of an absorbing mass of known volume and mass. (From Mayneord.[34])

2. In treating carcinoma of the cervix uteri with a dose of 6,000 mgh, the integral dose is calculated as about 9.8

megagram-röntgens, neglecting the absorption by the filters in which the radium is packed.

Measurements of Volume Dose

Measurements of volume dose have been attempted by Boag,[1] using the model constructed by Grimmett.[7, 8] This model consists of spaced plates 6 millimeters thick, of density 0.985, graphited and spaced 2 millimeters apart by thick washers of

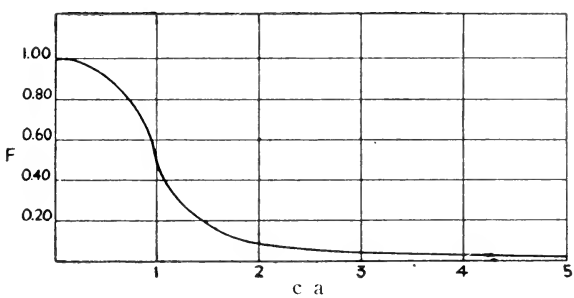

FIG. 3. Curve relating

$$F\left(= 2a + \frac{a^2 - c^2}{c}\log_e\frac{a + c}{a - c}\right)$$

to $\frac{c}{a}$ where c is the distance of a point source of radium from the center of a sphere of radius a. (From Mayneord.[14])

the same material (cellulose acetate) as the plates. Alternate plates are connected together, thus forming two groups of plates, each of which is connected to opposite poles of a battery with a sensitive galvanometer in circuit, to measure the total ionization current collected from all the air-gaps, i.e., from the whole body under radiotherapeutic conditions. Under these conditions, guard rings were found to be necessary to prevent insulation leakage, and allowance had to be made for their effect. Moreover, the absorption conditions for a wide range of wave lengths and various angles of incidence of the X-ray beam had to be similar to those for the human body. These points were all

dealt with, and curves were constructed from which volume doses delivered with X-rays of HVL 2 to 4 millimeters Cu can be estimated quickly and fairly accurately. Boag's measurements indicate that the volume dose depends principally upon the area and site of the field. The FSD linear dimensions of the patient and HVL of the beam have much less effect.

Photographs of the model are shown in figures 4 and 5, and curves representing some results in figures 6 and 7 from Boag.[1]

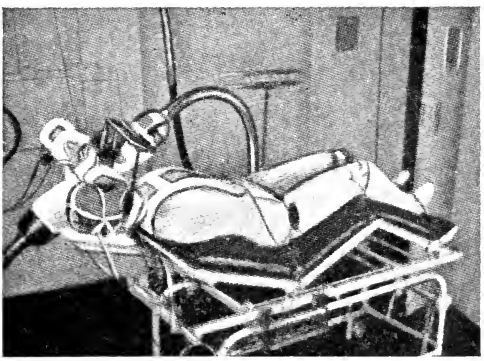

FIG. 4. Grimmett's ionization-chamber "man" in position for treatment to the head. (From Boag.[1])

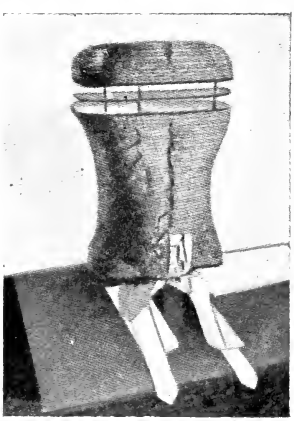

FIG. 5. Photograph showing the general appearance and method of construction of the trunk of Grimmett's ionization-chamber "man." (From Boag.[1])

Mayneord and Clarkson [15] also constructed a wax model for making measurements to estimate the volume dose when the whole body is irradiated. The actual measurements were made in slabs filled with the suggested powder mixture of Spiers,[17]

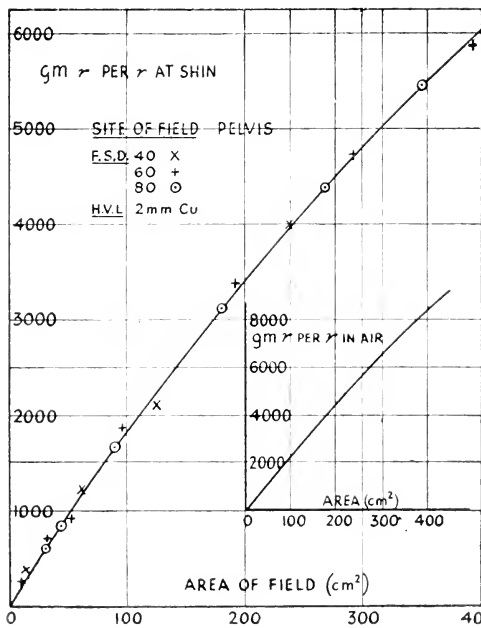

FIG. 6. Relation of volume dose to field area for irradiation of the pelvis. Inset curve shows relation for röntgen dose measured without scatter, which is linear up to 200 square centimeters. (From Boag.[1])

and estimated both by the average-dose method and by planimeter measurements of the areas between isodose curves in the body-section (figure 8). Their results are represented graphically in figures 9 and 10, which show the volume dose in gram-röntgens per röntgen to the surface of the body (70 kilograms) for various half-value layers. It is seen that there is a rapid rise up to HVL = 0.2 millimeter Cu (= about 100 kilovolts with 0.15 millimeter Cu filter) followed by a less rapid change.

Value of the Conception of Volume Dose in Radiotherapy

The volume dose might conceivably help in deciding on modifications of technique, and might help in correlating physical dose with general effects of radiation.

It must be realized, however, that the physical methods hitherto described for estimating volume dose suffer from certain inaccuracies. The chief of these are due to the fact that allowance is not made, in the physical methods, for the variable tissues and their densities in the human body, while biologically one cannot expect uniform behavior of various tissues for a given physical dose.

Physical Factors

The author has attempted elsewhere to show the effects of certain physical factors on volume dose.[3, 4]

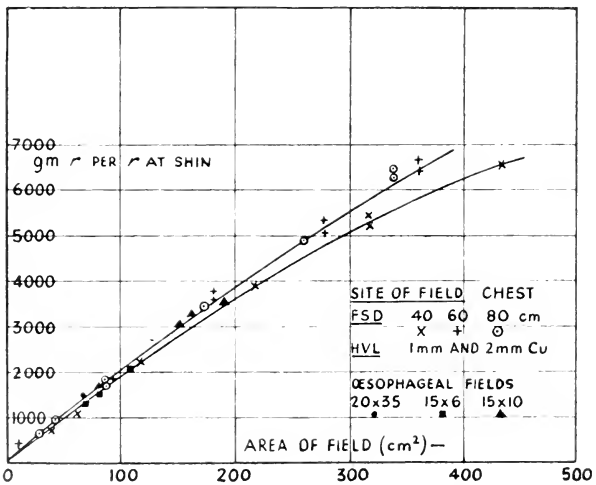

FIG. 7. Relation of volume dose to field area for chest irradiation. The lower curve is for the shorter FSD (40 centimeters). (From Boag.[1])

TABLE II

EFFECT ON VOLUME DOSE OF INCREASED FSD (CARCINOMA OF ESOPHAGUS, 40 CENTIMETERS FSD AND 100 CENTIMETERS FSD)

200 kv 1.5 mm Cu HVL Field size 15 × 4 cm²		Tumor dose = 6,000 r Eight fields
FSD = 40 cm Field dose = 3,400 r		FSD = 100 cm Field dose = 2,800 r
r cm³/cm²/r	Field thickness (cm)	r cm³/cm²/r
13.4	1 19	11.79
13.4	2 19	11.79
13.82	3 22	12.47
13.82	4 22	12.47
13.82	5 22	12.47
13.82	6 22	12.47
15.3	7 30	13.6
15.3	8 30	13.6
112.68		100.66

TOTAL ENERGY ABSORPTION

$$3{,}400 \times 60 \times 126 \times \frac{92}{76.3}\ \text{r cm}^3 = 3.11 \times 10^7\ \text{r cm}^3 \quad (125\%)$$

$$2{,}800 \times 60 \times 101 \times \frac{92}{76.3}\ \text{r cm}^3 = 2.05 \times 10^7\ \text{r cm}^3 \quad (100\%)$$

Field Area

The volume dose is almost proportional to the field area.

Focus-Skin Distance

A comparison is made in Table II of the volume dose using two techniques for treating carcinoma of the esophagus, the only difference between them for a given tumor dose being the difference in FSD. These estimates are based on Happey's

method [10] and it should be pointed out that Boag's graph (figure 7), for a similar technique, shows no appreciable difference with the two FSD and gives a rather higher value (36 megagram-röntgens) than either of the two techniques compared above.

The Arrangement and Number of Fields

The author has discussed [4] the effect of these factors for two sets of conditions:

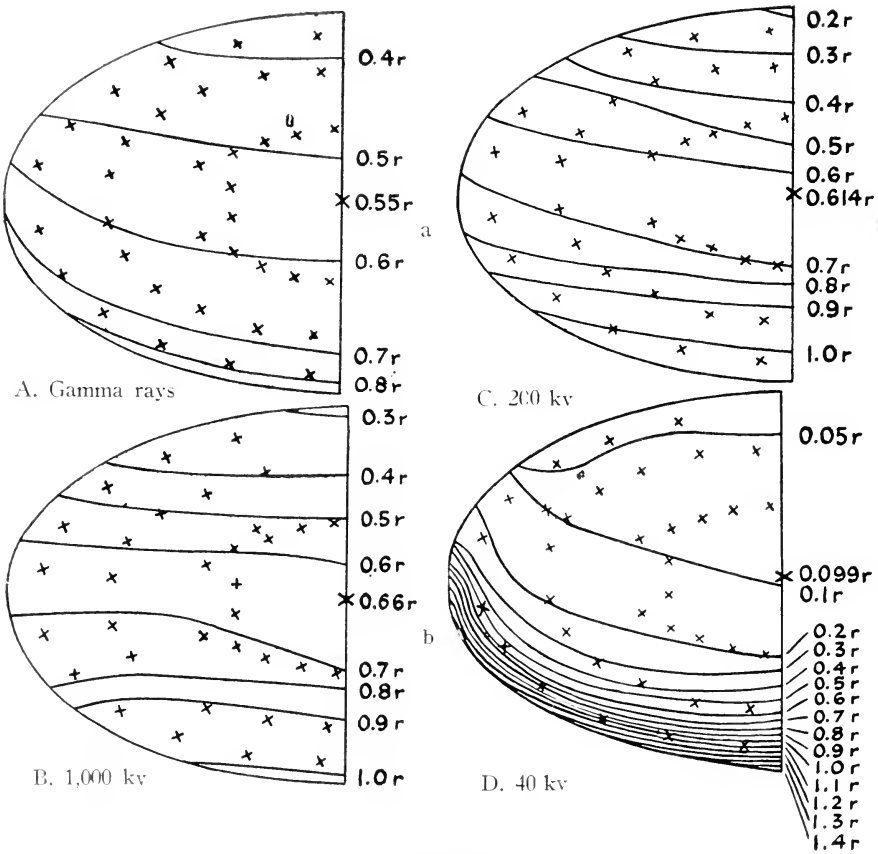

FIG. 8. Isodose distributions in a cross-section of the trunk for various qualities of radiation. (From Mayneord & Clarkson.[15])

Quality of the Beam

The effect of the quality of the beam as determined for whole-body radiation has been mentioned already (see figures 9, 10). Also Phillips [16] demonstrated that for a given tumor dose, there is a considerable difference in volume dose between techniques using 200 kilovolts and 1,000 kilovolts (see table III).

TABLE III

200 kv	For a tumor dose of 6,000 r	1,000 kv
2,400 r	Dose per field	1,620 r
5,030 r	Max. skin dose	3,400 r
67	Volume dose (megagram-r)	41

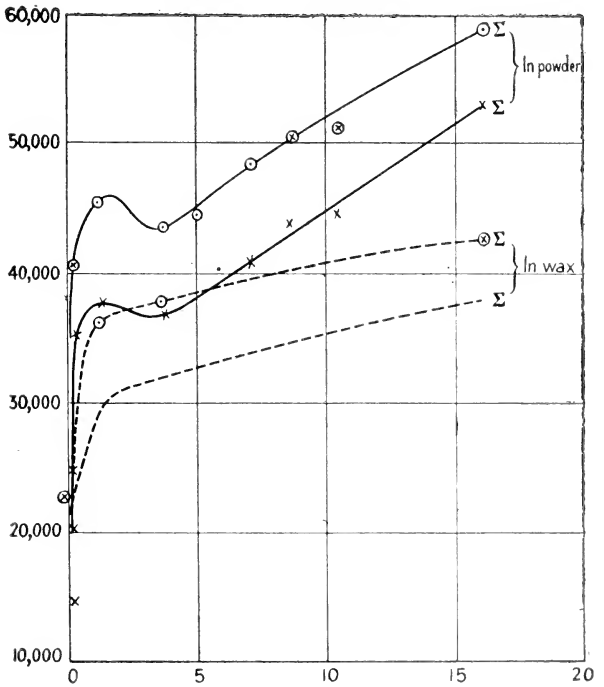

FIG. 9.*

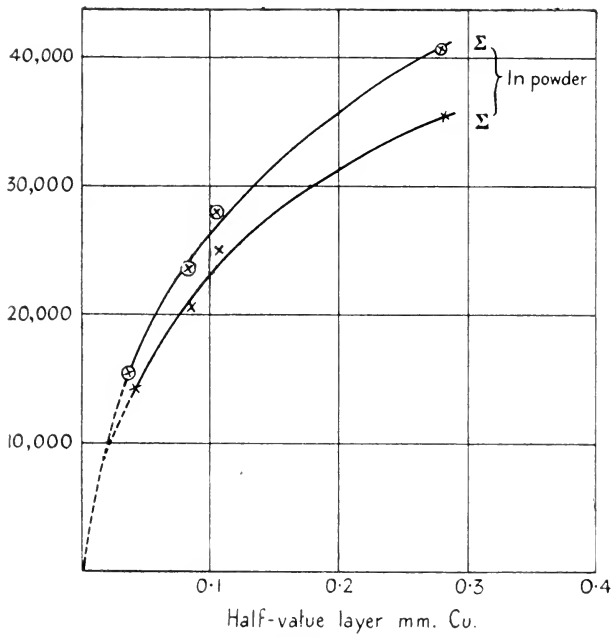

FIG. 10.*

* Figures 9 and 10 show a comparison of the values of integral dose obtained in a model patient constructed wholly of wax and in a model constructed of Spiers' mixture for various radiation qualities. (From Mayneord and Clarkson.[15])

a. Using Ungar's [18] conception of the economy quotient, it can be shown that the greater the homogeneity of dosage, the smaller the volume dose. Ungar gives examples of arrangements of fields for treating a case of carcinoma of the cervix in relation to the "economy quotient" and the volume dose. The economy quotient is the ratio of the minimum tumor dose to the difference between the maximum and minimum tumor doses, and is a measure of the efficiency of the technique. It seems that, other things being equal, the arrangement which gives the greater economy quotient gives the smaller volume dose. Since the economy quotient is highest when the difference between the maximum and minimum tumor doses is smallest, it follows that the greater the homogeneity, the smaller the volume dose (see figure 11).

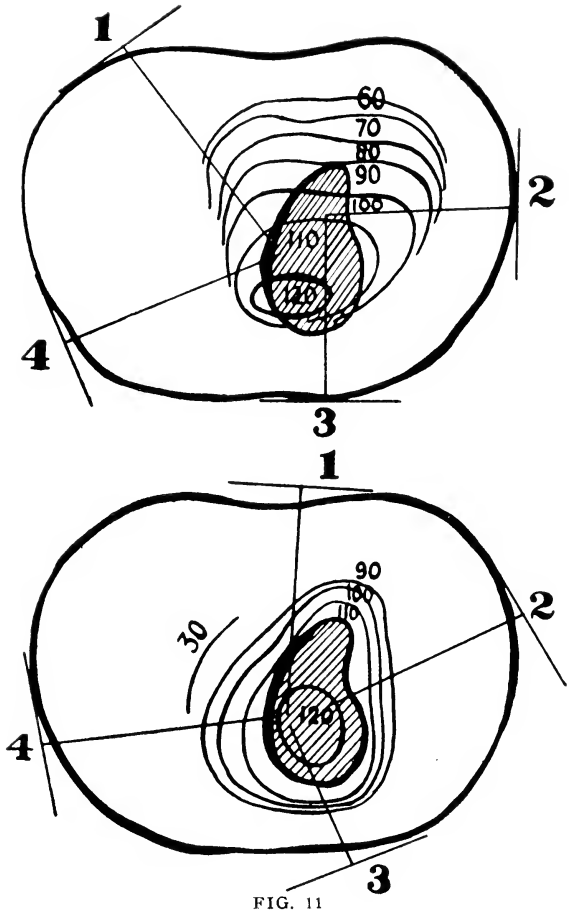

FIG. 11

TOP

$D^{t}_{\text{max.}} = 120\%$

$D^{t}_{\text{min.}} = 110\%$

$D^{t}_{\text{max.}} - D^{t}_{\text{min.}} = 30\%$ (heterogeneity factor)

$\dfrac{D^{t}_{\text{max.}} \quad D^{t}_{\text{min.}}}{\text{Het. Factor}} - \dfrac{90}{30} = 3$, the economy quotient

BOTTOM

$D^{t}_{\text{max.}} = 120\%$

$D^{t}_{\text{min.}} = 110\%$

$$\text{Economy quotient} = \frac{110}{10} = 11$$

Volume dose = 4.36 megagram-r

(From Ellis.[4])

b. Using two wedge fields as described by Ellis and Miller [5] (see figure 12), the volume dose for 1,000 r tumor dose calculated by me from measurements made by Boag,[1] is 1.42 megagram-röntgens. An appropriate technique to achieve the same treatment without wedge fields would be to use two lateral 10 × 8 square centimeter fields and one 6 × 4 square centimeter, e.g., to the skull. Under these conditions, the volume dose for 1,000 r tumor dose is 2.4 megagram-röntgens—obviously higher than that for the wedge fields.

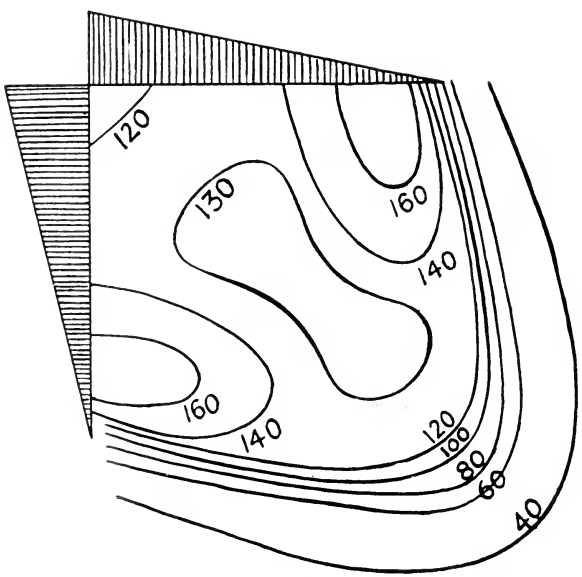

FIG. 12. Diagram of the isodose distributions produced by combining two X-ray beams at right angles, using wedge filters. (From Ellis and Miller.[5])

Volume Dose and Tolerance Dose

Mayneord and Clarkson [15] by their work on whole-body irradiation have put the energy absorption by the body under such conditions in true perspective, and a new aspect of the conception "tolerance dose" has emerged. For whole-body irradiation, the volume dose relationships for 40 kilovolt, 200 kilovolt, and

gamma radiation respectively are in the ratio of 15 : 35 : 40, for a wide beam enclosing the body, and a very large FSD—i.e., the conditions under which radiation is received by medical workers. In other words, for a given dose in "röntgens" to the skin—which is the present method of estimating tolerance dose—the energy absorbed by the body may vary considerably from one type of radiation to another. Since the biological effect considered in the internationally accepted figure of 10^{-5} r per second is a general effect rather than a local one, it would seem more accurate to aim at a volume dose estimation rather than a surface dose. It is interesting to note that the international figure for diagnostic X-rays (10^{-5} r per second) is three times that for gamma rays, and that this ratio, decided by experience, is of the order of the ratio of the volume doses of 40 kilovolt X-rays and gamma rays.

The following table (IV) shows the influence of technique on the volume dose in treating cancer of various sites.

TABLE IV

TECHNIQUE AND TOTAL ABSORPTION OR VOLUME DOSE. HVL-0.15 MM CU FSD-40 CM

Region	Dose 1,000 r	Fields No. cm²	Total absorption r cm³
Tonsil	4.5	2 × 10/8	7.77×10^6
		2 × 6/4	—
Fauces	4.0	2 × 10/15	11.26×10^6
		2 × 6/4	—
Larynx	5.0	2 × 6/8	—
		1 × 6/4	4.53×10^6
Brain	4.0	2 × 10/8	—
		1 × 6/8	11.97×10^6
Bladder	5.6	8 × 8/10	17.24×10^6
Pelvis	3.0	2 × 10/15	25.97×10^6
(supplement to radium)	3.0	2 × 10/15	—
Esophagus	6.0	8 × 15/4	31.1×10^6
Lung	4.0	4 × 10/15	30.3×10^6
Lung	5.5	5 × 6/8	19×10^6

The discrimination now possible between volume dose and surface dose should permit of new standards. That limiting the permissible general radiation should be a volume dose, and that limiting the local radiation a surface dose, which might presumably be higher than the figure used hitherto, which, in effect, has no real value for those working with radium.

Correlation of Biological Effects with Volume Dose

The ultimate practical value of the conception of volume dose will depend on the possibility of using it as a criterion for modifying technique, and as a means of obtaining more knowledge of the action of radiation. The physical factors hitherto discussed indicate the manner of influencing volume dose by technical variations.

Modification of technique will be considered by a radiotherapist only if the general effect of the radiation is of such magnitude as to interfere with the delivery of a local dose. General effects,

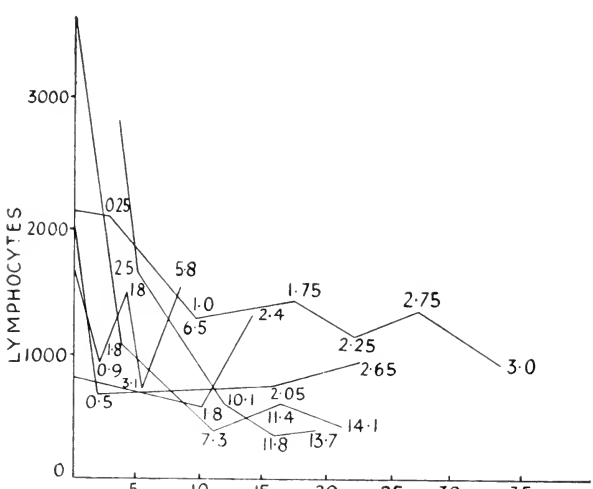

FIG. 13. Lymphocyte Counts in Individual Patients

Abscissae = days after commencement of radiation. The volume doses received are indicated on the curves. Note that although the trend is marked, each curve shows a rise at some time during treatment. (From Ellis.[4])

as distinct from local effects, however, might be due to the local effects of radiation. Thus, the local effect of radiation on the mouth and esophagus might have a profound effect indirectly on the general nutrition, the lighting-up of local infection might also have a marked general effect, while local edema in such specialized structures as the lung and brain might have a marked effect on general well-being. Moreover, the variable structure of the human body makes estimates of the usual accuracy demanded in physics almost impossible. In addition, different regions of the body differ in sensitivity, while the variation from one human being to another, due to metabolic, physical and psychological differences, conspires, with the influences mentioned above, to make difficult the correlation of biological phenomena with volume dose. Nevertheless, some attempts have been made.

The Volume Dose Limiting Radiation Technique

In table IV the volume dose for lung and esophagus of about 30 megagram-röntgens in one month is near the limit of what the patient can tolerate. Levitt,[11] in an account of trunk-bath radiation, finds that the maximum dose to the surface which can be tolerated is 1,500 r (measured with backscatter), though treatment under such conditions has not to be stopped because of local effects, e.g., on skin. This corresponds to a volume dose of about 30 megagram-röntgens in 6 weeks. Phillips[16] found that 40 megagram-röntgens was less than the maximum dose that could be tolerated in about 4 weeks in treating a rectum. At the London hospital, I find that treatment to the whole abdomen permits of a volume dose of about 40 megagram-röntgens in 3 weeks, so that it appears that a patient will tolerate a large volume dose to a smaller part of the body more readily than to a large part.

Apart from therapeutic conditions such as these, it does not seem from table IV that the volume dose is likely to limit technique as at present developed. It is possible to imagine conditions, however, under which such limitation might occur. Sup-

pose, for instance, that instead of being delivered in one month, a volume dose of 7 or 8 megagram-röntgens is to be given to a patient in treating a tongue in one day. It might be that, under such conditions, volume dose is a limiting factor. Such a possibility is not inconceivable in the light of the hypothesis suggested by Gray [6] that the number of fractions rather than the total time is more important. If this is true, then techniques might be developed necessitating the administration of very large doses in many fractions in a very short time.

What Biological Phenomena Can Be Correlated With Volume Dose?

The phenomena must be general, as distinct from local, and may be subjective or objective.

Subjective phenomena such as malaise, nausea, vomiting, and headache are very difficult to correlate, especially since so many of these symptoms might be produced by general upsets not due to radiation.

Objective phenomena may be measurable or not. Here we shall consider measurable phenomena only. They may be divided into (*a*) blood counts, (*b*) other measurements.

Blood counts are the easiest tangible evidence to obtain of the effects of radiation.

Ellis [3] tried to correlate the blood counts, corpuscular volume, and other factors, with volume dose. No correlation was possible. Figure 13 shows types of lymphocyte counts obtained. Althought there is an average trend, individual counts behaved very differently, even rising during relatively rapid administration of radiation at some part of every curve. Other types of cell are much more erratic. Thus correlation in individual cases is impossible. From the work of Bush,[2] however, there appears almost a mathematical correlation. Figure 14 is based on average lymphocyte counts of 26 cases treated for carcinoma of the mouth, pharynx and larynx. The possibility of individual variations as in figure 13 still, of course, exists. Experience of abdominal-bath treatments provides the same type of curves as

in figure 13. Thus the volume dose cannot be correlated with the lymphocyte count (and still less with other cell counts) in individual cases.

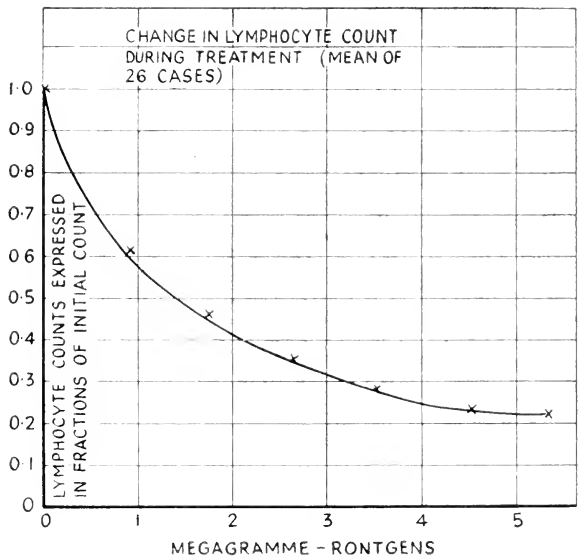

FIG. 14. Curve of average lymphocyte counts of 26 patients all treated by a similar technique related to volume dose in megagram-röntgens. (From Bush.[2])

The effect of X-rays on the blood concentration of ascorbic acid in animals and patients has been investigated by Kretzschmar,

TABLE V

Diagnosis	Treatment (200 kv) (tumor dose)	Ascorbic acid mg % in plasma	
		Before	Immediately after
Breast carcinoma	Post-operational X-ray 300 r	0.501	0.435
Breast carcinoma	Post-operational X-ray 300 r	0.836	0.794
Mediastinal tumor	X-ray 350 r	0.303	0.286
Breast carcinoma	Pre-operational X-ray 1,200 r	0.420	0.336

working with the author.[4] There is no doubt that X-ray treatment reduces the ascorbic acid content of the blood and of the tissues in animals, and the ascorbic acid content of the blood in patients. Table V shows a diminution of the plasma ascorbic acid during treatment in three breast cases and a case of mediastinal tumor.

The technical arrangements for the breast cases are similar in all three patients, and it is obvious, on a superficial examination of the figures, that there is a qualitative but not a quantitative correlation with volume dose even in these few cases.

It seems likely that the chemical changes which occur in the body soon modify any substances which might be formed, so that it might be impossible even to achieve biological correlation, although the most hopeful line of attack on the problem would be to try to estimate breakdown products, such as adenosine, as being the possible initial substances. Other effects seem likely to be secondary, whether chemical, cytological or physiological, and as such will not offer any real correlation.

ACKNOWLEDGMENT.—The illustrations are reproduced from the *British Journal of Radiology* by kind permission of the editor and of the authors concerned.

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ON TECHNICAL METHODS IN X-RAY THERAPY

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General Survey

X-RAY therapy is often roughly divided into various classes—contact therapy, superficial X-ray therapy, deep X-ray therapy, supervoltage therapy—yet these classes, and the various methods within each, all have certain physical principles in common. Firstly, it is desired to produce a chosen distribution of X-ray dose through a patient's tissues by combining the necessary number and arrangement of fields. It may be considered adequate to produce more than a certain minimum dose throughout a region, such as a tumor, with as little as possible elsewhere, without caring what the maximum in this region may be. A more stringent requirement is that the dose be uniform throughout the region. Ungar [37] has shown that under certain conditions, the total radiation absorbed by the body is a minimum, for a given tumor dose, when that dose is uniform throughout the tumor. A general requirement is that the dose at the skin, where each beam enters, shall not exceed a certain value, account being taken of all contributions from other beams. There may also be other regions where it is particularly necessary to keep the dose small.

Secondly, it is desired to keep the radiation dose absorbed by all the healthy tissues as small as possible in relation to that absorbed in the treated volume. This requirement not only influences the manner in which the X-ray fields are arranged to give the desired dose distribution; it also largely determines the class of therapy chosen. If a lesion is near the surface of the body, or accessible through a body cavity, or with the aid of

surgery, it is generally better to use a beam of less penetration and small focus-skin distance, so that the dose in the healthy tissues beyond the lesion diminishes rapidly with the depth in the tissues. A rough measure of this total body dose is obtained by summing the product of dose and volume throughout the body, though it is evident that this is only a rough guide, as the susceptibility to radiation of each element of volume as well as the dose there determines the aggregate effect.[6]

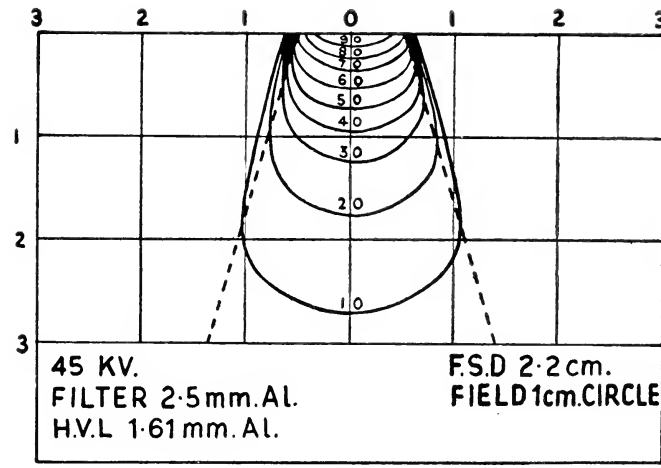

FIG. 1a. Isodose Curves for a Contact-Therapy Field

Field 1 cm circle, focus-skin distance 2.2 cm, radiation generated by 45 kv and filtered by 2.5 mm aluminum, HVL 1.6 mm aluminum (Mayneord[20])

The possible ways of combining X-ray fields to produce a desired distribution are studied with the aid of isodose charts. Typical charts are shown in figure 1*a* (for a low-voltage contact-therapy tube), and figure 1*b* (for a deep-therapy tube).[20] The dose distribution in a plane through the body due to a certain field is described by curves, which each join points of the same dose rate expressed as percentages of that at the center point of the field on the skin. Strictly speaking, these charts are not obtained by measurements in the human body, but in a "phantom" constructed of material the absorption and scattering of X-rays

of which approximate to that of tissues. Generally water is chosen, but sometimes wax, mixtures such as rice flour and sodium bicarbonate, and "pressedwood"—compressed wood-pulp boards—are used. Also, for the sake of standard conditions, the

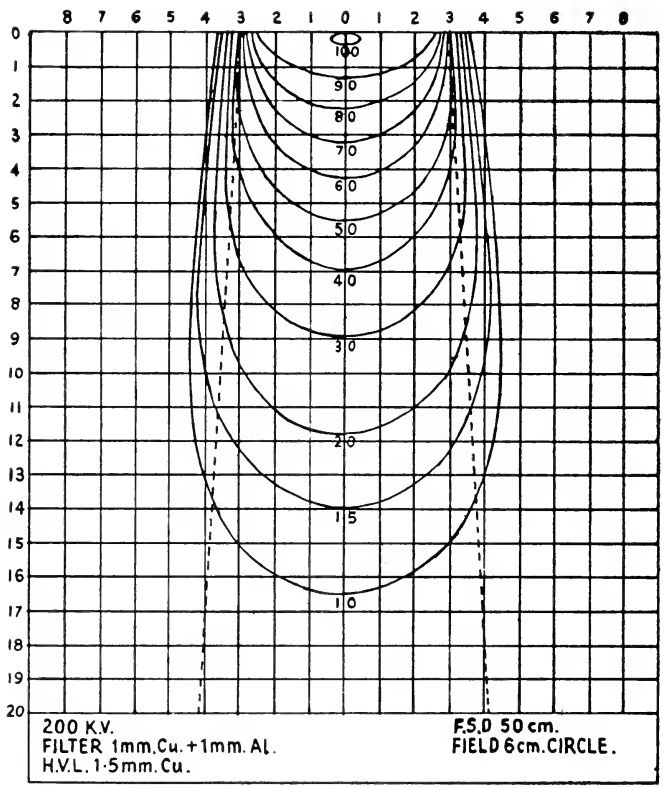

FIG. 1b. Isodose Curves for a Deep-Therapy Field

Field 6 cm circle, focus-skin distance 50 cm, radiation generated by 200 kv and filtered by 1 mm copper and 1 mm aluminum, HVL 1.5 mm copper (Mayneord [20])

measurements are made in a phantom large enough to approximate to a semiinfinite slab. Deviations from these charts which are likely to occur in practice, due to the nature of the human body, are considered later.

When a suitable distribution of fields has been chosen to give

a desired dose distribution on paper, means must be found to direct the X-ray beams sufficiently accurately to give this distribution in practice. If the absorption of the radiation in the healthy tissues is to be a minimum, beams no wider than necessary must be used. This makes accurate aiming very important. Rarely is more than one tube used at a time; usually a single tube is directed successively in the desired ways. This may be done by adjustment of the tube applicator to skin markings, with orientation of the tube to calculated angles. To assist in this, numerous beam-direction devices have been developed. Alternatively, jigs can be made, which are attached to the patient in fixed positions, and aid in the correct adjustment of the tube. Finally, methods must be mentioned in which there is a relative rotation of X-ray tube and patient, so that the axis of rotation and the X-ray beam pass through the tumor roughly at right angles to each other.

The desirability of beams being no wider than necessary was mentioned earlier. A broad beam provides a greater depth dose than a narrow beam, as the dose is enhanced by the scattering from a greater block of tissue. Beams broader than the tumor cross section have been used to give an adequate tumor dose at a depth, but it is preferable to use more beams with a cross-fire technique, or use a more penetrating radiation, so that the minimum beam width will suffice.

Illustrative Dose Distributions

a. Single fields. These are suitable for treatments where the maximum dose must be given to the surface. In this case, it is desirable that the dose rate should decline rapidly, and an easily absorbed X-ray quality, i.e., one generated by a relatively small kilovoltage, is therefore chosen—the so-called Chaoul or contact therapy. Meredith [23, 24] has shown that the dose received by the first millimeter or so of tissue is appreciably altered by secondary radiation from the applicator and metal parts in the tube, and can be reduced in relation to the dose at 5 millimeter depth by spraying the applicator with aluminum paint and covering the tube window with aluminum foil.

b. Multiple fields. When it is desired to produce a relatively uniform dose distribution through a volume, or to dose a tumor at a depth to a greater degree than the skin at the area of entry of the X-rays, it is evident that a number of beams must be used which all include the tumor, but enter through different skin areas. The simplest case is that of two oppositely directed beams. This is useful in the treatment of the lip, eyelid, or nose, by contact therapy, and gives a fairly uniform dose distribution.[11] It has been discussed by Smithers [14] and by Wilson.[43] With the usual deep-therapy conditions—40 to 100 centimeters FSD (focus-skin distance), about 1 millimeter copper HVL (half value layer)—a dose varying between 90% and 105% of the skin dose (the sum of contributions from both fields) can be obtained through a thickness of about 12 centimeters, i.e., the diameter of the average neck.

Two fields at right angles give a region of maximum dose on the bisector, and nearer to the apex of the angle than the point of intersection of their axes. Wilson [41] has shown that this can be put to advantage, for example, in the treatment of a tumor of the lung, situated near the anterior chest wall (figure 2).

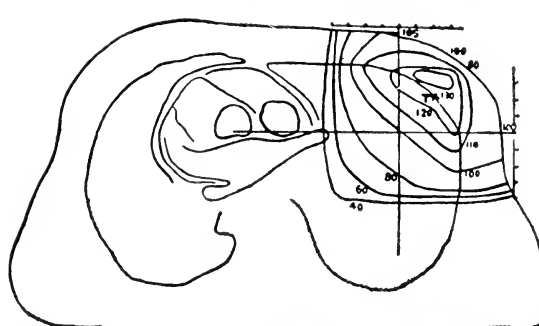

FIG. 2. Fields Prearranged Using Dose Contours

Tumor uniformly irradiated with maximum dose equal to 120% of maximum skin dose. 2 10 × 8 cm fields only

Irradiation of a tumor of the lung near the anterior chest wall by two fields at right angles. The maximum dose occurs on the bisector of the angle between the fields, but nearer to the apex of the angle than the point of intersection of the axes of the two beams. The fields are arranged to give this region of maximum dose at the site of the tumor (Wilson [41])

Skill in arrangement of multiple beams is acquired by a study of existing dose distributions, of model isodose surfaces,[21] and by trial arrangement of isodose charts and modifications of these arrangements. A few examples are given below. When the beam axes are coplanar, the case is simpler. Wilson [41] has shown an arrangement of three fields to give a good dose distribution for treatment of a larynx (figure 3). A case in which it is desired to keep the X-ray dose low over a region is in the treatment of the cervix uteri by combined X-ray and radium. Intrauterine and vaginal radium applicators, which give an adequate local dose, give too little to the more distant parts of the pelvis, which must therefore be dealt with by X-rays. The beams are directed to give maximum effect at the lateral wall of the pelvis, but be limited where the gamma rays are effective, the two together giving a uniform distribution. Reference should be made to papers by Walker,[40] and Sandler [32] for diagrams which give the dose distribution throughout the pelvis.

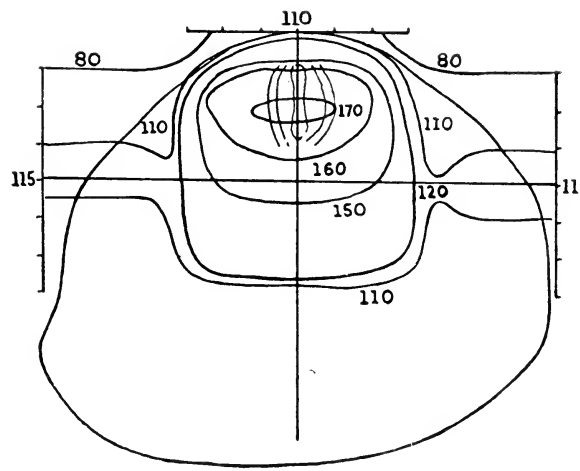

FIG. 3. Fields Prearranged Using Dose Contours

Larynx uniformly irradiated with a dose equal to 140% of maximum skin dose

Arrangement of three fields with coplanar axes to give a relatively uniform dose distribution through the larynx 1.4 times that of the maximum skin dose (Wilson [41])

More complicated cases of summation of three and of four beams, whose axes are not coplanar, have been given by Lamerton and Mayneord [14] and by Ungar [39] respectively. Ungar develops methods of treating vertebrae with 200 kilovolt radiation which give a dose at the lesion about 1.4 times as great as that at any skin area, except for certain small field overlaps not exceeding 5 square centimeters.

The method of rotating the patient (or tube) carries the multiple-beam technique to the limit, where the skin area of entry of the beam becomes a continuous belt round the patient. Nielsen [27] has described the application of this method in the treatment of cancer of the esophagus. The patient sits on a stool which rotates him once in about 15 minutes about an axis along the esophagus, which is 50 centimeters from the tube focus. A narrow beam is used, and to insure that it includes the esophagus the shadow pattern of this beam is viewed on a fluorescent screen. With radiation of 0.9 millimeter copper HVL, the skin dose on the anterior and posterior surfaces is 40% to 50%, and in the axillae 25% to 35% of the central dose. The longer radius from the axis of rotation to the axilla gives the skin in this region a greater linear velocity, so that it more quickly crosses the X-ray beam. Jensen [17] has described irradiation of the pelvis with a tube which rotates through 180° about an axis in the supine (and then prone) patient. Various modifications are possible in these methods—the shutter can be closed during part of the rotation, the angular velocity can be varied at different parts of the arc, and by tilting the beam axis at an angle to the axis of rotation, first in one direction and then in the other, the tumor can be irradiated through two zones of skin to provide a still greater ratio of tumor to skin dose. In the last case, however, the position of the maximum dose may be shifted along the axis of rotation away from the point of intersection of the beam axis.

c. Wedge fields. Ellis and Miller [7] have shown that an X-ray beam can be so modified by a wedge-shaped filter that two such fields at right angles, with the thick edges of the wedges contiguous, give a fairly uniform dose distribution through the block

of tissue of which the two fields are adjacent sides. The dose declines rapidly outside this block. The single field with the wedge-filter, and the two fields added at right angles, are shown in figures 4*a* and 4*b*. To produce a field like 4*a*, the wedge must cause a very considerable absorption, so that the useful dose rate is seriously diminished. However, if adequate dose rate is available, the arrangement is very convenient for the irradiation of lesions situated a few centimeters deep to the skin, and is specially suitable to use with a jig to give accurate direction of the beams.

When a number of fields are chosen to give a uniform dose distribution, a complete set should be administered to a patient at one treatment, and not at intervals of a day or so.

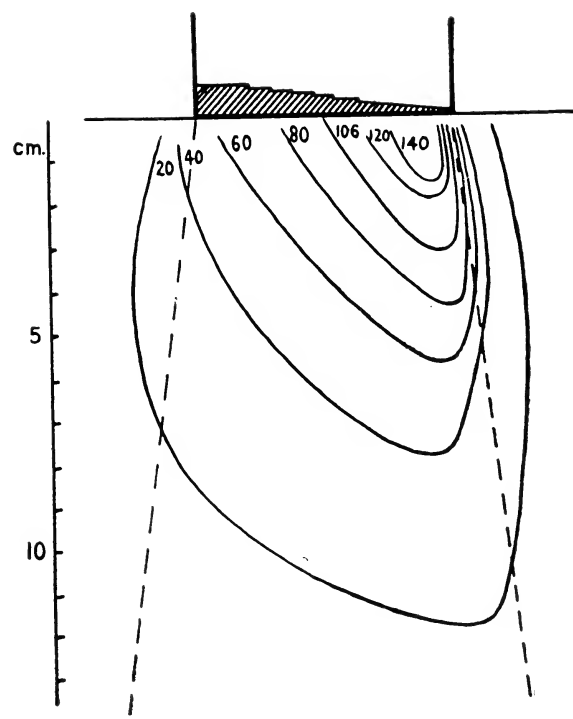

FIG. 4a. Isodose Curves as Modified by a Brass Wedge-Filter of Maximum Thickness 6.3 mm. Field 8 × 8 cm, Focus-Skin Distance HVL of the Radiation 1,5 mm Copper (Ellis and Miller [7])

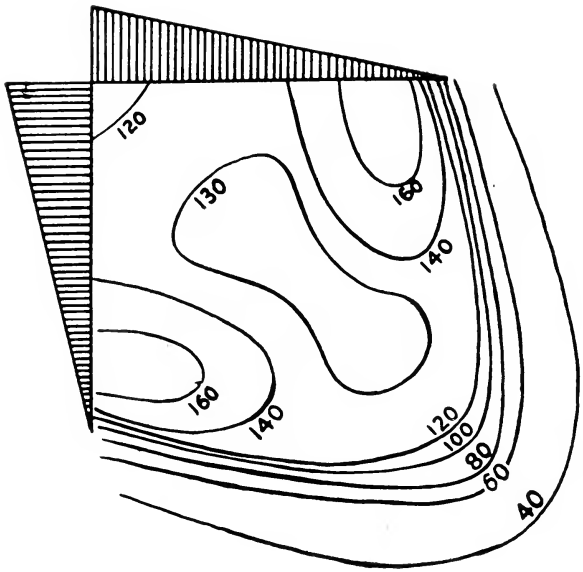

FIG. 4b. Dose Distribution of Two Fields of Type Illustrated in Figure 4a, Arranged at Right Angles, the Positions of the Thick Edge of the Wedge Being Contiguous. The Distribution Is Fairly Uniform Through the Block of Tissue Enclosed by the Fields and Declines Rapidly Outside (Ellis and Miller [7])

Methods of Study of the Dose Distribution from a Number of X-ray Beams

Most X-ray treatments require for their study the summation of the dose distributions of several beams. If the axes of these beams are coplanar, the distribution in that plane can be found by superimposing, in the correct relative positions, isodose charts drawn on transparent sheets, and summing them in succession at the points of intersection of the curves. A convenient method is that of Ungar,[38] who cut blue-base film (discarded diagnostic X-ray films freed from gelatin) to the shapes of isodose curves, and stacked them, so that points which had, for example, percentage dose rates of 60 to 70 had six thicknesses of film below them. Put on a viewing box, the depth of color showed the

range within which the percentage dose lay, and when one set for each beam was overlapped, the summation isodose curves could be drawn on a superimposed celluloid sheet by consideration of the depth of color.

For a knowledge of the dose distribution throughout a volume, a summation of dose in parallel planes is desirable. Also, if the X-ray beams are not coplanar, isodose curves in planes which do not contain the beam axis are necessary. When the beam has circular symmetry, there are geometric methods by which isodose curves in any plane can be drawn from those in a plane containing the axis. However, Mayneord [18] has devised an instrument, the "dose contour projector," which enables this to be done much more easily. Flanders [10] has described methods by which sections through isodose surfaces can be made visible by arranging a thin plane sheet of light to cut semitransparent models. The isodose curves in the required section can be sketched in with the aid of a camera obscura, and this method can be used with beams which have not circular symmetry.

Another instrument devised by Mayneord [18] is the "dose finder," which aids in the study of dose distribution in three dimensions. A dummy applicator is adjusted to a shell moulded to the shape of the part of the body under treatment. The shell is then moved 20 centimeters from the applicator, into which is plugged a plane carrying isodose curves (when there is circular symmetry), so that they occupy the correct position in space in relation to the applicator. A rod, with pointers at right angles 20 centimeters apart, is so arranged that when one pointer is adjusted to a chosen point in the shell, the other pointer gives the corresponding position in the region of the isodose curves. The plane carrying these curves is rotated about its axis until the pointer touches it, and the dose is read at the point of contact. Rectangular fields can also be studied with a slightly more complicated arrangement.[21, 42] Light beams have been used instead of mechanical pointers.[34, 42] From a study of each field in turn, the dose distribution due to a number of beams can be plotted in a number of parallel planes through the treated region. These can be drawn on glass plates, which also carry anatomical

drawings, and stacked in correct relation to each other, so that a three-dimensional representation of the dose distribution and anatomical features is obtained.[21]

Means of Realizing a Desired Dose Distribution

If the paper plan of fields to produce a chosen distribution of dose is to be successful, the fields must be applied to the patient accurately. Various appliances have been devised to make this easier and quicker. First, the center of the region it is desired to treat must be located radiographically—by relating it to bone or soft-tissue shadows, by insertion of an inactive gold seed, skin clip, small balloon catheter containing iodine, lead-shot catheter, lipiodol, or gelatin-barium pellet, or by barium- or thorium-air contrast, according to the site. Skin markings are used to give two lines which intersect at this point. Or the vertical depth below a skin marking can be found by standard radiographic methods. This localization must be done with the patient in the exact position he is to occupy during treatment.[12]

The X-ray tube can then be set to angles measured by a "parallelogram beam director" or "arc beam director," which is removed before adjustment of the tube, or to lines scribed on a protractor spanning the patient, or arc attached to the tube. Simplest of all, a sheet of cardboard is cut to fit the contour of the body, and the lines along which the applicator should be directed are drawn on it.

A second method is the use of a calliper, fixed to the tube, which carries a pointer coincident with the beam axis, which can be made to slide to touch the patient at the point of emergence. Green's calliper will also indicate points at known distances normal to the beam axis—a help when setting glancing fields—while Grimmett has adapted a calliper to give audible warning if the patient moves appreciably from the correct setting.[4, 5, 12, 13, 44]

Mayneord [19] has described an optical device which shows the exit point of the beam axis by a light spot on the patient. A small lamp can be arranged in an applicator to give a beam

of light along what is later the X-ray beam axis. A tube with cross wires and sighting aperture, at the other side of the room, is aligned with this light beam. The tube can also throw a light beam back in the same direction, so that, when the patient is adjusted to the applicator, a light spot on the patient shows the position of emergence of the beam. The use of this appliance in the treatment of esophageal growths is described by Adams.[1] It eliminates error due to whip in mechanical callipers, but has the disadvantage that the patient must be adjusted to the applicator, which must not be moved out of line with the light beam.

By "jig" is meant an appliance which can be fitted to a patient in a reproducible position, and which has surfaces or sockets in correct positions, to which the applicator is adjusted. A simple illustration is the jig to insure that two wedge fields are applied to a patient correctly at right angles. The jig is formed of two "perspex" (transparent plastic) plates, each the size of the applicator end, and fixed at right angles to each other. It is adjusted on the patient so that the block of tissue it is desired to treat is within the right angle. Skin markings are made so that it can be replaced in the same position. A metal replica is substituted for the perspex one, and any space between it and the skin is filled with "radium compo" (see below), a thermoplastic material. The radium-compo mold is detached from the metal replica, and used in the same position in the perspex jig. The fact that the radium compo has taken the shape of the body, together with the skin markings, makes it easy to replace the jig in the same position for each treatment. It is a simple matter to bring the X-ray-tube applicator into contact with each plane surface in turn.

Flood and Smithers [11] illustrate a nose built up with a wax mold to form a parallel-sided slab to aid in the correct adjustment of two opposed fields.

Another method is to produce a rigid shell, to fit the part of the patient's body under treatment, from plastic materials—nidrose, plaster bandage, or bexoid—and to cast on it wax sockets into which the applicator will slip in correct positions.[5]

The radium compo or wax not only helps in the correct fitting of the jig to the patient, but also fills up air spaces with tissue-like material, so that the standard isodose charts give the correct dose distribution.

It is also necessary that the correct quantity of dose should be given to each field. Frequently, this is done by making a daily measurement of the X-ray output of the tube, and then controlling the doses by stop watch and adjustment of the tube milliamperes and kilovoltage. The latter are often difficult to keep in correct adjustment, especially when radiographers must watch more than one tube, and the switching on and off of tubes affects the line voltage. The aggregate error in a dose may be considerable, and can be avoided by the use of an integrating dosemeter with an ionization chamber built into the master cone of the tube on which the various applicators fit. Such a dosemeter has been developed by Farmer.[9]

Theory and Practice

It is evident from the above discussion that much effort can be spent on the study of dose distributions based on sets of isodose curves. It is, therefore, well to consider to what extent the actual dose distributions obtained in the human body may differ from the charts. The latter are usually based on measurements made in water, so that one step is to consider what differences are to be expected in the body. However, although in the ideal, water-phantom measurements should be made for each individual tube and applicator, in practice this is too time consuming, and usually a radiotherapy center assumes that published charts of depth-dose values for the same quality of radiation, focus-skin distance, and field area, will apply. Tables of depth-dose values based on a survey of published values have been compiled by Mayneord and Lamerton,[22] and by Quimby.[28]

There are considerable differences between British and American values. This may be due to the use of different phantom materials—pressedwoods, wax, and rice flour, in addition to water; to different types of ionization chambers—the thimble

chamber and the extrapolation chamber;[8] or even, perhaps, to the prevalence of a different type of tube in the two countries. Oil-immersed tubes, where the beam emerges through a layer of oil, seem to give a more rapid diminution of dose rate with distance, near the tube, as the oil, by scattering, acts as a secondary source nearer than the focus. Spiers[35] has compared the behavior of a number of materials with water, as phantom materials. Paraffin wax and rice flour differed in the 200 kilovolt range, and pressedwoods in the 100 kilovolt range.[3] The most suitable substitute for water (suitable also for the filling of scatter-bags) for the 200 kilovolt range was a mixture by weight of about 60% rice flour and 40% sodium bicarbonate.

When jigs are fitted to the body with wax molds, it is important that the wax should behave towards the X-rays in the manner of water. Some of the dental waxes are much too absorbent, being loaded with elements of relatively high atomic number. If a dosemeter is immersed in a water-phantom, and a piece of wax, etc., is interposed between the dosemeter and the X-ray source, the change in dosemeter reading is an index of the difference of the wax from water. Slabs 3 centimeters thick gave the following diminution of dose rate: parabar (gum kauri, stearine, and magnesium silicate), 12%; perspex, 4%; radium compo (gum kauri, stearine, and charcoal powder), 1.7%.

If it is desired to use isodose charts in the study of treatment of parts of the body of smaller dimensions than the phantom, e.g., the neck, then the body must be built up with scatter-bags approximately to the full size. Reinhard and Goltz[31] have studied the changes produced by the lack of an adequate thickness. With radiation of 0.9 millimeter copper HVL, about 5 centimeters of material beyond a point of measurement is necessary to give adequate backscatter there; differences could be observed 8 to 10 centimeters preceding the exit surface. The exit doses were less than those in a deep phantom by 20% for a 10 centimeter thickness, 29% for a 20 centimeter thickness, and 16% for a 30 centimeter thickness.

Sometimes a better dose distribution can be obtained by discarding scatter-bags. Reinhard and Goltz[30] have shown how

isodose curves for beams incident at an angle to the skin, are affected by omitting scatter material from the wedge-shaped space between applicator and skin. Considerably greater depth doses were obtained towards the margin of the beam remote from the applicator edge in contact with the skin.

Even though it is not possible for a radiotherapy center to explore, in a water-phantom, all the fields used, a few check measurements should be made, as wide deviations from published values may occur. It cannot even be assumed that an applicator end is filled with radiation; sometimes strips as wide as 1 centimeter at the sides are almost devoid of radiation. This might be particularly detrimental when glancing-field techniques are used. Studies of the distribution of dose rate in air across various fields have been published by Thayssen,[36] Jacobsen,[16] and Attlee and Trout.[2] Sometimes fields are badly asymmetric. Ways in which these can be improved by specially designed filters have been described by Spiegler,[33] Meredith and Stephenson,[26] and Flood and Smithers.[11]

There still remains the possibility that dose distributions in the human body may differ from water-phantom measurements. The bones are more absorbent, particularly of the radiations of longer wave length, and beams which are tangential to, say, the ribs or skull, are likely to be considerably affected. The lungs and air cavities, on the other hand, will give a greater transmission than water. Quimby, Copeland, and Woods [29] made an extended series of measurements with 200 kilovolt radiation filtered by 0.5 millimeter copper and 2.5 millimeters aluminum, both in a cadaver and in the vaginas of patients who were irradiated both from the anterior and the posterior surfaces of the pelvis. Backscatter factors agreed well with water-phantom values for all fields of irradiation. Depth doses in the pelvis were also in agreement, but through the chest they became progressively greater. Measurements in the thigh agreed with water measurements until the bone was reached, beyond which they were up to 30% less. Measurements of radiation transmitted through the head of the humerus also gave definitely lower depth dose values.

The present author has measured the transmission of radiation of quality 0.9 millimeter copper HVL passed anteroposteriorly through the midregion of a patient's lung. A dosemeter sandwiched between the applicator and chest wall measured a backscatter factor of 1.33, compared with the water-phantom value 1.31. The dosemeter was then arranged at the beam's exit point on the posterior surface 17 centimeters from the applicator, and scatter-bags were packed around it to give a measurement comparable with that at a depth of 17 centimeters in a water-phantom. The depth dose was 20.5% compared with 11% in water. The fact that the backscatter factor was unaltered suggests that the diminution of scatter from any particular part of the lung is compensated by the less absorption of this scattered radiation on its way to the point considered. Accordingly, it is assumed that any point in the lung will receive the same amount of scattered radiation as the corresponding point in water, but the primary beam will be less absorbed. If the primary beam has passed through a distance d centimeters of lung tissue of density ϱ grams per cubic centimeter this is equivalent in absorption to only ϱd centimeters of water. The radiation which reaches any point in the water-phantom can be divided into primary and scattered radiation by the method of Meredith and Neary.[25] At 17 centimeters deep in water, a surface dose of 131 provides a primary beam dose of 2.20 and a scattered radiation dose of 12.8. The absorption coefficient in water of the primary beam is 0.19 centimeter^{-1}, and if we assume there is a 12 centimeter path in lung tissue of density about 0.3 this is equivalent to 3.6 centimeters of water. Therefore the primary beam value 2.20 must be increased by a factor $e^{+0.19\times3.4} = 5.44$, i.e., it becomes 12.0. The total dose should therefore be 24.8, and the corresponding depth dose 19%. This agrees reasonably with the measured value 20.5%, and suggests that this method could be used to deduce doses in lung tissue.

Conclusion

It has been the purpose of this paper to survey what seem to the physicist the best technical methods in X-ray therapy.

However, they have been developed in many centers, and it is doubtful whether there is any one center which employs, as a routine, a very large proportion of them.

Each radiotherapist develops his own methods. There are, for example, many skilled radiotherapists who prefer to direct the beam by judgment, using no special device, except perhaps, to indicate the position and direction of the central ray. It may be argued that physical methods can be developed beyond the clinically useful point, and readers should refer to a communication by Jacobs [15] on this question.

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ON TECHNICAL METHODS IN RADIUM THERAPY

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Introduction

TECHNIQUE in the therapeutic use of radium has been developed as a result of the changing outlook of the therapist. Surgeons were quick to employ radium when proper appliances had been devised for containing and manipulating this substance, but the tendency now is towards a diminishing use of radium by surgeons for implantation into the tissues. Dermatologists were no less ready to treat lesions of the skin with preparations of radium that could easily be applied to the surface of the body. By suitable choice of metal enclosure, the therapist could carry out this kind of work with beta-plus-gamma or pure gamma radiation. This technique survives, but it is unusual to use beta-ray sources except for lesions which are essentially skin lesions. Gynecologists have been perhaps the most outstandingly successful of radium therapists, because their work has led to far less actual surgery in uterine cancer, and the miseries of uterine hemorrhage promise to be a thing of the past.

The advances in technique fall into natural groupings which have been determined in one of two ways, e.g., a new technique may be developed as the result of a new medical point of view, for instance, the substitution of surface for interstitial applications largely arose from the view that damage to the tissues was to be avoided at all cost; or again, a new technique was developed as a result of the ingenuity of physicists in preparing radon sources which can sometimes be used in preference to

radium. But no amount of ingenuity in itself can make any headway in treatment unless it is embodied in an instrument or in a process which convinces the therapist of its undoubted utility and safety.

External Irradiation

The range of this method varies from the application of a few milligrams in the form of a capsule, to the use of 10 grams at a time. At the present time, considerable diversity of opinion exists about the utility of these gram units (the use of the deplorable term "bomb" for these units is happily declining). What need is there for mounting 5 or 10 grams of radium into a single unit as a gamma-ray source when this type of radiation can so nearly be duplicated by X-rays? The argument may, however, be presented with equal logic the other way round; why go to the trouble of installing complicated and expensive apparatus which will almost certainly have to be discarded after 10 years' service, when one can have a most useful source of radiation requiring little apparatus and a minimum of servicing by a staff of engineers, a source, moreover, that shows an inappreciable decline over the same period of time?

As a matter of fact, there are very good reasons why one source does not exclude the other. It is true that the quantitative yield of penetrating X-rays from a modern tube at a quarter of a million volts far exceeds that from a 10-gram radium unit (perhaps 10 times as big), but the latter has many advantages. It is often easier to apply to the patient, it is especially suitable when repeated and prolonged treatments are needed, and its servicing is so effective that one can almost say that these units do not suffer from breakdowns. So it may reasonably be expected that these units, ranging from 1 to 10 grams of radium, will be more and more used, provided that the present downward trend in the cost of radium continues.

Intracavitary Irradiation

The introduction of radium (and radon) into the natural cavities of the body when they are the seat of disease has been

developed on lines which insure, as far as possible, an adequate dose to the malignant regions with no overdose to the normal contiguous structures. This is most successfully done, perhaps, in the treatment of cancer of the uterus and in buccal cancer, but when growths originate in the rectum or esophagus, there are greater difficulties in insuring the necessary conditions.

In the treatment of uterine cancer, radium is put into the body of the uterus, the cervical canal, and the fornices, by means of special applicators containing radium in platinum thick enough to insure that practically homogeneous gamma rays are being used. Supplementary to this disposition of the radium, every effort is made by the use of packs to keep the normal tissues well away from the zones of most intense irradition. This is also attempted when radium is applied to the rectum in cases of malignancy; one of the most successful appliances is that devised by Margaret Tod, who arranged the radium inside a pneumatic device which could be expanded *in situ;* this helps to push the normal structures away from the irradiated zones.

For growths of the esophagus, the device of Souttar allows the introduction of radium into the lumen of the esophagus, but immediate contact is prevented by means of a Souttar's tube, which holds the radium axially. A valuable measure of control and protection is afforded by this device.

Interstitial Radium

Dominici was among the first to introduce radium enclosed in platinum into the tissues; the method was developed so that large volumes of tissue such as occur in mammary cancer were penetrated at many points by radium tubes 6 centimeters or more in length with a diameter of several millimeters. An extensive though not uniform irradiation of the malignant process occurred under these conditions, but the disadvantages of the method, with its associated trauma, brought interstitial work into disfavor, and today, it is probably true to say that if radium therapy can be carried out without recourse to interstitial methods then it is so done. Nevertheless, there are several

sites where such methods are still the best; for instance, lesions of the tongue where, owing to involuntary movement, it is almost impossible to use any other method properly.

No account of interstitial methods in treatment would be complete without mention of radon technique. The gas from radium can be purified so completely that one can handle quantities that represent extreme purity; the volume of 1 curie is just less than 0.6 cubic millimeter, and one gram of radium in solution can yield 25 curies during the course of a year, so that the total volume of pure gas is only 15 cubic millimeters; the refinements of technique allow this to be shared among no less than 10,000 capillary tubes which, when mounted in platinum, serve as gamma-ray sources, their lengths ranging from 5 millimeters to 3 or 4 centimeters.

In any technical discussion upon the use of radon, it soon becomes apparent that, in spite of contraindications, it continues to be used because objections are outweighed by advantages. It can be said that the outstanding advantage is the adaptability that attends its use; in other words, the size, shape, content, and filtration can be altered to suit the clinical need of the moment; moreover, radon "seeds" can be inserted into the tissues and left there without danger to the patient. Against this, we have the decline of its activity, which renders it unsuitable for treatment which lasts more than a few days, the high cost of running a radon center, and the danger to technicians engaged in the work of purification and concentration of the radon.

Therapeutic Aims and Methods

The three outstanding technical methods of using radium (and radon) in treatment have been discussed. It remains to say something of what is the aim behind these methods. Whatever the radiotherapeutic method in treating malignant disease, the aim is certainly to destroy all malignant cells, but it is equally certain that in many cases this is quite imposible if any regard is paid to the normal tissues of the body of the patient.

In most cases, this is due to the fact that growths are ill-defined in their extent, and this being so, it is evident that unless irradiation is extended well beyond the probable limits of the growth, some of the malignant cells will escape. We are, in fact, dealing largely with probabilities, not certainties, in the treatment of malignant disease; and an experienced radiotherapist is more likely to discern these probabilities than an equally clever but less experienced one. On this basis, it is evident that technical methods are developments of ingenuity in the best means of balancing the manifold considerations that are involved in the irradiation of a malignant growth.

There is indeed a wide difference in outlook between those who, for instance, plan an extensive irradiation of a breast tumor by the implantation of radium needles, and those who seek the same end by the use of externally applied gamma radiation which can be repeated at intervals determined by the day-to-day response of the organism. It is the latter working philosophy which originated in the French School, and which has been given a rather different orientation by the work of Spear and his colleagues of the Strangeways Laboratory, Cambridge; here, in fact, is a technical method which combines the virtues of sound biological intuition with the asset of rigid physical control.

If technical methods are to be improved, there must be a happy balance between biological probabilities and physical certainties; it is well, however, not to insist too much on the latter. Isodose curves are usually derived from measurements upon media having about the same density as the average of the tissues concerned in treatment, but there need be no insistence on the general crudeness of any such similarity. Any assessment of the differential response of the various structures of the body to irradiation is a matter not for the physicist but for the radiologist. It need not be emphasized that judgment upon this crucial matter will depend not only upon the clinical sense of the radiotherapist, but on his pathological knowledge. It is one of the greatest claims to eminence in the field of radiotherapy, that the French School, led by Regaud, and now by Lacassagne, has so persistently maintained that this pathological knowledge,

not only of the nature of malignant growths, but of their individual reactions to irradiation, should be the basis of the scientific method.

A few words may be said about technical methods in radium therapy other than in malignant disease. One of the most successful applications is in the treatment of uterine hemorrhage, and it is somewhat remarkable that, in spite of the generally good results obtained, there is a considerable difference in the dose employed at different clinics. Early in the study of this condition, it was found that the dose required to bring about a cessation of the dominant symptoms varied with the age of the patient. The following quotation is taken from Elizabeth Hurdon, *Cancer of the Uterus* (London, 1942).

"The treatment of simple metropathic hemorrhage depends partly upon the age of the patient, but the severity of the anemia due to hemorrhage, and the presence of myomata, have also to be considered. The cases are divided into three groups in relation to the age incidence and the reproductive function:

Group I	Adolescent cases—patients under 20 years of age.
Group II	Child-bearing period—patients from 20 to 40 years of age.
Group III	Includes the menopausal, 40 to 50 years of age, and post-menopausal cases.

Typical doses for each age group are as follows:

Group I	250 to 300 mg hr
Group II	600 to 750 mg hr
Group III	1,100 to 1,200 mg hr

Screenage is 1 mm platinum and 1.5 mm rubber."

It will be seen that the biggest dose found necessary in the treatment of this condition is 1,200 milligram hours (50 milligrams for 24 hours), yet there are many British workers who consider that treatment is not adequate with less than 48 hours'

exposure, using 50 milligrams of radium. The question arises, in view of the fact that the technical methods are practically identical, as to why this wide disparity of doses continues to operate. If the bigger dose is indeed necessary, how is it that 97% of the menopausal cases cited by Hurdon remained well without further treatment? On the other hand, if the shorter exposure is adequate, what purpose is served by a more severe one?

Technical Methods in the Future

The methods which have been most highly developed technically up till now are the methods developed in the use of the gram units and in the use of radon; both big and small quantities call for specialization in design and management.

Advances in pure science in the last 15 years have shown the feasibility of making ordinary substances radio-active, and the time may soon be at hand when these will be used in medical treatment as well as in research. Advances in applied science during the last year have drawn attention to the possibilities of using atomic power on a more liberal scale than we have so far enjoyed. Mere power, however, has not the first claim in the selective list of requirements among radiotherapists; what is primarily wanted is some form of energy which will give a wider margin of response between normal and malignant tissues, and at the same time be easily adapted to the purely technical demands of those called upon to treat malignant growths in any part of the body.

MILLION-VOLT THERAPY

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Introduction

UP TO the year 1930, the maximum voltage X-ray equipment available for X-ray therapy was of the order of 200 kilovolts. With such equipment, it had been demonstrated that in some types of cancer it was possible to attain a cure without irreparably damaging the patient. It was not known whether the failure in many lesions in certain sites was due to a difference in radiosensitivity, or whether it was due to the impossibility of delivering a sufficiently high dose to the lesion. The problem was not a simple one, being complicated by many factors.

No matter how high a dose is administered to a lesion, there are always some malignant cells left intact, and these have to be overcome by local normal cells if the lesion is to be eradicated. This can take place only if the normal cells have been less damaged by the radiations than have the malignant ones—that is, if the normal cells are less radiosensitive. Whether this radiosensitivity factor varied with the wave length of the radiations was not known, but the hope that this might be the case warranted investigation into the unexplored shorter wave lengths.

For optimum results, damage to the normal tissue surrounding the malignant zone should be reduced to a minimum, otherwise blood supplies to the normal cells in the zone of destruction will be cut, reducing their effectiveness. This requires a rapid decline of the X-ray dose outside the zone of required destruction, and it was forecast that this could be accomplished with the

shorter wave lengths, due to the sharper delimitation of the beam edges.

A third factor arises which might be called the patient's vitality, over which the therapist has only some small control; namely, in making certain that the total radiation energy absorbed by the patient is a minimum commensurate with the necessary lesion dose.* Provided that all stray radiations have been excluded, the energy absorption during the treatment then becomes a question of the most effective geometric distribution of the required X-ray beams, both physically and clinically, and of the physical properties of the radiation used.

Treatment at wave lengths shorter than those obtained with a 200 kilovolt equipment had been carried out in the use of radium on surface lesions, interstitially, in body cavities, or in mass in the radium-bomb units. The nearest approach to the methods employed in X-ray therapy are those of the radium bomb. The main difference is that owing to the low gamma-ray output from radium bombs, treatments can be carried out only at short distances from the patient, limiting the use of the bomb to lesions at short distances from the skin surface. In order to obtain the same radiation intensity as that emanating from a 200 kilovolt tube operating at 10 milliamperes 40 centimeters FSD [Focus-Skin Distance], 1.0 millimeter copper HVL, 1,000 grams of radium would be required.

However, it had been established from theory and experiment that the shorter the wave length of the X-rays, i.e., the higher the voltage applied to the X-ray tube, the more penetrating the rays would be and the less the absorption would vary with the density of the medium. One of the problems in 200 kilovolt therapy was, and is, the distortion, due to intervening bone, of the theoretical dosage distribution by an unknown factor. With the shorter wave lengths this unknown factor should become less disturbing.

* The lesion dose is the average dose throughout the lesion specified in röntgens. It is estimated from a mathematical analysis of the dose distribution in the patient, arrived at by the summation of dose-distribution charts for each X-ray beam. These charts are obtained by ionization-chamber measurements in a water-phantom.

X-ray Equipment: Some Technical Considerations

By 1933, a few experimental high-voltage X-ray equipments had been constructed in the United States, operating at voltages up to one million, but they were too unreliable in operation to give biological and clinical results which could be assessed. Usually these tubes had at the most only two fixed beam-directions, necessitating tilting of the patient to the tube, in order to accomplish cross-fire techniques. This method is deprecated in Britain, since it is argued that unless the patient is prone, supine or, for a restricted number of sites, sitting up, it is impossible to know the exact position of the various body organs. Angulation of the tube to the patient is therefore demanded as one of the essential features of an X-ray tube.

The main difficulty encountered in sealed tubes in the attainment of higher voltages was that the increased electrical stresses applied to the electrodes and envelopes extracted occluded gas from them, resulting in internal electrical breakdown between the electrodes, and often in the puncturing of the glass envelope. In one or two instances, tubes were supplied to withstand 350 kilovolts, but they were never really robust.

In 1932, a pair of 200 kilovolt steel and porcelain, demountable X-ray tubes, continuously evacuated by their attached oil diffusion-pumps, were installed in Sheffield Radium Center. The oil diffusion-pumps operated on the newly developed low-vapor-pressure Apiezon oils, and did not need the expensive liquid air traps required on mercury-vapor condensation pumps. Continuous evacuation and demountability made possible the cheap replacement of target and filament by any mechanically minded member of the X-ray department. Instead of the usual sealed-off thermionic rectifiers in the attached high-voltage generator, a pair of continuously-evacuated demountable rectifiers was fitted.

With the advent of these new oil diffusion-pumps, and the demonstration that continuous evacuation was feasible and reliable, the development of high-voltage continuously-evacuated

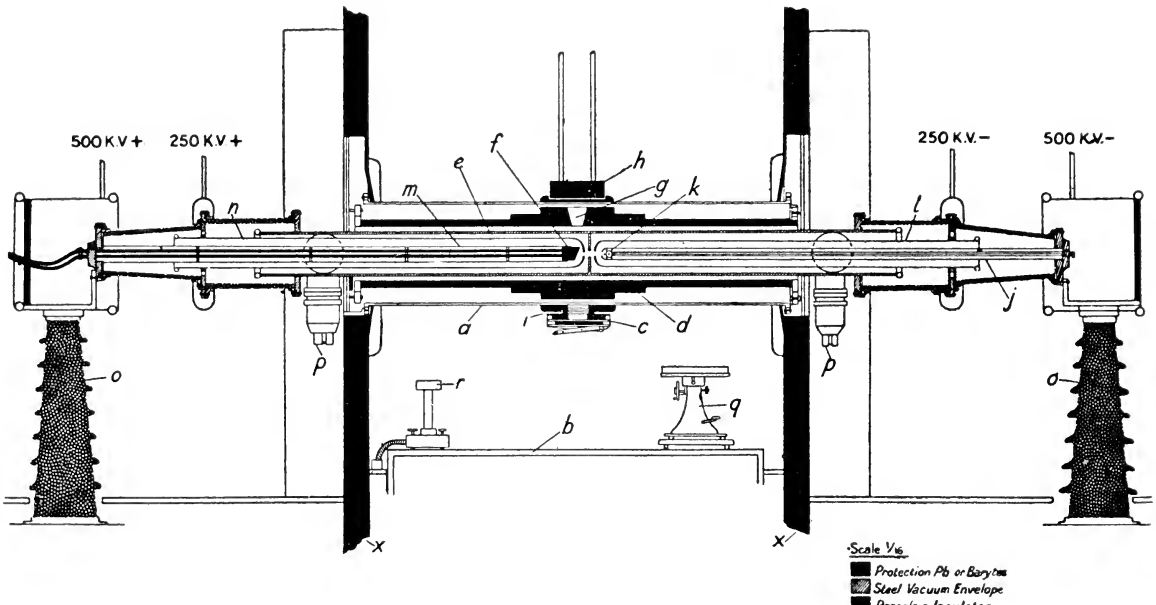

FIG. 1a. Diagram of Million-volt X-ray Tube

tubes became an economical proposition. These tubes had walls and envelopes electrically better than those of the sealed-off tubes, but they had previously been barred by their prolonged gassing.[1, 3, 5]

Million-volt Equipment at St. Bartholomew's Hospital, London

The hospital is indebted to the foresight of its Radium Committee, the generosity of Mrs. Meyer Sassoon, and the technical skill of the Research Department of Messrs. Metropolitan-Vickers Electrical Co., Ltd., Manchester, for envisaging and making available the million-volt plant installed in the hospital in 1936. The equipment was guaranteed to operate at 600 kilovolts d.-c. 3 milliamperes, with the proviso that continuous operation at one million volts would be aimed at. In the first hour after final erection, 700 kilovolts 4 milliamperes was attained, but at voltages greater than this, the tube became unstable in operation.[1]

During the next two years, while many modifications and additions were made to the tube, treatments were carried out at 700 kilovolts, giving the medical and physical staff an insight into the problems to be encountered at higher voltages. By 1938,

a Rotable applicator cylinder
b Moving floor
c Adjustable diaphragm for limiting size of emergent beam
d 8-ton lead protection cylinder, used as shutter by rotating
e Steel tube vacuum envelope
f Gold or copper target head
g Aperture in lead cylinder
h Lead block suspended from roof, blocking upwards beam, when shutter in "safe" position (as shown)
i Parallel plate ionization chamber across beam
j Cathode support tube
k Six-element filament assembly
l Negative mid-potential steel sheath
m Target support tube
n Positive mid-potential steel sheath
o Support insulators
p 04 (vacuum) pumping plants
q Treatment couch
r Control pedestal for tube angulation and floor movement
x Barytes X-ray protection walls between treatment room and H.T. rooms

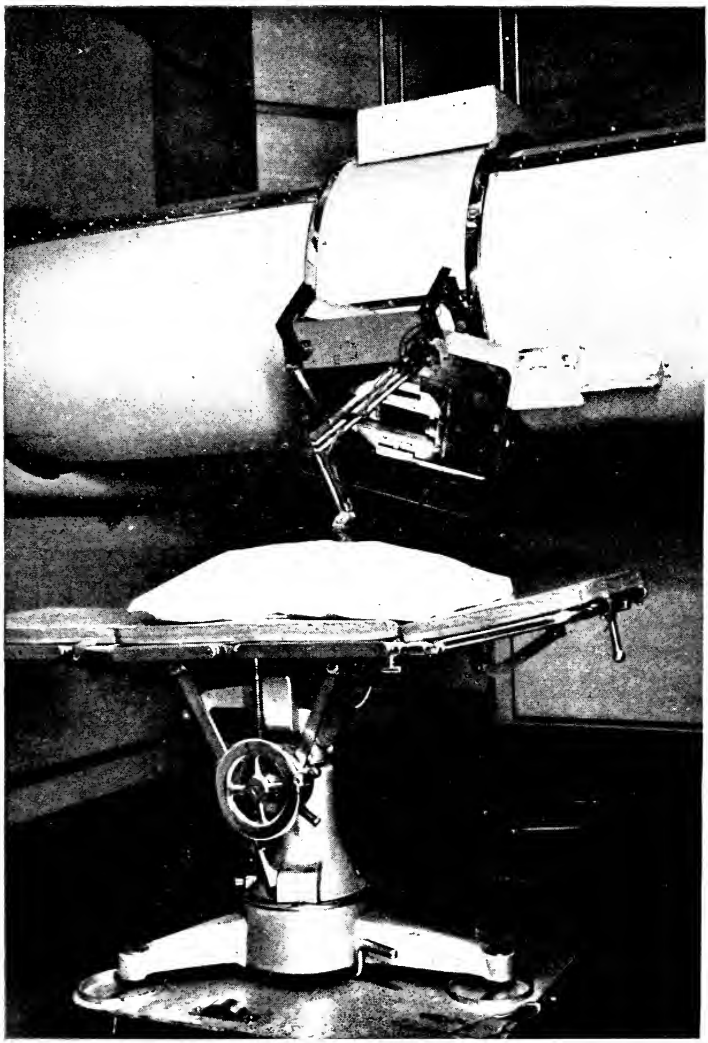

FIG. 1b. MILLION-VOLT X-RAY TUBE

Tube in the treatment room, showing the light-centering device and diaphragm

the plant was operating continuously at one million volts and since then some 10,000 hours of operation have been accomplished in spite of many near misses by bombs and V-weapons. Although there was considerable damage to the buildings on many occasions, the plant suffered little and at no time were treatments not carried out on schedule, except when power supplies were interrupted.

The equipment is so designed that, as far as possible, methods of treatment previously employed at 200 kilovolts can be repeated with the new tube . The tube (figure 1 *a, b*) spans the treatment room (X to X) and from the center of its span can emerge the X-ray beam, the direction of which can be varied from pointing vertically downwards to 110° upwards. This is accomplished by rotation of the outer sheath of the tube (a). Adjustment of the patient to the tube beam is accomplished by making the center part of the treatment room floor (b) under the tube traversible vertically through 7 feet [about 2.2 meters]. This is necessary, since it would have been difficult to traverse the 32 feet long [about 9.75 meters] tube, which weighs nearly 12 tons [about 12,192 kilograms]. The minimum FSD obtainable with ease is 60 centimeters, comparable with that used at 200 kilovolts.

Beam limitation at 200 kilovolts is done by lead-lined boxes called applicators, fitted with end limiting stops of the required size. At a million volts and 100 centimeters FSD, such applicators, to be effective, would weigh some 200 pounds [91 kilograms] and would be rather expensive and difficult to change. An adjustable diaphragm (c) was therefore fitted on to the tube outer sheath, built up of twin 1.5 inch [about 3.8 centimeters] thick adjustable lead stops, giving any beam size from 5×5 to 40×40 centimeters at 100 centimeters FSD. It is possible to use the diaphragm down to 60 centimeters FSD, but beam positioning then becomes awkward. The diaphragm has a light-beam device attached, indicating the size and position of the X-ray beam in space. The X-ray beams obtained from the diaphragm are not perfect, since they have penumbral edges caused by combination of a large focal spot, 2.5 centimeters, with the position of the stops at half the distance from the focus,

when used at 100 centimeters. The advantages, however, outweigh this imperfection, and in the future a light secondary diaphragm may be added.

Inside the outer sheath (a) on which is mounted the diaphragm, is a protective lead cylinder (d), which itself surrounds the steel vacuum envelope of the tube (e). This lead cylinder, which weighs 8 tons, gives an effective protection of 6 inches of lead in any direction relative to the focal spot on the target (f). The protection is so effective that with the tube operating at full excitation—one million volts 4.5 milliamperes—the X-ray leakage into the treatment room is only one half of tolerance dose (10^5 röntgens per second), a degree of protection rarely encountered in 200 kilovolt tubes. The lead cylinder is also used as the X-ray shutter of the tube. There is one aperture in the lead cylinder opposite the target head, which aperture (g) in the safe position points upwards into a six-inch-thick lead block suspended from the treatment room roof. This block prevents the emergence of the X-rays upwards into the treatment room. Providing the treatment room doors are shut, the whole of the lead cylinder can be made to rotate by pushing a control button in the control room, and by automatic interlocks it stops rotating when its aperture is aligned to that of the diaphragm on the outer sheath, so permitting the emergence of the X-ray beam in the required direction through the diaphragm stops. Just behind the diaphragm is mounted a three-plate ionization chamber (i), which indicates on an instrument on the control desk either the X-ray intensity or the dose given during an exposure. Mounted on the control desk are also direct-reading kilovoltmeters, indicating the actual kilovoltage applied to either end of the tube and the sum of these, irrespective of load current. These are electrostatic voltmeters which operate from a definite proportion of the kilovoltage applied to each end of the tube, obtained from oil-immersed resistance potentiometers connected from each end of the tube to earth.

The high voltage for the tube is supplied by two 500 kilovolt Cockcroft $\pm$ d.-c. generators, comprising transformer, condensers, and four continuously-evacuated thermionic rectifiers

each, and operating from the a.-c. mains. All vacuum and electrical operations are indicated on a power-station type of illuminated diagram, facilitating fault finding.

The treatment and high-tension rooms are enclosed in walls built of some 125 tons of interlocking barytes bricks, so effectively preventing the egress of X-rays, that it is possible to store films within a few feet of the treatment room.

In this equipment, we have a simple, controllable, safe source of high-voltage X-rays, not quite as hard as the gamma rays from radium, but equal in intensity, under the same geometrical conditions, to 7,000 grams of radium.

During the war no development work on X-ray tubes and equipment has been possible in Britain, but in the United States, a number of different types of high-voltage X-ray equipments have been produced, one in particular being very compact, tube and resonating transformer being housed in a tank some 6 feet [1.8 meters] long and 4½ feet in diameter. It is also of interest to note that during the German occupation of Norway, Norwegian engineers and physicists constructed and operated a 1.5 million volt Van de Graaff generator and multiacceleration tube.

Physical Investigations on Operating Conditions

When the treatment of patients with the million-volt plant commenced, there were few physical data available regarding the properties of the short-wave length rays so generated, and a complete investigation had to be made to find the optimum operating conditions to attain (1) the shortest economical wave length and (2), at the same time, the best geometric arrangement to give the highest % depth dose in the patient, with a reasonable X-ray intensity. Since the primary object of the whole investigation was to find whether the radiosensitivity of malignant cells, *in vivo*, increased with reduction in the X-ray wave length, the tendency was to bias (1) in preference to (2).

The properties of generation of X-rays, by the stopping of high-speed electrons by a target, are such that, although the electrons have all, in our case, a million volts equivalent velocity,

the emergent X-ray beam is a heterogeneous one composed of wave lengths varying from the shortest, which has a quantum energy equivalent to that of the original electron, to rays which just come through the tube wall. The peak intensity is at about 700 kilovolts, and the mean about 450 kilovolts equivalent. Passing such a heterogeneous beam through single or composite metal filters, the long wave lengths are absorbed to a greater degree than the short wave lengths, resulting in a hardening (shortening) of the average wave length of the emergent beam. What is more important, however, is that the very soft (long) wave length rays are completely removed. These cause considerable damage to the first few millimeters of tissue and, as they do not penetrate further, they do not contribute to the lesion dose.

It was found that there was little difference between lead and tin filters, the lead, if anything, being slightly more efficient. Backing of the lead filter by tin and copper was not found necessary, presumably since the 4.2 millimeter steel wall of the tube effectively removed the anomalous lead radiation.[7]

The distribution of dose in the patient is a much more complicated problem and, to simplify physical investigations, it is carried out in a medium which has the same electron density as the average of all the body components. Water is one such medium, while there are others of more complicated nature.[10] The relationship between (a) the dose at any point in the medium to (b) the dose at the surface of the medium at the beam center, when expressed as a percentage, is called the Percentage Depth Dose (%DD), while the chart giving the %DD-distribution in a plane by lines joining points at equal dose levels is called an isodose. The dose at a depth is made up of many components, and for general purposes here they can be divided up into three: direct beam, backscatter, and forward scatter. The direct beam is that part of the dose originating from the ionization produced at the point by absorption of X-rays from the part of the main beam which has penetrated to the depth. Backscatter is the dose originating from secondary X-rays scattered back from the part of the medium beyond the point of measurement, while forward

scatter is from secondary scatter from the part of the medium above the point of measurement.

Investigation into the variation of %DD with filtration of the X-ray beam indicated that not only was the lead filter the most efficient in increasing the %DD, but also that the maximum efficiency was between 0 and 1 millimeter of added filter. With heavier filters, the improvement was linear but less noticeable. (See figure 2, curve 4.) It will be noticed that the criterion of efficiency is the improvement of %DD in a 10×10 centimeter

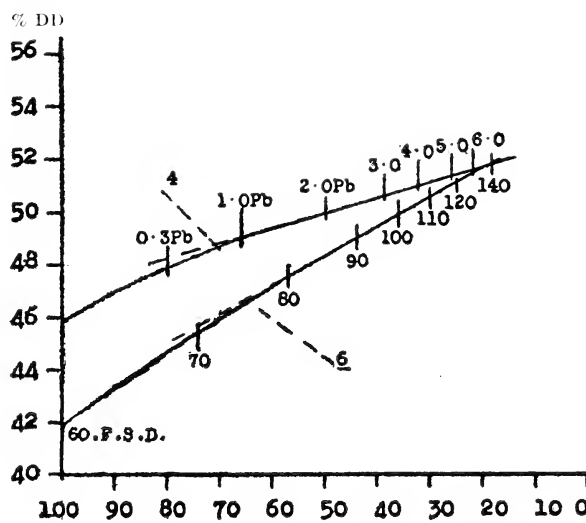

FIG. 2. Percentage of Beam Intensity Left

Abscissae = % intensity. Ordinates = % depth dose at 10 cm depth

Curve 4. Percentage of depth dose with increasing lead filtration, filter thickness marked on the curve, plotted against residual beam intensity. 10×10 cm, 100 cm FSD, 1,000 kv.

Curve 6. Percentage depth dose with FSD, FSD, marked on the curve, plotted against residual beam intensity. 10×10 cm, 2 mm lead added filter, 1,000 kv.

field at 100 centimeters FSD plotted against percentage of the beam intensity left. The improvement of the %DD with FSD is given in figure 2, curve 6, which shows that the maximum efficiency of improvement is produced between 60 and 80 centi-

meters FSD; improvements at distances greater than this being slower but appreciable. If %DD improvement were the main object, the optimum condition would be about 0.5 millimeter added lead filter and as long a FSD as possible, since the efficiency of improvement is greater by FSD than by filtration at this voltage.

In our case, however, where the main investigation was whether there was an increase in radiosensitivity of lesions with reduced wave lengths, a harder beam obtained with a 2 millimeter lead filter was decided on, with a FSD of 100 centimeters, giving an X-ray output of 40 röntgens per minute, comparable with the output of 200 kilovolt equipment.

Physical Advantages of the High-Voltage Beam

Since previous experience had been confined to 200 kilovolt X-rays, the main interest physically lay in a comparison between the behavior of the beams in a phantom, and an attempt has been made to formulate reasons for the differences. The main improvement with reduction in wave length is the increased penetration, but the %DD is a complicated feature in which variation of back- and forward scatter, FSD, depth, absorption-coefficient, and field area all play a part, and an attempt was made to sort out these effects by measurement and calculation. Figure 3 gives the proportions of direct, back- and forward scatter obtained as a percentage of the depth dose on the beam-center-line for 10×10 centimeters beams at 40 centimeters FSD 200 kilovolts and 100 centimeters FSD 1 million volts. At the surface at 200 kilovolts, the dose is 71% direct, 29% backscatter, while at 1,000 kilovolts, it is 93% direct and 7% backscatter. As we progress through the phantom at 200 kilovolts, the direct-beam component decreases more rapidly not only relatively, but also absolutely, while at 10 centimeters depth it becomes even less than the backscatter component. At 1,000 kilovolts, the backscatter component remains only a small portion of the dose. The forward scatter in both cases increases rapidly and is of the same order.

The direct component of the beam can be represented by I_d and is

$$I_d = I_a e^{-\mu d}\left(\frac{F}{F+d}\right)^2$$

where I_a is the air dose at the surface—FSD; F; μ, the absorption-coefficient and I_d the dose at depth d, due to direct beam. Both the backscatter and forward scatter components will increase with field area up to a maximum, beyond which any further added beam area will not contribute to the central dose, since it will be beyond the range of the secondary scatter.

From the curves and the above, certain forecasts can be made. (1) Since the penetration, i.e., the direct beam, is higher at 1,000 kilovolts, and the greater portion of the dose at all depths is due to direct beam, the depth doses will be greater than those met with at 200 kilovolts (the forward scatters being nearly the same). Not only will this be the case but, since at 1,000 kilovolts so little of the dose at a depth depends on scatter, there should be little change in %DD with field area, quite contrary to 200 kilovolt experience, where the %DD is governed to a greater extent by the backscatter and hence by field area. Further, the improvement with 1,000 kilovolts will be the greater, the greater the depth. At 200 kilovolts, there is little change in %DD with FSD beyond 50 centimeters FSD, and this can be understood by examining the information in figure 3. Since the direct-beam contribution is a small portion of the dose at the depth, any variation in its value due to alteration in F (in the formula) will be masked in the %DD by the small part it takes in the whole. At 1,000 kilovolts, on the other hand, the direct contribution even at 20 centimeters depth is over 50% of the dose, so increases in the direct component by increase in the FSD will be appreciable in the %DD.

Figure 2, curve 6, indicates that the last deduction holds, while figure 4 indicates that the forecasts about relative %DD at 1,000 kilovolts and 200 kilovolts are along the lines indicated. The gain in small field sizes is particularly noticeable, being as

high as 50% increase at 10 centimeters depth for a field 20 square centimeters. This opens up many new avenues in treatment design, which will be indicated later. Even for large beams, the improvement, though small (about 12%), is of importance

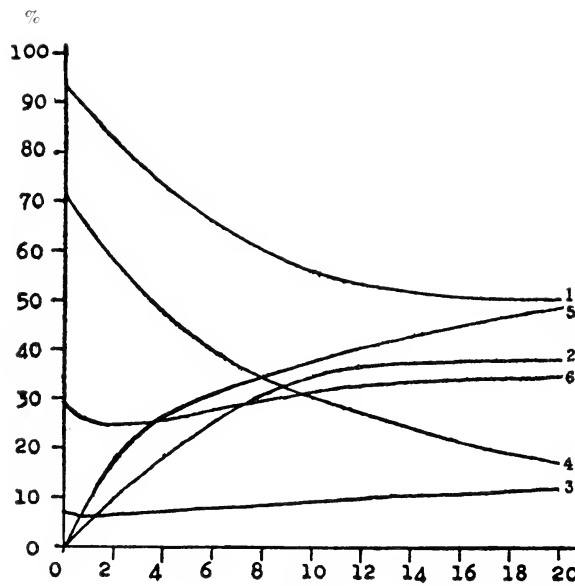

FIG. 3.

Abscissae = depth in cm
Ordinates = components as % of % of depth dose
1. 1,000 kv direct beam component as a % of the % of DD
2. 1,000 kv forward scatter as a % of the % of DD
3. 1,000 kv backscatter as a % of the % of DD
4. 200 kv direct beam component as a % of the % of DD
5. 200 kv forward scatter as a % of the % of DD
6. 200 kv backscatter as a % of the % of DD

in many cases of opposed-field technique. Further, with the reduction in backscatter, and also since the forward scatter is, with the higher voltages, more in the forward direction, the high-voltage X-ray beams show a much sharper delimitation on the geometric edge of the beam and a flattening of the isodose contours.

All these physical improvements make posible many alterations and refinements in techniques developed for 200 kilovolt therapy, and some methods quite inapplicable at 200 kilovolts have been introduced. There is one other factor which has to

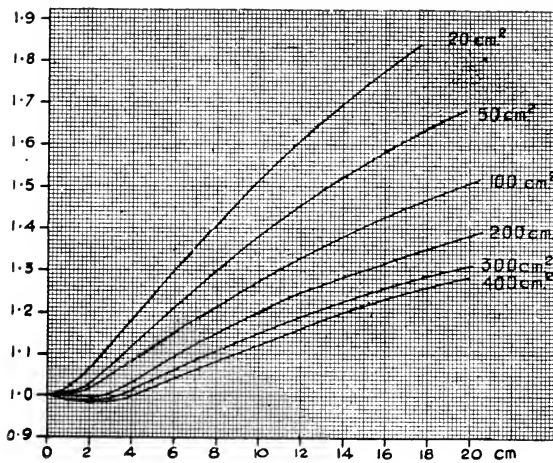

FIG. 4.

Abscissae = tissue depth in cm

Ordinates = ratio $\frac{\text{tissue dose 1,000 kv X-rays}}{\text{tissue dose 200 kv X-rays}}$

Ratio of the tissue dose with 1,000 kv DC. X-rays (9.0 mm Cu HVL) to that with 200 kv DC. X-rays (2.0 mm Cu HVL) for the same input skin dose at 100 cm FSD and various field sizes

be brought in, out of sequence, before it is possible to discuss alterations in treatment technique, viz., skin reaction.

Alteration in Skin Reaction

Tests were carried out on corresponding skin surfaces on patients with X-ray beams of identical dimensions under the same physical conditions except for the beam qualities. The control beam was one of 300 kilovolts (3.35 millimeters Cu

HVL), while the experimental beam was 1,000 kilovolts (10 millimeters Cu HVL). The dose required in one sitting to produce the same skin reaction was 50% greater with the 1 000 kilovolt than with the 300 kilovolt beam. Theoretically, only part of this alteration in skin response can be accounted for by the reduction in the photoelectric absorption in the sulphur in the skin with the shorter wave lengths, the remainder being so far unexplained, unless it is due to a radiosensitivity change. The results conform well with those encountered in gamma-ray treatment. This reduction in skin response also opens up improvements in technique, but more especially makes possible a reduction in the skin reaction which has undoubtedly an indirect effect on the patient's well-being, during and after treatment.

Modifications in 200 Kilovolt Techniques Possible by Employing Million-volt X-rays

1. Whereas it was impossible to employ small fields in the treatment of small lesions buried deep in the body, e.g., rectal carcinoma, owing to the poor depth dose of such fields, at 1,000 kilovolts, it becomes possible and economical to employ multiple small fields, even through the remote lateral skin surfaces.

2. In intrinsic carcinoma of the larynx, it is customary and necessary at 200 kilovolts to employ three fields—two opposed laterals, and an anterior field. At 1,000 kilovolts only the two opposed laterals are necessary, which simplifies and increases the accuracy of the technique.

In this type of case with two opposed beams, it is found that blocks of tissue up to 14 centimeters thick receive nearly uniform irradiation throughout by two opposed million-volt X-ray beams.

3. In many cases at 200 kilovolts, it is found necessary to employ beams angulated in three dimensions (spinal cord and bladder). So far, at 1,000 kilovolts, it has not been found necessary to employ such beams except in a few brain cases where the eye has to be avoided. Setting up beams accurately in three dimensions and calculating the necessary isodoses is a difficult

process, and one which should be avoided unless the most elaborate equipment and calculating devices are available.

4. Where originally at 200 kilovolts it was quite impossible to attain a uniform and sufficient dose owing to the patient's size, e.g., carcinoma of the breast of a large woman, even with the small increase in depth dose in large beams at 1,000 kilovolts, few cases have been encountered where it is impossibe to administer a greater uniform dose to the lesion than to the skin.

5. Where, at 200 kilovolts, lesions have had to be approached by beams through organs, the damaging of which incapacitates the patient, e.g., glancing beams in carcinoma of the esophagus damaging lung tissue, at 1,000 kilovolts, most of the lesion dose can, because of the increase in depth dose and the reduction in skin response, be contributed by the anterior and posterior fields, leaving only a small portion to be administered by the glances through the lung.

Comparison of the Physical Data Obtained for Treatment of Carcinoma of the Rectum

Figure 5 gives the cross-section outline at the level of the pubic crest in the case of carcinoma of the rectum. This type of case has been chosen because it shows very well many of the advantages of million-volt therapy, when compared with 200 kilovolt therapy. The case is treated with ten 18×8 centimeter beams at the angles indicated, each field being given 100 units of X-rays on the skin. On the left half of the section is shown the isodose if the case is treated at 200 kilovolts with the usual 40 centimeter FSD and Thoraeus filter. On the right-hand side is the isodose if the patient is treated at 1,000 kilovolts 100 centimeters FSD, 2 millimeter lead filter (HVL 9.3 millimeter Cu).

The differences are obvious. The lesion, which is a small one, is surrounded by the 370% contour at 1,000 kilovolts and by the 250% contour, approximately, at 200 kilovolts, indicating a 50% improvement with 1,000 kilovolt rays in the lesion dose, for the same input dose on each field. Outside the lesion, the

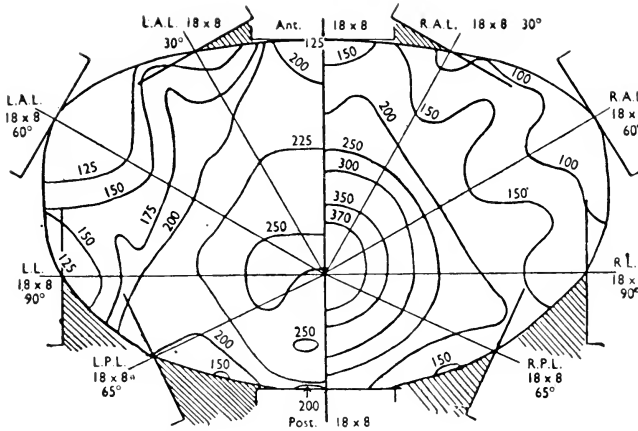

FIG. 5. Isodoses on a Transverse Section of a Carcinoma of the Rectum

a. 10—18 × 8 40 cm FSD fields with 200 kv DC. X-rays (HVL 2.0 mm Cu)

b. 10—18 × 8 100 cm FSD fields with 1,000 kv DC. X-rays (HVL 9.0 mm Cu)

dose declines rapidly at 1,000 kilovolts, whereas at 200 kilovolts, even up to the skin, the dose is still 80% of the lesion dose, unnecessarily causing damage to normal tissue and disturbances to the patients. The maximum skin dose is the same in both cases. If, now, 6,000 r is to be given to the lesion in 5 weeks, the following results are obtained:

Data	1,000 kv	200 kv
Lesion dose (5 weeks).....	6,000 r	6,000 r
Dose per field.....	1,620 r	2,400 r
Dose per day.....	650 r	960 r
Maximum skin dose.....	3,400 r	5,030 r
Integral dose*.....	40 Mgr	65 Mgr

It is doubtful if it would be possible to attain 6,000 r at the lesion, at 200 kilovolts, since the skin dose is probably above the tolerance, also the dose per day is high and would impair the patient's vitality. The integral dose is a measure of the dose absorbed by the patient, being the sum of the products of volumes of tissue and their respective doses. 40 Mgr is nearly

* Megagram-röntgens.

the upper limit and it is doubtful if many patients would survive 65 Mgr.

Similar conclusions can be arrived at for other lesion sites, and as a matter of routine all cases are isodosed at a million volts, each case being treated as an individual case with its individual problems.

Effect of the Variation of Density through the Body

Considerable investigation has shown that at 200 kilovolts the isodose curves calculated for treatments have always erred on

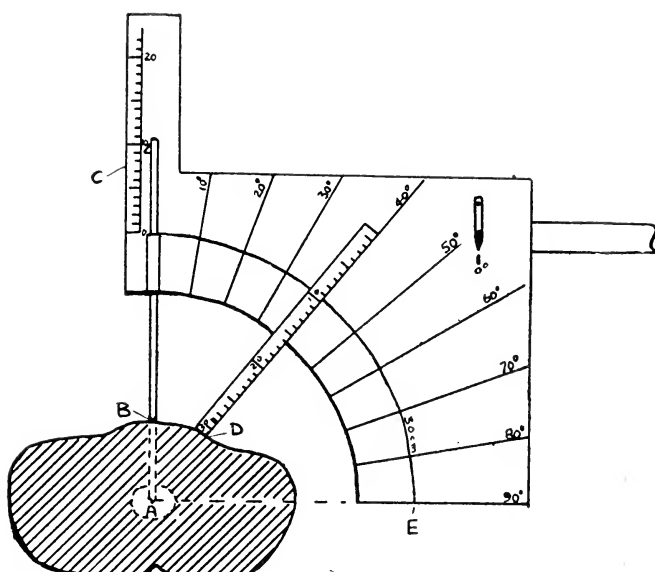

FIG. 6. Pin-and-Arc Device

the optimistic side, particularly where beams have had to pass through bone. At 200 kilovolts, a particular skull absorbed 15% more than the same thickness of tissue, while at 1,000 kilovolts there was only 4.5% more absorption. This would mean that in the treatment of a brain tumor at 200 kilovolts, the lesion dose might be at least 15% lower than calculated. A particularly

bad case came to light in an investigation into distribution, in the course of postoperative radiation in carcinoma of the breast, where, at 200 kilovolts, the measured dose was one-third of that calculated, mainly due to the fact that the angles of the beams, at that particular point, were the same as the ribs.

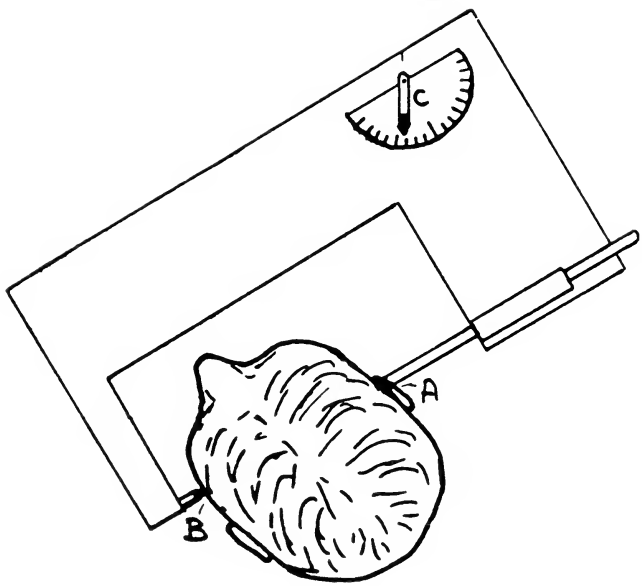

FIG. 7. Device for Measuring the Angle of a Line Joining Two Points

At a million volts, discrepancies have been small and rarely more than 10%. This may be partly due to the fact that so little of the dose at a depth depends on scatter, and the surrounding conditions do not therefore affect the dose to any appreciable degree.

Because of these discrepancies, there is sometimes a tendency to feel that the complicated and sometimes laborious calculation of the theoretical distribution of radiation is unnecessary. It must be pointed out that the cases quoted are the worst encountered, and that unless investigations commence from some mathematical basis, particularly when analyzing a group of sim-

ilar cases, it will be impossible to draw any dosage conclusions, or to attempt by models to simulate the actual patient and so solve the troublesome features mathematically. At a million volts, the variations are disappearing, and an assessment of results of different geometric methods of treatment is considerably helped by a full physical investigation.

Aids to Accurate Technique

The light beam indicating the position and size of the X-ray beam can be made to travel along the axis of the tube and, by rotation of the outer sheath of the tube, at right-angles to the tube-axis. These two movements are often of assistance, giving an accurate idea in many cases of the position of the emergent beam. Beam direction has been kept as simple as possible, there being no three-dimensional angulation of beams if it can be avoided, and the patient is either parallel or at right angles to the tube-axis. The "pin-and-arc" device* of Dobbie [6] is used for all angular directions, while a very simple device** is used

* The pin-and-arc device is, in effect, a large protractor, mounted on a stand with its center removed and a retractable central pointer fitted. In the sketch (figure 6), the pointer is shown dotted at the center of the protractor (point A). Rays are marked on the protractor panel at one-degree intervals radiating from A, with zero vertical. The protractor is set in the correct position with the aid of a plumb-bob attached at the right-hand top corner. If it is required to direct the center of a beam at a definite angle through a point inside a patient, the location of this point relative to a skin-mark vertically above it being known, the device is used as follows. In the sketch, the point to be aimed at is A, and it is, say, 9 centimeters below the skin mark B. The retractable protractor central point is raised 9 centimeters from its zero point, as indicated on the scale at C, and the device is arranged so that the point is in contact with the skin mark B. The point A in the patient is then at the center of all the protractor rays and, if the required angle is produced backwards onto the patient's skin, the central point of entry, D, of the X-ray beam is obtained. The depth (AD) of the point A from the central point of entry (D) of the beam is obtained by measuring the distance of D from a 30 centimeter arc E, inscribed on the protractor from the center A. (AD = 30 centimeters less DE centimeters.)

** See figure 7. A hoop, U-shaped, is fitted with a fixed point A, and an adjustable pointer B on the other arm of the hoop, adjustable so that the distance between A and B can be varied. On the hoop is fitted a protractor and plumb-bob C, which reads 0 degrees when AB is vertical. If in the sketch the center line of a beam has to enter at A and emerge at B on a patient's head, the hoop points are adjusted to these points and the plumb-bob protractor reading is taken. This gives the angle required relative to the vertical. With the known divergence of a beam's edge the device can also be used if the required in-and-out positions of the beam edge are known.

for measuring the angle in space of the line joining two points on a patient. This takes the place of an emergent pointer, which, to be of any use, must be really rigid, a difficult mechanical problem at the relevant distances. Instead, the ingoing and outgoing points required are marked and their angle is measured directly and set on the tube.

X-ray photography at 1,000 kilovolts on patients has served as a further check on arrangements, the films obtained being quite readable, and various bony markings just being visible. The films are slightly improved if 2 millimeters of lead is placed between the patient and the film. This tends to eliminate the scatter. The softer the scatter, the more it obliterates the detail, since the film response is greater for the longer wave lengths. The film should be given 2 r. This technique has been particularly successful in carcinoma of the rectum, where a lead-loaded catheter in the rectum indicates the required features.

Conclusion

Even with the limitation that 200 kilovolt techniques have been followed, significant differences in favor of million-volt therapy have been found in the treatment of certain cancers, e.g., of maxilla and breast. There are striking differences in carcinoma of the rectum, where, in at least a third of the cases treated at one million volts, disappearance of the growth has occurred, while at 200 kilovolts it is extremely rare for this type of cancer to show any response at all.[9]

Whether the improved clinical results in the types mentioned are directly due to the change in wave length of the bombarding rays, or to the improved and simplified arrangements made possible by the physical properties of these rays, it is impossible to say, as the two effects cannot be separated. However, both the physical and clinical results are such that they lend support to the view that a further increase in voltage to the 5 to 10 million-volt range, is likely to give still better clinical results.

ACKNOWLEDGMENT.—The author wishes to thank Dr. N. S. Finzi, director of the X-ray departments, St. Bartholomew's

Hospital, for permission to publish this article, and acknowledges the clinical work of Mr. Ralph Phillips, M.S., F.R.C.S., medical officer in charge of the therapy departments, summarized herein.

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PROTECTIVE METHODS IN RADIOLOGY

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Introduction

WITHIN a few years of the discovery of X-rays and radium, it had been established that the rays might be injurious to the health of the user. Many workers, through ignorance or indifference, developed burns and dermatitis, while some even lost their lives. In 1915, following a discussion on protection for X-ray workers, the Röntgen Society devised a set of suggestions regarding safety measures, but during the next few years, due either to continued indifference of the workers or to a large increase in the amount of X-ray work undertaken by hospitals as a result of the war of 1914–18, there occurred a series of fatalities which greatly disturbed public opinion. This led to the formation in 1921 of the British X-ray and Radium Protection Committee, which issued its preliminary report (Memorandum No. 1) in July, 1921. Other committees were set up at about the same time in other countries, e.g., the Safety Committee of the American Roentgen Ray Society, and the Commission du Radium, initiated by the Académie de Médecine.

The preliminary report of the British Committee not only indicated the way to ensure efficient protection against X-rays and radium gamma rays, but also drew attention to the necessity for suitable working conditions, condemning the practice of locating X-ray departments below ground level, where natural lighting and ventilation were often inadequate. In Memorandum No. 2, issued by the committee in December, 1921, heads of X-ray departments of hospitals and other institutions were strongly advised to safeguard themselves and their staffs by

insisting upon inspection of their departments, and of the various protective appliances, by the National Physical Laboratory.

Influence of Early Protection Recommendations on the Design of Sets

The British Committee insisted that a primary precaution in all X-ray work was to surround the X-ray tube as completely as possible with adequate protective material. As lead had a high absorptive value and was easily procurable and workable, it became the common practice to place the tubes in lead-lined boxes. These were, however, heavy and clumsy, and hindered the radiologists in their work. Accordingly, efforts were made to reduce the size and weight, without sacrificing any of the protection. These efforts led to the introduction of the so-called "self-protected" tube, of which the first example was produced by N. V. Philips' Gloeilampenfabrieken, Eindhoven, Holland.[3] The main body of the tube was a chrome-iron cylinder, to which glass was sealed directly. Surrounding the cylinder was a lead sheath of sufficient thickness to absorb practically all the primary radiation from the target, with the exception of the useful X-ray beam.

Another unsatisfactory feature of early X-ray tubes and high-tension generators was the risk of electrical shock associated with their operation, since various parts of the equipment, working at several thousand volts, were often exposed. The British Committee suggested various precautionary measures, such as the introduction of earthed metal guards, the reduction of the high-tension conduit system to a minimum, and the mounting of the overhead conductors as high as possible, out of harm's way. These measures, though obvious, had not previously been generally adopted. A further advance was made in regard to high-tension protection by enclosing the tube and transformer in a single container and immersing them in oil. Generally speaking, such units were somewhat limited in regard to movement. In 1928, Bouwers [4] designed shock-proof equipment which overcame this disadvantage. The tube was mounted in an earthed

case and connected to the high-tension generator by means of shock-proof cables. This permitted the tube to be freely moved with respect to the generator. In recent years, particularly with super-voltage X-ray equipment, operating at voltages of 1 million volts or more, there has been a reversion to the scheme of enclosing the tube and generator in a single earthed metal tank. Reduction in the size of the apparatus has been achieved by using freon gas [6] or air under high pressure [22] as the insulator.

Incidentally, the shielding of high-tension parts has led to improvements in another aspect of safeguarding the health of X-ray workers. It had early been observed that workers in X-ray departments complained of headaches and exhaustion, and of inflammatory conditions of the respiratory tract. These effects were attributed to nitrous fumes and ozone, generated by brush-discharge from sharp angles and points on the high-tension system. Subsequent experiments indicated that such effects as irritable cough, exhaustion, and blood changes occurred if the ozone content of the air exceeded 0.5 milligram per cubic centimeter. It was concluded that the effects observed in X-ray workers bore a great resemblance to the symptoms of ozone poisoning. Clearly, the introduction of shock-proof systems, with the consequent elimination of brush-discharge, led to a further improvement in working conditions.

International Recommendations

At the first international congress of radiology, held in London in 1925, the question of international agreement on the main principles of protection was discussed. Three years later, at the second international congress, held in Stockholm, the British Committee submitted its recommendations as a basis for agreement, and these were accepted with but few changes. The International Commission [10] stated that its recommendations were designed to "deal only with the more essential matters involved, minor questions of detail being left to each country to elaborate. The question of seeking legal authorization for such recom-

mendations is left to each country to deal with as appears to it best."

Most countries have, up to now, preferred not to take legislative measures. In Great Britain, the safety measures recommended by the British X-ray and Radium Protection Committee [4a] receive the support of State Departments, such as the Ministry of Health and the Ministry of Labor and National Service, but those in charge of X-ray and radium departments are not compelled to adopt the safety measures nor to submit to inspection of their departments by the National Physical Laboratory. The recommendations have, however, in general, been followed by hospital authorities and factory managements, while the manufacturers of X-ray equipment have played an important part in the progressive improvement in conditions by designing equipment and departments in conformity with the committee's proposals. It may be mentioned that the Ministry of Labor and National Service issued an Order No. 703 on April 1st, 1942, regarding the health and safety provisions for factory workers engaged in the use of radioactive luminous compounds. The Order does not, however, specify any tolerance doses, and the inspections of luminizing departments which are carried out by the National Physical Laboratory on behalf of the Ministry are based upon the tolerance doses suggested by the British Committee.

In the United States, safety recommendations are prepared by the Advisory Committee on X-ray and Radium Protection.[22a, b]

Tolerance Doses for Ionizing Radiations

In toxicology, it is important to know what quantity of a particular poison can be tolerated without ill effects. The same position holds for ionizing radiations of all types, particularly those of a more penetrating character, since complete protection against them is, in the light of practical considerations, impossible. Before any protective schemes can be formulated on a sound basis, it is necessary to survey the various types of work undertaken with ionizing radiations and to have a com-

plete knowledge of the ill effects which such radiations can produce. It is further necessary to know what quantity of each type of radiation a person can receive continuously without suffering any ill effects. This quantity is called the "tolerance dose." A subsequent task in formulating the scheme is to try to express the particular tolerance dose in terms of a specifiable and reproducible biological standard, which in turn can, for preference, be measured in terms of a physical unit.

Of the present protective schemes, it can be said that they are built on as sound a basis as existing knowledge of the ill effects of various radiations permits. As more evidence regarding blood changes and genetic effects comes to light, it may be necessary to amend the present estimated tolerance doses and, consequently, the protective schemes themselves.

As regards the effects of X-rays, clinical observations in different countries led to various estimates of the tolerance dose in terms of a somewhat uncertain surface biological effect, namely, the erythema. An average value of the figures published between 1925 and 1928 indicated that a person could tolerate a dose in 3 days corresponding to $\frac{1}{1{,}000}$ of the amount of radiation required to produce an erythema. Meanwhile, work had been in progress with a view to establishing a physical unit for the measurement of quantities of X-radiation. In 1928, the röntgen (r) was accepted internationally as the unit of X-ray quantity. Shortly before this, Küstner [15] circulated a questionnaire to a number of institutions which were using deep-therapy apparatus (which, at the time, operated mainly at 200 kilovolts), asking them to state the amount of radiation which produced an erythema. The average of the values given to Küstner, when translated into röntgens, was 600 r. The tolerance dose thus corresponds to $\frac{600}{1{,}000}$ röntgens in 3 days, or 0.2 r per day. This value is at present accepted as the basis of the recommendations of the International and British Committees. On the other hand, the American Advisory Committee on X-ray

and Radium Protection take a value of 0.1 r per day as the tolerance dose.

At the fifth international congress of radiology, held at Chicago in 1937, the definition of the röntgen was modified in such a way that it became a unit of gamma rays as well as of X-rays. As regards the tolerance dose of radium gamma rays, the early evidence indicated that it was likely to be of the same order of magnitude as that for X-rays. Accordingly, we find that the current recommendations of the International and British Committees state that "the evidence at present available suggests that a person in normal health can tolerate with impunity exposure to X-rays and radium gamma rays to an extent of about 0.2 international röntgen (r) per day or 1 r per week." In this respect, the American Advisory Committees have again chosen the lower tolerance dose of 0.1 r per day.

Integral Dose and Tolerance

It will be seen that the present tolerance doses are expressed in terms of the radiation falling upon the surface of the body. It has been emphasized by Mayneord [17] and others that the total quantity of energy absorbed throughout the body of an irradiated person, or "integral dose" as it is called, is of considerable importance, both physically and clinically. For a given dosage rate of radiation (expressed in röntgens per unit time) incident upon the surface of the body, the dosage rates at various depths in the body will be greater the more penetrating the radiation. It follows, therefore, that the integral dose per unit surface dose will depend on the quality of the radiation.

A suggested unit of integral dose is the gram-röntgen, which is the quantity of energy absorbed when 1 röntgen of radiation is delivered to 1 gram of air. Mayneord and Clarkson [18] have drawn attention to the possible importance of integral dose in protection problems. For X-rays excited at 40 kilovolts (Siemens' "Doglas" therapy tube with no added filter; HVL of 0.037 millimeter Cu), they find that the integral dose is of the order of 13,000 gram-röntgens per röntgen measured on the patient's

anterior surface. For X-rays excited at 200 kilovolts (Philips' therapy tube with 1.1 millimeters Cu added; HVL of 1.35 millimeters Cu), the value is about 46,000 gram-röntgens per surface röntgen. Again, for 1,050 kilovolt X-rays (Metropolitan-Vickers' tube with filtration of 4.22 millimeters steel + 2.0 millimeters Pb + 2.0 millimeters Al; HVL of 10.4 millimeters Cu), the integral dose is 51,000 gram-röntgens per surface röntgen, while for radium gamma rays (filter equivalent to 1.3 millimeters Pt; HVL of 16 millimeters Cu), the value is 59,000. This variation of the integral dose indicates that it may, in future, be necessary to express the tolerance dose of X- or gamma radiation in terms of the integral dose, measured in gram-röntgens, rather than in terms of the surface dose, measured in röntgens. Alternatively, since in practice it will be the surface dose which is likely to be measured, it may be necessary to adopt different values of the tolerance dose, expressed in röntgens, for various qualities of radiation.

Genetic Effects

At this stage, it would be well to consider briefly the effects of ionizing radiations on genes and chromosomes and the influence which this knowledge may have in fixing limits to the amount of radiation which a person should be given. It is known that all types of ionizing radiations produce mutations, either of the individual genes or of the chromosomes, the rate of mutation being linearly proportional to the amount of radiation received. That is to say, no matter how small the given dose, there is a chance that a mutation may occur, although that chance will be very small. There is, therefore, no such thing as a tolerance dose for genetic effects, if one interprets the phrase "tolerance dose" in its ordinary sense, namely, that the human body suffers no ill effects from such a dose. The genetic effects of radiation are accumulative and irreversible since, apparently, the mutation of a stable gene leads to another gene which is equally stable.

As the majority of hereditable changes are recessive in char-

acter, any inherited qualities do not become evident unless a mutated gene meets another like itself. Muller [20] has calculated the chances of the meeting of two genes originating from independent mutations and has found that, on the average, at least 30, but more probably 100, generations would pass before a recessive abnormality of a seriously harmful nature would manifest itself by this process. There would thus be a "latent period" of 900 to 3,000 years. Muller has also calculated the chance of the meeting of two genes descended from the same original mutated gene, taking into account the degree of inbreeding. It is found that the latent period in this case is of the order of 5,000 years. It should be mentioned that spontaneous gene mutations occur naturally, and that these may be produced by the effects of natural radioactivity.

Ignoring the ionization produced by the radioelements in the air, since the ions are largely due to alpha rays, which can have little effect on the body, it can be shown that the remaining ionization due to cosmic rays and to beta and gamma rays from radioelements in the air [9] corresponds to a dosage rate of 2.2×10^{-9} r per second, or to 0.0002 r per day of 24 hours, or to 0.07 r per year. If all spontaneous mutations are caused by natural radiation—and this fact has not been established—then the natural mutation rate can be said to correspond to the irradiation of the whole human race throughout past ages at the rate of 0.07 r per year, that is, to doses up to 5 r during the lifetime of each person. If then, from now on, only a fraction, e.g., 1%, of the race is exposed to ionizing radiations, either as workers or as patients, it seems logical to deduce that the natural mutation rate would at the most be only doubled even if each person in this minority received, on the average, 500 r in his lifetime.

In assessing the permissible dose on which to base future protection schemes, it will be necessary to know what fraction of the race is to be subjected to artificial radiation and what increase of the spontaneous mutation rate is justifiable, offsetting the degree of race degeneration against the benefits bestowed by radiation. It does appear, however, that the suggestion made in an earlier paper by Muller [19] that the dosage rate should be

reduced to 10^{-8} r per second is much too cautious. Assuming a working week of 35 hours, and 48 working weeks per year, in conformity with the International and British Recommendations, Muller's figure corresponds to 0.06 r per year, which is slightly less than the natural radiation intensity. Hence, if the whole human race were exposed to an additional intensity of 10^{-8} r per second, the mutation rate would not be doubled.

The regulations of the Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege recommend that, for the genital organs, the daily dose should not exceed 0.025 r. This is one-tenth of the ordinary tolerance dose accepted by the German X-ray Society. Jaeger and Zimmer [11] considered that, as the number of workers using ionizing radiations in 1941 was still a relatively small proportion of the total population, even this value of 0.025 r per day represented a very cautious attitude.

Risks by Inhalation or Ingestion

We now turn to the consideration of other classes of radiation workers, namely, those who may suffer injury from radioactive materials which have been inhaled or ingested. As regards radon, the British X-ray and Radium Protection Committee [4a] recommend that "the radon of the air in laboratory, factory, workshop or other working quarters should not exceed a concentration of 10^{-10} curie per liter." As regards radium in the body, the Committee recommend that if, after the person has remained away from work for 48 hours, "radon then be found in a concentration of even 10^{-11} curie per liter, it is presumptive evidence of radium in the body and the operator should at once discontinue such work." In the National Bureau of Standards Handbook H.27 on the *Safe Handling of Luminous Compounds*, much lower tolerance levels are advised, namely, "the radon concentration in the atmosphere of workrooms shall not exceed 10^{-11} curie per liter," and "no one shall be engaged as a dial painter who shows more than 0.1 microgram of deposited radium as revealed by the expired air test." It is stated that the latter figure corresponds to 10^{-12} curie of radon per liter

of expired air. Assuming that the tidal respiratory volume per minute is 5 liters, it can be calculated that, if all the radon formed from 0.1 μg of radium in the body appeared in the breath, the radon concentration of the expired air would be 2.5×10^{-12} curie per liter. The American figure of 10^{-12} curie per liter thus assumes that 40% of the radon is liberated. On the same basis, the British figure of 10^{-11} curie per liter corresponds to 1 μg of radium in the body.

It must be mentioned, however, that the ratio of the liberated to the trapped radon varies considerably, not wholly in relation to the length of time during which the radium has been deposited. In examining luminizers, the National Physical Laboratory, therefore, measures not only the exhaled radon but the gamma radiation from the disintegration products of the trapped radon, as this is the only way in which to assess accurately the total amount of radium in the body.

There is much conflicting evidence regarding radium poisoning:

1. Evans [7] reported that 7 persons carrying between 0.02 μg and 0.5 μg for 7 to 25 years revealed no clinical symptoms of chronic radium poisoning. Similar examples can be quoted from the results of tests made at the National Physical Laboratory on workers who have been engaged in luminizing for periods up to 30 years. In one case, a person who worked full time on actual luminizing for 30 years was found to have 0.7 μg radium in her body, and there were no apparent ill effects.
2. Opposed to the above is the evidence that fatalities have occurred when the radium burden was above 1.2 μg.
3. The "normal" amount of radium in the body is between 0.01 and 0.015 μg. Expressing this in another way, Jones and Day [12] calculate that the normal radium content of the body produces 0.025×10^6 ions per cubic centimeter of tissue per second. For comparison purposes, they show that the radiation tolerance dose of 1 r per week produces 2.69×10^6 ions per cubic centimeter per second, while a

radon concentration of 10^{-10} curie per liter in the atmosphere produces only 0.00008×10^6 ions per cubic centimeter per second.

4. The air of the Joachimstal mines contains from 20×10^{-10} to 60×10^{-10} curie of radon per liter, and occasionally as much as 200×10^{-10} curie per liter has been measured. Yet lung carcinoma among the miners is attributed to the dusts of arsenic and chromium, and not to the radon.

These conflicting facts indicate that much more evidence is required before the tolerance doses for radium in the body and for radon and radium dust in the air of the workshop can be regarded as satisfactory.

Neutrons

There is another type of ionizing radiation, the neutron, against which adequate protection must be found. The neutron is approximately the same size as the proton (the nucleus of the hydrogen atom), and if the two collide, the neutron surrenders a large part of its energy to the proton, which recoils along a short path. Neutrons are thus effectively slowed down in hydrogenous material, such as tissue. The recoiling protons produce ions in the tissue, the ion density along the proton track being far more intense than along the tracks of the electrons which are liberated in tissue by the passage of X- or gamma rays.

Comparisons have been made of the biological effects of X-rays, alpha rays, gamma rays, and neutrons.[8, 16] These raise the problem of the measurement of neutron doses. Since neutrons liberate far more ions in tissue than in the same mass of air, it is not possible to measure neutron doses directly in röntgens. The accepted practice is to define an "equivalent röntgen" of neutrons as the dose which produces the same number of ions per unit volume of tissue as a dose of 1 röntgen of X- or gamma radiation. On this basis, it is found that the ratio of gamma-ray energy to the neutron energy required to produce a biological reaction varies from about 1.5 to 9, according to the reaction studied.

On the other hand, the ratio of X-ray energy to gamma-ray energy shows much smaller variations, the average value being about 1.5. Clearly, further experiments will have to be made before a tolerance dose for neutrons can be established.

Reference is made in Smyth's report on *Atomic Energy*,[21] to the fact that the National Defense Research Committee of the United States set up a health group, one of whose tasks was to carry out research on the effects of radiations on persons engaged in the operations associated with the atomic pile. The results of the investigations of the group have not yet been announced, but doubtless the knowledge of radiation effects will have been greatly increased.

Elaboration of Protective Schemes

When the tolerance dose for a particular type of radiation, say, X-radiation, has been established and is measurable in terms of a physical unit, the subsequent procedure in determining the protection in any instance is to measure the dosage rate of the radiation received at a specified point in terms of the unit adopted, to determine the transmission values of the radiation through various thicknesses of various absorbing materials, and finally to calculate the thickness of the chosen absorbent which is required to reduce the transmitted radiation received at the point in question to the tolerance dosage rate.

It is well known that X-rays and radium gamma rays are absorbed more effectively by lead than by any other common material. Hence lead or lead-impregnated materials, such as rubber and glass, have generally been used to secure protection. It is also customary to express the required protection in terms of lead and to determine the "lead-equivalents" of other absorbents.

When using X-ray equipment, steps must be taken to safeguard the operator against three types of radiation. In the first place, the tube itself must be protected in all directions other than that of the useful beam. Secondly, if the direct beam is pointed at the operator, as is often the case in screening a

patient or object, a protective barrier must be placed in front of the operator. Thirdly, since all objects which are placed in the path of the direct beam scatter the radiation in all directions, the operator must be protected against this secondary radiation, either by means of a protective barrier or by relying on remoteness from the scattering objects.

Many papers have been published regarding the outputs of X-ray tubes operating under various exciting conditions. The results have been summarized by Kaye and Binks [13] and Binks [2] for exciting voltages up to 2 million volts. For tubes with "reflection" targets, that is, where the X-radiation is emitted at right angles to the electron stream, the outputs with a filtration of 0.1 millimeter copper are 2.1×10^{-4} (kilovolts)$^{1.8}$ r per minute per milliampere at 1 meter over the range 75 to 200 kilovolts, while with a filtration of 0.5 millimeter copper, the outputs are 1.7×10^{-5} (kilovolts)$^{2.1}$ r per minute per milliampere at 1 meter over the range 200 kilovolts to 2 million volts. For tubes with "transmission" targets, i.e., tubes in which the direction of the X-ray beam is a continuation of the electron stream, the X-ray outputs with a filtration of 0.5 millimeter copper are 2.1×10^{-6} (kilovolts)$^{2.6}$ r per minute per milliampere at 1 meter over the range 600 kilovolts to 2 million volts.

Turning to the corresponding question of the gamma-ray outputs from known quantities of radium sealed in containers having a screenage equivalent of 0.5 millimeter platinum, the outputs can be calculated on the basis that the quantity of radiation received in 1 hour at 1 centimeter from a "point source" of 1 milligram radium is about 8 röntgens. For distances other than 1 centimeter, the calculations are based on the inverse square law of radiation.

The preceding data on X-ray and gamma-ray outputs refer to the intensities of the direct beams. Far fewer measurments have been made of the intensities of scattered radiation,[2] but one or two examples will illustrate the magnitude and importance of the intensities of scattered radiation encountered in practice. The dosage rate at the side of a patient who is screened in the couch position is usually of the order of 100×10^{-5} r per second. The

daily tolerance dose of 0.2 r would, therefore, be received in just over 3 minutes, which is about the time taken on one patient only. Hence the need for a protective screen on the side of the couch. In the case of X-ray therapy, the intensity of the scattered radiation at 1 meter to the side of a patient, who is exposed to 200 kilovolt X-rays from a tube run at 30 milliamperes and having a filtration of 0.5 millimeter copper, is about 250×10^{-5} r per second, corresponding to a dose of 0.2 r in 80 seconds.

The absorption of direct and scattered X-rays and gamma rays in various materials has been determined experimentally by workers in many countries. For direct X-rays excited at voltages up to 5 million volts and for radium gamma rays, theoretical values have also been obtained [13] for absorption in lead and for the lead equivalents of barium concrete.

From a knowledge of the outputs of X-ray tubes, working under various conditions of excitation, and from a knowledge of the degree of absorption of the rays in lead, it is a simple step to calculate the thicknesses of lead required to reduce the radiation at any point to the tolerance amount. Binks [2] has prepared a simple nomogram, relating kilovoltage, milliamperage, distance, and the amount of lead protection. By means of this, it is possible to find the amount of lead required to give adequate protection for any tube voltage between 200 kilovolts and 3 million volts, for any tube current between 0.5 and 30 milliamperes, and for any distance from the tube between 0.5 and 10 meters. A similar nomogram has been prepared [2] for the determination of lead protection against radium gamma rays. The corresponding protective thicknesses of other materials, such as brick, concrete and barium concrete, are also known.[14]

During the war, there was a rapid increase in the number of workers engaged in luminizing instrument dials and in the average quantity of radioactive luminous compound handled by each worker. As previously mentioned, the Ministry of Labor and National Service issued an Order in April, 1942, giving fairly detailed instructions to employers and employees regarding the protective arrangements which are to be adopted in luminizing departments. The main features are:

1. Protection against gamma radiation from the radium paint issued to each operator and against gamma radiation from the main stock of luminous compound possessed by the firm.
2. Protection of the exposed parts of the body against beta radiation. Each operator is to work behind a lead-glass screen, thus preventing beta radiation from the luminized object from reaching the face.
3. Local ventilation on each working bench, so as to remove radon and radium dust from the vicinity of the operator.
4. General ventilation of the workroom to remove radon and radium dust.
5. Provision of special clothing for use in the workroom.
6. Periodical cleaning of bench tops and equipment.
7. Personal hygiene.

Similar proposals were put forward in America in the Bureau of Standards' Handbook H.27.

Reference has already been made to the fact that neutrons can be decelerated in hydrogenous materials and are ultimately reduced to thermal velocities. The "thermal neutrons" are easily absorbed, in capture processes, by elements such as cadmium and boron which, in turn, become temporarily radioactive. In this phenomenon, we find a method of protecting personnel against neutrons, produced by heavy particles accelerated by apparatus such as the cyclotron. Tanks of water up to 1 meter thick, or stacks of paraffin wax blocks up to about 70 centimeters thick, are placed round the neutron source, most of the slow neutrons being absorbed by salts of cadmium or boron introduced into the water or wax. Any gamma radiation which is liberated is absorbed in a final sheet of lead.

Tests on Radiation Workers and Inspections of Radiological Departments

Since the introduction of the first report of the British X-ray and Radium Protection Committee, the National Physical Lab-

oratory has continued to carry out inspections of radiological departments. Ionometric measurements are made at all points likely to be occupied by personnel and, if the dosage rate at any point is found to be in excess of the tolerance amount, methods of remedying the defective equipment or of improving the technique are suggested.

During the war, the Ministry of Health was disturbed at the increasing number of reported cases of low leucocyte counts and, towards the end of 1942, consulted the Laboratory with a view to the establishment of a dosage service. On the basis of many years' experience gained in the use of photographic films for monitoring the doses of radiation received by members of its own staff, the Laboratory organized a dosage film service on behalf of the Ministry. Later the service was extended to workers in Scotland and in Northern Ireland. In March, 1943, the Factory Department of the Ministry of Labor and National Service circularized industrial radiological departments, advising the managements to make use of the same film service.

Up to the present time, nearly 2,000 medical workers at about 550 hospitals and nearly 1,000 industrial workers at about 150 firms have been examined by the film method, many of the workers having been tested at three-monthly intervals, and a few continuously. The results show that over 70% of hospital X-ray staffs and over 90% of industrial X-ray staffs receive less than one-tenth of the weekly tolerance dose. When a film test indicates that the wearer has received an excessive dose and the result has been confirmed in a repeat test, the Laboratory sends representatives to inspect the radiological department concerned. In some cases, it is found that the equipment is defective; in others, that the technique is faulty. But it should be remarked that it has been found necessary to inspect only 9 hospital X-ray departments and only 12 industrial X-ray departments. There appears to be no need, therefore, for alarm regarding the low leucocyte counts. Indeed, Britton [5] found a low leucocyte count in 29% of the 552 counts on 68 apparently healthy nurses not exposed to radiation. He stated that this appeared to be a war effect of unknown cause.

The films which are issued to radium workers are half covered with sheet lead 1 millimeter thick, which absorbs any beta radiation. The shielded half of the film thus records the gamma-ray dose, whereas the unshielded portion records both beta and gamma radiation. In the case of luminizers, it has been found that there is a large beta-ray effect, and subsequent inspections of many of the departments have revealed that most of the dose is due to contaminated benches and clothing. In the majority of cases, the total doses are now well below the tolerance level.

It seems possible to use the film technique for the measurement of neutrons which fall on the body. Fast neutrons would be slowed down in the tissue and would "evaporate" from the surface of the body with thermal velocities. If the film is covered with a thin foil of, say, cadmium, rhodium, or indium, which have a high-capture cross section, these elements would capture the neutrons, becoming radioactive and emitting ionization radiations which would blacken the film. The radioactivity should, preferably, be short-lived, so that there would be no need to take into account the lapse of time between the initial irradiation of the film and the photographic development.

The inspections of luminizing departments also include tests of the radon concentration of the air of the workrooms, and tests of the radium in the bodies of luminizers, part of the radium being assessed by means of the alpha rays from the radon contained in the exhaled air and part by means of the gamma rays from the subsequent disintegration products of the radon trapped in the body. Similar tests have been carried out by Jones and Day.[12]

It will be apparent from the foregoing review that, while there is much to be learned about the tolerance doses for various types of ionizing radiation, and while there is an ever-growing number of radiological workers using an ever-widening range of man-made radiations, sufficient experience has already been gained to be able to tackle the new protection problems with high hopes of evolving effective safety measures.

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INDEX

A

B

C

D

E

F

G

H

I

J

L

M

N

R

S

T

U

V