LYNDON A. PEER, M.D.

Transplantation of Tissues

VOLUME I

CARTILAGE BONE
FASCIA TENDON MUSCLE

Transplantation of Tissues

CARTILAGE, BONE, FASCIA, TENDON, AND MUSCLE

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VOLUME I

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Foreword

I can think of no one who is better qualified to present a book on Transplantation of Tissues than Dr. Peer. He is a happy combination of practical surgeon and scientific investigator, and thus is able to bring to his medical colleagues research information that will aid them in their daily tasks in the treatment and rehabilitation of patients.

An example of this ability to apply experimental findings for clinical use was demonstrated when Dr. Peer invented "diced cartilage grafts" after noting in human experiments that cartilage grafts became bound together in the form of a plaque after transplantation in abdominal fat. He was the first to use diced cartilage to repair skull depressions and other facial defects, and later devised methods which successfully utilized the multiple transplants in such diverse fields as ear reconstruction, ankylosis of the hip joint, spina bifida, recurrent abdominal and inguinal hernia, and large losses in the chest cage. Diced cartilage grafts and Dr. Peer's principle of introducing them into perforated vitallium molds to preform or shape the cartilage are accepted surgical procedures in many clinics here and abroad. He has examined and reported the histological findings in a larger number of autogenous and homogenous human cartilage grafts than any other investigator.

The book tells, as far as present knowledge goes, just what happens to various types of tissues, heterogenous, homogenous and autogenous, when transplanted into animals and humans. Dr. Peer has introduced each separate tissue, such as cartilage, bone, etc., with a preliminary chapter describing the structure of the tissue from a histological and surgical standpoint. He has also, I believe, for the first time succinctly divided all experimental work under that in animals and that in humans, sharply differentiating between the two, since what happens in the animal is not always exactly so in the human. After discussion of the basic experimental data relating to transplantation of each particular type of tissue, a chapter follows on the practical or clinical application of these data in the treatment of specific conditions.

The book correlates and evaluates a vast amount of material that has been heretofore scattered throughout the literature. This will make it a valuable tool both for those doing research work and for clinicians engaged in the varied fields of tissue, gland, and organ transplantation.

Robert H. Ivy, M.D.

Preface

It is now some thirty years since Harold Neuhof wrote his excellent book on "The Transplantation of Tissues," and until this time no attempt has been made to present a similar comprehensive treatise on the subject dealing with all varieties of tissues. During these decades research has brought tissue grafting into relationship with various other scientific fields, and a mass of experiemntal and clinical data has accumulated. It therefore appears timely to gather the material together, and evaluate its contributions to advancement in our knowledge of this dynamic and expanding science.

The form a book assumes is determined by the reader for whom it is intended. After considerable thought I decided to present the material in a manner designed to be readable and informative for the physician, surgeon, and medical student. This decision was probably wise, for my training and attitude are those of a clinical histologist, and all of my experimental work has been done with human transplants in human recipients.

Advances in medicine and surgery usually follow new concepts which are made possible by research information in different branches of science; when this information is correlated and applied for clinical use in man the new period arrives. It is evident that a new dynamic era of surgical replacement therapy utilizing the transplantation of tissues has now begun.

The already successful homotransplantation of embryonal endocrine glands in children and adults for the replacement of deficient glands, and the treatment of aging individuals who have lost their drive and interest in life are no longer fanciful. The possibility of permanent successful homotransplantation of skin in severely burned patients, the temporary success of whole organ transplants, the transplantation of embryonal teeth, and the clinical success of auto-, homo-, and even hetero-arterial grafts are becoming accepted advances in medical and surgical care.

It is now generally recognized that homogenous grafts of cornea, bone, and cartilage have a wide and expanding field of usefulness in clinical surgery. Diced cartilage segments either shaped in vitallium molds or introduced directly for such diverse conditions as hernia, new joint surfaces, and large losses in the thoracic cage have a wide application, which is not appreciated by the average clinician.

Thus it appears that we are on the threshold of a medical and surgical era which is destined to affect clinical practice profoundly. With a greater understanding of the behavior of cells, especially by employing tissue transplantation techniques, a new science that might be called "clinical histology" will probably develop. Because of the great advances in tissue transplantation today the science of "clinical histology" will logically become an integrated part of the medical college curriculum of the future.

In Volume I, the material is presented in a somewhat positive way for teaching purposes. The simplification, however, is based on microscopic evidence collected over a period of many years, and this evidence is correlated with clinical experience, and the gross appearance of the grafted area. Whenever my facts and theories differ from generally accepted opinions the latter are presented as accurately as possible.

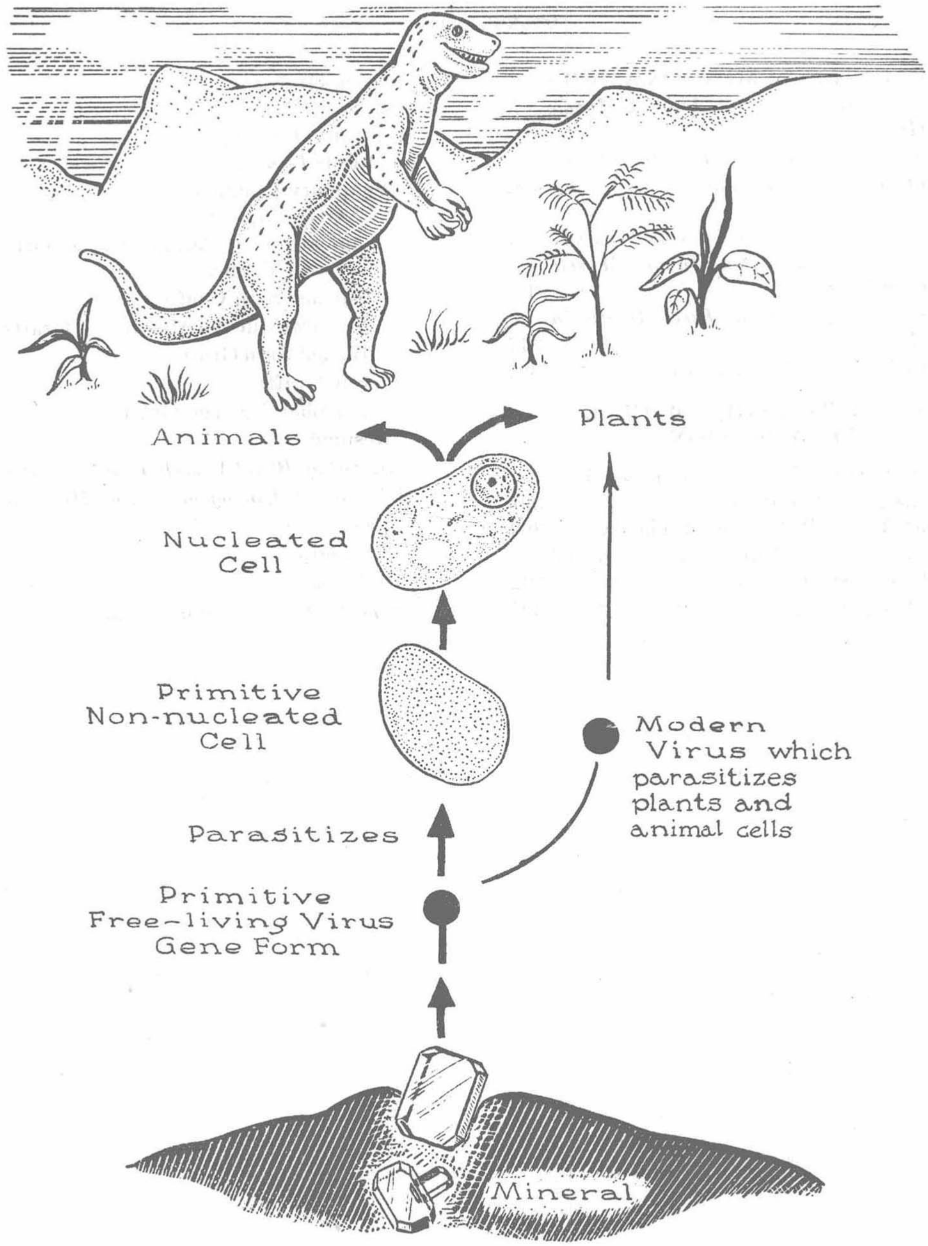
Various additional aspects of cell structure and cell behavior will be described by a number of selected authorities in Volume II, which is to be published subsequently.

I wish to express my indebtedness to scientific friends for their interest and helpful counsel, and in particular to Miss Ruth Pullen, R.N., for her skilful drawings in clarifying the text, and to Miss Emma A. Buehler, B.A., M.A., for compiling the literature, editing, and her many constructive suggestions.

Dr. William G. Bernhard, director of laboratories at St. Barnabas Hospital, contributed valuable advice regarding the fixation of tissues and the microscopic interpretation of many sections. My former residents in plastic surgery all participated in portions of the experimental work (Dr. John Van Duyn, Dr. John Walker, Jr., Dr. Francis Marzoni, Dr. Max Pegram, Dr. Armand Genest, Dr. Robert Hagerty, Dr. F. S. Hoffmeistr, Dr. Clare Johnson, Dr. M. Shahgholi, Dr. Alvin Mancusi-Ungaro, and Dr. Blair Rogers).

The author welcomes this opportunity to express a deep sense of appreciation to Dr. George H. Lathrope of Morristown, and Dr. Royce Paddock of Newark, who have encouraged him in his clinical and experimental investigations over a period of many years.

L.A.P.



"Possible Evolutionary Chain from Minerals to Plants and Animals"

The primitive free-living virus gene form, originating from a mineral, parasitizes a co-existent primitive non-nucleated cell and by co-operative effort with the cell gives rise to a nucleus containing genes. The nucleated cell evolves into multicellular organisms which give rise to plants and animals.

Alternately, some of the primitive free-living virus gene forms give rise to the present-day viruses, which can be active and reproduce only within the bodies of susceptible plant and animal cells. Evolution of this primitive free-living virus gene form also gives rise to the more complex and larger viruses, rickettsiae, and bacteria. (Modified from Stanley.)

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PART I

General Considerations

CHAPTER 1

The Importance of Understanding Tissue Cells

The field of tissue transplantation is one of the most rapidly expanding frontiers of experimental and clinical medicine. Transplantation of tissues offers a wide range of new therapeutic advantages not only to the surgeon but to the internist, endocrinologist, cancer research worker, and many other scientists as well.

When properly chosen and applied, the newly-developed methods of tissue auto-, homo- and even heterotransplantation[1] furnish the physician and the research man with improvements upon preexisting forms of therapy and experimentation that open up innumerable new possibilities for hormone replacement, substitution of organs, growth of experimental cancer cells, etc.

It seems plausible that a knowledge of, and an interest in, the activities and biophysiologic environment of the several billions of cells that collectively make up the human being should help to enlarge the horizon and increase the understanding of the medical student and the physician, both of whom are concerned with the health of man.

Carefully controlled studies have already been made in which tissue-cultured embryonic adrenal and parathyroid glands have been transplanted to humans and to animals. These homotransplanted embryonic glands have survived permanently, taking over the functions of the diseased or absent glands. One patient with Addison's disease now survives without hormone injections as a result of having received such a transplanted embryonic adrenal gland.

Some patients have been relieved of hypoparathyroidism and tetany by the transplantation of embryonic parathyroid glands, but the cures and improvements have not always been consistent. *These successful results at any rate demonstrate that the science of homotransplantation is no longer in the realm of hypothetical speculation.*

Research in this field has developed to such a degree that surgeons no longer look with hesitancy upon the problem of how to transplant, for example, a kidney or a piece of skin but rather upon the problem of *how to induce these homotransplanted tissues to survive permanently*. The real crux of the matter lies in these words—"survive permanently."

One might say that no adult tissue exists which can be successfully and permanently transplanted from one human being to another, preserving its normal structure and

[1] Heterotransplantation has little if any clinical uses at this time. It is extremely valuable, however, in cancer and other forms of research. For instance, human cancer cells may be transplanted and studied in the rabbit and in other animals.

function intact in a living state. The successful experiments mentioned above were performed with the use of embryonic glands removed from stillborn babies.

There is a great need to solve the problem of homotransplanting adult tissues. One can see quite readily that many tissues would be ideally suited for use in permanent successful transplantations from one human to another, e.g., skin, kidneys, endocrine glands, bone, blood vessels, cartilage, cornea, hair, etc. Naturally, in most cases such tissues would be furnished by recently-deceased healthy young adults killed in accidents or by disease unrelated to the health of the tissues mentioned, or by infants who die as a result of unrelated disease. Because the supply of tissues from stillbirths is a limited one, the entire field of homotransplantation must, of necessity, approach the problem of the successful utilization of adult tissues. There is, of course, the possibility that embryonic tissues might be grown in tissue-culture media (a tissue-culture bank) and transplanted to children or adults whenever homotransplants were indicated.

There is also the possibility that small portions of tissue, such as skin, might be grown into large sheets in tissue-culture media and later applied as a covering autograft (in the same patient) to replace large skin losses.

Certainly further experimental work with autografts, which are generally successful, should be correlated with our expanding knowledge regarding the behavior of homotransplants. *The behavior of autogenous grafts is an important yardstick in evaluating the fate of similar homogenous transplants.* One might critically remark that both research workers and clinicians tend to undertake experimental and clinical application of homografts before they are informed regarding the known behavior of similar autotransplants.[2] This is not unlike plunging into pathology without a thorough knowledge of histology.

Research in tissue homotransplantation has already solved some of the difficulties which arise when the surgeon transplants a kidney or skin from one human to another. *The chief problem, however, of getting such a tissue to survive permanently is far from being solved.* As an example of how misleading information on this subject can be, the average surgeon and the average layman think that corneal transplants are generally successful. It must be remembered, however, that a good one-third of these transplants fail because of the so-called "*mal de greffe*" or graft sickness, a vague term which is used to describe the sudden onset of a series of events which cause destruction and clouding of the transplant, often within twenty-four hours. Is this sudden change for the worse due to an "immunity reaction" on the part of the patient directed against the foreign proteins in the transplant? Research is only now beginning to explore just such a possibility. This is important research, for one may make this categorical statement: *Whoever solves the method by which skin may be permanently transplanted from one human to another, preserving its normal architecture and its living cells* (perhaps by preventing this hypothetical "immune reaction" from taking place) *also solves the problems underlying the successful permanent homotransplantation of any tissue or any organ from one human to another.*

One may conclude from these examples given and from others not mentioned that future advancement in medicine will be closely associated with a knowledge of the structure and behavior of cells.

The physician who has a thorough understanding of the physiologic requirements of living cells is not apt to undertake surgical manipulations that are harmful or useless, nor will he prescribe drugs or other forms of therapy that adversely affect tissue cells.

Unfortunately, the average practicing

[2] There is much that is not known regarding the behavior of autografts.

physician and surgeon seems to have little knowledge of, and consequently little interest in, *the structure and normal activities of tissue cells.* At medical meetings and in hospital dining-rooms many doctors show an interest in discussions about abnormal cell activity when this is directly related to a patient's symptoms or is evident in the production of gross abnormal findings such as grapefruit-sized tumors or abscesses containing a liter of fluid. Interest fades, however, when the discussion turns to microscopic observations, and attention is directed to those small living entities that collectively form and maintain all human tissues. A discussion of physiologic and pathologic changes on the cellular level is too speculative for the average surgeon, who too often thinks of the structures that he manipulates in much the same manner as the craftsman who works with cloth or blocks of wood. The physician does give a fair amount of attention to the circulating system that nourishes and drains the tissues themselves, and usually he is aware of the importance of the cellular elements in whole blood, because these are vitally necessary for the control of shock or the success of an operation. He is not usually interested, however, in the cell groups that are actually supplied by the circulating system unless they are diseased.

It is difficult to determine just why a practicing physician should departmentalize his mind in such a manner that his early histological training in medical school is later applied to pathologic problems but is largely ignored when he deals with normal tissues. This, in part, may be due to the gap in teachings in medical schools between academic histology and pathology, on the one hand, and surgery and medicine, on the other.

Pathology deals with abnormal tissue cells. Because all pathologic conditions usually arise from normal cell groups, the structure and behavior of normal cells should be understood in order to better comprehend the abnormal cells. It is quite easy, however, to be so impressed with the *abnormal* that we lose our conception of *normal cell types,* and the physiologic requirements necessary for their survival and good health.

Thus, even after six years of postgraduate study in our stream-lined American Board system of training, senior surgical residents show an astonishing ignorance of the tissues which they manipulate, and of the requirements of living cells in these tissues.

It is an established fact that certain tissue cells when transplanted as free grafts tend to react in a specific manner. Some cells will always survive a favorable transplantation procedure, whereas some will only partly survive the transfer and others will never survive. Wide surgical undermining of tissues, relaxation incisions, or the shifting of tissues on attached pedicles will naturally affect the survival of cells, depending upon the extent to which their vascular and lymphatic circulations are interfered with, plus many other non-surgical factors. The cells in some tissues such as cartilage, skin, and fascia tend to survive free transplantation just as readily when severed from their original blood supply as when they are transplanted with an attached blood supply. The exact opposite is true, however, of the cells in fat and muscle grafts.

It is not uncommon to observe a skilled surgeon who performs an excellent operation from a technical standpoint but who transgresses one of the biological laws of tissue transplantation, with an operative failure as the result. A free fat graft improperly handled during an operation, for instance, will fail to "take" despite the skill of the transplantation procedure. Fat cells, as a point of explanation, are undeniably sensitive to even the slightest amount of trauma during a surgical operation. When poorly-handled fat grafts are transplanted to a new host site, host connective tissue will often replace the graft. In general, grafts will also fail if their environment is radically altered. Thus, even skin grafts, which are composed of hardy, keratinized epithelial cells, tend to wither away when they are buried beneath the body surface. If these grafts are provided with even a small communication to the skin surface, they tend to survive, and as such they have been employed as a substitute lining—for example, in reconstruction of the urethra. Conversely, tissues such as fascia, tendon, and bone, which normally live buried under other body tissues, do not tend to survive when transplanted to the skin surface. With a better understanding of many poorly-known general facts about tissue transplantation the practicing physician and research worker would be in a better position to apply this knowledge to the perfection of improved methods for tissue grafting on both the clinical and laboratory level.

The entire field of free tissue transplantation has many important clinical applications. The doctor who practices in areas where there are no large medical institutions can still contribute valuable knowledge about the behavior of human tissue cells in transplanted grafts. The only equipment he needs is a compound microscope and his own individual powers of observation. When a favorable opportunity presents itself, with the consent of the patient or the patient's relatives, a tissue can be buried for varying lengths of time in the abdominal wall and later removed for microscopic examination. The conclusions drawn from such studies may be much more valuable than the numerous conflicting reports that now appear in the literature, and the fruits of such a study should have a stimulating effect on the investigator. Certainly in astronomy many significant contributions have been made by the amateur. Similarly the concepts and theories of a physician who does not consider himself an expert in tissue transplantation may be important; hypotheses are the soul of science and may be extremely valuable even if they eventually prove to be wrong.

The physician who develops this interest in normal and abnormal tissues and their transplantation will gain an understanding of cell behavior which can be applied clinically. In addition he may possibly help to contribute to the great fund of medical knowledge inherited from previous investigators, both living and dead.