Transplantation of Tissues | PEER

VOLUME II

SKIN, CORNEA, FAT, NERVES, TEETH, BLOOD VESSELS,
ENDOCRINE GLANDS, ORGANS, PERITONEUM, CANCER CELLS

Transplantation of Tissues

SKIN, CORNEA, FAT, NERVES, TEETH, BLOOD VESSELS, ENDOCRINE GLANDS, ORGANS, PERITONEUM, CANCER CELLS

Edited by

Lyndon A. Peer, M.D.

Clinical and Research Director, Rehabilitation
Center for Plastic and Reconstructive Surgery,
Saint Barnabas Medical Center, Newark, N. J.

with Twelve Contributors

Volume II

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DEDICATION

To the memory of Dr. Milton Adams, whose untimely death is a great personal loss. He contributed in a large measure to plastic surgery and enriched life for all who enjoyed his friendship.

Contributors

Sterling Bunnell, M.D.
Late Consultant to the Surgeon General of United States Army, to the United States Navy and to the Alaska Department of Health.

Ramón Castroviejo, M.D.
Clinical Professor of Ophthalmology, New York University Post-Graduate Medical School; Chief of the Department of Ophthalmology, St. Vincent's Hospital; and Director of the Corneal Clinic of New York City Eye and Ear Infirmary, New York, N. Y.

Miklos Cserepfalvi, M.D., D.D.S.
Beneficiary of Rockefeller Foundation's Program for Aid to Hungarian Refugees Seeking to Establish Themselves in the United States; Saint Barnabas Medical Center, Newark, N. J.

Ralph A. Deterling, Jr., M.D.
Associate Attending Surgeon, Presbyterian Hospital, New York; Associate Clinical Professor of Surgery, College of Physicians and Surgeons, Director of Surgical Research Laboratories, Columbia University, New York, N. Y.

E. J. Eichwald, M.D.
Director of the Laboratory of Experimental Medicine, Montana Deaconess Hospital, Great Falls, Mont.

Harold S. Fleming, D.M.D., M.Sc., D.Sc.
Research Associate, Department of Pathology, Yale University School of Medicine, New Haven, Conn.

David M. Hume, M.D.
Professor of Surgery and Chairman of the Department, Medical College of Virginia, Richmond, Va.

Abdol H. Islami, M.D.
Assistant Director of the Post-Graduate Department and Director of the Division of Experimental Surgery, Seton Hall College of Medicine and Dentistry; Consultant in Experimental Surgery, Saint Barnabas Medical Center, Newark, N. J.

P. L. Krohn
Nuffield Senior Gerontological Research Fellow and Honorary Professor, University Medical School, University of Birmingham, Birmingham, England.

P. B. Medawar, D.Sc.
Jodrell Professor of Zoology, University College, University of London.

Mary S. Parshley, Ph.D.
Research Associate in Surgery, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Lyndon A. Peer, M.D.
Clinical and Research Director, Rehabilitation Center for Plastic and Reconstructive Surgery, Saint Barnabas Medical Center, Newark, N. J.

Blair Oakley Rogers, M.D.
Instructor in Plastic Surgery, New York University College of Medicine, New York University-Bellevue Medical Center; Consultant, Tissue Culture Department, Saint Barnabas Medical Center, Newark, N. J.

Preface

The wide variety of transplants discussed in this second volume, *i.e.*, organs, endocrine glands, cornea, cancer cells, etc., has necessitated a group presentation since no single individual has more than a general knowledge concerning the behavior of all these tissues and their clinical application. My colleagues, however, have conformed to the same general pattern of presentation as in Volume I. Thus experimental work on animal tissue is separated from experiments with humans, since the two are not always the same.

The clinical application of research findings is again emphasized so that practitioners may take from the text suggestions of practical value in medical or surgical care. An example of such practical application is the clinical use of diced cartilage grafts, which is described in Volume I. These grafts when investigated experimentally were found to be extremely valuable in the repair of persistently recurrent hernias in cases where tantalum mesh fragmented, and dermal and fascial grafts proved to be inadequate in preventing recurrence. Although diced cartilage is better than dermal grafts for severe types of recurrent hernia, it is not as suitable as buried dermis for the repair of other conditions, which are described under clinical uses of skin.

Each contributor to this volume describes how tissue, organ or gland transplants may be grafted and the success, limitation or failure of the procedures

Unfortunately, many physicians tend to regard the study of tissue structure and cell behavior in free grafts as a somwehat impractical subject, detached from clinical medicine and surgery. In fact the exact opposite is true as evidenced by the many valuable contributions arising from studies of cell behavior which are in general use today.

One cannot overemphasize the importance of understanding the behavior of autografts, as described in Chapter 1, "Cells and Tissues." This is not only an important standard in evaluating the fate of homografts but also provides a basis for successful clinical use of the patient's own tissue. Statements that "the behavior of autografts is well known" are extremely optimistic, and further study is required to clear up controversial aspects of the subject. This may result in more satisfactory clinical management of, for example, free nerve, peritoneum, fat, muscle and preformed autogenous blood vessel grafts.

The surgical need of shifting or transplanting tissue from sound parts of the body to a defective part is fundamental, but in some patients normal tissues cannot be spared. Grafts have therefore been taken from other living individuals, from recently deceased, healthy young adults killed in accidents, or from still-born infants (embryonal tissue).

This rapidly expanding field of homografting, which appeared fanciful in the past, has a growth potential which should not be ignored. It is generally believed that the behavior of skin homografts indicates the behavior of other soft tissue homogenous transplants. Emphasis has therefore been placed on skin, the behavior of which is easy to follow because it is on the surface of the body. Recent work demonstrating the long survival of skin grafts exchanged between mother and child,* and the possibility of rendering human embryos or newborn infants tolerant to a parent's skin by an injection of living cells from the parent offer new avenues of approach for successful homografting. Children who tolerate their mother's skin may also tolerate other tissues such as endocrine glands, cartilage and kidney. It is now established that homografts exchanged between identical twins or transplanted to individuals with agammaglobulinemia behave like autografts. These and other experimental findings indicate that successful homografting with a wider variety of tissues may soon be possible. Heterografting is still in the field of experimental surgery, but homografting of blood, cornea, cartilage, bone, and blood vessels is an accepted procedure.

* Grants from The John A. Hartford Foundation and The Victoria Foundation were of material aid in furthering these research studies.

Transplantation of tissue, like immunology, has attained both scientific and clinical significance and the well informed practitioner is expected to have a general understanding of the subject. This has been somewhat limited in the past because of technical words used by research workers to describe experimental procedures in transplantation. Such special terminology serves to facilitate the exchange of information between pure scientists, but it tends to exclude the clinician. In this volume, as in Volume I, the material is presented in a simple, direct manner with a minimal use of specialized terminology. Research and clinical work are two sides of the same coin and should not function as separate entities. Certainly the fully competent physician must have one foot in the laboratory and the other in clinical medicine; the same may be said of research workers who, like physicians, tend to become narrow technicians in restricted fields.

The second volume begins with an introductory chapter, "Cells and Tissues," which comprises a review of Chapters 2 through 7 and Chapter 30 of Volume I, with modifications based on recent work. This was included in Volume II on the advice of a number of professional friends, who thoughtfully suggested that the rather simplified method of presentation would serve to orient the physician and surgeon for the chapters which follow, and make him feel at home with tissue transplantation.

The editor takes pleasure in expressing a deep sense of appreciation to the contributors to this volume, who have so ably presented their subjects in an understandable and concise manner. These colleagues deserve credit for any success that the book may have. Three chapters were written by associates in the Rehabilitation Department of Saint Barnabas Medical Center. Others are by selected authorities, all of whom are well known in the field of transplantation.

Once again I acknowledge my indebtedness to Dr. George Lathrope and Dr. Royce Paddock for encouraging me in my early transplantation studies of human tissues, and to Dr. William Bernhard, Director of Laboratories at Saint Barnabas Medical Center, for advice regarding microscopic interpretation of many tissue sections. Dr. Robert Ivy, editor of *Plastic and Reconstructive Surgery*, aided in various ways, and an old friend, Dr. Clarence Straatsma, stimulated my efforts in completing this volume by his favorable comments in reviewing Volume I.

Dr. George Schicks, as executive director of the Saint Barnabas Medical Center, generously provided laboratory and hospital facilities for the experimental work.

Miss Ruth Pullen, R.N., contributed drawings illustrating cell behavior in transplants and made valuable suggestions regarding them; Miss Emma A. Buehler, M.A., compiled the literature and assisted in the editing of the volume.

To my associate, Dr. John C. Walker, Jr., who aided in experimental investigations, and to all of my former residents I am indebted for cooperation in carrying out portions of the work.

With deep regret the editor announces the demise of Dr. Sterling Bunnell, who contributed the chapter "Transplantation of Nerves" in this volume. Dr. Bunnell was the father of modern hand surgery and his death is a great loss to medicine.

L. A. P.

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CHAPTER 1

Cells and Tissues

LYNDON A. PEER

THE CELL AND SMALLER LIVING UNITS

Cells

Modern scientific thinking did not first produce the concept of very small units of life nor did it develop the idea of a cell theory. Early Greek philosophers, particularly Aristotle and Theophrastus, speculated that "all animals and vegetables are constituted by a few elements which are repeated in each one of them." While they were largely concerned with substances that could be seen with the naked eye, such as the roots, leaves, and trunks of trees, and the tissues and organs of animals, the basic concept of large structures composed of and arising from smaller elements was established.

Robert Hooke (1), an Englishman, first described the cell as a unit of structure in 1665. Examining the texture of a cork through magnifying lenses, he observed that it contained many small compartments arranged in a honeycomb-like manner. Hooke noted the presence of limiting cell walls but gave little thought to "juice" or content of these cells.

The cell theory, which postulates that all plants and animals are composed of small units of life, was introduced by two German investigators, Schleiden and Schwann, in 1838 and 1839. They emphasized the significance of the jelly-like content of cells. Robert Brown, a botanist, in 1831 discovered the nucleus in cells. Purkinje in 1839 gave the name "protoplasm" to the basic substance of animal embryos, and seven years later von Mohl applied the same term to vegetable cells. Thus the gelatinous substance found in all cells became known by this name. These original investigations gave rise to the protoplasm theory which states that the cell is an accumulation of a living substance—protoplasm—limited in space by a cell membrane and containing a nucleus. The cell is now accepted as the fundamental unit in the structure of both plants and animals, just as the atom is accepted as the fundamental unit in chemical structures. Obviously the atoms in the molecules in the cell are made up of protons, neutrons, and electrons. This makes cells similar to inorganic matter with the important exception that a cell is *living* and inorganic matter is *dead*.

Recent studies utilizing polarization, diffraction, and ultramicroscopic and electron microscopic techniques have revealed many smaller complex structures in cells, bacteria, and rickettsiae. Microdissection and biochemical research has disclosed some of the possible functions and chemical composition of certain specialized particles found in the protoplasm. Thus the cell, which was formerly regarded as a simple structure, is now evaluated as an extremely complex center of diverse chemical activities.

Ultramicroscopy and electron microscopy now permit investigators to observe the "filterable viruses" that hitherto have been known only by their ability to pass through fine filters or by the pathologic alterations that they cause in human and plant tissue cells.

Viruses

According to Stanley (2) there is no single criterion by means of which viruses can be differentiated from bacteria, but the virus has been segregated by means of certain general characteristics. Among the most important of these are its small size, the ability to reproduce or multiply within the living cells of a given host, the power to change or mutate during multiplication, and the property of reproducing or growing in artificial media containing susceptible host cells.

Viruses vary in size from 300 to 10 millimicrons. Certain small viruses are smaller than the accepted protein molecules and conversely, some large viruses such as the vaccinia virus are larger than some of the smaller living organisms.

In general the small viruses seem to have more primitive or simpler structures than the large viruses, whose complexity of composition, structure, and function increases with their size. Because of this apparent direct relationship between the size of a virus and its complexity, it has been suggested by Stanley (2) that the viruses provide a link between inorganic molecules and organisms and thus create an evolutionary pathway leading from simple elements such as the electron to massive, highly complex structures such as man.

The exact status of the virus has caused considerable controversy among biochemists and pathologists, some believing that it is viable or alive, and others that it is non-viable or inanimate. Some virologists believe that the smaller viruses, the crystalline ones in particular, are

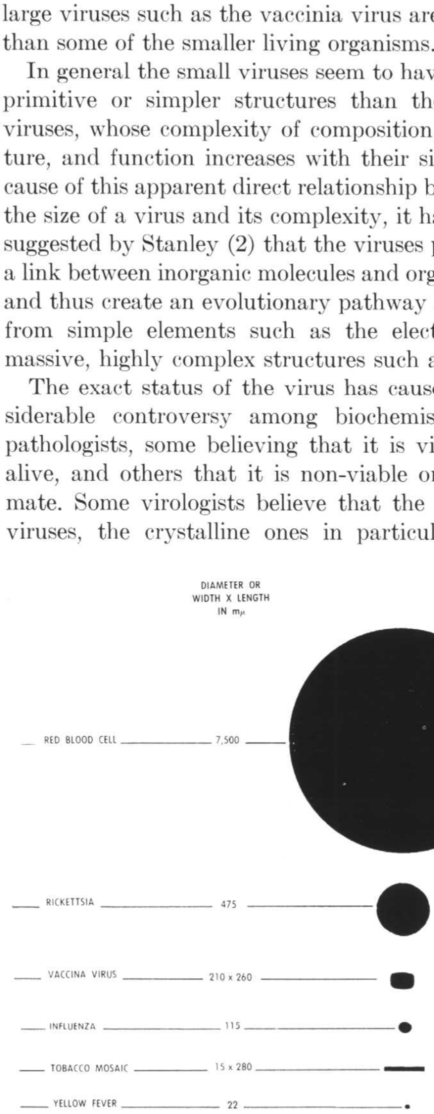

FIG. 1. The size and form of various viruses compared to a human red blood cell. Diameter or width × length in mμ. (Modified drawing from T. M. Rivers: Viral and Rickettsial Infections of Man. J. B. Lippincott Company, Philadelphia, 1948.)

non-living and represent end-products manufactured by their host cells through autocatalytic processes (3). Other virologists endow them with a sort of "half life" between the living and the non-living state. Dogmatic beliefs regarding that which is living and, alternately, that which is non-living have been subjected to some rather rude jolts in recent years, and for this reason precise distinction may be subject to later change.

An example of this difficulty in presenting exact evidence to demonstrate that *a structure is either living or dead may be seen in the tobacco mosaic virus. This small entity in its extracellular state is a pure anhydrous crystal devoid of any water content whatever. When the virus gets within a susceptible host cell, however, it has the ability to reproduce and to change or mutate during multiplication, thus resembling a living structure.*

Genes

Direct chemical analysis of whole chromosomes demonstrates that they are largely composed of nucleoprotein (4), which suggests that the genes also probably contain a large amount of nucleoprotein. Thus a similarity in structure can be drawn between the gene and the more primitive small viruses which are also composed largely of nucleoprotein.

Another similarity between genes and viruses is their power of self-duplication, which is dependent upon the presence of certain substances found in living cells. Both genes and viruses multiply only within specific cells where certain necessary substances are available and the environment is satisfactory. One important difference, however, is the fact that genes are found only within a living cell, whereas the virus can exist extracellularly (in a chemical sense).

Genes and viruses are also within the same general size range (5), and both can undergo mutation, giving rise to new forms which have altered biologic characteristics. These new forms moreover retain their power of self-duplication (5).

Rickettsiae and Bacteria

A number of human infections are caused by microorganisms called "rickettsiae." These are intermediate in size and other characteristics between bacteria and viruses. Studies with the electron microscope reveal the structure of rickettsiae to consist of an apparent limiting

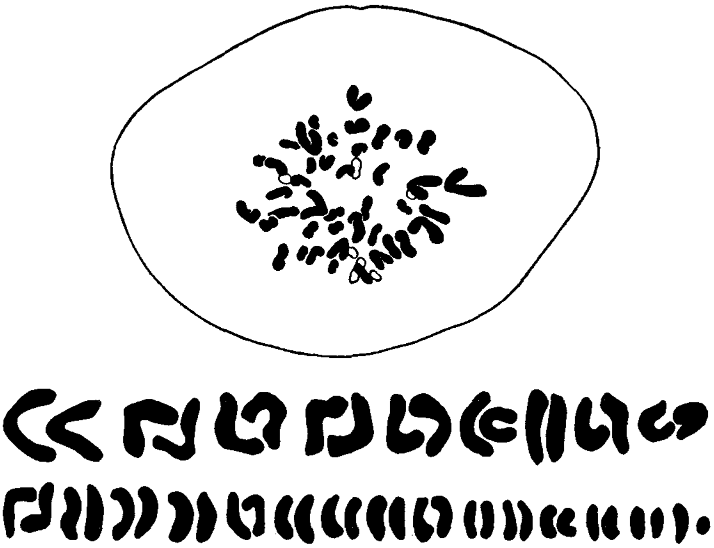

FIG. 2. *Above.* The chromosomes in a human cell. ×3000 (Koller). *Below.* The twenty-four pairs of human chromosomes; a drawing based upon thirteen male nuclei. (From Evans and Swezy's *Chromosomes of Man.*) These drawings show the chromosomes as relatively short, thick bodies, which are characteristic of the stage just preceding cell-division, during which they can be counted and their individual appearance discerned. At an earlier stage they are long, thin filaments. (From J. A. Fraser Roberts: An Introduction to Medical Genetics, p. 2. Humphrey Milford, Oxford University Press, London, 1940.)

membrane surrounding a protoplasm-like substance which contains a number of dense granules. A distinct and recognizable nucleus has not been observed. The rickettsiae are visible in microscopic preparations as coccobacillary forms and, like viruses, they multiply only within susceptible cells.

Bacteria were formerly thought to be the simplest and lowest of all living forms beyond which life did not exist. Exmination in previous years with the ordinary compound microscope failed to reveal a nucleus or any other structure within the substance of bacteria. Examination with the electron microscope and special staining reagents, however, has demonstrated the presence of bodies within bacteria that apparently are equivalent to the vesicular nucleus in typical cells (6). Hence a bacterium is now called a bacterial cell. Some botanists regard the bacteria as plants which, like fungi, do not contain chlorophyll; others believe that they are intermediate forms between plant and animal.

THE HUMAN TISSUE CELL

The findings of Schleiden concerning the constitution of living matter in plants were confirmed in and extended to animals by Schwann who, for the first time, used the term "cell theory" for the concept that animals as well as plants are aggregates of cells arranged in accordance with definite laws. The cell theory was then rather quickly applied to explain the structure of unicellular organisms, spermatozoa, and that of the ovum, from which—by division of cells—the organism is developed.

The main difference between plant and animal cells is that the former contain chlorophyll, which is so vitally sustaining that the food it synthesizes supports all organic life on the earth. Certain plants, such as the fungi, do not contain chlorophyll, but those which do not have it must steal its products from other plants in order to exist.

The cell principle includes two concepts: 1) that the bodies of all plants and animals are composed of cells and the products of cells, and 2) that new cells are derived only by the division of preexisting cells. Speculating on how the primitive ancestral types from which all modern plants have been derived were first brought into existence, biologists have come to favor certain hypotheses. The most plausible one seems to be that the first living organisms upon earth were derived