INTERNATIONAL ACADEMY OF PATHOLOGY MONOGRAPH

THE PERIPHERAL BLOOD VESSELS

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by 15 authors

Edited by J. LOWELL ORBISON, M.D.

Chairman and George H. Whipple Professor of Pathology, University of Rochester School of Medicine and Dentistry, Rochester

and DAVID E. SMITH, M.D.

Chairman and Professor of Pathology, University of Virginia School of Medicine, Charlottesville

THE WILLIAMS & WILKINS COMPANY

BALTIMORE · 1963

Library of Congress Catalog Card Number 62–21398

Composed and printed at
Waverly Press, Inc.
Mt. Royal and Guilford Aves.
Baltimore 2, Md., U. S. A.

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Contributing Authors

LESLIE B. AREY, PH.D.
Robert Laughlin Rea Professor of Anatomy, Emeritus, Northwestern University Medical School, Chicago

PHILIP BARD, PH.D., SC.D.
Professor and Director of Physiology, The Johns Hopkins University School of Medicine, Baltimore

CHARLES G. COCHRANE, M.D.
Helen Hay Whitney Foundation Research Fellow, Division of Experimental Pathology, Scripps Clinic and Research Foundation, La Jolla, California

DON W. FAWCETT, M.D.
Hersey Professor of Anatomy, Harvard Medical School, Boston

FRANCIS J. HADDY, M.D., PH.D.
Chairman and Professor of Physiology, University of Oklahoma Medical Center, Oklahoma City

ROBERT M. HARDAWAY, M.D.
Colonel, Medical Corps, United States Army, and Director, Division of Surgery, Walter Reed Army Institute of Research, Washington

GEORGE M. HASS, M.D.
Chairman of Pathology, Presbyterian-St. Luke's Hospital, and Professor of Pathology, University of Illinois College of Medicine, Chicago

CARL R. HONIG, M.D.
Assistant Professor of Physiology and Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York

JOHN ESBEN KIRK, M.D., PH.D.
Associate Professor of Medicine and Director of Research, Division of Gerontology, Washington University School of Medicine, St. Louis

WILLIAM C. MANION, M.D.
Chief, Cardiovascular Pathology Branch, Armed Forces Institute of Pathology, and Veterans Administration Central Laboratory of Anatomic Pathology and Research, Washington

DONALD G. MCKAY, M.D.
Delafield Professor and Chairman of Pathology, College of Physicians and Surgeons of Columbia University, New York

HERBERT MESCON, M.D.
Chairman and Professor of Dermatology, Massachusetts Memorial Hospitals and Boston University School of Medicine, Boston

ALBERT QUINTILIANI, JR., M.D.
Research Fellow and Senior Teaching Fellow in Dermatology, Massachusetts Memorial Hospitals and Boston University School of Medicine, Boston

FLOYD R. SKELTON, M.D., PH.D.
Chairman and Professor of Pathology, State University of New York School of Medicine, Buffalo

LEON SOKOLOFF, M.D.
Chief, Section on Rheumatic Diseases, Laboratory of Experimental Pathology, National Institute of Arthritis and Metabolic Diseases, Bethesda

Foreword

The Peripheral Blood Vessels is the fourth of the series of Monographs in Pathology initiated by the International Academy of Pathology in 1959. Its various chapters are expansions of presentations made in May 1962 at the annual meeting held in Montreal, where the principal course was entitled "Pathologic Physiology and Anatomy of the Peripheral Vessels." This course was a continuation of the educational program of the International Academy in a form that began in 1953 under the especial guidance of Dr. F. K. Mostofi, Secretary-Treasurer of the Academy. It was organized by Dr. J. Lowell Orbison, who has contributed greatly to all aspects of the educational program of the Academy during the past several years as Chairman of the Educational Committee. He also is principal editor of this volume and contributes from his active and continued interest in the field an informative *Preface*, which demonstrates his thoughtful planning of the course and careful selection of the various topics so capably treated by the invited participants.

The Council of the Academy has sponsored the publication of this and previous Monographs to provide a permanent reference source for the subjects especially presented at the meetings of the Academy. The goals are to assemble material of the finest scientific standards and educational value relative to the structure and function of the peripheral blood vessels in health and disease, as well as to representative modern technics for research in the field, and to make a presentation in a form that will be of continuing benefit to the entire scientific community as well as to those who attended the meeting.

DAVID E. SMITH
Series Editor

Charlottesville, Virginia

Preface

The study of peripheral vessels and peripheral vascular disease over the past several years has greatly extended our knowledge of normal and altered structure and function. Though our knowledge is still fragmentary, and investigations are progressing rapidly, this presentation was planned in the belief that a selective compilation of information available at this time would be useful to the general student and to the specialist. The aim of this Monograph is to summarize the literature on the subjects presented and to make available the major references without attempting a comprehensive review. In many instances, the summary of the older literature serves as a background for a more detailed presentation of recent developments.

The subject matter of the Monograph has been divided into two major categories: the normal, and the abnormal or pathologic. The first category has been subdivided into presentations of development, structure, chemical composition and function. The second category includes two subdivisions: one based on etiologic factors influencing the development of peripheral vascular disease, and the other based on the manifestations of peripheral vascular disease. By such a classification, it is possible to present relatively broad topics rather than discussions of specific diseases. Hence, under etiologic factors, the topics of nutritional and metabolic, hormonal, immunologic and infectious factors are discussed; under manifestations, the topics of thrombosis, purpura and collagen disease make up the subject matter. It is inevitable that in any organization duplications and arbitrary separation of related material will occur. To keep separation of related subjects to a minimum in certain major areas, some deviations from the basic plan of the Monograph have been allowed. For example, the effects of sex hormones on atherosclerosis are included with the discussion of atherosclerosis under nutritional and metabolic factors, rather than with hormonal factors. Similarly, electrolyte alterations in hypertensive vascular disease are included with the discussion of hypertension under hormonal factors, rather than with nutritional and metabolic factors.

It has been necessary to be selective in both topics and subject matter, and it is hoped that the judgments used in selection have been well made. It should be noted that little is presented on either the veins or the lymphatics. Such an exclusion was not planned, but arose from the fact that relatively little new work has been reported on either of these subdivisions of the peripheral vascular system. The subject of neoplasia has not been included for similar reasons. Another subject that it has not been possible to include, even though it is of increasing interest and importance, is that of the naturally occurring vascular diseases of lower animals.

If one were to attempt to epitomize the theme that our newer knowledge has superimposed upon our previous concepts of vascular structure and function, it might be described by such terms as complex, intricate and amazingly precise. Dr. Arey has enumerated 15 ways in which the final structure of the vessels of the

adult may develop. Dr. Fawcett has illustrated several quite different kinds of capillaries, each characteristic of its site. Dr. Kirk presents extensive evidence to indicate that the chemical composition of morphologically similar vessels is quite different, to say nothing of the chemical differences in morphologically different vessels. Drs. Bard, Haddy and Honig join forces to illustrate that the factors influencing vascular function at the cellular, tissue and central nervous system levels are almost beyond enumeration. Although it is too early to assess the meaning and interrelationships between these separate but surely related observations of normal structure and function, it is certain that these advances in our knowledge will affect our understanding of abnormal structure and function in ways that we can now only guess.

As our knowledge of normal structure and function advances rapidly, so also does our understanding of altered structure and function. Each contributor to that part of the Monograph dealing with abnormal structure and function has illustrated this fact with many examples. More specifically, the fact that our knowledge about the etiologic factors influencing vascular disease has advanced at great speed is illustrated by the presentations of Dr. Cochrane on immunologic factors, Dr. Hass on metabolic and nutritional factors, Dr. Skelton on hormonal factors and Dr. Manion on infectious factors. Despite this rapid increase in our knowledge of etiologic factors influencing vascular disease, there is only scanty information on the mechanisms by which these factors influence vascular metabolism to produce the changes observed. Similarly, we have an increasing body of knowledge about the kinds of etiologic factors that influence the manifestations of vascular disease. The presentations by Dr. McKay on thrombosis, Dr. Mescon on purpura and Dr. Sokoloff on collagen disease demonstrate this point very well. Yet again we are only beginning to gain knowledge of the mechanisms by which these factors work to produce the manifestations of altered vascular structure and function.

It seems clear that there needs to be an increasing emphasis upon studies designed to elucidate the mechanisms by which etiologic factors act upon the vessels, and that these studies will be most successful when they are based upon our increased knowledge of the normal vascular metabolism and structure.

J. Lowell Orbison

Rochester, New York

Contents

Chapter 1

The Development of Peripheral Blood Vessels

LESLIE B. AREY

Blood vessels are, of course, organs. In this instance the primary tissue is endothelium. All else is auxiliary tissue, which, in vessels larger than capillaries, becomes added so as to provide support, resistance, flexibility, elasticity or contractility. The source of the auxiliary tissues is clearly mesodermal or, more specifically, mesenchymal. By contrast, the origin of endothelium was not so obvious to early investigators and remained in dispute for may years. By long custom the primitive cellular tissue that gives origin to endothelium is named angioblast. Indeed, by some, even the individual, formative cells have been awarded this designation.

An account of the development of blood vessels subdivides into two major categories. First, there are certain general principles of development, which encompass the following topics: (1) the origin of angioblast, (2) the source of vessels within the embryo, (3) the development of provisional capillary plexuses wherever definitive vessels will later appear, (4) the emergence of secondary, larger channels within such temporary plexuses, (5) histogenetic advances, providing auxiliary coats that meet the special mechanical demands of particular local regions, (6) causal development. Second, there is the special development of vessels, which traces the developmental history of individual vessels or types, including the secondary alterations that produce the final, permanent pattern.

General Features

Germ Layer Origin of Endothelium. The earliest vascular primordia in most vertebrate embryos are clusters of cells arising on the yolk sac, between the splanchnic mesoderm and entoderm (Fig. 1*A*). These blood islands are at first compact masses (Fig. 1*B*), but they soon separate into peripheral cells that become endothelium and into more centrally located cells that produce a short lived line of primitive blood cells (Fig. 1, *C* and *D*).

The intermediate location of this angioblastic tissue occasioned prolonged controversy, extending even into the present century, as to whether the mother tissue is mesoderm or entoderm.[31] Eventually the proponents of mesodermal affinity prevailed. In the human embryo, for example, early vessels that arise in certain locations preclude an entodermal ancestry. Such examples are vascular primordia on the body stalk[5] and primitive chorion[15] (Figs. 2 and 3). Likewise, the unconform-

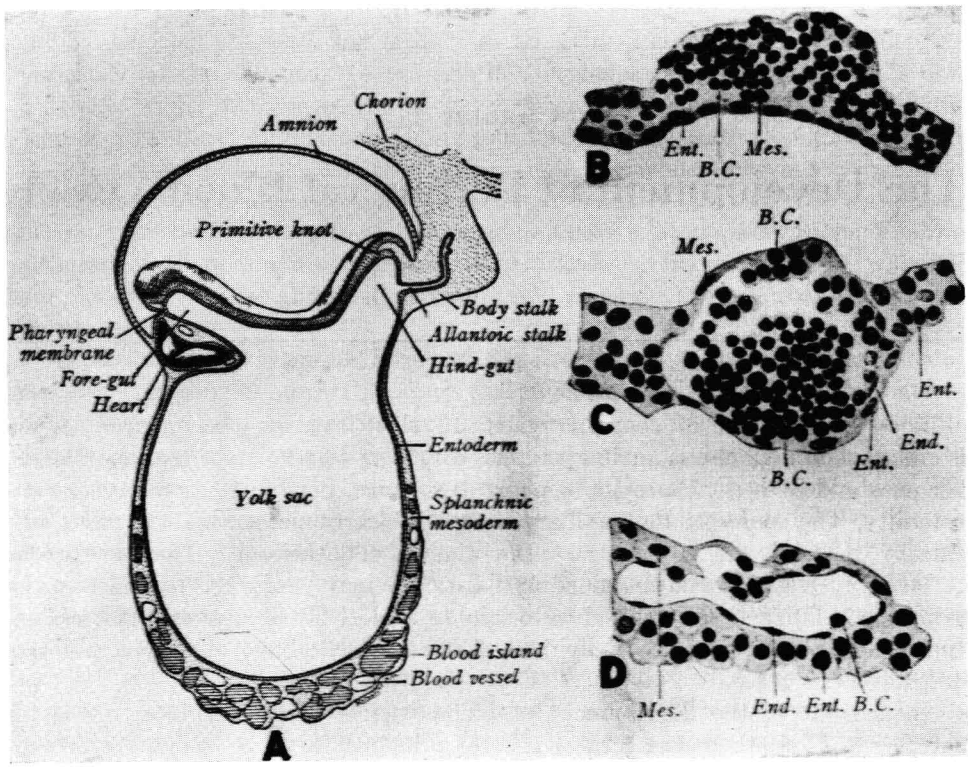

FIG. 1. Development of blood vessels from blood islands in the yolk sac of early human embryos. *B.C.*, blood cells; *Ent.*, entoderm; *Mes.*, mesoderm. *A* is reproduced from Prentiss, C. W. *A Laboratory Manual and Text-Book of Embryology*. Philadelphia, W. B. Saunders, 1915; *B*, *C* and *D* are reproduced from Evans, H. M., in *Manual of Human Embryology*, ed. by Keibel, F., and Mall, F. P., vol. 2, Philadelphia, J. B. Lippincott Co., 1912.

ing development of the umbilical vein in the somatic mesoderm of the body, separated by coelom and splanchnic mesoderm from entoderm, is incontestable.[37] An alternative interpretation has been advocated for the origin of this tissue. Thus, 50 years ago, Minot,[27] believing that all endothelium was descended directly from yolk sac angioblast, viewed it as a special creation with a specific function, assignable neither to entoderm nor to mesoderm. Two decades later, in his study of angiogenesis in the chorion, Hertig[15] similarly emphasized the simultaneous origin of mesoderm and angioblast by delamination and differentiation from the trophoblast. This separate primary origin, rather than a derivation secondarily from mesoderm, was not accepted by Bloom and Bartelmez[4] in a subsequent restudy of the same problem.

Source of Endothelium within the Embryo. The earliest vascular primordia of most vertebrates arises on the yolk sac and consolidates into a plexus. This plexus spreads over the yolk sac and appears to extend directly into the embryo. Such progressive vascularization led to an interpretation that credited the early blood islands of the yolk sac with being the sole mother tissue from which arose, by growth

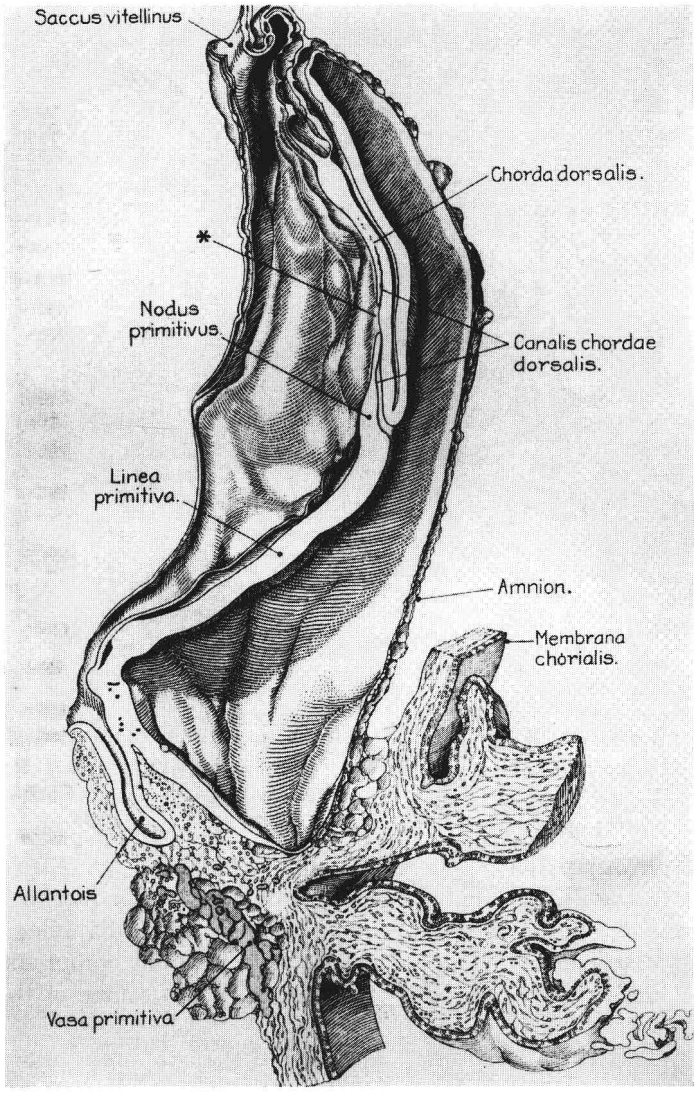

FIG. 2. Vascular primordium in the body stalk of a presomite human embryo, shown in hemisection. Reproduced from Heuser, C. H. *Carnegie Contrib. Embryol. 23:* 251–267, 1932.

and spreading, all blood vessels—both extraembryonic and embryonic.[16] It was to this specific stem tissue that the name "angioblast" was originally applied. Its supposed destiny, as the only tissue endowed with the capacity of vessel formation, was the basis of the doctrine called the "angioblast theory."

The specificity of yolk sac angioblast in intra-embryonic vasculogenesis was attacked through developmental studies by various workers, notably Huntington[18] and McClure.[26] These investigators maintained that mesenchyme throughout the embryo is capable of organizing into endothelium as needed, separate primordia linking into vascular channels (Figs. 3 and 4*A*). They argued that the injection of

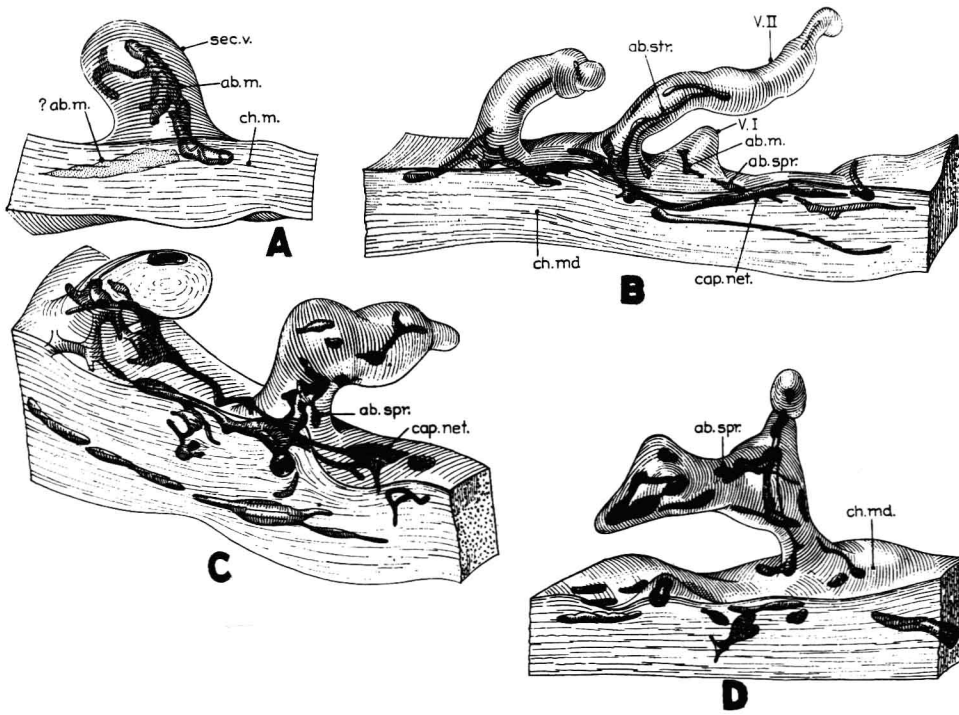

FIG. 3. Developmental stages of blood vessels forming in the chorion and chorionic villi of presomite human embryos. Reproduced from Hertig, A. T. Angiogenesis in the early human chorion. *Carnegie Contrib. Embryol. 25:* 37–81, 1935.

blood vessels already patent, the method employed by proponents of the angioblast theory (chiefly the Johns Hopkins group), obviously could give no information concerning the existence of unconnected vascular primordia lying beyond the limits of physical patency (Fig. 4*B*). That vessels could sprout and grow was conceded, whereas the real question, they urged, is the source of the tissue that does the growing.

Experimental attacks eventually annihilated the stubborn adherents of the sovereign role of extra-embryonic angioblast. For example, Reagan[29] isolated completely a portion of the chick's embryonic body at a time before its vascularization occurs. After a period of incubation, endothelial-lined vessels or spaces invariably occurred (Fig. 5). More recently Jolly[19] obtained blood vessels, developed *in situ* from the mesenchyme, in explants of rat embryos.

Although Dr. Sabin,[33] the leader of the latter day angioblast school, eventually came to accept the local origin of blood vessel endothelium within the embryo, she and her followers never admitted the validity of the same method of development for lymphatics.

After a time, when the embryonic circulation is once fully established, the vascular system is extended further solely by sprouting and growth. This production of a capillary plexus by sprouting, and its subsequent transformation, has been

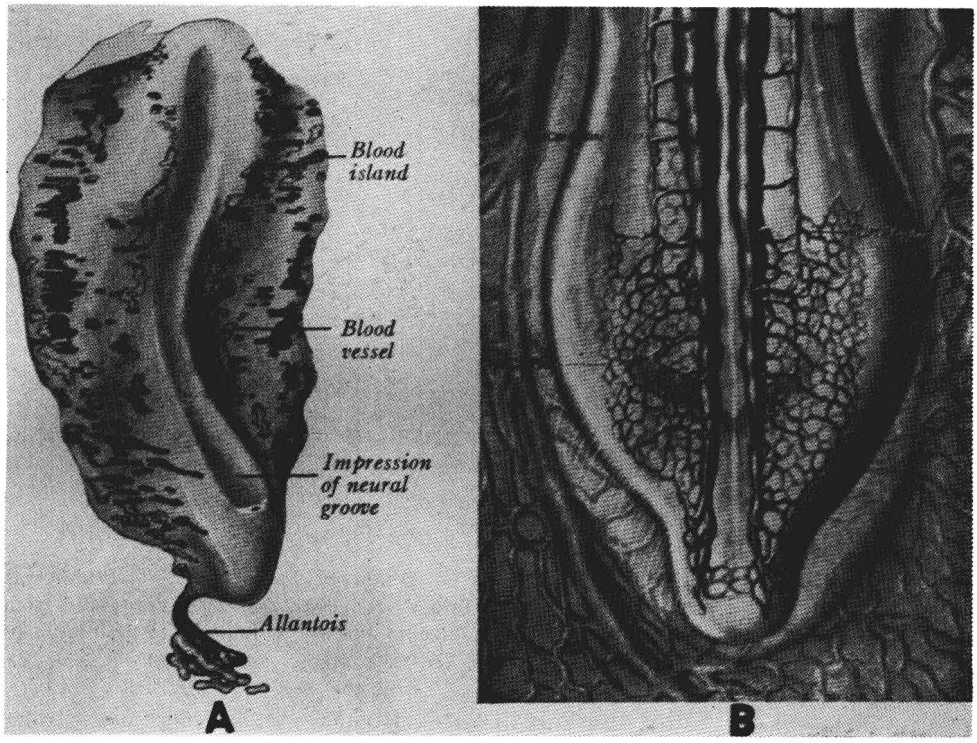

FIG. 4. The origin and growth of blood vessels. *A*, Model of a human embryo of two somites, showing the location of isolated blood islands (*dark masses*) and hollowed vessel primordia (*light areas*). *B*, Injected vessels in the organizing caudal region of a chick embryo. *A* is reproduced from Ludwig, J. *Gegenbauer's Morphol. Jahrbuch 59:* 41–104, 1928; *B* is reproduced from Evans, H. M., in Prentiss, C. W. *A Laboratory Manual and Text-Book of Embryology*. Philadelphia, W. B. Saunders Co., 1915.

demonstrated by Arnold[2] in the tail of the living tadpole and by Sabin[35] in cultured chick blastoderms (Fig. 6). A similar process of the laying down of a capillary plexus by sprouting occurs during the regenerative stage of wound healing. Such information has been established by Sabin[34] in a study on the results of intestinal anastomosis in adult dogs. She described how the endothelium of vessels reverts to cells like embryonic angioblasts, and how these undergo great multiplication of their nuclei. From such modified vessels solid masses of angioblasts, like those of the embryo,[35] grow out. Lumina are acquired, as in the embryo, through the liquefaction of cytoplasm. New vessels emerge, first taking the form of capillary plexuses and then becoming arteries and veins. Direct confirmation of the general principles of growth by sprouting and the transformation of plexuses has been furnished by Clark *et al.*[11] through the direct observation of healing within transparent chambers inserted in the rabbit's ear.

Role of Primary Capillary Plexuses. As early as 1868, Aeby[1] was led to conclude that vascular variations in the adult depend on the prior existence of a meshwork of capillaries in which there is a competition for supremacy and survival. The

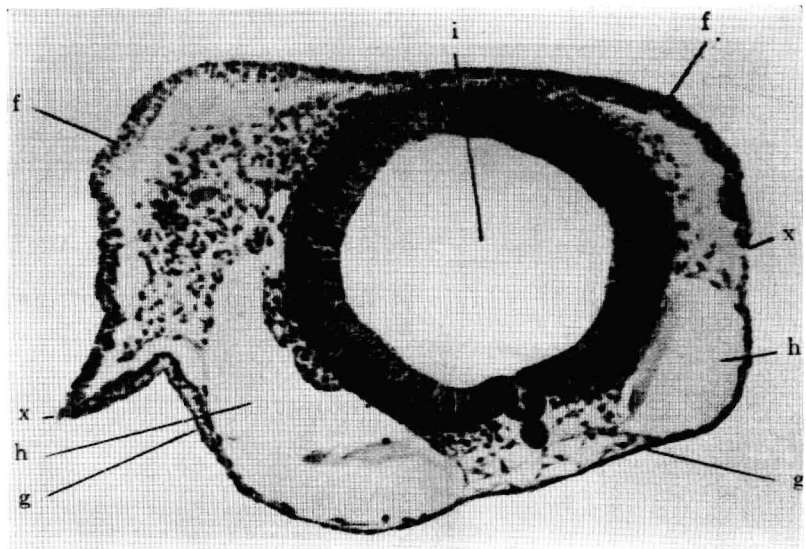

FIG. 5. The independent development of aortae (*h*, *h*) in a portion of a chick's body that was isolated before any vessels could have spread into it from the yolk sac. Reproduced from Reagan, F. R. Vascularization phenomena in fragments of embryonic bodies completely isolated from yolk-sac entoderm. *Anat. Rec. 9:* 329–341, 1915.

contrary concept of the direct outgrowth of definitive vessels, as such, found strong adherents in Ruge[32] and Hochstetter.[17] In 1893, however, the studies of Thoma[38] began to turn the tide in favor of the necessary existence of provisional capillary plexuses. In 1909 Evans[13] published convincing illustrations showing how the injection of living embryos could demonstrate the presence of an intricate vascular meshwork wherever a vessel was to appear and the gradual selection of a definitive channel in it (Fig. 7). This sequence of plexus and enlarging channel was utilized even where the position of a vessel, such as the aorta, is apparently determined by heredity (Fig. 4*B*). Only in a few instances (most strikingly in the dorsal segmental branches of the aorta) do definitive vessels first occur as single tubes. The sequential stages represented by a provisional temporary plexus, the development of a major vascular pathway within it and the concomitant atrophy of unused parts of the plexus constitute an important concept in the understanding of angiogenesis.

Evans[14] concluded that "the cause of the early appearance of vessels in a multiple, capillary form is to be found in the view that this represents the fundamental method of vascular growth, and that larger vessels only come into existence secondarily *when the number of capillaries induces an increased supply of blood.*" In this situation, certain fortuitously located capillaries enlarge into artery and vein. These larger vessels are to be considered as mere service pipes supplying and draining the capillary bed. For this reason, "the cause for the rich vascularity of a tissue cannot be sought in its possession of larger vessels, but rather in the influences which have brought about a more abundant growth of capillaries in it."

The original concept of Aeby[1] that a homogeneous capillary mesh pervades all the tissues of the body at an early period is contrary to fact. Capillaries spread out from primary vascular centers, such as the aortas, into areas not yet vascular.