ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Volume 16A

THE ARTERY AND THE PROCESS OF ARTERIOSCLEROSIS PATHOGENESIS

The Artery and the Process of Arteriosclerosis

Pathogenesis

The first half of the Proceedings of an Interdisciplinary Conference on Fundamental Data on Reactions of Vascular Tissue in Man April 19-25, 1970, Lindau, West Germany

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PLENUM PRESS · NEW YORK-LONDON · 1971

The second half of the proceedings will be published as
The Artery and Process of Arteriosclerosis: Measurement and Modification (Volume 16B of this series).

Library of Congress Catalog Card Number 70-163284

SBN 306-39091-4

A Division of Plenum Publishing Corporation
227 West 17th Street, New York, N.Y. 10011

United Kingdom edition published by Plenum Press, London
A Division of Plenum Publishing Company, Ltd.
Davis House (4th Floor), 8 Scrubs Lane, Harlesden, NW10 6SE, England

Printed in the United States of America

PREFACE

The present volume contains the first half of the edited transcript of a six-day Conference, "Fundamental Data on Reactions of Vascular Tissue in Man," held April 19-25, 1970, in Lindau, West Germany. The remainder of the proceedings, dealing with the epidemiologic, clinical and preventive aspects of arteriosclerosis, will be published in a second volume.

The Conference was held under the auspices of the International Society of Cardiology, the International Cardiology Foundation and the European Atherosclerosis Group. The aim of the Conference was to achieve a synthesis of present knowledge concerning arteriosclerosis. Therefore, workers were brought together from several countries and from various disciplines that do not ordinarily intercommunicate for free exchange of data and ideas. Six broad subject areas were introduced by single papers; three of them are included in this volume. In the discussion which followed each formal presentation, the participants attempted to reconcile disparate data and interpretations and to reach a clear identification of important areas of ignorance and of crucial questions for future research.

The format of the proceedings does not follow precisely that of the Conference itself. The formal papers are included, somewhat abbreviated, and excerpts of the discussion have been gathered under a series of topics arranged in logical sequence. Therefore, the quoted statements do not necessarily appear in order or in the place in the program where they were made. Principal issues, syntheses and unanswered questions are interspersed among the topics as editorial comments.

The Lindau Conference took place less than six months after the Second International Symposium on Atherosclerosis in Chicago (Atherosclerosis, Proceedings of the Second International Symposium, Edited by Richard J. Jones, Springer-Verlag, New York, Heidelberg, Berlin 1970). Despite the proximity in time and the substantial overlap in participants, the Lindau meeting reflected a further step in understanding the pathogenesis of arteriosclerosis. Each presentation of data was exposed to a more or less leisurely examination and critical

comment by interested participants of varying background and experience. Unfortunately, the remarks of some of the participants did not come through clearly enough in the tape recording of the Conference to enable them to be transcribed and included in the Proceedings. Apologies are therefore offered to these contributors. The full list of participants follows:

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The expenses of the Conference and of the preparation of the Proceedings were covered by generous contributions from the following organizations and firms:

Alabama Heart Association
American Heart Association
British Heart Fund
Fannie E. Rippel Foundation
Federal Republic of Germany
City of Lindau
Office of Naval Research
Oklahoma Medical Research Foundation
University of Heidelberg
University of Texas Medical Branch at Galveston
Ayerst Laboratories
Bayer A.G.
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CIBA Pharmaceutical Company
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Merck, Sharp and Dohme Research Laboratories
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Squibb and Sons Pharmaceutical
Unilever Research Laboratories
Upjohn Company
Warner-Lambert Foundation

Arrangements for the meeting were accomplished under the direction of Professor Gotthard Schettler and Dr. Gunter Schlierf. The warm and generous hospitality of our German hosts is gratefully acknowledged. The staff for the Conference was led by Mrs. Cora Gillett, and included Miss Jane Henson, Miss Carol Wehner, Miss Anneke Rieben and Miss Anita Reinartz. The editing of the Proceedings was greatly expedited by the able editorial assistance of Miss Helen Goodell, and by the expert and devoted secretarial work of Miss Jane Henson, who typed the final manuscript, and who, with Mrs. Barbara Altstatt and Mrs. Harriet Ross, also managed the lengthy correspondence preliminary to the Conference. Miss Mary Steichen and Miss Elizabeth Fitzsimmons provided valuable assistance to Miss Henson in organizing and developing the manuscript. Thanks are offered to all of these ladies.

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Chapter 1

THE STRUCTURE OF ARTERIES, GROWTH ADAPTATION AND REPAIR:

THE DILEMMA OF NORMAL

Opening Address by Dr. John French

Sir William Dunn School of Pathology, University of Oxford, England
(Dr. French died shortly after the Conference and before he had an opportunity to edit his remarks for publication and provide illustrations and bibliography. Therefore his words appear here substantially as he spoke them.)

I shall concentrate on points that appear to me basic to an understanding of the pathogenesis of atherosclerosis in man. Thus in the first place, I shall consider only the main arteries, i.e. the elastic arteries, the aorta, pulmonary, common carotid, subclavian and common iliac, and the larger muscular or distributing arteries. And secondly, I would like to emphasize the fact that there are differences depending upon different hemodynamic factors in the large arteries in large animals, as opposed to the large arteries in small animals. I hope these points will emerge and will be kept in mind.

It is usual to consider the arterial wall in terms of three coats or tunics: the intima, media and adventitia, but in following this systematization it needs to be kept in mind that this division may, from a functional point of view, be arbitrary and that in practical terms the whole arterial wall is operating as a single functional unit adapted to its specific role at that particular site in the arterial tree.

If we begin at the inner surface of the arteries, we can note that this interface between circulating blood and the arterial wall is exposed throughout life to the possibility of deposition of solid material from the potentially coagulable blood and also subjected to injury from hemodynamic forces. Looked at this way, the remarkable thing is perhaps, not so much that the arteries occasionally lose their patency, but that they do so relatively rarely in relation to the total number of years at risk. This raises the question, then,

what is the nature of the homeostatic mechanisms which in general ensure that the arterial surface remains smooth and its cellular lining intact?

It is, of course, fully established that the arteries are lined by a flattened pavement of endothelial cells. This endothelium is almost certainly all of the continuous type, i.e. the cells closely opposed at their junctions without the gaps or fenestrations in the endothelium that may appear at some sites in the peripheral vascular bed.

The protection which endothelium provides against deposition from the lumen may be largely passive, that is to say that it presents a surface that does not normally activate either blood coagulation or the adhesion of platelets, but the physico-chemical basis for this property of the endothelial surface is not fully understood. Earlier proposals that the surface properties of endothelium depended on the adsorption of a protective layer of protein from the plasma or the secretion of a so-called cement substance on to the surface have not been supported by electron-microscopic observations in which standard methods of fixation and staining had been used. However, a thin coating of material which stains with the dye ruthenium red, and is therefore thought to be rich in polysaccharide material, has been demonstrated on the luminal surface of the capillary endothelium. It is also present on the surface of arterial endothelium.

This extraneous coating is probably analogous to the so-called glycocalyx, to use Stanley Bennett's term, which is well known to occur on the surface of many types of cells and is well developed on the luminal surface of the blood vessels in some invertebrates (Bennett, 1963). Its precise composition in the mammalian endothelium is not known but it may well be responsible for the surface properties of the wall and its maintenance may be one of the important functional properties of the normal endothelial cell. This work with ruthenium red suggests in a way a revival in a somewhat modified form of what I mentioned just a moment ago as the secretory hypothesis of a protective layer on the surface, though Dr. Copley has recently claimed that this ruthenium red staining material could still represent the fibrinogen or fibrin which, he previously argued, covered the endothelial surface. This question, I think, is still open.

Evidence that endothelium plays an active role in the prevention of surface deposit has been gained from studies on the fibrinolytic mechanism. The presence of a plasminogen activator was first demonstrated in venous endothelium by means of the fibrin plate technique introduced by Todd (Todd, 1959) and this has been followed up by other workers, including Warren in Oxford (Warren, 1963). It is now clear that this activity is present also in, and can be extracted from, the endothelium lining the aorta, though it is possibly present in lower

concentration in the aortic endothelium than it is in the venous endothelium. This fibrinolytic activity associated with endothelium might be important in regulating any deposition of fibrin on the surface, particularly where the experiments of Ashford and Freiman have indicated (Ashford and Freiman, 1968). There may be a local activation of the coagulation mechanism at the surface of an injured endothelial cell. The cell is not destroyed, the findings suggest, but the surface membrane is broken, then you can demonstrate fibrin formation at that site of injury if fibrinolysis is suppressed. Incidentally, the relatively high activity of fibrinolytic properties in the adventitia of arteries can probably be related also to the endothelium of the vasa vasorum. Whether endothelium may play an active role in the prevention of platelet adhesion other than by covering up the collagen fibers or basement membrane beneath it, is uncertain. Endothelial cells contain phosphatases which can break down ADP and, since this substance is involved in platelet aggregation, these endothelial enzymes might possibly be concerned in the dispersal of any small platelet aggregates that form at the surface, but it is not at present, to my knowledge, known whether ADP is directly involved in adhesion at the vascular surface, as distinct from aggregation, or whether platelets can indeed adhere tenaciously at all unless underlying collagen or basement membrane is exposed by endothelial damage.

The next point I should like to take up is how the structural integrity of the endothelial layer is maintained in spite of the hemodynamic forces which are continuously acting on it. In the elastic arteries, which are subjected to stretching of the wall during systole, the cells presumably have some measure of extensibility and are sufficiently firmly attached to one another at their periphery to prevent them being pulled apart with each pulse movement. However, if the cells are not injured within the normal limits of stretching, there is evidence from the recent work of Dr. Fry (Fry, 1968) in the United States, that the endothelial cells may undergo structural damage at sites where there are high rates of shear at the surface or turbulence of flow. It can therefore be expected that there will be greater wear and tear of the endothelium at certain sites in the arterial tree and that there must be some way in which potential destruction by wear and tear is compensated for in the vessel that remains normal.

The ability of endothelium to regenerate has usually been considered in relation to the repair of relatively large defects of the endothelial surface caused by experimental injury, or in relation to the organization of the surface of arterial protheses, or the organization of mural thrombi. Endothelium grows in these situations and it is established that endothelium can indeed regenerate by mitotic division of cells from the intact edges of the defect. I would just remind you of some experiments by Poole, Sanders and Florey (Poole and Sanders et al., 1958) in which they scraped the endothelium off from a 2 cm. length in the abdominal aorta of a rabbit and within

a day or two noted endothelial cells beginning to spread over that area. They demonstrated mitotic figures in endothelial cells just behind the growing edge.

If we think of this as preserving the integrity of the endothelial surface, this growth in this way is a process which takes time to complete, depending on the size of the defect. Actually, with that 2 cm. length defect in the rabbit aorta, it took up to a year for it to be fully completed, but experiments with smaller defects by other workers - Bjorkerud in Sweden (Bjorkerud, 1969), for example - have shown that quite small defects of the endothelium will stimulate mitosis around them within a day or two, and they may be completely covered within a week. But there is still the question of what is happening during this interval.

During the healing process, cells from the circulating blood platelets and leukocytes adhere to the surface, but it is not known clearly whether this serves any temporary protective function. This adhesion of platelets is usually considered only as a pathological process which under the appropriate conditions of blood flow will lead to thrombosis. The proposal has been made that the leukocytes, presumably monocytes, from the circulating blood can, by colonizing the surface, give rise to new endothelium. This is a difficult question which, I feel, still really lacks conclusive proof, whether endothelium can regenerate from circulating cells.

When experimental injury is less severe, as for example when a rubber coated clamp is used to compress a vessel, gross destruction of the endothelium may not occur but individual injured cells, rather than whole groups of cells, then undergo shrinkage and are gradually displaced by cell division in the surrounding endothelium. This seems to be the most likely way in which injured or effete cells could be replaced in the normal artery without the creation of temporarily denuded areas. In this regard, recent studies using tritiated thymidine and autoradiography to demonstrate endothelial cells engaged in DNA synthesis have indicated that the endothelium is undergoing a continuous slow replacement and that the rate of turnover is higher near the sites of branching, for example, where it can be anticipated that the greater hemodynamic stress might lead to shorter cell survival. Dr. H.P. Wright (Wright, 1971) is doing experiments on this subject using a guinea pig aorta. The animals had been injected with tritiated thymidine 24 and 16 hours before sacrifice. The labelling rate of the endothelial cells was greatest over the arch, and at the bifurcation. After creating an artificial aortic constriction a higher rate of labelling appeared in that region than in the control. This work has yielded the tentative information that normal endothelial cells survive between 100 and 180 days, but that in some regions, subject to particular hemodynamic stresses, this survival time is shorter, and in Dr. Wright's experiments ranging there from 60 to 120.

Now turning to the sub-endothelial space, i.e. the space between the endothelium and the internal elastic lamina, in the main arteries of small mammals such as the mouse, rat or rabbit, the outer surface of the endothelium is very close to the internal elastic lamina and in most regions only a narrow zone of ground substance and possibly a few fibers separate these two structures. This description of the intimal architecture applies only to the vessels in a small animal. The intima is much thicker in comparable vessels of large animals. Thus in man and in many other large mammals, it is only in the fetus or the new born that this close approximation of the endothelium and the internal elastic lamina can be seen in the aorta and main distributing arteries, and in the adult the thickness of the sub-endothelial zone varies widely in different regions and possesses a considerable population of cells and fibers.

Differences in intima between small and large mammals

Since during the development of arteries, the elastic tissue which extends to form the ultimately continuous internal elastic lamina appears first as small islands in the position of the endothelial basement membrane, or the shared basement membrane of endothelium and smooth muscle, it seems likely then that the internal elastic lamina and basement membrane could basically be analogous structures and have primarily a supporting function for the endothelium. The interposition of ground substance may allow some slip of endothelium over the lamina when the arterial wall extends or contracts.

Thickening of intima in man with growth

The intima of the aorta in adult man forms about 1/6th of the total thickness of the wall, and it is not a simple structure. It consists of a network of fibro-elastic tissue supported in a mucinous ground substance. In its deeper part, the elastic fibers are coarser and are associated with smooth muscle cells to give a rather poorly defined edge to the internal elastic lamina. In the coronary arteries in man, there is an apparent penetration by smooth muscle cells of the space between endothelium and internal elastic lamina during childhood to form this so-called musculo-elastic layer which we see also in the pig. This formation occurs first in relation to the orifices of proximal branches, but later extends widely to form a substantial part of the total thickness of the wall. Then, in man, and to some extent in the pig, an elastic hyperplastic layer composed of circularly directed elastic fibers with relatively few cells among them, forms on the luminal side of the muscular elastic layer, so the intima is getting thicker. And finally in the third decade of life, an additional connective tissue layer is formed immediately beneath the endothelium.

The functional significance of the thickened intima in large arteries with its relatively loose texture and longitudinal orien-

Nutritional role of thickened intima vs response to injury -- perforation in internal elastic lamina

tation of cells and fibers, is not obvious to me, at any rate. In part, it may be an adaptation to longitudinal stress and extension in arteries. It has also been proposed that this thickened intima acts as a sponge which imbibes plasma filtrate from the lumen and that the passage of the pulse wave then has a milking effect which serves to squeeze the filtrate outwards through the wall. In this way it might have a role in the nutrition of the thick wall of large arteries, if the thickening provides a little nutrition, pumps so to speak. But on the other hand there are many features of this intimal thickening which are consistent with a response to injury. Thus, where the thickenings first appear, for example in the proximal part of the coronary arteries in growing animals, there are always discontinuities in the internal elastic lamina at the deep edge of the intima, an apparent protrusion of smooth muscle cells from the media into the sub-endothelial space and an increase in these regions in the metachromatic staining of the ground substance. This has been demonstrated to be a standard response to injury in vessels.

It may therefore appear that a simple elastic lamina close to the endothelium may represent the ideal construction for an artery, and in fact is adopted in the small mammals, but that such a construction may not be strong enough to meet the increasing stretching forces which act on the inner part of the wall of an artery as its diameter increases with growth in the large mammals and beyond a certain size evidence of injury and repair will always be found at certain critical points in the arterial tree in the large mammals including man. If this is so, then it becomes extremely difficult to draw a line between growth changes and pathological changes in the structure of the intima. A change that always occurs in the artery of the pig, for example, would, if you saw it in the rabbit, be interpreted as a response to some extraneous injury.

Adaptation to stress vs injury and repair. The dilemma of normal

The mechanical properties of the arterial wall can largely be accounted for by the structure of the tunica media. The requirements in the media differ as between the elastic and the muscular arteries, but in each situation they are met by the combined action of elastic tissue, collagen and smooth muscle, each with distinctive properties when examined in isolation. The tunica media of the large muscular arteries, which of course are under fine neural control, consists very largely of smooth muscle cells arranged spirally in concentric layers, but as Burton has pointed out, there is a need for the combination of muscle, collagen and elastic fibers to provide stability. A few bundles of collagen fibers are present between the muscle cells of the media of the muscular arteries and some loose

networks of elastic fibrils are arranged circumferentially, but the main concentration of elastic tissue is in the well defined internal elastic lamina between media and intima and, less constantly, in an external elastic lamina between the media and adventitia.

Characteristics of the internal elastic lamina in muscular vs elastic arteries

There may be some advantage in having the elastic membranes of the muscular arteries condensed to a single dominant lamina but it does appear that a relatively strong internal elastic lamina has secondary effects that are relevant to some of the problems in arterial disease. You could say that on the one hand an intact internal elastic lamina appears to restrict the migration of cells from the media into the sub-endothelial space, and that the thickening of the intima by the cellular migration may occur when that internal elastic lamina becomes defective. So we might think of it as having a restraining influence on any migration of cells from the media into the intima. Then, on the other hand, it is usually stated that the presence of fenestrae in the lamina means that it does not present a barrier to the passage of plasma filtrate through the wall. There are fenestrations in the internal elastic lamina in the rabbit aorta that range in width from 2 to 7 micra. Nevertheless, in cholesterol-fed rabbits very little cholesterol is found beyond the internal elastic lamina. Thus it does seem to provide a pretty sharp limit to the extension of cells and to the movement of lipid material presumably coming from the lumen. These properties of the internal elastic lamina in relation to permeability and restraint certainly warrant further investigation.

In the elastic arteries as exemplified by the thoracic aorta, there are different functional demands on the media. By exerting the so-called Windkessel effect, these vessels maintain the blood pressure during diastole and ensure that there is a continuous forward flow of blood. The structural adaptation to this situation is seen in the preponderance of elastic tissue with muscle playing a relatively minor role in regulating tension in the elastic laminae. And in contrast with the situation in muscular arteries, there are in the thoracic aorta multiple concentrically arranged laminae, evenly spaced throughout the media. These concentric laminae are cross-connected by elastic fibers and inter-leaved with circumferentially arranged smooth muscle cells and thin collagen fibers.

According to Wolinsky and Glagov, (Wolinsky and Glagov, 1964) the construction of these arteries is such that tensile forces are distributed uniformly throughout the wall so that any focal defects in one of the laminae could occur without there being any overall effect on the properties of the wall. These same workers also propose that each of these elastic laminae with its adjacent compartment

containing collagen and smooth muscle can be considered as a functional unit in the media of the aorta. The number of units required in a particular vessel would then depend on the total tension in the wall. Bearing in mind that the tension in the wall depends on the radius as well as the pressure, it is understandable that while a mouse may require only five such units in the wall of its aorta, the rabbit requires 20, and adult man about 60. Since the thickness of the units is fairly constant, it is obvious that the structures required to meet the greater tension in the wall of the aorta in large mammals can only be accommodated in a much thicker wall (say 0.3 mm thickness of aorta in the mouse, 1.2 mm in man).

The greater thickness of the walls of the main arteries in large mammals introduces problems in the nutrition of the wall which are not encountered at all in small mammals. It appears that the nutrition can be maintained from the lumen if the total thickness of the wall in the adult animal does not exceed approximately half a millimeter, so there is no need for vascularization of the media of the aorta, and indeed it does not occur in such animals as the rat or the rabbit. Where the wall exceeds this critical thickness, as in man for example, the wall is partly vascularized by medial vessels. These medial vessels can only extend as far inwards, apparently, as the pressure gradient across the wall will allow. Thus, regardless of species, there is always an avascular zone in the inner part of the wall of the arteries and in those species requiring vasa vasorum, this zone appears to have a remarkably constant structure, as Wolinsky and Glagov have shown (Wolinsky and Glagov, 1964), being made up of approximately 29 of the structural units already described.

The vasa vasorum and the avascular zone

I expect that later speakers will discuss the formation of elastin and collagen in the arterial wall, particularly this interesting question of the whorl of smooth muscle cells in histogenesis and the way in which these fibers are modelled or remodelled during body growth. I have also neglected to discuss the cells of the adventitia. We have emphasized endothelium and smooth muscle, made a passing mention of fibroblasts in adventitia, but of course in pathological lesions the macrophage is a very important cell and, no doubt, there will be some discussion later as to the potential origin of phagocytic macrophages in the arterial wall.

But just to conclude, if I may, I would like to return to a very brief consideration of what Anitchkov described as the lymph stream through the wall of arteries, implying a continuing flow of plasma from the lumen to the lymphatics of the vasa vasorum. His was a physiological concept upon which many theories, particularly the filtration hypothesis of atherosclerosis have been based, and yet I can find remarkably little factual data in the physiological lit-