THE CONDUCTION SYSTEM OF THE HEART

STRUCTURE, FUNCTION AND CLINICAL IMPLICATIONS

edited by Wellens, Lie and Janse

THE CONDUCTION SYSTEM OF THE HEART

STRUCTURE, FUNCTION AND CLINICAL IMPLICATIONS

edited by

H.J.J. WELLENS, M.D.,
K.I. LIE, M.D. AND M.J. JANSE, M.D.

H. E. STENFERT KROESE B.V. – LEIDEN
1976

ISBN 90.207.0576.8

Photoset by Interprint (Malta) Ltd. Printed in The Netherlands.

PREFACE

This monograph had its genesis in a workshop on the specific conduction held in the spring of 1975.

The meeting was organized to discuss present knowledge on structure and function of the cardiac specialized tissues with emphasis on their clinical implications. Since much new information was presented, the participants agreed to prepare manuscripts and make their material available for publication. This has resulted in a book in which the cardiac specialized tissues are discussed by different specialists: the electron-microscopist, anatomist, pathologist, physiologist, physicist and clinician. Apart from their interest in the cardiac conduction system the participants shared the opinion that their contribution should be relevant to the understanding and treatment of patients with cardiac arrhythmias. The book should be useful for the clinician, the morphologist and the physiologist.

The workshop took place at the University Department of Cardiology, Wilhelmina Gasthuis, Amsterdam, The Netherlands. This is the home ground of one of the most outstanding electrocardiologists of our time, Dr. Dirk Durrer. By pairing genius and originality with endless fund of energy and dogged persistence he made several important contributions to modern cardiac electrophysiology. In recent years he created a cardiological institute where workers from various disciplines cooperate in the study and treatment of cardiac disease. Several of his pupils participated in the workshop and contributed to this volume.

In appreciation and thankfulness we want to dedicate this book to Dr. Dirk Durrer.

Hein J. J. Wellens
K. I. Lie
Michiel J. Janse

LIST OF CONTRIBUTORS

Masood Akhtar, M.D., Cardiovascular Program, U.S. Public Health Service Hospital, Staten Island, N.Y.

Maurits A. Alessie, Department of Physiology, University of Amsterdam.

Robert H. Anderson, M.D., Cardiothoracic Institute, Brompton Hospital, London.

Irany de Azevedo, M.D., Cardiopulmonary Department, The Lankenau Hospital, Philadelphia, Pa.

Arthur L. Bassett, Ph.D., Department of Pediatrics and Pharmacology, University of Miami Hospitals and Clinics, Miami, Fla.

Anton E. Becker, M.D., Department of Pathology, Wilhelmina Gasthuis, Amsterdam.

Jacques Billette, M.D., Department of Physiology, University of Montreal, Montreal.

Felix I. M. Bonke, Department of Physiology, University of Amsterdam.

Frans J. L. van Capelle, Ph.D., Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam.

Antonio Caracta, M.D., Cardiovascular Program, U.S. Public Health Service Hospital, Staten Island, N.Y.

Agustin Castellanos, Jr., M.D., Department of Cardiology, University of Miami School of Medicine, Miami, Fla.

Philippe Coumel, M.D., Hôpital Lariboisière, Paris.

R. Coutte, M.D., Hôpital de la Salpêtrière, Paris.

Paul F. Cranefield, M.D., Ph.D., Department of Pharmacology. College of Physicians and Surgeons of Columbia University, New York, N.Y.

Rudolf Th. van Dam, M.D., Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam.

Anthony N. Damato, M.D., Cardiovascular Program, U.S. Public Health Service Hospital, Staten Island, N.Y.

J. Cl. Demoulin, M.D., Hôpital Universitaire de Bavière, Liège.

Pablo Denes, M.D., Cardiology Section, Abraham Lincoln School of Medicine, University of Illinois College of Medicine, Chicago, Ill.

Ramesh C. Dhingra, M.D., Abraham Lincoln School of Medicine, University of Illinois College of Medicine, Chicago, Ill.

Henk J. M. Dohmen, M.D., Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam.

Eugene Downar, M.D., Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam.

C. Dragodanne, M.D., Hôpital de la Salpêtrière, Paris.

Henry N. Dreifus, Cardiopulmonary Department, The Lankenau Hospital, Philadelphia, Pa.

Leonard S. Dreifus, M.D., Cardiopulmonary Department, The Lankenau Hospital, Philadelphia, Pa.

Marcelo V. Elizari, M.D., Service of Cardiology, Ramos Mejïa Hospital, Buenos Aires.

Nabil El-Sherif, M.D., Veterans Administration Hospital, Miami, Fla.

Daniel Flammang, M.D., Hôpital Lariboisière, Paris.

Guy Fontaine, M.D., Hôpital de la Salpêtrière, Paris.
R. Frank, M.D., Hôpital de la Salpêtrière, Paris.
John J. Gallagher, M.D., Clinical Electrophysiology Laboratory, Duke University Medical Center, Durham, N.C.
Henry Gelband, M.D., Department of Pediatrics and Pharmacology, University of Miami Hospitals and Clinics, Miami, Fla.
Robert Grolleau, M.D., Department of Cardiology, University of Montpellier.
Claude Guimond, M.D., Department of Cardiology, University of Montpellier.
G. Guiraudon, M.D., Hôpital de la Salpêtrière, Paris.
Ronald R. Hope, M.B., F.R.A.C.P., Veterans Administration Hospital, Miami. Fla.
Michiel J. Janse, M.D., Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam.
Jackie Kasell, Clinical Electrophysiology Laboratory, Duke University Medical Center, Durham, N.C.
Henri E. Kulbertus, M.D., Hôpital Universitaire de Bavière, Liège.
Richard Langendorf, M.D., Michael Reese Medical Center, Chicago, Ill.
Sun H. Lau, M.D., Cardiovascular Program, U.S. Public Health Service Hospital, Staten Island, N.Y.
Ralph Lazzara, M.D., Veterans Administration Hospital, Miami, Fla.
Julio O. Lázzari, M.D., Service of Cardiology, Ramos Mejía Hospital, Buenos Aires.
Raúl J. Levi, M.D., Department of Electrocardiography, Ramos Mejía Hospital, Buenos Aires.
K. I. Lie, M.D., Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam.
William J. Mandel, M.D., Department of Cardiology, Cedars of Lebanon Hospital Division, Los Angeles, Calif.
E. Neil Moore, D.V.M., Ph.D., F.A.C.C., School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pa.
Robert J. Myerburg, M.D., Division of Cardiology, University of Miami School of Medicine, Miami. Fla.
Onkar S. Narula, M.D., Division of Cardiology. The Chicago Medical School, Chicago, Ill.
Kristina Nilsson, Department of Pediatrics and Pharmacology, University of Miami Hospitals and Clinics, Miami, Fla.
Alejandro Navakosky, M.D., Department of Electrocardiography, Ramos Mejía Hospital, Buenos Aires.
Alfred Pick, M.D., F.A.C.P., F.A.C.C., Michael Reese Medical Center, Chicago, Ill.
Paul Puech, M.D., Department of Cardiology, University of Montpellier.
Ricardo A. Quinteiro, M.D., Department of Electrocardiography, Ramos Mejía Hospital, Buenos Aires.
Kenneth M. Rosen, M.D., Cardiology Section, The Abraham Lincoln School of Medicine, Chicago, Ill.
Mauricio B. Rosenbaum, M.D., Service of Cardiology, Ramos Mejía Hospital, Buenos Aires.
Manfred Runge, M.D., I. Medizinische Universitäts Klinik, Hamburg.
Jeremy Ruskin, M.D., Cardiovascular Program, U.S. Public Health Service Hospital, Staten Island, N.Y.
Benjamin J. Scherlag, Ph.D., Veterans Administration Hospital, Miami, Fla.
Francien J. G. Schopman, Department of Physiology, University of Amsterdam.
Reinier M. Schuilenburg, M.D., Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam.
Will C. Sealy, M.D., Duke University Medical Center, Durham, N.C.
Joseph F. Spear, Ph.D., School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pa.
Harold C. Strauss, M.D., Duke University Medical Center, Department of Medicine, Cardiovascular Division, Durham, N.C.

Ruey J. Sung, M.D., Department of Pediatrics and Pharmacology, University of Miami Hospitals and Clinics, Miami, Fla.

A. C. Tans, M.D., Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam.

Paul Touboul, M.D., Hôpital Cardiologique, Lyon.

Jørgen Tranum-Jensen, M.D., University of Copenhagen, Anatomy Department, Copenhagen.

Raymond C. Truex, Ph.D., Department of Anatomy, Temple University, Philadelphia, Pa.

Andrew G. Wallace, M.D., Division of Cardiology, Duke University Medical Center, Durham, N.C.

Yoshio Watanabe, M.D., Fujita Gakuen University School of Medicine. Toyoake, Aichi.

Menashe B. Waxman, M.D., Department of Medicine of the University of Toronto. Toronto.

Hein J. J. Wellens, M.D., Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam.

Arnold C. G. Wenink, M.D., University of Leiden, Leiden.

Jay R. Wiggins, Ph.D., Department of Pharmacology, College of Physicians and Surgeons of Columbia University, New York, N.Y.

David O. Williams, M.B., M.R.C.P., Veterans Administration Hospital, Miami. Fla.

Andrew L. Wit, Ph.D., Department of Pharmacology, College of Physicians and Surgeons of Columbia University, New York, N.Y.

Delon Wu, M.D., Abraham Lincoln School of Medicine, University of Illinois College of Medicine, Chicago, Ill.

Iwao Yamaguchi, M.D., Department of Cardiology, Cedars of Lebanon Hospital Division, Los Angeles, Calif.

Douglas P. Zipes, M.D., Indiana University School of Medicine, Indianapolis, Ind.

CONTENTS

Myocardial infarction

ANATOMY AND ELECTROPHYSIOLOGY OF THE DEVELOPING CONDUCTING SYSTEM

1
THE DEVELOPMENT OF THE CARDIAC SPECIALIZED TISSUE

ROBERT H. ANDERSON, M.D., ANTON E. BECKER, M.D.,
ARNOLD C. G. WENINK, M.D., AND MICHIEL J. JANSE, M.D.

INTRODUCTION

It is a reasonable premise that knowledge of the development of any system provides a sound basis for the comprehension of both its normal and abnormal structure. It can also be argued that awareness of the morphogenetic nature of components of any system can provide some evidence relative to its function. In our opinion, all of these statements hold good for the cardiac specialized or conducting tissue. However, there is considerable divergence of opinion regarding the precise origin of certain parts of the conducting system, in particular the atrioventricular junctional area, while controversy continues to rage concerning the extent of specialized structures within the atrial tissues. Review of the relevant literature shows that in many cases these disagreements relate more to differences in interpretation than to variation in observations, while other arguments relate more to definitions and semantics. In this review we will present our own observations relative to the development of the cardiac specialized tissue. These have been based on histologic study of human embryos and specimens of congenitally malformed human hearts, together with combined morphologic and electrophysiologic studies of human fetal hearts. Where any topic is contentious we shall refer to the results of previous investigators. However, we shall not attempt to provide an exhaustive review of prior studies of development of the cardiac specialized tissue. Rather we will attempt to provide an outline of embryogenesis which we hope will facilitate interpretation and aid comprehension of the subsequent contributions to this book.

EARLY STAGES OF DEVELOPMENT

At the stage at which the heart is represented by a straight tube (approximately 2 mm CR length—3 weeks intrauterine development—Horizon X), various segments are recognizable. These can be designated, following the precedent of Keith (432), as sinus venosus, primitive atrium, primitive ventricle, bulbus and truncus. Each of the segments is separated by a constricted ring, and close examination of these rings reveals that they are histologically distinct from the walls of the intervening segments (fig. 1a) (62, 920). A close parallel to this situation is to be found in the hearts of lower vertebrates where some authorities hold the junctional tissues to be specialized (658). In contrast, others contend that conducting tissues are only observed in birds and mammals (179). Nonetheless, examination of the precise effect of cardiac looping and development on the disposition of

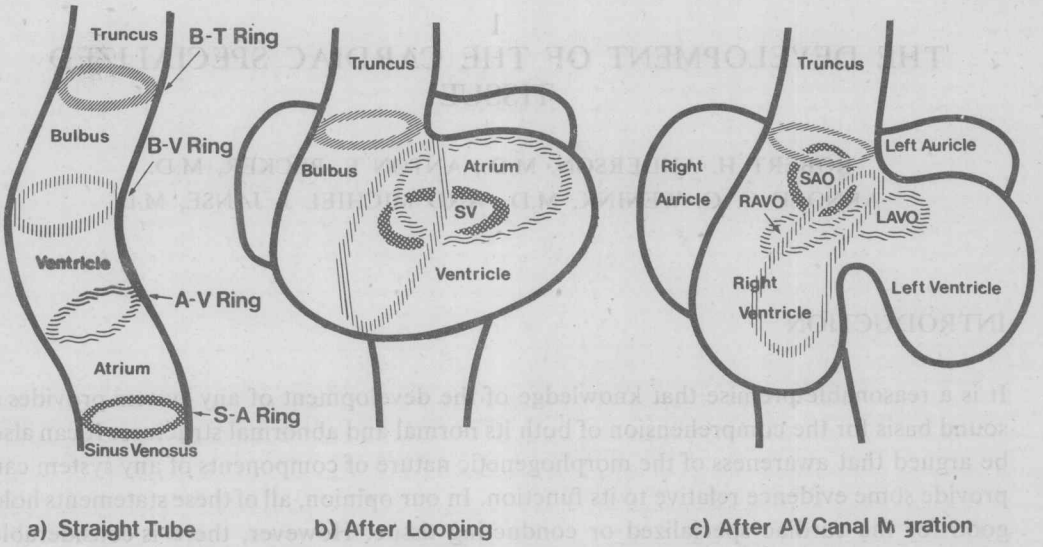

Fig. 1. Diagrams showing the effect of looping upon the rings of specialized tissue separati .g the components of the primitive heart tube, viz: sinus venosus, atrium, ventricle, bulbus and truncus. The four rings, the sinuatrial (SA), atrioventricular (AV), bulboventricular (BV) and bulbotruncal (BT) rings are indicated by differing varieties of cross-hatch or stipple, and these symbols will continue to be used throughout the subsequent diagrams. After looping (fig. 1b), the formation of the inner curvature brings the AV, BV and BT rings into close apposition. After canal migration, the SA ring is brought into contact with the AV ring posteriorly, while the BV ring is now juxtaposed to the AV ring in both medial and lateral parts of the right bulboventricular junction. These ring appositions are of considerable significance to subsequent development of AV junctional specialized tissues. Other abbreviations: SAO = sinuatrial orifice. RAVO = right atrioventricular orifice. LAVO = left atrioventricular orifice.

these junctional rings is of considerable significance to the subsequent formation of conducting structures (fig. 1).

Absorption of the sinus venosus into the right atrium places the sinuatrial ring in the posterior wall of the right atrial chamber. It impinges postero-inferiorly upon the atrioventricular ring, which following formation of the right ventricle is itself in apposition to the anteriorly situated bulboventricular ring in two sites, one septally and the other laterally (fig. 1c). Since the looping process produces an exceedingly short inner curvature of the heart, the cono-ventricular flange, it follows that atrioventricular, bulboventricular and bulbotruncal rings are all in close apposition at this point (fig. 2). This concept of disposition of the rings is dependent upon the premise that the definitive right ventricle is formed in part from the primitive ventricle and in part from the bulbus. Although some maintain that the right ventricle is an entirely bulbar structure (868), our own studies do not support this contention (34). Furthermore, if the primitive ventricle does contribute to both ventricles, as we believe, then the posterior ventricular septum is formed de novo from the primitive ventricle and is not a bulboventricular structure. As we shall show, conducting elements formed astride the posterior interventricular septum are of particular

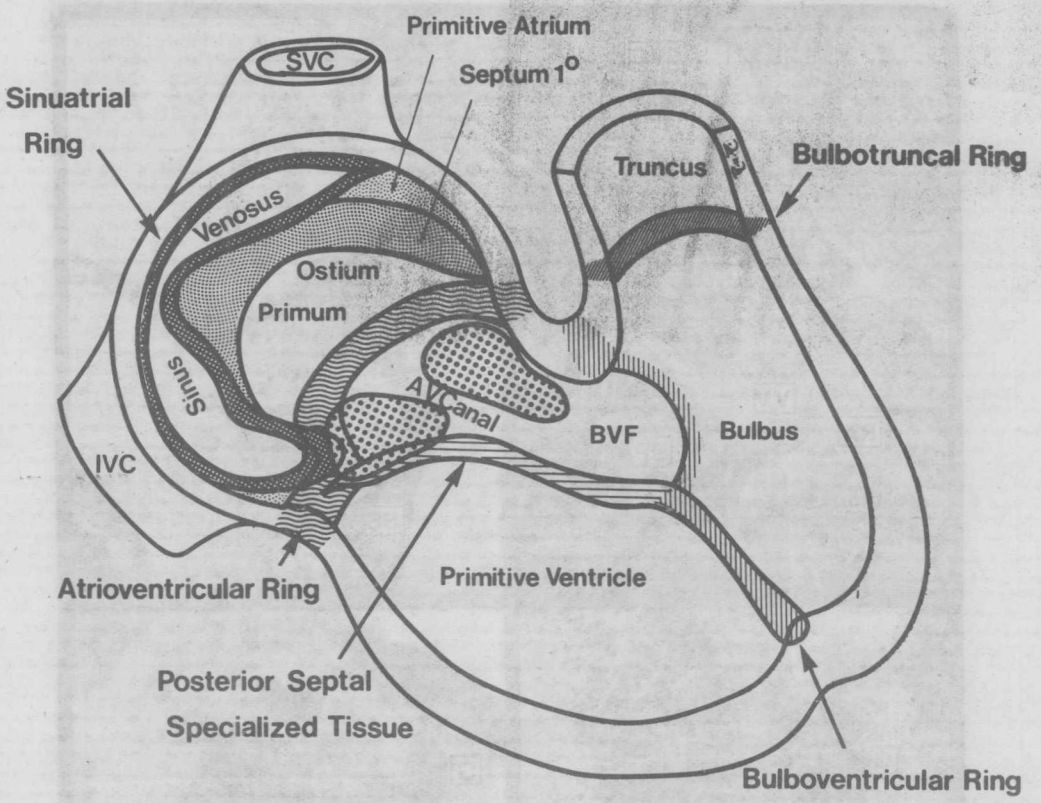

Fig. 2. Diagram illustrating the disposition of specialized tissues following looping and canal migration, but prior to fusion of the endocardial cushions (bold stipple). The specialized rings are in the same symbols as for figure 1. The atrial septal primordia are depicted by various forms of hatching (primitive atrium, septum 1°). The heart is dissected as viewed from its right side looking through the as yet unseptated ostium atrioventriculare. The primitive ventricle is shown as though septated by the posterior septum. The primordium of the compact node is astride this septum (posterior septal specialized tissue). Although drawn in a differing cross-hatch, our results indicate that this tissue is derived from a posterior invagination of the atrioventricular ring. Note that the sinuatrial ring is in the posterior atrial wall. SVC = superior vena cava. IVC = inferior vena cava. BVF = bulboventricular foramen. 1° = primum.

significance to development of the junctional area. In the ensuing account, therefore, we will presume that the right ventricle is derived in part from the primitive ventricle and in part from the primitive bulbus.

CONDUCTING TISSUES PRIOR TO COMPLETION OF ATRIOVENTRICULAR SEPTATION

Study of embryos in the stage at which fusion of the endocardial cushions is about to occur (Horizon XV) is of major significance to concepts of subsequent development of the conducting tissues. At this stage the septum primum is growing down to the cushions and is

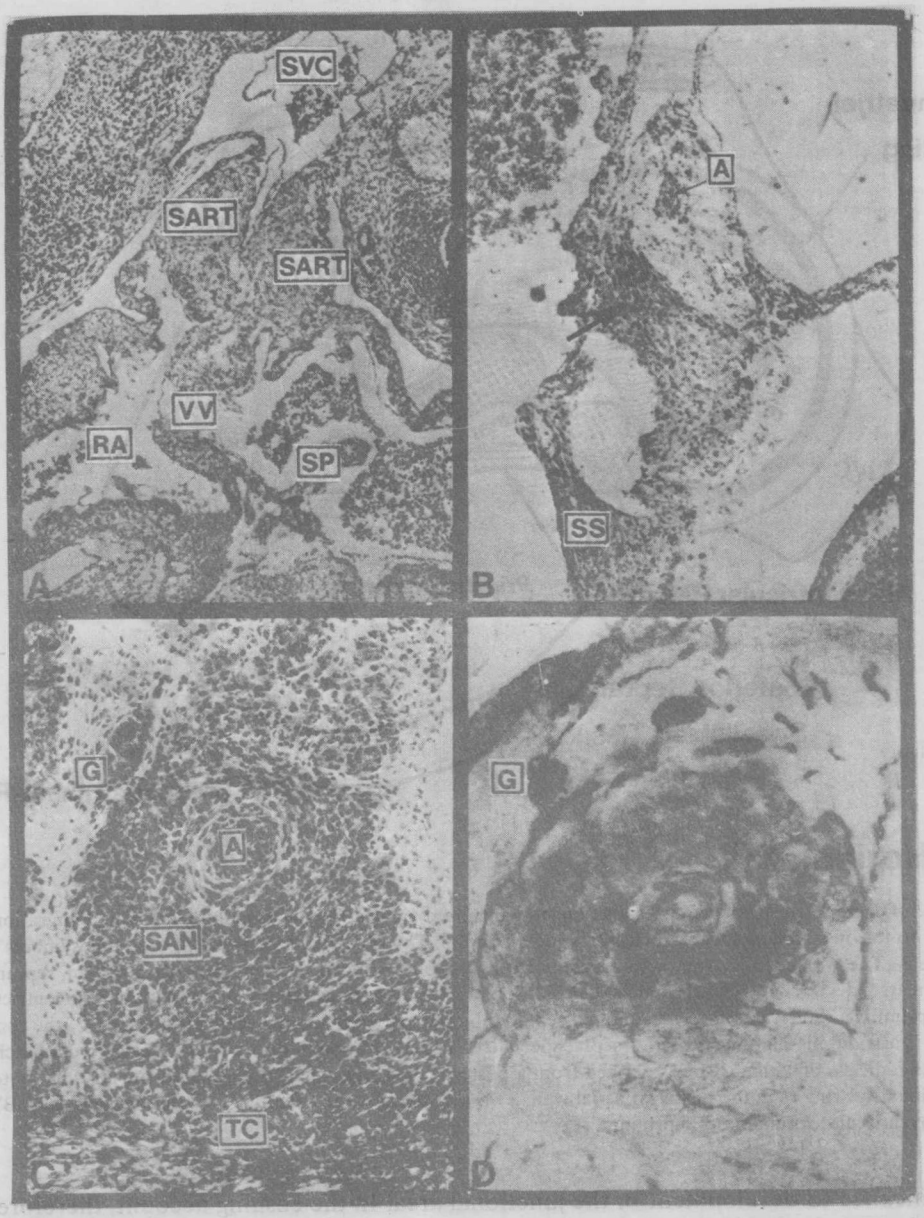

Fig. 3. Photomicrographs illustrating the development of the sinuatrial node. At approximately six weeks of development (fig. 3a) the sinuatrial ring tissue (SART) is thickened at the junction of the superior vena cava (SVC) with the right atrium (RA). Note the prominent venous valves (VV) depending from the sinuatrial junction and the perforated septum primum (SP) which is an outgrowth from the primitive atrial tissue. At approximately 8 weeks of development (fig. 3b) the sinuatrial ring thickening is confined to a small area of tightly packed cells (arrowed) above the septum spurium (SS). The cells do not surround the prominent artery seen at the cavo-atrial junction (A). By 10–12 weeks of development (fig. 3c and d) the cells have proliferated and now surround the nodal artery (A). The sinuatrial nodal cells (SAN) are minimally differentiated from those of the crista terminalis (TC) in histological terms (fig. 3c). However, an adjacent section processed for cholesterase activity (fig. 3d) shows that the nodal cells are ChE positive and are supplied by ChE containing nerves. Note the ganglion cell body which is also ChE positive (G).