PATHOLOGY FOR THE PHYSICIAN

By

WILLIAM BOYD

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Preface

THE preface to a new edition should inform the reader of any respects in which the book has changed. Such in part is the object of the present preface. In addition, however, I wish to take the opportunity of expressing some thoughts relating to pathology at the present day and our changing concepts of this discipline.

In many respects this is a new book rather than a new edition, although the pictures at least give it a familiar appearance, and the description of many of the lesions remains unchanged. The rewriting of large sections seemed to be the only satisfactory solution, instead of merely adding new material here and there, and thus patching the old suit to make it look like new. It is particularly in the section on General Considerations which opens each chapter that the newer cytological, physiological and biochemical aspects of the subject are considered. This will be evident more especially in such chapters as those dealing with the kidney, the respiratory system, the blood, and the endocrine glands. It would certainly be absurd to discuss the morphological changes of the adrenals in disease without first considering their physiology and biochemistry, or describe carcinoid tumors of the bowel without a reference to the subject of serotonin. I have called the book "Pathology for the Physician" in place of "The Pathology of Internal Diseases" as formerly, because I wished to present pathology as a sum total of its parts rather than as the pathological changes in the organs in "internal diseases," whatever those may be.

The rewriting has been done with the graduate rather than the undergraduate student in mind, the physician or internist rather than the pathologist, the young rather than the old. A Table of Contents has been introduced at the beginning of each chapter with the object of systematizing and classifying the material in a way which may be helpful to those unfortunates who have to face the ordeal of satisfying the examiners for the Specialty Boards of the United States and those of the Royal College of Physicians in Britain, in Canada and in Australia. The value of classification is seen in such chapters as those dealing with diseases of the kidney, the blood, the nervous system and the bones.

The references have also been changed, being now arranged alphabetically instead of under subjects. Most of the old ones have been discarded, because the old are contained in the new. The names of the authors whose work is described are given in the text, which seems more satisfying than the coldly impersonal method of referring to them by number. In the list of references I have put the year before the volume, which is not usual in North America, because to the reader, although not to the librarian, the year of publication is of major interest. The references are those which I have found most useful and which may prove of similar value to those who may wish to read more widely.

New chapters have been written on diseases of muscle and the internal environment, a separate one written on diseases of joints, and the chapter on the kidney has been placed immediately after those on the heart and arteries because of the increasingly intimate correlation between cardiovascular and renal disease.

The book may be regarded in one way as a companion to my own "Pathology for the Surgeon." No book should contain everything, for if it does it defeats the object for which it was written. A certain amount of overlapping has been unavoidable, because often a disease is found to be in the borderland dim between medicine and surgery. Indeed what is surgical today may become medical tomorrow, and often the process is reversed. In some instances, particularly in the case of the bones and joints, material from "Pathology for the Surgeon" has been incorporated with little or no change. I wish to express to the publisher, the W. B. Saunders Company, my appreciation for this courtesy, which has

saved me the thankless task of rephrasing much of this material.

A clinical-pathological conference worthy of the name does not consist merely in the presentation of two sides of a problem, but in bringing them together, so that the one will explain the other. So it should be in a book on pathology. This of course involves a consideration of disordered function as well as disturbed structure in the organs principally involved. It is for this reason that I have devoted so much space to normal and disordered function in the section on General Considerations which introduces each chapter, and why I have tried, even more than in previous editions, to correlate the lesions found at autopsy with the symptoms which characterized the disease during life.

More than a quarter of a century has elapsed since the publication of the first edition. In the intervening years the headlong rush of medicine, and in particular of the basic sciences which have come to form such an integral part of medicine, has left us all a little breathless, a fact of which the author of such a book as this is painfully aware. The growth of medical information has been compared to that of bacteria, which show a lag at the beginning of growth and then multiply at a logarithmic rate. Modern medicine seems to have reached the logarithmic phase. In medicine, as with Alice Through the Looking Glass, "it takes all the running you can do to keep in the same place. If you want to get somewhere else, you must run twice as fast as that."

Our concept of pathology has changed almost beyond recognition since I was an undergraduate, and very materially since the first edition of this book was published. It has long been recognized that the description of a dead body is of no value as an isolated piece of information, a fact indeed which was fully realized by the great masters of the past, including Virchow and Cohnheim. The purpose of pathology is not merely to learn a set of facts about things, but to study the causes of things and why things happen. An account of the morbid anatomy, whether gross or microscopic, must now be associated with physiology, biochemistry, histochemistry, cytochemistry, electron microscopy, and, most important, with the clinical manifestations during life which reflect the pathological physiology. It then becomes indeed pathology of the living, not of the dead, with attention directed to what may be called the biochemical lesion. Pathology conceived in this sense is the basic science concerned with the understanding of disease, and no clinician is better than his pathology. Without a sound knowledge of the hidden processes of disease as revealed by pathology, the physician, as Osler said many years ago, will flounder along in an aimless fashion, hitting now the malady and again the patient, he himself not knowing which.

Moreover, the picture of disease itself has changed to a remarkable degree in many instances. Diseases of major importance in the past have been largely displaced from their evil eminence by modern therapy. The examples of syphilis and typhoid fever at once suggest themselves. Morbid anatomy itself is not unchanging, and for this change chemotherapy is again responsible. We now see a type of vegetation in subacute bacterial endocarditis, vascular occlusive lesions in long-continued tuberculous meningitis, and late manifestations of diabetes mellitus which were never encountered in the past. The lesions of pulmonary tuberculosis encountered in the autopsy room are quite different from those seen formerly, and the lesions following streptomycin therapy are again different from those treated with isoniazid. But the picture is not always a rosy one. The antibiotics, the sulfonamides, steroid hormones, blood transfusions and other life-saving measures may be two-edged weapons, and we are now confronted with a growing list of iatrogenic lesions caused by the physician himself, which might be called the pathology of therapy. This is the penalty of progress, and it illustrates the truth of the saying that virtue itself turns vice when misapplied.

In recent years, with the great upsurge of the basic sciences, there has developed an insidious tendency to downgrade the place of pathology as a discipline of major importance to the clinician. This tendency is understandable when pathology is regarded as synonymous with morbid anatomy, the pathology of the dead. But the term pathology connotes now, as it has done in the

past, the comprehension of disease. It was Virchow, the supreme master of morbid anatomy, who defined disease as "the course of vital phenomena under altered conditions," and what outlook could be more modern? Lesions may explain symptoms but not disease; they may answer the question "how," but not the much more profound question "why."

When the archæologist studies the ruins of Pompei he does not confine himself to a consideration of ruin and decay long after life has ceased, but he endeavours to reconstruct the life of the people who lived there. That also is the aim of the present day pathologist. This opens the wide field of pathological physiology with its maze of fascinating paths along which it is delightful to roam in search of the answer to that question "why," but in whose maze it is fatally easy to become lost. The true objective of pathology is not merely to describe lesions and thus assist in making a so-called diagnosis, which in the past has too often been merely a matter of applying convenient labels which help to classify the narratives of illness, but rather to describe and explain the disease process, the manner in which the anatomical lesions are responsible for the disordered function. It should be the study of, not just the diagnosis of, disease. In the penetrating words of Liebow, "modern pathology may be paraphrased as investigative medicine, not merely the study of the morphology of diseased organs." One has only to think of the story of carcinoid tumors of the bowel to realize that morbid anatomy is not dead, and that there is no such thing as a "routine autopsy."

I have spoken as if disease was only a group of lesions or of biochemical disturbances, thus falling into the trap of on the one hand the morbid histologist who can only see disordered cells and on the other hand that of the electrolyte expert who has only an eye for the ions. Perhaps this mistake is natural coming from a pathologist. But the good physician knows that disease is more than this; it is something that happens to a sick person. As the old French proverb puts it: "There are no diseases, but only sick people." There is always the psyche to be considered as well as the soma, the person as well as the potassium. Two thousand years ago Socrates said: "It is the great error of our day in the treatment of the human body that the physicians separate the soul from the body," or in the modern and memorable words of Francis Peabody: "The care of the patient is caring for the patient."

In conclusion I am happy to acknowledge the helpful advice and criticism I have received from Dr. Calvin Ezrin of the University of Toronto in the preparation of the chapter on the pituitary, and from Dr. James A. Dauphince of the same University in the chapter on the internal environment, as well as from Dr. J. F. A. McManus, Dr. S. Richardson Hill and Dr. Howard L. Holley of the University of Alabama for similar assistance in the chapters on the kidney, the thyroid and adrenals, and the arteries and joints respectively.

As in previous editions I am indebted to my publishers, Messrs. Lea and Febiger, for the readiness with which they have agreed to my many requests as to format, some of which may have appeared to them unreasonable, and for enabling me to include references to work published during the past two or three months.

WILLIAM BOYD

Toronto, 1958

Contents

PATHOLOGY FOR THE PHYSICIAN

"Those who have dissected or inspected many bodies have at least learned to doubt; when others, who are ignorant of anatomy and do not take the trouble to attend to it, are in no doubt at all."—MORGAGNI

Chapter

1

Diseases of the Heart

OF all the ailments which may blow out life's little candle, heart disease is the chief. The statistics of the Metropolitan Life Insurance Company show that 600,000 people die of this disease in the United States every year, and that 1 out of every 3 of the population living at the age of ten years will succumb to organic disease of the heart.

Every physician knows that cardiac symptoms more often have an emotional than an organic basis. My colleague, Dr. Allan Walters, has pointed out to me that the simple everyday words of our language illustrate the relation of the emotions to the heart. We say that a person is heavy-hearted, hard-hearted, heartless, good-hearted, that his heart aches with loneliness, flutters with alarm or stops with fear, that it is in his mouth or in his throat or in his boots. This is, of course, only another way of saying that the nervous system has a profound influence on the cardiovascular apparatus. In this place, however, we are concerned only with the structural lesions of heart disease.

The four common organic diseases of the heart are rheumatic disease, subacute bacterial endocarditis, cardiac infarction, and hypertensive heart disease. Congenital heart disease, although comparatively rare, must be included in any list of important cardiac

disabilities, because of the part which surgery now plays in its treatment.

RHEUMATIC DISEASE OF THE HEART

Rheumatic fever is the major agent in cardiac pathology, and this for several reasons. It is the most frequent cause of acute inflammatory lesions in the heart. It commonly results in a chronic valvular disability which is a burden to the patient for the rest of his days. And it is the common precursor of subacute bacterial endocarditis. In the United States, next to accident it is the leading cause of death in children of school age and ranks second only to tuberculosis as a killing disease in young adults.

Pathology of Rheumatic Fever.—Our conception of the essential pathology of rheumatic fever has undergone an interesting evolution. For centuries the acute arthritis flitting from joint to joint has been well recognized. About a hundred years ago the relationship of valvular lesions to acute rheumatism was established, but these lesions were thought to be sequelæ of the acute disease, and not a primary manifestation as we now know them to be. Rheumatic fever is now known to be an inflammatory condition of the fibrous tissues involving first and foremost the heart, and, as a rule, the joints, the subcutaneous tissue, occasionally the brain and probably certain other organs. Regarding the relative importance of the cardiac and the arthritic lesions, it has been wittily said that rheumatism is a disease "which licks the joints, but bites the heart."

The disease pursues a somewhat different course in children from what it does in the adult. In children the joint pains may never appear. The child suffers from tonsillitis and a sore throat, these are replaced by chorea, and some fine day a heart murmur is discovered. In the adult the intensely painful swelling of the joints is much more characteristic, fever is higher and skin lesions are much rarer. It must be emphasized, however, that rheumatic fever is principally a disease of childhood; about 75 per cent of the cases occur before the age of twenty years. Conversely, about 95 per cent of heart disease in children is rheumatic.

Etiology.—The problem of the etiology of rheumatic fever is a rather curious one. There is general agreement that the disease is the result of infection with beta hemolytic streptococci group A. The difficulty is to prove this. The evidence in favor of a streptococcal etiology falls into three groups. (1) The demonstration of elevated titers of streptococcal antibodies, such as antistreptolysin and antistreptokinase, in patients with rheumatic fever, indicating recent contact with streptococci. (2) The effect of the treatment of acute streptococcal infections with antibiotics and sulfonamides in reducing the incidence of rheumatic fever. (3) Epidemiological evidence. Acute streptococcal infections in children are not infrequently followed by an attack of rheumatic fever. A person who has had rheumatic fever is likely to have an exacerbation after subsequent streptococcal infections.

C-reactive protein is always present in the serum in acute rheumatic fever, whilst the reaction is completely negative in normal persons. It will of course be realized that the test is in no way specific for rheumatic fever. The name comes from the fact that the blood of patients with pneumococcal pneumonia contains a protein which reacts with the carbohydrate (hence the C) of the pneumococcus to form a precipitate long before any antibodies to the pneumococcus can be detected. The protein has been isolated in crystalline form, and rabbits are immunized with the pure substance with the production of an antiserum. A simple precipitin test with the antiserum, which can be done in the doctor's office, will show the presence or absence of C-reactive protein. The test, which is indicative of an inflammatory or tissue-destroying process, gives a better correlation than the other indices of inflammation, namely the erythrocyte sedimentation rate, the leukocyte count, and the temperature (Roantree and Rantz). Any positive reaction may be considered abnormal. It is particularly in doubtful cases of acute rheumatic fever that the test has proved its value.

The incidence of rheumatic fever parallels in a striking manner the incidence of hemolytic streptococci in the throat and also the incidence of streptococcal diseases such as scarlet fever in which the primary infection

is in the upper part of the respiratory tract. This incidence is affected to a marked degree by climate. In the tropics, where hemolytic streptococci are rarely found in the throat, scarlet fever is unknown and rheumatic fever is very uncommon. In the north temperate zone where the climate is cold and damp it has been shown that, as the frequency curve of rheumatic fever rises, the incidence of hemolytic streptococci in the throats of the population shows a corresponding increase. Both are rare in children of the wealthy but common in children of the poor. Children who suffered from repeated attacks of rheumatic fever in New York remained perfectly free when removed to the tropics (Coburn).

A moment's thought will show that none of this is conclusive evidence. Certainly none of Koch's postulates have been satisfied. It is true that the Lancefield group A of beta hemolytic streptococci can be isolated from the throat of many persons with acute pharyngitis in whom rheumatic fever has subsequently developed, but throat cultures often give negative results when acute rheumatism develops. Of particular significance is the isolation of hemolytic streptococci from acute lesions of the heart valves, although most workers have failed in this attempt.

The truth is that rheumatic fever cannot be compared with such infections as diphtheria or streptococcal cellulitis where the etiology and pathogenesis is simple and evident. In rheumatic fever as in acute glomerulonephritis *host factors* as well as streptococcal infection are all-important. The classic infection with hemolytic streptococci is an acute process characterized by constitutional symptoms and local lesions, often suppurative in nature, at the site of invasion. These manifestations pass away, and the patient makes a recovery, which is complete *or only apparent*. For in a certain number of cases, after a period of quiet and calm lasting up to 6 or 8 weeks, an entirely new train of symptoms and lesions make their appearance. These differ in different persons, taking the form of rheumatic fever, acute glomerulonephritis, or still other disease complexes. These later manifestations must be attributed to host factors, changes in the tissue of the nature of hypersensitization, so that they develop an allergic inflammatory reaction to minute amounts of streptococcal antigen. Thus the development of rheumatic fever requires the presence of living streptococci throughout convalescence. It is prevented when penicillin therapy of streptococcal pharyngitis is delayed until a week or 10 days after the onset of the infection. This eradicates the streptococci, but does not affect the anti-streptolysin response (Cantanzaro *et al.*).

There can be little doubt that accessory factors play an important part in the etiology. Reference has already been made to the influence of geography. Rheumatic fever is a disease of poverty. This may be explained in part by overcrowding which encourages the spread of infection, in part by food deficiency, especially vitamin C (Rinehart). As rheumatic fever is one of the collagen diseases, it is possible that the response of the tissues may be under the influence of hormones, particularly the adrenal corticoids.

The classical picture of rheumatic fever is frequently absent. This serves to explain the well-known fact that so many patients who develop chronic rheumatic heart disease give no history of an antecedent acute attack. This is particularly true of the disease in childhood. It is unfortunate that no really good laboratory tests for the condition are available. The clinical signs and symptoms may be suppressed by therapy, and the sedimentation rate, C-reactive protein and other laboratory evidence of infection return to normal, but they again become abnormal when therapy is discontinued, showing that the disease has been suppressed but not cured.

From what has been said it will be apparent that rheumatic infection must be much more common than the cases diagnosed clinically would indicate. Rheumatic heart disease is much more common than acute rheumatic fever. Between 1950 and 1955 only 2 cases of rheumatic fever were admitted to the Vancouver General Hospital, but mitral stenosis was a common finding at autopsy, often as an incidental finding without clinical symptoms pointing to the lesion.

The acute disease is rare before the age of two and after the age of thirty years, the

peak of incidence being about the age of seven. Attacks in the adult are usually in the nature of a recurrence. Indeed recurring attacks are the rule rather than the exception, for once the special tissues have become sensitized, any pharyngeal infection with group A streptococci may precipitate an attack. It is said that a second attack may be expected within one year of the initial attack in 40 per cent of cases. Evidence of the persistence of the allergic state is seen in the frequency with which Aschoff bodies are encountered in biopsies of the atrial appendix removed during the operation of mitral commissurotomy.

The Lesions.—The basic lesion of rheumatic fever is fibrinoid degeneration and necrosis, a change in the ground substance and collagen as a result of which the connective tissue assumes a lattice-like appearance with some of the staining characteristics of fibrin. The fibrinoid material is composed of an acid mucopolysaccharide-protein complex. This connective tissue change appears to be a fundamental manifestation of allergic reaction, and is observed in other lesions of the vascular system, in particular periarteritis nodosa and disseminated lupus erythematosus. For this reason the two latter conditions have been classed with rheumatic fever as the *diffuse collagen diseases*. The fibrinoid lesion with the inflammatory cells which accompany it form the Aschoff body, which is the hall mark of rheumatic fever.

It must not be thought that pathological opinion accepts without reserve the view that the Aschoff body is of collagenous origin. Some excellent observers in the past and a few at the present day believe that the lesion is the result of destruction of myocardial fibers and that Aschoff cells evolve beneath the sarcolemma from primary injury to these fibers. The consensus of opinion, however, favors an origin from ground substance and collagen fibers (Ruebner).

There are five main components of the rheumatic nodule:

1. The center is composed of a small amount of necrotic material. This consists for the most part, as Gross has shown, of swollen and fragmented collagen.

2. Around this center are grouped the Aschoff cells, peculiar large endothelioid cells with one or several vesicular nuclei, and cytoplasm with characterically ragged edges. Naked masses of cytoplasm may be present. The cytoplasm of the Aschoff cells stains a brilliant red with Pappenheim's pyroninmethyl green, but the tissue must be specially fixed in alcohol. These cells constitute the most characteristic feature of the lesion. They are probably derived from the histiocytes or resting wandering cells, members of the reticulo-endothelial system. The giant cells resemble those of Hodgkin's disease rather than the multinucleated giant cells of tuberculosis (Fig. 1).

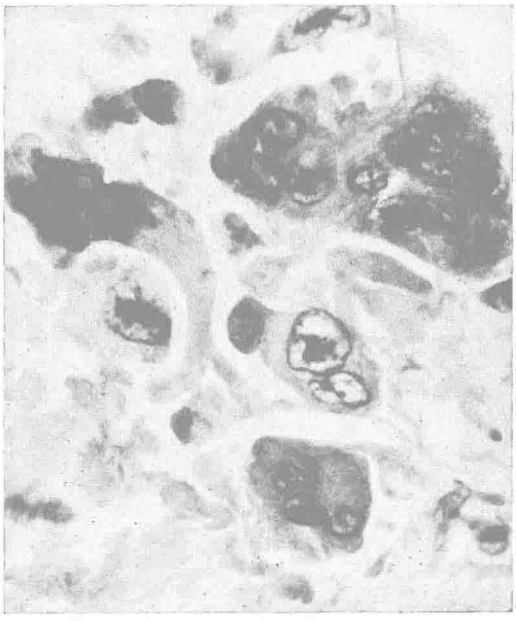

FIG. 1.—Multinucleated Aschoff cells of various sizes. × 900.

3. The Anitschkow myocyte (Fig. 2) is often found in large numbers in the cardiac lesions, although not in rheumatic lesions elsewhere. It is a cardiac histiocyte, which in inflammation shows increased cytoplasm, a highly characteristic serrated bar of chromatin in the center of the nucleus, and fibrils radiating from the bar to the periphery.

4. Lymphocytes and plasma cells are to be seen in varying numbers, together with an occasional polymorphonuclear leukocyte. Occasionally, as Clawson points out in his review on the Aschoff body, the polymor-

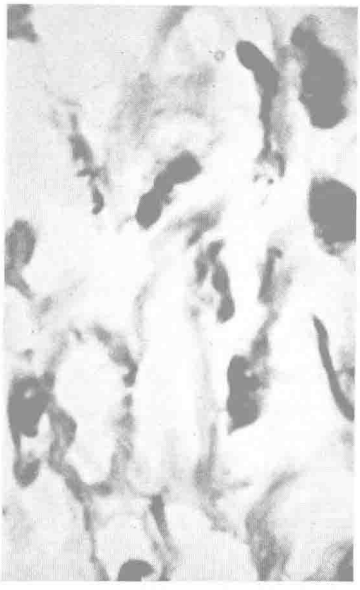

FIG. 2.—Antischkow cells. × 750.

FIG. 3.—Aschoff body in the myocardium. There is a lemon-shaped collection of inflammatory cells in the interstitial tissue, with destruction of the muscle fibers. × 150.

phonuclears are so numerous that the lesion is practically an abscess.

5. A fibroblastic proliferation more or less marked in degree is always present.

The Aschoff body varies greatly in size; there may be only a few cells, or it may be visible to the naked eye. It may be round, but frequently in the myocardium it is elongated or lemon-shaped (Fig. 3). It bears a definite relation to the adventitia of the small branches of the coronary arteries, not perivascular in the sense that the cuff of inflammatory cells in syphilis or encephalitis lethargica is perivascular, but nevertheless lying alongside the wall of a vessel as it runs in the interstitial tissue between the bundles of muscle fibers (Fig. 4). The cells of the Aschoff body are mainly the result of local proliferation, but it cannot be denied that probably some of the small round cells and certainly the polymorphonuclear leucocytes are to be regarded as evidence of the exudative type of reaction. Edema, frequently seen in the valves, is another manifestation of this reaction. It is, however, in the joints and in the pericardium that exudation is seen to the best advantage.

Interest in the Aschoff lesions has been reawakened by the opportunity provided by the removal of biopsy specimens of the left atrial appendage in the course of operations on the mitral valve. The proportion of active lesions vary considerably in the reports of different workers. Clark and Anderson in 78 cases operated on in the Toronto General Hospital found Aschoff granulomas in 50 per cent of cases and basophilia (metachromasia with toluidin blue) probably due to sulphated mucopolysaccharides even more frequently. In 10 of the cases, no lesions were found. In another large series the figure was 41.6 per cent (Luse *et al.*). The average of many surgical reports is 46 per cent (Thomas *et al.*). On the other hand, Tedeschi and his associates in a series of 400 cases found only 2 per cent of active lesions, the others being healed or healing rheumatic carditis (17 per cent) or chronic non-specific carditis (81 per cent). The difference is probably due partly to varying interpretations of what constitutes an active or a heal-