THE YEAR BOOK *of* PATHOLOGY *and* CLINICAL PATHOLOGY

(1958-1959 YEAR BOOK *Series)*

EDITED BY

WILLIAM B. WARTMAN, B.S., M.D.

Morrison Professor of Pathology, Northwestern University;
Director of Laboratories, Passavant Memorial Hospital;
Senior Attending Pathologist, Chicago Wesley Memorial Hospital;
Consulting Pathologist, Children's Memorial and Veterans Administration Research Hospitals, Chicago.

THE PRACTICAL MEDICINE YEAR BOOKS

This volume is one of the 15 comprising the Practical Medicine Series of Year Books founded in 1900 by G. P. Head, M.D., and C. J. Head, and published continuously since then. The complete list follows:

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INTRODUCTION

Last year, many kind readers of this little book wrote letters telling me how much they had enjoyed the Introduction with its account of my quinquennial brain dusting. It is probably unnecessary, but nonetheless pleasant, to tell of the pleasure these letters gave me and to record my appreciation of the trouble the authors took to write them and of the kind things they said.

This year, when I began to write this Introduction, my first thought was to give an account of how I went to the Seventh International Cancer Congress in London in July of 1958, and of how afterward my mother and I motored through Brittany. But, successful as the Congress was and delightful as the Brittany journey proved to be, I have finally decided not to do so for fear that a second diary account might prove anticlimactic. Besides, I have gathered two special articles which I am certain you would much rather read than anything I can write—Sir Roy Cameron's article on the centenary of the publication of Virchow's Cellular Pathology and Robert Kark's account of Richard Bright to mark the hundredth anniversary of his death.

And now to the pleasant task of acknowledging my debt to my colleagues at Northwestern University—to Willard T. Hill for help with the selection of the papers on tumors, to Francis Tenczar with those on hematology, to Edward Fitzsimons with the ones on clinical chemistry and to Robert B. Jennings for papers on the kidney. They gave me generous help indeed and the opportunity to rub my wits against theirs—things which have added immeasurably to the value of this book.

"No man is an Island, entire of itself."—*Devotions,* John Donne (1573-1631)

WILLIAM B. WARTMAN

► The year 1858 was important for Medicine for it saw the death of Richard Bright, the first printing of Virchow's *Cellular Pathology* and the death of his great teacher Johannes Müller. I knew of no one to mark the centenary of Müller's passing, which is a great regret for he had specially great powers of mind and of these he gave freely to his pupils with surprising results—Helmholz, Billroth, Virchow! I was more fortunate, however, in having two good friends to help me mark the centenaries of Bright and Virchow. Professor Robert M. Kark, of the University of Illinois, let me use part of his special biographical note on Richard Bright, which you will discover in the section on the Kidney.

The importance of Virchow's *Cellular Pathology* is made specially clear by Sir Roy Cameron, of the University of London, in the following paper. Professor Cameron's book on the *Pathology of the Cell* has an unquestioned position and with his many papers has put him in the position of the leading British scholar of Virchow, his times and his book. I have a great feeling of debt to Professor Cameron, as I know you will have, for the time and trouble he has taken to write this special article for the YEAR BOOK.—Ed.

Special Article

A CENTURY OF CELLULAR PATHOLOGY

SIR ROY CAMERON*

This year we have seen the completion of a century of astonishing investigation since the publication, on Aug. 20, 1858, of Rudolf Virchow's *Die Cellularpathologie*. Apart from a few papers on the subject by German writers in the *Deutsche medizinische Wochenschrift* and a special commemorative session arranged by the Society of Clinical Pathologists in London in October, 1958, little notice has been taken of a great moment in the history of pathology. It seems fitting that we pause for an instant while we take stock of the idea that lies behind this inspired generalisation. At that moment, the young Virchow—he was only 37 years of age—was rapidly approaching the summit of his fame. Despite many political and personal vicissitudes, he had fought his way to the top. He had accepted the leading post in pathology in Berlin on his own terms, which included a new Pathological Institute at the Charité and almost complete autonomy. The time was appropriate for a statement of his views on the principles of pathology, and no more fitting

*Department of Morbid Anatomy, University College Hospital Medical School, London.

occasion could have presented than a course of lectures to general practitioners. The words were spoken, and cellular pathology was born.

Elsewhere I have shown that Virchow's theory rests on six propositions and I trust that I may be forgiven if I quote these propositions for they lie at the back of what I wish to discuss.

1. Cells are the units of life.
2. The tissues of the living organisms are built up from cells, organs in turn are composed of tissues. But the organism is essentially a cell state.
3. Cells receive their nutriment from blood vessels, abstracting nourishment from the blood of their specific vascular territories.
4. Cells, too, are units of disease. Unhealthy cells show impairment of their powers of nutritive attraction and contribute noxious ingredients to the blood, thus producing dyscrasias and metastatic disease.
5. Cells possess irritability as long as they are living. Response to irritation may be functional, nutritive and formative.
6. Disturbance of function may result in exhaustion and fatigue; nutritional upset is shown by hypertrophy, cloudy swelling and inflammation or passive changes such as degenerations and necrobiosis. Formative disturbance gives hyperplasia, pus formation, tuberculosis and neoplasms.

Of these six propositions, no one will take exception to 2 and 5, although some obscurity must persist with the use of the term "irritation" until we decide what is meant by functional stimuli and whether all three varieties share something in common. Probably this will turn out to be chemical, a product of some sort of activity of the cell. But we are not so sure that cells are the units of life since the borderline between life and death is not so sharply definable as we had previously believed, and we are hard put to include viruses within the classic grouping of cells. Nor are we prepared to accept, in its entirety, Virchow's third proposition. That they receive their nutriment from blood vessels goes without question, but not everyone would agree that certain districts belong to one cell, others to another cell, and so on. We have become used to the idea of switches in functional activity within vascular territories as shown so brilliantly by Richards in the case of glomeruli and postulated, with a fair amount of likelihood, for the liver lobule and the brain. Various considerations have led some of us to favour the idea of more composite groupings within the tissues than isolated cells. Arguing from painstaking and precise studies of

the vascular arrangements in the intestine, spleen and liver, Franklin Mall long ago postulated units of tissue possessing anatomic location but ill-defined in extent. He emphasised the prime importance of the capillaries for functional activity of a tissue and applied Thomas's histomechanical principle relating new formation of capillaries to variations in blood pressure in the capillary areas to all such relationships. Mall especially stressed the plasticity of the capillary system. "So we must conclude," he wrote in 1906, "that in a child the liver structure is entirely rearranged each year which calls for a destruction and regeneration of at least a billion capillaries and towards puberty ten times this number." Nevertheless, he clearly accepted Thomas's statement that "it is the organ itself which determines the quantity, the rate of flow and the pressure of the blood flowing through it." As the result of our investigation of variations in cell injury responses according to environment, Mehrotra and I thought that some sort of unit, which we called a "field," was needed to express "the dual relationship between cells and their immediate environment which we see so clearly in action when the effects of local injury are studied." Recent work by Dr. Khyu-Sun Rhee and myself on splenic regeneration inclines us more and more to the "field" or "unit" idea but leads us to place emphasis on the parenchymal cells of the "field" rather than on their blood vessels. In the case of the spleen, for instance, minute groups of pulp cells can be successfully grafted into another environment of the parent animal. Although they become dissociated from their original blood vessels at the time of grafting, they soon establish a new set of sinusoids through the differentiation of their reticulum cells and the formation of new capillaries by the vessels around the graft. Virchow may well have been correct in assuming the existence of specific vascular territories but too rigid a view of their nature cannot be maintained. Nor, indeed, is it desirable, for the essence of many pathologic processes is the adaptability of cells to a new environment and the moulding of that environment to their needs.

When we approach Virchow's proposition that cells are units of disease we feel the need for radical readjustment mainly because of the rise of biochemistry. In the past 50 years has emerged the idea of the organelle, and investigators now plot the function and structure of these minute

components with the utmost confidence. Already some progress has been made in transferring the "seats of diseases" from the cell to its organelles and precise biochemical maps can be constructed which indicate the exact sites at which injurious agents produce their blocks and disruptions (Christie and Judah; Gallagher, Judah and Rees). And we accept, with increasing conviction, the likelihood of specialised regions in the cell which are concerned with the transport of oxygen, water and nutritive substances, the removal of waste products and the maintenance of osmotic equilibria. Thus we speak of "pumping stations" for water, sodium and potassium, although no one knows where these are located; we think of mitochondria as cell dynamos from which energy is distributed to the microsomes, ergastoplasm and nucleus and we postulate specialised "patches" at the cell surface where certain functions are concentrated. Immunology, too, has furnished evidence for the manufacture of cell products under the appropriate stimulus and the release of these products into the body fluids whereby they are enabled to exert their specific action at localities far removed from the site of their formation. Even more remarkable has been the isolation of hormones from differentiated cells, crowned by the discovery of their exact chemical constitution in some cases, and their synthesis in the laboratory. These, too, may exert noxious effects on vulnerable tissues when they enter the blood stream in certain concentrations, thus fulfilling Virchow's dictum.

One hundred years of research has dealt harshly with the sixth proposition. Though we may agree, at any rate in a broad sense, that nutritional upset lies behind hypertrophy, we soon find ourselves in difficulties when we consider individual cases such as the pregnant uterus or the anoxic bone marrow. Recent studies suggest that some forms of cloudy swelling may indeed come from nutritional disturbance (Spector), as may also be the case with other degenerations and necrobiosis. Inflammation, however, must be placed in a group of its own while progress in bacteriology has clarified the nature of pus formation and tuberculosis. No longer need we speak of formative disturbance as the cause of neoplasia since the discovery of carcinogenic chemical agents, and hyperplasia and hypertrophy bid fair to be placed in somewhat similar groups, though our lack of accurate knowl-

edge here is scandalous. Nor should we go on repeating, parrot fashion, that disturbance of function leads to exhaustion and fatigue, knowing quite well that the only example comes from muscle behaviour and that, even in this instance, we know next to nothing of its real nature.

On the whole, then, Virchow has come out of the hundred years with fair success. Nothing has emerged to disturb the position of the cell at the centre of the theory of disease. It is inevitable that fresh developments in technique and novel points of view will lead to a shift in focus and the scrapping of obsolete or clumsy terminology. That, in my opinion, is precisely what is about to happen at the present time. Pathology is badly in need of stock-taking if it is to keep in step with its sister sciences and avail itself of all that they have to offer.

► [In the November number of the *Journal of Clinical Pathology* you will find a delightful account by Sir Roy of the condition of affairs in the year 1858. The whole number of the Journal is given over to papers on cellular pathology. Three interesting papers in German came out in the *Deutsche medizinische Wochenschrift* (83:361, 364, 370, 1958).—Ed.]

GENERAL PATHOLOGY

Synergism and Antagonism between Simultaneously Occurring Diseases—General Review of Ways in Which Diseases Modify Each Other is presented by Carl E. Taylor[1] (Harvard Univ.). Diseases occurring together have three possible patterns of behavior: (1) they may be greater than the sum of their independent effects (synergism); (2) one may limit the effect of another (antagonism); or (3) an end result may occur that would be expected from each disease separately (asynergy). The principal mechanism is modification of host resistance. Immunity is too often considered synonymous with acquired resistance because of its dominant role in infections. Other defense mechanisms are important.

Most congenital anomalies facilitate invasion. Pancreatic fibrosis with pulmonary cystic disease is often associated with bronchiectasis and pulmonary infections, congenital heart disease and patent ductus arteriosus with subacute bac-

(1) Chicago M. Soc. Bull. 61:257-266, Oct. 4, 1958.