Publications of the
Wellcome Institute of the History of Medicine

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New Series, Volume XXIII

British Contributions to Medical Science

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General Editor: F. N. L. POYNTER, PH.D., D.LITT., HON.M.D.(KIEL)

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The Woodward-Wellcome Symposium
University of British Columbia
1970

Edited by William C. Gibson, M.D., D.Phil.(Oxon.)

London
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BRITISH COLUMBIA is a thriving and progressive state which cherishes its British connexions and traditions. Its university, with a spacious campus that cannot be surpassed for the natural beauty of its surroundings of mountains, water and forests, has been growing at a rate that testifies to the concern of its citizens for higher education. That the Health Sciences have taken the lead in this phenomenal growth is to a large extent the result of the vision and dynamism of the members of faculty. Their enthusiasm and confidence have inspired massive and generous financial support to which the university is indebted for some of its finest buildings. Among these the Woodward Library is notable as a centre of medical humanism and scholarship which is bound to leave its impress on all medical graduates of the university. For Professor Gibson it was a dream come true, for it embodies his own convictions, first nurtured when he was a graduate student at Oxford, of the great value of medical history to medical education.

There are many occasions in the history of science when new discoveries have sprung from a chance observation made by the prepared and alert mind. It is Professor Gibson's belief, as it is mine, that an acquaintance with the ways in which our present scientific and medical knowledge has originated and developed is one of the most useful contributions to preparing the young doctor for his life-work, whether it be in the laboratory, the hospital or in general practice. His perspectives are extended beyond the routine methods and techniques, his horizons enlarged beyond the immediate environment and his intellectual life deepened and enriched. Professor Gibson has himself written a book on the medical discoveries made by medical students, and it is deservedly well known. In the Woodward Library his own students have been able to learn not only from their living teachers but from many of the great men of the past who are long since dead. This is their true heritage, and those students who are privileged to share in it become thereby not academic medical

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Gibson should seek my aid in making the arrangements for the British speakers at his proposed meeting, both to avoid covering ground already well covered and to avoid the delays that might arise from the great distance between Vancouver and London. Unfortunately, commitments elsewhere prevented my own attendance at this meeting, but my British friends and colleagues assure me that it was indeed a memorable occasion, organized to perfection on the spot. Some of their papers I was able to read before they were delivered; others I have read for the first time before sending this volume to press. Taken as a whole, I think it will be agreed that they present a record of a most substantial contribution to the advancement of knowledge and human welfare, a record of which any country might justifiably be proud. At a time when the foreign press is avidly discussing what they call 'the British apathy' and 'the decline of Britain', it is well for the world to be assured—for some of the history in the following pages is very modern—that it is but a transitory phase. The intellectual achievements discussed in these papers are less a product of a great imperial past than they are of a native intelligence and creative energy that at times throws up a genius.

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THIS VOLUME consists of papers read at a symposium held at the University of British Columbia in June 1970 on contributions to medicine made by British scientists. The occasion was the opening of an extension to the Woodward Biomedical Library on the campus at Point Grey. The Wellcome Trust of London and the foundation endowed by the late Mr. and Mrs. P. A. Woodward of Vancouver made it possible to bring the distinguished visitors from abroad. They were joined by scholars from the University of British Columbia in two days of presentation of the varied aspects of this broad subject. All were able to be present on the day preceding the symposium to hear Lord Brock pronounce the new building open, and to witness the moving ceremony at which Sir John Eccles, F.R.S., Nobel Laureate and an Honorary Lecturer at U.B.C. unveiled the portrait of his teacher Sir Charles Sherrington, O.M. This handsome painting by Eves was given to the University by Sir Charles' son, Carr Sherrington of Belmont, Surrey, and his family.

In continuation of the theme of the symposium, a permanent museum is being established in the Sherrington Room of the Woodward Library, wherein memorabilia relating to British contributions will be displayed. Among these will be a collection of letters received over a lifetime of ninety-five years by Sir Charles from the eminent scientists with whom he had worked and those whom he had trained, together with his honorary degree parchments and other possessions. Also gracing the room is a large portrait of the Canadian medical scientist Dr. Frank Fairchild Wesbrook, Sherrington's confrere at Cambridge, and first president of U.B.C. Contemplating the room no doubt with satisfaction, is a copy of the Royal College of Physicians portrait of William Harvey, presented to the Library by the late Dr. Donald Paterson, Professor of Pediatrics at Great Ormond Street, London, and later at U.B.C.

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General Medicine

by

K. BRYN THOMAS

THE HONOUR of the invitation to give this first paper upon so auspicious an occasion as the opening of this splendid Woodward Library is one which I must own to leaving me very conscious of my deficiencies in knowledge of the subject upon which I have to speak. My title refers to 'General Medicine' but when one begins to consider this in some detail one is forced to ask 'What is general medicine?'. Should I give a discussion of those aspects of clinical medicine normally dealt with by the general physician, be he general practitioner or hospital consultant? With all deference to my physicianly colleagues, I submit that this would cover a narrow field, though admittedly an important one. In any case, following speakers are to tell of many activities which, though of a specialist nature, fall to the lot of the general physician. Should I produce an account of the background to which British medicine has contributed, the work of the physiologists, pathologists, biochemists, or other-ologists, who have added so much to knowledge? Or should one discuss the contributions of a select few, an élite band of leaders, whose work has pointed to new roads for others to follow? The field is obviously vast, for one can include all these and more, and therefore I have been forced to a degree of selectivity, but at the same time, I have to cast my net widely so that no large fish (small though his pond may be), shall remain unnoticed. This is of course impossible, and omissions will abound. Accordingly, I should like to discuss my subject under some headings which may not immediately appear to be the concern of 'general medicine', for I shall bring in such topics as contributions to general medical education, to research and what is perhaps most important, to epidemiology and preventive medicine. Later speakers will fill in many gaps in matters which I can mention only briefly.

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Henry VIII's Medical Act of 1511 had been designed to limit the activities of quacks and non-qualified people, by allowing medical practice only to graduates of Oxford or Cambridge. They would be licensed by the Bishop of London or the Dean of St. Paul's, a privilege which these clerics held for some two hundred years. But on 23 September 1518 the king granted the charter of incorporation of a college of physicians of London. The petition requesting a charter had been presented by three royal physicians, John Chambre, Thomas Linacre and Ferdinand de Victoria, with three lesser-known physicians and one great name, that of Cardinal Thomas Wolsey, Lord Chancellor of England, who was then at the height of his power. Linacre was his personal physician, and became the first president of the College, a position which he held until his death in 1524, when he left part of his house to the College as a meeting place and library. Linacre therefore has a firm place in English medicine; though his claims as a medical humanist were not fully recognized save on the Continent, and his ideal of a union between Greek learning and medicine did not materialize, his translations went into many editions in Europe. There is, however, no doubt that the works of Galen were a powerful influence upon English medicine at this time, though revolutionary forces were already at work, and the effect was not perhaps what Linacre would have desired.

The stimulating effects of Linacre's work may, however, be seen in the rising interest in medicine which manifested itself by the publication of such books as the first anatomical treatise in England by David Edwards, 1532, and the translations of further Galenic texts by John Caius, the second English medical humanist. Caius had studied in Padua, as a contemporary of Vesalius, with whom he at one time shared lodgings, and though they had parted on bad terms, Caius was thus able to modify his Galenic beliefs by an admixture of Vesalian modernism, even though details from his autobiography reveal that some Galenic anatomy still remained with him. He must

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Later speakers will deal more fully with Harvey's work.

With the turn of the seventeenth century medical men came more and more to see the need for knowledge of basic anatomy and physiology; and in London and Edinburgh, at any rate, it was the surgeons who largely filled this need. The eighteenth century saw such men as the Monros, William Cheselden and, above all, the Hunters and their students, avidly dissecting, drawing and writing, and incidentally producing those splendid folios which are among the high glories of medical art. Cheselden's *Osteographia*, 1733, Smellie's *Tables of Obstetrics*, 1754, and William Hunter's *Anatomy of the Human Gravid Uterus*, 1774, are unsurpassed.

Allied to the increasing knowledge of anatomy was the realization that structure is subservient to function and, as Harvey had taught, that knowledge of the normal is a prerequisite to study of the abnormal.

For the major part of the eighteenth century medical teaching in England was organized on a basis of apprenticeship, and teachers vied with each other not only to acquire students, but also to obtain posts at the larger hospitals, whence their pupils followed them for training and for posts as house-doctors. The majority of these pupils would qualify to practise by taking the membership examination of the College of Surgeons, which had separated itself from the Barbers in 1740 and received the Royal Grant in 1800.

At this period very little medical teaching took place at Oxford and Cambridge, and no other university medical facilities existed except in Scotland. Even there it was customary to incorporate one's doctorate of Leyden, Padua or other continental university. The College of Physicians of Edinburgh had been founded in 1681, and three years later the Town Council set up three chairs. During the eighteenth century, the Edinburgh school became an important centre of teaching, notably under the influence of William Cullen (1712–1790), mentor and friend of William Hunter. This school took over the mantle of that of Leyden, largely under men who had been trained at the latter university by the great Dutch teachers Sylvius, Boerhaave and Albinus. Cullen was also responsible for the foundation of the Medical School at Glasgow in 1744.

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Another important aspect of medical improvement which deserves brief mention, was the acquisition of great libraries, particularly in the eighteenth century. Thus Harvey himself, Hans Sloane, founder of the British Museum, Richard Mead of whom Johnson said that he walked in the sunshine of life more than any other man, William Hunter, Anthony Askew, third owner of the Gold-Headed Cane, and many others of lesser note, made great collections of medical, scientific and classical literature without which to study is to wander in an arid desert. The tradition is continued in the great modern medical libraries of Britain as well as here in British Columbia.

The continual pressure to improve standards of medical education led to the passing of the Medical Act of 1858 after much lobbying and persuasion, ably promoted by the fiery Thomas Wakley, then editor of the *Lancet*, the journal which he founded in 1823. Among the provisions of this Act was the setting up of a General Medical Council, a body responsible for standards of training and discipline, which also held the register whereby a practising certificate was awarded after the student had completed the prescribed training and had received his degree or diploma. The General Medical Council still exercises these exact functions, at present under the presidency of Lord Cohen of Birkenhead; and though it tends to make the headlines only over some particularly newsworthy piece of indiscipline on the part of some frailer member of the profession, its independent watch over professional and educational standards is one of the mainsprings of the high ethical nature of medical practice in Great Britain: providing a pattern and character which has been studied and carried to many other parts of the world, especially to those whose ties to the mother country are based upon large numbers of emigrant professional men. Time and discretion prevent one from entering into discussion upon the present rather controversial activities of the General Medical Council.

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> It generally begins with a chilness and shivering, which are followed by heat, thirst, restlessness and other well-known symptoms of a fever— in a few hours the patient is seized with a violent pungent pain in one side in the parts adjacent to the ribs . . . ; a frequent cough afflicts him . . . so that he sometimes holds his breath to prevent the first efforts of coughing. The matter expectorated at the beginning of the disease is small in quantity, thin and frequently streaked with blood: but in the course thereof it is more copious and more concreted and likewise mixed and coloured with blood.

No later physician could give a more succinct or accurate description, and it was this accuracy and minuteness of Sydenham's which enhanced later British medicine. Sydenham was not greatly appreciated by his immediate contemporaries, but in the eighteenth century his English medical descendants were enormously influenced by his writings, though one must plainly state that at this time, as at any other, the crossing of international boundaries brought powerful influences from the Continent, notably those of Hermann Boerhaave of Leyden. Nonetheless, Boerhaave himself stated that no reading had improved his knowledge more than that of Sydenham, whom he frequently perused, and whom he picturesquely described as 'the ornament of England and the Apollo of the Art'. Thus the English physicians contemporary with Boerhaave in the period 1720–1740 received from the Continent a re-inoculation of Sydenham's methods, and the results may be seen in their writings. We may take as example John Fothergill, the Quaker physician who lived from 1712–1780 and who studied under Monro *Primus* at Edinburgh and briefly under Boerhaave himself. It is worth noting also that Alexander Monro, first of the dynasty of anatomists at Edinburgh, was among the first to teach students at the bedside to observe signs and symptoms, a direct legacy from Sydenham which he had received from Boerhaave. Fothergill's most famous paper was his *Account of the Putrid Sore Throat* published in 1748, the original description of the ulceration of diphtheria. His description of the disease is of a similar standard to that of Sydenham, and he covers in detail the ulceration, the increasing delirium and the suffocating dénouement. The palatal paresis of diphtheria was described a few years later by John Huxham of subsequently discharged as the secretions of disease. Listen to him on pleurisy —

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There are many well-known examples of the application of medical knowledge to industrial disease. A famous example is the notable discovery of the cause of 'Devonshire Colic' by Sir George Baker, who showed that lead in vessels and pipes used in the manufacture of cider was responsible for the disease. Needless to add the vested interests and the production workers saw this as a threat and for a while opposition was fierce. I have digressed from clinical medicine, though I shall return to the topic of epidemiology. Eighteenth-century medicine offered an increasing knowledge of the signs and symptoms, descriptions and nomenclature of hitherto undescribed diseases. Of treatment little can be said. Galenic purging, vomiting and bleeding were widely employed and a common saying was 'it wrought both up and down'. Of specifics only three existed—that ancient poppy, opium; the mercury of Paracelsus, and the later cinchona bark, romantically but incorrectly associated with the fevered Spanish duchess of that name.

But treatment depends upon a more fundamental knowledge of disease than mere description. Under the influence of the Hunters and others, and stimulated by Morgagni's great work *De Sedibus et Causis Morborum*, which was translated into English in 1761, clinicians were turning to pathology and to the examination of the dead.

Matthew Baillie, nephew and pupil of the Hunters, published his book *Morbid Anatomy* in 1793. The fine copper-plates to this work were executed by William Clift, John Hunter's last assistant who became curator and preserver of Hunter's great museum, and include one of an emphysematous lung supposed to be that of Samuel Johnson. Baillie was a distinguished physician who wore himself out in the daily practice of medicine, in teaching, and in the post-mortem room. His book broke new ground in pathology. It was the first to deal exclusively with this subject and the first systematically to describe the morbid changes in each organ in different diseases, relating these changes to the symptoms shown before death. Baillie's descriptions of peritonitis, of the lungs in pneumonia, and of cirrhosis of the liver, among many others, were original in every sense, and the book was thus early sewn. Many became permanently sickly and many died.' As Sir Arthur MacNalty pointed out, 'Evil has many descendants, and the appalling conditions which prevailed before reform came inevitably weakened healthy stocks and national stamina'.

There are many well-known examples of the application of medical knowledge to industrial disease. A famous example is the notable discovery of the cause of 'Devonshire Colic' by Sir George Baker, who showed that lead in vessels and pipes used in the manufacture of cider was responsible for the disease. Needless to add the vested interests and the production workers saw this as a threat and for a while opposition was fierce. I have digressed from clinical medicine, though I shall return to the topic of epidemiology. Eighteenth-century medicine offered an increasing knowledge of the signs and symptoms, descriptions and nomenclature of hitherto undescribed diseases. Of treatment little can be said. Galenic purging, vomiting and bleeding were widely employed and a common saying was 'it wrought both up and down'. Of specifics only three existed—that ancient poppy, opium; the mercury of Paracelsus, and the later cinchona bark, romantically but incorrectly associated with the fevered Spanish duchess of that name.

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The Mid-Nineteenth Century

The leaders of the profession at this time were associated with the large teaching hospitals, most of which had been established during the previous hundred years. Now though one immediately considers London in this context, one must remember the older schools of Edinburgh, Glasgow and Dublin, together with the newer medical colleges at Sheffield, Liverpool, Manchester, Leeds, and later several others. We may take as an example the rising Dublin school, founded by John Cheyne (Cheyne-Stokes respiration), Abraham Colles and Robert Adams (Stokes-Adams heart block 1827). Here, in the 1830s, Robert Graves (exophthalmic goitre, Graves' disease, 1835) and William Stokes, Regius Professor, were responsible for allowing students access to patients at the Meath Hospital; they initiated the system of clerking which is still so prominent a part of the clinical teaching of the medical student. These men, too, with Thomas Hodgkin—who like them, had sat at Laennec's feet—introduced the stethoscope and Auenbrugger's percussion into clinical examination. At first, however, auscultation did not make the headway it deserved, and it was the younger men such as Charles J. B. Williams and James Hope, among other prominent British doctors, who were enthusiastic for its use.

Occasionally too there appeared the greater genius such as James Mackenzie, who revolutionized cardiology, who was to live through the first quarter of the present century and who spent nearly all his life in general practice in Burnley, a small Lancashire manufacturing town.

The middle years of the nineteenth century were thus an important era in British medicine. At Guy's hospital the great triumvirate of Bright, Hodgkin and Addison were at work and it will be worthwhile physician, with Osler himself as the prime example, was far from scorning this background. I have tried to show how the seventeenth- and eighteenth-century medical teachers bred their students to acute observation of the patient. Add to this the teaching offered by Baillie, Bowman and their kind, and it will be seen that the British physician of the mid-nineteenth century was able both to hold his own with any in the world and to send out his young men to a far-flung and rapidly developing Empire to continue and to improve upon, the work of their masters.

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> though after the most active symptoms of arachnitis, we often find nothing but serum infiltrated behind the arachnoid, we at times meet with a coagulable effusion, or one that is puriform. Rostan has given several such cases . . . others are given by Cruveilhier; and some examples are recorded and figured in Dr. Bright's splendid work.

The point one is labouring in each of these instances is that here were practising medical men whose realization of the limitations of their calling was not by any means confined to lack of diagnosis or even of treatment. It was a realization that beneath these outward needs—and most important needs too in relation to the patient—were the needs of the physician himself to know and understand the cause of the disease at which he was looking. The traditions of observation and recording set by such men are alive today in British medicine and rank as high as any detailed actual description of disease, however apposite and fundamental.

Specific Diseases

Castiglioni remarked that 'the history of medicine is not a catalogue of names of physicians, celebrated or otherwise, or a list of curious indications or the search for a grain of truth in the dusty volumes of ancient authors'. Rather we must realize that 'in its broadest sense the history of medicine is a study of diseases: cause, diagnosis and treatment': and one must now consider in a little detail one or two specific diseases, arbitrarily chosen.

Tuberculosis is perhaps an obvious choice, but the influence of British physicians upon the disease has been considerable. Opportunities for its study in Britain were all too common.

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Hippocrates considered tuberculosis to be the most grave of all diseases, regarding phthisis or pulmonary tubercle as a disease in the absence of any true knowledge of contagion this is exactly what it might appear to be. Morton regarded prophylaxis and early treatment as important.

> the great business is to take all possible care, for in this so slippery a state of health they are wont to fall headlong into a fatal consumption . . . but alas physicians have very seldom an occasion to advise about preventing this distemper (when at the beginning it may be cured as well as other diseases, although by neglect it proves fatal) the sick person seldom imploring Aesculapius' help before it has run so far as to be a fatal case and then he expects miracles from the Art of physic when it is more convenient for them to have a good council of a minister about the future salvation of their souls and the advice of a lawyer about making their last Will.

Morton was followed by Benjamin Marten, who in 1720 published his *New Theory of Consumptions*; though this leaned largely on Morton, he nonetheless produced an inspired, but ignored, guess as to causation.

> the original and essential cause then . . . may possibly be some certain species of animalcula or wonderfully minute living creature that by their peculiar shape or disagreeable parts are inimical to our nature, capable of living in our juices and vessels and which being drove to the lungs by the circulation of the blood, or else generated there from their own ova or eggs, with which the juices may abound or which being carried about by the air, may be immediately carried to the lungs . . . The curious, having considered the new world of wonders that microscopical observations have opened to our view, will easily conceive the possibility of very minute animals being not only the original and essential cause of this but of many other diseases hitherto inexplicable . . .

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A British physician who contributed to the pathology of tuberculosis was noted by Matthew Baillie. This was William Stark (1740–1770), a pupil of John Hunter. Stark's *Works* were edited posthumously in 1788. His descriptions of tubercles and of fibrosis of the lungs were confirmed and enlarged upon by Matthew Baillie, and gave a great stimulus to the study of the pathological anatomy of disease.

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I have taken tuberculosis as my example of what British medicine has done for one important disease. Time does not permit me to go into detail upon other similar examples. I can but mention such diseases as cholera—of which the great epidemics of the first half of the nineteenth century were important factors in stirring the medical and public conscience in matters of social medicine, to the extent of setting up the General Board of Health in 1848 and the passing of the Public Health Act in 1875.

I should mention the deficiency diseases, from Francis Glisson's description of rickets in 1650, from James Lind's magnificent experimental trial of the effect of fresh vegetables on scurvy, to the discovery of the vitamins by Sir Frederick Gowland Hopkins: to this must be added the work of Archibald Garrod, whose book the *Inborn Errors of Metabolism*, 1909, showed the important fact that constitutional variation can occur in function as well as structure, giving rise to what he called 'chemical malformations', alkaptonuria, cystinuria and other metabolic disorders. This book was among the most important of the early twentieth century. Then I should discuss smallpox, in which the contribution of Edward Jenner to the conquest of the disease by vaccination in particular, and to medical thinking in general, was on a par with that of Harvey.

Cholera

No historical disease indicates more acutely than cholera the potentialities of preventive medicine in the face of overwhelming disaster, contemporary methods of general medicine being completely unable to cope with the situation. And no epidemic, or rather, series of epidemics (with the possible exception of the yellow fever situation in Panama) has led more surely to advances in control than did those hands of the Medical Officer of Health. In the near future, the formation of new Area Health Boards is to alter the administration, bringing together the Regional Boards and the Local Authorities. In practice, control of the disease will still be the concern of the Medical Officer of Health. In 1962 Sir Arthur MacNalty reported a decline in mortality of 65 per cent in the previous fifteen years, and says 'in our own time we are witnessing the decline of a deadly disease'. How gratified Sydenham, Bodington or Robert Philip would be.

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Smallpox

This ancient disease appeared in England at an early date, and its contagious nature was recognized in the thirteenth century. Curiously, Sydenham's miasmatic concept of acute fevers did not allow for 'contagion', though his studies in the geography and spread of epidemics and of the rhythmical nature of their recurrences make him a pioneer epidemiologist. Nevertheless, Osler described him as still remaining one of the most trustworthy authorities on the disease.

By the end of the seventeenth century, epidemics of variola were common and in the eighteenth century the disease was endemic in most European cities and towns. Children were the chief sufferers and the London Bills of Mortality show a high death rate. Boerhaave was the first to *prove* the contagious nature of the disease, but the earliest large scale attempts at control took place in England. Inoculation with variola virus is an ancient practice, originating in the East, though known in parts of Britain. It was introduced with considerable publicity in 1721 by Lady Mary Wortley Montagu, wife of the British Ambassador to Turkey, where she noted its practice among Eastern families. She had her own children inoculated and the practice rapidly spread. Many physicians, including Sir Hans Sloane, endorsed it, and the royal seal of approval was set upon it in April 1722, with the inoculation of the young princes and princesses of George I. Inevitably controversy ensued, with the anti-inoculationists pointing to the risk of spread and to the possibilities of increased mortality. Nevertheless 897 inoculations noted by 1728 resulted in only seventeen deaths.

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Deficiency Diseases

For several centuries British doctors have played leading roles in dealing with the diseases now known to be caused by nutritional deficiencies, culminating in the work of Gowland Hopkins, Mellanby, Drummond and MacCarrison in the early years of the present century.

Rickets

It is 320 years since Francis Glisson of Cambridge gave his classical description of rickets in *De Rachitide sive morbo puerili qui vulgo* the Rickets *dicitur*. Daniel Whistler too had described the disease in his doctoral thesis of 1645. His paper is far less verbose than is that of Glisson, and equally exact, but it failed to attract much attention. Glisson described sixteen main findings, including the enlargement of the epiphyses and the knotty swellings in the chest cage, with the noteworthy observation that the whole bony system is flexible like wax that is rather liquid, so that the flabby and toneless legs scarcely support the weight.

Though the value of cod liver oil in rickets has been known for many years, it was not till 1903 that Leonard Findlay produced artificial rickets in puppies, and only in 1918 did Edward Mellanby state that 'rickets is a deficiency disease due to the absence of an accessory food factor'. Vitamin D was subsequently isolated from McCollum's fat-soluble factor.

Scurvy

Almost 220 years ago the publication of another epoch-making book occurred. James Lind (1716–1794) had seen the ravages of scurvy among seamen in the long eighteenth-century voyages of discovery. Anson's expedition of 1740 suffered a scorbutic morbidity of 75 per cent while the channel fleet had 2,400 cases in a ten week cruise in 1779. In the bicentenary year of Cook's voyages and at a point close to Nootka*, it is appropriate to note that Cook's scurvy rate was very low. But he was a brilliant commander, who obtained fresh food whenever possible. Even so, he himself was divided on the issue as to whether malt and wort were equally efficacious, and his doubts contributed to the long delay in the conquest of scurvy. The publication of Lind's book *On Scurvy* in 1754 with its definitive

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nothing but a muscle differing but little from other muscles'. He postulated a nitro-aerial salt without which life cannot be maintained and which is derived from the inspired air. This important contribution was only to be fully appreciated 100 years later with the discovery of oxygen by Joseph Priestley of Birmingham, and with the fundamental work of Lavoisier on respiration and combustion.

The interest in gases which Priestley stimulated manifested itself in the opening of such establishments as the Bristol Pneumatic Institute which Thomas Beddoes set up at Bristol in 1798, under the research superintendence of Humphry Davy, then but twenty years old. Here were performed a remarkable series of experiments on gases, including hydrogen and oxygen and nitrous oxide. Davy in 1800, in experimenting upon himself with nitrous oxide, described the exhilarating effects of the gas, and made the well-known observation that 'as nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place'. Over forty years were to elapse before Horace Wells, the American dentist, tried the experiment. Davy's work on gases went much further than this. His book *Researches, chemical and philosophical, chiefly concerning nitrous oxide*, 1800, is a magnificent record of experimental research conducted with skill and acumen.

Seventy years were to elapse before respiratory and cardiac physiology again became an object of active research, under the inspiring guidance of Sir Michael Foster (1836–1907), professor of physiology at Cambridge. Among Foster's pupils were Walter Gaskell (1847–1914) who demonstrated the cardiac effects of vagal stimulation: J. N. Langley (1852–1925) who performed important experimental work on the autonomic control of cardiac action and respiration: those master experimental neurologists, Charles Sherrington and Henry Head were products of Foster's school, as was Joseph Barcroft (1872–1947) who wrote an important work on the respiratory function of the blood in 1925 and investigated the consumption of oxygen in the tissues: and John Scott Haldane, (1860–1936) who in 1892 gave to both physiologists and respiratory clinicians the all important techniques and apparatus for gas analysis, and for the determination of haemoglobin values in 1901. Haldane's journey to Pike's Peak in 1913 as the culmination of his studies on the chemical nothing but a muscle differing but little from other muscles'. He postulated a nitro-aerial salt without which life cannot be maintained and which is derived from the inspired air. This important contribution was only to be fully appreciated 100 years later with the discovery of oxygen by Joseph Priestley of Birmingham, and with the fundamental work of Lavoisier on respiration and combustion.

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This is of a truly pioneering simplicity and Snow's work made possible considerable advances in anaesthetic techniques.

In considering the advances made in medicine by British doctors, I have tried to cover a few subjects in some depth rather than to give lists of comprehensive discoveries. I have omitted much. For example, the contribution to dermatology from the days of Daniel Turner (1667–1742) who wrote *De Morbis Cutaneis* in 1714 and who received the first medical degree to be awarded from Yale in 1723, through Henry Jackson (1750–1816) who in 1792 made the first attempts to classify skin diseases by pathology: to Robert Willan (1757–1812) and Thomas Bateman (1778–1821) who in the first decade of the nineteenth century determined the classical nomenclature of skin diseases which is still in use.

The Antibiotic Drugs

I will end with a brief note on the antibiotics, though I cannot do justice to so vast a subject.

The term antibiotic was coined as long ago as 1889 by Vuillemin, when certain living organisms were found to produce antibacterial substances, and many such organisms have been described since the time of Lister, who was himself interested in the antiseptic properties of a penicillium. Joubert in 1887 showed that following a sewing of aerobic organisms in a culture of anaerobes for example, the anthrax bacillus will inhibit the growth of the latter. Many other similar examples could be cited. Frost in 1904 introduced an ingenious technique whereby a collodion membrane kept two organisms apart, while diffusion of an antibiotic substance from one inhibited the other. Even extracts of penicillin were isolated as when, for example, Gosio in 1896 produced an antibacterial crystalline substance from a *Penicillium*, and a French medical student, Duchesne, described a mould active against bacterial infections.

It may also be noted that certain enzymes have been accredited with antibacterial properties. Thus Joyce and Donaldson in 1917 described the 'Reading bacillus', now known to be *Clostridium sporogenes*, which produced a proteolytic enzyme. Their work was of proven value in the wounds of World War I. More lately the protease streptokinase has been introduced into wound surgery. These are not antibiotics, but digestive ferments which remove dead or dying tissue.

This is of a truly pioneering simplicity and Snow's work made possible considerable advances in anaesthetic techniques.

In considering the advances made in medicine by British doctors, I have tried to cover a few subjects in some depth rather than to give lists of comprehensive discoveries. I have omitted much. For example, the contribution to dermatology from the days of Daniel Turner (1667–1742) who wrote *De Morbis Cutaneis* in 1714 and who received the first medical degree to be awarded from Yale in 1723, through Henry Jackson (1750–1816) who in 1792 made the first attempts to classify skin diseases by pathology: to Robert Willan (1757–1812) and Thomas Bateman (1778–1821) who in the first decade of the nineteenth century determined the classical nomenclature of skin diseases which is still in use.

The Antibiotic Drugs

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The Social Environment of British Medical Science and Practice in the Nineteenth Century

by

RUTH G. HODGKINSON

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The nineteenth century was to be in many ways a glorious age. In practically every sphere of life and for every section of the community it was a period of upheaval and acceleration. And there was close from the doctors, from reformers and from the new breed of Members of Parliament. Often it came in response to an urgent need or imminent catastrophe, but it was not always so. And historians who categorize on this forget the long time lapse before an idea became legislation. However dilatory, and for many reasons, the era of cooperation between medicine and the State was gradually brought into being.

So we now turn to the involvement between medicine, the people and the State created by industrial, agricultural and population changes. In 1800 there was an estimated population of nine million. By 1850 it was eighteen million and by 1900 thirty-three million. There was not only the problem of a tremendous natural increase in numbers but more so of an imbalance. Through the enclosure of land and more scientific farming, there occurred a great shift of people from rural areas to the towns and in addition there was the migration of domestic industry workers to the rapidly expanding industrial centres. Therefore the extensive conurbations which developed in Lancashire, Yorkshire, the Midlands and in southern Scotland had to cope with great natural increases in population, the flotsam and jetsam of society which flocked to them in search of work, the displaced village worker and also immigrants from overseas. Millions of starving Irish came, and later in the century political and Jewish refugees from continental Europe. Therefore there was a vast amalgam of people, used to different environments, ways of life and thought. The problem of integration was acute with important social, psychological and medical implications.

There has been enough rhetoric on the repulsive British urban areas. Speculators threw up conglomerations of shoddy back-to-back dwellings, where overcrowding, water supply, methods of sewage and refuse disposal and burial created great health hazards. Personal hygiene and cleanliness were impossible. Contagious and epidemic diseases found fertile breeding grounds. Family life barely existed. Promiscuity was general, so was very early childbearing. Malnutrition, food adulteration, poisoning, alcoholism produced great medical problems and all affected succeeding generations. Infanticide was very common, so was the abandoning of children and orphanage. In sum: life was nasty, brutish and short. The expectation of life was eighteen to twenty-five even in mid-century in some areas, and in addition to the high mortality rate there was impaired physique and from the doctors, from reformers and from the new breed of Members of Parliament. Often it came in response to an urgent need or imminent catastrophe, but it was not always so. And historians who categorize on this forget the long time lapse before an idea became legislation. However dilatory, and for many reasons, the era of cooperation between medicine and the State was gradually brought into being.

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As Britain was a great seafaring nation, one must briefly recall the plight of the sailors in their coffin ships, for whom no real medical care or safety regulations were provided until the 1870s, and of the passengers who were herded together in emigrant ships to Australia or North America. For them conditions only improved through individual agitation, often from doctors or local Boards of Health, who found one solution was the payment of ships' doctors on a basis of 'per live head' at the destination. As English commerce began to flourish, so the special difficulties of the ports were intensified. In addition to the strains imposed by urbanization, the ports were points of entry for many epidemic diseases, particularly cholera and smallpox. They were also points of entry for immigrants. The predicament of Liverpool invaded by hordes of starving Irish who could only be housed, a whole family together, in one dark damp cellar room, a den of fever or tuberculosis, is the classic example. But chaotic conditions regarding overcrowding and disease characterized most seaports.

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was a clearer recognition of the problems and an attempt to solve them. And there was the development of an incorruptible and more efficient civil service, both local and central, without which nothing could have been accomplished.

As community health was the most necessary branch of medicine in the nineteenth century, the general practitioner and the medical teachers who were interested in public health had the greatest role to play. A great number of the medical élite, the hospital 'consultant', the scientist, the teacher, involved themselves in public health and occupational medicine. As State intervention developed, it depended on the employment of the expert and special bodies. Doctors were the first experts used in many practical fields—because they had long personal contact and extensive experience of a wide range of needs. On special bodies, doctors were appointed to the Factory Inspectorate, the Poor Law Inspectorate, the Prison Inspectorate, as well as being used by the General Board of Health and later the Medical Office of the Privy Council as official investigators. And when the State personal medical service was established in 1834, many a humble Poor Law Medical Officer became a good public servant and a new important force, fighting for positive health measures and in the lead for sick care for the masses.

A very important innovation of the nineteenth century was the government inquiry, either on a national level or into a specific problem or a special area. Investigations were undertaken into conditions in factories or mines, the employment of women and children, occupational diseases and hazards, into sanitary conditions and public nuisances in towns, housing, the operation of the Poor Law and into the problems of the medical profession. All used laymen but also the expert. The rise of the expert had begun, so had a new role for the doctor, for he could give the most compelling evidence. There were far more inquiries than is generally realized because a large number were ignored and the material rested in obscurity to provide a mine of information for researchers today. But the reports of the main Select Committees and Royal Commissions made public official data, the facts and statistics which were so forceful that they could not be ignored. The revelations of the Children's Employment Commission of the 1840s and the almost annual Reports of the 'sixties shocked the Victorian conscience. So did the Royal was a clearer recognition of the problems and an attempt to solve them. And there was the development of an incorruptible and more efficient civil service, both local and central, without which nothing could have been accomplished.

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Indeed sections of education, factory and poor law legislation added together would produce a charter for child care and welfare, which by the end of the century presented quite a large, though still seriously inadequate, programme. This progress was of utmost value for the pediatrician, and without it he could not effectively have advanced his particular service nor his individual science.

This is only one example of the interdependence of personal and public welfare. Closely involved with the factory and education enactments was public health legislation. From the middle of the century the Nuisances Removal and Sanitary Acts and the Public Health Acts, especially those of 1848 and 1875, gradually removed the worst excrescences. For success there had to be effective administrative machinery. The creation of new Boards of Health in the cities and the rationalization of old local health authorities (there had been seven types including the fire service in the villages) followed closely on the setting up of the General Board of Health in 1848. This became the medical office of the Privy Council in 1858 and of the Local Government Board in 1871. The success of the British endeavour in the public health field is chiefly due to the outstanding achievements of two brilliant public servants. First, there was Edwin Chadwick, the indefatigable administrator who moved from Poor Law to Public Health because he saw the close connexion between the two. And then there followed John Simon. Simon, by training a surgeon and pathologist, but most important a scientist, soon turned to devote his entire life to Public Health. He was the instigator of many fruitful investigations employing individual doctors or teams to inquire minutely into every field of health. Often he cajoled private practitioners or hospital teachers with special knowledge to help, but the Health Inspectorate were his chief servants.

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State interference which indirectly greatly affected the health and wellbeing of the people, government activity, the medical profession and medical science came through the General Registration Act of 1836 with its amending Acts to enlarge the scope of census returns and the accuracy of registrations. Doctors were most closely involved in this great potential for progress although they did not always give complete or honest answers. (And medical science had not progressed sufficiently to make this possible.) The pictures obtained every ten years were imperfect and statistical analysis was still in its infancy; but taking death registration for example, a local and national survey of the causes of mortality was obtained. This aided Public Health reformers, those combating occupational ill health, disease and accidents, those interested in maternal and child welfare and medical practice and research. From mid-century there developed a profound examination and use of vital statistics by social reformers and medical men. In addition, Dr. William Farr's essays appended to the Registrar General's reports were monumental studies analysing census information. They too constituted a real break-through for medical and allied fields.

As Britain was the first country to industrialize, she was also the pioneer in both industrial medicine and factory legislation and these were closely related. Already in the late eighteenth century doctors and some laymen pointed to the consequences of the barbaric exploitation of women and children—and men. Government intervention began in 1802 but early Factory Acts were difficult to enforce for 'laissez-faire' had its strongest protagonists in the industrialists. Against them, William Cobbett in 1833 protested in Parliament that England's prosperity was based on the labour of 300,000 little girls. The Act of that year forbade the employment of children under nine years of age, established the Factory Inspectorate and introduced the Certifying Factory Surgeons. From the time of the Ten Hours hospital requirements was undertaken by the Poor Law Board in 1865 when they instituted the Cubic Space Committee to inquire into the desiderata of air, light, number of beds and sanitation in workhouse medical wards. This was the first committee of any kind consisting entirely of experts in the country's history—and these experts were the doctors.

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Last in surveying the close connexion between State activity, the health and welfare of the people and medical practice and science, we have to turn to medicine itself. After protracted controversy within the profession and difficult parliamentary sessions, the Apothecaries Act of 1815 successfully initiated the regularization and improvement of medical education, qualification and practice. Partly by compulsion, partly by its own efforts the profession began putting its house in order. And the greatest impetus was given by the Medical Act of 1858. The setting-up of the General Medical Council, as a controlling body to scrutinize practice and education and to suggest improvements in both, ensured progress towards a higher and more uniform standard, especially after its powers were extended in the following decades. The Act of 1858 was also a charter for the people, as it was intended to be, to help them choose competent practitioners and receive efficient treatment. The term 'general practitioner' had been coined in the first decade of the nineteenth century but only now began to be used widely. It is important to note that the State doctors, the Poor Law Medical Officer and Medical Officer of Health had to possess the double qualification in medicine and surgery and to be registered, so that the poor often had better qualified attendants than the wealthier sections of the community. However, it was not until 1888 that city Medical Officers were compelled to have special public health qualifications and this was not universal until as late as 1892.

Courses in Public Hygiene or Public Health were only slowly introduced. The Dublin and Edinburgh medical schools provided lectures and practical experience early in the century, but in England the pioneer, St. Thomas's in London, began a special course only in the 'fifties. In 1872 Dublin established a Diploma in State Medicine. In 1875 Cambridge offered the first Diploma in Public Health in England. The suggested title had been State Hygiene but the word 'State' was anathema to Victorians. The requirements for these qualifications were in the future to be taken as a standard by North America and all British colonies. But throughout the nineteenth century medical schools did not provide special courses for infectious diseases which were so predominant. Nor was any organized system of practical training insisted upon by the Government. The nearest await progress in medical science. Meanwhile, the Lunacy Commissioners did major work.

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Having studied how the State reacted to health questions and the unavoidable and salutary involvement of medicine, we must now review independent response and interaction within the private sector. As with medical science, the British achievement in social medicine depended very heavily on outstanding personalities, or public action generated by private endeavour. On the other hand, in lauding individuals or societies there is State involvement, for reformers were often government employees paid for their services, or the success of their ideas depended entirely on government enactments.

First, there were individuals who received national recognition: Edwin Chadwick, Dr. John Simon, Dr. Kay-Shuttleworth, Dr. Southwood Smith, Dr. Thomas Wakley, and Lord Shaftesbury who for fifty years fought for factory and mine workers, chimney sweeps, lunatics and public health. There was the little-remembered Dr. Rumsey who with great prescience for decades advocated a single comprehensive State health service. All these people battled for reforms in many fields. They understood the inter-relation of problems and that their solution depended on the integration of ways of improvement. Therein lay their greatness. There were local men thoroughly cognisant of local anomalies and working for their amelioration. In Manchester, there was Dr. Percival who formed the first Board of Health in the country, in 1795, from a group of volunteers; and Dr. Ferriar, Dr. Gaskell, Dr. Roberton and Dr. Kay-Shuttleworth who were involved in every social and health problem. In Leeds, there was Dr. Thackrah whose investigations in the 1820s and early 1830s earned him the title of 'the father of industrial medicine'. Elsewhere, men were at work and much was being investigated voluntarily and without financial reward. And there were strugglers into the chemistry of the nervous system. Government-sponsored research provided great stimulus to private research, and this occurred at the time when another revolution—the medical—had got under way. But this again was no isolated phenomenon, nor was it generated spontaneously. Much of it must be viewed in the context of all the preceding problems and the general acceleration in solving them which come within the broad interpretation of social medicine.

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Doctors read papers frequently; and Florence Nightingale was a most active member for fifty years. But every influential society contained a large number of medical men. They therefore received and gave much accurate and compelling information, and in turn realized their involvement in spheres often, though wrongly, regarded as outside their speciality. It is essential to stress the importance of all members with different interests learning from and helping each other.

In an age of nascent specialization there naturally arose the need for particular societies. In the mid-fifties the Metropolitan Medical Officers of Health Association was formed: the nucleus of the subsequent national society. Through John Simon this was closely linked with research. The Poor Law Medical Officers also established an association to struggle not only for their own rights, status and higher pay, but also for better care for their patients. Of special importance was the founding of the Provincial Medical and Surgical Association in 1832 which became the British Medical Association in 1856. Originally it was a fighting body and established several committees to deal with improving medical education, public health and the training and selection of Poor Law doctors. In 1868 the British Medical Association formed a committee on public medicine under one of the leading physicians in the country, Henry Acland, Regius Professor of Medicine in Oxford. This became a great pressure group for a long time for improving public health legislation, local health administration and death registration. It worked closely with the Social Science Association; and the General Medical Council itself came under its influence regarding special qualification for Medical Officers of Health. The British Medical Association thereby gave professional recognition to those who practised in the public health field. In the last decades of the nineteenth century its bias in State provision was strongly towards environmental rather than individual curative care.

The social history of medicine of the nineteenth century should include what the people who were most sadly involved thought and tried to do for themselves, and not only what was offered to them. So, briefly, at the other end of the scale of societies, there were the clubs of the working class, started through necessity and influenced by the teaching of self-help. The poor had a variety of self-help plans, Doctors read papers frequently; and Florence Nightingale was a most active member for fifty years. But every influential society contained a large number of medical men. They therefore received and gave much accurate and compelling information, and in turn realized their involvement in spheres often, though wrongly, regarded as outside their speciality. It is essential to stress the importance of all members with different interests learning from and helping each other.

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Physicians such as Southwood Smith had by this time recognized and publicized the knowledge that typhus was a product of poverty and insanitary homes and towns, and that the mortality rate increased noticeably with every trade depression. They were also aware that the incidence of tuberculosis was closely correlated with poverty and especially with overcrowding. Regarding cholera, Budd and Snow demonstrated that the infecting agent, although its identity was not known, could be controlled and isolated, and that the supply of pure water and efficient sanitation had reduced or actually eradicated the onslaught of epidemics. It may even be postulated that had the bacterium of cholera been discovered earlier, England would have been a far less healthy place at the end of the century, for the extensive field which the 'sanitarians' covered would not have come within their reforming activity. English physicians before the bacteriological age gave the world a clear lead in sanitary science and the wide field of Public Health. Epidemics, environmental diseases and occupational hazards provided a great stimulus to medical science. But the scientific revolution and its impact cannot be reviewed here, nor can the significance for the individual doctor and the patient of the developments for example in nosology, anaesthesia, aseptic surgery and aids to diagnosis such as auscultation and percussion. Even so, the curative potential in medicine and surgery at the end of the nineteenth century was limited, for the greatest proportion of doctors were slow in accepting innovations or did not have the means. The nineteenth-century revolution really bore fruit in the twentieth.

But in the field of social medicine, doctors helped the people and thereby medical practice in another way: by expressing an individual concern and by individual activity. To give but one example: Thomas Hodgkin (of Hodgkin's disease) was an eminent Guy's physician and a scientist but he also felt a deep involvement with all aspects of human welfare. He gave lectures to the Mechanics' Institute in one of the poorest sections of London, on every approach to health and personal hygiene, taking extremely wide definitions. These were published in a large volume and ran to a second edition. He studied and wrote on the training and method of selecting Poor Law Medical Officers, and on conditions in factories and hours of labour. (He protest against the circumstances which allowed 'fevers' to decimate whole areas.

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For the fortunate and for professional people, the publications of learned societies, the 'Transactions' or 'Proceedings' were of outstanding significance. The papers by Farr, Chadwick, Simon and Florence Nightingale for example, with their dramatic presentation of facts and statistics, shocked the government into action. And knowledge originally obtained by the relatively few was disseminated via the press. The working men's papers also snatched pertinent information for their causes.

Particular emphasis must be given here to the *Lancet* and the *British Medical Journal*, but there were many other medical journals and hospital reports which far more than today provided ammunition for all activities related to social medicine. From 1823 when Wakley, the 'Battling Surgeon', founded the *Lancet*, there was no field, no movement for reform which was not discussed in long editorials or articles. The journal was the voice of the small doctor and the eminent man. One has only to look at the index of a single volume taken at random. In addition, the *Lancet* undertook scientifically conducted inquiries with its team of special investigators. Of particular significance and with far-reaching salutary results were the inquiries of the 1860s into workhouse medical wards. Through these the government instituted its own investigations and the important Metropolitan Poor Act of 1867 followed. The *Lancet* reports on occupational disease and on the sweated trades, published over several years in the 1880s, resulted in a long House of Lords inquiry and again in legislation. Both the hospitals and medical education were subjects of detailed studies in the 1890s and extremely long informative and important during this era. Individuals were very prone to writing to Members of Parliament and government departments directly, and they received personal replies. That this was frequently effective is revealed in manuscript letters of doctors and health reformers. But above all, there was the influence and power of the printed word. Newspapers, broadsheets, journals and periodicals published information regarding grievances and their amelioration and this affected every sector of the community and included all fields. The enormous quantity of detailed analyses written and read by the educated middle class in their 'Quarterlies' and 'Reviews' is remarkable. Implicated again therefore in every sphere of progress was the promotion and advance of education.

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People were living longer, not as yet through medical advances but because their homes and towns were healthier and their standard of living had risen. Economic history should not be ignored by medical historians. After England became the workshop of the world, the economic prosperity made reforms possible and many improvements a matter of course in the fields of public health and occupational health. Also the explosion of curiosity gathered momentum so that every branch of science and technology provided fresh ideas and the means for advance.

By the beginning of the twentieth century, the whole field of preventive medicine was established. In 1874, there had been half a million deaths and Simon had pointed out that a quarter of a million were due to preventible disease. By 1900, the local government board was obtaining nearly 2,000 Annual Reports from local Medical Officers of Health. Industrial medicine and occupational diseases were also receiving significant recognition. Further, by the close of the century there were 4,000 Poor Law Medical Officers, 1,300 medical officers for education authorities, 2,000 factory surgeons and after 1911 the vast army of general practitioners engaged in the National Insurance service. Few doctors were as yet engaged full-time in any of these spheres. But none of the offices had even existed in 1800.

Despite the legislature's dramatic failure to establish a comprehensive health system when the moment was opportune in 1911, the involvement and contributions required of individual doctors, the medical profession and medical science assumed even greater dimensions. Medicine for long so narrowly conceived had within a century emerged from being a personal sickness service to become a dynamic partner with the social sciences. England here gave a clear lead to the world.

The people too became more involved with their own welfare. By the end of the century, they began to think in terms of Rights. They were growing conscious of their right to decent housing, decent environmental conditions, pay and pensions. They grew wise to the effects of malnutrition and became interested in efficient personal medical care. And education, trade unionism and working class political movements had made them aware that the means to satisfy their needs existed. They were also from then on anxious to participate in making improvements for their wellbeing. In the realms of medical

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The ideal of the 'whole doctor' is still with us. The nineteenth century demonstrated that where fear could not motivate individuals sufficiently, nor philanthropy or private effort cope adequately, then the State and the doctor marched together. Medical science can, and must continue to elucidate and interpret problems and suggest answers. But it is now only practicable for the State to provide the finance, the rationalization and coordination of all health and welfare services. The individualism of the scientist and the practitioner need not be stifled nor their work impeded; on the contrary, progress should gather momentum. The experience of the United Kingdom medical profession made it the practical pioneer in social medicine. When involvement is becoming more profound, will the British doctor meet the challenge and give a lead in furthering the complete health of mankind?

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Anatomy and Pathology

by

A. H. T. ROBB-SMITH

I FEEL DEEPLY honoured to be invited to participate in this symposium and yet I will confess that at first I was somewhat surprised that I should be asked to discuss two such disparate themes as anatomy and pathology. I soon realized that, as ever, Professor Gibson was very right in his allocation, for until quite recently normal and morbid anatomy were closely intertwined, the anatomist in his dissections discovering visceral abnormalities, while the physician or surgeon would learn and display the normal anatomy of the body while carrying out examinations on deceased patients; furthermore the concept of pathology as the study of the nature of disease at first was linked with morbid anatomy, but later was broadened to embrace bacteriology, haematology and chemical pathology and out of this evolved the diagnostic aspect of pathology.

To attempt a comprehensive review of British contributions in this immense field is clearly impossible and so I can but offer you a series of vignettes, and it may well be that I shall by this approach overlook matters of moment; furthermore I shall select as far as I am able those contributions which had a contemporary impact whether as original discoveries, new concepts or in the field of medical education.

Accordingly there is little to discuss until the early seventeenth century; it is true that John of Gaddesden's *Rosa Anglica*, written early in the fourteenth century, was by reason of its style a popular text for over 250 years; it was the first English medical book to be printed—at Pavia in 1492—and continued to be reprinted for over a century. It was the medieval counterpart to Osler's *Textbook*; easy to read, written from practical experience, though with a greater emphasis on therapy, while the aetiology or pathology of the various maladies were explained in terms of humoral dysfunction. In anatomy

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More important, not so much for what was said, but for their effect, were the writings of Dr. Walter Charleton (1619–1707), an Oxford graduate, physician both to Charles I and Charles II and President of the Royal College of Physicians; he was a versatile and prolific writer, on a whole range of subjects from the age of Stonehenge, wine, zoological classification, to anatomy and pathology, but it is his *Physiologia* of 1654 that released the inhibitions surrounding the atomic philosophy. In the Elizabethan period, a group of brilliant English scientists, led by Thomas Harriot had developed the atomism of Epicurus as a mechanical philosophy to facilitate their experimental observations, which were impeded by scholastic Aristotelianism, but atomism and its supporters were under grave suspicion of atheism, as the very concept called in question the immortality of the soul. Charleton was a man of outstanding piety and he set out to show that the atomism to which he adhered was not only philosophically sound but theologically purified, indeed a doctrine to promote piety; he used the word physiologia not in Fernel's sense of a study of the normal functions of the living, though in fact he did write the first English text on this subject—his *Natural History of Nutrition, Life and Voluntary Motion* (1659)—but in the wide sense of natural philosophy. Charleton's *Physiologia* made atomism respectable at a critical time, for it enabled scientists like Boyle and Newton to carry out their researches openly, without the very real danger of accusations of blasphemy, while in medical sciences it opened the way for the iatro-mechanical schools from which evolved vitalism. I felt it desirable to call attention to these two British contributions to the understanding of the nature of disease because they reveal the groping towards functional studies which in the future were to be of greater import than simple morphological observations and because it is often thought that after Fernel's *Pathologia* (1554)—the first attempt to display organic abnormality in disease—nothing of moment was achieved until Morgagni's great work two hundred years later.

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Edinburgh School of Pathology, Thomas Young one of the greatest intellects in medicine, Philip Syng Physick who brought the Hunterian tradition to the United States, and Edward Jenner, who in his modest way, mirrored most closely his master's enquiring mind. But there is one other of John Hunter's pupils to be named—the Reverend John Clinch, who had been at school with Jenner at Cirencester and remained his firm friend. He came out to Newfoundland as a missionary practising medicine as well; just before he left, Hunter wrote to Jenner, 'Give my compliments to Clinch and I hope to see him before he sets out for Newfoundland. If I do not, let him think of the white hares, to take a buck and doe and send them to me.' Whether the hares ever arrived I do not know, but Jenner sent Clinch some of his cowpox threads which he used effectively on some seven hundred people and was the first to use Jennerian vaccination in the new world.

As I mentioned a moment ago, Alexander Monro (1697–1767), trained under Cheselden, founded the Edinburgh Anatomy School and in due course arranged that his son, Alexander Monro *secundus* (1733–1817) should succeed him; he was a highly successful physician as well as a brilliant anatomist—commemorated by his foramen which is appropriate for he made important discoveries in the nervous system, and when he came to retire, following the family tradition, his son Alexander Monro *tertius* (1773–1859) took over the chair, but he was quite incompetent and this opened the way for the private schools. John Bell (1763–1820), a very able surgeon, soon attracted pupils, and in 1793, published his *Anatomy of the Human Body*, beautifully illustrated by his brother Charles' superb drawings, which became the first great textbook of anatomy, but he was so successful that James Gregory, the Professor of Medicine, organized a campaign of abuse and invective, that forced John Bell to give up his teaching and so he became the leading Scottish surgical consultant. Charles Bell attempted to take over his brother's classes, but the opposition was too strong and so he removed to London and succeeded to the Hunterian Windmill Street school; apart from his abilities as a teacher and artist, he was a first-class investigator, in particular in relation to the nervous system, discovering the motor function of the anterior roots which laid the foundations for subsequent developments in mapping out nerve paths and centres in the brain and cord.

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Thomas Hodgkin (1798–1866), Richard Bright (1789–1859) and Thomas Addison (1793–1860), whose achievements in clinicopathological correlations are rightly commemorated eponymously. In order to pursue his studies on renal disease, Bright established in 1842 one of the first clinical research units with a laboratory attached to the ward where the patients' urine and blood was examined by his students, Golding Bird (1814–1854) and George Rees (1813–1889), whose interest in the subject had been inspired by William Prout (1785–1850), rightly called the father of chemical pathology. The kidneys were examined by another of Bright's students, George Robinson (1821–1875) who published a paper on *Granular Disease of the Kidney* before his twenty-first birthday. The great triumvirate at Guy's were physicians who illuminated their clinical observations by morbid anatomy, though Hodgkin, who was not very successful in practice, spent more of his time in the museum with his microscope, than in the wards; but the London Colleges, which were going to evolve into the University of London, were appointing academic professors and it was from them that stemmed the study of experimental pathology, largely in abeyance since the death of John Hunter. The first medical lectures at University College were given in 1828, while the Medical Department of King's College, founded to counteract the godless non-sectarian Gower Street establishment, was opened in 1832.

The first professor of anatomy, morbid anatomy and surgery at University College was a quarrelsome Glaswegian, Granville Sharp Pattison (1791–1851) who was dismissed by the Council after four years and returned to the United States where he had already enjoyed a similar professorial settee and was later Professor of Anatomy at Philadelphia and New York. He was succeeded as Professor of Morbid Anatomy by Robert Carswell (1793–1857), who had been one of John Thomson's assistants in Edinburgh. He issued a coloured atlas of morbid anatomy with his own drawings, and though aesthetically inferior to Cruveilhier's great atlas, it reveals a more profound knowledge of pathology. Carswell had to abandon the chair owing to ill health, but he set a high standard which successive holders have certainly maintained. After some initial appointments, anatomy at University College London, became the responsibility of the brothers Quain, Richard (1800–1887) being concerned with des-

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A very important event in the development of morbid anatomy was the founding of the Pathological Society of London in 1846 by a group of physicians from Guy's and University College which continued to flourish until 1907 when it merged with other societies to form the Royal Society of Medicine. Its transactions have been called a museum in print and form an invaluable store house of information.

This was also the period of prebacteriology, when men were looking for the cause of communicable diseases and sepsis, wondering whether it was the environment or a specific agent and gradually amidst all the confusion and controversy ideas became clearer, and in this British scientists played their full part: Budd, a Bristol physician; Snow, a London anaesthetist; Sir John Simon, a surgeon pathologist; Lord Lister, another surgeon; Burdon Sanderson, a medical officer of health for Paddington; and there were distinguished men ranged against them, also conducting experiments to uphold their views on spontaneous generation or heterogenesis, men like Hughes Bennett, Charlton Bastian and Lionel Beale.

I shall not attempt to give an account of this work, though it would have been profitable to consider the achievements of Sir John Simon in pursuading recalcitrant politicians and civil servants to support scientific research, or of the importance of the Brown Institution, the first laboratory established in England for experimental pathology, which is apparent even by naming the Professor Superintendents: Burdon Sanderson, W. S. Greenfield, C. S. Roy, Victor Horsley and Charles Sherrington.

However, I must mention one of the opponents of the germ theory, not because of his ideas on the subject but because of his influence on clinical pathology in England and in this country. Lionel Smith Beale (1828–1906), before he qualified spent two years as a research assistant to Sir Henry Acland who was trying to persuade the University of Oxford that science was a proper part of academic education and it was here that Beale realized the potentialities of the microscope as a diagnostic weapon. On qualification he became resident physician at King's College Hospital, where he did an enormous amount of important research and gave lecture demonstrations on the 'Microscope in Medicine'. At the age of twenty-four he succeeded Bowman

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It was Osler's friend Francis Shepherd (1851–1925) who revolutionized anatomical teaching at McGill, gaining international recognition, and until his retirement in 1914, was Dean of the Medical Faculty, and it was Osler who encouraged Whitnall to exchange Oxford for Montreal. However, after Osler left for Philadelphia, pathology had to wait for a few years for its revival, though one should not forget that Bishop's College admitted women students, amongst them a Miss Maude Abbott and that Sir Andrew Macphail (1883–1966) was Professor of Pathology there.

It was a matter of considerable good fortune that when Canada decided that it was time to appoint professional pathologists, she looked not to the orthodox morbid anatomy of the Scottish schools but to the experimental pathology of Cambridge. You will be aware that Sir George Humphry, the Professor of Anatomy, anxious to establish a department of physiology at Cambridge, attracted Michael Foster, one of William Sharpey's pupils at University College and of the flowering that took place. The Professor of Pathology was C. S. Roy who shared in this experimental approach and it was one of his most brilliant pupils, George Adami, who came to McGill in 1893 as the first Strathcona Professor of Pathology and there could not have been a happier choice; he revolutionized the teaching and the practice of pathology. His *Principles of Pathology* expressed in a masterly manner the very philosophy of the subject, while his textbook written with his assistant, the poet pathologist John McCrae, became the standard text for medical students; his writings stimulated young pathologists all over the world and his pupils filled the chairs of pathology of the Canadian and American medical schools. He appointed Dr. Maude Abbott as curator of the Pathological Museum and it was a specimen in that museum of a remarkable congenital heart, placed there in 1823 by Dr. Andrew Holmes, one of the founders of the McGill School, that stimulated Dr. Abbott to become the world authority on this condition. But George Adami was not the only pathologist that Cambridge gave to Canada. Frank Wesbrook, a this came his work on bacterial endocarditis and the anatomical changes in congenital bicuspid aortic valves—but I must stop this catalogue which has emphasized, I hope, some of Osler's personal contributions to morbid anatomy and clinical pathology quite apart from the importance he attached to these subjects in medical teaching.

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Another of Adami's lecturers was Oscar Klotz who was appointed to the Chair of Toronto in 1923 but before considering the effect of this appointment I must go back to an earlier Toronto period. Arthur Ellis, son of the Professor of Chemistry, graduated there in 1908, spent some years at the Rockefeller Institute and then was in charge of a mobile laboratory with the C.A.M.C. and there is a photo of him on leave in Oxford, with the Consoler General, little thinking that twenty-five years later he himself would become Regius Professor and play a part in re-opening 'The Open Arms'. Sir Arthur Ellis became the Director of the Medical Unit at the London Hospital, but he was at heart a pathologist as his important work on kidney disease shows. He was also influential in attracting Canadian pathologists to Great Britain—Hugh Maitland, a distinguished virologist, left Toronto to become Professor of Bacteriology at Manchester, and another virologist from Toronto, my colleague Freddie MacCallum whose long-standing interest in virus hepatitis has clarified its complexities; speaking of colleagues, I cannot omit Roy Vollum, a Rhodes scholar from this university, who died a month or so ago, famous for his work in tuberculosis and leprosy.

When Klotz returned to Toronto, he had already held two chairs and was internationally famous both for his work on atherosclerosis and his knowledge of yellow fever. He was a stimulating and inspiring teacher both for students and the research workers he drew to Toronto; he certainly had a profound influence on Banting, Best, Macleod and Collip. It is interesting to note that at the first meeting of the Canadian Physiological Society held in Toronto on 19 October 1925, there was a paper on the experimental production of coronary thrombosis and myocardial degeneration by Hall, Ettinger and Banting, and another by Collip and Selye on acute fatty liver following partial hepatectomy, thus upholding Michael Foster's view of the essential unity of pathology and physiology; as he said, what would be thought of meteorology if it were divided into two separate sciences dealing respectively with fine and bad weather? Probably Klotz's most distinguished pupil was Lyman Duff who succeeded to the Strathcona chair in 1939 and so continued the Adami tradition with his work on atherosclerosis which is maintained by his pupil More today. His opposite number in bacteriology was E. G. D. Murray, a fiery Cambridge man who under Montreal's

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Professor Gibson, I recognized that I was quite incapable of carrying out the task which you so generously allotted to me 'British Contributions in Anatomy and Pathology', as the field was too great and my knowledge insufficient, and so as you will have realized, I have cheated and for the last part of this address have restricted myself to Canadian contributions in these fields and I fear by ignorance or forgetfulness, may well have omitted some important names and if so I can but apologize. I hope I have shown, if only superficially, the importance of interplay between all the fields of biological endeavour, pathologist to that hospital and has played a major role in the development of clinical pathology as a special discipline. Well, as you know, Boyd was appointed and by his writings and his art of teaching has revolutionized the comprehension of pathology throughout the English-speaking world. He succeeded Klotz as Professor of Pathology at Toronto and since I met him last, he has been with you at U.B.C., and is now enjoying his retirement at Willowdale. At this time there was not only superb teaching in pathology at Toronto, but in anatomy as well, for Boileau Grant was bringing the subject alive, illuminated by his flare for anthropology. This teaching tradition has been maintained by the present holder of the chair Arthur Ham, whose enthusiasm and research has been directed towards fine structure. It is interesting to see that at last the anatomists have wrested back histology, stolen from them by William Sharpey over a hundred and fifty years ago, and the resurgence of research that has resulted from this; in part due to the new dimension provided by the electron microscope, first made a practical proposition by Albert Prebus and James Hillier in Professor Burton's old department at Toronto, but also by intelligent looking. A magnificent example of this is the discovery of the significance of sex chromatin by Murray Barr and his colleagues at Western Ontario in 1949; this dark staining mass at the side of the nucleus has been apparent for the last hundred years to every microscopist looking at a cell stained in the most ordinary way, but it was Barr who discovered that it was only to be seen in females and from this observation has developed a vast and important field of research in intersex and gonadal endocrinology. It is a discovery which would have delighted the heart of John Hunter with his interest in hermaphrodism and thrilled Sir William Osler who had recognized the platelet in just such a way.

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Tropical Medicine

by

ANTONY DUGGAN

THE CONTRIBUTION which you have invited me to describe is a vast and complicated tapestry of human endeavour woven by innumerable hands across the face of the earth and fashioned by that strange combination of genius and serendipity which has attended so many of the great achievements of science. This tapestry was woven in many pieces, for until comparatively recently those who fabricated it were scattered throughout the world, often working in isolation and conducting their enquiries with little more than their self-determination and, let us admit, their eccentricities, to urge them on. While our clinical disciplines were being forged in the great teaching hospitals of the nineteenth century, only an occasional portent of tropical medicine could be discerned, far away, in recesses of the world known only to missionaries and explorers. To help us thread our way from these inconspicuous beginnings to the attainments ultimately reached, I shall, from time to time, highlight a single continuous line of progress down the years, and try to show how it reflected the nature and the circumstances of British endeavour in the many other departments of tropical practice and research.

The line which I have chosen is that of trypanosomiasis, and the earliest British contributions to this subject were those of Thomas Atkins,[4] a naval surgeon who described the neurological symptomatology of sleeping sickness in 1734 and Thomas Masterton Winterbottom,[97] likewise a mariner, who in 1803 observed the cervical adenopathy common in that disease, a sign which still carries his name. During the next eighty years many more clinical references were made to this condition, largely by medical officers of the military forces who manned trading posts along the West African coast.

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Trypanosoma evansi, the first known blood-borne pathogenic protozoon.[37] In 1885 D. D. Cunningham[29] described, but did not name, the causal organism of that ancient affliction, oriental sore, and in 1887 David Bruce on a visit to Malta demonstrated a bacterium now known as *Brucella melitensis* in the spleen from a case of undulant fever.[13]

Meanwhile, at the Conference of Berlin in 1885, the western powers affirmed their intentions of promoting the moral and material well-being of native populations in newly-annexed territories overseas. The French, under the impetus of Pasteur and Laveran, who had already achieved immortality by discovering the parasite of malaria, soon established the Saigon Institute in Indo-China under the direction of Calmette in 1889, but the British responded with less alacrity; but in that year a doctor by the name of Patrick Manson returned home to Scotland after an absence of twenty-three years in the Far East. During his last years there he had practised in Hong Kong and had become Dean of the proposed College of Medicine in 1887. One of his earliest pupils was Sun Yat Sen, of whom more was to be heard. Manson had had a singularly successful career, and intended to retire, but his fortunes became seriously affected by the fall in the exchange rate of the Chinese dollar, and thus he came to London and set up in practice in 1890. Like so many tropical clinicians of that time, he was a born naturalist and he had already made three important discoveries in the field of parasitology, having to his credit fundamental contributions on filariasis,[60] paragonimiasis[62] and sparganosis.[26] In all this he had been greatly supported by T. Spencer Cobbold who had done so much to systematize the subject of helminthology, and in whose judgement the discovery of filariasis was a complex series of observations for which Wucherer, Lewis, Bancroft[25] and Manson deserved equal merit. Of the three British workers it was Manson who not only established the law of filarial periodicity, but by an inspired rather than logical piece of reasoning concluded in 1877 that the vector of the parasite was a night-biting mosquito.[61]

The concept that insects conveyed disease to man was not new. Several tribes in West Africa had associated tsetse flies with the transmission of sleeping sickness for so long that the belief had passed into tribal lore. Lancisi[50] in 1717 advanced the theory that mosquitoes might carry the agents of disease. In 1806 Ninian Bruce[15]

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By 1894 Manson was convinced that British progress in tropical medicine was being outrun by the Germans and the French. Of the great fundamental discoveries up to that time, only in filariasis research could it be said that the British had played a major part. Perhaps the greatest blow to his esteem was the contribution to the knowledge of plague made in Hong Kong by the Swiss Yersin[99] and the Japanese Kitasato,[49] pupils of Pasteur and Koch respectively. In April of that year Manson had his historic meeting with Ronald Ross. Manson's mosquito/malaria hypothesis, influenced by his researches into filariasis and expounded by him in the Gulstonian lectures in 1896,[63] had already begun to germinate in his mind, and his friendship with Ross and the guidance which Manson gave him during his subsequent researches in India finally led to the demonstration, in 1897, that the malaria parasite developed in a mosquito.[84] At practically the same time MacCallum,[56] of Ontario, working with bird malaria, explained the significance of the parasite's exflagellation.

The drama surrounding these discoveries and Manson's subsequent experiments has been described from many points of view including that of Manson's son-in-law Sir Philip Manson-Bahr,[65] and the sequence of priorities, with which we are hardly concerned, is debated even to this day. But there can be no doubt about the telegram which Manson received in September 1900 which ran 'Salute Manson who first formulated mosquito/malarial hypothesis'. The cable was signed by Grassi, leader of the Italian school of malariologists. Manson had not seen a malaria parasite before 1890 and it is remarkable that he should have merited such an acknowledgement only ten years later.

Another contribution of a totally different kind was made in those stirring times. In October 1896 Manson and the surgeon James Cantlie, a friend from his Hong Kong days, rescued their former pupil Sun Yat Sen from his imprisonment in the Chinese Embassy in London. The destiny of this young man was thus diverted from a barrel at the bottom of the Thames to the first Presidency of the Chinese Republic. Perhaps an equally important development, however, was Manson's appointment to the British Colonial Office in 1897, a post which gave him access to that remarkable statesman, Joseph Chamberlain, who was quick to realize the paradox that the Second World War, and for part of this time published its own journal which was called *Climate*.

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It would take many hours to describe fully the events of this momentous decade, the last of the nineteenth century. In all things the influence of Patrick Manson was the driving force in establishing the basis of scientific tropical medicine and the means to disseminate it by precept and example throughout the world. Little wonder that in August 1913 at the International Congress of Medicine in London he was hailed, not by a Briton but by Raphael Blanchard of Paris, as the 'Father of Tropical Medicine'.[10]

As things turned out, his accomplishments came only just in time. From 1896 onwards a great epidemic of sleeping sickness had been fulminating in the Congo basin and it is now generally believed that between 1896 and 1906 half a million people lost their lives on this dire account. Possibly as an extension of the disease from this area, British possessions on the northern shore of Lake Victoria became involved in an outbreak of large proportions. Possibly the first to note this event were two missionary brothers, Albert and Howard Cook,[27] who practised at a hospital in Mengo, Uganda, and whose excellent work has been recognized only in recent times. The Lake Victoria outbreak was confirmed in 1901, and the response of Manson and his co-workers was immediate.

In 1900 Manson had been made a Fellow of the Royal Society and undoubtedly due to his influence and that of Joseph Chamberlain the Society dispatched a Commission to investigate the disease, the cause and transmission of which was then unknown. The Commission had, of course, no means of controlling the outbreak, and the afflicted population was reduced from three hundred thousand to about a third of that number by 1908, but in the years between the Commission's arrival and the end of the epidemic, Castellani[19] established that the causal organism was a trypanosome and Bruce,[14] who had shown in 1895 that cattle trypanosomes were transmitted by tsetse flies, proved that sleeping sickness was carried by the same agent. Meanwhile, Dutton[35] of the Liverpool School demonstrated trypanosomes in the blood of a sick European in the Gambia, and it remained only for Adams[1] to propose that this condition, known as trypanosomal fever, was the early stage of the epidemic disease on the shores of name proudly among the major medical research establishments in Asia. In India the Pasteur Institute was opened at Kasauli in the same year.

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The period between 1900 and the outbreak of the Second World War might be termed that of colonial tropical medicine. The official reports of experts on Commissions and in research institutions conveyed the British sense of moral responsibility for health in tropical dependencies. In 1909 Sir William Osler exclaimed, 'Surely no nation in history has ever had such a load of responsibility towards the health of people overseas'.[71] Hitherto, official medical services had been based upon the cantonment system and orientated towards the prevention of high mortality rates among officials. Within a decade of the establishment of tropical medicine as a special discipline determined efforts were being made to alleviate suffering among all those living wherever British rule held sway.

Neither were these efforts solely those of officialdom. There was opportunity for a more enlightened kind of philanthropy than the frenetic urges of the nineteenth century which had sent innumerable explorers and missionaries to their deaths. Henry Wellcome, industrialist and confidant of the explorer Stanley, visited the Sudan in 1901, only three years after Kitchener's pacification, and established his research laboratories at Khartoum under Andrew Balfour in 1902. His famous floating laboratory was taken up the Nile by Charles Wenyon in 1907, and his first museum was presented to the Sudanese Government in 1912.

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After the First World War British commitments in Africa were greater than ever before. Efforts to obtain an improved drug for sleeping sickness were redoubled and the Colonial Office subscribed no less than £50,000 for the investigation of methods of treatment. Research organizations were set up in East and West Africa for investigation into trypanosomiasis of man and animals. One such department was established in Northern Nigeria under Johnson and Lloyd in July 1921, and this enterprise was replaced by a control organization ten years later. In Uganda in 1927 Lyndhurst Duke became the first director of the Trypanosomiasis Research Institute, and its descendant, the present East African Tsetse and Trypanosomiasis Organisation, still continues to contribute to the knowledge of tsetse and trypanosomiasis from the Nile to the Zambesi.

Great epidemics of sleeping sickness struck the British territories in Africa, particularly in Nigeria and Tanganyika, during the 1930s, and no efforts were spared to overcome these outbreaks. In Eastern Africa the whole strategy of the fight against tsetse fly became integrated with land reclamation and resettlement, and in Nigeria a grant of £95,000 was made in 1936 from colonial development funds to undertake a classic experiment in trypanosomiasis eradication had given an impetus to modern chemotherapy. Although the German worker Paul Erhlich was the chief force in the experimental work involved, H. Wolferstan Thomas of McGill University, working at the Liverpool School, tested the arsenical atoxyl, which had previously been used for the treatment of skin diseases.[91] Having given it to himself in large intravenous doses, he and Breinl recommended its use against sleeping sickness in 1905[92] and it was thereafter used for treatment until the introduction of suramin sixteen years later, a product of traditional German research work into the aniline dyes. It is interesting to recall that David Livingstone had suggested the use of arsenic in 1858[55] for the treatment of the wasting disease of cattle conveyed by tsetse bite which is now known to be a form of trypanosomiasis, and that the aniline dyes were introduced by another Englishman W. H. Perkin in 1856[72] who stumbled on aniline purple while trying to synthesize quinine, and commercialized his discovery at a factory near Hounslow. From this chance synthesis by a somewhat eccentric British chemist the azo dyes on which Erhlich worked, came into existence.

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A great deal of research was performed in British laboratories during the colonial period. In the field of protozoology, Dobell and Wenyon, the Director-in-Chief of Wellcome's Laboratories, redressed the balance of authority which continental workers had obtained during the nineteenth century. Dobell's classic work *The Amoeba Living in Man* was published in 1919[33] and Wenyon's monumental *Protozoology* which has recently been reprinted without the change of a syllable, appeared in 1926.[94] In 1925 a malaria reference laboratory was established at Horton near London and experimental work of the highest class has emanated from this institution ever since. In the following year the Ross Institute was opened and was amalgamated with the London School of Hygiene in 1934.

During these years which saw the flowering of the Manson tradition, there was continued awareness of the obligations which the establishment had to fulfil. Manson-Bahr, the son-in-law of Sir Patrick Manson, said at a meeting of the Cambridge Medical Society in 1936,[64] 'On no other people does a burden of Imperial responsibility rest so heavily as on the inhabitants of this small island', and Worthington[98] in 1938 drew a convincing picture of all that was involved in discharging those obligations in Africa alone.

Yet in spite of the efforts of men such as Andrew Balfour,[7] one may remain impressed as much by the lack of overall co-ordination in the work, as by the energy and ingenuity of those responsible for it, sharing, perhaps, the wonderment of the German writer Stoye[89] who believed the British Empire to be the outcome of the not easily intelligible English character and therefore as unsystematic and as illogical as the Englishman himself. But in those days the British contribution to tropical medicine was based, like the colonial system, on a great variety of scattered units in which every officer from the Governor downwards was pledged to foster local interests. Nothing of this could be sacrificed on the grounds of administrative simplification. When Stanton, the Canadian, left Malaya in June 1926 to which broke out among Tamil labourers in 1915. This finally proved to be the same condition that Whitmore had described in Rangoon a few years before.[95] Stanton, after a prolonged study, named the disease melioidosis[87] and, with his successor William Fletcher, compiled a monograph on the subject which still remains the standard work.

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In 1943 the United Nations held a Conference at Hot Springs, Virginia, at which the Food and Agriculture Organisation was conceived. It is to the credit of the British that one of the key documents of this Conference was *Nutrition in the Colonial Empire*, a far-seeing report published in 1939 but largely ignored owing to the exigencies of the international conflict. This Organization, now known as FAO, held its first conference at Quebec in 1945 and the involvement of British experts in so many of its activities during the last twenty-five years was a portent of a new international era. The immediate problems were vividly defined by Platt[73] who showed that the British responsibilities involved 66 million people in 44 territories spread over 2¼ million square miles.

Once the War was over the British found themselves in the anomalous position of having an impressive tradition in tropical medicine and greater curative and technical resources than ever before, while being committed to a policy of imperial disestablishment. In 1947 this process began with the achievement of world status by India. It has been emphasized by Sir George McRobert that this development had been long anticipated. Indeed, Lord Elphinstone, speaking of the Indian Empire in the middle of the nineteenth century, said that the 'most desirable death for us to die should be the improvement of the natives to such a pitch as would render it impossible for a foreign nation to retain the government'.[67]

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Meanwhile, in New Guinea the Australian worker Zigas and the American Gajdusek[100] discovered the extraordinary neurological syndrome of kuru and opened up a completely new field of exciting scientific speculation and research into slow virus infections of the central nervous system.

With the advent of the 1960s came the modern political age, and within a few years the colonial apparatus became virtually extinct. With the birth of new tropical nations the realization dawned that in those countries a balance must be kept between the improvement of health and the other processes of social and economic development. Although the ideal of communicable disease control, which was the principal aim of classical tropical medicine, could be fully justified on scientific and humanitarian grounds, the expense of eradicating these infections was far greater than had been foreseen, and indeed required resources of global proportions. In the preface to his classic work Dobell writing of the fundamental problems of human amoebiasis stated that no one man could ever succeed in solving the problem. These prophetic words can also be applied to malaria, sleeping sickness and leishmaniasis. Notwithstanding Manson's early triumph, Beaver[9] has recently expressed his belief that filariasis remains the most elusive of all the helminthological problems. As Ayé reminded us in his presidential address to the 23rd World Health Assembly, almost two-thirds of mankind are still exposed to all the diseases which have accompanied their development.

The British contribution to this situation is difficult to define. To begin with, the very nature of tropical medicine has changed; secondly the active participation of great international agencies has promoted such an intermingling of workers that national distinctions have been almost swept aside. Thirdly, the last decade has brought scientific discoveries whose significance has infiltrated into the realm of medicine everywhere, and lastly we are living in a period so close to these before this puzzling disease was being investigated throughout tropical Africa by sophisticated methods of cardiological investigation. Davies also instigated the first cancer registry in Eastern Africa and in 1958 Denis Burkitt[16] described the malignant lymphoma which bears his name, the cytological and virological aspects of which have since occupied the attentions of research workers all over the world.

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At the second Commonwealth Conference held at Kampala in 1968, the agenda included matters concerning family planning which was considered of such importance that the papers on this subject occupied 100 pages of the Conference Report.[74]

Since political self-determination has come to the tropics, British aid has been used for building and equipping hospitals, training doctors, nurses and technologists, and supplying specialized staff. The Ministry of Overseas Development supports twenty-one lectureships at London and Liverpool and makes it possible for their holders to be posted overseas when required. Links have been formed between British and overseas medical schools. An early association was established between Great Ormond Street Hospital for Sick Children and Mulago Hospital in Uganda. Arrangements between the Glasgow Medical School and the University of East Africa made it possible to establish in Nairobi the sixth medical school in commonwealth Africa.

Close links have been forged between the Liverpool School and Thailand, and between the Royal Postgraduate Medical School and the Medical Institute at Chandigarah in India.

Financial provision has enabled a 900-bed hospital at Mulago in Uganda to be opened in 1962, and the opening of the Queen Elizabeth Hospital in Hong Kong in 1963. More recently £2.8 million has been made available to the University Hospital of the West Indies, and nearly £3.5 million for hospitals in Malta, Mauritius, Fiji and the Maldive Islands.

In recognition of population growth as a retarding factor in development the Ministry has established a Population Bureau for aid in family planning. In financial terms, £100,000 has been provided for the International Planned Parent Federation and £40,000 to United Nations for population investigations.

Grants for co-operation with W.H.O. and U.N.I.C.E.F. totalled £2 millions from British sources in 1969. In terms of medical and veterinary research specifically directed to tropical problems, £870,000 sponsored courses. Australian assistance to Malaya was accompanied by Malaysian assistance to Hong Kong, India helped Uganda, and Nigerian facilities were provided for Gambia. Here in Canada nearly half the overseas students in medical schools are from the Commonwealth.

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Close links have been forged between the Liverpool School and Thailand, and between the Royal Postgraduate Medical School and the Medical Institute at Chandigarah in India.

Financial provision has enabled a 900-bed hospital at Mulago in Uganda to be opened in 1962, and the opening of the Queen Elizabeth Hospital in Hong Kong in 1963. More recently £2.8 million has been made available to the University Hospital of the West Indies, and nearly £3.5 million for hospitals in Malta, Mauritius, Fiji and the Maldive Islands.

In recognition of population growth as a retarding factor in development the Ministry has established a Population Bureau for aid in family planning. In financial terms, £100,000 has been provided for the International Planned Parent Federation and £40,000 to United Nations for population investigations.

Grants for co-operation with W.H.O. and U.N.I.C.E.F. totalled £2 millions from British sources in 1969. In terms of medical and veterinary research specifically directed to tropical problems, £870,000

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Biochemistry

by

J. H. QUASTEL

I HAVE THE privilege of addressing you on British contributions to biochemistry. It is not possible to do justice to this subject in the time at my disposal. I have therefore decided to deal with some early aspects of the growth of biochemistry in Britain, to dwell on a few items with which I am personally familiar and to give some of the highlights as I see them today.

Although biochemistry was born of two parents, chemistry and biology, it was nourished almost entirely in its early days in Britain by physiology. If we turn to the classical text on physiology written by Michael Foster towards the close of the last century, we find in it a section entitled 'The Chemical Basis of the Animal Body'. This section, composed by Sheridan Lea, epitomizes what might be considered to be the biochemistry current in the late Victorian era. It considers the animal body to be a mixture of various representatives of three large classes of chemical substances, namely, proteins, carbohydrates and fats, but it also considers the animal body 'as made up on the one hand of actual living substances and on the other hand of numerous lifeless products of metabolic activity'. 'We know nothing,' he states, 'about the molecular composition of the active living substance but when we submit it to chemical analysis we always obtain from it a considerable quantity of the material spoken of as protein.' Thus current thought, at the time, envisaged the living cell as made up of something endowed with life or having the essence of life, together with a variety of lifeless products such as might be found at any time on the laboratory bench. A revolution in this line of thought was to take place in the next two or three decades and this was due in no small measure to the development of biochemistry in Britain. It must not be thought, however, that

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Thus we can say that events of importance in the development of biochemistry did take place in Britain during the last century but the focus of activity lay in Germany. Major changes were about to take place in Britain and they were set in motion by Hopkins and his colleagues in Cambridge and by Harden and his colleagues in London.

The turning point for biochemistry in Britain came at a meeting of the Physiological Society of Cambridge in May 1898. Here, Michael Foster, then Professor of Physiology in Cambridge, invited Hopkins, who was at the time a physician in Guy's Hospital, London, to Cambridge to develop teaching and research on the chemical aspects of physiology, a subject which had fallen on evil days. One of Foster's pupils, Sheridan Lea who was engaged in this work, had fallen ill and his place had to be filled. It must be remembered that, at that time, biochemistry, as a recognized branch of scientific study, existed nowhere in the world under that name, though, as already mentioned, the subject, as a branch of physiology, had achieved a measure of independence, not without opposition, in continental Europe. Hopkins accepted Foster's invitation, together with a large fall in salary, for he had to abandon his medical practice and we have to be grateful to his wife that she did not dissuade him, but, on the contrary, encouraged him in this venture. The isolation and identification of tryptophan, as a new amino acid constituent of most proteins, was an important achievement in itself, but it had great consequences for it led to the opening up of a new chapter in biochemistry. Hopkins set about testing the importance of individual amino acids, and particularly tryptophan, in the protein part of a diet. Hitherto the concept of an adequate diet had been in terms of proteins, fats and carbohydrates and scant attention had been paid to anything but crude energy values. But Hopkins and Willcock, in 1906, included Thudicum, the founder of neurochemistry, whose treatise *Physiological Chemistry of the Brain* appeared in London in 1884. He and his colleagues isolated and characterized many of the substances present in brain and gave them names, such as cephalin, phrenosin, sphingomyelin, sphingosine, cerebronic acid, with which we are all familiar today. After Thudicum's death in 1901 systematic work on the chemistry of the brain practically stopped and did not start again until almost thirty years later with a re-awakening of interest in Britain, particularly in South Wales, and in Germany.

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Another investigator, among so many who had fallen under the spell of the teaching and inspiration of Hopkins, was Laidlaw who worked on the fate of tyramine in the body, and Dale and Laidlaw investigated the extremely powerful action of histamine, which their work on ergot had just revealed. What is now called biochemical pharmacology was being opened up in Britain. Laidlaw's later work was outside the normal field of biochemistry and was concerned with immunity reactions, particularly of viruses, and he discovered that influenza was a virus disease.

Many examples can be given of Hopkins' influence on a whole generation of biochemists in Britain and testify to the enormous effect on scientific development of a school of science that has an inspiring teacher and investigator at its head.

Apart from his work in the field of nutrition, Hopkins developed a theme which was fundamental to the development of biochemistry. When Hopkins entered the field of biochemistry, he found it dominated by the idea of 'biogen' a great molecule within which obscure, and possibly incomprehensible, chemical changes were taking place.

Hopkins did his best to show how processes of intermediate metabolism might be dissected into recognizable chemical reactions catalysed by enzymes whose numbers were growing every day.

lack of exercise, or forms of infections, were not the cause of rickets and that a dietary deficiency was a primary essential cause. He showed that there was something present in cod liver oil but lacking in vegetable oils that was essential for the prevention of rickets. Later work, outside Britain, by McCollum, Steenbock and others showed that calciferol (Vitamin D_2) was the causative factor and nowadays commercial vitamin D is obtained by irradiation of ergosterol. Mellanby's pioneer work, following that of Hopkins, is one of the outstanding points of new departure in the advance of biochemistry in relation to nutrition and was profoundly stimulating of further enterprise. Perhaps, however, Mellanby's greatest contribution to biochemistry in Britain was his influence on biochemical support when he became Secretary of the Medical Research Council. Many, including myself, owe much to his help and encouragement. In fact the Medical Research Council in Britain, under the leadership of such men as Fletcher and Mellanby has had a major influence on the growth of biochemistry in Britain.

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Many examples can be given of Hopkins' influence on a whole generation of biochemists in Britain and testify to the enormous effect on scientific development of a school of science that has an inspiring teacher and investigator at its head.

Apart from his work in the field of nutrition, Hopkins developed a theme which was fundamental to the development of biochemistry. When Hopkins entered the field of biochemistry, he found it dominated by the idea of 'biogen' a great molecule within which obscure, and possibly incomprehensible, chemical changes were taking place.

Hopkins did his best to show how processes of intermediate metabolism might be dissected into recognizable chemical reactions catalysed by enzymes whose numbers were growing every day.

sinks, effective fume cupboards, adequate shelf space, a good balance room and a splendid library. Such luxuries we did not have in the old laboratories and yet, there, much of importance emerged. Glutathione for example was born there.

While these events which I have briefly described were taking place in Cambridge, momentous events were occurring in London. The Lister Institute was one of the few places in England where biochemistry was taking its new form and Harden and his colleagues were at work on the chemistry of fermentation. Buchner in 1897 in Germany had made the fundamental discovery that yeast juice, which was cell-free, could bring about the conversion of glucose into alcohol, thereby disproving the contention of Pasteur that the act of fermentation was indissolubly connected with the life of the yeast cell. In fact, the discovery by Buchner, together with the earlier work of Wöhler, did much to demolish the concept of vitalism, i.e. that there existed a 'vital force' or 'spirit' accounting for the difference between living and lifeless matter. Such a vitalistic theory was completely prohibitive of ordinary scientific investigation and was partly responsible for the lack of progress in the field of biological chemistry in those early days. Buchner's discovery of zymase, the enzyme associated with glucose breakdown into alcohol, introduced a new experimental method for the investigation of alcoholic fermentation. Harden, working at the Lister Institute, at the turn of the century, showed that growing bacteria could split glucose into acetic acid and ethanol in equimolecular proportions, but this work drew little attention. The pure bacteriologists did not appreciate what the work was about and others had little interest. However, the situation swiftly changed when Harden and Young in 1905 made the discovery that the enzyme zymase would not convert glucose into alcohol unless another substance, called the co-ferment, was present and that phosphate had also to be present. Harden might not have made his advances, had he not abandoned the gravimetric estimation of CO_2 used by Buchner and others and substituted a volumetric method which enabled him to study the kinetics of the processes involved, using short time intervals. The separation of the co-ferment was achieved by use of a special gelatin filter, for the procedure of dialysis was too slow. With this filter, zymase remained on the outside and the co-ferment passed through. Each substance was inactive without the other being present.

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metabolism in the animal cell may be traced back to the fundamental studies of Robison on the significance of phosphoric esters in yeast fermentation. Warburg goes so far as to say that his yellow enzyme (the flavoproteins), and the pyridine nucleotides, TPN and DPN, may never have been isolated had it not been for the availability of the Robison ester. What is sure, is that the development of what is termed the hexose monophosphate shunt in carbohydrate breakdown, due largely to the work of Warburg and Lipmann on the one hand and of Dickens in Britain on the other, was dependent on the initial pioneer work of Robison.

As we contemplate the march of events in British biochemistry since the end of the first world war, we see notable advances that lead directly to the modern era of biochemistry. We see the recognition of the cytochromes playing a basic role in respiratory systems, the study of microorganisms as living units and not simply as a means to bring about chemical changes in substances to which they are exposed, the increased study of enzymology as a distinct field of biochemistry, the advance in knowledge of the molecular structure of important biological substances such as the sterols, thyroxin, the nucleotides, ascorbic acid, and the isolation of hormones such as insulin. Whilst great events were taking place in Continental Europe, particularly in the schools of Warburg and of Euler and of others, biochemistry advanced rapidly in Britain.

Keilin's work on the cytochromes about 1925 brought together apparently opposing schools of thought, those of Wieland and of Warburg in Germany, in the field of cell respiration and made possible modern ideas on the mode of electron transport in the cell. Keilin came into the field of biochemistry from biology where he had accomplished outstanding work on the biology of insect larvae, both free-living and parasitic, and he discovered the absorption bands of cytochrome in the thoracic muscles of insects such as the blow-fly, the wax moth and the honey bee at a time when he was quite unaware of the earlier, wrongly-discredited, work of MacMunn. Keilin came into biochemistry in the early twenties innocent of any knowledge of the subject, and in those very early days, when I knew him well, we shared together my own meagre knowledge of the subject. In fact we were both blessed with what is graciously termed an open mind, so far as biochemistry was concerned. Keilin's open mind served him well, metabolism in the animal cell may be traced back to the fundamental studies of Robison on the significance of phosphoric esters in yeast fermentation. Warburg goes so far as to say that his yellow enzyme (the flavoproteins), and the pyridine nucleotides, TPN and DPN, may never have been isolated had it not been for the availability of the Robison ester. What is sure, is that the development of what is termed the hexose monophosphate shunt in carbohydrate breakdown, due largely to the work of Warburg and Lipmann on the one hand and of Dickens in Britain on the other, was dependent on the initial pioneer work of Robison.

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Keilin's open mind served him well, almost wholly taken in what they could perform as agents of chemical change in the substances to which they were exposed. The introduction of the technique of using washed suspensions of bacterial cells by a group of us in Cambridge had important consequences in the development of biochemistry. It was first demonstrated in 1924 with suspensions of *E. coli* that a reversible equilibrium exists in these cells between succinate and fumarate. This came as a surprise because it was thought that the enzyme acted only on succinate to activate its hydrogen atoms. The demonstration that fumarate could be activated by the same enzyme to take up hydrogen was something quite new. This demonstration of the reversible nature of succinic dehydrogenase was soon followed by its confirmation with muscle tissue by Thunberg in Sweden, and by the demonstration, in many laboratories, of the existence of other reversible dehydrogenase systems. The idea of activation of hydrogen being the significant property of dehydrogenases disappeared and led to the modern concept of the activation of the molecule when combined with its enzyme. The discovery of fumarate as a hydrogen acceptor had another consequence, for the idea arose that fumarate might play the role of a hydrogen acceptor, replacing oxygen, in the growing bacterial cell. And so, for the first time, purely synthetic media were devised for the anaerobic growth of *E. coli* and other organisms and it was realized that oxido-reduction systems must play a role in the energetics of the developing cell and that oxygen must be considered only as one form of a terminal hydrogen acceptor. The demonstration of oxido-reduction systems as sources of energy for living cells set the stage for the appearance of intracellular hydrogen carriers, which we prophesied in 1929, and which came as a result of the later work in Germany that showed the carrier properties of the pyridine nucleotides. This work was materially advanced by Stickland in Cambridge who showed that in the strict anaerobes amino acids play the role of oxidation-reduction systems. Probably one of the best known results arising from the study of washed suspensions of *E. coli* was the demonstration of inhibition of enzymes by substances allied in chemical structure to the enzyme substrate, substrate analogues or anti-metabolites as they are now often called. The most familiar finding was the malonate inhibition of succinic dehydrogenase. The demonstration of this phenomenon had far reaching consequences, for the malonate inhibition of succinic almost wholly taken in what they could perform as agents of chemical change in the substances to which they were exposed. The introduction of the technique of using washed suspensions of bacterial cells by a group of us in Cambridge had important consequences in the development of biochemistry. It was first demonstrated in 1924 with suspensions of *E. coli* that a reversible equilibrium exists in these cells between succinate and fumarate. This came as a surprise because it was thought that the enzyme acted only on succinate to activate its hydrogen atoms. The demonstration that fumarate could be activated by the same enzyme to take up hydrogen was something quite new. 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The demonstration of this phenomenon had far reaching consequences, for the malonate inhibition of succinic crystals were difficult to reconcile with the accepted sterol structure. Rosenheim and King then arrived at the modern structure of cholesterol and the bile acids. This revolutionized the chemistry of the saponins, the cardiac glycosides, sex hormones and adrenal corticoids.

In 1932 all the resources of the laboratories of Haworth in Birmingham were used to determine the structure of vitamin C, which four years previously Szent-Gyorgyi had isolated from adrenal cortex and from orange juice. Haworth and Hirst showed that the substance, which was called ascorbic acid when its vitamin activity had been finally established, had the structure as we know it today and they synthesized the vitamin at about the same time as Reichstein synthesized it in Switzerland.

In this period Kennaway in London made his important discovery of the carcinogenetic properties of certain groups of hydrocarbons, a finding leading to much investigation in the vexed problem of carcinogenesis. And in this period also came the work of Robert Hill, in Cambridge who showed that when chloroplasts are illuminated, in the absence of CO_2, water is split to form oxygen so long as a suitable hydrogen acceptor, such as a pyridine nucleotide, is present.

From Canada, also, came momentous findings. The work in the early twenties on the isolation of insulin by Banting and Best in co-operation with Macleod and Collip had tremendous consequences on therapy in the hormone field, the later work of Collip on the parathyroid hormone, of Selye on the hormones associated with stress and of Copp of this University on calcitonin are well known. Insulin has even been synthesized recently by the joining together of two inactive halves of the molecule by Dixon also of this University. Indeed, Canadian biochemists have shown a definite penchant for the hormones but I should hasten to say that this is not their only contribution to biochemistry.

Although much of the extremely important work on hormones in recent years has been done outside Britain, many of the developments in the subject have been accomplished in Britain, from the time of the initial pioneer work on secretin by Bayliss and Starling just after the turn of the century to the relatively recent work of Wigglesworth on the insect hormones. We owe the very name 'hormone' to W. B. Hardy, of Cambridge, a pioneer in the field of colloid chemistry and crystals were difficult to reconcile with the accepted sterol structure. Rosenheim and King then arrived at the modern structure of cholesterol and the bile acids. This revolutionized the chemistry of the saponins, the cardiac glycosides, sex hormones and adrenal corticoids.

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We may quote perhaps one more development that took place in this period in Britain and that is the development of neurochemistry. Although Thudicum carried out his classical work about 1880, the systematic investigation of the brain on modern biochemical lines did not occur until the thirties. It was shown in Oxford by Peters that thiamine is essential for pyruvate oxidation in the brain, but the discovery of the coenzyme activity of diphosphothiamine was made outside Britain. In a laboratory of a mental hospital in Cardiff, S. Wales, it was shown in systematic studies directed towards problems of mental disorder that brain oxidations are greatly dependent on glucose, that glutamate is also a fuel for the brain, that acetylcholine, already established by Dale and his colleagues as a transmitter in the nervous system, is synthesized in the brain at the expense of glucose and pyruvate oxidations, that amine oxidase exists in brain, amine analogues can block the activity of the amine oxidase, and that barbiturates can effect notable inhibitory effects on cerebral metabolic processes. The concept was put forward that cerebral amine metabolism may be involved in mental aberrations. This formed a stimulus to further neurochemical work in America and elsewhere.

Work on fatty acid metabolism, which had been developed in Britain by Leathes and Raper, though the main findings had come from outside Britain through the pioneer investigations of Knoop and of Dakin, received a considerable stimulus by the finding made in Britain in 1935, that fatty acid oxidations can be quantitatively investigated by the use of liver slices. This work showed that acetone bodies cannot wholly arise from butyric acid formed during fatty acid oxidation by a process of β-oxidation, as was previously thought, and that another explanation was required to explain the formation of acetone bodies from fatty acids. The slice technique made possible quantitative measurements that could not be made with anything like the same accuracy with the old perfusion methods. The results and conclusions obtained with this technique stimulated work chiefly in America where the early advent of isotopes had already indicated the dynamic state of body constituents and which now for the many biosynthetic processes in the cell. Thus, whilst it is not indispensable for life, for strictly anaerobic organisms can exist without it, it seems to be essential for normal operations in the aerobic cell.

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Another technique of the greatest importance for biochemistry, which evolved in Britain, was the use of the X-ray diffraction pattern. The first serious work on proteins by X-ray diffraction studies began in the mid-thirties with Bernal's work in Cambridge, England. Perutz, an Austrian then in England, started work in 1937 on haemoglobin, that forms crystals suitable for crystallographic analysis, and Kendrew in 1947 carried out work on myoglobin. Perutz then demonstrated that several synthetic polypeptide chains, containing only one amino acid, exist as α helices, thus supporting Pauling's view, put forward in 1951, in America, that a helical configuration is an important element in protein structure. Perutz's experiments on protein structure led to his adding a heavy atom such as gold or mercury to a protein molecule and he was then able to compare the original with the loaded protein by X-ray diffraction pictures. He was able to obtain a two dimensional projection of haemoglobin looking through a depth of about forty atoms. The work of Perutz and Kendrew in 1953 and 1959 showed that the molecules of myoglobin and haemoglobin are enormously complicated with amino acids folded as α helices in some regions and very irregularly in others.

Other examples of the application of X-ray analysis data carried out in Britain, probably well known to you all, are the elucidations of the structure of Vitamin B_{12} and of penicillin by Dorothy Hodgkin.

But perhaps the most exciting of all such work involving X-ray found that this method could be used on strips of filter paper, the method began to be used everywhere. Separations by chromatography are now commonplace and no modern biochemical laboratory can be without the means to accomplish chromatographic analyses and separation. It has developed to such a stage that automatic, and very expensive, amino acid analysers are commonly used, and today it is possible to analyse a protein completely in a matter only of hours. Chromatographic techniques are current for lipids of every sort, and for all manner of intermediates met in cell metabolism. The method has been used with great success by Sanger for the establishment of the amino acid structure of proteins. Sanger's work in Britain has been a milestone in the study of proteins for it demonstrated that each type of protein contains a specific arrangement of amino acids. This led to important developments in the study of immunoglobulins and in our ideas of biochemical evolution.

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Nutrition

by

H. M. SINCLAIR

1. INTRODUCTION

NUTRITION INCLUDES, first, dietetics and the disorders that result from foods that are wrong in quality or quantity; secondly, it includes the digestion of foods; and thirdly it includes the metabolism of aliments and nutrients. It is convenient to retain the word aliment for the chemical compounds in foods that are used for the production of energy in the body, and the word nutrient for relatively specific compounds such as essential amino-acids, vitamins and certain inorganic elements.

Nutrition obviously includes therefore topics that will be mentioned elsewhere, by Dr. Bryn Thomas under 'Medicine', by Dr. Alfred Franklin under 'Paediatrics', and by Dr. Quastel under 'Biochemistry'. In considering my subject under the three sections of dietetics, digestion and metabolism I shall try to avoid repetition of what will be included by others. This I may claim as a partial excuse for my omissions. But a more real one is that I have not had easy access to the original sources of information now that the books I formerly possessed are, I am glad to say, so excellently housed here in the Woodward Library through the generosity of Mr. H. R. MacMillan.

2. DIETETICS

Medicine, as the Hippocratic Corpus pointed out, arose from dietetics. Indeed the Pythagoreans, borrowing from Egypt, observed what foods suited men best in health and disease; they preferred diet to drugs, and that Pythagorean manifesto called the Hippocratic Oath puts surgery as a last resort even for renal stone. Their interest in the diet of athletes, as later that of Galen with gladiators, helped empirical observations in dietetics which were admirably incorporated into the *Regimen* of Salerno and brought from there to Britain by the

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Lancaster and Woodall

In 1591 James Lancaster (?–1618) sailed round the Cape to the East Indies in command of ships belonging to the Company of Merchant Adventurers, formed nine years later into the East India Company. His crew suffered severely from scurvy, which he attributed to 'their evil diet at home'. When in 1601 he sailed in command of the first fleet of four ships to the East Indies for the newly-established Company he tripled his crew so that replacements would be available for those who died. They were needed, for when he approached the Cape most of the sailors in three of his ships were suffering severely from scurvy, but not in his own ship: 'And the reason why the general's men stood better in health than the men of other ships was this: he brought to sea with him certain bottles of the juice of lemons, which he gave to each one as long as it could last, three spoonsful every morning fasting . . . By this means the general cured many of his men and preserved the rest.' The Directors of the Company in London, with a natural concern for the health of their sailors in view of its economic consequences, ordered at their Court meeting on 13 August 1607 the provision of lemon juice. Five years later John Woodall was appointed the first surgeon-general of the Company (1612). In 1617, the year after he had become surgeon to St. Bartholomew's Hospital, he published *The Surgion's Mate or Military & Domestique Surgery* (1617). Woodall was a surgeon who was interested also in the cure of plague; and apart from the *Surgion's Mate*, he later wrote *Viaticum, the Pathway to the Surgion's Chest* (1628) for the younger surgeons of the East India Company. He regarded surgery as the most important branch of medicine, and placed diet second, with drugs coming third and last. Because there was no practical guide for a young apprentice surgeon in the Company, he wrote his book 'in want of some more learned and expert then [*sic*] himselfe', the cost being defrayed by the Company. The book fulfils admirably this practical aim, but there is no evidence that Woodall advanced in any way the method of preventing and curing scurvy that was practised in the Company before Woodall joined it. Indeed, Woodall follows Lancaster almost word for word:

> The use of the juyce of Lemmons is a precious medicine [for the scurvy] and well tried, being sound and good, let it have the chiefe place, for it will deserve it, the use whereof is: It is to be taken each morning, two or

Lancaster and Woodall

In 1591 James Lancaster (?–1618) sailed round the Cape to the East Indies in command of ships belonging to the Company of Merchant Adventurers, formed nine years later into the East India Company. His crew suffered severely from scurvy, which he attributed to 'their evil diet at home'. When in 1601 he sailed in command of the first fleet of four ships to the East Indies for the newly-established Company he tripled his crew so that replacements would be available for those who died. They were needed, for when he approached the Cape most of the sailors in three of his ships were suffering severely from scurvy, but not in his own ship: 'And the reason why the general's men stood better in health than the men of other ships was this: he brought to sea with him certain bottles of the juice of lemons, which he gave to each one as long as it could last, three spoonsful every morning fasting . . . By this means the general cured many of his men and preserved the rest.' The Directors of the Company in London, with a natural concern for the health of their sailors in view of its economic consequences, ordered at their Court meeting on 13 August 1607 the provision of lemon juice. Five years later John Woodall was appointed the first surgeon-general of the Company (1612). In 1617, the year after he had become surgeon to St. Bartholomew's Hospital, he published *The Surgion's Mate or Military & Domestique Surgery* (1617). Woodall was a surgeon who was interested also in the cure of plague; and apart from the *Surgion's Mate*, he later wrote *Viaticum, the Pathway to the Surgion's Chest* (1628) for the younger surgeons of the East India Company. He regarded surgery as the most important branch of medicine, and placed diet second, with drugs coming third and last. Because there was no practical guide for a young apprentice surgeon in the Company, he wrote his book 'in want of some more learned and expert then [*sic*] himselfe', the cost being defrayed by the Company. The book fulfils admirably this practical aim, but there is no evidence that Woodall advanced in any way the method of preventing and curing scurvy that was practised in the Company before Woodall joined it. Indeed, Woodall follows Lancaster almost word for word:

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voyage round the world in 1740–1744 lost during three months more than half his men from scurvy on one of his ships, and on his own, the Lieutenant could muster only six men capable of working out of more than 200 who remained alive. Lind states that only seamen, and 'no physician conversant with this disease at sea', had undertaken to throw light upon the subject, and clear it from the obscurity under which it had lain in the works of physicians who practised only at land. He was physician and seaman.

> But as it is no easy matter to root out old prejudices, or to overturn opinions which have acquired an establishment by time, custom, and great authorities; it became therefore requisite for this purpose, to exhibit a full and impartial view of what had hitherto been published on the scurvy; and that in a chronological order, by which the sources of those mistakes might be detected. Indeed, before this subject could be set in a clear and proper light, it was necessary to remove a great deal of rubbish.

He follows this by an excellent description of scurvy, its causes and the method of preventing it. His third part contains selected passages from authors and a chronological *Bibliotheca scorbutica*.

The excellence of the book is of course enhanced by the description of Lind's classical experiment.

> On the 20th of May 1747, I took twelve patients in the scurvy, on board the *Salisbury* at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all . . . Two of these were ordered each a quart of cyder a-day. Two others took twenty-five guts of *elixir vitriol* three times a-day, upon an empty stomach; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a-day, upon an empty stomach; having their gruels and their other food well acidulated with it, as also the gargle for their mouth. Two of the worst patients, with the tendons in the ham rigid . . . were put under a course of sea-water. Of this they drank half a pint every day, and sometimes more or less, as it operated, by way of gentle physic. Two others had each two oranges and one lemon given them every day. These they eat with greediness, at different times, upon an empty stomach. They continued but six days under this course, having consumed the quantity that could be spared. The two remaining patients, took the bigness of a nutmeg three times a-day, of an electuary recommended by an hospital-surgeon, made of garlic, mustard-seed, *rad. raphan.*, balsam of *Peru*, and gum myrrh; using for common drink barley-water well acidulated with tamarinds . . .

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Rickets

Other nutritional diseases have been excellently described by British authors. It is difficult to understand why rickets suddenly became common in Britain about 1620. Sir Thomas Browne (1605–1682), for instance, in his *A letter to a Friend, upon occasion of the Death of his Intimate Friend* (1690) states that the mutual friend suffered in his youth from rickets, 'a disease then newly arrived in this country'. The Bills of Mortality of John Graunt (1620–1674), first published in 1662, also indicate the sudden increase, though there might be an artefact in this in view of the way the Bills were collected. But Sir Thomas Browne has evidence that might be taken to disprove the sudden appearance; and he himself does not comment on the conflict. In his *Notes on Certain Birds found in Norfolk* he states that 'many [rooks] are killd for their Liuers in order to cure of the Rickets'. If this was folklore in Norfolk, the disease must have existed there for a long time. The folklore is soundly based, for I found the livers of rooks contained about 30 I.U. of vitamin D per 100 g., which is a little less than livers of ox or pig contain, and more than livers of calf or lamb.

The first description of rickets was given by Daniel Whistler (1619–1684) in his thesis on graduation at Leiden in his twenty-sixth year: *Disputatio medica inauguralis, de morbo puerili Anglorum, quem patrio idiomate indigenae vocant The Rickets* (1645). Bootius (1600?–1653?) showed that the disease was common in Ireland (*Observationes medicae de affectibus omissis*, 1649). Glisson (1597–1677) gave an excellent account of the disease and in chapter 22 of his book described infantile scurvy (*De rachitide sive morbo puerili, qui vulgo The Rickets dicitur*, 1650); he does not mention Whistler, although he probably knew of his thesis. The disease became known on the continent of Europe as 'the English disease' in view of the prevalence in Britain, and it may be that the decline in the consumption of fish caused by the Reformation was mainly responsible for the sudden increased incidence of the disease. Bland-Sutton (1855–1936) cured the rickets that frequently killed the lion cubs born in the London fruit juices. As both authorities pointed out, it was often accompanied by and confused with rickets. Since the bones are very painful, cases of infantile scurvy are not seen infrequently in orthopaedic clinics.

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Zoo with cod liver oil and crushed bones (1889), but did not follow up his discovery. That rickets was caused by a vitamin deficiency was proved experimentally by Sir Edward Mellanby (1884–1955) who produced the disease in dogs (1918), although he considered that the antirachitic nutrient was 'either fat-soluble A, or has a somewhat similar distribution to fat-soluble A' (1919). After McCollum and his colleagues in Baltimore had proved the existence of vitamin D, this was crystallized from irradiated ergosterol at the National Institute for Medical Research at Hampstead, London (Bourdillon *et al.*, 1930), four years after Rosenheim and Webster (1926) had proved that irradiation of ergosterol formed the vitamin.

The effect of sun-light in preventing rickets was thus explained, and there had been many early observations about this. In particular, Palm (1890) concluded from the distribution of the disease that sunlight should be regarded as a therapeutic agent. The effectiveness of this was proved by Chick and her colleagues in a study of children in Vienna just after the First World War (Chick *et al.*, 1923).

The Nineteenth Century

In the middle of the last century nutritional work in Britain was trivial compared with the exciting advances being made in France and Germany. In biochemistry the dominant figure was Liebig (1803–1873) in Munich; in physiological chemistry Claude Bernard (1813–1878) in Paris; in physiology Ludwig (1816–1895) in Zürich, Helmholtz (1821–1894) in Königsberg; in pathology Virchow (1821–1902) in Würzburg. But some British contributions may be noted. Lawes (1814–1900) and Gilbert (1817–1901) began their association at the former's Rothamsted estate in 1843, Lawes being rich in money and Gilbert in experience having been a pupil of Liebig. They studied the conversion of food in lower animals, proving for instance that in the pig carbohydrate could be converted into fat. As early as 1852 they disputed the view of Liebig that protein was the source of muscular force, quoting extensive experiments on such lower animals as pigs, pugilists, cab-horses, hunters and fox-hounds.

Edward Smith

But the dominant figure in Britain was the remarkable Edward Smith (1818 ?–1874) whose contributions have recently been excellently reviewed by Dr. Carleton Chapman (1967). We may note in particular three of these. In 1859 he invented an instrument to measure inspired air and to collect carbon dioxide in the expired air; he was the first person who studied human respiratory exchange during exercise, and his work was acknowledged by Pettenkofer in the following year (a reprint of an important and rare work by Pettenkofer, colleague of Voit, with an inscription to Claude Bernard, is in the Woodward Library). Smith's apparatus was re-discovered by J. S. Haldane (1860–1936) and Pembrey in 1890, and by Haldane in 1892; Haldane and Priestley (1880–1941) in their classical work *Respiration* (1905) do not mention Smith; Haldane's papers are in the Woodward Library, and his colleague, C. G. Douglas, told me he knew nothing of Smith. For his experiments on the action of foods on respiration Smith was elected Fellow of the Royal Society in 1860, together with Joseph Lister, Francis Galton and Brown-Séquard.

A second great contribution of Edward Smith was the establishment of the first scientific dietary standard. The American Civil War caused the cessation of exports of cotton, and the industry which employed two million people was quickly in poverty. Famine and 'famine fever' (typhus) resulted. Fortunately Britain had Sir John Simon (1816–1904) as Medical Officer to the Privy Council, an appointment arising from the Medical Act of 1858 which created the General Medical Council; and Simon was second only to Sir Edwin Chadwick (1800–1890) as reformer of the public health in the nineteenth century. Simon sent Sir George Buchanan to study the fever and in 1863 Edward Smith the famine, with the following enlightened terms of reference:

> *Questions.* At the named places, and at current retail prices, and distinguishing the case of separate persons from that of members of families, and having regard to the season of the year as well as to the habits of factory populations in ordinary times—
>
> 1. What is the least cost per head per week for which food can be bought in such quantity and in such quality as will avert starvation-diseases from the unemployed population?
>
> 2. What, with special reference to health, would be the most useful expenditure of a weekly minimum allowance granted exclusively for the purchase of food?
>
> 3. What, with the same special reference, would be the most useful expenditure of small additional sums, say 25 and 50 per cent. on the minimum granted for the same exclusive purpose?

in diet. McCarrison's classical researches on goitre, iodine deficiency and infection led him in 1914 to study wider aspects of deficient food, and McCay's recently published book encouraged him to pursue classical researches that were harassed by stupid officials in the Indian Medical Service to which McCarrison belonged. McCarrison purposely chose a technique different from that being followed by others. Biochemists were studying rats or mice on purified diets, as will be mentioned presently. But McCarrison realized that though a single deficiency was responsible for diseases such as rickets or scurvy, other nutrients were likely to be deficient as well; and less-marked deficiencies, alone or in combination, might be responsible for ill health without the production of a specific deficiency disease. In his own words: 'My own method, on the other hand, has been to observe the more general symptomatic and pathological effects of faulty food on the animal body as a whole, and thereby to ascertain what forms of human illness might reasonably be attributed to it.' This was an excellent approach, complementary to that of Hopkins or McCollum or other biochemists. Hopkins told me that he thought McCarrison's work had been greatly under-rated; but Mellanby dismissed it scornfully, telling me that McCarrison was never elected a Fellow of the Royal Society because his work was unscientific in that he did not know the content of the diets he studied. This showed considerable lack of vision in Mellanby: there is still an urgent need for the epidemiological comparison of the health of persons on different diets with their diseases, and then to find the significant differences between those diets. On a very much lower plane I may mention that I, friend of and co-author with McCarrison, had the opportunity during some nutritional work for the Royal Canadian Air Force in World War II of comparing in Northern Canada the product of cholesterol ingestion in Canadian Indians and Eskimos with that in young British pilots being trained at the same latitude, and so confirming my conclusion that atherosclerosis and coronary heart disease were related to the quality of fats in the diet and not to the quantity as was later maintained by Dr. Ancel Keys when he worked with me in 1951–1952. McCollum, a chemist, saw as Mellanby failed to do the significance of McCarrison's work and at his own request contributed to a volume I edited on that work in 1953. Another contributor was Aykroyd who succeeded McCarrison as Director in diet. 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Jameson (1885–1962). His mastery of nutritional problems made it unimportant that the Ministry of Food was not always wisely led: one Minister spent two days with me in Oxford to learn about nutrition, and since vitamins could be 'destroyed' he could not understand why they did not crawl on legs. But in 1940 Lord Woolton (1883–1964) was appointed Minister of Food, a man of scientific training who had seen malnutrition in his social work in Liverpool, and a man of great practical ability. He, with his highly practical if rather unscientific scientific adviser, Sir Jack Drummond (1891–1952), provided the perfect supplement to Sir Wilson Jameson at the Ministry of Health. It is a great tribute to these three that in wartime Britain the nutrition of the people improved. They rightly received the Laskei award for contributions to medicine.

Purified diets

William Stark

I have mentioned above that the converse of the epidemiological approach of McCarrison is the study of purified diets. One of the best examples is the experiments of William Stark (1740–1770). He was a pupil of Adam Smith, Black and particularly of William Cullen, himself a pupil of the great Boerhaave (1668–1738) at whose University of Leiden Stark graduated in 1766 after studying under John Hunter (1728–1793). Smyth, who posthumously edited Stark's works in 1778, rightly stated that 'His Experiments in Diet are the first, and will probably long remain the only Experiments of the Kind . . . They will be considered as the corner-stone of a great building, to be finished at some after-period of time, when men will be found of equal fortitude, perseverance and self-denial with our Author, actuated by a similar zeal for promoting useful knowledge'. Two years after returning from Leiden, he started his dietary experiments in June 1769 at the age of twenty-nine, encouraged by Sir John Pringle (1707–1752) and Benjamin Franklin (1706–1790). His first experimental diet was bread and water, and to his second he added sugar but at the end had a molar extracted for toothache and 'the gum appeared somewhat black'; in his third experiment he replaced sugar with olive oil, but his gums became increasingly swollen and black, and he had petechiae and follicular hyperkeratosis on his legs.

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> A Series of Experiments on the QUANTITY OF FOOD, Taken by a Person in Health, compared with the quantity of the different secretions during the same period; with CHEMICAL REMARKS ON THE SEVERAL ARTICLES. By JOHN DALTON, F.R.S. (Read March 5th, 1830) During my residence at Kendal, nearly 40 years ago, I had at one time an inclination to the study of medicine, with a view to future practice in the medical profession. It was on this account chiefly, but partly from my own personal interest in knowing the causes of disease and of health, that I was prompted to make such investigations into the animal economy as my circumstances and situation at the time would allow. I had met with some account of Sanctorius' weighing chair and of his finding the quantity of insensible perspiration compared with the quantity of aliment; and it occurred to me that the differences of constitution and of climate might occasion very considerable modifications which it would be desirable to ascertain. The following train of experiments were accordingly instituted for the purpose.

Fordyce and Prout

It was of course the work mainly of Liebig that made possible the interpretation of such experiments in chemical terms, but some British contributions were made. Cruickshanks (1745–1800) had in 1797 published his chemical studies of sucrose, and at the same time the important experiments of the brilliant George Fordyce (1736–1802) were made. He, like Stark, was a favourite pupil of Cullen, and therefore inherited the Boerhaave tradition of chemistry and medicine; he like Stark studied at Boerhaave's University of Leiden. His friend Wells, a very competent judge, regarded Fordyce as being more skilled in medical sciences than any other person of his time. He carried out the striking experiment that was communicated to the Royal Society by Sir Charles Blagden (*Phil. Trans.* 1775, **65**), in which he (with Blagden, Sir Joseph Banks and two others) entered a room that was heated to 260°F. In his *A Treatise on the Digestion of Food* (1791) he described his pioneering nutritional experiments with chicks and canaries, in which he discovered *inter alia* that laying birds needed calcareous substances in their diet. Some seventy years later, in 1863, Sir William Savory (1826–1895) first used rats for nutritional studies: two rats fed on lean veal and water died after thirteen and twenty-three days respectively.

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Dr. Cicely Williams, whose life was written by Ann Dally in 1968 (*Cicely, The Story of a Doctor*), is a medical practitioner of dauntless courage and deep compassion for children in underprivileged countries. Her heroism in Japan during the Second World War is here irrelevant. In 1935 she gave the first accurate description of one of the most important nutritional diseases today, protein deficiency in children, which she named 'kwashiorkor'.

Another Oxford graduate is Professor Dorothy Hodgkin, O.M. (1910–) who, a cousin of the biochemist Sir Charles Harington, became interested in biochemistry at the age of sixteen through reading a small book on the subject, and has brought her brilliant technique of X-ray crystallography to biochemical problems such as the elucidation of the structure of vitamin B_{12} in 1955 (for which she received the Nobel Prize), and recently of insulin.

3. DIGESTION

The main contributions to this important branch of nutrition have been made in countries other than Britain. Boerhaave (1668–1738) appears to have been the first to use a stomach tube for treating poisoned persons. In 1783 John Heysham, a Carlisle physician, passed a tube into the stomach of an hysterical patient who had difficulty in swallowing. Another similar patient was fed by John Hunter four years later (1772) through an eel-skin tube in the stomach. The stomach tube was in fact well established before the rival claims to its invention by Evans (1823), Jukes (1822) and Bush (1822).

After the classical experiments on digestion conducted by Boerhaave's pupil de Réaumur (1683–1757) on his pet buzzard, John Hunter (1772) concluded from his studies *post mortem* of patients and of fish:

> These appearances of the stomach after death throw considerable light on the principles of the digestion: they show that it is not mechanical power, nor contractions of the stomach, nor heat, but something secreted in the coats of the stomach, which is thrown into its cavity, and there animalifies the food, or assimilates it to the nature of the blood. The

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3. DIGESTION

The main contributions to this important branch of nutrition have been made in countries other than Britain. Boerhaave (1668–1738) appears to have been the first to use a stomach tube for treating poisoned persons. In 1783 John Heysham, a Carlisle physician, passed a tube into the stomach of an hysterical patient who had difficulty in swallowing. Another similar patient was fed by John Hunter four years later (1772) through an eel-skin tube in the stomach. The stomach tube was in fact well established before the rival claims to its invention by Evans (1823), Jukes (1822) and Bush (1822).

After the classical experiments on digestion conducted by Boerhaave's pupil de Réaumur (1683–1757) on his pet buzzard, John Hunter (1772) concluded from his studies *post mortem* of patients and of fish:

> These appearances of the stomach after death throw considerable light on the principles of the digestion: they show that it is not mechanical power, nor contractions of the stomach, nor heat, but something secreted in the coats of the stomach, which is thrown into its cavity, and there animalifies the food, or assimilates it to the nature of the blood. The

of 1655, at the age of about twenty-nine years and with no university education, he came to Oxford. By his genius he attracted great scientists such as Willis, Laver, Wren, Wilkins, Petty and Mayow. Patterson (1931) has given a very critical account in his work on Mayow's *Respiration* in which he suggests that Mayow merely summarized the discoveries mainly of Boyle and his circle. Patterson refers to an anonymous tract: *Novae Hypotheseos De Pulmonum Motu, et Respirationis Usu Specimen*; he mentions the Leiden edition in the library of the Royal College of Surgeons and adds that it 'seems also to have been published in London' since there is an account of it in *Phil. Trans. Roy. Soc.* of 17 April 1671. I had a copy of the exceedingly rare London edition of 1671 which is now in the Woodward Library, and it would well repay study; Boyle is mentioned extensively in it.

Richard Lower (1631–1691), friend of Boyle and brilliant assistant in Oxford of Willis, in 1669 showed that dark venous blood when passed through the lungs became bright, like arterial blood; he suggested that the blood absorbed from the air a definite chemical substance necessary for life, and that this was the main function of the passage of blood through the lungs. Hooke (1635–1705), who carried out experiments with Lower, had shown in 1667 that animals could be kept alive by blowing air through their lungs with bellows.

John Mayow (1641–1679) probably stands as an experimenter between the denigration of Patterson and the adulation of Beddoes, Gotch, Haldane and many others such as Robb-Smith who has just stated that his work was 'epoch-making'. His *Tractatus duo* (1668) was published when he was twenty-seven, and included his account of experiments on respiration and his description of rickets. In 1674 he expanded it into his *Tractatus quinque*; four years later he was elected F.R.S. on the proposal of Hooke and he died the following year. He is best known for his discussion of the 'spiritus nitro-aereus' which other members of Boyle's circle had shown to be absorbed by the blood, and which was, of course, oxygen.

Discovery of gases

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Inborn errors of metabolism

The son of Sir Alfred Garrod made one of the greatest contributions to metabolism of the present century when he introduced the concept of inborn errors of metabolism, the history of which I have discussed elsewhere (Sinclair, 1962). But Sir Archibald Garrod had a great predecessor.

In 1814 Joseph Adams had published a brilliant book entitled *A Treatise on the supposed Hereditary Properties of Diseases, containing Remarks on the unfounded terrors and ill-judged cautions consequent on such erroneous opinions*. Written at the beginning of the last century, before Pasteur's work had elucidated the nature of infections, this treatise is a very remarkable one, but it has been largely ignored. Adams distinguishes between diseases present at birth ('congenital or connate', or 'hereditary or family diseases') and those that arise afterwards ('hereditary of family susceptibilities to certain diseases').

> If the family or hereditary susceptibility is such, that the disease, though not existing at birth, is afterwards induced without any external causes, or by causes which can not be distinguished from the functions of the economy, such a state may be called, A DISPOSITION to the disease. But if the susceptibility . . . is so far less than a disposition as always to require the operation of some external cause to induce the disease; this minor susceptibility may be called, A PREDISPOSITION to the disease.

Even more interesting than these important distinctions are his remarkable passages on evolution by natural selection, nearly half a century before the publication of Darwin's masterpiece. For instance:

> We must at once see, that if no provision had been made in the construction of animals to prevent it, hereditary diseases would by degrees have become universal; whereas there is every reason to believe, that they lessen in the human race, as Society improves: and we shall see that so important an end is not left to the uncertainty of human institutions . . . Another provision arises out of climate; which we have seen is, in some cases, the only means of exciting a diseased susceptibility into action. Those constitutions, which are peculiarly susceptible of such diseases as are excited by climate, fall an early sacrifice; hence, the propagation

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The work of Adams and of Garrod was little known, although recently the latter has received the attention it deserves. Yet a couple of years ago one of the greatest present authorities on inborn errors of metabolism could in a lecture on them state that Garrod did all his work at St. Thomas's Hospital (where he never worked) and omit to mention that Garrod was Regius Professor in the University in which the lecturer was demonstrating his ignorance of the history of medicine. Garrod was successor of Osler in Oxford and contemporary of Sherrington, both of whom made notable contributions to the history of medicine, as has William Gibson, a pupil of Sherrington in Oxford. For this important and neglected subject, tools are required and academic appointments for those willing and able to use those tools. Oxford has in the Bodleian Library the tools, but the University ignores the history of medicine: Singer was slighted in Oxford and that great scholar E. T. Withington was ignored; had Oxford been interested in the history of medicine the University could have had the libraries of Osler, D'Arcy Power, F. J. Cole and others. Here the tools are provided by the magnificent Woodward Library, and this and the enthusiastic intelligence of Professor William Gibson ensure the brightest future for the study of the history of medicine.

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Obstetrics and Gynaecology

by

F. E. BRYANS

NO BRANCH of medicine can claim a longer history than midwifery. For many centuries the art was handed down from generation to generation of women who jealously guarded their scanty knowledge. Remarkably little advance was made from ancient times until the sixteenth century because of reluctance to challenge the authority of respected traditions and the works of the few medical writers who moulded medical thinking. Even such authors as Galen, whose influence lasted many centuries, knew little of anatomy and physiology of the human. It is not surprising that there was little change in the practice of the uneducated midwives in such a sterile and unquestioning period of history. A search for truth emerged in Europe in the late fifteenth century when Leonardo da Vinci and other artists demonstrated a superb understanding of anatomy and committed their studies to excellent anatomical plates. Vesalius in 1543 published the most authoritative anatomical text to that time, and fostered the growing place of accurate dissection and the teaching of anatomy in medical education.

William Harvey, who is best known for his classical description of the circulation of the blood in 1616 and the publication of his major work, *De Motu Cordis* in 1628, came under the influence of this school of anatomists during his studies in Italy. Late in his life he published a second, although less distinguished, work in 1651 entitled *De Generatione Animalium*. The chapter on labour (*De Partu*) is the first original work on midwifery to be published by an English author, and justifies the description that has been given to Harvey as 'Father of British Midwifery'. That part of the book relating to fertilization and embryology was based on studies of the chicken and it is not surprising that it contains some erroneous assumptions

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In 1670, Hugh Chamberlen tried to sell the secret in Paris while on a visit to a then leading French obstetrician, Mauriceau. In order to test the value of the forceps he was being asked to buy, Mauriceau set an almost impossible task for the over-confident Hugh Chamberlen when he asked him to deliver a thirty-eight-year-old dwarf exhausted by eight days of labour with the foetus dead, the cervix only partially dilated, and the pelvis so distorted by rickets that the hand could not pass through it. Although Chamberlen had boasted that he could deliver her within a quarter of an hour, he gave up exhausted after four hours of fruitless effort. In 1693, the Chamberlens finally sold their instrument to a Dutch obstetrician and the secret was then out. The Chamberlens apparently made few improvements in the design of their forceps during their century's control. In the light of the rapid and important further developments in the design and application of obstetrical forceps that occurred within the fifty years following the general release to public knowledge of the forceps, the withholding of this important scientific advance for a hundred years seems particularly to be regretted.

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A junior contemporary of William Smellie was another Scot from Lanark, William Hunter, who was the younger brother of the famous John Hunter. He was a man of small stature but cultivated manner and obvious intelligence. He went to London as a young man, where he studied midwifery under Smellie and then established himself in a large and fashionable obstetrical practice. His main contributions to obstetrics and gynaecology lay in his continuing interest in anatomy. His publication *The Anatomy of the Human Gravid Uterus* in 1774 represented the most authoritative and accurate description to that date, surpassing in anatomical quality even the plates of Smellie. William Hunter claimed the discovery of the placental circulation which was also claimed by his own brother John. A dispute between the two brothers led to their separation and a quarrel that was never settled.

The history of midwifery of the eighteenth century centres around the continuing rivalry between man midwives and women midwives. The traditional view fostered by the jealously possessive women midwives was that the presence of a man in the labour room was an outrage against female modesty. In a long uphill fight that was aided by the obvious contributions of men of superior education and intelligence such as Smellie and William Hunter, the acceptance of men in obstetrical practice was finally achieved. In this connexion it is interesting to remember that Queen Victoria was the first queen of England to be delivered by a man, although William Hunter had been present in an adjoining room when Queen Charlotte, the wife of George III, was confined in 1762. By 1800 the man-midwife was well established in the practice of well-to-do women, but for the most part the poor people continued to be cared for by the uneducated, self-appointed women who made up the very indifferent quality midwife of that time. The relatively low place given to obstetrics in medical education can be appreciated when it is recognized that as late as 1886 it was possible to become a licensed doctor without training in obstetrics. Following the acceptance of obstetrical instruction into a medical school curriculum, there developed a group of leaders in obstetrical education who led the way to improved standards both for doctors and midwives. Although some progress was made in raising the standards of midwives during the nineteenth century, it was not until 1902 with the passage of the 'Midwives Act' that

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Maternal Mortality

Traditionally maternal mortality has been described as the yardstick of obstetrical practice. Little factual information about maternal mortality was available in Britain until the first statistical report on this subject was published in 1837, and the story it told was a grim one. The first half of the nineteenth century could be described in the words of Charles Dickens: 'It was the best of times—it was the worst as an obstetrical anaesthetic which led him in the autumn of 1847 to begin a search for a better agent. With two colleagues, Thomas Keith and James Matthews Duncan, Simpson would meet in the dining room of his own home at the conclusion of a day's work. A number of different agents were tried until on the evening of 4 November, 1847, an agent named chloroform was placed in a cup which was then immersed in water to increase its volatility. The experimenters proceeded in their task of inhaling the vapours and noting the effects. They soon recognized the potency and effectiveness of this agent which caused initial excitation followed by confusion and sleep. Exhilarated by his new discovery, Simpson employed chloroform in the confinement of the wife of a medical colleague four days later, the child subsequently being named 'Anaesthesia'. Within a month he was addressing his medical colleagues at Edinburgh extolling the virtues of anaesthesia and his new discovery chloroform. The ensuing controversy over the use of anaesthesia in obstetrics has had few equals in the annals of medicine. Anaesthesia was violently opposed by many of the clergy as well as his medical peers. Simpson was forceful, articulate and logical in his rebuttal to the criticisms directed at him. The controversy carried on, with Simpson and the modern place of anaesthesia gradually gaining the upper hand. However, it was not until 1853, when Queen Victoria received anaesthesia at the time of the birth of her eighth child, and her subsequent praise for its benefits, that the scales of popular acceptance were decisively tipped in its favour. Not long afterwards Simpson was made a Baronet and the inscription on his Coat of Arms read 'Recto Dolore' (pain conquered). When he died at the age of fifty-eight in 1870, a measure of his stature in the community is revealed in the fact that there was a day of public mourning in Edinburgh with its shops and university being closed.

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The second most important cause of maternal mortality has been post partum haemorrhage due to a failure of the uterus to maintain a state of sustained contractility. A major advance came with the availability of oxytocic drugs which have a specific effect on uterine muscle to increase its contractions and thereby limit bleeding. In 1906, Sir Henry Dale, a renowned pharmacologist and physiologist and a Nobel Laureate in Medicine, observed the effect of an extract of the posterior lobe of the pituitary gland on the uterus of a female cat which he was studying for another purpose. The uterine blanching indicative of strong contraction was an unexpected finding but to the observant Henry Dale it stimulated an interest that led to the isolation and purification of oxytocin, the uterine contracting principle of the hormone of the posterior pituitary gland. The second oxytocic drug in obstetrical usage, ergometrine, was discovered by Chassar Moir of Oxford. For centuries an oxytocic effect had been recognized from the taking by mouth by man or animals of grain infected with a fungus called ergot. Although crude extracts with weak oxytocic effect were obtained as early as 1918, the active principle ergometrine was not isolated until 1935. Problems relating to indications and dosage plagued the early use of these agents but once the potency of the extracts had been standardized and bitter clinical experience had demonstrated the dangers, oxytocin and ergometrine became extremely valuable drugs in obstetrical practice that have saved countless lives by the control of obstetrical haemorrhage.

The maternal death rate in Britain as in other countries has shown a remarkable decline in the past thirty years. This is partly attributable to advances in knowledge and improvements in diagnostic and therapeutic techniques but to an even greater measure it is due to the making available of a higher standard of obstetrical care to more and more women, to the improvements of the general health and nutrition of the childbearing population and to the greater role in obstetrical by Lister, but earlier advocated by Holmes and Semmelweis, the mortality rate from puerperal sepsis gradually declined. However, the major drop was delayed until the introduction of chemotherapy with such drugs as prontosil in 1935 and later penicillin, that wonderful discovery of Sir Alexander Fleming and its application by Howard Florey, which began to make its mark in obstetrics about 1944, and led to a further reduction in the ravages of puerperal sepsis.

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large ovarian tumour, and Dr. Marion Sims, who in 1850 demonstrated that vesico-vaginal fistulae, the tragic result of poor obstetrics, could be closed by ingenious surgical techniques and newer suture materials, set the stage for the new field of operative gynaecology. Anaesthesia was just beginning at this time with the first major surgical procedure carried out under ether anaesthesia being performed in December of 1846, and in 1847, as already noted Sir James Y. Simpson introduced chloroform into obstetrical and surgical practice. There was no great rush to carry out abdominal surgical procedures, but over the next decade significant forward steps were taken by a few bold surgeons.

There is little doubt that the ovarian tumour was the first battlefield whereon the safety of abdominal surgery was tested and won, and with the gradual emergence of this operation as a practical procedure the door was opened to further intraperitoneal operations. Spencer Wells of London is credited with having placed ovariotomy on a sound footing. By 1864 the operation was generally accepted by the profession and by 1880, Wells had performed his one thousandth operation. His biographer, D'Arcy Power, refers to him justifiably as 'the originator of modern abdominal surgery'.

Surgery of this era in Britain was profoundly influenced by yet another force and that was the work of Joseph Lister, who as Professor of Surgery at the University of Glasgow, was working towards his classical contribution on the antiseptic principle in surgery which was first formally presented in 1867. He was convinced that wound infection, the serious hazard of all surgical procedures, could be reduced by proper application of antiseptic technique to the operating room and surgical wards. Great controversy surrounded the introduction of such a radical idea, and it was interesting that some of the leading characters of our story were intimately involved in the battles of that time. Personal animosities ran deep in those days, and clinical judgments were unquestionably influenced.

The famous Sir James Y. Simpson was a senior contemporary of Lister in Edinburgh. Although Lister was an inoffensive and scholarly man, his Chief in the Department of Surgery, James Syme, was an old rival of Simpson having opposed his appointment to the Chair of Midwifery years before. One can only speculate upon the reasons, but it is interesting to note that both Simpson and one of his more prominent pupils, Lawson Tait, later of Birmingham, who became a leading large ovarian tumour, and Dr. Marion Sims, who in 1850 demonstrated that vesico-vaginal fistulae, the tragic result of poor obstetrics, could be closed by ingenious surgical techniques and newer suture materials, set the stage for the new field of operative gynaecology. Anaesthesia was just beginning at this time with the first major surgical procedure carried out under ether anaesthesia being performed in December of 1846, and in 1847, as already noted Sir James Y. Simpson introduced chloroform into obstetrical and surgical practice. There was no great rush to carry out abdominal surgical procedures, but over the next decade significant forward steps were taken by a few bold surgeons.

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Our story began with the introduction of careful observation in anatomy and physiology by Harvey and Hunter. These chiefly related to the mother, for as long as pregnancy represented a substantial threat to the welfare of the mother, the foetus was of only secondary interest. As maternal mortality rates declined, a hitherto lacking interest in the foetus developed so the final chapter of our story that deals with the past twenty-five years has seen a return to the science of reproduction and a diminished stress on the technical aspects of the specialty. Although interest in maternal physiology continues, the focus of the current challenge is the foetus and its intra-uterine environment. Sir Joseph Barcroft, a distinguished physiologist who had made important contributions in other areas, turned his interest in later years to this field. His book published in 1946 *Researches in Prenatal Life* based upon the studies of his team at Cambridge on foetal sheep had a major influence in stimulating a growing interest in developmental physiology. Important schools of foetal physiology emerged at St. Mary's Hospital, London, under Huggett and at the Nuffield Institute for Medical Research in Oxford where Geoffrey Dawes and his co-workers continue to be leaders in the field.

With a clearer understanding of foetal metabolism and development, a more direct clinical approach to the intra-uterine human foetus has been possible. This is best illustrated in Rh incompatibility where Bevis of Sheffield in 1952 demonstrated the value of a study of amniotic fluid as a guide to the severity of the involvement of the child. Liley of New Zealand further demonstrated how repeated samplings of amniotic fluid could guide the management of a pregnancy complicated by Rh incompatibility and in 1963 pioneered the field of foetal surgery by demonstrating that an intra-uterine blood transfusion was a practical and sometimes life-saving procedure.

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Advances in General Surgery

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LORD BROCK

IN PRESENTING British contributions to advances in surgery it is important to consider how such a vast subject should be dealt with. It seems desirable to avoid a long list of names and especially a long list of operative contributions. I have decided, therefore, to include only those who would seem to have made some fundamental contribution to the science of surgery. Examples of progress in the art of surgery, that is essentially the initiation of new operations or new techniques, will be included only if they introduced or consolidated some basic advance.

For this reason I am going to pass over the many names in the earlier centuries and choose as my first example Peter Lowe who lived from about 1550 to 1612. His place is secure in medical history as the founder of the Faculty of Physicians and Surgeons of Glasgow, now the Royal College of Physicians and Surgeons. In 1596 he published his book on *A Discourse of the whole Art of Chyrurgeri.*

Although Peter Lowe used the actual cautery in amputation for gangrene he appears to be the first in English to refer to ligation of arteries in amputation.

I have included Peter Lowe because he was so much ahead of his time in his definition of surgery. Thus in 1745 the *Medical Dictionary* compiled by Dr. Robert James defines surgery as 'The part of Medicine which is employed in manual operation'. Dr. Johnson relied upon this book for many of his medical definitions and in his *Dictionary of the English Language* published in 1755 we find that surgery is 'The act of curing by manual operation' and a surgeon is defined as 'One who cures by manual operation'. Even before Dr. Johnson surgeons were more enlightened than lexicographers as Peter Lowe

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> The art of operating can be gained by little experience, but the art of knowing how to operate, of understanding which cases demand operations and which bid us abstain, the proper times and settings for performing them, the various modifications which they derive from a host of circumstances, the consequences which go with them and the means of alleviating the consequences, that is the difficult art of surgery, that is its science, the rest is mere skill. Surgery is unmeasurable, it borrows all the precepts of medicine, or rather shares them in common, for the healing art is a tree whose branches are medicine and surgery; everywhere these branches interlace and mix.

These remarks were made by Bichat in his lectures at the Hôtel Dieu in Paris in 1795. I wish to remind you of the Fernel-Paré medal which had been struck about this time. Although not a British action or contribution, its relevance to my theme is such that I do not wish to pass over it. The medal sought to commemorate the union of Medicine and of Surgery which had been separated for many centuries, the separation being worse in France than in England. It was originally struck in 1744 during the monarchy and had been made for the foundation of the Royal School of Surgery in that year. It is remarkable that at the height of the Terror in France this same medal should have been struck again, by the Republic, to confirm the union of Medicine and Surgery, and their centuries-long conflict was to be ended by a Republican decree in 1794.

At approximately the same time events in London were also taking an important new turn. The uneasy union between Barbers and Surgeons directed by Henry VIII in 1540 was finally ended in 1745 when the Company of Surgeons was formed, only in its turn to be succeeded, after a half century of unsatisfactory life, by the Royal College of Surgeons in 1800. A more academic body replaced the poorly organized Company that retained too much of the pattern of the old City Trade Guilds.

But a new concept of surgery had been in the minds of these mid-eighteenth-century surgeons who engineered the break from the Barbers and which culminated in the thought, philosophy and endeavours of John Hunter.

Surgery had begun as a crude act that developed gradually into an art and remained essentially so until the eighteenth century when John Hunter, by his energy, his example and his genius, crystallized and directed thought towards the absolute need for science in surgery.

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As Hunter's influence spread into the nineteenth century it encountered the tremendous expansion of clinical study of that remarkable age.

In surgery there were Charles Bell, Benjamin Brodie, James Paget and others who contributed to the science as well as to the craft of surgery. One of the most celebrated of those inspired immediately by Hunter was Astley Cooper. The closing words of Sir Charters Symonds' Hunterian Oration in 1921 and with Astley Cooper as his subject were:

> The Hunterian era awoke in the minds of men a desire to explore the old ground by new methods, and so unearth the truth so long concealed. There was the spirit of adventure, like that which animated the Elizabethan explorers, the ambition of the healthy human intellect to extend the range of vision and knowledge.

Astley Cooper introduced no new philosophy, policy or practice into surgery, but was the perfect exponent of the scientific approach to surgery, combined with skilful and successful practical ability. Unlike Hunter he was an excellent, indeed outstanding, clinical surgeon.

His contributions are almost too numerous to enumerate but one must mention his great contributions to arterial surgery. In his day this chiefly involved ligation of the principal large arteries; his approach to these operations was always founded on extensive preliminary animal experimentation, observation and dissection. This was so in his case of successful ligation of the common carotid artery. The first issue of the Guy's Hospital Reports in 1836 contains a long and important article on his researches on carotid and vertebral artery ligation and also an account of the end results of two of his earlier outstanding cases.

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obscurity that it is only fair to Astley Cooper that we should recall this effort he made.

In addition to his contributions to arterial surgery we must remember, but can only mention his outstanding basic work on hernia, on the breast, on fractures and dislocations, on the testis and the thymus. But one apparently small achievement cannot be omitted.

The Royal College of Surgeons possesses one of his manuscript museum catalogues at the end of which are short notes about a young man 'admitted into Guy's Hospital on April 9th, 1817 with a diseased thumb which Mr. Cooper amputated between the phalanges. He then cut off a healthy piece of integument from the amputated part and applied it to the base of the stump where he secured it by means of adhesive slips.' The autograft was completely successful and, although the case appears to give him priority in free grafting, it has an even deeper significance. The case was never published but present at the operation was Franz Reisinger of Bonn, who wrote: 'This case gave me excellent encouragement to attempt similar experiments with the cornea' (Reisinger, 1824). His experiments on rabbits and chickens failed, as did many other attempts with differing techniques until Zirm in 1905, eighty-eight years after Astley Cooper, was successful with a corneal homograft (Rycroft, 1965).

A great plant from a small seed—and how much else grew and flourished in a similar way from his work and example?

Although Astley Cooper carried Hunter's work forward and projected much of it into practice he, like Hunter, was restricted by the limitations placed on the proper expansion of surgery by the absence of anaesthesia and by the ever-present fear of infection.

Lister, his task happily lightened by the introduction of anaesthesia, changed all this and completed the work begun by Hunter, carried nobly forward by Astley Cooper, but still awaiting the touch of Lister's genius to set the seal on its success. Lister was in great part fortunate that the time was ripe for his epoch-making research. The stage was not fully set in Hunter's or Cooper's day for the conquest of sepsis and for the release of surgery from the bonds that bound it. It had to wait for Pasteur to provide the critical basic facts of microbiology. Lister's work was the finest flower of Hunter's inspiration and example. It was Astley Cooper who carried the torch of progress from Hunter to Lister.

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I have now reached the era of modern surgery, of post-Listerian surgery, essentially the surgery of the twentieth century, and have presented what I think to be the background for assessment of further contributions. A difficult task faces me, not only in selecting those contributions that are genuinely worthy but in selecting those that are wholly or substantially British. The whole world has contributed to advances in surgery, as in all science, and it is often difficult to apportion credit to one country alone for an advance. I can only suggest certain contributions which I consider are worthy of special mention. Obviously others might cite different ones and reject the ones I select. At the same time, although I would give the greatest credit to advances based on contributions to the science of surgery, I must include certain ones based predominantly on the *art* of surgery. This selection is a task I shrink from when I contemplate the thousands of excellent and commendable surgeons who confront me. I can only beg your indulgence.

The contribution of an important advance often rests in fact not on an isolated piece of work or a flash of inspiration but on the summation or the example over many years of a man's work and thoughts.

In this connexion I first mention William Arbuthnot Lane who lived from 1856 to 1943. Lane's reputation is now rather at a discount, probably because of his later years when his adventures in abdominal surgery were not acceptable and when he was associated with the New Health Society. We should not allow these activities to detract from the splendid work of his earlier years. Foremost I place his great influence on and contributions to the treatment of fractures. His insistence on the desirability of accurate anatomical reduction of the displaced fragments was fundamental and was in complete contrast to the earlier practice in which the doctor was supposed to 'set' the fracture; this setting usually consisting of a splint that was often in the nature of a talisman. There is no question of the correctness of his teaching that the first step in good treatment should be full correction of the anatomical abnormality. Lane was a brilliant technician and to up whose chief pre-occupation was with the art or craft of surgery. Happily reason has reasserted itself and the science of surgery is now widely respected as the only and the essential method by which the art can advance.

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He was a clinical surgeon and his position rests essentially on his technical skill and his personality. In his later years he fully realized and taught the absolute need for basic surgical research.

Another surgeon whose contributions rest in great part upon technical achievement and personality was Sir William Macewen (1848–1924) of Glasgow; here again we must relate his contributions to his whole way of life. As specific items we remember his classical osteotomy and his pioneering of autogenous bone grafts, both of which he introduced and established in the decade 1880–1890. Another Scotsman whose contribution consisted of his influence on the development of a school of surgery was Sir David Wilkie of Edinburgh. His place in furthering surgical science is commemorated by the Wilkie Surgical Research Laboratories.

I cannot leave the influence of the Edinburgh school on the progress of surgery without recalling the contributions of Sir James Learmonth who, in addition to training young surgeons in a scientific approach, added to our knowledge of the surgery of arterial disease, particularly in regard to operations upon the sympathetic nervous system.

The systematic development of the surgery of the sympathetic nervous system owes much to the basic contributions of Telford and Stopford of Manchester. But the stimulus for recognition of the potentialities of sympathetic nerve surgery both in Britain and in the United States came from the basic work of the Australian surgeon and anatomist, Royle and Hunter, whose writings on the alleviation of spastic rigidity go back to 1924. Their work served as an inspiration to the participation of many in this field.

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of malignant disease and in the principles that should govern its management and treatment.

In a comparable fashion I must include the contributions to the treatment of rectal cancer, progressive over many years, of Lockhart Mummery and Ernest Miles. The radical operation evolved by Miles, and strengthened by the pathological classifications of Cuthbert Dukes, is a contribution that must not be overlooked.

Our work often rests on the work of others and the contributions of one man support, inspire and advance the work of those who follow him. One of the best examples of such a sequence is the founding and the evolution of prostatic surgery by British surgeons.

The pioneer work of Sir Peter Freyer at the very beginning of the century was preceded by that of McGill of Leeds. Moynihan states (1928) that he was acting as house surgeon to McGill when he did his first prostatectomy in March 1887 and that in 1889 at the British Medical Association meeting in Leeds, McGill showed a number of old men each holding a jar containing his prostate and that these specimens still exist. He comments that no serious controversy is possible on the question of priority.

We have to acknowledge the progression from this quick blind procedure to the more deliberate technique of Sir John Thomson Walker which still left much to be desired in the discomfort and risk to the patient, and thence to the simple but brilliantly successful procedure of the retropubic prostatectomy of Terence Millin which has been a boon and a blessing to many. Terence Millin has returned to or rather retired to his native Eire. His great contribution came when he was working in London.

In a similar manner it is difficult to single out any one surgeon from a sequence or succession of surgeons who have advanced the surgery of amputations. I do not refer to the work of the pre-Listerian surgeons whose activities included many amputations, and many of whom are associated by name with particular operations. I have in mind successive surgeons who have worked at the limb-fitting centre at Queen Mary's Hospital, Roehampton. This work sprang essentially from the large number of amputations done during the First World War and done after the manner of amputations of some surgical antiquity that were learnt from the standard textbooks of surgery. The drawbacks arising from these amputation methods were revealed by the study of of malignant disease and in the principles that should govern its management and treatment.

In a comparable fashion I must include the contributions to the treatment of rectal cancer, progressive over many years, of Lockhart Mummery and Ernest Miles. The radical operation evolved by Miles, and strengthened by the pathological classifications of Cuthbert Dukes, is a contribution that must not be overlooked.

Our work often rests on the work of others and the contributions of one man support, inspire and advance the work of those who follow him. One of the best examples of such a sequence is the founding and the evolution of prostatic surgery by British surgeons.

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Before I leave the advances springing from the work of surgeons within Great Britain I must remind you of yet another change in the achievement of progress. I have instanced the earlier days when advance was inspired or sprang from the efforts of one surgeon. I have given examples of advance due to progressive corporate work. We are now moving essentially to the achievement of advance by team work. Often inspired, directed or 'led' (that is the usual word today) by one surgeon, advance often rests upon the work of a team. This is especially so in the advances being achieved in transplantation surgery. The contribution of any one surgeon is essentially technical or organizational; the success of his operation will rest in great part on the control of immune reactions. Success in transplantation rests on the work of many surgeons from many countries but advance from British surgeons has come from the work of Professor Roy Calne of Cambridge University on liver transplantation. I have to remind you that not only has he achieved encouraging clinical success but by his research he has made important observations on the apparent low tendency of the transplanted liver to provoke drastic immune reaction.

Although I must declare a personal interest I think that my presentation of progress from British surgeons cannot omit mention of the successful establishment of cardiac surgery. We should not forget the early fundamental contribution of Sir Henry Souttar who succeeded with mitral valvotomy as long ago as 1925. The time was not then really ripe for successful cardiac surgery which had to wait upon the advances in thoracic surgery and thoracic anaesthesia, many of which were achieved between the two wars by British surgeons especially Tudor Edwards and Roberts at the Brompton Hospital. O'Shaughnessy who lost his life from a German bomb in France early in 1940 had already led the way to the surgical treatment of coronary ischaemia by his introduction of cardio-omentopexy.

The application of the basic surgical step of the relief of an obstruction to the successful relief of valvar obstruction in 1948 opened the flood gates to the development of closed and open heart surgery that other British surgeons are recognized in the McIndoe Research Centre at the Queen Victoria Hospital, East Grinstead, where so many of the war pilots were treated and where important fundamental research continues.

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In addition to directing the Toronto School of Surgery, William Gallie himself made an important contribution in his introduction of living suture material (fascia lata) in the repair of hernia. Although in some ways a technical step in furthering the art of surgery it carries an overlay of scientific achievement that becomes even more manifest when we contemplate the many additional uses of autografts of fascia lata culminating in the fashioning of fascia lata for heart valve replacement.

I count very high the contribution made by those two other Toronto surgeons, Shenstone and Janes, of one-stage tourniquet lobectomy in 1930. I can well remember the state of thoracic surgery before Shenstone and Janes' contribution because I was studying thoracic surgery with Dr. Evarts Graham at St. Louis at the time they reported their remarkable series of eleven cases of lobectomy for bronchiectasis with only two deaths. One could appreciate at once the fundamental advance that had been made in this loathsome disease. Tourniquet lobectomy is now a thing of the past having been displaced by individual ligation techniques. Bronchiectasis as a surgical condition has in great part disappeared owing to the advent of antibiotics. But in spite of this the value of Shenstone and Janes' work lives on because it was their operation that enabled surgeons to become familiar with intrathoracic techniques of all sorts. Their work provided the great stimulus to the rapid development of thoracic surgery that we saw in the 1930s and which paved the way for the development of cardiac surgery. For this reason I place their contribution very high. In case you protest that it was not an advance in general surgery, which is my remit today, I reply that it was a great advance in the general principles of surgery and resulted in many advances in the means of making difficult surgical techniques safer, such as improvements in anaesthesia, in avoiding, controlling and replacing blood loss and in many other things that enabled thoracic surgery to evolve as a part of general surgery, guided as I have said, by the general principles of surgery the observance of which is essential to all true progress.

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British Physiology: Some Highlights, 1870–1940

by

JOHN C. ECCLES

A. INTRODUCTION

I HAVE HAD no difficulty in deciding when to begin my survey of the history of British physiology. Appropriately, in 1970, we can celebrate the centenary of its beginning. As stated by Sir Edward Sharpey-Schafer, in his *History of the Physiological Society* (*1876–1926*), before that time there were no physiologists in Britain whose 'names were worthy to be mentioned with those of Magendie, Claude Bernard, Müller, Helmholtz, Ludwig, to mention but a few of the brilliant physiologists of France and Germany'. Then in 1870 at T. H. Huxley's suggestion, Michael Foster (1836–1907) was invited to be Praelector in Physiology at Trinity College, Cambridge, and Burdon Sanderson (1828–1905) succeeded Foster as Professor of Practical Physiology at University College, London. Both had been inspired and trained as physiologists for several years by William Sharpey who had been professor of General Anatomy and Physiology at University College since 1836, and whom Sharpey-Schafer (1927) regards as the forefather of modern physiology in Britain. From 1870 onwards the stream of British physiology has flowed continuously and with ever increasing strength.

Michael Foster's achievements at Cambridge derived from his extraordinary ability to attract a succession of great scientists and to guide them into fields of research that suited them. Gaskell, Langley and Sherrington immediately come to mind, but one has to remember also the magnificent physiological achievement of Trinity College from Foster's time to the present with such a sequence as Lucas, Dale, Fletcher, Head, Hill, Adrian, Roughton, Rushton, Hodgkin

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His high standing in the physiological world of that time did not derive from his researches, which were few and not particularly notable, but from his personal influences and his books. His *Textbook of Physiology*, published in 1877, was the first authoritative textbook in the English language, and was moreover well written with his characteristic lucid style of exposition. Later he published a remarkable book, the *History of Physiology*, which I found to be required reading even in my day at Oxford, though I wished it could have been continued to the more interesting later periods of physiology.

Meanwhile another distinguished centre of physiology was developing at University College, London, in the continuing Sharpey tradition that was maintained by Burdon Sanderson on his appointment in 1870 and then by Schäfer from 1883 to 1899. This developing distinction was in large part due to two young colleagues, Bayliss and Starling from the 1880s onwards. Starling became the Jodrell Professor in 1899 and with Bayliss continued the great tradition of University College until their deaths in 1924 and 1927, when the tradition continued with A. V. Hill and then Lovatt Evans.

At this stage also Oxford was developing, firstly with Burdon Sanderson who had come on from London in 1883 and then with Gotch and Haldane who was later joined by Douglas and Priestley. After 1913 Sherrington and his pupils made Oxford the world centre of neuro-physiology. Before his Oxford period Sherrington had already made Liverpool foremost in the world in the physiology of the central nervous system.

This brief introductory sketch will give some impression of the exultant state of British physiology late in the nineteenth century and well into the twentieth century. The great *Textbook of Physiology* edited by E. A. Schäfer (later Sir Edward Sharpey-Schafer) is a witness of the remarkable state of British physiology, with Volume I in 1899 and Volume 2 in 1900. There is a total of 2,400 pages in this amazing book. It was the most advanced text in the world at that time and is a most valuable reference book even to this day because with its meticulous index and its immense bibliography one can quickly find all the references up to that time in any field of physiology. Large sections were written by some of the best authorities in the world, for example 250 pages by Schäfer; 220 by Sherrington; 150 by Gotch; 140 by Langley; 130 by Starling, 100 by Burdon Sanderson and so on.

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British physiology can be traced back to quite humble experiments in 1878 in which Langley (1852–1925) was studying the secretion of the submaxillary gland to stimulation of the chorda tympani and the cervical sympathetic. Contrary to the earlier work of Heidenhain on the dog, he found that in the cat both nerves gave a similar secretion, the difference in volume arising on account of their respective vaso-dilator and vaso-constrictor actions. This interest in salivary gland physiology led to pioneer electrophysiological investigations on the action potentials of glandular secretion by Bayliss and Bradford (1885), and then to Barcroft's (1872–1947) pioneer work on the metabolism of the submaxillary gland at rest and during and after stimulation of the nerves. In three classical papers (1901) he made for the first time a sound critical and quantitative study of the metabolism of an organ at rest, and of its variations during changes of activity occasioned by nerve stimulation or treatment with drugs. Then with collaborators he made studies by the same technique of blood-gas exchange on the metabolism of the kidney, pancreas and heart.

2. *The Respiratory Function of the Blood*

These investigations led to a study of blood as an oxygen carrying system. The relationship of oxygen pressure to the amount of oxygen combined to the haemoglobin, the so-called oxygen dissociation curve, was determined with great accuracy. In 1910 A. V. Hill developed a theoretical explanation of the S-shaped curve which is so important for the efficient carriage of oxygen at a high pressure. In 1912 Peters (1889–) made very accurate determinations of the ratio of iron to oxygen, showing that it was in fact stoichometric in the ratio of FeO_2. According to Hill's theory there was variable aggregation of the haemoglobin so that there were between two and three atoms of iron per aggregate. All of this work was published in 1914 in Barcroft's famous monograph, *The Respiratory Functions of the Blood*. Much later Roughton continued at Cambridge with refined investigations on the chemistry and physical chemistry of haemoglobin and its various gaseous combinations.

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4. *Anoxia*

An unresolved problem bedevilling all these studies of respiratory control was the effect of anoxia on respiration. In fact this problem remained an enigma until much later when the carotid body was shown by Heymans to be a chemical sense organ exciting the respiratory centre and being sensitive to anoxia as well as hydrogen ions and CO_2. Meanwhile the study of anoxia led to international co-operation in four memorable mountaineering expeditions in which fine work was done on the physiology of acclimatization to high altitudes and on the disturbances responsible for mountain sickness. British physiologists played a leading role in all these expeditions. Barcroft was the leader of the Teneriffe (1910), Monte Rosa (1911) and Peruvian Andean (1922) expeditions, while Haldane led the Pike's Peak expedition (1911). Barcroft gave his inimitable presentation of his expeditions in 'The respiratory function of the blood. Part 1. Lessons from high altitudes (1926)' while Haldane gave an account of the work of the Oxford School and of the Pike's Peak expedition, in particular, in his classic monograph (*Respiration*, 1922). There was for many years a strongly fought controversy between the Cambridge and Oxford schools with respect to the manner in which oxygen is transferred from the lung alveoli to the blood capillaries, the former school believing in diffusion, the latter in an inward secretion under conditions of good acclimatization to oxygen deficiency. In retrospect there can be no doubt that it is another example of Oxford being a 'home of lost causes', though this was never admitted by Douglas!

5. *Muscular Activity: Heat and Lactic Acid*

The production of lactic acid in the normal contraction of an isolated muscle was first established in 1907 by Fletcher (1873–1933) and Hopkins (1861–1947), and in the anaerobic state there was a corresponding disappearance of glycogen. Furthermore they showed the Bohr phenomenon (O_2 uptake increased by loss of CO_2 in the lungs, and vice versa in the tissues) it was found that O_2 uptake by haemoglobin in the lungs aided the dissociation of CO_2, while O_2 loss in the tissues aided in the uptake of CO_2.

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The heat production of nerve offered a most exacting challenge to A. V. Hill. His first attempt in 1912 failed to detect any temperature change during intense activity of isolated nerve. Much later an exquisitely sensitive thermopile enabled the heat production to be investigated in detail (Downing, Gerard and Hill, 1928), and since that time Hill and his associates have continued to perfect the technique so that measurements of the intensity and time course of the heat production have come to be of great significance in relation to the understanding of the metabolic events in nerve.

7. *Physiological Adjustments of the Circulation*

Brief reference should be made to two other very significant discoveries in the field of energetics.

Starling devised and used the heart-lung preparation in 1910 to 1914 in order firstly to study the action of the heart as a pump under fully controlled conditions, and then as a means of controlled perfusion of other organs. His most important discovery was that within limits the more the heart is distended with blood, the stronger is its contraction. As he pointed out, Hill found that within limits skeletal muscle also contracts more strongly the more it is extended. Starling's 'Law of the heart', as it has come to be called, is certainly important as a basic mechanism in enabling the heart to cope with the great variations that occur in circulation rate during extreme physiological conditions.

Another emergency mechanism was shown by Barcroft to relate to the blood reservoir function of the spleen. During rest the spleen fills with blood that is virtually stagnant therein, but during exertion the sympathetic outflow and the secreted adrenaline constrict the smooth muscle of the splenic capsule, so pouring blood into the general circulation. This unique discovery was found to merit a Nobel Prize in 1933 and 1936, but surely Barcroft deserved a Prize much more for his tremendous contributions to the 'Respiratory Function of the Blood'.

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C. HORMONES AND INTERNAL SECRETIONS

Several pioneer and outstanding contributions have been made by British physiologists.

1. *The Suprarenal Medulla and the Posterior Pituitary*

Special recognition must be given to Oliver and Schäfer (1850–1935) for the discovery in 1894, 1895, that watery or alcoholic extracts of the medulla of the suprarenal produce, on intravenous injection, a very powerful contraction of arteries so that there is an enormous increase in blood pressure. Moreover, if the vagi are cut, there is also an acceleration of the heart. They showed that both of these actions were direct and not via the nervous system. Contraction of mesenteric arteries was observed with a direct application of the extract. Their experiments were carried out with great skill and physiological acumen, and quantitative estimates were made relating the content of the gland and the physiological action. For example 10^{-6}g/kg of extract would produce a large physiological effect. They also reported that the respiration became shallower, an effect that is now recognized as being a reflex mediated by the excitation of the carotid sinus by the high blood pressure.

Also in 1895 Oliver and Schäfer reported that extracts of the pituitary gland had a vasopressor action directly contracting the arteries, but in contrast to the suprarenal extract there was no cardiac acceleration. In 1909 Dale (1875–1968) showed that one active principle from the pituitary caused contraction of many varieties of smooth muscle, that in arteries, uterus and spleen particularly, and so differed from the more restricted action of the suprarenal extract, which was restricted to the smooth muscle excited by the orthosympathetic system.

Much later the physiological action of another active principle of the posterior pituitary, the anti-diuretic hormone, was very elegantly investigated by Verney. He showed that in the hypothalamus there are receptors sensing very precisely the osmotic pressure of the plasma. If this is raised, there is a discharge of nerve impulses to the posterior pituitary and the secretion of the antidiuretic hormone that restricts water excretion by the kidneys and so counteracts the raised osmotic pressure. Verney has in this way demonstrated a very efficient physiological control.

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1. *The Suprarenal Medulla and the Posterior Pituitary*

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Also in 1895 Oliver and Schäfer reported that extracts of the pituitary gland had a vasopressor action directly contracting the arteries, but in contrast to the suprarenal extract there was no cardiac acceleration. In 1909 Dale (1875–1968) showed that one active principle from the pituitary caused contraction of many varieties of smooth muscle, that in arteries, uterus and spleen particularly, and so differed from the more restricted action of the suprarenal extract, which was restricted to the smooth muscle excited by the orthosympathetic system.

Much later the physiological action of another active principle of the posterior pituitary, the anti-diuretic hormone, was very elegantly investigated by Verney. He showed that in the hypothalamus there are receptors sensing very precisely the osmotic pressure of the plasma. If this is raised, there is a discharge of nerve impulses to the posterior pituitary and the secretion of the antidiuretic hormone that restricts water excretion by the kidneys and so counteracts the raised osmotic pressure. Verney has in this way demonstrated a very efficient physiological control.

sponses of the individual nerve fibres, employing for this purpose either the electrical disturbance measured by a capillary electrometer or the contraction of the attached muscle. Gotch (1902) was the first to suggest that, when the intensity of stimulus applied to a nerve was varied, the resulting variations in the size of the response are attributable to the number of fibres conducting impulses and not to any variation in size of the impulse in a fibre. This fundamental all-or-nothing concept was corroborated and developed by Lucas (1909). Further work of Adrian and Lucas (1912) showed that, following a conducted nerve impulse, there is a refractory period that first was absolute for a millisecond or so with no response to stimuli, then relative with a progressive recovery of excitability for five to ten milliseconds, and often a supernormal phase of excitability. This fine analytical work on nerve and muscle was collected by Keith Lucas in his book *The Conduction of the Nervous Impulse* that was revised by Adrian and published in 1917 after Lucas' tragic death in 1916.

This pioneering work on nerve fibres was greatly hampered by the inadequacy of techniques until valve amplification and oscilloscopes made it possible to record impulses in single nerve fibres. Nevertheless Adrian and Zottermann (1926) were able to record the impulses in single afferent nerve fibres from muscle and to show that the frequency progressively increased the more the muscle was stretched. The general concept developed that the unitary impulses in nerve fibres effectively signalled intensity of stretch applied to the receptor organs of muscle in two ways: increase in the number of receptors discharging along their afferent fibres; increase in the frequency of discharge in any one fibre.

A further factor of great importance is the rate of adjustment of different species of receptor organ to a steady stimulus. This adaptation, as it is called, was found to be extremely rapid in some cutaneous receptors, for example, that consequently require vibration for a continuous discharge, whereas it can be much slower for other cutaneous receptors and muscle receptors. In a later investigation Adrian and Bronk showed that the same two factors—number of discharging motoneurones and the frequency of discharge—were responsible for the grading of reflex responses. Adrian and his colleagues in Cambridge investigated a wide range of receptor organ discharges including sponses of the individual nerve fibres, employing for this purpose either the electrical disturbance measured by a capillary electrometer or the contraction of the attached muscle. Gotch (1902) was the first to suggest that, when the intensity of stimulus applied to a nerve was varied, the resulting variations in the size of the response are attributable to the number of fibres conducting impulses and not to any variation in size of the impulse in a fibre. This fundamental all-or-nothing concept was corroborated and developed by Lucas (1909). Further work of Adrian and Lucas (1912) showed that, following a conducted nerve impulse, there is a refractory period that first was absolute for a millisecond or so with no response to stimuli, then relative with a progressive recovery of excitability for five to ten milliseconds, and often a supernormal phase of excitability. This fine analytical work on nerve and muscle was collected by Keith Lucas in his book *The Conduction of the Nervous Impulse* that was revised by Adrian and published in 1917 after Lucas' tragic death in 1916.

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Dale in 1914 reported that there was a close resemblance between the action of acetylcholine and that of some divisions of the sympathetic system. Elliott (1904) had already proposed that the orthosympathetic system could act by liberation of adrenaline on smooth muscle and Dale pointed out that acetylcholine was even more powerful in actions which were complementary and antagonistic, i.e. the parasympathetic system.

Dale (1938) referred to this preliminary stage of the chemical transmitter hypothesis in the following dramatic manner:

> Such was the position in 1914. Two substances were known, with actions very suggestively reproducing those of the two main divisions of the autonomic system; both, for different reasons, were very unstable in the body, and their actions were in consequence of a fleeting character; and one of them was already known to occur as a natural hormone. These properties would fit them very precisely to act as mediators of the effects of autonomic impulses to effector cells, if there were any acceptable evidence of their liberation at the nerve endings. The actors were named, and the parts allotted; a preliminary hint of the plot had, indeed, been given ten years earlier, and almost forgotten; but only direct and unequivocal evidence could ring up the curtain, and this was not to come till 1921.

This reference was of course to the first report of Loewi's discovery that acetylcholine was the chemical transmitter from the vagus to the heart.

A particularly fine series of experimental investigations (Feldberg and Gaddum, 1934; Feldberg and Vartiainen, 1934; Dale, Feldberg and Vogt, 1939; Brown, Dale and Feldberg, 1936) led to the extension of the chemical transmitter hypothesis to sympathetic ganglia and neuromuscular junctions with acetylcholine as the transmitter (Dale, 1935, 1938).

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3. *Central Nervous System*

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The problem that Sherrington here outlined was to occupy him for most of his scientific life and one which he pioneered alone. He was fascinated by the perfection of animal movement and sought to understand the intricate organization of the central pathways responsible for it. He had early realized that the whole control was central, the muscles being merely good servants of the central nervous system. Hence the control and right ordering of movement could be understood only in terms of the *Integrative Action of the Nervous System*. As early as 1898 he expressed his views in the poetic phrase: 'Reflex action by its spread develops a combined movement, synthesizes a harmony.' In a later, more precise analysis he studied the responses of the individual muscles and compiled lists both of those muscles which contracted in the flexor reflexes and of those muscles that relaxed. Further investigation revealed that virtually the same two classes of muscles gave complementary responses in such other types of reflex action as the crossed extensor reflex and the flexor and extensor phases of reflex stepping. Thus arose the general concept that all flexor-type muscles contracted together in reflexes and hence were synergists, as also with all extensor-type muscles.

It is remarkable how surely Sherrington discovered the way so that there was a steady progress in understanding with almost no occasion for retracing of steps. When we examine his work in an attempt to discover the secret of his amazing success, we can find several clues.

First, meticulous study of structure precedes and goes on simultaneously with the functional study. Sherrington's concepts were always formulated in terms of known structures and he showed great insight in grasping the essential structural features in the vast maze described by neurohistologists. For example it is to him that we owe the name and the physiological concept of the synapse (1897, in *Textbook of Physiology*, Foster and Sherrington).

Secondly, his investigations were not ends in themselves, but always it seems that he had before him the great problem: How does the nervous system work not only in isolated units but also in its functional entirety? This gave a meaning and a direction to his work as well as guidance in the choice of research problems. One can survey his life's effort as the ordered strategy of a campaign.

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Again he seemed to have an intuitive grasp of the essential functional features of the nervous system and he coined such appropriate factor'. Herein he ventured still further in his attempt to explain inhibition.

> It is still early to venture any definite view of the intimate nature of 'central inhibition'. It is commonly held that nerve-excitation consists essentially in the local depolarization of a polarized membrane on the surface of the neurone. As to 'central excitation', it is difficult to suppose such depolarization of the cell-surface can be graded any more than can that of the fibre. But its antecedent step [facilitation] might be graded, e.g. subliminal. Local depolarization having occurred the difference of potential thus arisen gives a current which disrupts the adjacent polarization membrane, and so the 'excitation' travels. As to inhibition the suggestion is made that it consists in the temporary stabilization of the surface-membrane which excitation would break down. As tested against a standard excitation the inhibitory stabilization is found to present various degrees of stability. The inhibitory stabilization of the membrane might be pictured as a heightening of the 'resting' polarization, somewhat on the lines of an electrotonus. Unlike the excitation-depolarization it would not travel; and, in fact, the inhibitory state does not travel.

We are indebted to that same lecture for a masterly summing up of the essence of his life's work on the nervous system:

> The role of inhibition in the working of the central nervous system has proved to be more and more extensive and more and more fundamental as experiment has advanced in examining it. Reflex inhibition can no longer be regarded merely as a factor specially developed for dealing with the antagonism of opponent muscles acting at various hinge-joints. Its role as a co-ordinative factor comprises that, and goes beyond that. In the working of the central nervous machinery inhibition seems as ubiquitous and as frequent as is excitation itself. The whole quantitative grading of the operations of the spinal cord and brain appears to rest upon mutual interaction between the two central processes 'excitation' and 'inhibition', the one no less important than the other. For example, no operation can be more important as a basis of coordination for a motor act than adjustment of the quantity of contraction, e.g. of the number of motor units employed and the intensity of their individual tetanic activity. This now appears as the out-come of nice co-adjustment of excitation and inhibition upon each of all the individual units which co-operate in the act.

The excerpts that I have given from Sherrington's writings illustrate the amazing prescience of his imagination. As I read them there is hardly any modification that I would like to make in the light of all that has been discovered since that time.

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After the war, great developments ensued at Cambridge, London, Oxford and many other universities. The most notable achievements seem to me to have been in analytical studies on simple isolated systems using the most advanced biophysical techniques. Thus Hodgkin and Huxley were conjointly awarded the Nobel Prize in 1963 for their discovery of the ionic mechanisms responsible for the nerve impulse, but many other British investigators were also in the forefront in this new field of neurobiology: Rushton, Keynes, Katz, Fatt, and more recently Miledi.

As I survey in retrospect this amazing development of British physiology during the one hundred years from 1870, I am convinced that the Physiological Society has been the greatest factor in this success. In fact I regard it as an ideal of what a scientific society should be. It is informal, yet is efficiently organized. There is an excellent atmosphere of personal friendliness; yet those presenting scientific papers or demonstrations are subject to the most searching criticisms; what surprises visitors is the tradition that these criticisms must be free of personal attack and that they must be accepted with good grace. There is a characteristic sporting atmosphere in the way that hard knocks are given and received! The society is remarkable for its truly democratic spirit, where the youngest member ranks with the most senior. I have been a member since 1929 and was in regular attendance until I left England in 1937. In recent years I always try to attend if I am in Europe, and I am much encouraged to see how the fine old traditions are continued, almost exactly as I first knew them in the 1920s. And so we can be assured that the stream of British physiology will flow even more strongly as it continues into its second century.

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Pharmacology

by

W. D. M. PATON

PHARMACOLOGY CONCERNS itself with the study of the responses of biological systems to, and their control by, chemical substances, with the special aim of improving therapeutics. The underlying motives of a pharmacologist need to be understood, for its history to be interpreted. If at the heart of physiology lies the idea of normal function, then at the heart of pharmacology is the idea of control by chemical substances; either as a means of perturbing the system (as a physicist uses temperature and pressure, or a physiologist ablation or nerve section) so as to throw light on the system and to test our understanding of it, or in order to improve its functioning. Logically, the ability to control should follow understanding of function; but, as the instances of curare, eserine, digitalis, anaesthesia and antibiotics show, the ability to control often comes first, posing problems or even creating new fields of investigation. In turn, a new functional understanding feeds back to improvements in control, in therapy. In all this, there is a closer link with chemistry than appears at first sight, and pharmacologists have always tried to think, whether fruitfully or not, at the molecular level. A more practical chemical link has always been in the background, that pharmacology underpins the pharmaceutical industry; this is a subject on its own, and I will only say that major pharmacological contributions have come from British pharmaceutical houses—perhaps it is right for an old Hampstead denizen to mention The Wellcome Foundation as a particular example.

It is pharmacology understood in this way, therefore, whose British development is to be considered. But there is another general point to be made; namely how young the subject is in its modern sense. One can see three phases of development. The first goes back to the dawn of history, wherever drugs have been used to heal or to palliate, to

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Until that last burst, one could almost have said, with Oliver Wendell Holmes in 1860, 'Throw out opium, which the Creator himself seems to prescribe, throw out a few specifics which our doctor's art did not discover, throw out wine which is a food, and the vapours which produce the miracle of anaesthesia—and I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind and all the worse for the fishes.' But from 1935 it is a different story. One may note, too, that the British Pharmacological Society was founded in 1931, and that until then there were, in England and Wales, only three chairs in the subject.

But if the subject is only, in its modern form, about forty years old, it is too recent to be able to stand back from and assess; and there is, too, no body of scholarly analysis to draw on, such as now exists for other sciences. There is a start—a review by J. H. Gaddum kill, to change mood, or for magic (whether to produce invisibility, strength, suspended animation or invincible love); and indeed, a component of magic still lingers on in the placebo effect. But it comes of age as an experimental science during the beginning and middle of the nineteenth century, with the analysis by Magendie of strychnine's action, by Claude Bernard of curare and carbon monoxide, with the anaesthetics, and with Crum Brown (1838–1922) and T. R. Fraser (1841–1919) in 1868 on the structure-action relationships of quaternary compounds. Yet it is curious that for a long time after this period, despite successful analyses of drug action, introductions of synthetic compounds into medicine, and deep chemical insight, the subject never really got going. I have discussed elsewhere whether it was in some way hampered, or whether the soil (particularly the state of chemistry) was not quite ready. But it seems clear that something happened around 1930. To quote one illustration: if one analyses the pharmacopoeias (Fig. 1) in Britain (and the Royal College of Physicians' pharmacopoeia merges quite smoothly into the British Pharmacopoeia), one sees first a severe pruning of the old galenicals, then the introduction of materials partially purified by extraction in water (extracts) or alcohol (tinctures); but only recently has come the great burst of pure substances, by tablet, capsule or pure enough for injection, the rise of synthetic compounds and the astonishing growth of successful therapeutic agents.

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There is another type of induction, not from patterns of bodily action, but from patterns of chemical structure. It begins with Crum Brown and Fraser's astonishing paper of 1868, in which they showed that quaternizing atropine, morphine, thebaine, strychnine, codeine and other alkaloids with methyl iodide removed the characteristic action of the drug, and replaced it with a curare-like action. It was the first correlation of a particular type of pharmacological action with a particular type of molecule, and it, too, pointed forward to cholinergic neuromuscular transmission. Crum Brown and Fraser other as the eye or the toe) were linked by a common reactivity to curare alkaloids. Similarly, in Langley's (1852–1925) and Anderson's (1865–1928) hands, autonomic ganglia were found all to be sensitive to nicotine, first being excited then paralysed, and voluntary muscle was also found to be sensitive. Hence there were two systems of structures, nicotine-sensitive and muscarine-sensitive, the names implying a chemical similarity in the effector structures concerned. Into this situation comes H. H. Dale's (1875–1968) marvellous 1914 paper, on the esters and ethers of choline, where he shows that *both* systems have a deeper link, that of a shared responsiveness to acetylcholine. Combine this with his shrewd observation that even a massive dose of acetylcholine had a transient action in the body (so that the body must have some means of dealing with it—he suggested an esterase), and the stage is set for the discovery of the underlying truth—that at all the neuro-effector junctions concerned, acetylcholine was the chemical transmitter. The method is essentially inductive, discovering an aspect common to a variety of anatomical structures. A similar inductive process, initiated by T. R. Elliott's (1877–1961) comparison between the effects of adrenaline and of sympathetic nerve stimulation, led ultimately to the identification of noradrenaline and other catecholamines as neurotransmitters. So, too, Dale's discovery of 'adrenaline reversal' by ergot paved the way for the later generalization of α and β catecholamine receptors. These were major contributions in themselves; and they gave a characteristic flavour to much British pharmacology, a broad method of approach, using many responses in the whole animal, coupled with careful analysis to identify securely the precise points at which a drug was in fact active. One hopes that they are not the last gifts of pharmacological induction to physiology and medicine.

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Bioassay

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Biostatistics

A need in bioassay is to be able to compare the potencies of drugs, whether to assay the amount of transmitter released, to compare the activity of two chemically related substances, or to establish the activity of an international therapeutic standard such as insulin or digitalis. This raises a very general question—that of handling data with the variability that is part and parcel of living tissues. The solution to this began with Francis Galton (1822–1911) and D. MacAlister, when they showed that cumulative curves of response had a characteristic ogive form (Fig. 3). This was exploited by J. W.

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some specific end-point, as distinct from measurements of some graded parameter such as blood pressure height or contraction), in a manner now widely practised. It also contributed to a great advance in the precision of biological measurement, and in the estimation of limits of confidence in those measurements.

Another British statistical development of great importance for medicine came into pharmacology from epidemiology: the method of the clinical trial. Lest it should be forgotten, I should like briefly to mention it. Bradford Hill and his colleagues had the responsibility in the 1950s of determining for the Medical Research Council the efficacy of streptomycin in tuberculosis. Their papers on the subject remain a magnificent introduction to similar problems today. They laid down that, for such a trial, there must be (1) clearly defined criteria for admission to the trial; (2) clearly defined criteria for judging clinical response—the criteria in both cases being required to reduce variability of response and ensure sensitivity to the drug as far as possible. Hence their initial choice of advancing bilateral parenchymatous disease in young adults. Further to eliminate conscious or unconscious bias, they introduced (3) a system of controlled randomization, whereby sizes of control and test groups were kept of comparable size, yet any patient had an equal chance of belonging to either group, and (4) they introduced assessment of results by observers ignorant of the treatment assigned. It is perhaps a pity that of these rules, today it is sometimes only the last which, sometimes obsessively, is honoured in the single, double or treble-blind investigation!

Receptor Pharmacology

Last I would like to mention what I think may ultimately prove to be the deepest scientific contribution by British pharmacology—the work on the drug receptor. I have already mentioned the very high potency of acetylcholine, and that one can associate particular chemical structures with particular actions. A. R. Cushny was the first to establish that with drugs such as hyoscyamine and adrenaline one optical isomer was more active than the other. These and other ideas were all pulled together by A. J. Clark (1885–1941) in his great monograph *General Pharmacology*, to support the idea already formulated by J. N. Langley, that drugs combined in the tissues with some specific end-point, as distinct from measurements of some graded parameter such as blood pressure height or contraction), in a manner now widely practised. It also contributed to a great advance in the precision of biological measurement, and in the estimation of limits of confidence in those measurements.

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Cardiology

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CLEARLY NOT only British cardiology but British physiology began with William Harvey. I shall therefore divide my account of British contributions to cardiology into sections on physiology, common forms of heart disease, and treatment.

Cardiovascular Physiology

The more one immerses oneself in Harvey's work the more astonishing does one find him. Genius, of course, by definition astonishes; it would not be genius unless it did. Yet one cannot help wondering how this orthodox physician, throughout his life traditional and authoritative in outlook, introduced a new concept of the circulation of the blood based on innumerable new observations and original experiments, successfully bound together by that very new form of inductive logic which his contemporary, Francis Bacon, was striving so eloquently to get accepted.

Moreover, in Harvey's view his achievement in *De Motu Cordis* was of only secondary importance to his greater project on generation. For him the preservation of the body by the distribution of the blood by the heart in circulation was of secondary importance to the creation of the body by the heart and blood in its generation. This outlook he makes clear in many passages in *De Generatione Animalium*; and he states it succinctly towards the end of his second letter to Riolan, in the passage where he briefly recapitulates his description of the circulation. 'Before long,' he writes, 'I shall have occasion to lay before the world things that are more wonderful than these, and that are calculated to throw still greater light upon natural philosophy.'[1] He refers, of course, to his *De Generatione*.

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And Harvey chooses *De Generatione Animalium*, not *De Motu* and distended with blood that the cavities of the ventricles equalled those of a bullock's heart in size. Such is the force of blood pent up.' One is justified I think in seeing in these examples Harvey reaching out towards a relationship between raised blood pressure in the aorta and heart (pump) failure.

One further example of Harvey's suggestive developments of his circulatory theme is contained in his brief description of an experiment in which, having engorged the veins of his arm with a 'medium tight' ligature he plunges the arm into snow for some minutes. Then, releasing the ligature he observes the time interval before a feeling of faintness occurs, commenting:[5] 'You will perceive by the cold blood returning to the heart with what speed the current flows.' Though we may dispute his end-point Harvey leaves us in no doubt as to the purpose of the experiment, measurement of the arm-heart circulation time. But he gives no actual measurement of this time. Indeed I think this illustrates the reason why so many of Harvey's developments of his concept of the circulation have escaped recognition, for he so rarely made any attempt to quantitate his results. With one great exception, his estimate of cardiac output, Harvey never made measurements. In this he was so consistent that it can be recognized as part of his outlook. He was not a quantitative mechanistic scientist like Sanctorius or Galileo, but a qualitative experimental biologist like Aristotle.

The Cornishman Richard Lower (1631–1691) saw his own contribution as a development of Harvey's work. He makes his position clear in 1669 in the dedication to his *Treatise on the Heart* when he writes:[6] 'Harvey, in so far as it concerned his magnificent discovery of the circulation described the structure of the heart and movement of the blood in a way that left practically nothing to be added. But just as in the Ptolemaic hypotheses of the heavens smaller epicycles are allotted to the planets indispensable for the explanation of observed facts, so in the system of the human body there are points not mentioned in Harvey's circulation which need consideration.' Apart from this surprising reference to his persisting belief in the Ptolemaic astronomical system Lower here refers to gaps in Harvey's exposition amenable to further investigation. These were three: the stroke volume of the heart, the quantity of circulating blood, and the colour contrast between venous and arterial blood.

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Lower recognized that inflammation and fatty disease of the heart muscle could lead to failure, as also could 'oppression from outside' from pericardial effusion.[8] 'When the envelope is full in hydrops cordis the walls of the organ are compressed on all sides by the surrounding fluid to such an extent that they are unable to dilate sufficiently to receive the blood, the heart beat diminishes greatly until at length it is completely suppressed and syncope and death result.' Thus Lower describes the phenomenon of cardiac tamponade, though omitting its venous signs. He also describes a case of adherent pericardium producing the symptoms of 'pain dyspnoea syncope and death'. At post mortem the 'thick, opaque, hard' pericardium[9] had clearly hindered the heart's movement. Here, too, Lower omits to mention any signs of venous congestion. Even though in his experimental studies of arteries and veins, he ligated the inferior vena cava and noted at autopsy how the abdomen contained 'a large quantity of serum as if the animal had suffered long from ascites', he did not see this as part of the syndrome of congestive failure of the heart. He just failed therefore to reach the concepts of left- or right-sided heart failure. Nevertheless he clearly achieved very considerable developments in cardiovascular physiology as Harvey had left it.

Stephen Hales (1677–1761) a clergyman in Teddington, held the view that,[10] 'the all wise Creator has observed the exact proportions of number, weight and measure in the make of all things.' This was the essential principle behind what he called his 'statical way' of investigating nature. He applied it to botany in his work, *Vegetable Staticks*, and to the movement of the blood in his later work, *Haemastaticks* of 1733. But Hale's statick way was by no means easy. Others before him had attempted it. Perhaps the best known of these was Giovanni Borelli, mathematician, physicist, and pupil of the mechanistic school of Galileo. Borelli developed his mechanistic view of the physiology of movement over many years, his great work *De Motu Animalium* being published after his death, in 1680–1681. Borelli advanced on Lower in attempting to make an estimate of the force of ventricular systole. Assuming that an equal weight of muscle has equal force of contraction, and finding that the mass of heart muscle equalled that of the masseter and temporal muscle of one side, Borelli assessed the force of the heart muscle as equal to half that of the lower jaw, which he measured. Multiplying this figure of 150 lb. by an arbitrary

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Newton's *Principia* Book II, proposition 36, a proposition used by Newton to calculate the velocity of water running out of a hole at the bottom of a cylindrical vessel (Fig. 1). Correcting these calculations purely theoretically, Jurin concluded that the force of the left ventricle was 9 lb. 1 oz. and the right 6 lb. 3 oz. Thus when Stephen Hales undertook his Haemostaticks he had good reason to comment,[11]

> Several ingenious persons have attempted to make estimates of the Force of the Blood in the Heart and Arteries, who have as widely differed from each other as they have from the Truth. Finding, therefore but little satisfaction in what had been attempted on this subject by Borelli and others, I endeavoured about twenty-five years ago by proper Experiments to find what was the real force of the Blood in the crural arteries of Dogs, and about six years afterwards I repeated the like Experiments on two Horses and a fallow Doe . . . Having of late years found by Experience the Advantage of making use of the Statical Way of Investigation into the Nature of Vegetables . . . I was hence induced to hope for some success if the Same Method of Enquiry was applied to animal Bodies . . . Since we are assured that the Animal Fluids move by Hydraulic and Hydrostatic Laws, the likeliest Way therefore to succeed in our Enquiries into the Nature of their Motions is by adapting our Experiments to those Laws.

Hale's first experiment tells how, 'he caused a Mare to be tied down alive on her Back', and how, 'having laid open the left Crural Artery about three inches from her belly I inserted into it a brass Pipe'. He then made measurements of the height of the column of blood in twenty-five 'trials' after letting out blood in different quantities. By making a wax cast of the ventricles, he estimated stroke volume.

Taking Harvey's and Lower's estimate of 2 oz. as the stroke volume of the ventricle of man, and Keill's estimate of the area of the aorta, Hales calculated the velocity of the blood in the aorta of man, and suggested that the column of blood in a tube fixed in the carotid artery of man would rise $7\frac{1}{2}$ ft. From this he calculated the force of the left ventricle on contraction as 'a weight equal to 51.5 pounds'. Hales arranged his cardiovascular measurements and estimates in different animals including man, in a very instructive table[12] (Fig. 2). He was well aware that the force of the heart varies with peripheral vascular resistance, and this he located in the 'capillary vessels', defining a capillary as being 'twice the diameter of one red globule of Leeuwenhoek'.

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During the first half of the nineteenth century two parts of Harvey's circulation claimed particular attention, the capillaries and the great veins.

All workers previous to Marshall Hall of Nottingham had confused arterioles with capillaries. Hall clarified this position in his *Essay on the Circulation*[16] of 1831, published a year before his more renowned paper on *The Reflex Function of the Medulla and Spinal Cord*. Hall clearly distinguished arterioles and venules from capillaries, and described arterio-venous shunts. From this stage investigation of the capillaries was carried out in Germany by histologists like Krause, and by Ludwig and Heidenhain. It was from the latter's view of capillaries as filtering or secreting membranes involved in the exchange of tissue fluids that Starling at University College, London, in 1896 revealed that the balance of forces regulating the quantity of circulating fluid consists of the capillary filtration pressure against the osmotic pressure of intravascular plasma.[17]

Starling's other great contribution also sprang from the work of Ludwig, his pupil, Fick whose 'principle' has become so famous, and Otto Frank who worked on the dynamics of heart muscle. Through his brilliant development of the heart-lung preparation Starling in 1915 came to state that, 'the law of the heart is that the mechanical energy set free on passage from the resting to the contracted state depends on the area of chemically active surfaces, i.e. on the length of the muscle fibre.'[18]

To these important controlling factors in Harvey's circulation James Carson of Liverpool in 1815 added recognition of the vital effect on venous return played by the negative pressure in the pleural cavity. By this, writes Carson,[19] 'Blood in the large venous trunks is relieved from a part of the ordinary pressure in the direction of the heart; it necessarily takes the course in which it meets with least resistance . . .' This work was later repeated by Barry in 1826.

The twentieth century has revealed that expansion of knowledge of cardiac physiology depends not only on techniques for the study of isolated hearts and heart-lung preparations, but on studies of the tree, and that resistance to blood flow is located peripherally. Quantitative estimates of blood pressure and other factors controlling blood flow had to await Poiseuille's undergraduate work of 1828, and that of 1846.[15]

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He concludes his paper with a section entitled 'Reflections on the preceding cases', in which he gives special attention to the relation between the quantity of blood reaching the lungs and infant survival. He discusses, too, the effects of congenital heart disease on growth. He is particularly interested in the relationship between congenital deformity of the foetus and intra-uterine survival, attributing many miscarriages at the third month to 'some uncompensated defect'.

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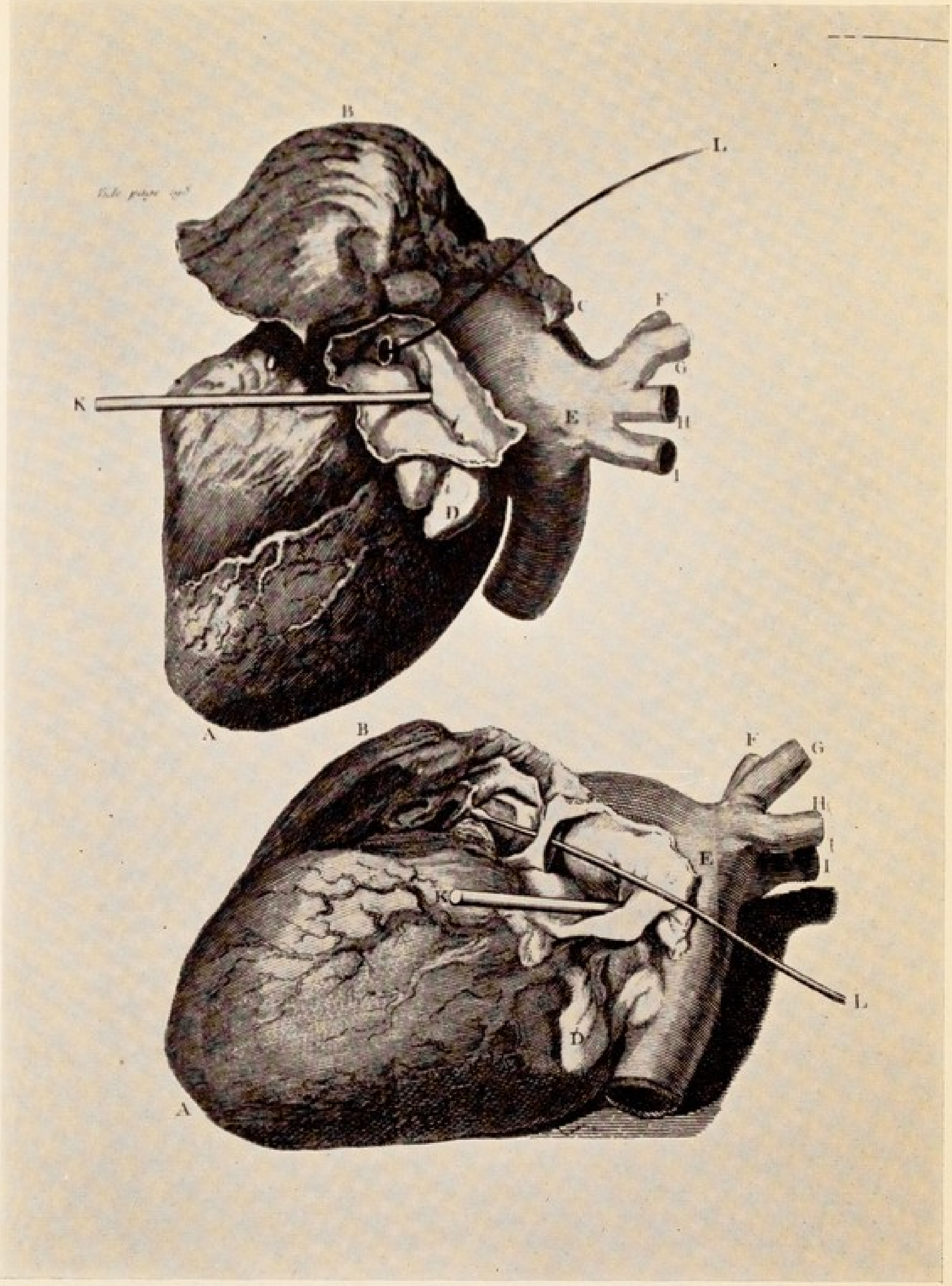

Figure 3 William Hunter's case of congenital heart disease; with pulmonary atresia (indicated by the bent bristle) patent ductus arteriosus (shown by the rod) and atrial septal defect (not shown). From *Medical Observations and Inquiries*, 1784, vol. 6, 296.

(*Facing p. 216*)

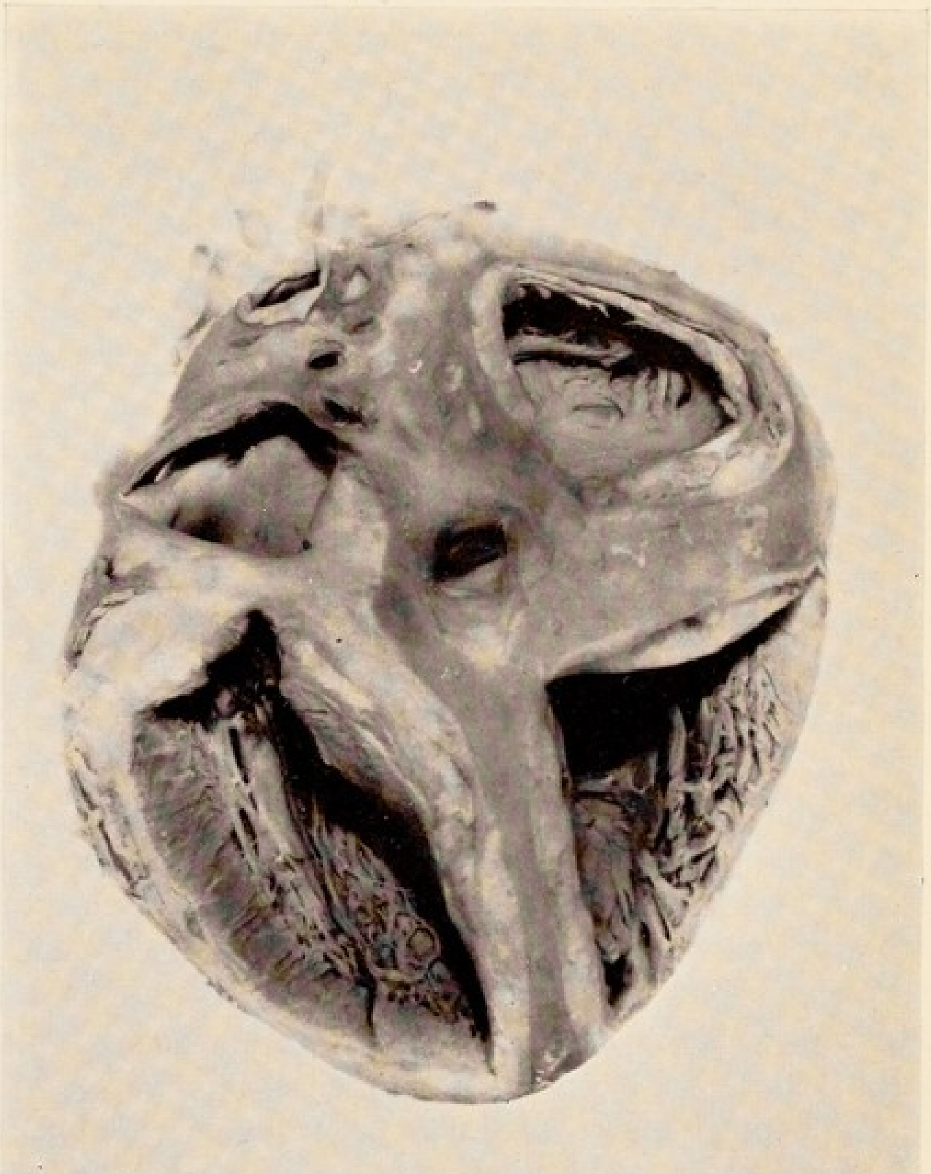

Figure 5 The preparation of the enlarged heart which David Dundas presented to the Royal College of Surgeons of England in August 1808 to exemplify disease of the heart, 'always connected with or subsequent to, an attack of rheumatism'. The heart shows an adherent pericardium, and vegetations on the mitral valve. Reproduced by courtesy of the President and Council of The Royal College of Surgeons of England.

production of thrills and murmurs to achieve a diagnosis of pulmonary stenosis in life. Not until 1858 when Thomas Peacock produced his *Malformations of the Human Heart*[29] was further advance made. Peacock, a devotee of the morbid anatomical approach of Corvisart and Laennec, collected specimens and physical signs of congenital heart disease with all the assiduous patience one might expect from an honest, diligent and austere Quaker. His contribution consisted of an embryological classification of types of congenital heart disease into: malformations due to 'arrest of development at an early period of foetal life', malformations occurring 'at a more advanced period', and malformations occurring 'during the later periods'. To these he added such conditions as ectopia cordis, absent pericardium, and abnormal primary vessels. He concluded the work with a section on clinical diagnosis and treatment. Peacock did not classify congenital heart disease into acyanotic and cyanotic types for the good reason that he did not believe that cyanosis was due to the mixture of venous with arterial blood by a shunt mechanism, but to obstruction of pulmonary blood flow. He seems to have been but little influenced by the Scottish group of workers.

Peacock's work constituted a vital stage of development of the subject of congenital heart disease. He was the first to organize the subject comprehensibly into a whole. Maude Abbott described his work in 1908 as, 'the first comprehensive study covering the whole field'. For nearly another century, however, congenital heart disease remained almost entirely a subject of merely academic interest. Then anaesthetists found techniques of respiratory control with the open chest. This heralded surgical treatment, first in the form of ligation of the patent ductus arteriosus by Gross in the U.S.A. and by Tubbs in England, in the same year 1939. Holmes Sellors and Brock pioneered the surgical attack on pulmonary stenosis in 1947. British cardiac surgery entered its present era with the introduction of the diagnostic aids of angiocardiography and cardiac catheterization in the following years.

Rheumatic Carditis

Early recognition of rheumatic heart disease in Britain presents a story similar in many ways to that of congenital heart disease. It gradually emerged at the hands of several men rather than appearing dramatically in the grasp of one.

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Hunter failed to appreciate the association between rheumatism and heart disease yet his Museum contains several specimens retrospectively recognizable as such. One is a typical example of mitral stenosis;[31] it is accompanied by a clinical history obtained from Heberden who describes the patient's substernal pain as a true example of angina pectoris. There is also a specimen of rheumatic mitral and aortic disease[32] on which John Hunter makes the remarkably enlightened comment that the regurgitation occurring at the mitral and aortic valve orifices must produce a retrograde motion of the blood into the left ventricle, the left atrium and pulmonary circulation, so 'producing that darkness in the face, which stagnation extends to the right side of the heart, then through the whole veins of the body'. There is no evidence that Hunter further developed this remarkable insight into the haemo-dynamics of left and right ventricular failure.

Though Hunter, who had been called in to see the above case by Heberden 'to give a name to the disease' clearly failed to call it 'rheumatic' in 1781, Pitcairn used the term a few years later, in 1788, and Matthew Baillie recognized rheumatic carditis between 1794 and 1797 when he produced the second edition of his book on *Morbid Anatomy*. Here he writes:[33] 'The causes which produce a morbid growth of the heart are but little known; one of them would seem to be rheumatism attacking that organ.' In a footnote he adds, 'Dr. Pitcairn has observed this in several cases'.

About this time, 1790 to 1800, at least four persons were investigating the relationship between rheumatism and heart disease; Jenner, Pitcairn, Wells and Dundas. Jenner's paper was lost, Pitcairn died without publishing his observations, Dundas published first in 1808 and Wells in 1812.

In 1806 David Dundas presented at the Royal Medical and Chirurgical Society's first session, a paper entitled, 'An Account of a peculiar Disease of the Heart'.[34] At the same session John Abernethy gave a paper entitled, 'On a diminution in consequence of disease of the Area of the Aperture by which the left Auricle of the Heart communicates with the Ventricle of the same side.' At that time neither Dundas nor Abernethy had an inkling of the fact that they were describing different stages of the same disease. Dundas it will be noticed did not give a name to the heart disease he was describing, but he did associate it closely with rheumatic fever. He observes that he has seen nine such

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> Dear Sir, The preparation of the enlarged heart which I brought to the College a fortnight ago is to exemplify a disease of that organ which is not described by any author that I am acquainted with, but from the number of cases which have fallen under my observation is, I apprehend, very frequent in this country. The most remarkable circumstance of this disease is its being always connected with, or subsequent to, an attack of acute rheumatism.
>
> The patient complains of great anxiety and oppression at the praecordia, has generally a short cough and difficulty in breathing, which is so much increased by motion, or by any exertion, as to produce an apprehension that the smallest increase of the motion would occasion fatal effects.
>
> The difficulty in breathing is also aggravated by taking even a small quantity of food. He prefers lying on the back, complains of a great palpitation of the heart, and violent pulsation of the carotid arteries, accompanied with noise in the ears and giddiness of the head. The action of the heart is often so strong as to be distinctly heard, and to agitate the bed the patient is in so much that I have counted the pulse of the person by looking at the curtains of the bed.
>
> Towards the conclusion of the disease symptoms of water in the chest take place. The legs become oedematous, and frequently a considerable quantity of water is accumulated in the cavity of the abdomen.
>
> In some cases the disease has been very rapid in its progress, not lasting above four or six weeks; in others it has run on for one or even more than two years. I have only seen one person who has recovered, and I have opened nine persons who have died of the disease.
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> The heart has been uniformly much enlarged in bulk; in one case water was found in the pericardium, in all the others the pericardium adhered to the heart. The heart itself was sometimes nearly three times the size of a healthy heart. The muscular structure is not increased in thickness beyond what it commonly is, so that its powers of action are not augmented proportionally to its bulk. It has also been generally found of an unusual pale colour, and very soft and tender in its texture.

It will be readily appreciated that when Wells came across Dundas's contribution he felt that his own collection of cases had lost much of its value. Nevertheless he did publish his observations, and was the first to use the title, *Rheumatism of the Heart*.[30] Here he cites seven specially those of the right side. The left ventricle is slightly hypertrophied, and there are some soft vegetations adhering to the mitral valve; the tricuspid valve is dilated and its margin slightly thickened. The pericardium is thickened and totally adherent; it shows recent fibrinous exudate.' The accompanying letter commences:

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Coronary Disease

Apart from retrospective diagnoses of cardiac ischaemia by medical historians, and isolated references to calcified coronary arteries at post mortem without clinical correlation with symptoms, the story of coronary disease must begin with Heberden's well-known description of angina pectoris delivered to the College of Physicians in London in 1768, published in 1772,[37] under the title, *Some Account of a Disorder of the Breast*. This title conveys to us the information that Heberden had no idea of the site of origin of the pain he so brilliantly described. His suggestions in this regard are contained in three sentences: 'It may be a strong cramp, or an ulcer, or possibly both.' He suggests here no site of origin of the 'ulcer' or 'cramp'. He then states: 'The pulse is at least sometimes not disturbed by the pain, and consequently the heart is not affected by it.' At this time (1768) he regrets that he has as yet seen no post-mortem examination of a case. Later, in 1782 in the description of angina pectoris found in his *Commentaries*[38] Heberden omits the sentence exonerating the heart. By this time he had seen nearly one hundred cases, and now ascribes the pain to, 'the class of spasmodic not inflammatory complaints.' He has seen one post-mortem, 'on the body of one who died suddenly of the disease, in which a very skilful anatomist could discover no fault in the heart, in the valves, arteries or neighbouring veins, except some small rudiments of ossification in the aorta'. Thus, though Heberden became suspicious of the heart as the source of anginal pain he never confirmed it.

The 'skilful anatomist' referred to by Heberden was John Hunter. In a personal search I have found disease of the coronary arteries recorded in five autopsies performed by John Hunter between 1757 and 1779. In these he records white necrotic endocardial patches, necrosis of papillary muscles, two cardiac aneurysms, and one disease with its mitral and aortic valvular lesions, for though lesions such as mitral and aortic stenosis had been frequently described previously their relationship to rheumatism had not. Bouillaud's studies of the varieties of endocarditis, a term he himself introduced and defined, revealed the stages of development of chronic rheumatic heart disease.

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Parry's work on angina exerted considerable influence on Allan Burns in Glasgow. This is reflected in his chapter on Disease of the Coronary Arteries in his book on *Diseases of the Heart*, of 1809.[45] This chapter opens with the words, 'Let us inquire into the consequences which result from loss of contractility of the coronary vessels'. Burns sums up the position at the time thus: 'To Drs. Heberden, Jenner and Parry we owe most of our information respecting this most fatal complaint.' He adds that he thinks he can add little to the pathology of syncope anginosa beyond what Parry has already said. Nevertheless he does add very significant evidence, which consists of the experiment of tying a moderately tight ligature round a limb and, 'calling it into vigorous action'. Burns is struck first with the weakness of the muscle so exerted, then with the pain, and compares both the weakness and pain so produced with the state of the heart muscle in the presence of rigid, narrow coronary vessels.

Burns rejected Everard Home's explanation of John Hunter's anginal pain which attributed the pain to neuralgia from pressure of the cardiac nerves against the ossified arteries. Nevertheless this concept of angina as a neuralgia dominated the first half of the nineteenth century.

From 1809 to 1850 interest in the coronary arteries flagged not only in Britain but all over Europe. In contrast interest in rheumatic heart disease was intense. The reason for this is simple; whereas valvular heart disease presented problems soluble by the new methods of auscultation and percussion, coronary heart disease was conspicuously negative in these features. It was accepted that the coronary arteries nourished the muscle of the heart, and that when they failed to do so a condition called 'fatty degeneration' of the heart set in. Until Virchow in 1858 introduced the pathological concepts of necrosis and thrombosis 'fatty degeneration' was a term which disguised a variety of ischaemic changes in heart muscle.

An exception to this general statement was provided by the graduation thesis of Erichsen in 1842[46] in which he set out to find an experimental answer to the question, 'what effect the arrest of the coronary circulation would have upon the action of the heart'. Erichsen ascertained that ventricular action continued for an average coronary arteries were found to be extensively ossified. Thus was Jenner's tactful prediction justified by events.

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Allan Burns[50] in 1809 gave a detailed case history of a man of forty with syncope and oppression of the chest. During paroxysms of breathlessness, 'the pulse fell from its usual standard of 70 to 80 at first to 18 then to 12, and in the end it was as low as 10 beats in the minute. In this situation he remained for several years . . .' writes Burns. He concludes the detailed case history as follows: 'One night he supped heartily, went to bed, and slept two hours, when he suddenly awoke convulsed, and almost instantly expired. Before his wife, alarmed by his struggles could procure assistance he was dead.' At autopsy Burns found a huge heart which he describes as, 'an unseemly mass, its huge auricles and broad ventricles were longer than those of an ox . . . all the cavities were equally dilated . . . the heart weighed two pounds'. Burns here advances on all previous reports in that unlike his predecessors he insists in attributing this patient's symptoms to dilatation of the heart and not cerebral disease or epilepsy.

The close association between epilepsy and bradycardia was significantly noticed by Robert Reid in 1824, when he wrote:[51] 'The first symptom of an attack of epilepsy is the suspension of the action of the heart and consequently an intermission of the pulse which may continue from a few seconds to about three minutes, which was the longest period of intermission I have yet seen.' Reid proceeded to speculate that during the period of what he called 'epileptic quiescence of the heart' blood accumulates in the cerebral hemispheres producing an irritation responsible for the epilepsy. His treatment of the attack was most interesting to us today, for it consisted of 'regular compression of the upper abdomen with the closed fist towards the spine while the patient is firmly supported in the back'. This treatment Reid reported as having been adopted with 'gratifying success' in the case duced his pulse-watch. It is surprising that with this instrument he failed to note either very slow or very fast pulse rates. Such slow pulse rates were reported by Gerbezius in 1691 and Morgagni in 1761 in patients diagnosed as epileptics. The first British case was reported by Thomas Spens[49] of Edinburgh in 1793. Once more the diagnosis was epilepsy with a ventricular rate as low as 10 per min. Autopsy revealed no cardiac lesion, and Spens attributed the syncope and bradycardia to the 2 oz. of watery fluid found in the cerebral ventricles which he called hydrocephalus.

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In parallel with this histological attack ran the investigation of electrical potential changes in the heart. Augustus Désiré Waller, son of the Waller after whom Wallerian degeneration is named, was at first a practitioner in Kensington, later turning to physiology. His interest in haemodynamics led him to an investigation of the variations of electrical potential which arise in the human heart, using Lippmann's capillary electrometer. It was in 1887, at St. Mary's Hospital, London, that Waller[57] demonstrated the human electrocardiogram to Einthoven and others, showing them that leads could be taken from anywhere on the surface of the body. Einthoven, using the string galvanometer which had been invented by Ader in 1897, produced human electrocardiograms in 1903.

Meanwhile, in 1883, James Mackenzie had constructed an instrument for obtaining simultaneous recordings of venous and arterial pulses, the polygraph. With this he analysed cardiac arrhythmias into different prognostic groups, observing his patients over many years in general practice to establish his facts. In his *Study of the Pulse*[58] of 1902 he distinguished in particular sinus arrhythmia and extrasystoles from what he called 'auricular paralysis' and 'failure of the ventricle to respond to the stimulus after auricular systole', terms later translated into auricular fibrillation and heart block.

Always anxious to keep clinical medicine within the field of observation by the five senses Mackenzie, with some success, set about searching for physical signs for differentiating the cardiac arrhythmias. He was as keen to abolish the necessity for using his own polygraph as any other specialized instrument. It is not surprising therefore to find that Mackenzie did not welcome the turn of events in the opposite direction denoted by the introduction of the electrocardiograph. With this instrument Thomas Lewis in 1909[59] produced convincing electrical evidence of that atrial change called 'fibrillation'. Direct visual confirmation of the nature of this movement had to await Lewis' experiments on the heart of a horse on Bulford Plain, reported in 1912.[60] 'The chest was opened', he writes, 'while the heart was still beating, and I obtained a clear view of a fibrillating auricle brought to this state, not by experimental interference, but by disease. We now know that auricular fibrillation may occur and persist as a manifestation of disease.' Even Mackenzie acquiesced.

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matter lies in the fact that Withering did not have sufficient evidence to justify him claiming that he had already demonstrated this salutary power of digitalis over the heart. It is only with retrospective hindsight that we can see this to be so.

The action of digitalis on the heart was concealed throughout most of the nineteenth century. It has yielded its secrets reluctantly. This is manifest in Lauder Bruntons's work on it which led him to the conclusion that digitalis produced arteriolar constriction. This work, however, led him directly to his trial of amyl nitrite for angina pectoris in 1867. He relates the story thus:[62]

> The first vaso-dilator investigated was nitrite of amyl. Its power of flushing the face was noticed by Guthrie in 1859, and B. W. Richardson observed that it caused dilatation of the capillaries in the frog's foot; but it was Dr. Arthur Gamgee who first discovered its power of lowering blood pressure. It was under his direction that I had been carrying out my experiments on digitalis, and I used to submit myself to Dr. Gamgee for experiments on the effect of nitrite of amyl on my own pulse from which he made sphygmographic tracings.

Having thus acquired skill in taking and interpreting sphygmographic tracings Lauder Brunton took some on a patient with angina pectoris in the Royal Infirmary, Edinburgh, noting what he called the 'change in tension' during each attack (Fig. 6). He then tried to lower the pressure in the patient's vessels with amyl nitrite. He writes,

> To my delight the experiment proved a complete success. As I administered the nitrite of amyl which my friend Dr. Gamgee had given me, the patient's face became flushed, the pulse, instead of being small and thready became full and bounding, and the pain almost instantaneously disappeared . . . In 1876 along with Mr. Tait I discovered that nitroglycerine had a similar action upon the circulation, but I used to get such an awful headache that I hesitated to give it to patients, and while I was still hesitating Dr. Murrell employed it in a case of angina with great success.

It will be noticed once more that a number of persons played important parts in this discovery of the action of nitrites in angina pectoris.

In conclusion I would like to draw attention to perhaps the most striking feature of these British contributions to cardiology, their slow emergence through the work of a number of men, sometimes working together but often separately. True there are isolated personally triumphant contributions like those of Harvey, Hales and Withering, matter lies in the fact that Withering did not have sufficient evidence to justify him claiming that he had already demonstrated this salutary power of digitalis over the heart. It is only with retrospective hindsight that we can see this to be so.

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Paediatrics

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IN THE Palazzo Medici Riccardi in Florence is an unlit room, the Medici private chapel with its altar on one wall. The other three walls were enriched in 1469 by a fresco, the masterpiece of Benozzo Gozzoli, depicting 'The Journey of the Three Kings to Bethlehem'. Against a varied landscape, here wooded, there bare rock, slowly marches a long winding train of camels, horses, mules and men. Some of the men stand out by reason of their size or their position in the line, some for their colouring. The artist suggests the presence of an unseen host, hidden from view by the contours of the land. Painted by the light of a lantern, all remains in darkness until the guide turns his spotlight on a hill, a tree, a rock, an animal, a man.

This is an allegory of history. The historian views the life and the work of many men, as they pass through a varied landscape, now favourable and now unfavourable. He lights the picture piece by piece, traces the path of the procession, the beginnings small and distant, the foreground dominated by today.

British paediatrics like the fresco has had its march of many men, finding little bits of treasure by the way, knowing in general what they were seeking. The Kings on their journey knew exactly what they sought. They found it. Did they, I wonder, know any more clearly than we do the value and the purpose of what was found?

The British contribution to paediatrics stirs our pride. Like the masterpiece of Benozzo Gozzoli, it belongs to the world.

THE CENTURIES OF PREPARATION

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The latter part of the sixteenth century saw a turning point. The preparation for the press of classic texts and the dissemination of book learning led editors to succumb to the temptation of interspersing observations of their own. With Thomas Phaer's *Boke of Children* (1553) comes not only the first paediatric book with any originality in the English language but the work of one who declares a true paediatric interest—'my purpos is here to do theim good that have moste neede, that is to saie, children'.

Phaer was born of Flemish stock in Norwich in 1510. He studied at Oxford and Lincoln's Inn, publishing a legal work, *A Boke of Presidentes* in 1543. He was appointed Solicitor to the King and Queen's Majesties in the Court of the Welsh Marches, was Member of Parliament for Cardigan for the last two sessions of Philip and Mary and the first of Elizabeth and seems also to have practised medicine in Kilgerran, Pembrokeshire for twenty years before applying for his B.M. at Oxford early in 1559, eighteen months before his death. His reputation is perhaps greatest as the translator into English verse of the first nine books and part of the tenth of Virgil's *Aeneid.* A well intentioned man, keen 'for defence of my country language', he wanted 'phisicke to come forth in Englishe'. Like many later paediatricians he is a man with a mission.

Phaer lists thirty-nine diseases with which children are 'chefely vexed and greved'. These are the things that happen to children that can be seen and recognized, external rather than internal medicine, in the language of today signs and symptoms rather than diseases. The list, not surprisingly, has changed but little from the time of ancient Greece.

THE CENTURY OF IDENTIFICATION (XVII)

Early in the seventeenth century a new disease appeared among the infants in the south-west of England, destined to remain a mystery for three hundred years. Rickets, known at the time as the English

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Whatever was happening through the period of the Napoleonic Wars, after the hungry forties rickets abounded. Samuel Gee reckoned in 1868 that '30.3 per cent of sick children under two years of age (attending the Hospital for Sick Children, Great Ormond Street) are rickety'. In his private practice he recognized it too in the children of the comparatively rich.

Cod liver oil was first used in medicine at the Manchester Infirmary about 1772 for patients with chronic rheumatism, as an external inunction and then 'an accidental circumstance' writes Dr. Robert Darbey to Dr. Thomas Percival (Percival 1789) 'discovered to us a remedy . . . the cod, or ling liver oil, taken by mouth'. Cod liver oil, oleum aselli, first appeared in the *Pharmacopoeia* in 1777. In 1807 S. A. Bardsley gave it with benefit in warm table-beer to women who had rheumatism, possibly osteomalacia, after childbirth. In a treatise on cod liver oil published in 1841 John Hughes Bennett states that he learned of its value, not in Manchester, but in Germany. A visiting professor from Marburg had copied its use from English practice. One of his Dutch pupils is said by Hess (1929) to have reported the cure of three rickety infants by cod liver oil in 1826. Bennett revived the British interest in the oil. Six years after his book was published the pharmacy accounts of St. Bartholomew's Hospital show the first purchases in 1847 (Franklin, 1954). By 1877, 811 gallons at five shillings were bought. Samuel Gee wrote (1868) 'in cod liver oil we possess a pharmaceutical agent worthy of a place beside iron, Peruvian bark and mercury'. These were the specifics for the green-sickness, quartan agues and the pox.

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The battle was waged not only in the journals but at a personal confrontation before the Section of Children's Diseases at the Royal Society of Medicine between Mellanby and Paton on 27 February 1920. Mellanby presented his proofs that deficiencies in the diet caused rickets in dogs and that this disease was preventable and curable by fat soluble vitamin. He was attacked from the flank by Paton who, refusing to accept the evidence, maintained that the cause was lack of sunshine and exercise.

When it came to children rather than dogs or rats the matter was convincingly settled by the 'Studies of rickets in Vienna 1919–22' (M.R.C., 1926). The team, led by Dr. Harriet Chick and including the paediatrician, Helen Mackay, conducted a therapeutic trial in the wards of Clemens Pirquet. As he confesses in the Preface he had long regarded rickets as due to an infection and comparable with childhood tuberculosis, which had attacked every Viennese child by the age of fifteen years. Rickets became severe if caught early, if resistance was lowered by an inherited disposition, or if susceptibility was increased by any means. In the third year of the study the sight of a large number of hand-fed infants growing in his wards without the expected disease convinced him of the value of cod liver oil. This was the answer to those who, like Robert Hutchison, the apostle of common sense, could taunt Mellanby in public in 1920 with a 'reminder' that 'vitamines are the latest dietetic stunt'.

King Edward VII said of tuberculosis, 'if preventable, why not prevented?' It is interesting to speculate why fifty years after Mellanby rickets still damages child health.

The medical history of the second half of the seventeenth century is dominated by Thomas Sydenham in medicine and Walter Harris in paediatrics. Both men were involved deeply and personally in the troubles of their time, Sydenham fighting in youth for Cromwell and Harris moving from the Anglican to the Roman Church and back. Both were clinical observers, both attempted to reduce acute diseases into a system, and both succeeded in devising a practical method of treatment. Sydenham's immediate claim to fame after his death rested on the posthumous 'Processus Integri', the method of curing almost all diseases, which guided doctors for more than fifty years.

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Cortex Peruviana, Jesuit bark, was brought to England from Antwerp where it had been used since 1643 by James Thompson, merchant, in 1658 (Mercurius Politicus, 1658). Eight years later in 1666 Sydenham published his 'method of curing fever'. Quinine is given only a lukewarm recommendation, and a fatal effect of its use is recorded. By the third edition in 1676 bark is recommended for quartan agues. Meanwhile Talbor, a scholar of St. John's College, Cambridge, who had been an apothecary's apprentice in Cambridge, had settled in Essex. His success with the bark in curing agues brought him to London where he sold his cure as a secret remedy, eventually curing King Charles II. Recommended to Paris, he treated the Dauphin with success and was persuaded to sell his secret to Louis XIV for two thousand Louis d'Or in 1679. Talbor, knighted by Charles, died in 1681.

Sydenham, keen clinical observer that he was, conceded that the bark possessed a secret virtue destroying the seeds of the disease and acted without any 'sensible evacuation', yet there remained four good reasons why the drug met strong opposition. The Jesuits were responsible for it, hardly a good recommendation. Some supplies may have been prepared from the wrong tree. Sir Robert Talbor had sold it as a secret remedy, while practising without a College Licence. And perhaps subconsciously and most importantly because if it did succeed its success was inexplicable on the basis of Hippocratic pathology. It was a treatment by neither contrary nor similarity, and no humoral change nor evacuation could be detected. For Walter Harris Jesuits bark remained 'a nine-day wonder', 'the greatest Catholicism or panacea extant' and the standby of 'the ignorant tribe of impudent empiricks'. In 1683 Harris published *Pharmacologia Anti-empirici or a Rational Discourse of Remedies both Chymicall and Galenical.* While the patients' fever abated with quinine, that of the doctors grew great. Convulsed with argument, spewing out words, the doctors defended their cherished illusions with the same blindness and obloquy with which they have always tried to conserve their methods and their ways of thought. In the end the truth that agues, especially quartan intermittents, responded to the proper use of quinine, could no longer be denied. At that point the humoral theory of disease began its final slow disintegration.

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Cortex Peruviana, Jesuit bark, was brought to England from Antwerp where it had been used since 1643 by James Thompson, merchant, in 1658 (Mercurius Politicus, 1658). Eight years later in 1666 Sydenham published his 'method of curing fever'. Quinine is given only a lukewarm recommendation, and a fatal effect of its use is recorded. By the third edition in 1676 bark is recommended for quartan agues. Meanwhile Talbor, a scholar of St. John's College, Cambridge, who had been an apothecary's apprentice in Cambridge, had settled in Essex. His success with the bark in curing agues brought him to London where he sold his cure as a secret remedy, eventually curing King Charles II. Recommended to Paris, he treated the Dauphin with success and was persuaded to sell his secret to Louis XIV for two thousand Louis d'Or in 1679. Talbor, knighted by Charles, died in 1681.

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Thomas Coram opened his Foundling Hospital in 1741 to preserve the lives of babies left to die on the dung heaps of London; and Jonas Hanway investigated the high death rates of the parish babies. Both had experience of the unsatisfactory techniques employed in rearing babies by hand and believed that even wet-nursing was open to serious abuse. Both enlisted Parliament's aid, Coram for a Charter of Foundation for his Hospital and Hanway to ensure the inclusion of all parish poor under the age of four years within Bills of Mortality. An attempt to improve the care of infants by parental education was made by William Cadogan who wrote a letter to one of the Governors of the Foundling Hospital, published anonymously by order of the General Committee in 1749. Entitled *An Essay upon Nursing and the Management of Children from their Birth to Three Years of Age*, this revolutionary twenty-eight-page pamphlet guided infant care for the next century. The traditional practice of keeping an infant too warm was condemned and Cadogan attacked the 'Flannels, Wrappers, Swathes, Stays etc. . . . almost equal to its own weight . . .' applied as if Nature had produced her chief work, a human creature, so carelessly unfinished as to want those idle aids to make it perfect.

Another valiant attempt to improve the lot of infants was due to Dr. George Armstrong, brother of Dr. John Armstrong, the Poet. Both were Edinburgh graduates and both made the southward journey to London, John in 1732 and George, in 1745 as a refugee from Prince Charles's unsuccessful Rising. John was probably editor and translator of *A Full View of all the Diseases Incident to Children* published anonymously in 1742. This contained a new translation (his own?) of Walter Harris' *De Morbis Acutis* and of Boerhaave's *Treatise on Diseases of Children*, with English abridgments of Sylvius on thrush, Willis on epilepsy, Sydenham on smallpox and measles, Andry on worms, Burton on the chincough, Glisson on rickets and Wiseman on the King's Evil. A compendium of all that was best in paediatrics at the time, the book was designed to encourage doctors to take over wrought in England during the century. Superstition made way for sophistication, coarseness for gentility and, although the gaming clubs of the wealthy and the gin alleys of the poor characterized the Georgian scene, there was a strong and effective background of genuine charity in thought, word and deed. In paediatrics two important reformers interested themselves in the fate of the unwanted baby.

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The story of the Universal Dispensary for Children opened in 1815 by John Bunnell Davis and of Charles West's foundation in 1852 of the Hospital for Sick Children in Great Ormond Street have been recounted in detail in 'The evolution of hospitals in Britain' (Franklin, 1964).

In 1784 while George Armstrong's book was still in print a new British contributor published a *Treatise on the Diseases of Children*. Michael Underwood was born in 1737, studied at St. Georges Hospital and in 1779 was surgeon to the British Lying-in Hospital, now the British Hospital for Mothers and Babies, Woolwich. He practised successfully in midwifery, gynaecology and in diseases of infants and children, becoming Physician to the Prince of Wales, afterward George IV and attending Princess Charlotte's birth. In 1801 aged sixty-four he retired to live in seclusion until his death in 1820. Extracts from the 122 volumes of his diary were published in 1823. The rather morbid entries include many meditations on religious subjects.

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The difficulty was a clinical one. Swelling of the gums, characteristic of adult scurvy, was rare, beading of the ribs, thought to be diagnostic of rickets, was common. Some epiphyses were swollen, although at first it was not regarded as significant that scurvy swelling unlike rickety swelling was asymmetrical. The nature of this curious infant disease, resembling rickets, yet differing, and of its relation to haemorrhage under the periosteum, was settled brilliantly by Thomas Barlow (1883). He had analysed thirty-one cases, noting their special character and his views cannot be better expressed than in the title of his paper in the *Medico-Chirurgical Transactions*—'On cases described as "acute rickets" which are probably a combination of scurvy and rickets, the scurvy being an essential, and the rickets a variable element.' Cheadle had found potato helpful in treatment, Gee lemon juice and potato. William Baly (1843) had, it must be remembered, cleared scurvy out of Her Majesty's Prisons by a liberal addition of lightly-cooked potato to the diet. Barlow favoured orange juice, and after Barlow's Bradshaw Lecture on 'Infantile scurvy and its relation to rickets' (1894) the real argument was over.

American paediatricians were not so easily persuaded. The American Paediatric Society's (1898) collective investigation on infantile scurvy in North America analysed records of 359 babies. The majority report blamed prolonged use of unsuitable diet, especially of proprietary foods. A minority report by Augustin Caillé drew attention to the danger of heat treatment of milk and insisted on the value of fruit juice. Barlow's final separation of scurvy from rickets was amply justified.

The nineteenth century witnessed the beginnings of preventive paediatrics. Jennerian vaccination got into its stride. Infantile scurvy was recognized and was treated with orange juice. Cod liver oil for a time was used to cure rickets. Rickets remained, however, along with tuberculosis of bone, a major cause of physical handicap.

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M.R.C.S. in 1857. After a post-graduate trip to Paris, he joined his father's unqualified Liverpool practice in 1858, the year of the Medical Register Act. Temperaments clashed and soon the younger man set out on his own, quickly earning a well merited reputation for saving lives and limbs. Hugh Owen Thomas preached a gospel of rest, fresh air and conservation. He was a craftsman, the damaged or diseased joint of each patient to him a unique problem, demanding its own solution. Splints and apparatus were custom built by a metal worker and a leather worker under the master's own eye.

Thomas had married in 1864 a Miss Jones. Childless they took some interest in her nieces and nephews. The eldest of them, Robert Jones, had been born in 1857, and when it was decided in 1873 that he should enter medicine, it was natural that he should study in Liverpool living in the house of his uncle and aunt and attending the Liverpool school of medicine. Five years later he qualified at the age of twenty-one as a licentiate of the Royal College of Surgeons in England. At once he joined his uncle in the busy practice that occupied the whole of every weekday, with a free clinic on Sundays.

Thomas was a genius, an individualist who went his own way; he preferred speed to anaesthesia, and distrusted Lister's carbolic spray. What he wrote was recognized by the perceptive few, ignored by the many, who saw him only as a crank. When he died in 1891 at the early age of fifty-seven, his legacy was that he had inspired two men, his nephew Robert Jones and one John Ridlon of New York and later Chicago who was able to carry the message effectively across the Atlantic. Hugh Owen Thomas planted the tree, Robert Jones tended it and by his strong and upright character and his genial personality gathered a mighty harvest for all who wished to share in it. 'If Owen Thomas was a pioneer of orthopaedics', wrote Dr. Charles Macalister, 'it was his nephew, Robert Jones, who ultimately became responsible for making it a special branch of surgery.'

In 1919 at the end of a great war that had taught many lessons in surgery of trauma of bones and joints, Robert Jones with G. R. Girdlestone, pupil and disciple, published a key paper in the *British Medical Journal* on 'The cure of crippled children. Proposed national scheme.' 'Many thousands of children otherwise doomed to the life of cripples,' they wrote, 'will be redeemed to health, and others, though not fully cured, enabled to become self-supporting citizens, and given

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What this British innovation has achieved in setting an example to the world is great indeed. But times change. The 'very relative cleanliness' that politely described the squalor of slum housing earlier in this century has given place to modern flats with fitted carpets. A new lesson has had to be learned, too, from the world of psychiatry and the words of John Bowlby. As the age for prevention and treatment has been lowered, so more and more crippled children have entered the longstay hospitals while still needing for their emotional development the close embrace of the family circle. The price of medical and surgical treatment has increased and now includes emotional deprivation. Robert Jones took pity on the incurables despised and rejected by physicians, the foreground of whose mind was filled with acute disease and whose hospitals were designed for the short-stay patient destined to be quickly dead or better. But even physicians learn. The cause of the crippling too has changed. Rickets, tuberculosis, social diseases, have ceased to cripple. Anterior poliomyelitis is prevented. Congenital limb defects, cerebral palsy, muscle and rare nerve diseases and spina bifida remain, and these are not diseases of debility or bad environment, but genetic or acquired in the womb or the delivery room. Evenly spread through the social classes many live in good conditions. It is not in long-stay institutions run on hospital lines with big wards and little mothering that young children can best grow in happiness, self-reliance and 'in their capacities'.

The British have always been pioneers in the care of children with handicaps. Education and child health act and react upon each other. After the establishment of compulsory education by the Elementary of anterior poliomyelitis, the same techniques have revolutionized the orthopaedic treatment of spina bifida. What the surgeon sought for his child patients was 'happiness, a self-reliant outlook and the greatest possible capacity', so work and play were available and preparation for life. Macalister has described (1930) the foundation of the Children's Hospital at Heswell planned by Robert Jones and himself, taking its inspiration from a Home for Incurables. Home environment in the Liverpool of the last years of the nineteenth century was 'clamour, very relative cleanliness, and improper feeding...' What was incurable at home recovered under good hygiene. So began an increasing residential accommodation for crippled children run on hospital lines in the country and 'under scientific and sanitary auspices'.

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Sooner or later even the most important concepts cease to be productive. If they apply widely, as in the case of the bacterial cause of disease, the concept overshadows all. Any other explanations of disease are hindered until observations bring to light enough phenomena that still cannot be explained. Patients clearly vary in their reaction to bacterial attack, and so once more interest is awakened in temperaments, tendencies, constitutional predispositions.

Garrod, whose researches like Pasteur's began in chemistry, published his first paper in 1892 on urinary pigments. Six years later this work brought him in touch with a child with alkaptonuria. Bowel bacteria were believed at the time to cause this disturbance of tyrosin metabolism. 'One afternoon while walking home from the Hospital thinking about these problems,' wrote a pupil, Dr. George Graham (1936) 'it suddenly occurred to him that alkaptonuria might be due to a chemical error on the part of the body, which might be present throughout life. The proof of this hypothesis was unexpectedly easy as the mother of one of his alkaptonuric patients was pregnant.' Staining of the new baby's napkin was noted on the second day of life and homogentisic acid found in the urine about a week later. Garrod had also observed the frequency of the disease in the progeny of first-cousin marriages, suggesting inheritance according to the laws codified by Mendel whose work had been discovered and republished by Bateson in 1900. In this manner an inspiration was confirmed by an observation. A new concept took shape, of inborn errors of metabolism. This subject was chosen by Garrod for his Croonian Lectures before the Royal College of Physicians in 1908, by which time he had added to his list albinism, cystinuria and medicine owes to Morgagni, could be linked with a clinical picture during life. Then another Frenchman, his starting point the new and fast growing science of organic chemistry, had found in fermentation the proofs of the existence of a vast unknown silent living population, the bacteria. Now the seeds of disease could be isolated, grown in test tubes, stained with dyes, gazed at down microscopes and used for preventive treatment. The rewards in understanding acute disease and epidemics were at once seen to be great and promised to be greater. That there were many chronic infections like tuberculosis and syphilis, led to hopes that these external agents could be blamed for almost all diseases. The seed claimed attention rather than the soil.

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The application of genetic science to medicine and to paediatrics owes no special debt to Britain. Antenatal and perinatal care owe a great deal.

The British doctors who first contributed to paediatrics were mostly skilled in midwifery. As more detailed knowledge was gathered about disease, pathology and physiology, it was natural for general physicians to play a larger part. Samuel Gee claimed that the 'great landmarks in the subject had been discovered and expanded by general physicians rather than by specialists'. He was thinking narrowly of disease arising in childhood, acute rather than chronic. He was not thinking of handicaps acquired before, during and soon after birth. Their avoidance owes much to two obstetricians, J. W. Ballantyne of Edinburgh and Eardley Holland of London.

Ballantyne was born in 1861 at Eskbank, Midlothian. His father kept a nursery garden. He qualified M.B., C.M. at Edinburgh in 1883 and in 1885 became senior assistant to the Professor of Midwifery. His next post in 1890 was Lecturer on diseases of infancy in the School of Medicine of the Royal Colleges. The direction of his interests is shown by the title of his two-volume work, published in Edinburgh in 1895—*The Diseases and Deformities of the Foetus: an attempt towards a system of antenatal pathology*. The topics were general dropsy, elephantiasis, ichthyosis, sclerema and skin diseases generally. In 1902 and 1904 appeared two further volumes on *Disease and Deformities of the Foetus*, a mine of information derived from the literature and from personal observation, which needs to be explored even now by anyone writing on these subjects. Begun, he tells us, in active curiosity, as his interest deepened he regarded his studies as part of preventive medicine. One ante-natal bed was allowed in 1901 in the Royal Maternity Hospital, his ante-natal clinic was officially to doubt his memory, that it was in Garrod's wards at St. Bartholomew's that Darrow and Howland first realized the importance of electrolytes in the blood and of blood volume in disease. Garrod had returned from considerable work with adult dysentery. Darrow's studies helped to make safe the use of intravenous fluids, written of as dangerous in standard paediatric textbooks even as late as 1929. Such treatment making its demands for micro- and then for micro-micromethods of blood analysis has not only advanced paediatric treatment but has made possible much of the new science of neonatology.

The application of genetic science to medicine and to paediatrics owes no special debt to Britain. Antenatal and perinatal care owe a great deal.

The British doctors who first contributed to paediatrics were mostly skilled in midwifery. As more detailed knowledge was gathered about disease, pathology and physiology, it was natural for general physicians to play a larger part. Samuel Gee claimed that the 'great landmarks in the subject had been discovered and expanded by general physicians rather than by specialists'. He was thinking narrowly of disease arising in childhood, acute rather than chronic. He was not thinking of handicaps acquired before, during and soon after birth. Their avoidance owes much to two obstetricians, J. W. Ballantyne of Edinburgh and Eardley Holland of London.

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History plays the eunuch unless the past, linked with the present, helps to create the future. Four men have played vital parts in British paediatrics because their work, bridging a century, helped to create new attitudes. John Thomson (1856–1926), successful in practice in Edinburgh, brilliant clinician, 'opened doors' for many doctors by his practical concern for the families of mentally handicapped children. He taught that diagnosis was not enough and that parents should be given patient explanation and long-term support. Leonard Parsons, cultivating paediatric science in Birmingham with his studies in coeliac disease and in haematology, showed to obstetricians as well as to paediatricians the importance of antenatal paediatrics. James Spence, immortalized by the *Thousand Family Studies*, brought scientific paediatrics from the bedside to the fireside in the family's home, because he believed in the value and the importance to health of the wholeness of the family and of the interactions between its members. Donald Paterson, the Canadian, is best remembered as a teacher, a stimulator of paediatric activity and the founder of the British Paediatric Association.

The contributions of three women can appropriately end this survey. Helen Mackay, Cicely Williams and Mary Sheridan. Each represents a different facet of the total function of Child Health in any society, Helen Mackay the traditional pre-occupation with disease, its causes and treatment, with a strong flavour of its social effects on family life. Cicely Williams was concerned with diseases of ignorance arising out of cultural idiosyncrasies, Mary Sheridan with a new way of looking at the behaviour development of normal children as a means of identifying abnormal behaviour in its earliest stages.

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Cicely Williams pioneered paediatric concern for child health in developing societies, not as an extension of home based medical care, but in its own right. And at the same time she paved the way to much scientific study of protein starvation.

Mary Sheridan qualified in Liverpool in 1922 and after post-graduate paediatric study joined the Cheshire public health service in 1926. The point of departure for her achievement was that despite four years of paediatric training she remained puzzled by routine questions of assessment and management of handicapped children. She found herself testing the vision of five-year-old school entrants and of mentally backward children on charts on which they could not recognize the pictures. She had the humility to accept the fact of ignorance and the ingenuity and patience to design useable charts. Later she moved to Manchester where she began to work on hearing tests in the same spirit, writing half a dozen plays the while.

She realized how little she knew about the recognition of hearing problems in children. Starting from a modest appreciation of her own lack of knowledge she soon found that she was not alone. Earlier work there had been in many countries. Philip Franklin in London, in a hearing clinic which he organized at the Infants Hospital, Vincent Square, now part of the Westminster Hospital, had shown how failure to develop speech was often due to deafness and that some 'dumb' children diagnosed and even institutionalized as mentally defective, were in fact of high intelligence but needed sensory stimulation before their first birthday. This aroused interest but did not lead to any general action until Mary Sheridan, having carefully observed the normal programme of hearing responses in infancy, devised a screening test suitable for general use at six months.

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Mary Sheridan's work coincided with a burst of enthusiastic revolution in the care of crippled children. Lastly Edward Mellanby in 1919, away from his laboratory and his dogs, braves the assembled children's specialists of London to take the penultimate step in the prevention of rickets by showing it to be a vitamin deficiency and by proving that vitamins are more than 'the latest dietary stunt'.

To label the centuries is a tempting task. The sixteenth turning from the old to the new ended the 'ages of preparation'. The search for new objectives, which required to be recognized and defined, earns for the seventeenth the title 'century of identification', while in the eighteenth human reason discarded altogether its historic props and tried to 'go it alone'. Sometimes called the age of reason, it is more accurately entitled the 'century of ratiocination'. All this reasoning led men to some solutions which the nineteenth and twentieth busily exploited. These 'centuries of solution' ought, if the plans go right, to lead to the 'age of perfection'. If the wrong problems have been identified and false reasoning has by some dreadful chance led to faulty solutions the next centuries may earn the titles of 'frustration' or even 'annihilation'. But let us hope that, having reached the foreground of the fresco, the procession of British scientists and physicians contributing to child health, are really marching on towards an age of 'perfection'.

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Genetics

by

JAMES R. MILLER

BIO-MEDICAL SCIENCE has become so complex; so many disciplines and so many individuals from different nations contribute to any given problem that it is often difficult, if not impossible, to trace the origin and evolution of a particular concept, hypothesis or idea, or even to determine the beginnings of a specific field of study. The beginnings of genetics are much better defined than they are for many of the disciplines discussed during this symposium. Although pre-Mendelian studies were made in the general field of variation, it is generally conceded that Mendel's experiments and concepts were of an entirely different kind. As Stern and Sherwood[1] in their book *The Origin of Genetics* have stated 'Gregor Mendel's short treatise "Experiments on Plant Hybrids" is one of the triumphs of the human mind. It does not simply announce the discovery of important facts by new methods of observation and experiment. Rather, in an act of highest creativity, it presents these facts in a conceptual scheme which gives them general meaning. Mendel's paper is not solely an historical document. It remains alive as a supreme example of scientific experimentation and profound penetration of data.' Although Mendel's publications appeared between the years 1866 and 1873, it was not until 1900 that they were dramatically drawn to the attention of the scientific world. An English biologist was there at the very beginning and he was shortly to be joined by an English physician, and together they were going to set the stage for many distinguished British contributors to the science of genetics, both in its fundamental aspects and as it relates to man and his well-being.

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William Bateson

The English biologist was William Bateson (1861–1926) and it was of the basic terminology of the new science, including its name—genetics. He was able to see the potential significance for genetics, not only with respect to its application in animal and plant improvement but in the welfare of human beings. In his book *Mendel's Principles of Heredity—A Defence*, first published in 1902 and which is generally conceded to be the first textbook in genetics, he made the following statement: 'An exact determination of the laws of heredity will probably work more change in man's outlook on the world and his power over nature than any other advance in natural knowledge that can be clearly foreseen'.[6]

Although at present many would believe that advance in nuclear physics must be assigned first importance, it is conceivable that in the long view Bateson's prediction will prove to be correct.

In 1908 he assumed the Professorship in Genetics at Cambridge, and his inaugural lecture contains an extension of this discussion on the social significance of genetics. The reading of it sounds very similar to much of the discussion which we read today concerning the potential value and hazards of eugenics and so-called 'genetic engineering':

> Some will say perhaps this is all very well as a scientific curiosity, but it has nothing to do with real life. The right answer to such criticism is of course the lofty one that science and its applications are distinct: that the investigator fixes his gaze solely on the search for truth and that his attention must not be distracted by trivialities of application. But while we make this answer and at least try to work in the spirit it proclaims, we know in our hearts that it is a counsel of perfection. . . . And surely to the study of Heredity pre-eminently among all the sciences we are looking for light on human destiny. To pretend otherwise would be mere hypocrisy. So while reserving the higher line of defence I will reply that again and again in our experimental work we come very near indeed to human affairs. . . . No sociologist can examine the pedigrees illustrating the simple descent of a deformity or a congenital disease, and not see that the new knowledge gives a solid basis for practical action by which the composition of a race could be modified if society so chose. [7 (pp. 31–32)]

In this lecture also appears a statement which has been the motto of geneticists ever since, '. . . if I may throw out a word of counsel to beginners it is: treasure your exceptions! When there are none the work gets so dull that no-one cares to carry it further. Keep them always uncovered and in sight. Exceptions are like the rough brickof the basic terminology of the new science, including its name—genetics. He was able to see the potential significance for genetics, not only with respect to its application in animal and plant improvement but in the welfare of human beings. In his book *Mendel's Principles of Heredity—A Defence*, first published in 1902 and which is generally conceded to be the first textbook in genetics, he made the following statement: 'An exact determination of the laws of heredity will probably work more change in man's outlook on the world and his power over nature than any other advance in natural knowledge that can be clearly foreseen'.[6]

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The American geneticist, George Beadle, in his Nobel Prize address[11] makes it quite clear that the work which he and his colleagues did leading to the development of the 'one gene-one enzyme' hypothesis, for which the Nobel Prize was awarded, had its roots clearly in the studies of Garrod. In fact the work of Beadle and Tatum really constituted the rediscovery of the same phenomenon of which Garrod was aware forty years earlier. This phenomenon of independent rediscovery is essentially what happened with Mendel's work. De Vries and Correns did not come upon Mendel's work until they themselves had repeated the essence of his experiments. Beadle has stated that he and Tatum were unaware of Garrod's findings until they were well into their experiments on Neurospora and had developed their concepts on the relation between genes and enzymes.

Garrod, therefore, can be considered the 'Father' of what has become known as biochemical genetics. By the study of the disease alcaptonuria he formulated many of the basic principles of biochemical genetics, particularly the concept that a specific gene determined a block in a metabolic sequence, with deleterious consequences of: (1) the failure of certain compounds to be synthesized beyond the block, and (2) the accumulation of compounds which would normally be metabolized. Alcaptonuria is a disease characterized by excretion of homogentisic acid which normally is broken down into aceto-acetic acid. Garrod postulated that the splitting of the benzene ring of homogentisic acid was carried out by a specific enzyme and that '. . . in alcaptonuria this enzyme is wanting'. While he did not state that a defective gene was responsible for the fact that the enzyme was 'wanting', it seems quite clear, as Beadle has pointed out, that the relation between the two was implicit in Garrod's thinking, and it is obvious from his writings that the concept of the relation between the gene and a specific enzyme reaction was his.

In 1908 when he delivered his Croonian lectures before the Royal College of Physicians he had extended his studies to include in addition to alcaptonuria three other diseases—albinism, cystinuria, and porphyrinuria. Although there was some early appreciation of the significance of his work, this petered out after 1920 and in the next two decades there was never any reference to the work in standard genetic texts, and only a handful of individuals, notably J. B. S. Haldane,[12,13] seemed aware of the potential significance of the

The American geneticist, George Beadle, in his Nobel Prize address[11] makes it quite clear that the work which he and his colleagues did leading to the development of the 'one gene-one enzyme' hypothesis, for which the Nobel Prize was awarded, had its roots clearly in the studies of Garrod. In fact the work of Beadle and Tatum really constituted the rediscovery of the same phenomenon of which Garrod was aware forty years earlier. This phenomenon of independent rediscovery is essentially what happened with Mendel's work. De Vries and Correns did not come upon Mendel's work until they themselves had repeated the essence of his experiments. Beadle has stated that he and Tatum were unaware of Garrod's findings until they were well into their experiments on Neurospora and had developed their concepts on the relation between genes and enzymes.

Garrod, therefore, can be considered the 'Father' of what has become known as biochemical genetics. By the study of the disease alcaptonuria he formulated many of the basic principles of biochemical genetics, particularly the concept that a specific gene determined a block in a metabolic sequence, with deleterious consequences of: (1) the failure of certain compounds to be synthesized beyond the block, and (2) the accumulation of compounds which would normally be metabolized. Alcaptonuria is a disease characterized by excretion of homogentisic acid which normally is broken down into aceto-acetic acid. Garrod postulated that the splitting of the benzene ring of homogentisic acid was carried out by a specific enzyme and that '. . . in alcaptonuria this enzyme is wanting'. While he did not state that a defective gene was responsible for the fact that the enzyme was 'wanting', it seems quite clear, as Beadle has pointed out, that the relation between the two was implicit in Garrod's thinking, and it is obvious from his writings that the concept of the relation between the gene and a specific enzyme reaction was his.

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Galton's interest in these matters relating to human variation came late in his life, and really constituted a second career. The first part of his life included training as a physician and explorations in Africa. For his geographical studies in Africa and for astronomical observations he was awarded the gold medal of the Royal Geographical Society. In 1856, at the age of thirty-four years, he was made a Fellow of the Royal Society.[15] It was after this that he became interested in all aspects of human variation, and measured an enormous number of human attributes, both mental and physical. As Newman[15] aptly states '. . . his activities actually were neither limited nor classifiable'.

The beginnings of a systematic study of human genetics can actually be traced to Galton, and his two books *Hereditary Genius* (1869)[16] and *Natural Inheritance* (1889).[17] He realized the difficulties of measuring many human characteristics, particularly those associated with mental attributes, and he was the first to use Shakespeare's phrase 'Nature versus Nurture' to describe the human condition. He himself favoured the nature side of the argument, and suggested that familial concentrations of individuals with particular kinds of outstanding skills, e.g. the Bach family, was attributable to biological rather than cultural inheritance. His interest in human variation led him to see the value of twins in such studies. He grouped twins into two categories 'similar' and 'dissimilar', and concluded correctly (as later confirmed by embryological and genetic studies) that the former resulted from a single fertilized egg, and the latter from two eggs fertilized independently. His studies were the first of a long series which used twins in an attempt to analyse the 'nature-nurture' problem.

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Presumably because it was an American publication and sufficiently obscure to meet his purpose!

Sir R. A. Fisher

Undoubtedly the most outstanding individual in the biometrical or statistical side of genetics in Great Britain was R. A. Fisher (1890–1962). This was a brilliant individual, trained in mathematics and statistics. He was introduced to genetics as a consultant to biologists in general in the field of bio-mathematics, and was immediately captivated by the mathematical and statistical problems posed by genetic theory. It is said that C. D. Darlington in particular interested Fisher in the fascinating challenges posed by genetics. He was largely responsible for bridging the gap between the 'blending inheritance' group of Pearson and the Mendelians, by demonstrating that the results obtained by biometricians were a logical consequence of Mendelian inheritance in a classical paper 'The correlation between relatives on the supposition of Mendelian inheritance', published by the Royal Society of Edinburgh in 1918.[21] He followed Carl Pearson as Galton Professor at University College in 1933, and in 1943 succeeded Punnett as the Professor of Genetics at Cambridge. While at the Galton Laboratory his interest in determining genetic linkage in man led him to work on human blood groups as possible marker genes. The product of these efforts with G. L. Taylor, R. R. Race and Ruth Sanger, was the unravelling of the genetic complexities of the Rhesus blood groups.

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As Penrose has pointed out[20] one aspect of the English tradition in this discipline has involved the assembling and publication of detailed data on human pedigrees with a diversity of genetically determined diseases. For example, Galton and Pearson founded *Biometrika*, the *Annals of Eugenics* (now the *Annals of Human Genetics*) which for decades was the only journal devoted solely to problems of human genetics, and the *Treasury of Human Inheritance*. These journals served as an outlet not only for the works of the staff of the Galton Laboratory and colleagues such as Haldane, who was Professor of Genetics in London in 1933 and in 1937 became Professor of Biometry at University College, but for a number of English physicians who were outstanding in their own specialities, and who were acutely aware of the significance of genetics in the causation of many of the diseases with which they came in contact.

The statistical bent of English human genetics was strong, influenced primarily by Fisher and Haldane. Penrose was a physician who was influenced greatly by his associations with Fisher and Haldane and made major contributions to the statistical analysis of many problems of human variation. Among his many outstanding efforts was the unravelling of the maternal age effect in the aetiology of mongolism, or Down's syndrome as it is now called after Langdon Down, another British physician who first described the condition. In addition Penrose through his systematic research brought to the area of mental retardation a biological outlook which has only recently been appreciated.

The present incumbent, Harry Harris, in a sense breaks the tradition of a strong statistical approach of the Galton Laboratory because his own outstanding contributions have been in the area of biochemical genetics, the work begun by Sir Archibald Garrod in the first decade of the century. However, it should be pointed out that Harris has extended these studies, and the major contributions made by him and effect in originating and moulding the science of human genetics.'[20] This modest statement made by L. S. Penrose, who occupied the Chair for a period of twenty years, does not do justice to the real impact of this laboratory on human genetics not only in Great Britain but throughout the world. The Chair has been occupied by Carl Pearson, R. A. Fisher and L. S. Penrose before the present incumbent, Professor Harry Harris, assumed the office several years ago.

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Court-Brown and his co-workers in Edinburgh in human cytogenetics must be ranked as outstanding contributions to our knowledge in what has come to be an extremely important area of human genetics. The determination of the model for the structure of DNA by Watson and Crick, which has been called by many the most significant contribution since Mendel's work, was carried out in Great Britain; although not all British in the sense that Watson was an American, the work was done at Cambridge University fifty years after Bateson and Punnett and their colleagues had been busy establishing the groundwork for the new science of genetics.

Cyril Clarke and his colleagues at Liverpool have been in the forefront of the study of the Rh story and the development of immunological techniques which have gradually led to the control of erythroblastosis foetalis.[29] Finally I should like to mention Mary Lyon and her theory of differential inactivation of the X-chromosome. Dr. Lyon, a geneticist at Harwell, developed her theory after observations on the behaviour of X-linked mutants in the house mouse,[30] and a review of the literature relating to the activity of X-linked genes in the human being.[31] Although there is still some discussion and dispute about the extent of the inactivation and its nature, there seems to be no doubt that the phenomenon is a real one, and that the theory put forth by Lyon has made a major contribution to our understanding of the activity of genes in mammals. It should be pointed out that not only is this idea of theoretical significance but it is used in practical ways in genetic counselling of families in which X-linked mutants are segregating.

Perhaps it is appropriate to end this brief review by pointing out that genetics as a whole has been characterized as a field which attracts people from many disciplines; some have stayed and been converted from their discipline, and others have come and made a major contribution but have then returned to their own field of endeavour. The British tradition has perhaps been dramatic in this way, and also in the fact that significant contributions to British medical genetics have been made not only by physicians but also by individuals who regardless of their background and training were concerned with understanding the sources of the variation—both normal and abnormal—which exists in human beings. It is perhaps a commentary on the liberal attitude of British medicine that these contributions from

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by

WILLIAM C. GIBSON, M.D.

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Let us not forget the immortal Harvey, who in 1628 discussed that borderland, psychosomatic medicine, in the following terms: 'Every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart.'

Harvey's interest in the nervous system was not in any way passing or superficial. He laboured mightily to rid his mind of Aristotelian and Galenic theory by appealing to neurological phenomena seen in his own patients. He says, as translated by Gweneth Whitteridge: 'Like speech in delirium are the convulsions of an epileptic, the jumpings in the first sleep of the night, the jerkings which result from touching something in sleep, and the restless tossing in fevers.'

Later he continues:

> The use of nerve is to communicate to the brain that which is perceived by the senses, that a judgement may be made; . . . movement is then the characteristic of that which is itself sensitive. Another point to be considered is its regulation and its motor faculty. As a result of which chickens with their heads cut off move as, so also, men in delirium and drunkards, but they move with a disorderly action and not with the harmony and rhythm necessary for work. . . .

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Willis' contemporary, Richard Lower, was an early student of the circulation of the cerebro-spinal fluid and investigated the problem of hydrocephalus. Nor should we hurry past the English Hippocrates, Thomas Sydenham, whose description of chorea in 1686, Osler so much admired. Chorea also occupied the attention of Mead and Cullen. Both Sydenham and John Locke have left good descriptions of trigeminal neuralgia. Five years later Robert Boyle was to relate in his *Experimenta et Observationes Physicae* the case history of a knight who fractured his skull as a result of a fall from his horse. The right-sided hemiplegia which resulted was cured after a 'splinter' of bone was removed. As Boyle says—'was not pull'd out without a great Hemorrhage, and such a stretch of the Parts, as made the Patient think his Brain it self was tearing out'.

Boyle's questioning of this patient showed remarkable neurological insight. He writes:

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Boyle concluded with the shrewd clinical reflection: 'that . . . he was very frequently let Blood; that he wanted not Appetite to his Meat; that for the most part he slept indifferent well; and, which was more remarkable, upon so great a Hurt of the Head he did not Vomit, nor had afterwards any Convulsions'.

Isaac Newton, too, was cited by William Cullen (1712–1790) as author of the idea that 'all bodies however solid, are enveloped with a subtile Ether which likewise pervades them'. Cullen asks: 'Now may we not suppose that the Medullary Fibres from their Original Confirmation have a Subtile Ethereal Fluid adhering to them like the Magnetism.' Cullen's strength lay in his conviction—held by all his sect calling themselves 'neuropathologists'—that the brain, not the heart, was the governor of the body.

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In 1783, another Edinburgh scholar, Alexander Monro *secundus*, published his great work *Observations on the Structure and Functions of the Nervous System*. His comments herald the beginning of the end of a chapter in transmission in the nervous system. He said: 'most authors have supposed that the nerves are tubes or ducts conveying a fluid secreted in the brain, cerebellum and spinal marrow. But, of late years, several ingenious physiologists have contended that a secreted fluid was too inert for serving the offices performed by the nerves, and, therefore, supposed that they conducted a fluid the same as, or similar to, the electrical fluid.'

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The name of Augustus Volney Waller (1816–1870) is well known to all students of the nervous system. This Kentish medical undergraduate working in Paris, first described the passage of blood that if he cut off the head of a turtle and touched the nose, breathing movements ensued. And thus he came to generalize that one message sent into the spinal marrow reflected another one along the motor pathways. For this work, on what would today be called 'reflex action of the spinal cord', he was awarded his fellowship in the Royal Society. He is also remembered for his pioneer studies on artificial respiration of more than a century ago.

My teacher Lord Florey became interested in Hall's early difficulties with the Royal Society as a result of a rash statement which I made in a lecture on Hall and his fellow investigators. Florey, as President of the Royal Society, was keen to see justice done. After digging into the archives he concluded: 'Marshall Hall seems to have had his difficulties with the Society because what I take to be his discovery of reflex action was turned down by the Council of the R.S., and there is in the archives of the R.S. library a printed note which he sent to all members of Council, complaining of their behaviour. It would seem that the Council made a grave error here.'

Clinical observation has been the specialty of British students of the nervous system since Harvey's day. One circumscribed example of this great capacity which needs no emphasis because it is so self-evident is the description of 'The Shaking Palsy' by the little general practitioner of Hoxton Square in London. In his brilliant biographical sketch of Parkinson, William McMenemey has given us the background to the classic work on *paralysis agitans*. Trained under the apprenticeship system, James Parkinson soon realized, as Jean Fernel had realized, that he needed to learn much more. It was at John Hunter's lectures in London that he learned to think about the tough, unsolved problems in diagnosis and treatment. His wits were sharpened by association with fellow students there, such as Henry Cline, destined to be a distinguished surgeon at St. Thomas' Hospital.

Parkinson wrote books on chemistry, on fossil remains, and gave us the first description in English of fatal perforation of the appendix. His political pamphlets, signed 'Old Hubert', against the despised Edmund Burke, simply convulse the reader today with the marvellous invective. But far above all this literary outpouring stands Parkinson's little classic of sixty-six pages, published in 1817, on the disease which bears his name today. It may not be out of place in this audience to remind you of the pioneer work in the Kinsmen Laboratory of this that if he cut off the head of a turtle and touched the nose, breathing movements ensued. And thus he came to generalize that one message sent into the spinal marrow reflected another one along the motor pathways. For this work, on what would today be called 'reflex action of the spinal cord', he was awarded his fellowship in the Royal Society. He is also remembered for his pioneer studies on artificial respiration of more than a century ago.

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His life has been so beautifully chronicled by Lord Cohen of Birkenhead, and his work so well described by Liddell and by Granit, that it would be redundant to add personal reminiscences from his last pupil. However, Sir John Eccles and I hope to produce, eventually, a volume entitled *The World of Charles Sherrington*, so that generations who did not know him may come to appreciate his many-sided character as well as his scientific achievements. Meantime, the Sherrington Room of the Woodward Bio-Medical Library will perpetuate what we have started here in our symposium, an exhibition of British contributions to Medical Science.

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