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EDWARD CHARLES DODDS

13 October 1899–16 December 1973

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BY F. DICKENS, F.R.S.

EDWARD CHARLES DODDS, Baronet, for nearly 50 years one of the foremost medical biochemists of his day, becoming a President of the Royal College of Physicians, a Vice-President of the Royal Society and a Master of the Worshipful Society of Apothecaries of London, was born in Liverpool on 13 October 1899. He was the only child of Ralph Edward Dodds and Jane Dodds (née Pack), who both had close connections going back over many years with Darlington, to which town Charles Dodds (the name by which he was always known) moved with his parents while he was still very young.

At that time his father was in the retail footwear business. The family fortunes seem to have fluctuated considerably, and his father's place of business to have changed more than once. Unfortunately Charles left no autobiographical notes and I am indebted to his son Ralph and his cousins the Misses Elinor Doris and Mabel Varley, who are artists now living at Malvern Wells.

Charles had an aunt, Mrs Richmond, his father's sister, who also lived in Darlington and whom they frequently visited even after the family had left for London. It was through Mrs Richmond that Charles met his future wife Constance Elizabeth Jordan, daughter of Mr J. T. and Mrs Katherine Jordan who were close neighbours and friends of Mrs Richmond. The Jordan family were well known business people in Darlington where they owned considerable property. Like Charles, Constance was an only child. They were married in 1923 and set up their first home in a flat in Maida Vale, London.

Charles's mother was a person of great charm, one of a fair-sized London family who boasted an ancestor who was a Lord Mayor of that city. Her father, also named Charles, was a successful businessman and his brother, George Pack, was a dentist in Harley Street. After his father's death, George helped the Dodds family financially. Her brother, Edward Pack, had a very successful tailoring business off Oxford Street, London. He seems to have been the 'wealthy uncle' to whom Charles Dodds referred in some of his later writings; he also helped Charles during his student days. Whereas Charles's mother and father wished him to enter medicine as a career, his uncle Edward, understandably but fortunately unsuccessfully, in view of Charles's later prowess, urged that it
would be much safer for him to go into the tailoring business. However, the parental wish was made good, though no doubt at some sacrifice on their part, for they seem to have been far from affluent at the time.

Charles's father, Ralph Edward Dodds, was frequently away from home on business. The family finally moved to London in 1910 or 1911, living at Chesham, Buckinghamshire, when Charles was entered as a pupil at Harrow County Boys' School. His father had a variety of occupations and when World War I came he enrolled in one of the welfare services on the Eastern Front, finishing up in Istanbul. While there, he purchased, presumably from a Russian émigré, a rather splendid gold cigarette case, by Fabergé, which Charles later inherited. This valuable piece seems to have been responsible for a lifelong appreciation of similar objets d'art, including old silver and paintings of which Charles gradually acquired a fine collection. His father also brought back to this country a large silver-plated oriental table which Charles later presented, together with a very fine chandelier, to the Worshipful Society of Apothecaries, where they may still be seen.

Shortly after the Dodds family moved to London his father entered Charles, on 21 January 1911—the opening day—at the newly built Harrow County School for Boys, situated in Gayton Road, Harrow. This was one of the first of such state secondary schools; the fees were kept low, originally only £2. 6s. 8d. per term, and there were at first only 70 boys, the 28 in Form I including Charles who took a prize in history and geography in his first year. This early interest in historical matters survived throughout his life. The numbers increased very rapidly and within a few months the School had 118 pupils and continued to expand over the years up to the present day.

Charles's father chose well, for the School had an outstanding first headmaster, Mr Ernest Young, B.Sc., F.R.G.S., who came from the near-by and better known John Lyons School at Harrow. In the very few references which Charles has left concerning his schooldays, he has particularly praised the teaching of science at the School, and their excellent laboratories. This reputation has been maintained to this day under their present headmaster, Mr J. R. Avery, M.A., F.R.S.A., who has kindly put me in touch with two of Charles's contemporaries at the School—Mr F. Warburton, F.C.A., and Mr Reginald Cole—from whom my information about his schooldays is derived. The School in 1932 produced a Book of commemoration, 1911–1932 which was 'Dedicated to the Old Gaytonians whose names are inscribed on our War Memorial' and was printed and published by Mr J. G. Cockerton of West Ealing, himself an Old Gaytonian. Reference to this book gives some further information about Charles's schooldays.

The School from its foundation onwards enjoyed visits from a remarkably distinguished group of speakers at their annual speech days—for example in 1914 Sir Herbert Tree, the famour actor, witnessed a performance by the School of a scene from A Midsummer Night's Dream. Concerning this, the local press reported that 'the antics of Bottom [Dodds] caused the greatest amusement to Sir Herbert'; as the Book of commemoration comments, 'an interesting light on the subsequent career of a distinguished Gaytonian'. It is perhaps relevant that
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in after life Charles was in conversation a most witty and amusing raconteur and mimic, though it must be admitted that in his public lectures he never acquired quite the same fluency, in spite of his vast experience. He was in fact essentially a shy person, but this was not at all obvious to those who did not know him well, who might easily form the false impression on first acquaintance that he was inclined to be rather abrupt and offhand. He was in fact a most warm-hearted and companionable man.

His two schoolfellows have told me that Charles was known as ‘Tommy’ at school, that he was essentially a ‘loner’ in modern slang, and that as he considered all sporting activities a waste of time, he was inevitably considered ‘a swot’. They remember him as ‘a lumpish lad, toiling to school with a monster satchel of books’. Not that he was unsociable, in fact his fellow pupils, not much interested in his academic abilities which were even then outstanding, still remember how much they were impressed by his immense confidence in class. He would not be suppressed and one or two of the masters were nettled by his proclivity to ‘answer back’, so that he became known as a character to be reckoned with. These qualities of independence of mind and originality, together with an element of defiance of accepted views, continued to be characteristic of him in later life. At school he became a prefect and captain of his house, and he seems to have thoroughly enjoyed his schooldays. He always retained a great affection for the School which he revisited on several occasions. The Harrow Observer for 26 January 1971 published a full report of the School’s Diamond Jubilee Commemoration, which was attended by more than 1000 past and present pupils, among whom was ‘Sir Charles Dodds, a former President of the Royal College of Physicians’. The School publishes a most impressive science journal Enquiry and Charles contributed an article ‘The science of biochemistry’ to the 1970 issue in the course of which he discusses the conception of biochemistry as an independent discipline beginning in this country with Sir Frederick Gowland Hopkins and his department of biochemistry at Cambridge. He goes on to describe the work of the Courtauld Institute of Biochemistry and also some recent advances in antibiotics. The seventh issue of the same journal for 1971 contains a Foreword by the present headmaster, Mr Roy Avery, in which he quotes from a letter from Sir Charles as follows:

‘If I remember correctly, the first science teacher was Mr Carran who taught physics and chemistry. The laboratories were, to us youngsters, fascinating places. I did science the whole of the five years that I was present at the school and I left in 1916 to enter the Middlesex Hospital Medical School in October of that year. The standard of teaching of physics and chemistry was so high that I could have passed the 1st M.B. the day I entered the Medical School’.

Early days at ‘The Middlesex’

In fact, Charles did not obtain one of the three annual major entrance scholarships to the Middlesex Hospital Medical School in 1916—these were awarded: one in science to Samson Wright (who in 1930 became Professor of Physiology

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in the Medical School) and two in classics to David A. Patey (later Senior Surgeon to the Hospital), and to Richard O. Swaine, both of whom became lifelong friends of Charles. He did, however, obtain the Class Prize in chemistry and a Certificate in physics for 1916–17. In 1916 the number of General Students entering the Middlesex was only 37 and the Official Record of his attendance at lectures was phenomenal—in chemistry, physics and biology he missed only one out of a total of about 250 lectures; this is on the assumption (by no means certain) that the ‘signing-on’ procedure was immaculate.

Charles was called up for Army service, full-time in London University O.T.C., on 19 July 1917. His health record had not been good and while still at school, in 1913, he had been sent to Margate to recover from an illness. While in the O.T.C. he contracted pneumonia as a result of a long route-march, so that the Medical School records contain the entry: ‘Exempt for 6 months on account of health; returned 12 December, 1917.’ There is some confusion about the exact period, Charles himself having spoken of a total of 18 months’ military service; perhaps he was also in the O.T.C. while still a student, but no records are now available owing to the war-time conditions prevailing at the time.

On his return to Medical School, Charles was faced with a serious financial problem owing to the fact that his father’s business had failed. As already mentioned, his uncle helped him with a loan and Charles had himself to provide the remainder by acting as demonstrator and by coaching medical students. At that period the teaching at the Middlesex Hospital Medical School was, as with most other medical schools, run on very amateur lines, and in primitive buildings, as judged by present-day standards. Charles has given a graphic description of the situation at this period in his Second Astor Lecture delivered in 1964 on the occasion of the Golden Jubilee of the Bland-Sutton Institute of Pathology (272):

‘Geographically the whole of the Hospital and Medical School were contained in the island site bound by Goodge Street, Cleveland Street, Nassau Street and Riding House Street and even this did not belong entirely to the Hospital as the South-West and North-West corner sites were occupied by businesses. Furthermore, the Nurses Home and the residence quarters for medical staff were also on this site. The Medical School consisted of some buildings on the Riding House Street aspect. The only original one remaining of the 1914 days is the building at the North-East corner which is connected by the bridge to the Courtauld Institute—a much later addition, and also the entrance of the Medical School in Riding House Street and the buildings West of that. This very small area housed the departments of chemistry, physiology, physics, biology, anatomy and pathology. There was one circular lecture theatre which dealt with all the needs of the students. The total number of students in the School was about 200 including occasional ones running into 20–30 per annum. Again, the students and their conduct of those days bore no resemblance to those of today. In the pre-1914 period, and in fact right up to the last war, there was no pressure on students to get qualified quickly and the whole pace was much more leisurely. In the pre-1914 days the paying of fees could either be
annually or by what was known as a ‘composition’ fee which I think was £150. Discerning parents could pay this and the School undertook to keep the student until he qualified. This led to the evolution of what used to be termed the “chronic” student and medical schools used to vie with each other as to who had the most chronic student. In those days we at Middlesex held the record with a student who was unqualified after 15 years. This seems incredible to people who have been brought up in the post-1945 era. Contrary to the belief, it was not that students in those days were unintelligent, it was just that they did not do any work and used the Medical School as a kind of club where they could meet their friends, receive letters, etc. It is also interesting to note that when the parents could stand it no longer and applied sanctions, these students quickly qualified and almost without exception turned out to be first-class doctors.

‘The staff of the Medical School was minute compared with that of today. There were of course no Professors and very few recognised teachers and many of them were part-time. For example, the lecturer in Physiology, Dr. Strickland Goodall, was a cardiologist with a very busy private practice and he taught physiology and its various branches and also biology, with one assistant. Chemistry and physics were taught by Dr. Kellas, again with only one assistant’.

It was Dr A. M. Kellas to whom Charles became demonstrator and who taught Charles both inorganic chemistry for 1st M.B. and organic chemistry for 2nd M.B. Kellas was a distinguished mountaineer who had collaborated with J. S. Haldane at Oxford in respiratory work. There seems little doubt that this contact was responsible for Charles’s great interest in respiration in his earliest researches. Kellas himself died of heart-failure in the preliminary reconnaissance of Mount Everest during the summer of 1921. He is reported as having been a great teacher, although his strong Scottish accent was apparently none too easy for Sassenachs to understand. Dr R. O. Swaine recalls that he used to retire all day to his private room behind the chemistry lecture theatre and there was much speculation as to whether he fasted the whole time. He was always immaculate with a well-waxed moustache and wearing a frock coat, and his demonstration experiments at lectures invariably went off successfully having been set up by his sole technician, Reggie Blake, who afterwards joined Dodds when he was appointed Chemical Pathologist. Reggie was a kind of Admirable Crichton who was an adept at improvisation—on one occasion later when we had run out of large vessels for the preparation of insulin, he returned with three large enamelled baths. When Charles, aghast at the expense (for money was exceedingly short in those days), remonstrated, Reggie blandly remarked that there was no need to worry as he had them ‘on approval’ and would return them to the shop next morning, well cleaned, after use.

The first Professor of Physiology was appointed in 1919; he was a Dr Swale Vincent from Winnipeg and had published work on the organs of internal secretion—the ductless glands. Dodds, who had obtained distinction in physiology and pharmacology in the March 1919 2nd M.B. part II, was appointed
assistant to the new professor, thus contributing something towards his fees as a student. As already mentioned, a further source of income he found in coaching, at which he became renowned because of his phenomenal success with students in their examinations. This particularly applied to the Primary Examination for the Royal College of Surgeons. At that time a large number of doctors from abroad, especially from Australia and New Zealand, were supported by their governments in attending special courses held at some London medical schools, designed to overcome the formidable hurdle which this examination proved to be in restricting entry to the surgical profession. Attending the Middlesex course there were on occasion perhaps as many as 50 such embryo surgeons, so that Charles was in great demand as a coach in physiology and biochemistry.

The latter subject had hardly been generally recognized by medical schools as a discipline on its own, being regarded rather as a minor branch of either physiology or pathology. In any case, it was not a subject in which Professor Swale Vincent had much interest, and so it happened that the first Director of the Bland-Sutton Institute of Pathology at the Middlesex, Dr Carl H. Browning (who was elected F.R.S. in 1928, and who died only 3 years ago at the ripe old age of 90), decided to appoint in 1919, Dr E. L. Kennaway as the first Assistant in Chemical Pathology to the Hospital and to provide him with accommodation in this fine new Institute. It is true that only two or three rooms were then available for the whole of biochemistry, including routine work and teaching, but this was a far-sighted and fruitful appointment by Browning of a man who later, as Sir Ernest Kennaway, F.R.S., became a most distinguished world leader of cancer research, the discoverer of the first pure chemical carcinogens, and Director of the Research Laboratories of the Royal Cancer Hospital. It marked also a turning point in the life of Charles Dodds, who was appointed in 1920, while still a medical student, under Kennaway and who succeeded him in the following year: ‘Demonstrator in Biochemistry, E. C. Dodds, M.R.C.S., L.R.C.P.’ according to the Medical School records. When Kennaway left for the Cancer Hospital, Dodds was appointed Lecturer in Biochemistry for the session 1921–22 having then passed the Primary F.R.C.S. Examination in 1919; he soon acquired also the M.B., B.S., with honours, of London University, the Ph.D. January 1925, the M.D. July 1925 and the M.R.C.P. in 1927; a remarkable record. In those days he had an amazingly accurate photographic type of memory; after reading once through a book or an article he could quote its contents quite effortlessly—‘including the footnotes’, as he himself once said. He also had the facility of very rapid reading; for example, he was able to read and mark a large batch of examination scripts in a fraction of the time taken by his more laborious colleagues, but the marking was none the less accurate as proved by a comparison of the results. His memory stood him in good stead on one occasion when he was introduced to Mr Samuel Augustine Courtauld by the then Dean of the Medical School, Alfred Webb-Johnson (later Lord Webb-Johnson and a President of the Royal College of Surgeons). The Dean had, not without guile, arranged for the three of them to be invited to dinner by Sir John Bland-Sutton. Sir John was not only one of the most distinguished surgeons of his day, but he possessed a
remarkable knowledge of comparative anatomy and pathology, as well as owning a most imposing Egyptian-style house in Brook Street. Mr Courtauld's ancestors came over with the Huguenots and included famous designers in silver and in textiles; one was among the earliest subscribers to the Middlesex Hospital in 1746. Mr S. A. Courtauld himself was no mean classics scholar, having published a translation of the *Odes* of Horace. During the course of the evening he began to quote from one of the *Odes*, but was unable to remember the ending. Charles had learnt his classics from a Roman Catholic priest who must have done a good job for it enabled Charles to complete the quotation; a performance that clearly made a great impression on Mr Courtauld, who shortly afterwards yielded to Webb-Johnson's eloquent appeal to endow in 1925 a professorship for Charles—the Courtauld Chair of Biochemistry—and to provide the funds for building a new Institute of Biochemistry for the Medical School, opened in 1928 only 18 months after building operations started, of which he was the first Director.

So it was that Charles Dodds became, at the age of 25, the youngest professor in the University of London; and when he retired in 1965 he was its senior professor having enjoyed 40 years continuous service in the same Chair. In fact he never seemed to wish to work elsewhere and 'The Middlesex' was, throughout, his great pride and joy, as well as the mainspring for his scientific career.

**The opening of the Courtauld Institute of Biochemistry**

The official opening was on 14 June 1928, the chair being taken by H.R.H. Prince Arthur of Connaught, Chairman of the Board of Governors, who accepted from Mr S. A. Courtauld the gift on behalf of the Hospital, and Mr S. G. Asher accepted on behalf of the Council of the Medical School. The building consisted originally of five stories, of which the ground floor and basement were at first used for purposes other than biochemistry, the ground floor being a much-needed students' restaurant. The remainder of the building, including the sixth floor which was added later, was exclusively devoted to biochemistry. The student laboratory was on the first floor; here all practical teaching of biochemistry was done, the lectures being delivered in a communal lecture theatre on the opposite side of Riding House Street, which was shared with other disciplines. At that time, chemistry was taught by Professor W. B. Tuck, and this continued up to the outbreak of World War II, in a separate department housed in the older medical school buildings. As was not unusual at that time, the teaching of chemistry was almost completely divorced from the later activities of the students and little attempt was made to bring these aspects together, although such departments had sometimes made great contributions to science and to medicine. The changes produced by the war resulted in the end in a useful healing of this breach, as we shall see later.

The address at the Opening Ceremony was delivered by Sir Archibald Garrod, F.R.S., a physician widely famed for his identification of the inborn errors of metabolism, a most happy choice of speaker. In his remarks (Garrod 1928) he said:
For more than a century past every medical man has had, in his consulting room or near it, a shelf with a few bottles of reagents, a spirit lamp, and some test tubes, with which to carry out certain simple chemical investigations which form part of clinical routine. That shelf is the prototype of this great Institute, with which the munificence of Mr Samuel Courtauld has enriched the Middlesex Hospital; and the contrast between prototype and achievement is no greater than that between the medical chemistry of a hundred years ago and the biochemistry of today.

Sir Archibald then reviewed the applications of the science to diseases such as diabetes, gout, impaired function of liver and kidney, as well as to the growing knowledge of nutrition and vitamins. His concluding remarks were true and prophetic:

'Medicine may be looked upon from several distinct standpoints, but, in importance, the chemical standpoint is second to none, as is becoming more clearly recognized from year to year. Biochemistry is not merely a useful preliminary subject of study for the medical man, but is part of the very essence of his science, and, through his science, of his art.

'We know that members of different genera and species of animals and plants differ from each other in chemical structure and chemical life, and evidence is accumulating that no two individuals of a species are any more identical in chemistry than in form. It would seem that there is a chemical basis for those departures from type which are styled mutations, and I for one believe that the liabilities of certain individuals to, or their immunity from, certain maladies—what may be called their diatheses—have chemical origins. Undoubtedly the mechanisms by which the body protects itself against bacterial invasions or poisons introduced are, for the most part, chemical; and it is not necessary to point out the importance of the parts played in the animal economy by such chemical substances as hormones and vitamins. If all this be true it is obvious that a chemical outlook is needful for the comprehension of morbid processes, and that there are unlimited openings for research in biochemistry.'

Sir John Bland-Sutton, the famous Middlesex surgeon, then proposed, and the newly appointed Professor E. C. Dodds seconded the vote of thanks to Sir Archibald. All the speakers seem to have emphasized the very intimate connection with the clinical work of the hospital, symbolized by the bridge across Riding House Street leading from the Hospital to the Institute, which principle under Charles Dodds has always been at the centre of its teaching and research.

The opening of this great Institute at that time, when it was probably unique among such departments of Medical Schools in this country, represented a great act of faith on the part of the moving spirits, chief of whom was Alfred Webb-Johnson. As Dean of the Medical School he was convinced that the fuller integration with the University of London was an essential stage in development, and to that end he instituted several new professorships and the provision of suitable new buildings. He was one of a number of distinguished sons of the Hospital who had access to a wide circle of influential and generous benefactors,
including for example, in addition to Mr Courtauld, Sir John Bland-Sutton, Lord Astor of Hever, Lord Cobbold, Mr Philip Hill and many others. In addition, the Cancer Research Campaign, from its earliest days, and such bodies as the Medical Research Council, the Nuffield Foundation and Wellcome Trust, have given continuous support over the years. Sir Charles himself, after he became Director of the Courtauld Institute of Biochemistry, found himself faced with the necessity to provide for a large number of research grants, most of which were not forthcoming from depleted university sources, in order to staff this large building—from the original half-dozen the graduate staff rose to be 42. This he did with conspicuous success for he too had the gift of attracting support from similar benefactors, reinforced by his wide and ever-increasing contacts with important figures in industry, at home and abroad, as will be mentioned later.

THE DEVELOPMENT OF BIOCHEMISTRY AT ‘THE MIDDLESEX’

Until the opening of the Courtauld Institute conditions were cramped even for the small staff which in 1923 consisted of Charles Dodds (lecturer), Wilfred Lawson (organic chemist, formerly personal assistant to Professor (later Sir Robert) Robinson at Liverpool) and myself a newly fledged Ph.D., together with one newly qualified medical student and a couple of technicians. Both Lawson and I were fortunate to be appointed as there was already a post-war slump in the employment of chemists and correspondingly enormous application lists, although the salary offered was only about £250 per annum and, in my case, the appointment ‘for one year only’. In fact, we both remained for many years. We were all about the same age—very young and no doubt rather brash—and conditions were a strange mixture of complete informality in our mutual relationships with an absolutely rigid discipline over hours of work and similar matters, such as most young workers would not be willing to accept today. We were housed in three rooms in the Bland-Sutton Institute, of which Professor James McIntosh had recently become Director in succession to Dr Carl Browning. This accommodation was nominally for chemical pathology and in addition there was one teaching laboratory for about 25 students. Dodds was transferred, as already mentioned, from physiology to assist Dr Kennaway in teaching and research in biochemistry as well as in routine clinical biochemistry for the Hospital. Dodds himself has written of this period, or a little earlier, in his 1964 Astor Lecture (272):

‘There was no provision whatsoever for research in the basic sciences such as physiology and biology and of course biochemistry in those days did not exist as a subject in the Medical School. A little elementary chemical physiology was taught in the same laboratory that was used for experimental physiology and botany and zoology. Racks of reagents were put out when chemical physiology was to be done and their resemblance to the condiment containers on the lunch and dinner table led later workers to refer to this as “cruet” biochemistry.’
When Kennaway departed to the Cancer Hospital in 1921 and Dodds was appointed Lecturer in Biochemistry in his place, with characteristic vigour he at once tackled both the teaching and research deficiencies and also the inadequacies in the provision of clinical biochemical services for the Hospital.

His views on the teaching of chemical subjects to medical students were ahead of his time. They are summarized in an article (198) he wrote for the *British Medical Journal* entitled 'The teaching of chemistry' (1949), stressing the need for all branches to be under a single authority. These views he was able, after World War II, to put into practice, appointing for the purpose a small but select group of lecturers, three of whom have since become professors in the Medical School. In addition, Mr Philip Hill, a close friend, left in his estate provision in 1946 for the Philip Hill Professorship of Experimental Biochemistry, of which I was the first holder. Altogether Dodds's contribution to both the teaching and scientific activities of the Medical School was phenomenal.

As regards clinical biochemistry, a startling change had overtaken medicine during the war years and immediately after, especially as a result of developments in the United States. Clinicians were now asking increasingly for more numerous and more comprehensive chemical analyses in the study of their patients. No such pressure had existed before and the analytical methods then in use were laborious and slow, as well as demanding trained chemists for their satisfactory performance. For example, one or two hours' skilled work was necessary for the titrimetric determination of a single blood-sugar value, and the other analyses were equally unsuited for routine use. From 1919 onwards the volume of such work increased steadily, not always to the gratification of some of the older physicians, one of whom was reputed to have returned the analytical data asking that they should be expressed in grains per gallon! But the final factor necessitating a revolution in methods was the introduction of insulin in 1923. 'Blood analysis', as Dodds himself has said, 'which in the past had been looked upon as rather an advanced luxury, now became an absolute necessity in the treatment of patients with diabetes.'

The answer he found in the introduction into this country of the colorimetric methods of clinical analysis developed during the war years in the U.S.A. by Otto Folin. Dodds himself, Lawson and I, and our young medical colleagues (at first Dr J. I. Collier, later joined by Dr Daniel T. Davies) did all these analyses in one small room—temporarily provided within the Bland-Sutton Institute, together with one larger laboratory for general purposes including all research, and a smaller room used for urine analysis.

Folin's original published descriptions of his methods were unfortunately far from clear and contained a number of printing errors, for example in the method for determination of uric acid in blood. After Lawson had no success with this, Dodds wrote to Folin who admitted it was incorrect and thereupon sent a revised analytical procedure which worked satisfactorily. There was clearly a need for a well presented book describing both the newer methods and their clinical application and this was written jointly by Dodds and Dr George Beaumont, a physician in the hospital. *Recent advances in medicine*, of which the
first edition was published in 1924, proved a best-seller and went through 13 editions up to 1952, being subsequently continued from 1964 to the present time in a different form and under new editorship. This book had a most profound influence, both in this country and abroad, on the widespread adoption of these methods.

Thus Dodds was already acquiring recognition as a leading exponent of clinical biochemistry in this country, and his first signal public honour came when Lord Dawson of Penn, the King's Physician, called in Dodds during the illness of King George V. For a young man barely 28 at the time this was a great mark of confidence, and for his services he was, in 1929, awarded the M.V.O.

In March 1932 Dodds had an extended tour of clinics and laboratories in North America, Mr Courtauld having presented him with a generous cheque for this purpose. This gift and the value of these visits were acknowledged by Dodds in two longish articles in the *Middlesex Hospital Journal* which he wrote on his return, and which show how much he was stimulated and impressed, for example, by the Columbia Medical Center, the Rockefeller Institute, the Mount Sinai Hospital, the Mayo Clinic in the U.S.A., and in Canada McGill University, the Montreal General Hospital, and finally Toronto University and Toronto General Hospital; each of the latter having a Department of Physiology under the direction of Professor J. H. Best. There can be little doubt that this visit greatly influenced Dodds's later planning; for example, a small ward for determination of basic metabolic rate of patients was set up in the Courtauld Institute, with a sister in charge and proper nursing facilities, and this has been enlarged and remains a valuable facility to the Hospital under the control of Dr Arthur Miller, now Reader in Chemical Pathology.

Reference has already been made to the exponential rate of growth in the demand for clinical biochemical data for the hospital. Dodds has given a brief summary of this situation in his article in his old school magazine, *Enquiry*, for 1970 (see also ref. 278):

'Since 1920 there has been an enormous growth in the need for chemical analysis as an aid for the diagnosis and treatment of human diseases and it is interesting to note that in 1921 the total number of requests for analyses received by the Courtauld Institute amounted to 1060, whilst in 1969 the figure was 200,000.'

(By 1973 it had reached a third of a million per annum.)

'The clinician requires in practically every case detailed analysis of blood and other biological fluids in order (a) to help him make a firm diagnosis, and (b) to check on the treatment. Only those who lived through the period can realize the difficulty and complications.... The whole of this was changed through the introduction in 1958 of the American machine known as the Autoanalyser. By the use of this extremely ingenious piece of apparatus drops of blood, separated by air bubbles, are passed through polythene tubes to the reacting vessels which eventually produce the colorimetric reaction for the required ingredient to be estimated.... At a modern institute some 80%, if not more, of the routine work is done on this
type of machine ... and there is no doubt that automation has literally changed the face of clinical biochemistry.'

It is worth commenting that at the time of its first introduction into this country there was considerable opposition to the Autoanalyser, of which the analytical principles went quite contrary to the accepted ideas then prevailing; and the fact that it has now been generally adopted must owe a good deal to the bold and controversial outlook which Dodds always brought to bear on any new venture such as this. The decision once made, however, he left all detailed checking and practical testing to his staff whom he trusted entirely to work out such problems, giving them a completely free hand to do so. This policy of decentralization helps to explain how he so successfully undertook such an astonishing variety of activities over the years. Of course, there was inevitably a debit side in that he abandoned all personal experimental work at an early age, although as his own early research work shows this was not through any lack of skill at the bench on his part.

EARLY RESEARCHES

Respiratory

Reference has already been made to the great influence which Dr A. M. Kellas exercised on Dodds's early respiratory studies. As a famous climber, Kellas must have appeared to him as a romantic figure and, as already mentioned, it was through Kellas that Dodds made the acquaintance of Dr J. S. Haldane with whom Kellas had collaborated in Oxford. The fact that the great Haldane, at that time the leading figure in respiratory physiology, visited Kellas and from the first took a keen interest in Dodds's earliest ventures into research, left a lasting impression on the young Dodds, to which he often referred in his later writings. Characteristically he began by challenging in 1921 an observation of Haldane's that the percentage content of carbon dioxide in the residual (alveolar) air at the end of an expiration remained at a remarkably constant level in any one individual. Dodds published a number of papers during the period 1921–24 which revealed that although, as Haldane had shown in 1905 the alveolar CO₂ did tend to fall steadily during starvation, the effect of a meal was to bring about a definite though transient increase in CO₂ content in normal subjects, and since this did not occur in those (achlorhydric) subjects who did not show the normal secretion of hydrochloric acid by the stomach, it was concluded that this rise in alveolar CO₂ was related to this phase of gastric secretion. The duodenal secretion of alkali, which occurred later, was accompanied by a return of alveolar CO₂ to more normal resting levels. Corresponding changes in the titrable acidity of the urine had been known for many years and were referred to as 'the alkaline tide', accompanying the partaking of a meal. These effects were not then universally recognized as correct, but in several publications Dodds was able to show that following overnight fasting, the taking of breakfast was regularly associated with increased alveolar CO₂ and with increased alkalinity of the urine, except in achlorhydric subjects. On the other hand, when not following a period of fasting
such changes were negligible or even undetectable. As most observers had, for convenience, based their observations on the effect of lunch, their negative results could probably be explained by the complication of residual effects from their earlier meal.

Haldane reported at a meeting of the Physiological Society that he had been able substantially to confirm Dodds's findings. The matter has, however, been the subject of controversial opinions for many years and perhaps the prevailing view of modern respiratory physiologists may be summarized by saying that although Dodds's findings were qualitatively probably correct, the extent of the increase in alveolar CO₂ which he reported was too great to be quantitatively accounted for completely by the secretion of hydrochloric acid in the stomach.

It is perhaps not without interest that at least until recently the venerable Haldane gas analysis apparatus used by Kellas and Dodds was still in existence at the Middlesex Hospital Medical School. Those who have struggled to obtain accurate results with this difficult and infuriating machine will need no further proof of the experimental prowess of Dodds in those far-off days!

**Gastric secretion**

Simultaneously with the respiratory work just described, Dodds took part with Dr Izod Bennett in the extensive studies of gastric secretion by means of the fractional test meal. Bennett, who later became Dean of the Medical School, was a physician from New Zealand who had worked with Dr Ryle at Guy's, a well known specialist in this technique. For this test, the patient came fasting to the Hospital, was persuaded to swallow a fine rubber tube and then given the so-called meal (usually of gruel), specimens of the stomach contents being removed by syringe at timed intervals. By examination and titration of the samples thus withdrawn, the course and extent of gastric secretion could be followed more accurately than was possible hitherto. Dodds and Bennett became so adept at swallowing these Ryle tubes that they regularly demonstrated on themselves to reluctant patients to show how easy it was! In the earlier days after we had removed to the newly built Courtauld Institute, it was a common sight each morning to see numbers of such outpatients undergoing this not very pleasant investigation.

During 1921–25 Dodds published, in part with Bennett, the results of these studies, and in 1930 with Dr J. D. Robertson who had by then become his Assistant Chemical Pathologist, he returned to the question of the origin of lactic acid in the stomach. This was the kind of highly controversial matter into which Dodds delighted to plunge with gusto. There had been over the years much discussion about the origin of this lactic acid, which was often associated with achlorhydria, and concerning which Dr H. MacLean in particular had maintained that its presence might be regarded as diagnostic of gastric cancer. Some workers had even suggested that it could have arisen through the aerobic glycolysis of the tumour tissue itself a property of malignant tumours that had recently been described by Otto Warburg in Berlin. Dodds and Robertson, however, were able to make a close study of 73 cases and they also proved by
isolation and analyses from 7 patients of the zinc salt of the acid, together with measurement of its optical activity, that it was in fact the DL-lactate and therefore almost certainly arose by fermentation occurring in the stomach contents, since the tumour would have excreted the optically active D-acid. This important finding, which received confirmation from their experiments in which they incubated gruel with a small amount of stomach contents from a patient, shed considerable doubt upon the validity of the occurrence of gastric lactic acid in the differential diagnosis of gastric carcinoma. For a long period, however, fractional gastric analysis continued to be regularly used in clinical laboratories.

It is one of the curiosities of medicine that such an apparently firmly established investigative procedure should by now have almost completely disappeared from use. In this, the very thorough studies by Dodds and his colleagues must have assumed an important role, though improved diagnosis by X-ray and other newer types of clinical examination no doubt also played a great part.

EARLY ENDOCRINE RESEARCH

Insulin

Dodds first became involved in work on the internal secretions in 1923. A couple of years before, Banting and Best in Toronto had set in train their momentous work, for the first time providing a workable method by means of which insulin could be prepared in a stable and clinically usable form from the pancreas. As is well known, earlier workers had been largely frustrated by the proteolysis of the hormone brought about by contact during extraction with the external pancreatic secretion, trypsin. Up to 1923 patients were still regularly dying of diabetes in the Hospital, since the earliest available supplies of the hormone were quite inadequate to meet the needs of the clinicians. In October of that year, I was appointed ‘to assist Dr. Dodds in the preparation of insulin for the patients in the Hospital’. It is perhaps one of his most typical actions, that Dodds instead of merely duplicating the methods used by Banting and Best, and later improved by Collip, which used alcohol as both extraction medium and trypsic inhibitor, broke away from this by starting two entirely new approaches. The first, and less successful, was by aqueous extraction in the presence of various chemicals which lessened the trypsic destruction of the hormone. The second, which was successful enough to enable us to prepare insulin for a long period of use in the Hospital and also for later commercial production by Boots at their Nottingham works, started with the direct addition of picric acid to the minced fresh ox pancreas, which we personally collected from the slaughterhouses. The insulin picrate thus formed we found, purely empirically, to be more readily extracted by a 70% acetone/30% water solvent than were most of the inert protein picrates in the crude mixture. From this stage the conversion of the extracted picrate to hydrochloride presented no difficulty for it had been already achieved for a rather different purpose by Dr H. W. Dudley at the National Institute for Medical Research. The solution of the hydrochloride so prepared was assayed for hypoglycaemic action on rabbits, sterilized and bottled by us
ready for use. For both of us this was an exciting and stimulating time and for me a good introduction into new biochemical and physiological techniques; though the work had to be done between practical classes in the students’ laboratory and frequently went on until late at night.

As a result of these and a few lesser adventures into the hormone field, Dodds and I wrote a book in 1925 for Oxford University Press entitled *The chemical and physiological properties of the internal secretions*, from the Introduction to which perhaps one may be allowed to quote a rather significant passage:

‘Although it is as yet early to offer any opinion, it would appear that the recent work upon the ovarian hormone will prove to be of the very greatest importance... Here we have a body the injection of a few milligrams of which causes, within forty-eight hours, a solid column of cells to become a tube, in addition to the other cellular changes occurring in oestrus. That the subcutaneous injection of this hormone can influence so powerfully the growth of a series of epithelial cells is surely something entirely new. It is justifiable to say that hitherto no body has been isolated with such a powerful action upon the growth of cells, and it will not be surprising if this and similar bodies start a new era in the investigation of cell growth, and possibly of malignant disease.’

**Oestrogens: the ‘female sex hormone’**

The passage quoted above provides an indication of the intense fascination which the oestrogenic hormones always held for Dodds, as well as showing how penetrating was his vision into the future of this subject, at that time in its infancy. The comment is particularly relevant to his own later major work on the synthetic oestrogenic substances, but for the moment it is necessary to consider the earlier and more primitive researches which finally led him to such a successful outcome.

During this period (1923–30) we were more concerned with the preparation and purification of the crude ovarian or placental extract known at that time as the ‘female sex hormone’. In 1923 Allen and Doisy in the U.S.A. had produced from ovarian liquor folliculi and from placenta the most active extracts so far prepared and these authors brilliantly took advantage of the earlier cytological work of Stockard and Papanicolaou to devise a good assay system. Dodds, with Professor Samson Wright and myself, quickly confirmed their important findings and also obtained active material by other extraction methods; though it is easy to see in retrospect that our approach was based on a misguided view that the hormone, like others at that time known, would prove to be water-soluble. That aqueous preparation did prove active in these experiments and in contemporary work by others was due to the extreme activity of steroidal oestrogenic hormones, such that even their low water-solubility permitted active aqueous solutions. A valuable positive finding from this work was the development in 1930 by Allan, Dodds & Dickens (49) of a satisfactory assay method based on sound statistical principles which J. H. Burn and others were at that time developing. In the case of aqueous material, we found that a single dose was unable to
induce oestrus in ovariectomized rats, but a satisfactory assay resulted when the total dose was divided (usually into five or six portions) injected over a period of 3 days. This assay procedure was that used in all of Dodds's later work.

Tested in this way, the 'water-soluble' preparations made by the method of Allen, Dickens, Dodds & Howitt (44) which were termed 'oestrin', were undoubtedly active in inducing oestrus in castrated rats. Dodds & Robertson (54) tested these extracts on 86 women patients with no ill effects and with restoration of menstruation in 28 of 62 women who received the full dosage of 10 rat units per day over 50 or 60 days, a considerable advance. Since the rat unit was only about 0.01-0.02 mg the actual weight injected was quite small—a great improvement on previous crude oily preparations (rat unit 10–15 mg) which had produced unpleasant local reactions.

Valuable though this progress was, it was still a long way from the isolation of the pure oestrone which was accomplished independently by Doisy in the U.S.A. and by Butenandt in Germany at about the same time as the clinical trials by Dodds and Robertson were proceeding. This made it clear that the pure hormone (rat unit about 0.1 μg) comprised only 1% of our relatively crude material.

This early work by Dodds and his colleagues, however, had its main long-term value in the part it played (a) in establishing a satisfactory bioassay method and (b) in directing his further attention to the problem in such a way as to lead him eventually to prepare artificial substances which were equal or even superior in activity to the natural oestrogens. This work will now be described.

The synthetic oestrogens

Dodds began in 1932 this fascinating chapter of his discoveries with a very discerning observation based on the rapidly developing knowledge of the structure of the naturally occurring oestrogens, brilliantly developed by chemical workers of many countries such as E. A. Doisy, A. Butenandt, G. F. Marrian, E. Laqueur and A. Girard. These authors had begun to find that, contrary to the prevailing view held before that time, the activity of the oestrogenic hormone was not confined to a single chemical individual substance. The true chemical constitution emerged over a few years, crystalline oestrone being the first pure substance isolated, from urine of pregnant mares, by Doisy and by Butenandt. Then Marrian in England obtained oestriol, its hydration product, from human pregnancy urine, and this compound, though still oestrogenic, was less potent in tests on castrated rats. Later, it was recognized that the hormone occurring naturally in the ovarian liquor folliculi, from which it was first obtained crystalline by Doisy, was also a different hydrogenation product of oestrone, namely oestradiol. All three substances possessed a phenolic ring. A. Girard showed that, in addition, two substances which were more unsaturated in ring B of oestrone (equilin and equilenin) were also oestrogenically active, the latter having two aromatic rings, thus being a polycyclic derivative of 2-naphthol.

It occurred to Dodds that if such a wide variety of related chemical structures could possess in common the physiological action of being oestrogenic, it was reasonable to ask if there were not still further modifications of basic structure
which might still possess the same characteristic activity. He, therefore, cast around for related, preferably simpler, compounds, and having a well developed testing laboratory ready to hand in his Institute, based on the earlier work with natural oestrogens, he was fully equipped to test such materials.

Dr J. W. Cook (now Sir James Cook, F.R.S.) had at that time (1932) already established the chemical basis of an important link between certain polycyclic aromatic compounds and cancer induction in animals. Working with Sir Ernest Kennaway, Director of the Research Institute at the Royal Cancer Hospital, he had shown that the carcinogenically active substance in coal tar was such a compound, and that chemically pure 1,2,5,6-dibenzanthracene was capable of inducing cancer of the skin when applied to mice. Finally, the main active ingredient in coal tar was identified by Cook, Hewett & Hieger (1933) as 3,4-benzopyrene.

For the purpose of this historic piece of research, Cook had prepared a large number of pure polycyclic hydrocarbons and their derivatives, including some partly aromatic hydrophenanthrenes, possessing hydroxyl or ketonic groups. He has kindly given me an account of how Kennaway at the time was very desirous that he (Cook) should attempt the synthesis of oestrone, the final structure of which was still uncertain:

‘There was in fact evidence that the oestrin molecule had a fused ring alicyclic structure (probably tetracyclic) with one aromatic ring and with two polar groups at opposite ends of the molecule. There were also indications of the general shape and size of the molecule from X-ray diffraction studies. New hydrophenanthrene structures for the sterols and bile acids had just been proposed and supported and it was tempting to speculate that there might be a structural relationship between these and oestrogenic hormones.

‘I told Kennaway that structural investigation of oestrin was not sufficiently advanced to warrant any attempt at synthesis but that I had in my collection a number of compounds which had several structural features which had been shown to be present in the hormones—notably, a partly aromatic hydrophenanthrene structure with hydroxyl or ketonic groups. Kennaway approached Dodds, his former assistant, and asked if we could come and see him to discuss the possibility of his undertaking some tests for oestrogenic action. It was known that Dodds had readily available facilities for such tests in his laboratory.’

I think that it is fair to comment that there is some difference of opinion about whether Kennaway approached Dodds, as he certainly gave Cook to understand, or vice versa, as Dodds himself believed. The whole matter apparently arose in a series of telephone conversations between the two, and it will probably never be possible to clarify this point. Cook goes on to report the first actual meeting of the three of them in the following terms:

‘I well recall our visit to Dodds at the Courtauld Institute of Biochemistry on a dark November afternoon in 1932. I had picked out from my collection three compounds of the type mentioned in the preceding paragraphs and
diffidently handed them over with the feeling that I was wasting the time of a busy man. Dodds accepted the substances without enthusiasm and promised to undertake the tests. About a fortnight later he telephoned in some excitement and told me that one of the of the three had shown a positive response in 100 mg doses. This was 1-keto-1,2,3,4-tetrahydrophenanthrene, a considerable supply of which had been prepared by my assistant C. L. Hewett as an unwanted by-product obtained in the course of what proved to be an unsuccessful attempt to synthesise 3,4-benzopyrene! Encouraged by this result we assembled a larger collection of compounds from my store. Some of these showed oestrogenic activity, including two carcinogenic hydrocarbons. A high order of activity was shown by a diol related to 1,2,5,6-dibenzanthracene.

‘By this time confirmatory evidence of the structure of the natural hormones and of their relationship to the sterols was accumulating and Dodds was anxious to continue our collaborative work by seeking to prepare and test compounds more closely related in structure to the natural hormones. He offered the services of Wilfrid Lawson, a chemist in his Institute, to participate and to work under my guidance on chemical synthesis. I also encouraged my colleague Hewett to undertake synthetic studies in this field.’

Unfortunately the collaboration between Dodds and Cook was broken off and their researches took different lines from 1934 onwards, but not before a real start had been made towards the final goal.

The biological activity shown by 1-keto-1,2,3,4-tetrahydrophenanthrene, even though large doses were required, was indeed spectacular, as Cook’s comments above indicate. Not only did this compound induce full oestrus in ovariectomized rats (Cook, Dodds & Hewett 1933 (66)) but it also produced typical changes of plumage from the male to female type of pigmentation, when administered to capons (Cook, Dodds & Greenwood (78)). It was thus the first non-steroid synthetic compound to produce the major effects of the natural steroidal oestrogens. As Cook has also mentioned, it was only a few months before other more highly active compounds in the form of the diols such as 9,10-dihydroxy-9,10-di-n-butyl-9,10-dihydro-1,2,5,6-dibenzanthracene were added to the series; other, less active, members were neo-ergosterol, 5,6-cyclo-penteno-1,2-benzanthracene, 1,2-benzopyrene, calciferol and ergosterol (Cook & Dodds (67)). Some of these compounds, being also carcinogenic, were obviously not suitable for clinical trials, and others were too weak in their activity.

At this stage, Wilfrid Lawson joined the others and within a year a full paper embodying a whole range of similar 9,10-diols was published (Cook, Dodds, Hewett & Lawson 1934 (77)). The highest activity was shown by the di-n-propyl derivative, of which the rat unit was 0.025 mg. Hitherto activity had required the presence of the phenanthrene nucleus, but even this was proved unnecessary when other compounds, including several stilbene and diphenyl derivatives, were found quite active (Dodds & Lawson (99, 112, 113)). In most of these the presence of p-hydroxyl groups added greatly to the activity.
A very high oestrogenic activity was reported for the alkyl derivative of phenol known as anol (or \(\rho\)-hydroxy-propenylbenzene)—1 \(\mu\)g of this preparation was originally claimed to have the same activity as 1 \(\mu\)g of oestrone in the rat tests (Dodds & Lawson, April 1937 (112)). Two months later there appeared a retraction of this claim (Dodds & Lawson (113)), following negative findings for the activity of purified anol by other workers who had attempted to repeat this observation. This was a severe setback; but it was mollified when the mother liquor from which the apparently pure anol had been recrystallized was found to contain a very highly oestrogenic material: 'Anol polymerizes with the greatest of ease and it is possible that the active substance is a polymer' (Dodds & Lawson (113)).

This view proved to be correct, and it led more or less directly to the discovery of stilboestrol, a name first introduced by Dodds, Golberg, Lawson & Robinson (February 1938 (123)) to describe 4,4'-dihydroxystilbene, which they had by then found to be the mother-substance of a whole range of highly active oestrogens. The full details of this series were published in *Proceedings of the Royal Society* by the same authors in May 1939 (142). The reason for the collaboration between Dodds and Robinson's two laboratories was briefly mentioned in their February 1938 paper (123). After a description of Dodds & Lawson's earlier work already mentioned, and that of Campbell, Dodds & Lawson (January 1938 (122)) showing that di-anol, one of the possible dimerides of \(\rho\)-hydroxy-propenylbenzene, obtained by demethylation of di-anethole was oestrogenic to rats in doses as low as 50 \(\mu\)g, Dodds, Golberg, Lawson & Robinson (123) went on to say:

>'In the meantime an investigation had been initiated at Oxford, the object of which was to prepare possible oestrogenic agents bearing a close structural resemblance to oestrone (or oestradiol) but which should be capable of ready synthesis. In certain directions, especially in the diphenylethane and stilbene groups, we found it convenient to join forces in order to avoid duplication of work.'

Sir Robert Robinson and Wilfrid Lawson have kindly informed me recently just how this very fruitful collaboration came about. At that time (1938) both Dodds and Robinson were consultants to Boots and attended a meeting there under the chairmanship of Sir Jack Drummond, a personal friend of both. Dodds mentioned his problem and that the particular di-anol which he and Lawson had prepared had insufficient potency to account, even if it were present, for the high oestrogenic activity of their crude anol preparations. Robinson thereupon wrote the formula of another possible dimeride, namely 4,4'-dihydroxy-\(\alpha\beta\)-diethyl stilbene, and told Dodds that his D.Phil. student at Oxford, L. Golberg, had already prepared the dimethyl ether of this diphenol. He arranged for a sample of 1 g to be sent to Lawson, who was experienced in demethylation of similar compounds, and who by heating this material with alcoholic KOH in a sealed vessel at 205 °C produced the first sample of the pure diethylstilboestrol. The original specimen is still in Lawson's possession. It proved to be the most potent compound of this series of alkyl-substituted dihydroxystilbenes, being fully
active in inducing oestrus in ovariectomized rats in a dosage between 0.3 and 0.4 µg. This high activity was found to be associated with the trans-isomer, and was some 2–3 times as great as that of the naturally occurring oestrone in similar tests (Dodds, Golberg, Grünfeld, Lawson, Saffer & Robinson 1944) (155). In spite of the later description of a very wide range of other synthetic oestrogens by Dodds, Huang, Lawson & Robinson (1953) (218), diethylstilboestrol has proved the most important of the whole series of artificial oestrogens, being readily and cheaply prepared in quantity and having the very great practical advantage for clinical purposes of being fully active when given orally. The preparation of this substance therefore represented the culmination of the long and tenacious pursuit which Dodds carried out for some 5 years, the whole time against vigorous competition particularly from several powerful and highly equipped commercial organizations. There is little doubt that this factor was responsible for the evidently hastily written form in which some of these publications first appeared in print, but there can be no two opinions on their final great value.

Although diethylstilboestrol has held its own as a synthetic oestrogen, the work of Campbell, Dodds & Lawson (1938) (122) and Campbell, Dodds, Lawson & Noble (1939) (143) had already shown that another substance, hexoestrol, which lacked the double bond present in stilboestrol, being 4,4'-dihydroxy-γδ-diphenyl-β-hexane, was the probable contaminant conferring oestrogenic activity on impure anol. The latter paper included full biological tests on this substance. In tests for the induction of vaginal oestrus on ovariectomized rats it even surpassed diethylstilboestrol slightly in activity and showed a full range of all other biological effects associated with the natural oestrogens; like diethylstilboestrol it was active by mouth, far more so than was oestrone when given by the oral route.

In later tests these activities were compared for the human female in a series of clinical trials (Bishop, Kennedy & Wynn-Williams, 1948), which together with much other evidence has been reviewed by Dodds (1949) (195). The final conclusion seems to be that activities in the human and in animal tests are very different. Diethylstilboestrol was the most active in women, dienoestrol having only about one-quarter, doisynolic acid one-fifth and hexoestrol one-eighth of its activity. Finally, it should be noted that very high clinical activity is shown by some semisynthetic compounds such as ethinyl oestradiol, even when these are orally administered; most of these derivatives of the natural oestrogens, however, are protected by patents and very costly in use compared with diethylstilboestrol.

**Clinical uses of diethylstilboestrol**

The Therapeutic Trials Committee of the Medical Research Council Report (1939) found that as a result of extensive clinical trials diethylstilboestrol (now often loosely called stilboestrol) is capable of replacing the naturally occurring oestrogens such as oestrone and oestradiol in every way and, moreover, that it is intensely active when administered by the mouth as well as subcutaneously. The daily dosage varies from 0.5 to 5 mg. Menopausal symptoms may be controlled
by 0.5–1 mg orally daily. A slight amount of nausea may result but this usually passes off when the treatment is continued, though in a few cases it may have to be abandoned. Amenorrhoea and dysmenorrhoea have responded successfully, and a complete menstrual cycle has even been reproduced in a castrated woman with an oral dose of 24 mg (Dodds 1953 (219); Bishop 1953). Other actions of dosage with oestrogens include marked suppression of the secretion of anterior pituitary hormones; it is thought that this effect, or possibly the alteration of the sex-hormone environment of the organism, may account for their activity in treatment of carcinoma of prostate and breast.

By far the most spectacular effects of stilboestrol in cancer patients are seen in carcinoma of the prostate. As is well known, Huggins and co-workers in Chicago (1941) had begun to make the important discovery that similarly effective results to those of castration could be obtained by administration of powerful oestrogens in patients with carcinoma of the prostate. Stilboestrol proved an ideal substitute for the natural hormone. ‘Administration of 15–30 mg of stilboestrol daily will, in many cases, arrest the primary growth and resolve the secondary deposits, often with recalcification of metastases in bone. Whereas it is almost certain that stilboestrol does not lead to a permanent cure, it may, nevertheless, arrest the disease for many years—up to 8 [or more] years—so far as the prostate gland is concerned’ (Bishop 1953). In carcinoma of the breast, long treatment (3 or 4 months) proved usually necessary before any response was observed—and only a fairly small percentage of women so treated may be expected to respond. Nevertheless, these uses of stilboestrol have proved of immense value, especially in cases where surgical and radiotherapeutic treatments have proved unsuitable or unsuccessful.

The oestrogens are powerful drugs and correspondingly their use is not without risk. Some of the adverse aspects have only recently come to light, particularly with regard to their possible carcinogenic action. Dodds himself always maintained that such risks were slight or non-existent. As he wrote for a lecture given in Vancouver in 1971, in almost his last published work (Dodds 1972): ‘I must say that when the Thalidomide tragedy occurred I could not help feeling how lucky we were that there was no hidden toxicity in stilboestrol.’ Unfortunately, almost simultaneously, it was being reported that vaginal adenocarcinoma in young women was occurring in the U.S.A. associated with stilboestrol therapy of the mother during pregnancy, and these and a number of similar observations were recently reviewed in a leading article in *The Lancet* (1974). Although the risk as a percentage of those so exposed appears low, the widespread use of stilboestrol over past years in the treatment of threatened abortion in the U.S.A. means that there the final numbers may become serious. In this country no cases have yet been reported, probably because similar treatment with oestrogens early in pregnancy has not been customary here. Also recently the first cases of benign hepatoma have been reported in women taking oral contraceptive steroids (Leading article, *Lancet*, 1973) which normally include oestrogens. It is clear, therefore, that the negative results obtained in skin-painting on animals, to which Dodds often referred, were in fact insufficient evidence to exclude the
carcinogenic potential of the oestrogens in humans, while other animal experiments had already pointed to a possible risk.

Finally, one must refer to an astonishing omission from Dodds’s development of the use of oestrogens. As early as 1938, Parkes, Noble & Dodds (134) published a detailed account of how the use of diethylstilboestrol or ethinyl oestradiol in laboratory animals, if given before mating, would prevent nidation and pregnancy. This treatment would also terminate established pregnancy. Yet it was not until 1956 that Gregory Pincus began his now famous clinical trials on Puerto Rican women showing the highly efficient contraceptive action of pills containing progestogen plus an oestrogen, frequently ethinyl oestradiol (Pincus 1956, 1959); this has of course become a recognized and widely used form of contraception. This blind spot, as it now appears, in Dodds’s usually perceptive vision is perhaps accounted for by his fear of prolonged interference with the hormonal background of the woman, who may possibly take the treatment over nearly 40 years:

‘I personally as a biologist cannot believe that it is possible to interfere in a natural process for so long without something really serious happening’ (Dodds 1972).

Time alone will show if his fears were in fact well founded or otherwise. Clearly in this as in other aspects of oestrogen therapy it is necessary to balance the known great benefits against the element of risk.

OTHER RESEARCH INTERESTS

While there is little doubt that Dodds’s great contribution to biochemistry and medicine lay in his endocrine studies, he had many other research interests, besides the new developments in clinical biochemistry, some of which have been already mentioned.

Throughout his life he was a leading figure in cancer research, being for many years Chairman of the Scientific Advisory Committee of the British Empire Cancer Campaign. Those who served under him remember vividly how efficiently he conducted these meetings, at which large sums of money were allocated to universities, hospitals and individual scientists in record time, but always with scrupulous fairness. Beside his own work on the synthetic oestrogens, which played so great a part in the treatment of prostatic cancer, his other direct contributions to cancer research appear relatively minor. He critically studied from time to time a number of reputedly diagnostic tests for the presence of malignant disease, and although the results were mainly negative ones, this was a very necessary task. He inspired work, particularly by A. E. Kellie in his Institute, on the possible diagnostic value of urinary steroids in cancer on which he wrote an interesting review for the Annals of the Royal College of Surgeons in 1948, with the conclusion that at that time ‘research workers had very little to offer to the practical clinician’ in this field. This typically down-to-earth but essentially honest attitude was itself a necessary antidote to much wishful over-optimistic presentation of this and similar aspects of cancer research, which was not uncommon at that time.
Edward Charles Dodds

Dodds had always shown great interest in Addison's disease, having had the honour of delivering the first Addison Lecture at Guy's in 1946 as well as the Centenary one in 1960. It is, therefore, fitting that the other great advance, which emerged in his Institute, from the joint work of J. F. Tait and Sylvia A. Simpson, was the discovery in 1952 of aldosterone. Mrs Simpson (now Mrs Tait), a notably skilful experimental biologist, was a member of the staff of the Courtauld Institute who among her other activities had earlier been responsible for much of the testing for activity of Dodds's synthetic oestrogens. Dr (now Professor) Tait, as a physicist in the Medical School, was familiar with isotopic techniques, and the combined skills of these two workers enabled them to develop a method of estimating mineralo-corticoid activity by measurement of the ratio of excretion of $^{24}\text{Na}/^{42}\text{K}$. By their purification of this hormone from adrenal glands they were able for the first time to identify and, in 1954 jointly with Professor T. Reichstein (Simpson et al. 1954), to establish the chemical structure of the natural principle, which was very highly active in sustaining patients suffering from Addison's disease. Professor and Mrs Tait were both elected to the Royal Society in 1959. Dodds's other great interests were in nutrition and chemotherapy, as well as in the history of medicine; these aspects will be briefly mentioned later.

The International Unions

As a great traveller who had lectured in many countries Dodds not unnaturally became deeply involved in the activity of the International Unions. He was for several years Treasurer to the International Union of Pure and Applied Chemistry and later became Chairman of the Section of Biological Chemistry of I.U.P.A.C. of which he was formerly a member. The controversial manner in which in 1951 he became Chairman of this body is set out in R. A. Morton's *The Biochemical Society, its history and activities 1911-1969*, pp. 106-108. At the relevant period, the Biochemical Society was busily organizing an official application for the establishment of a separate International Union of Biochemistry which the late J. N. Davidson and myself travelled to Washington to present to the International Council of Scientific Unions in October 1951. Dodds had been invited by the Biochemical Society, of which he was Chairman 1951–52, to represent their interests at the New York XII International Congress of Pure and Applied Chemistry, which he was attending in September 1951 as a delegate of the British National Committee for Chemistry. At about the same period, draft statutes for the proposed new International Union of Biochemistry had been drawn up and submitted to the Royal Society with a view to the formation of the first National Committee for Biochemistry.

When Dodds arrived in New York he learnt that Tiselius, the Chairman of the Biological Chemistry Section of I.U.P.A.C., had been elected President of that Union, and Dodds was asked at short notice to accept the chairmanship in his place. This he did with some reluctance and on condition that it was minuted that he, Dodds, favoured an independent Union of Biochemistry. Nevertheless, this appointment led to much disappointment and some bitter criticism on his...
return from other supporters of the proposed new I.U.B., many of whom felt they had been badly let down and said so. Among those who took a contrary view was Professor A. Neuberger, a member of the Section Committee at the time, who has kindly informed me that Dodds, in the face of much opposition from chemists, stuck to his view favouring the establishment of the new Union throughout. By 1953, Dodds's Section of Biological Chemistry had come round to supporting the formation of the new I.U.B. and for this valuable aid he was given the official thanks of the Biochemical Society. Finally, this long drawn-out battle was vindicated by the formal constitution by the Royal Society of the British National Committee for Biochemistry in November 1955 and the official formation of the International Union of Biochemistry followed as soon as the Union rules permitted. In all this negotiation Dodds showed his strength of character, remaining, at least externally, quite unperturbed by the storm going on around him.

THE WORSHIPFUL SOCIETY OF THE APOTHECARIES OF LONDON

Sir William Wilcox persuaded Dodds to become a Yeoman of this ancient body in 1934. He became a Liveryman in 1937 and was elected to the Court of Assistants in 1941. After serving on the Committee of Examiners, he was elected Master in August 1947, serving in this capacity for two years. From 1947 to 1970 he was Custodian of the Cellars of the Society—an appointment that he much relished, being very knowledgeable, particularly on clarets. He delivered several lectures to the Society, including an interesting historical piece 'A physician in the plague year' given in 1965, the Gideon De Laune Lecture.

A stained-glass window in the Great Hall by Carl Edwards bears Dodds's coat-of-arms as a baronet—the first in the history of heraldry to include a chemical formula; needless to say that of diethylstilboestrol. The parlour adjoining the hall contains an excellent miniature of him by Lisa de Montfort. His long association with the Apothecaries undoubtedly gave him a special pleasure and delight in the ancient traditions of this City Company, as Sir Brian Windeyer said in his address at the Memorial Service, which was held in the near-by church of St Andrew's-by-the-Wardrobe on 13 February 1974.

THE ROYAL COLLEGE OF PHYSICIANS OF LONDON

Dodds's crowning medical honour was his election as President of the Royal College of Physicians in 1962, after he had served for several years as their Harveian Librarian, a position which his historical interests made memorable for him. He had worked hard for the College which at the time of his Presidency was going through an anxious time, having just moved to their new home in Regent's Park. Sir Cyril Clarke, the present President, has written (Clarke 1974) of 'the great contribution that he [Dodds] made to the Royal College of Physicians in stabilizing its finances at the time of the move to our new building. This was particularly exemplified by the special appeal he made to the pharmaceutical industry enabling the college to bridge the gap between its income and expenditure. Sir Charles himself always said that his greatest contribution was the
Edward Charles Dodds

foundation of "The Friends of the College". This is a body of people distin-
guished in industry, commerce and other walks of life to whom we can turn for
advice, not only in maintaining financial independence but also in surmounting
the various problems which face all charities and independent educational
organizations. The advice of the Friends is particularly helpful in these times of
stringency and we shall always be in his dept for bringing them into being.'

It is certain that Dodds himself regarded his election as President as the
greatest honour of his career, it being unique in the four and a half centuries
since the foundation of the College for a physician who was laboratory-based
and not engaged in regular clinical practice to be elected President. He looked
upon his election also as a tribute to the ever-growing importance of the science
of biochemistry to medicine.

FOOD AND NUTRITION

At an early stage of his career, Dodds became greatly interested in nutrition,
especially in relation to obesity. Indeed, he was sometimes a target for wits over
this, being by no means slim himself. In an old issue of the *Middlesex Hospital
Journal* there is verse accompanying a cartoon (suspected to be by E. G. L.
Bywaters—a good artist as a student; now an eminent Professor of Medicine)
showing Dodds smoking the small pipe which he then affected:

'The Modification of Dodds:
The little pipe you see portrayed,
Is far too small, and I'm afraid
Year after year it must get bigger
To counterpoise its owner's figure.'

He took such ribaldry in good part, but he was in fact deeply interested in the
problem posed by the observation that the same diet in two individuals could lead
to adiposity in one but not the other, and he devoted a good deal of work to study-
ing the basal metabolic rate and related physiology of such differing persons.
He was responsible with Sir William Jackson Pope, F.R.S. (71) for intro-
ducing in 1933, dinitro-o-cresol into clinical use as a metabolic accelerant and
thus as a slimming agent. Other nitrophenols had been used for this purpose, but
the new compound was thought to be considerably less toxic as shown in animal
tests. Dinitro-o-cresol was certainly highly active in humans when given by
mouth and, as Dodds & Greville (1933) showed, greatly increased the respiration
of tissue slices *in vitro*. Dodds & Robertson (1933) (74) showed that it raised the
b.m.r. of patients, though unlike doses of thyroid hormone it had no curative
effect in myxoedema. Unfortunately, it was not long before toxic effects after all
became apparent in the clinical use of the drug, which has now been abandoned.

It seems that it may have been through his friendship with the late Lord
Horder that Dodds from 1937 onwards became much involved in bread manu-
facture and flour-milling, although the synthesis of vitamin B₁ in that year by
Todd and Bergel in this country and by Williams and Cline in the U.S.A. and
its subsequent large-scale manufacture by Hoffmann la Roche, to which firm he
was a consultant, also played an essential part. Dodds, together with Lord

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Horder and Dr T. Moran, the Director of the British Flour Millers Research Association, published in 1954 a small book, *Bread*, which gives a full account of how the enrichment of white flour became standard practice in this country (as well as in the U.S.A.). The following extract from the obituary notice on Sir Charles written by Dr Moran for the *Flour Millers and Bakers Research Association Bulletin* (1974) aptly summarizes this important development:

‘From about 1920 onwards there was a growing and vociferous body of opinion from some doctors and “food reformers” stressing that white bread was nutritionally much inferior to wholemeal or high extraction bread; yet the bulk of the population preferred white bread. Dodds saw the obvious compromise and it was he who suggested to the milling industry that white flour should be enriched with vitamin B₁ (and by inference with any other of the B vitamins and minerals held to be desirable). Such a flour, enriched with B₁ and with calcium, was adopted by the Government in July 1940 and continued until March 1942 when shipping losses made it essential to raise the extraction rate to 85%. . . . Finally in 1956 the Panel under the Chairmanship of Lord Cohen of Birkenhead on the Composition and Nutritive Value of Flour declared that in the diet in this country there was no ascertainable nutritional difference between 80% National Flour and enriched white flour. Sir Charles’ original suggestion was thus endorsed.’

Dodds, as Chairman of the Food Standards Committee for their Report *Bread and flour* (1960), advised on the use of so-called ‘improvers’ added to flour to facilitate baking, in the light of Sir Edward Mellanby’s discovery (1946) that the use of agene (nitrogen trichloride) was capable of inducing hysteria in dogs. In a series of papers from Dr Moran and his colleagues (1947–51) it had been shown by its isolation that the toxic factor was methionine sulphoximine, formed by interaction of NCl₂ with methionine contained in the flour protein. These and similar studies have led to the replacement in bread-making of agene by other materials.

In July 1969 Dodds & Moran contributed an article (280) to the trade journal *Milling* which gives a useful broad survey of the present nutritional aspect of bread in the national diet.

Sir Frank Young, President of the British Nutrition Foundation, has kindly given me an account showing how Dodds played an important part in the establishment of the Foundation:

‘In November 1965 he was host at a luncheon party at the Royal College of Physicians in London, of which he was then President, attended by prominent members of the food industry and a number of scientists and medical men, all of whom recognized the need for the establishment of an authority on nutritional matters which was independent both of commerce and of government. As a result of this and subsequent meetings the British Nutrition Foundation was incorporated early in 1967, the promotion of research and education in the wide field of nutrition being the main aim of its activities. Under its first Director-General—the late Professor A. C. Frazer, C.B.E.—the Foundation quickly established itself as a source of
information available to those who sought an unbiased view of matters of current nutritional importance and interest, and although the Foundation suffered a grievous blow in the unexpected and early death of Professor Frazer in 1969, it continues to flourish. Sir Charles Dodds served three times as Chairman of its Council and was still active in the Foundation at the time of his death. As often was so, Dodds was far-sighted in these matters and clearly appreciated the importance of the growing interest in food and nutrition of an increasingly literate public who would welcome independent advice about nutritional matters. This the British Nutrition Foundation from its outset sought to provide.

Finally, his services to the Ministry of Supply Establishment at Porton, especially to the Microbiological Research Department, extended over many years, largely during the period when Dr David Henderson, C.B., F.R.S., was Director, having been persuaded originally by Sir Paul Fildes to join his group at Porton. Their reports were made to a Committee of the War Cabinet under the chairmanship of Lord Hankey. Dodds later took a great interest in the design of the outstanding new laboratories completed in 1951 to house the Department, and in the progress of the work there. An appreciative account of this is contained in the biographical memoir of the late Dr David Henderson (Kent & Morgan 1970). Dodds strongly supported the freer publication of work and public visits to the Department which are now its approved practice.

THE NATIONAL RESEARCH DEVELOPMENT CORPORATION AND THE PHARMACEUTICAL INDUSTRY

Dodds was a member from the first year of the N.R.D.C. in 1949 and remained on the Board until 1968, being subsequently a consultant. Among the projects which had his full support were the cephalosporin developments which subsequently proved to be the leading patents taken out by the N.R.D.C., and a major theme in their investments—and also work on ACTH, cortisone and later aldosterone.

In several of his writings, Dodds has expressed his regret that at the time of the discovery of stilboestrol, which the M.R.C. felt unable to protect by patents, the N.R.D.C. did not exist to do so—it would certainly have proved one of their more profitable ventures.

Dodds’s earliest interest in Beechams was brought about by Mr H. G. Lazell, then Chairman of MacLeans and later Chairman of the Beecham Group, to whom he was introduced through their mutual friend Mr Philip Hill in the 1940s. He became a consultant and strongly urged both of them to develop the Group’s research institute for pharmaceuticals. This led to the purchase in 1948 of the fine house at Brockham Park, Surrey, at which a little later the massive expansion of their research by the introduction of the semi-synthetic penicillins began. Dodds remained a consultant for more than thirty years.

Sir Ernst Chain has told me that while he was working in Rome as Head of the Biochemistry Department and of the International Centre for Chemical Microbiology, at the Istituto Superiore di Sanità, Dodds approached him in 1954
on behalf of Mr Lazell. At that time, Professor Chain had excellent fermentation facilities and it is well known how this led to the production of 6-aminobenzylpenicillin and later, with the aid of Mr F. P. Doyle and his colleagues at Brockham Park, 6-aminopenicillanic acid. A programme of work to prepare N-acyl derivatives had been devised partly by Sir Ernst Chain and Sir Ian Heilbron, and this was put into action at Brockham Park in 1959–60 to produce new penicillins, such as methicillin, which could not be made by conventional fermentation methods. The full history is given by Chain (1971) in his lecture ‘Thirty years of penicillin therapy’. This valuable therapeutic advance was in itself a complete justification of the excellence of Dodds’s advice, and there were other if less striking results from the formation of the research institute.

Final remarks

Broad as is the field covered by this memoir, it is incomplete in many ways which will be only too clearly apparent to those intimately acquainted with various special aspects of Dodds’s life. His interests ranged far and wide so that this must be so, in spite of help so freely given by very many friends. It is to be hoped that some of his robust and powerful character, full of sound common sense, as well as his penetrating intelligence and good judgement, has been made apparent. What is less easy to convey is his well developed sense of humour, lack of pomposity and good companionship in personal relationships. He was a true friend who earned the unstinted devotion of colleagues and staff alike. He never went back on his word. He worked hard and expected those with him to do the same. He was a good judge of character and chose his staff well; they respected him greatly and mostly remained for years. The high honours he earned did not change him. He was a generous man who liked the good things of life and a hospitable one who enjoyed being host to his enormous and varied circle of friends. His wide contacts with industry also made him a wealthy man, how much so probably came as a surprise to many of his friends.

His family life was a happy one and Lady Dodds was a constant support and help to him all through his working life. When she died in 1969 it was a terrible blow to him, though he had the great support of his son Ralph, who has succeeded him to the baronetcy, and his daughter-in-law Marion and their two daughters. Marion was the daughter of Sir Daniel T. Davies, K.C.V.O., a famous physician who had in his early days worked for a while in the Biochemistry Department at the Middlesex Hospital Medical School and who moved to the Coutauld Institute with Dodds to take charge of the Clinical Biochemistry Laboratory there in its first few years: one more example of how well he chose his friends and colleagues.

In writing this account I have had the benefit of correspondence and discussion with a very large number of Charles Dodds’s former friends and colleagues, as well as with his family and former schoolfriends. Some of these are mentioned in the memoir but I hope all will accept my grateful thanks.
Mrs Esmé Barron, his personal secretary over many years, very kindly typed this account and prepared the bibliography.

The photograph was taken by the Photographic Department of the Middlesex Hospital, to whom my thanks are also due.

Decorations, honorary degrees, medals, membership of learned societies and committees


Some endowed lectures given by Sir Charles Dodds


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