HERBERT MCLEAN EVANS 1882-1971
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In the constantly moving story of human endeavour and experience, there occur, or appear to occur, periods when the pace of change is accelerated and when, during a comparatively short space of time events of deep significance arise. The 89 years of Herbert McLean Evans's life (1882-1971) would seem to cover such a period. As one of the actors of the endocrine scene of the first half of the twentieth century, he strikes us with the startling impact of his vivid personality.

## ANCESTRY

HERBERT MCLEAN EVANS, anatomist, embryologist, endocrinologist and bibliophile was born on 23 September 1882 at Modesto, California, as the eldest of the three children of Clayburn Wayne Evans and his wife, Bessie, whose maiden name had been McLean. The father, a native of Alabama and a man of vigorous, rather than polished character, was an early graduate of the University of California Medical School which had been established in San Francisco in 1864 by that extraordinary surgeon of gold rush days, Herbert A. Toland (1809-1900). In due time Dr Evans became the leading physician and surgeon in the then small town of Modesto, with a population of 500 inhabitants, but now numbering 70,000. He is reputed to have been the first to do abdominal surgery in the Upper San Joaquim Valley and to have brought most of the babies in Stanislaws County into the world. Evans's mother was born near Baton Rouge in Louisiana; her family came from Appomatox, Va., where General Lee, the head of the Confederacy, surrendered to Grant in the mansion of her ancestor Wilbur McLean. Her father, Samuel Merriwether McLean, who was related to Merriwether Lewis, of Lewis and Clarke fame, also practised medicine in the Mother Lode county of California during the gold rush, and her brother, Robert McLean, the first native son of California to win a medical degree from its University, was Professor of Surgery and at one time Dean of the San Francisco Medical Faculty of the University. Bessie McLean Evans, like her brother Robert, was a person of refined manners and tastes, and her son evidently thought of her as having had a stronger and more enterprising influence than that of his father, between whose faith and his own he saw an ever widening gap. Herbert Evans thus began life in a strongly medical family and with a varied store of traits and temperament.

## SCHOOL AND COLLEGE YEARS

The record concerning Herbert Evans's early childhood is meagre in the extreme. In high school days his interests had turned towards science—indeed, to all the natural sciences, and to literature and history as well; and one can trace during the college years the growth of his interest in books. He attributed much of his early interests to the immensely tall Thomas Downey, a cultivated Irish high school principal in his home town, and to the excellent school library he had built up and which was then reputed to

house all the standard American journals—very unusual for a mere high school at the end of the nineteenth century. Besides his cultural interests, Downey's chief attribute which impressed the youthful Evans, was his physical capacity to throw the boys one after the other down the stairs. These activities were not very scientific, but were at least original; and as Evans has said, 'this is the age in which an influence is enormously important'.

Writing in later years Evans stated that he was undoubtedly better disciplined and better prepared for life from the teachings of this man and from such association as he had with him. And when, in his freshman year in the University of California at Berkeley in 1900, he received a visit from Mr Downey, he wondered who in the professorship was worthy of meeting his high school teacher. He chose Frederick Slade, the professor of physics, a man of sterling integrity with an active interest in matters of real dignity and importance, as the person most deserving of the honour. In this instance, Evans was seeking to prove that Slade possessed some of those qualities which he so admired in Downey.

This early exposure to books in boyhood was fortunate, for with his family background and strong pressure from his father it was inevitable that the young man should enter the medical profession, and that his college education should be directed to that end at the expense of cultural interests. Indeed, his father seems at first to have been dubious about letting him have more than the two years of pre-medical preparation then required. In the event his pre-medical education was extended, and the young Evans concentrated the rest of his college years on science, receiving his B.S. in 1904, at the end of his fourth year. Two factors matured him: the disapproval of his father and the consequences of his hunger for fame. Evans has told us how he and his father felt about his decision to extend his pre-medical education. ‘Of course', his father said, 'you will take that and then my boy, I hope you will be disposed at once to join me in practice in the town where you were born'. 'But inwardly,' Evans says, 'I had the idea, so famous was my father as a country practitioner, that I was certain that I would never rise to any fame, except to be old Dr Evans's son, and it struck me that I might do something on my own'. Here then was the Evans who at 23 said of himself that he could never devote himself half-heartedly to a cause: 'I must go at it headlong and lead the field'. This the young Evans made his creed, but if it gave him a line of conduct, it did not resolve his doubts about the practice of medicine, which as his reading increased, increased also. It was becoming more and more difficult for him to be satisfied with his father's unambitious plans for him, and he was passing through a difficult period, made the more difficult by his marriage.

Among his teachers at College, one who especially won his admiration was the celebrated palaeontologist, John C. Merriam who, during Evans's senior year in 1904, took him on a field trip to Idaho. The outcome of this trip was the publication in that year of a description of 'A new cestraciont spine from the lower Triassic of Idaho,' which Merriam had encouraged the young Evans to study. This was his first scientific adventure and it typifies the profound intellectual curiosity which he displayed at an

early age and which characterized his whole life thereafter, leading him into many highways and byways, interesting but unpredictable. His interest in palaeontology derived from his admiration for Karl Alfred von Zittel of Munich, who was J. C. Merriam's teacher, and on the completion of this his first scientific paper, as a student, he recalls that Merriam said to him: 'I know you were bored by that work, you are only interested in higher vertebrates'. 'Oh no', Evans replied, 'I might learn something from all'.

His college years had been bright. Not only had he acquitted himself creditably in his course work, but he had achieved what was more important to him at that time, distinction. As the gold medalist and outstanding student of his class during the senior year, he was one of the two student speakers (then customarily chosen) at the commencement exercises in 1904. Unfortunately, we possess no documentary relic of this address, which according to Evans was of five minutes' duration, and for which he was highly commended by the President of the University, Benjamin Ide Wheeler, save that he spoke on 'The importance of biological research for human welfare'.

Evans received his B.S. from the University of California at Berkeley in 1904. At the time of his graduation, the completion of an irrigation dam in the country where Modesto is, had so changed the agricultural prospects of the whole valley that, as Evans says, 'the land could grow seven crops of alfalfa a year instead of one crop of wheat'. To celebrate the event President Wheeler had been invited to perform the opening ceremony and to make an oration. Recalling the event to Sir Alan Parkes more than sixty years later, Evans went on to say: 'He was very eloquent but, more important for me, was the fact that the celebration was attended by Morse Stevens, a professor of history from Cornell and an authority on the French Revolution. At the celebration he coached Wheeler to persuade my father that I was doing the right thing to get a little better general education. At the end of his speech, Wheeler asked if there were such a man as Dr C. W. Evans in this community? Well, my father was the greatest physician there, and he came up and busted a gut almost, and wanted to know why he had been called for. ‘Well', Wheeler said, 'your son happens to be one of the two student Commencement speakers this year and I would like you to be my guest. I am giving a garden party for a man named Theodore Roosevelt and wish you to come'. My father was overpowered, and Wheeler went on to tell him a lot of stuff about what I'd done in the student honour society, which impressed my father very much, and he said: 'My boy, come up here'. And I came up and he said: 'Now look, this monkey business of yours with guinea-pigs and rabbits seems to have justified itself'.

Clayburn and Bessie Evans had planned that their son should remain in California to continue his medical studies. Thus, in the autumn of 1904, having earlier received his B.S., he enrolled in the medical school, in whose Berkeley laboratories he pursued the courses of the first year of professional study. The Professor of Anatomy was J. M. Flint, a surgeon who had done some anatomical research at Johns Hopkins and was a stimulating lecturer; his associates were Irving Hardesty, a productive histologist, and Robert Orton Moody, a competent teacher of gross anatomy. Another of

whom Evans spoke approvingly was Alonzo E. Taylor, the Professor of Pathology. But the outstanding scientist on the Berkeley campus during his pre-medical student days, probably the one who had the greatest influence on the twenty year old medical student and contributed most notably in the shaping of his subsequent interests, was the physiologist Jacques Loeb, whose brother Leo was the first to show (1907) that placentomata could be experimentally produced in the non-pregnant guinea-pig uterus, a subject which was later to consume a good deal of Evans's interest. It was Jacques Loeb's deliberately conceived biological experimentation which appealed most to Evans, and in later years he followed Loeb in his insistence that anatomy had been led astray by the enormous productivity of Johannes Muller in descriptive and speculative morphology, thus postponing the development of an experimental phase. Evans set about attending some of Jacques Loeb's courses although these were not primarily for freshmen, and as he has said: 'I cannot tell how much I enjoyed my freshman year. I would sneak into the back row at his seminar, because his fame touched us all'. But by the summer of 1905, Evans knew that the programme in medicine at Berkeley 'was so complete with lectures and likely to remain so during succeeding years, that there would be little free time to undertake that difficult task called discovery'. So it was that with this intention in mind and with his usual impetuous energy, and with funds provided by a Chapter of the Alpha Beta Psi fraternity, he undertook a visit of exploration to Harvard, where Charles Sedgwick Minot was the Professor of Anatomy and to Johns Hopkins in Baltimore, where Franklin Paine Mall held a similar position. 'Harvard and Hopkins', he says, 'struck me in those days as great lights in medicine, in our country, but I found Harvard had no free time at all, and Johns Hopkins gave a fourth of your time free, and this was an astonishing innovation'.

At this point in his life, Evans showed early signs of that assertive, though well founded, confidence in his own abilities which was to carry him so far, and at the same time bring about such bitter sorrow and disappointments. He wanted experience and he wanted to do research and to make a name for himself; entirely natural and praiseworthy ambitions of a young man at the outset of his medical studies. He could never turn definitely away from one thing to another; he always wanted them both.

There is no doubt that the intellectual climate at the medical school in California was uninspired, but it is certain that this was not the sole reason for Evans's wish to depart. There was the longstanding conflict with his father, and it is probable that these ups and downs and other family responsibilities conduced to Evans's decision; he had married on 17 September 1905. And so it was that in the autumn of 1905, having had the first year of medicine at the University of California at Berkeley, he decided to go to the Johns Hopkins Medical School in the second year of the curriculum, there to seek training in scientific medicine. Johns Hopkins, as the home of the new medicine, was easily the foremost medical school in America.

The transfer to Baltimore was against the wishes of his dominant father, as was his marriage, by elopement, to his college sweetheart, Anabel Tulloch, whose family also strongly disapproved of the marriage. Nothing could have been better designed to

produce a rift between father and son; his father was tormented by the fear that the young man's evident leaning towards science and the influence of the scientific atmosphere in Baltimore might turn him away from the practice of medicine. It says a great deal for their mutual affection, that it survived this unhappy experience. Herbert Evans had, however, another and far more weighty problem on his hand, a wife, like him tall and handsome and in her way as spirited as he. At that time, married medical students were unheard of at Johns Hopkins and most other medical schools in America. Fearing that he might not be admitted, Herbert concealed his marriage from the admissions office. He and Anabel set up housekeeping at some distance from the school, where in one of East Baltimore's little brick row-houses the bride from California's broad and verdant spaces was cooped up and separated from her husband all day long, among unintellectual neighbours, seeing nothing of his associates and activities, feeling lonely and neglected. Years afterwards each of them separately spoke to one of us (G.W.C.) about that strange interlude, he with an expression of remorse, she with a trace of lingering resentment, but each realizing that their sacrifice had helped to put him on the way to professional achievement. After about a year, the birth of their daughter Marian in the Johns Hopkins Hospital ended the deception and Anabel's isolation, although as the wife of an impecunious and intently busy student her lot was still far from easy.

## BALTIMORE 1905-1915

When Evans arrived in Baltimore, in the Autumn of 1905, to continue his medical studies, the Medical School of Johns Hopkins University and its Hospital were new and vigorous institutions. The Medical School, after it had benefited by President Daniel C. Gilman's far-sighted organization, had received full status as a postgraduate division of a great university, liberal education had begun to accrue, and by the time Evans had enrolled, teaching was on a plane superior to that at any of the other schools in America. It was nevertheless a strange new world for this young married student of 23. After the white marble walls of the Harvard Medical School and the new Peter Bent Brigham Hospital, which he must have seen on his visit of exploration to Charles Minot's laboratory in Boston, the Johns Hopkins Hospital Medical School building of Evans's day could not have been an imposing sight. Each storey was very high. There was no elevator except a small freight affair which had to be pulled up by hand. There was a hallway around the stairwell from which the various laboratories radiated. But for the eager young Evans, whose main interest was in the pursuit of science, such inequalities and inadequacies could be tolerated since these were fully compensated by the much more generous apportioning of free time for research that Johns Hopkins then offered.

At the time Evans went to Johns Hopkins, and for the seven years he spent there after taking his M.D. in 1908, the medical school had a glamour and a brilliancy of its own. Everyone was filled with the enthusiasm of a new experiment in medical education, and whatever anxiety as to the future may have troubled the older men, no signs were apparent in the new recruits who had thrown in their fortunes.

Further insight into Baltimore's chatoyant habits of this period, to which Evans was early exposed and with which he must have been familiar, since he lived in East Baltimore, may be gained from the following account by Paul D. Lamson [1], a contemporary of Evans who worked in pharmacology, close by the anatomy department where Evans spent most of his time while at Johns Hopkins: 'At just the time I went there (1914)', Lamson wrote, 'Baltimore was starting to grow up and to lose much of its old charm which, however, has been replaced by much of beauty. The automobile was coming in, and a few people were moving out of town, but many of the best families still lived in the city and sat on their doorsteps after dinner on warm evenings; and on the way home it was the custom for one to drop into the Maryland, Baltimore or University clubs, where one was sure to find friends. The University had not moved out to Homewood, and I lived and dined with a very pleasant group at the corner of Monument and Howard Streets. Each morning, we would walk across town to the school. As we began our pilgrimage, we would pass houses with beautiful doorways, the brass knockers and name plates of which were being polished by those fine old coloured men of the old school, and before we had passed the Washington monument we were sure to have been greeted with a "Goodmorning, Major, Colonel, General, or Admiral" which, in spite of its slight exaggeration, gave one a sense of importance' (it is unlikely that Evans needed this) 'with which to begin the day's work. Going over the hill and past the railroad tracks one saw those marvellous, great horses, eight or ten at a time, which pulled freight cars through the streets, but after this the glamour disappeared, as one had to watch his step to avoid the sewage drains which ran uncovered across the sidewalks in the famous Baltimore sewage system, and there was nothing left but a long climb up to the hospital, which tapered off from a very imposing front, to Dr Welch's laboratory across the street from Hanselmann's saloon, to which was attributed the entire success of the early Johns Hopkins groups'. Alas, all this has changed!

## THE MEDICAL FACULTY AT JOHNS HOPKINS (1905-1915)

Turning from these more general observations which apply to the Baltimore of Evans's day, we can the better assess the life and times at Johns Hopkins if we turn our attention to the scientific, intellectual, and cultural background of the years he spent in Baltimore (1905-1915). What memorable figures pass across the stage! Medicine was represented by William Osler (1849-1919) who was at once such an outstanding pathologist, internist, humanist, historian, bibliophile, and all-round scholar. It seems certain that it was, principally, Osler's stimulating, humanistic influence (though Harvey Cushing may have had a hand in this) which led subsequently to Evans's enthusiasm for the History of Science and of Medicine. Here we can draw on Evans's own recollections of the impact Osler made on him. 'Osler' he says, 'gave me a taste for the history of biology and then, much more important, for the history of medicine', But he goes on to say: 'The minute I got there [Baltimore] I regretted to learn that William Osler had gone to be Regius Professor of Medicine at Oxford, befriended by his brother Regius at Cambridge, Clifford Allbutt, who had a grand influence on Osler. When Osler

came back from his first year in Oxford and, in the amphitheatre at Baltimore, gave his lecture on Michael Servetus, I was so impressed that I determined forever to take an interest in the history of medicine'. Osler gave the lecture on Monday 11 May 1906, before the Hopkins Historical Society; though much admired, it has been criticized by experts for repeating some of the old inaccuracies. It is not unnatural to suppose that Evans probably began to interest himself in the history of science before he went to the University; as a boy, indeed a very young boy, if he really read the books in his school master's library.

At Johns Hopkins, surgery could claim the austerely scientific William S. Halsted (1852-1922), with whom Evans subsequently published his first paper in the field of endocrinology, and Harvey Cushing, who had already distinguished himself as the foremost brain surgeon of his day, and was then director of the Hunterian Laboratory of Experimental Medicine where Evans was to conduct his earliest researches on *The essential vascular changes in the hypertrophy following resection of large portions of the small intestine*.

Besides this triumvirate in medicine and surgery, pathology at Johns Hopkins triumphed in William Henry Welch (1850-1934), then generally recognized as the father of medical research in America, who so early insisted on the significance of adaptive processes in living material, and who, besides possessing an unbelievable memory, distinguished himself as a microbiologist and humanist. Osler had this to say of him: 'no man of his generation in the United States has so influenced the profession, not only by his administrative ability and his stimulating work in pathology, but much more by a personal unselfish devotion to its highest interests.' It is interesting and perhaps significant to note that while the influence of America's great pathologist on Evans was profound in that it stimulated and encouraged the latter's passionate curiosity about biomedical processes, and enlarged his vision in that search, it was not Welch's subject which ultimately captured his allegiance. A great teacher may, indeed, influence his pupil profoundly (as in this instance) without gaining a disciple.

The third branch of medicine, obstetrics and gynaecology, was represented by J. Whitridge Williams (1866-1931) who occupied the chair of obstetrics and by Howard Atwood Kelly (1858-1943), who was Professor of Gynaecology and a distinguished herpetologist. Although the latter never attained the scientific eminence of the remarkable group of clinicians on the faculty, he was a distinguished abdominal surgeon and, as the leading gynaecologist of his day commanded a handsome practice. His house and his manner of living were both quiet and distinguished and in the best taste. He contributed greatly to the establishment of his subject as a reputable branch of medicine and, in the manner of the time, was insistent in his advocacy of its more practical aims.

Kelly became enmeshed in a preposterous story which got abroad that he assented to Evans receiving his M.D., only on the condition that the latter would never practise midwifery. Here again fiction has gilded one of the incidents in Herbert Evans's

life into something wholly different from what the facts warrant. He was always the type of person who was watched and commented upon. Indeed one of the great difficulties of his biographers is in sifting the stories that were true from those that were apocryphal. It was a tribute to the vivid colour of his personality—he was invariably in the centre of the stage. In short, he had that indefinable quality, 'news value'.

Evans himself contributed to the persistence of such legends by his own apocryphal account of his expulsion from the medical school at the end of his third year. In a letter read on the night of 1 February 1941, on the occasion of the celebration of the sixtieth anniversary of William Howell's graduation from the Johns Hopkins University [2], at which he was unable to be present, Evans wrote:

`Duty in a foreign land (South America) will prevent my being present at the dinner in honor of Dr Howell. I have known, respected and, I may say, revered Dr Howell for thirty-five years in his role as teacher, mentor, guide and friend. My testimony must be that of every graduate of the School, but I have special and intimate grounds for my attachment. Expelled from the School at the conclusion of the third year for failure in surgical bandaging, obstetrical manikin manipulation and incompetence in the writing of prescriptions, I sought his advice. It was given with that combination of judgment and sympathy and with that the wayward returned to the fold to bless him and his alma mater forever thenceforth. May the Lord continue William H. Howell amongst us This is the fervent prayer of

Herbert M. Evans.'

No doubt he did neglect such practical routines, and cut classes withou regard to consequences, since from the first he felt little interest in the clinical courses, particularly when they took time from his researches. This: expulsion of which he speaks may well be the exaggeration of a lazy memory for in sober fact the records of the medical school do not mention any disciplinary action ever taken with respect to Herbert McLean Evans [3]. Yet one is prompted to ask whether, in the circumstances, he would have blatantly involved Howell in an episode which he knew to be wholly untrue. Or does it throw a new light on the 'second self' ? One almost feels that it is dramatic rather than narrative illusion that he has in mind. He has so individual a stamp upon every one of the six sentences—like Carlyle's letters; they have the 'writer's signature in every word, not only at the end'--that his visible presence would be superfluous.

Besides the clinicians at Johns Hopkins, Evans also came under the stimulating influence of the distinguished physiologist William H. Howell, as well known for his influence on medical education as for his studies on the mechanism of the clotting of the blood. Howell was also Dean of the Medical School in Evans's day, and it was part of his office to look upon medical education as a whole. He was, as Dean, interested equally in the teaching of the clinical and of the laboratory branches of the curriculum, and as educator he admitted no division between them, being convinced that the major clinics should be made, as the laboratory subjects already were, full University

professorships. He thus must have come to know Evans well and Evans him. And it is historically significant that in Howell's last year as Dean in 1911—Evans had then been qualified for three years—the discussions began in the medical faculty which two years later were to usher in that second great reformation in medical education in America, first put into effect at the Johns Hopkins medical school, namely, wholetime clinical chairs. In the autumn of 1913, the Rockefeller Foundation announced that the sum of one million and a half dollars had been given to the Johns Hopkins Medical School 'for the purpose of so organizing the departments of Medicine, Surgery and Pediatrics that the professors and their staffs might completely withdraw from private practice in order to devote their entire time to their respective departments.'

Amongst others who made up the first Faculty of the Johns Hopkins Medical School in Evans's day was John Jacob Abel, who will be remembered as the first pharmacologist in America. Besides his work on the active principles of the pituitary gland (which he mistakenly attributed to histamine), his isolation of the active principle of the thyroid as well as that of the adrenal medulla, though largely of a chemical nature, could scarcely have passed unnoticed at the time by the younger man. This was inevitable. Yet there is nothing to suggest that Evans was especially influenced by Abel, despite the opportunities offered by the close proximity of the latter's department to that of the German-trained professor of anatomy, Franklin Paine Mall, where Evans worked for most of his nine years in Baltimore.

Howell, Abel and Mall had come to the Johns Hopkins School at about the same time in 1893 at the launching of the new medical school. The latter two men, both German-trained, as was Welch, were given laboratories in two extra stories hastily added to the old Pathological, while Howell carried on the teaching of physiology across town in the Biological Laboratory on Howard Street. It was not until the Physiological Building was occupied towards the end of the century that the medical group became unified and all the teaching was carried out in East Baltimore, in, and adjacent to the Hospital.

These men who constituted the medical faculty at Johns Hopkins during Evans's Baltimore days, were not only profound scholars and men of high and noble minds; they were instructive teachers, tellers, explainers, helpers. In short, they were exciters of youth and by their writings and doings were profoundly influencing the minds and thought of the students of this period, but none more profoundly than that of Herbert McLean Evans; and the one who exerted the strongest influence was Franklin Paine Mall (1862-1917). On the other hand, it seems very unlikely that Mall himself could have failed to notice that this particular pupil was much above average in ability, and it may well be that he engaged his master's attention soon after arriving at Johns Hopkins. Mall's practical interests lay in research, in anatomy and physiology as sciences, sufficient ends in themselves. Not until Mall was sharing in the laboratory life and in the problems of Wilhelm His and Carl Ludwig in Europe did he feel an attraction that would not be denied. When he came to teach anatomy himself, his reforms in methods were all in the direction of encouraging research on the part of the students, of

stimulating them to find and solve problems for themselves. He had no time for the business of impressing upon passive minds the established relationships between anatomy and the practical arts of medicine; and this was precisely the attitude of Evans himself. His place was in the seclusion of the laboratory, never at the busy crossroads of medical practice; and while he developed a fruitful interest in the science of medicine he evinced but little manifest concern with its art.

It has always been assumed that Evans's relationship with Mall was close and that the latter was more than a teacher to the young medical student, for a fast friendship seems to have sprung up between master and pupil. Evans has this to say about the relationship: 'Someone once asked me what was the greatest thing I got out of my nine years in Baltimore ? And I said, Franklin Paine Mall let me walk across the town with him every night and described to me how they were trying to introduce the whole time system into the clinics. Then, too, I went at noon to a German Saloon where good beer was served and the men in the various parts of the medical faculty came there so that I got acquainted with them'. The German Saloon to which Evans refers was most certainly Hanselmann's, which stood across the street from Welch's laboratory and to which, as we have already noticed, was attributed the entire success of the early Johns Hopkins group! It is also evident from Evans's account that even at this early stage, he was not slow to seize the opportunity of meeting men of culture, not only in the field of medical sciences, which interested him especially, but in the more general realms of thought. There is a strong hint of this in his precise references during his evening walks with Mall.

In the compact community of Johns Hopkins at the time of Evans's graduation, it will be recalled that William Howell, with his intense interest in medical education, was deeply committed in the movement towards medical reform. Hence it is not unnatural to suppose that with his enquiring mind Evans's thoughts would be directed towards that broad subject, nor could he, voracious reader that he was, have overlooked the address on: ‘The Medical School as part of the University' which Howell gave at Harvard Medical School in 1909, and in which he arrived at the conclusion that the major clinics should be made full university professorships (chairs).

These were intellectually stimulating days in Baltimore; and for Herbert Evans they had a glamour and brilliancy of their own. At that time, Franklin Mall was in the fullness of his power. The maturity of his broad experience undoubtedly influenced Evans's thinking; and it was Mall who, more than any other, stimulated his passionate curiosity in human embryos and from whom he learned the importance of care in microscopic details. It is plain that the German-trained Mall had a forceful personality and a vigorous, creative mind, which could not fail to impress and inspire a pupil such as Evans, who had an equally distinguished personality. Then, too, the whole scientific life of the German-trained medical men on the faculty at that time made a deep impression on Evans. Their almost monastic devotion to scientific inquiry, their ability, assiduousness, the care and exactness with which they did their work in minute detail, and their desire to find out the truth of matters gave him very high standards for his

own development. 'The thing', he says, 'that influenced University education in America, from my point of view, more than any other, was the immense influence of Germany at the Universities and I think that started at Johns Hopkins'. With these strong pressures and his own passionate intellectual curiosity it is easy to see how his interests became definitely oriented towards the solution of biomedical phenomena, and although he was attracted to a great variety of problems having to do with medicine in general, his primary avocation seemed to be the study of the fundamentals of the living organism rather than the secondary changes brought about by disease.

## STUDENT RESEARCH

It would be natural to think of Herbert Evans as the medical student devoting his attention largely to anatomy and physiology and to the clinics at Johns Hopkins during his first year in Baltimore, but this is wide of the mark. He was certainly studying medicine in its widest meaning, but does not appear to have been bound to a strict adherence to courses. In his medical year at Berkeley, Evans had taken the usual course in human anatomy with dissection. At Johns Hopkins, at that time, second-year students were given continuing programmed instruction in that subject, but the professor, Franklin P. Mall, shrewd and subtle judge of men, allowed him to spend his time in the laboratory more or less as he wished. The result was that Evans spent more time in Mall's laboratory than in the clinics and soon found himself in the full swing of research. Mall, a master microscopist with an early interest in the pathology of human embryos, who had been trained by Wilhelm His and Carl Ludwig in Germany, was himself then engaged in research on the pattern of microscopic blood vessels in various organs and in embryos. From him Evans learned the techniques of injecting the vascular system with coloured fluids to make the vessels more readily visible. Working with finer and finer glass cannulae, under the microscope, he became, in due time, quite expert. His special status in the laboratory gave him much closer association with the departmental staff than he would otherwise have had. Mall, the most influential anatomist in America, had gathered about him probably the strongest anatomical research group in the English-speaking world, including Warren H. Lewis, Ross G. Harrison, Eliot R. Clark and Florence R. Sabin, all of them destined, as was Mall, to be members of the National Academy of Sciences. Like Evans himself, Ross G. Harrison was elected to the Foreign Membership of the Royal Society.

It was about this time that Herbert Evans was first accused of neglecting classes. The first incident which led to these allegations was when, as he put it, 'I began to work with him (Mall) to learn the technique of injection of the vascular system. I became so interested that I cut many classes, because I wanted to study the development of the vascular system in pig embryos. Some of the classes I cut occurred only once a week and struck me as trivial, so that my absence was not likely to disturb anyone. But I got into trouble. Even in my third year medical I cut courses I knew little about, and went to inject pig embryos to learn something about angiogenesis'. Yet the truth was that Herbert Evans was simply an enquiring mind in an age when most inquisitive intellectuals had to conduct their studies in that no-man's land between conformity and

non-conformity.

During this period the young Evans, though he had not yet completed his medical course, became engrossed in an investigation with the school's professor of surgery, which doubtless kindled an interest in endocrinology that was to last through his life. The beginnings were simple enough. One day the austerely scientific William Halsted came to Mall for help with a clinical problem. A patient of his, following an operation on the thyroid gland, had developed acute tetany. Knowing of surgical mishaps of the same kind, Halsted rightly conjectured that he had inadvertently either removed the inconspicuous but indispensable parathyroid glands along with the thyroid, or had tied off their blood supply. He felt that with more exact knowledge of the small arteries supplying the parathyroids, operations could be planned to conserve the glandules. Mall arranged for the eager young Evans to take on the problem under Halsted's supervision. The latter's thyroid resections were turned over to 'Mr Evans, a senior student from Modesto, California' for careful dissection and precise description of the vascular supply to the thyroid, and the all-important parathyroids. By injection and careful dissection of the branches of the thyroid arteries in a few cadavers, Evans solved the problem. 'I was pretty sure', he says, 'that they had removed more than just thyroid tissue'. Their paper, an authoritative article on *The parathyroid glandules: their blood supply and their preservation in operations upon the thyroid gland*, was published in the *Annals of Surgery* for October 1907. Thus it was that his name appeared, with Halsted as the senior author, while the junior author was still a medical student.

While Evans was thus exhibiting his remarkable talent for controlled experiment, Franklin Mall missed no occasion to foster Evans's research but had him write book reviews for the *Anatomical Record*, then being published from Mall's laboratory. These reviews, at this point in his career, already show the richness of his scholarship, and from them we get a glimpse of his underlying interest in the history of science and his familiarity with a wide variety of scientific topics.

In 1907, a year before Evans obtained his M.D., Mall was organizing jointly with Professor Franz Keibel of the University of Freiburg i.B., Germany, their great *Handbuch der Entwicklungsgeschichte* and its English counterpart, *Manual of human embryology*, to be written by leading investigators in Germany and America. A European embryologist who was to contribute a section on the blood vascular system was unable to do so and Mall entrusted the task to Evans—a quite extraordinary opportunity for so junior a person. Evans made good use of the occasion, and his early fame resulted from his chapters on this system in the German and English texts. Too ambitious merely to compile what was already known, he prepared himself not only by studying the literature of the subject and by examining well-understood embryos in Mall's collection, but also made original observations on the little known earliest development of the aorta and the other great vessels. By extremely skilful injection of vertebrate embryos (human, pig and chicken) working under the microscope, he proved, against the supposition of Hochstetter, and others, that these ultimately large channels begin, as do the peripheral arteries and veins, as a network of capillaries. Evans had by now at least

four papers to his credit, and all of these works revealed an extraordinary maturity, extensive scholarship and firm purpose.

DEPARTMENT OF ANATOMY JOHNS HOPKINS UNIVERSITY AND THE DEPARTMENT OF EMBRYOLOGY, CARNEGIE INSTITUTION

Immediately after his graduation in 1908, it would have been easy for the young Evans with his medical degree to take the usual road and start earning his living at once as a doctor, but that did not appeal to him at all. Instead, he joined Mall's department as an assistant in anatomy. By this step he confirmed what his father had been fearing for some years, that he would not return to Modesto to assist with and later take over the older man's practice. To Dr Evans senior this was a heavy blow, for he thought practice far more important than research. It was, doubtless, the feeling that his father undervalued his choice of career that instilled into Herbert Evans an urgent desire to impress his parents by success in his chosen work, and in later life to win the highest academic honours.

While he remained at Johns Hopkins, Mall, with grants from the Rockefeller Institute and from the Robert Koch (Sitzung) Stiftung, Berlin, arranged several times for Evans to go to Germany where by chance he started his apprenticeship to research on vital dyes. Most important of all, during a stay in Freiburg, doubtless to consult with Professor Keibel, he visited the experimental laboratory of Edwin Goldmann, which stood on the foothills of the Schwarzwald. Here he was fascintaed by Goldmann's novel experiments on *intra vitam* staining of animal tissues by acid azo dyes, then in progress. 'Seeing white mice that were stained every colour of the rainbow, living and behaving normally', so fascinated Evans that he thereupon resolved to consult his young chemist friend, Werner Schulemann 'to find out how the animals can tolerate such treatment, and whether the capacity of these cotton dyes to act as vital stains is due to chemical constitution or physical action'. Thus it was that Evans and Schulemann spent odd months over several years wandering in 'dyeland'. The dyes were supplied by Goldmann who obtained them from Paul Ehrlich. The latter, it would seem, was reluctant to disclose the identity of the dyes, for when Evans visited him in his laboratory he asserted: 'we cannot tell you the chemical nature of these dyes that you are so excited about, because we are involved in a legal affair with them that no one shall know their constitution'. 'This', says Evans, `so shocked me that anyone would work that way that I got up and left him in a hurry with Schulemann and we returned to Breslau to continue our work there'. How far this encounter with Ehrlich affected Evans's opinion cannot be known. What is certain is that he and Schulemann began to study the cytological aspects of vital staining with acid azo dyes, arriving after some years at a clear understanding that the storage of such dyes is a physical process of inclusion in macrophages, whose recognition as a special cell-line was much forwarded by Evans's work. Among the numerous dyes which Evans and Schulemann studied and which the former later introduced to America, one, T.1824, now called 'Evans blue', with some justification, proved so useful as a method of measuring the blood volume of living animals and human surgical patients, that there is little reason to believe that

search for a superior label for plasma would be worth while.

From the beginning a very close friendship had developed between Edwin Goldmann and Evans and the roots of more than the kindling of the latter's practical concern in vital dyes can be traced to their association. The pervasive influence of Goldmann, to whom Evans constantly recurs, both in his early manhood and in his tottering old age, is everywhere to be seen in his early scientific writings. But there are other signs of his awareness of Goldmann's guiding hand. Goldmann was a humanist who effected a deeply penetrating change in Evans, his terse style and trenchant observations providing inspiration and arousing admiration that apparently never lapsed. It was only natural, therefore, when Goldmann learnt that Evans was about to go to Italy that he would want to ensure that the latter knew something about the importance of Italy in the revival of learning. 'We will go', he said, Tor a walk to the foothills of the Schwarzwald every afternoon before you go to Italy (there were four sorties in all), and I am going to tell you what you have to get out of Italy. Have you ever heard of the great artist Giotto ?' Evans, in an interview with Sir Alan Parkes in 1967, recalled how his ears tingled at the mention of the name. Here then was Goldmann's chance to exhort the younger man that it was needful to study at some length the many phenomena of the Renaissance in Italy, because the history of that phase of evolution in the other western races turns almost entirely upon points in which the latter adhered to or diverged from the type established there. Against this background it is easy to see why Evans took seriously Goldmann's advice to go to Padua at the first opportunity, for here he would see not only the anatomical theatre where Vesalius, Fallopius and Fabricius of Aquapendente had taught and where our own Harvey was a pupil, but he could be introduced to the greatest by far of Giotto's undestroyed and undisputed enterprises, the series of frescoes with which the master of painted drama decorated the entire walls of the Chapel of the Madonna dell'Arena. Recalling, in later years, the events of his first visit to Padua, so Evans's account runs in this autobiographical fragment: 'I looked into the question of Giotto and I owe all this to the affection and concern for me that Edwin Goldmann had; he stuck with me and helped me for years'.

During his Baltimore days as a member of Mall's staff, the variety and scope of Evans's work was in itself extraordinary. Besides teaching he was busy with his work on vital staining, and with study of the blood vessels of pig and chicken embryos, and of human embryos when on rare occasions one of them was received in a sufficiently fresh state to be injected with india ink. Early in 1913 Mall, obtaining from the Carnegie Institution of Washington funds to support his large collection of human embryos and to develop research in that field, created the Department of Embryology of the Carnegie Institution. This was housed at first in the Johns Hopkins anatomical laboratory, and later in part of an adjacent new building. Evans became one of its research associates concurrently with his Johns Hopkins post, and devoted a good deal of his time to the sectioning of early human embryos and reconstructing them in wax from the sections, using the procedure of Wilhelm His, which Mall had introduced to Johns Hopkins. 'A

wearisome thing to do,' Evans said, 'compared with making the living embryo pump india ink as though it were blood to show you the multitudinous vascular channels that are always plexusing'. And he added: 'when I found by reconstruction two subclavian arteries instead of one going to the arm bud, Mall said: surprising there weren't more.'

This strong inclination to experimental rather then purely morphological research was a partial cause of his dropping a major project that Mall had suggested, a descriptive study of the human embryo during the period of somite formation. Another reason was that when Evans finally left Baltimore, Mall was unwilling to let him take with him, even for temporary use, the rare and precious serially sectioned embryos necessary for the study, one or two of which, at least, Evans had himself collected and laboriously sectioned during Mall's summer absences. Evans was disappointed and hurt by what he regarded as his chief's ungenerosity, and his relations with Mall were soured after the incident. When, however, a few years later Mall died in 1917 in the prime of his life with the rift still unhealed, Evans was deeply grieved. As a kind of penance for his part in the disagreement, he proposed to write a biography of Mall, hinting that this would be a profound analysis of a distinguished scientific mind (as indeed it might well have been), but the plan was in time forgotten. Evans's work on the embryos was, however, not lost. Several years later G. W. Bartelmez of the University of Chicago took up the study of the somite stage of human development, studying the Carnegie embryos in Baltimore and then going to Berkeley to secure Evans's collaboration and the use of his notes and drawings. The result was an important monograph on this phase of human development in the Carnegie Contributions to Embryology (1916) under their joint authorship.

For nearly the whole period after he graduated in medicine, Evans had no contact with practical doctoring; probably he never entered a hospital. But he had caught glimpses of the new world of medical science in the laboratories of the worthies—of Wilhelm His and Ludwig, of Ehrlich, Goldmann, Schulemann, of Keibel and Minot, of Halsted and Cushing, of Welch. And he certainly knew of Koch's cultivation of microbes on solid nutrient media, of his identification of the tubercle bacillus (for he had himself studied the histogenesis of the miliary tubercle using vital stains); of Metchnikoff's illuminating observations on the phagocytosis of foreign bodies by the amoeboid wandering cells in larval starfishes and in Daphnia; and of Hochstetter's monumental studies in angiogenesis. And he was training himself, as his papers of the period show, for 'the difficult task of discovery.'

## BERKELEY 1915-1962: HIS FIRST FULL PROFESSORSHIP

In 1915, when Evans was in his 33rd year, President Benjamin Ide Wheeler of the University of California offered him the chair of anatomy at Berkeley vacated by the departure of Flint in 1907 and his acting successor, Irving Hardesty, in 1909. Direction of the department had reverted to the worthy pedagogue Robert O. Moody, under whom Evans a dozen years before had studied gross human anatomy. It is not strange that Evans should have again attracted the attention of Benjamin Wheeler, a liberal and

intelligent promoter of scholarship and the arts and a person who did all he could to foster unbiased investigation by the scholars with whom he surrounded himself. Always optimistic and ambitious, there was thus every reason why a chair at the University at Berkeley under the patronage of her enlightened President should have appealed immediately to a young man of Evans's bent; especially since Wheeler had promised that he could go East once a year to attend some national meeting connected with medicine. More of a man in every way, Evans returned to Berkeley and to his first full Professorship. The decision required courage and faith, nevertheless; the accommodation at Berkeley was limited, there was little active research, animal facilities were painfully inadequate and anatomy was then taught only as it applied to the active work of the physician and surgeon, and this last was precisely the aspect of the subject which had the least appeal for Evans. Yet it is ironical that in later years Herbert Evans wished to be known as a physician and to be counted among the doctors of medicine.

Once established at Berkeley, Evans was more concerned with introducing scientific methods than with gross anatomy, and was intolerant of those who regarded the subject principally as the hand-maiden to surgery. This was hardly calculated to make him a popular incumbent in a department where dissections were considered of prime importance. Soon after his return to Berkeley, these 'hat rackers', as he called the protagonists of gross anatomy, reminded him that: 'the Medical Faculty doesn't regard anything in the anatomy department as important except gross anatomy'. To which he replied: 'Gentlemen, this isn't perhaps the growing point of our subject', and thereafter he says: 'I paid no attention to them'. Although this may have been said with a twinkle in his eye, and was perhaps more of a pose than reality, it was unfortunate, since as Saunders [4] has reminded us: 'the caustic expressions he used unwittingly scared many, so that his influence among clinicians was far less than it might have been'. Doubtless it was an overcompensation for the lack of understanding he engendered at Johns Hopkins as an independent and brilliant medical student undiplomatically flustering elderly clinicians.

It soon became evident that Evans was a man of independent judgement and was by character and outlook something of a non-conformist. His independence of thought, his subtle powers of persuasion, and his unruffled demeanour ultimately created something of a figure of mystery which, it must be admitted, Herbert Evans did nothing to destroy. In fact, he rather enjoyed being the enfant terrible. He was essentially a forceful character but with an underlying tenacity of purpose which, together with a splendid intellect, carried him forward in the pursuit of truth as he saw it.

Another reason for Herbert Evans's concern on his arrival in Berkeley, was the fact that in his zeal to build up the department and to strengthen the staff he had taken with him from Johns Hopkins two young people who had shown a competence for anatomical research and for whom he felt in some sense responsible. The initial team included: Katherine J. Scott (now Katherine Scott Bishop), a medical graduate of 1915 who had worked with him in Baltimore, and George W. Corner, who was just

completing an internship in the women's clinic. 'Gynaecologists ought to know more about the female reproductive cycle', said Dr Evans; 'come to Berkeley with me and do your gynaecology for a while on rats and rabbits'. Thus it was that Bishop and Corner joined Philip E. Smith, the only one of any distinction from the existing staff whom Evans had retained.

Later the group was augmented by the arrival of Miriam E. Simpson who had previously taken a Master's degree in the Department of Chemistry for her work on the organic chemistry of nitrogen. After working with Evans from 1918 to 1920 on the vital staining of circulating macrophages in blood, the results of which she published independently in 1921, Miss Simpson went to study medicine in Johns Hopkins where she graduated in 1923. Returning to Berkeley in the same year she re-joined a department in which, as a result of fruitful collaboration with Joseph A. Long of the department of Zoology and Katherine Scott-Bishop, the four main themes of Evans's experimental work for the rest of his career had now been established: (1) an abiding interest in the reproductive system; (2) the attempt to understand the regulation of growth and reproduction; (3) studies of nutrition as related to growth and reproduction; and (4) the systematic exploration of the hormones of the anterior pituitary gland. These topics were firmly developed in the fifteen-year period, 1915-1930, and in this development Dr Simpson, with her unique combination of chemistry and medicine, spearheaded an endocrine segment which was constantly productive during the thirty-seven years of Evans's incumbency, serving loyally and maintaining a firm esprit de corps in the department.

After his return from Baltimore, and recognizing Philip Smith's great abilities, Evans arranged for him a much lightened teaching schedule and in every possible way facilitated the research which ultimately won for Smith an international reputation and the chair of Anatomy at Columbia University. Associate Professor Moody, perhaps a little surprised by the inrush of all this youthful enthusiasm, retained charge of gross anatomy with Smith and one of the newcomers helping him. It was during this early period that Smith perfected his operation of hypophysectomy by the parapharyngeal route in the rat which became an invaluable procedure in research on the pituitary gland, and was destined to revolutionize endocrinology.

The work in Berkeley was first carried out with Wistar rats, but recognizing that these Eastern animals were obsolescent, Evans and Long, a quietly persistent worker from the department of Zoology, who for years had been studying the oestrous cycles of albino mice and rats, sought to improve the breed by back-crossing to a wild grey rat captured in the Strawberry Creek area of the Berkeley campus. The result was the famous Long Evans strain of rat, attractively hooded, vigorous, but gentle, sturdy prolific and remarkably uniform. 'The organization and maintenance of the model colony', as Lyons and Wilhelmi [5] have said 'were steps as significant for modern endocrinology as the establishment of Osborne and Mendel' "Yale" strain of rats was for the early work in nutrition at New Haven'. I was their common interest in reproduction that brought Evans and Long together at Berkeley in a partnership mutually beneficial;

Evans, with his penetrating mind and profound insight, providing the drive and Long, the older man, reciprocating by lending his unusual and patient skills.

With the staff thus fully manned, the reorganized department resumed its work in the autumn of 1919 in the small frame building, once the University's printing shop, that had been adapted for the teaching of human anatomy when the San Francisco earthquake and fire of 1906 forced the transfer of pre-clinical classes to Berkeley. Evans took teaching quite seriously, in his own way, which was tinctured with the pride of intellect he never concealed. His course in histology was radically new in its extensive use of fresh and experimentally prepared tissues along with the traditional fixed and routinely stained sections. In the class laboratory he was usually to be seen at the microscope beside one of the better students. With the general run he was tolerant, with the duller minds hardly so and occasionally sarcastic. He did not believe in lecturing on gross anatomy, 'a finished science', but his lectures on microscopic anatomy were superb from the standpoint of his staff, for whom they constituted a post-graduate course. As for the medical students, he was heard to say that he aimed his lectures at only the four or five best students in the class (of forty), tacitly implying that the assistant professors and instructors could take care of the rest.

Evans shared with his teacher Mall the inner conviction that self education is the only form of lasting value, the student learning the inductive method through personal investigation and research. For the best ten per cent, the instruction (or it might be more correct to say, the freedom to learn) provided by this brilliant professor opened new vistas in medical science. A member of the first class he taught at Berkeley, Elmer Belt [6] (now California's most distinguished urologist) wrote years later about Evans and his young associates: 'the effect of their scholarship and idealism upon the freshman class in medicine was electric. Each of us realized how great an opportunity it was to enter the study of medicine under their guidance and for us the study of medicine became an obsession. The routine work of gross dissection and histology was time-consuming but most of us, in addition, were stimulated to take up a separate problem in research. We were then led to seek out and read recent contributions to the literature concerned with our special subjects. This pursuit inevitably led us to doubt didactic textbook statements unless verified by our personal observations. This atmosphere of doubt and verification prevailed through the department and led to intense application. For most of us this was our first taste of scholarly research'. And to judge by results, it was the application of these very principles which made Evans a great investigator and built the characteristic school of Berkeley endocrinologists.

Departmental administration was for Herbert Evans a duty reluctantly borne. His compulsive urge to work intensively at research led him to put off administrative routine, the writing of articles against deadlines, and other less congenial tasks, until the last minute. Thus the course of departmental affairs was interrupted from time to time by minor or even major crises. There are many anecdotes from the early members of Evans's group. One of these in the early Berkeley days, somewhat mysterious to Evans's associates, evidently caused him great concern. He and his secretary were for several

days intently busy, occupied with account books and the adding machine. Evans's brother, a business man familiar with accounting, was called in; there were urgent messages to and from the University bursar's office. Probably the professor had overrun his budget. The trouble was that no one had ever taught Herbert Evans to keep his budget balanced. Not that he would have bothered to do so if he had known how. Evans was as impetuous in expending his budget as in so many other things and often the prudent rules of economy would go by the board. Unwise? Improvident? Perhaps, though there is a view of living that counts the grasshopper wiser than the ant, the feast worth the famine. To prejudice his researches for the sake of a few dollars was something the professor did not understand.

On another occasion he was overtaken by the deadline for an article long promised to an Eastern scientific journal. In despair he retired to the study at home, sent for the secretary and her typewriter, and dictated hectically for three or four days. Typed sheets were sent to the laboratory to be proofread by an assistant professor, the manuscript was assembled at home as the last pages were being typed, while Mrs Evans sat in the family car at the door, ready to dash to the Berkeley Southern Pacific Station to get the parcel on the Overland Limited for Chicago and the East. In spite of harassing episodes such as these, having a wife still willing to yield her impetuosities to his, junior colleagues anxious to be helpful, and a devoted secretary, Evans kept the Berkeley department of anatomy happily productive and himself went from one achievement to another.

By 1930 the work of Evans and his group could no longer be accommodated in the little grey building where he began at Berkeley in 1915, and the department of anatomy along with the research laboratories and animal colony were transferred to the newly built Life Sciences Building, further west on the Berkeley campus. Evans insisted upon a close geographical relationship between the experimenter and his animal colony. He roundly condemned remotely placed animal quarters, which he believed prevented adequate personal surveillance of all phases of the experiment. In the same year the University of California created an Institute of Experimental Biology, of which Evans became the first director, assuming at the same time the title of Herzstein Professor of Biology, in recognition of his achievement, in research, thus providing for him and for those he had gathered around him far ampler space and superior equipment. His laboratory had now reached the height of its prestige and he held sway over it much as would a Sultan.

As time went on, other capable investigators joined the two interlocking groups, notably, W. R. Lyons, Choh Hao Li, C. W. Asling, Richard I. Pencharz, K. Meyer and Gertrude van Wagenen developing the lines of study established after Evans came to Berkeley. An ever increasing number of visitors, men and women, from home and abroad also continued to come to visit and work in the laboratories; many came to study under him and his contacts with them are interesting in the light of their individual and sometimes amusing anecdotes. Evans was working very hard at this time; he himself says from 7 in the morning until 2 o'clock the next morning, which is

probably less of an exaggeration than it would seem, as his capacity for sustained mental effort was always phenomenal. His tireless energy, his invariable punctuality, the insatiable appetite for getting things done, were some of the things that in later years his easy-going students found most trying; yet there must be many who still have lingering memories of the oblique remonstrances that were sometimes left to bear silent testimony of a missed appointment: 'I called at 7 o'clock and you had not yet arrived—I called again at 7.30!!'

With his immediate associates Evans worked in close co-operation but not always in close harmony. One of them has written that because this was a period of group research in Evans's laboratory, the contributions of individual members might well be obscured or even forgotten. Such, indeed was the unfortunate episode which led to the feeling of bitterness which grew up between Herbert Evans and Philip Smith and for which the latter never forgave his erstwhile colleague. Perhaps it was with the lingering memory of such ups and downs, and with his critics in mind, that in his closing years he expressed the hope that the biographers of this memoir might be well disposed to him and concerned to draw distinctions important to him. For us who are so committed, we feel his life ought to be generously written, not without a sufficient mention of his many failings, but with a handsome recognition of his great merits and still greater aspirations.

Of his collaborators and pupils, Evans has this to say: 'All of the credit for anything I ever did was due to the wonderful individuals who surrounded me, and helped me,' and he continues; `If you investigate my scientific life, you will find that I have appropriated from colleagues and pupils 100% of my achievements'. But irrespective of the views his associates may have held individually, none of those who took part in this large and bold enterprise could ever forget Evans's own contribution through his choice of personnel and the provision of facilities for work, or his conferences in which divergent views were analysed and conclusions reached, and where also, the current events at the meetings of the American Association of Anatomists, and kindred bodies—relayed by a specially appointed envoy—were followed with close scrutiny.

Despite the strain of teaching and planning and organizing a new and rapidly growing department, mounting committee work, and the claims of his own researches, Evans yet found time to take a very active part in the life of the University, and to follow his pupils with close attention. He had a deft way of keeping in touch with the research work in the department. A new man was generally treated with the greatest cordiality the first day. But with the exception of those who came to work with him on his own problems, men, and women too, were simply turned loose and 'allowed to sink or swim'. `I neglected them soundly', Evans says. But here again this was perhaps more of a pose than reality, for as Dr Miriam Simpson explains: 'If students came to us to work we were apt to neglect them until we saw they wanted to accomplish something, and then we pushed them. We pushed them very hard, often harder than we should. So you can't say we neglected them'. Some went through a great deal of mental anguish

before settling down to a problem, but it was surprising how each did, how they absorbed the spirit of the professor, and after a very short time were working day and night. One needs only to go over the list of those who worked at his side and their accomplishments, as recorded in the long list of joint publications appended to this memoir, to see that whatever the methods of education were which Evans used they certainly were successful. After the newcomers had become acclimatized, Evans gave them very considerable responsibility and he himself generally kept in close touch. He has told us of the device which he used to encourage students. 'If', he says, 'an individual had entered on a promising line of research, he would be encouraged to follow it up. If he did it ably and it was accepted by a journal, and even praised, he would be the senior author, Simpson was second or third and myself fourth or fifth'. `Thus', Evans continues, 'the individuals' efforts were quoted, because they took their eggs to the same market I took mine to.'

Evans was a stern taskmaster and always gave painstaking attention to any paper that might result; his revisions were now and then tantamount to primary composition. He was especially particular about details of illustration, and bibliography—he was himself an accomplished artist—and also insisted that a scientific paper should have literary merit, claiming that the reader's attention should be engaged from the outset by having the problem presented in an engaging manner. 'Clarity', he says, 'is the only attribute good science has and science has this that it can be refuted'. But despite the attractiveness of many of his own scientific publications which combine erudition with readability, and show him as a master of his craft, there is no doubt that he tended at times to over-dramatize. Quick to praise when he felt it was due, he did not hesitate to criticize, or even rebuke if he thought some one had strayed, or had not given due credit to those who had preceded him. Now and again he offered brusque criticism when it would have been wiser or more dignified to remain quiet. At times, Evans seemed jealous of his own priority, and several who had had difficulties while on his staff have insisted that he could not face serious criticism. This contention perhaps ha a basis, since in his younger days he had candidly stated that he had set out to lead the field.

## THE ROCKEFELLER INSTITUTION

The progress of research in the new laboratories was temporarily interrupted when in 1932 Simon Flexner, Director of the Rockefeller Institute in New York (now Rockefeller University) invited Evans to spend a year at the Institute as a guest investigator; Evans was now approaching the peak of his career, and his rising reputation for endocrinological research perhaps sufficiently explains this rather unusual invitation, but he believed, as did many of the Institute's permanent staff, that it had been arranged to test his eligibility to succeed to the directorship. Flexner, 69 years old, would soon have to step down. Evans at 50 was of suitable age and obviously possessed the scope and courage to deal with difficult scientific problems and the ability to lead group research. He had just finished a two-year term as president of the American Association of Anatomists. Before scientific audience. he spoke with

impressive manner and style. Brilliantly persuasive as a teacher, his talent for lecturing without notes was unsurpassed for ease, brilliance, erudition and wit. He combined a remarkable breadth of know ledge with tremendous powers of expression. He knew his subject well and loved it. He was accurate, punctual, precise and untiring in patience over detail while the wealth of illustration, comparisons, simile and witty allusion: he used was unequalled. Hence his charm; you received information and you were amused at the same time. The material was assembled, not always neatly, in his well-stocked mind and would pour out in a remarkable stream of erudition dispensed with patent enjoyment and a measure of enthusiasm which always left a mark on his audience.

Evans took with him to New York Miriam E. Simpson and Richard Pencharz, then junior members of his Berkeley group. At the Rockefeller Institute he added a pharmacologist, E. L. Gustus, and a biochemist Paul R. Austin. Gustus recalls still his admiration of Evans's broad knowledge of science in general, his personal charm, and his encouragement of the younger men. In a personal letter to one of us (G.W.C.) Austin describes the characteristic drive and intensity of research under Evans's direction 'Dr Evans impressed everyone with his infectious energy and enthusiasm. He sent a technician to the Institution ahead of the rest of his group to get a rat colony started . . . This colony was soon supplemented by purchase of rats from outside suppliers so that at our peak of activity we had 700 21-day-old rats available every Monday morning for our assays . . . . As you will guess; the situation was pretty hectic at times and there were occasions when the rats drove the program rather than have the program limited to the rats. But we did get a lot of work done with a small group in the short period of eight or nine months'. The group, in fact, made significant progress in the purification of the follicle-stimulating hormone, FSH, of the pituitary gland, and in clarification of the synergism between this agent and the pituitary luteinizing hormone, LH (which they were then calling interstitial cell stimulating hormone, ICSH).

The minutes of the Board of Scientific Directors of the Rockefeller Institute do not reveal anything about this visit and none of the senior staff of that time survive to tell why nothing came of it, if indeed it was a trial run for the brilliant Californian. In all probability Simon Flexner and his advisers doubted whether Evans could subordinate his own progress of research to the broader task of leading the distinguished and diversified Institute.

## HERBERT EVANS'S SIXTIETH BIRTHDAY

Although Herbert Evans may have neglected his students soundly and thrown them in at the deep end, few went from the presence without a profound sense of loyalty to him and to the Department. Indeed, one of Evans's outstanding characteristics was his ability to inspire loyalty in the men and women who served him. This feeling persisted through the years and whenever occasion arose his friends, associates and students rallied around to do him honour.

In September 1942 Herbert Evans was to reach his sixtieth birthday. As early as

1941, a committee under the chairmanship of Dr Miriam E. Simpson began the preparation of a volume as a tribute to his leadership, his cultural ideals and his scholarly achievements [7]. It was intended that the volume should include papers representative of the range of interests which had characterized the forty years of Evans's scientific career from 1904 to 1942, namely Anatomy, Embryology, Physiology of Reproduction, Endocrinology, Nutrition, the History of Medicine, and the History of Science. The dedication of the volume to 'Herbert McLean Evans on his Sixtieth birthday', because it resuscitates the feelings and beliefs of those who were closest to him at the zenith of his career, can bear repetition. It reads in part:

`Your pursuit of truth and natural law has brought a fuller knowledge and understanding of fundamental problems in embryology, histology and physiology. Wisdom, the brightest jewel in the crown of scholarship, has joined originality, insight, and energy in your labors. . . . Your understanding and enthusiasm have inspired all who have worked with you and spurred them on to their utmost efforts. Your example continues to guide and stimulate them.'

Although wartime exigencies prevented many of his colleagues from England and the continent of Europe from participating, Essays in Biology contained 48 papers by 57 authors, all of whom acknowledged in some measure the contributions of Herbert Evans to their field. That of John Fulton, a bibliophile and medical historian like Evans, is typical of the rest. In this autobiographical fragment, Fulton writes [7]: 'Harvey Cushing once good-naturedly accused Herbert Evans of being "pituitary minded", and I believe that there was a prompt rejoinder from Doctor Evans to the effect that Cushing has lately transferred his "mindedness as well as his affection to the hypothalamus".' Had it been a three-cornered exchange, one might have suggested that these two seats of Cartesian turmoil are connected by silken threads of functional integration. In my mind's eye I can see Herbert racing around the sella turcica, peeping over the posterior clinoid or looking; menacingly up through the diaphragm—only to meet the penetrating gaze of a diminutive Harvey Cushing seated securely on the floor of the thin ventricle and exclaiming: 'What, Herbert more fractions ? Stop it—I'll stir up one of them from here, and create a case of diabetes that even Jack Peters cannot control.' And Fulton continues: 'What excuse can I offer for presenting the nervous system to Herbert Evans on his birthday? I fear he may not like it—but even so, he surely will be pleased by the thought that he and Cushing are still playing hide-and-seek with one another above and around the sella. And what game on the part of two men proved more richly rewarding to us all?'

## RESEARCHES

The titles of Evans's papers, more than 600 in number, themselves provide a commentary on his career as an investigator. His first, in 1904 was on a fossil fish spine from Idaho. In 1966 he wrote on the physiology and chemistry of growth hormone, and in between came papers which ranged in subject from the oestrous cycle of the rat to the pioneer history of vitamin E, and from a review on the liver in antiquity to requests for

embryological specimens. The scope and general interest of these sample pieces of his research are typical of what we find in the remaining contribution: which, apart from his earliest work, and notwithstanding their seeming diversity, are, as Saunders [4] put it 'all of a piece, held together by an internal logic and devoted to the solutions of the problems of reproduction and to the history of science'.

For Evans, a fundamental philosophy in all biological research was the 'Fragestellung', which, as his German-trained teacher Franklin Mall had taught him, was 'to know what to ask of Madame Nature; don't ask "why", but "how".' To Evans, 'why, is an indisputable question that only the Lord can answer', and as Sir Alan Parkes [8] once reminded him: 'You've got to go to Church to ask that, not to a laboratory'. This method of discovery advocated by Mall depends on the imagination as an essential link. It requires a faculty of guessing how a series of measurements or observations can be accurately described or subsumed in a law or formula. Bacon described it as 'learned sagacity'. It depends very much too on the talent or genius of the individual scientist and is individually only roughly predictable. One can say that a number of well trained clever men, provided with facilities, will certainly make useful progress in the investigation of a wide range of problems, but there is very little certainty in the forecast of whether any individual will discover any particular thing or what he will discover.

Different scientists give very different descriptions of how they have actually made discoveries. In Evans's case he had that 'learned sagacity' of which Bacon spoke—he knew what questions to address to 'Madame Nature'. But he was also fascinated by the role chance played in his own research, ascribing with pride the successful outcome of his work with the vital dyes to his lucky encounter with Edwin Goldmann's multicoloured mice. A lucky accident also led him to his remarkable demonstration, early in his career, of the distension of the lymph vessels in the skin of a human embryo—Mall's collection No. 448. The embryo, which was 5.5 cm long, was injected through the umbilical artery by Professor Max Broedel while the heart was still beating. It was then placed in formalin and left there for about a year. Evans then began to study the vascular injections in the skin vessels, and while working on it put the embryo into freshly made up 50% alcohol. To his amazement there appeared a wonderful injection of air in the skin, which proved to be a complete injection of the superficial lymphatic system.

Evans's first demonstration of vitamin E deficiency, the failure of laboratory rats to procreate, was, likewise, a chance observation in Pasteur's sense. The existence and indispensability of vitamin E might have been discovered in connexion with several other unnatural and diseased conditions now known to be produced when it is lacking. Indeed, deprivation of vitamin E is followed by a more baffling array of physiological abnormalities in different species than has ever been encountered with a single vitamin. And furthermore, although its first recognized function as an antisterility factor for the laboratory rat has been overshadowed by its demonstrated need in the maintenance of the structural and functional integrity of skeletal cardiac and smooth muscle, and, in some animals, the peripheral vascular system, yet, again by chance, none of these

disorders is as suitable for purposes of bioassay as is the restoration of fertility in a vitamon E-deficient female rat, a procedure which was developed by Evans and continues to be employed at the present time.

## BLOOD SUPPLY TO THE PARATHYROID GLANDULES

As an undergraduate in medicine, Evans had shown his investigative brilliance in his paper with Professor William Halsted, on the relationship of ablation of the parathyroids to tetany. That Evans was instantly and deservedly successful in this undertaking with the Johns Hopkins Professor of Surgery shows that there was, by the turn of the century, no general prejudice against the fashion of joint authorship of pupil and teacher; even those critics who theoretically disapproved, conceded that when the experiments were so interesting, 'we cannot have too much of him'. As further evidence of the interest these experiments of Evans engendered at the time, we find in the December issue of the Johns Hopkins Hospital Bulletin for 1907 (18, 333-336) two articles on the blood supply and anatomical relationships of the parathyroids in the sheep and goat, and in the horse respectively. Half a century later knowledge of these findings proved crucial in the isolation and characterization of the newly discovered thyroid hormone calcitonin.

## DEVELOPMENT OF LYMPHATICS AND BLOOD VESSELS

Before the study with Halsted was published Evans's imaginative genius had already discovered another enterprise on which he could exercise his consummate skills. In the August issue of the American Journal of Anatomy for 1907, there appeared a creditable account of the blood supply in the walls of the lymphatic vessels in man, illustrated with his own drawings made in the style of the great Johns Hopkins medical artist Max Broedel. In this he reported 'that lymphatic vessels possess a special blood supply when possessing a calibre far below that of blood vessels which have Vasa vasorum'. Evans was aware, however, that the results were known to earlier investigators anc had been referred to in the literature. In fact, he cited Dugald Alexander (1879) as being the first to have noticed a beautiful capillary plexus abou certain of the lymphatics in the rat's ear. Florence Sabin, who was also a member of Mall's department, and who was so conspicuously identified with the advances in knowledge concerning the development of the lymphatics may well have channelled these interests in Herbert Evans. The clue is provided by Evans himself, for he states: 'This investigation was merely pleasant by-path, as it were, in the larger problem of the intestinal vessels, the object of which was the study of the essential vascular changes in the hyper, trophy following resections'. But quite apart from these interests in the regenerative capacity of the intestinal vessels, another result of this study besides the possible limits of resection, was the change in behaviour of the animals under investigation. The importance of these findings to clinical practice were realized at once by Harvey Cushing in whose laboratory the resections had been performed, and in the annual report of the Hunterian laboratory for 1907, he cautioned 'animals previously amiable and friendly after their resections would often become belligerent and ferocious

to a degree'

Another significant accomplishment of this time was Evans's demonstration of the growth of lymphatic vessels into a malignant tumour of the intestine, published in August 1908. Here, by the use of India ink injections, he demonstrated the gradual progression of the new lymphatics out into the ultimate capillaries, thus providing one of the strongest proofs of the growth of lymphatics from the veins to the periphery, rather than from the periphery to the veins. He also asserted that 'it is the lymphatic capillaries, i.e. merely endothelial-walled vessels without valves and the finest vessels of the lymphatic system here which have shown the power of growth'. But in this, as is true also of his putative statement that it was 'entirely probable that in every instance regenerative or proliferative power in the case of the blood and lymph vascular systems is manifested primarily by their capillary bed', he was simply confirming, for man, what Langer (1868) and Ranvier (1895. 1897) had, respectively, discovered and rediscovered in the previous century concerning this method of growth of lymphatic capillaries in the tadpole's tail and in a series of studies on amphibian and mammalian embryos. It is, perhaps, worthwhile recalling in this connexion, that the final proof that lymphatics grow by sprouting of their endothelium, was provided by E. R. Clark (1909)—himself, like Evans, a member of Mall's staff—by watching the same tadpole's tail under the microscope for long periods of time.

In the meantime Evans had begun research on embryonic blood vessels. These studies must claim our deepest interest from what light they may shed on those general principles which govern the development of the vascular system throughout the body and as showing, furthermore, Evans's profound faith in the superiority of the method of injection over that of His's wax plate reconstructions, in the study of angiogenesis. Before taking his medical degree he completed a study of the earliest blood vessels in the arm buds of man, which was published in (December) 1908, and followed this up with one on the anterior limb buds of the chick. This was published in full in (May) 1909, as was his account in September of that year, of the earliest development of the aorta and the other great vessels in vertebrate embryos. In the first of these he observed the development of the subclavian artery in a human embryo of 28 to 29 somites, using the method of wax-plate reconstruction, and reported that 'all of its branches down to the digital are successively preceded in their development by zones of true capillary nets, out of which, in each instance the stem in question is ultimately derived'. This conclusion, it must be observed, almost exactly duplicates Goppert's prior account (1905, 1909) of the origin of these arterial channels in the arm of the white mouse 'auf der Grundlage eines capillaren Netzen'.

Evans was, however, well aware of the fact that: 'only when a method of investigation is used that would give the whole picture of all the vessels present in various parts of the embryo, including the capillary bed and even the endothelial sprouts, could the origin of these vessels be put beyond question'. It was for these reasons that he resorted to the method of India ink injections in his studies of the avian subclavian vessels and of the aorta and other large vessels in human embryos and in

those of the pig and chicken, which as he put it: 'would thus provide, at a glance, more information than could be more laboriously acquired by the wax-reconstruction methods', then fashionable in most embryological laboratories. 'The revelation due to such preparations,' he says 'has enabled me to see the capillary precursors of some of the more fundamental trunks of the body.' By employing the method of injection in the case of the human arm bud, it was possible 'to recognize, preceding the stage of subclavians, a more profuse outgrowth of capillaries from the lateral aortic wall than had previously been suspected'. In one case he was able to count eleven of these vessels streaming into the arm blastema where but three could have been expected had they arisen merely at intersegmental points. In other words, then, 'when the arm tissue is first supplied by vessels, and it is supplied very early, it is supplied merely by capillaries growing from multiple points and anastamosing to form a typical and simple plexus'.

Evans's fundamental observations on the fashioning of the aorta and other great vessels out of a chain of capillaries, which was the basis of his authoritative contribution to the Keibel-Mall Manual, attracted a great deal of attention, as a work that powerfully assisted in the eventual overthrow of Hochstetter's doctrine. Evans was, however, criticized by Hochsetter's supporters who claimed that the latter was at least partly justified by the simple conditions he saw in the vessels of the limb buds and tail of Triturus. where vascular trunks are remarkably simple and suffer a more or less direct transformation into arteries and veins. Yet, for a medical student to be recognized internationally as Evans was, is a sufficiently remarkable achievement. These were modest studies, but they serve to show that the diversification of Evans's biological interests began very early during his scientific career.

VITAL DYES AND THE BLOOD BRAIN BARRIER

In h905, Ehrlich and Shiga, then attempting the cure of trypanasome infections in laboratory animals, happened to find that the azo dye which they named trypan red could be injected in sufficient quantity into the living animal to kill the organisms of the disease without perceptible toxic effect on the cells or tissues of the host, themselves deeply stained. A yea] later, driven by the same quest, Nicolle and Mesnil, of Paris, discovered a similar effective compound, or 'good colour', as they called it, in trypan blue, a dye formed by the combination of two molecules of 1.8 amidonaphthol 3.6 disulphonic acid with one molecule of ortho-toluidine in alkaline solution, and hence may be represented by the formula:

The profound colour of the healthy animals which received the dye could not fail to attract the attention of the German and French investigators who set their respective pupils Goldmann and Boufard the intriguing problem of determining the form in which the dye persisted in the body Although Goldmann's initial experiments with trypan blue (1908-1913) established that the central nervous system cannot be stained by intravenous injection of vital dyes and created the concept of a blood-brain barrier, the fundamental question of how the dyes really act on the cells of the body what property

it is by virtue of which one of the members of this class c dyes is enabled to be a brilliant vital stain, whereas a closely related dye is complete failure, remained undisclosed.

It needed courage for Evans to start off his enquiries about vital dyes, but it did not take him long to show that alteration of the barrier, that is, storage of trypan blue in parts of the nervous system where it does not normally enter, is dependent upon inflammatory or necrotizing changes. Thus Evans was one of the first investigators to work in this field and his fundamental studies of the impairment of the blood-brain barrier following deliberate injury of the brain were begun independently, without knowledge of the fact that Goldmann and others were developing similar interests. His paper on the subject with John T. MacCurdy appeared in the *Berlin Klin. Wchnschr.* for July, 1912, a year prior to the publication of Goldmann's monograph *Vitalfarbung am Zentralnervensystem* in 1913. Evans recalls that when he reported to Goldmann that, during the healing of stab lesions in the cerebral cortex, the vital stains immediately coloured the brain substance, the latter said good-humouredly: 'I thought that might be one of my great discoveries and you boys have stolen it from me.' In later days there were some who were not so generous.

Before the study with MacCurdy was completed, Evans had begun other types of experiments with vital stains. In July 1912 he published a short communication with Fred Bowman and Milton Winternitz describing the histogenesis of the miliary tubercle developing inside the liver lobule in animals that were stained vitally with trypan blue. The results emphasized the importance of the Kupffer cells in the genesis of the tuberculous giant cell and its so-called epithelioid cell; 'the mononuclear cell thus entering most actively in the reaction is endothelial and not haematogenous'. The significance of these studies on the response of the hepatic endothelium to vital dyes was that they provided a starting point for Evans's subsequent experiments on the vital staining of the macrophages and vascular endothelium elsewhere in the body, since he believed that 'the reaction of these cells to foreign bodies of whatever size might provide a cue to the better understanding of their origin and function'.

## CHEMISTRY OF VITAL DYES

In the meantime, Evans, impressed with the brilliant advances in knowledge of the chemistry of aniline dyes, brought about by the enormous commercial importance which the dyes possess, had undertaken with Schulemann the monumental task of examining critically almost the entire number of possible dyes made from benzidine and similar bases united with the sulphonic acids of naphthylamines, naphthols and amido-naphthols, with a view to ascertaining how the dyes act on the cells of the body. They reported that the production of a vital stain with these dyes cannot be said to depend on any special component or chemoreceptor, of the dye molecule—as Ehrlich supposed—but is solely a function of the physical state of the dye solution; dyes approaching a true solution in character being brilliant vital stains, whereas those which are most highly colloidal cannot gain a sufficiently general distribution to produce such an effect. They emphasized, however, that this reaction is limited to particles of certain

dimensions, for those vastly more minute and speedily diffusing particles of acid dyes which form true solutions gain no admittance to the cell. By comparative measurements of the diffusion in gels, it was possible to recognize an intermediate group of dyes corresponding to a certain colloidal state which would act as typical tains. Using Wilborn's measurements they were able to predict the biological behaviour of the dyes.

MACROPHAGES

After his visits to Germany, Evans had come back to Johns Hopkins a convinced disciple of Edwin Goldmann and full of enthusiasm for the thoroughgoing German methods. The methodology which Goldmann taught or recommended had proved effective, but it could only have been effective in the case of a young man of very exceptional parts, as Evans evidently was. His mind worked with great speed and it was not long before he reported the result of studies on the reactions of endothelium, protoplasm and macrophages to vital dyes, which appeared almost simultaneously (1914) and which were to settle beyond doubt the origin and functions of the mononuclear phagocytes.

Although Metchnikoff had earlier (1892) proposed the term macrophages for the most varied assortment of blood cells and connective tissue cells, he sought no cytological criteria for the separation of these cells from the mononuclear blood cells. There was thus no clear indication of just what were the great phagocytes which Metchnikoff insisted upon as a cell class. The definitive results of Evans's experiments were presented in a highly influential publication on The macrophages in mammals, which appeared in May 1915. In this he described the entry of vital dyes belonging to the benzidine group into specific cells, in the cytoplasm of which the dye is concentrated in granules of differing intensity and dimensions; but under no circumstances does the living nucleus store dye. Using these physiological criteria rather than morphological ones, Evans united together very diverse elements into a common class and proposed that the macrophages 'be defined as those mononuclear cells, wherever they may be, lining vascular channels, resident in the connective tissues or entirely free, whose protoplasm constitutes a physical system characterized above all by its response to finely particulate matter'. 'In the case of particles of ordinary microscopic dimensions, this response (phagocytosis) is a behaviour shared equally with the polymorphonuclear elements of the blood. But towards the very much finer ultramicroscopic particles, the macrophages react in a practically specific way "drinking them in", as it were, and storing them either as free coagula in their protoplasm or as the inhabitants of watery vacuoles where they oscillate in ceaseless Brownian movement.' It is interesting that Evans showed that these fundamental physiological reactions of macrophages to the vital azo dyes were shared by the Hofbauer cells of human chorionic villi. Here in human embryos, they occur remarkably early, perhaps as early as any considerable mesoderm is laid down in the membranes, and may be seen scattered sparsely throughout the general mesenchyme of the embryonic body at stages of from 15 to 20 mm. Hence there was no reason to suppose that the macrophages represent a very recent and highly specialized cell class. The 'drinking in' to which

Evans refers is obviously the phenomenon of pinocytosis, a term introduced by Warren Lewis, who was also a member of Mall's staff.

Resuming work on the vital staining of connective tissue cells on his return to Berkeley, Evans quickly produced in collaboration with Katherine Scott a monograph, beautiful in its clarity and certainty, on the differential reactions of macrophages and fibroblasts to the acid azo dyes. His publications during this period were elegantly and artistically illustrated by his own hand after the style of that most celebrated medical illustrator, Max Broedel, whom Kelly, with the backing of Mall and Cushing, had brought to Johns Hopkins in 1894.

OESTROUS CYCLE IN THE RAT

While still in Baltimore, Evans's attention had been directed to the ovary by a reaction never seen in the healthy follicle. In mice vitally stained with trypan blue he had noticed that, apart from the macrophages which penetrate the zona pellucida of the degenerate ovum, the moribund cells of the granulosa of atretic follicles were also heavily stained with dye particles, sufficient at times to delimit the whole layer. Following this up at Berkeley, with confirmation of his findings in the rat, guinea-pig, rabbit, dog and monkey, and recognizing the profound importance of developing an infallible method of determining with exactitude the progress of the ovarian cycle, he sought information and assistance from Joseph A. Long of the Zoology Department, who for years had been studying the living eggs and ovulation periods of albino mice and rats. The length of the oestrous cycle in these animals was still a puzzle because the outward signs of oestrus are very inconspicuous, as compared with those of household and barnyard animals. Joseph Long, by an ingenious but (as it turned out) inadequate method had set it tentatively at eleven days. About this time (1917) Charles R. Stockard and G. N. Papanicolaou published a study of the oestrous cycle of the guinea-pig. They had revived a forgotten observation of H. Morau (1889), that the lining of the vagina undergoes periodic changes produced (as we now know) by action of the ovarian oestrogenic hormone. Such changes are revealed by microscopic examination of cells scraped from the vagina.

Evans has told us that Joseph Long had been working quietly on the rat and was using the method of vaginal smears long prior to the publication of Stockard and Papanicolaou's paper but he had not published anything on it. It is very probable also that Evans himself had known of the work of Morau and that of his teacher F. Lataste, a zoologist from Bordeaux. In 1889 Morau had demonstrated a quite unknown fact, namely a periodic change of the vaginal epithelium, from a multilayered cornified type through a mucified type, back to the initial stage; and with his teacher had correlated these cyclical changes with ovarian periodicity. However, the occurrence of cyclical morphological variations in a stratified epithelium seemed so incredible to the contemporaries of Lataste and Morau that their results were disbelieved and both were held in scorn. Morau died young, and Lataste, disgusted with his colleagues from Paris, discontinued his investigations and his career in France and adjourned to Algiers,

where, fortunately for posterity, he published in 1891 his: *Théorie de la gestation retardée.*

Using this simple and expeditious method of vaginal smears, Evans and Long, working together in the anatomical laboratory, soon found that the female rat has a quite regular cycle of about four days, and that the occurrence of oestrus and the time of ovulation can be determined by the vaginal test. This exciting discovery, obviously opening the way to a vast field of research in the physiology of reproduction, stimulated Evans to furious further activity in which the gentle and studious Joseph Long was caught up. Together they published twenty short communications which appeared in the Anatomical Record between 1920 and 1921. These were later brought together in a memoir The oestrous cycle in the rat and its associated phenomena, now a classic in its field. Anyone who studies the monograph will understand why much of Evans's spare time between 1920 and 1922 came to be devoted to its preparation.

The treatise was one of the most far-sighted expositions of its kind that had been written and remains so to this day. Here for the first time the whole reproductive life of the rat was carefully laid down. It is unsurpassed in care, clarity and grasp and opened up a vista of experiments to be done. Evans drafted it but in deference to Joseph Long's prior work, put his colleague's name first on the title page. When the manuscript was completed, so Evans's account runs in this autobiographical fragment: 'There was a great influenza epidemic after World War I, and Long was taken sick. When they propped him up in bed and he felt all right, I took him the manuscript and said: "this is your paper and you are the senior author", and he said: "I expected that since you put it all together, you would be the senior author; nobody ever treated me that way". I said: "we have to tell the truth occasionally, Dr Long, this is your work".'

The book has had a very great influence, partly because of the attention it directed, in conjunction with Stockard and Papanicolaou's study of the guinea-pig, to the ovarian-uterine cycle as a general phenomenon. It alsc made available for experimentation on the cycle, the albino rat, a mamma: that is inexpensive, hardy and easy to house, feed and handle. From this work stemmed directly the discovery, next to be discussed, by Evans, Scott. Bishop and Burr, of vitamin E, and almost as directly the isolation of the ovarian oestrogenic hormone by Edgar Allen and E. A. Doisy at St Louis and it helped greatly to stimulate the whole advance of our knowledge of the steroid hormones and the general chemistry of steroids. In the next few years the oestrous cycle of the mouse (Allen, 1922) and the longer 28-day menstrual cycle of the monkey (Corner, 1923) were revealed in rapid succession.

Not only did the monograph attain international fame; so also did the animals whose activities it described, for the Long-Evans standardize( strain of white rats with gray hoods is currently specified in many account of research on the physiology of the rat. These animals were descendants of cross made about six years previously between several white females and wild gray male caught in Berkeley, black, gray, and hooded varieties resulting. The colony had been fed with table scraps supplied daily from a large hotel, or from boarding houses, 'where' Evans says 'I went for my best food and,

on Sunday mornings when I'd meet President Wheeler with his top hat on, going to church, I would be carrying a bucket of selected table scraps'. He also relates, good humouredly, how on one occasion one of the boarding house women asked him, 'aren't you ashamed of yourself; a grown man like you getting scraps for varmints' ? 'Then', says Evans, 'I became the garbage king of Berkeley.'

While Evans and Long were diligently and laboriously concerned with the precise mechanism of the oestrous cycle in the rat and with the various steps in its reproductive activities, Long's chief, the senior Professor of Zoology, became increasingly annoyed by Long's frequent absence from his own laboratory, and both Mrs Long and Mrs Evans were even more disturbed by their husbands' lateness at dinner-times and absences at week-ends. One of the writers of this memoir (G.W.C.) was the embarrassed witness, in the rat room late one afternoon, of a dramatic entrance of the two ladies with a loud peremptory demand that their respective husbands should quit work at once and go to their homes where they belonged at that time of day.

## NUTRITIONAL STUDIES

Once having developed a standard strain of experimental animals and a practical method for following their cycles, and with the perspective opened by the discovery of vitamins A and B, essential for growth in the rat, Evans proceeded with various colleagues, 'to look into whether reproduction might have nutritive dependencies different in character from those adequate for growth to adulthood'. The early nutritional studies led, first, to the observation of permanent vaginal cornification as a useful criterion of vitamin A deficiency, and then to the discovery of a fat-soluble essential dietary factor, vitamin E in 1922; this was finally isolated and identified in 1935.

### Vitamins A and B

Evans and Long had previously shown that cornified cells normally appear during less than one-third of the oestrous cycle of the rat. Their constant presence in A-deficiency, first observed by Evans and Bishop in 1922, was considered by them to be yet another manifestation of the specific relationship between vitamin A and epithelial structures. This exaggerated cornification induced by lack of A does not represent a continuous state of oestrus, because ovulation and corpus luteum formation occur at intervals, as indicated by successful matings with normal males, but as Evans (1925) later showed fertilization and implantation may be impaired. At about the same time it had been asserted that vitamin B was likewise a requirement for the normal function of the testes, but investigations carried out by Evans (1928) after the recognition of the value of E did not support the claim.

### The history of vitamin E

In 1922 Evans and Bishop demonstrated that rats fed a synthetic diet containing correct proportions of protein, fats, carbohydrates, the known vitamins, and salts, grew normally and were in excellent physical condition yet were unable to reproduce. In

these animals mating would occur normally but pregnancy invariably terminated in foetal death and resorption. Mal rats also became sterile if fed the same diet by deterioration of the spermatogenic—sperm-forming-cells of the testis. Extensive studies of the reproductive systems of both males and females by Evans and Burr (1927) showed that whereas in the females placentation was the vital point of the disorder rather than the ovary or germ cells, in the male it was the gonad; sterility fin appeared and was followed by severe degeneration of the testis but not that of any other organ.

Evans and Bishop next turned their attention 'to the prevention rather than alleviation of these strange resorptions—a prevention which might disclose at once what individual natural foodstuffs carried the missin needed substance.' 'Good fairies', Evans has said, 'attended every phase of this quest,' for soon it was disclosed 'that elevation in the proportion of each of the constituents of the diet was without effect, yet various nature foods proved curative in the next following generation'. Since the addition of fresh lettuce to the lard diet then being fed to the animals was spectacularly successful, it appeared at first as if the antiscorbutic vitamin C, which was not essential for growth, was necessary for pregnancy, had it not been quickly shown that not the aqueous but only the fatty components of these leaves, the chlorophyll-rich green oil, had effected the 'cures'. Then to thei surprise, whole wheat, notably deficient in C, was equally remedia hence the concept that this vitamin was involved could no longer be sustained.

Evans has left us the full story of what then followed. 'The good fairies he says, 'accompanied me to the large Speery flour mill at a neighbouring town, Vallejo, where I found three great streams flowing from the milling of the wheat berry: the first constituted the outer cover or chaff; the second the endosperm, the white so-called flour; and the third which came in flattened flakes, stuck into such units by its oil content—the germ. Night had not fallen that day, before all these components were fed to groups of carefully prepared females—animals which had begun gestation on vitamin-E low diets and were fed both the watery and fatty solutions. Single daily drops of the golden yellow wheat germ oil were remedial. That an oil might enrich the embryo's dietary needs for vitamin A and vitamin D, the only fat-soluble vitamins then known, was negated at once when we added the well-known rich source of vitamins A and D, cod liver oil, an addition which did not lessen but increased and made invariable our malady'. These observations pointed clearly to the detection of the need for a new substance and since in the case of some food materials (e.g. wheat germ) the requisit quantities were small and extracts of those foods were efficacious, Evans and Bishop (1922) felt justified in announcing the existence of a new fifth member of the vitamin class to which the designation substance-X was provisionally attached. In 1924, in place of the original Factor X, Barnett Sure of Arkansas proposed the name vitamin E, as the next in series after E. V. McCollum's identification of the antirachitic vitamin D as a separate entity. 'Why', asked Sure, 'does Dr Evans keep on calling this vitamin X? It deserves the next serial letter. It is not A or D because they fed tons of that and got nowhere'. `I then called it E with reasonable speed', Evans concluded.

The first study of the chemical nature of the newly discovered vitamin was carried out by Evans and Burr in 1925. This indicated that, like vitamins A and D, vitamin E was to be found in the unsaponifiable portion of certain fats; that it was somewhat vulnerable to saponification; and that it was destroyed by bromination and acetylation, but not by hydrogenation. Vacuum distillation caused considerable decomposition, but solvent partition as between pentane and 92% methanol effected some concentration. Another approach to the understanding of its chemistry was opened by Evans and Burr's special study of the destructive action of certain fats on vitamin E, from which it appeared that diets ordinarily adequate for reproduction gave sterile animals if the diets contained fats which became rancid or if the usual mixed diets were treated with ethereal ferric chloride. Commenting on these findings thirty-five years after the publication of Evans's two papers with Burr in 1927, M. K. Horwit has this to say [9]: 'If those of us who came into this field later had paid better attention to this report, perhaps we would not have waited until 1956 to add fats containing more linoleic acid to the basal diet used in the Elgin project.' And he continues: 'Perhaps we of this generation should go back and read the papers of these early masters for the gems their papers contain.'

For a number of years after the earlier work by Evans and Burr, very little real progress was made towards isolation and chemical investigation of vitamin E, partly on account of the difficulty of fractionating the complex mixture of substances present in wheat germ oil and partly because of the rather troublesome biological test method. In 1936, however, Evans, together with Oliver and Gladys Emerson, was able to isolate from wheat germ oil as crystalline allophanates two alcohols, alpha- and beta-tocopherol, both of which showed vitamin E activity, although the relative proportion of the two active substances appeared to differ in different samples of oil. Alpha-tocopherol has the composition $C_{29}$ $H_{50}$ $O_2$ originally attributed to it by Evans, while beta-tocopherol has been shown by analytical and X-ray crystallographic methods to be a lower homologue of formula $C_{28}$ $H_{48}$ $O_2$. Soon thereafter the same alpha-tocopherol was isolated from cotton seed oil, and later still another substance, gamma-tocopherol, which appeared to be isomeric with beta-tocopherol and with similar biological properties was obtained from the same source. Further investigation by Evans revealed that only alpha-tocopherol is present in lettuce and that palm oil is qualitatively similar to cotton seed oil and contains no beta-tocopherol. In several other laboratories, tocopherols were isolated almost simultaneously from wheat germ oil, the beta- by Todd and his coworkers in Manchester (1937), neotocopherol by Karrer and his colleagues in Zurich (1938), and cumotocopherol by John in Gottingen (1937). The preponderance of beta-tocopherol in European wheat germ oil and of the alpha-form in that of California has never been explained.

After the isolation of vitamin E in purity, the name tocopherol wa proposed from the Greek Tokos (offspring), (ppm (to bear), an 'ol' to signify an alcohol. Evans has left us a full account of how the word came to be coined and of the primary role of the Emersons in the whole vitamin E story. 'I well remember', he says, 'their plea to me to

suggest a proper nam for their purified substance when success crowned their efforts. I promptly invited George M. Calhoun, our Professor of Greek to luncheon in Berkeley in our small Faculty Club'. 'Most scientists, medical men especially', said Calhoun, 'have been guilty of coining Greek-Latin terms, bastards of course and we might have to do this'. 'What does the substance do'? he asked. 'It permits an animal to bear offspring', I replied. 'Well, "child birth" in Greek is Tokos', he said, 'and if it confers or brings child birth, we will next employ the Greek verb pherein. You have also said that the term must have an ending; consonant with its chemical—'ol', it being an alcohol; your substance is 'tocopherol' and the pleasant task assigned me quickly solved and not worth the delightful four-course dinner you have arranged'.

Secure in their belief that the function of vitamin E was essentially limited to the reproductive mechanism, Evans and his associates (Burr and Althausen 1927) confidently asserted that 'we are convinced that the literature of the future will carry frequent reference to the existence of dietary sterility'. In 1928, Evans and Burr published their important paper of 'Development of paralysis in the suckling young of mothers deprived of vitamin E', in which they showed that the affliction in rats could be prevented by feeding large amounts of E to a mother throughout her lactation, thus establishing mammary secretion of the vitamin, or by giving small doses to the pups but only if administered before the 15th day. Here then was the first clear indication that the biological action of vitamin E extended beyond the sexual sphere into more general phases of nutrition. Yet Evans did not immediately follow up these early observations, even though his studies on 'The relation of vitamin E to growth and vigor', also published in 1928 had amply demonstrated that the late phases of body growth in the rat are impaired by lack of E, and that such animals frequently exhibited muscular atrophy. It was not until Marianne Goetsch and A. M. Pappenheimer (1930 had demonstrated the nutritional production of profound lesions in the musculature of rabbits and guinea-pigs that muscular dystrophy was recognized as the one syndrome commonly encountered in vitamin E deficiency in all species. It is frustrating to read how very close Evans had come to the correct solution and in later years this 'basic fallacy of the anti fertility vitamin' as he expressed it, gave him some cause for regret. 'There' he says, 'I made some of my most critical mistakes. I even called it the anti sterility vitamin. I overlooked the most significant thing about it. It had nothing important to do with reproduction. It had to do with the musculature.' But notwithstanding, had the physiological role of vitamin E not been extended beyond the confines of reproduction, the manner of its action would still be an intriguing problem, unsolved after half a century. And while vitamin E continues to be one of the most interesting mysteries of nutritional science, and even challenges the nutritionist for a new and broader definition of the term 'vitamin', its discovery and the long established method of its bio-assay, based upon the phenomenon of foetal resorption in the rat, will forever be associated with the name of Herbert McLean Evans.

## ANTERIOR PITUITARY FUNCTION

Evans's attention was next drawn to the hypophysis (pituitary gland) and its

remarkable endocrine effects. It had recently dawned upon the medical profession that a form of gigantism, acromegaly, resulted from pituitary overactivity usually caused by a tumour of the gland. During the period 1908 to 1909, Harvey Cushing, Evans's admired teacher in surgery at Johns Hopkins, had been working intensively on the pituitary body and had been experimentally removing the glands from dogs with startling effects on growth. In 1910, in collaboration with Samuel J. Crowe and John Homans, he issued an important monograph entitled *Experimental hypophysectomy*. In this they established that the pituitary of animals, although probably not essential to life, normally exerts an important influence on metabolic processes of the body. They described in detail the disturbances which follow partial or complete removal of the gland, one of which was an atrophy of the gonads and genital system in immature dogs, and correlated their findings with the corresponding symptoms in man. And by so doing paved the way for the clinical distinction, now fully recognized, between states caused by excess secretion of the anterior lobe (acromegaly and gigantism) and states of diminished secretion, such as occur when the pituitary is completely or only partially destroyed. Uncertainties still prevailed, however, for in his treatise, *The pituitary and its disorders*, published in 1912, Cushing has this to say: 'No one has definitely succeeded in simulating a fixed state of functional overactivity of the ductless gland series, whether by feeding experiments or by heterogenous transplantations . . . . Unquestionably there is some chemical process at work behind the actual glandular hyperplasia, and until this can be determined we must not only await the experimental reproduction of states of functional overactivity, but must also continue to speak of the glandular change as the primary incident in the process . . . . Acromegaly and gigantism have not unequivocally been proven to be expressions of hyperpituitarism (anterior lobe hyperplasia)'. Within a decade, however, answers were forthcoming.

Growth hormone

When Evans took over the Berkeley anatomy department in 1915, Philip Smith, already there, was becoming expert in extirpating the rudiment of the anterior lobe of the hypophysis of frog tadpoles, causing remarkable regressive effects on growth, on pigmentation and on the development of the thyroid and adrenal glands. The correct deduction from this work and from that of Harvey Cushing was made: the regressive effects upon growth were referred to the absence of a specific function, or rather, absence of a specific substance (hormone) produced by the anterior hypophysis. The evidence upon which this deduction was made, was in a sense negative, for as Evans has said: 'It is singular how long we had to wait for the positive accomplishment, i.e. the detection in anterior lobe tissue of a substance with which indubitable growth changes could be produced experimentally.' Yet there were good reasons for the delayed recognition of the material which is called the growth hormone. Firstly the substance itself is a complex body chemically resembling the proteins; secondly, it is extraordinarily labile; and, thirdly, its effects can be detected only when it is administered frequently, parenterally, and over a sufficiently long time interval, with adequate controls, to an adequately standardized animal form. These circumstances, the

extraordinary instability of the hormone itself, and the lack of a speedy, reliable, biological assay not only delayed the discovery of the hormone but continued to delay or prevent research in this field.

In 1920, Evans began experiments with extracts of the mammalian anterior lobe, at first with J. A. Long, and in 1921 prepared an extract by the simple procedure of trituration of the anterior lobe of the bovine gland with sand, the addition of Locke's solution, and centrifugation. The opaque, pink fluid obtained was injected daily intraperitoneally into young and mature rats. The reason for periodic dosage was that Evans wanted to mimic the natural conditions where the endocrines are constantly discharging small amounts of their products into the blood stream. Untreated littermate controls were maintained under identical conditions. An identical and optimal diet was given to both groups. The effects obtained in less than three months experimentation were sufficiently outstanding to lead Evans to announce that along with other effects (delayed sexual maturity, suppression of oestrus, and excessive luteinization of ovarian follicles), an outspoken acceleration of growth had been induced. This was referable to no other cause save the minute amount of organic substance which had been duly introduced. Before employing beef extracts, Evans says, 'We tried many substances, thyroid, thymus, ovary itself, corpora lutea, adrenal cortex, adrenal medulla, and posterior and anterior pituitary. From only one of these tissues did we secure characteristic effects upon ovulation—from the anterior pituitary—effects which were paralleled by still more striking changes in the body growth and in some of the internal organs beside the ovary, e.g., the adrenal.' A year later, Evans and Long reported a continuance of the initial growth response which finally led to gigantism. This was the first essential step towards recognition of the pituitary growth hormone. Similar observations were subsequently made in dogs by Evans, Meyer, Simpson and Reichert who induced acromegalic changes in the adult dachshund, but the disproportion of these creatures persisted and 'the animals were still condemned to a life under the bureau'. From this point onwards, the isolation and identification of the several hormones of the anterior pituitary was to be for forty years the main theme of Evans's research.

During 1923 Evans had devoted most of his spare time to the preparation of his Harvey Lecture, The functions of the pituitary gland, which he had been invited to give on 24 April 1924. In the lecture he summarized the experimental work which he had carried out at Berkeley with Long on the gigantism and other specific endocrine effects in rats by the injection of his crude alkaline extracts of the anterior lobe. This lecture, considered by some to be his greatest, was published in 1925, and by a happy coincidence in the same volume in which also appears that of his former teacher in pharmacology John Jacob Abel. The content of these two lectures puts into perspective the research interests of the teacher and the pupil, the one concerned with the posterior pituitary, the other with the anterior lobe. Although it has defects, Evans's lecture stands as a milestone in endocrine medical literature, and more particularly in the history of endocrinology, for it introduced a concept of endocrine function which did

much to clarify a rapidly growing subject that had not yet taken firm root.

Evans and Simpson now began a systematic effort to find methods for the extraction and purification of the hormone. They early recognized the value of aqueous alkaline extracts and the possibility of reducing the protein content of such extracts by neutralization with weak acids in the cold followed by centrifugation. The more detailed study of the pituitary and the use of hypophysectomized animals for testing of extracts received a powerful impetus with the discovery by Philip Smith in Evans's laboratory (1926) of a parapharyngeal approach to the hypophysis in rats which permitted an ablation of the anterior and posterior lobes without danger of brain injury and which was readily performed so that the necessary number of operated animals could be obtained. Preliminary studies on injection of growth hormone preparations into hypophysectomized rats had convinced Evans that they are unusually sensitive to the presence of the hormone. This procedure permitted the introduction by Evans and his group (1943) of a very sensitive bioassay for growth hormone which proved to be a milestone in growth hormone research. Immature female rats were hypophysectomized when 26 days old and, on the twelfth post-operative day daily intraperitoneal injection of the growth hormone preparation was begun and continued for four days. On the fifth day the right tibia was removed, split longitudinally at its proximal end after fixation in formalin, and stained with silver nitrate. While calcified tissue is stained dark brown the proliferating zone of the uncalcified epiphysial cartilage appears as a clearly defined white band; its thickness was shown to be very responsive to growth hormone; and a new definition of a growth hormone unit was then possible. It was probably no coincidence that in the following year, utilizing this assay in the control of the chemical process, a purified bovine somatotrophin (growth hormone) was obtained by Li and Evans (1944). Subsequently, Li, Evans and Simpson (1945) showed by the results of electrophoresis, diffusion, and solubility experiments that the hormone prepared from the alkaline extract of ox anterior pituitary is free from other active contaminants and behaves as a homogeneous substance. Thus a quarter of a century elapsed between the discovery that extracts of bovine pituitary glands stimulated growth in normal rats and the first isolation of a highly purified bovine somatotrophin.

The availability of purified growth hormone in relatively large quantities, enabled Evans and Simpson, and the Berkeley group which included Herman Beck, C. W. Asling and R. O. Scow, to confirm and extend a number of observations made previously with crude anterior pituitary extract or growth hormone concentrates. The clearest evidence of dissociation of the phenomena of increase in size from differentiation, was obtained from the study of osteogenesis in rats deprived of the pituitary or thyroid, and from replacement studies with pituitary growth hormone and thyroid hormone. The effect of growth hormone on the skeleton was chiefly to increase its size, by increase in length and diameter of the bones. Thyroxin, on the other hand, accelerated maturation of the skeleton in normal rats—closure of the epiphysial plates occurring before adult size was reached. These studies of endocrine influences on skeletal growth and differentiation, carried out by the Berkeley group between 1943 and

1950, were summarized by Miriam E. Simpson in the 'Thirteenth Harry Burr Ferris Lecture', presented at the Yale University School of Medicine, April 3, 1950, and serve as a model of careful exploitation of a new tool.

Luteinizing hormone (LH, ICSH)

Evans's principal collaborator in the continuing research on the pituitary hormones was Miriam E. Simpson. For the next twenty years their efforts were largely centered on the relations between the pituitary gland and the ovaries and many regard this work as his most original and important contribution to medical science. 'Our research', Evans has said, 'was primarily an attempt to show the relation of the various glands of internal secretion to the gonads and especially the ovary. And we were led into the field by the discovery of a remarkable four-day ovulation mechanism in the rat.'

In his work with J. A. Long on the growth hormone in 1921, Evans, a: briefly noticed above, had found that prolonged injections of their saline extracts of ox anterior hypophyses into rats delayed the onset of sexual: maturity and caused an immediate cessation of the 4-day rhythm, smaller doses permitting oestrus to recur at longer intervals, the larger doses inhibiting it altogether. At the same time an excessive amount of luteal tissue was formed by luteinization of ovarian follicles, which, as Evans showed three years later, was unaccompanied by ovulation. 'In all instances', he wrote, 'the ovaries instead of being underdeveloped weighed twice as much as the) did in control animals and exhibited great numbers of substantial corporal lutea. The uterus on the contrary weighed absolutely about half as much as it did in the normal controls. Histological examination of the gonads con firmed the presence of very abundant lutein tissue and demonstrated the formation of this tissue about the egg in unruptured, normal follicles and in atretic follicles. Ripe normal Graafial follicles were invariably absent! A powerful, specific stimulus to lutein cell transformation has thus been effected.' When injections were stopped the oestrous cycle was resumed after varying periods of time. Subsequently, Evans showed that the luteal tissue produced could perform all the functions normally associated with the corpus luteum. His long-term experiments may well have been complicated by immunological effects, but they provided the first direct experimental evidence that gonadotrophic substances could be obtained from the hypophysis. Here then was apparently a second hormone of that organ; its activity and its chemical structure must be distinguished by further research from those of the growth hormone.

Follicle-stimulating hormone (FSH)

The difficulty presented by Long and Evans's striking results, that while their extracts of the anterior pituitary stimulated growth they were antagonistic to sexual development, was in some measure defined, if not resolved, when in 1926 Philip E. Smith succeeded in perfecting the operation of hypophysectomy of the rat. He found that transplants of anterior pituitary were capable of restoring all of the normal functions to his hypophysectomized rats. However, extracts identical with those used by Evans were capable of restoring growth, but were completely unable to repair

ovaries or testes atrophied by hypophysectomy. Smith and Engle (1927) next administered anterior pituitary transplants to immature normal mice and rats and found that they produced precocious sexual development. Smith was also able to show that his transplants acted directly on the gonads and through them on the other organs of the genital system.

Commenting on Smith's hypophysectomies by the parapharyngeal route, Evans had this to say: 'He found the right spot on the base of the cranium to make a circular entry and there was an enormous advantage in the rat, namely, that you need not injure the brain from below because the diaphragma sellae separated the Turk's saddle from the brain. That was an immense advantage, because all the injury in the early hypophysectomies arose from lifting the whole brain to get under it. That was a basic error, and the animals went into a coma at once. Smith's hypophysectomy was a magnificent feat and demonstrated the invariable sequelae of a complete hypophysectomy. He could do fifty or sixty a day and I said to myself, "with ingenuity and chemical brains we can find out if all the different trophic effects are interrelated or if each is an independent entity". Then later, Smith injected chromic acid to injure that area and duplicated some of the hypothalamic syndromes'.

With the demonstration by Philip Smith in 1927 of the follicle-stimulating effect of fresh implants of the anterior lobe and knowing that the luteinizing effect could be obtained by the saline or alkaline extracts then available, the position was taken by many that there were two active gonad-stimulating principles in the anterior lobe; the factor shown by Evans and Long to cause luteinization of the follicle, and another factor which causes follicular stimulation as shown by Smith. A further complication was the finding by others that the urine of pregnant women contains a substance which when injected into female animals causes hyperaemia of the ovaries, growth of the follicles and, in some species, ovulation. This is the basis of the Aschheim-Zondek and Friedman tests for pregnancy. For some time the similarity of action of the urinary and the anterior pituitary hormones was quite confusing. To this problem Evans and Simpson devoted much attention during the earlier years of their collaboration, finally demonstrating that the urinary gonadotrophin (since shown to be produced by the chorionic part of the placenta) and the pituitary FSH are different substances. Efforts were then made to obtain a pure follicular factor from gland tissue by chemical methods, as Zondek reported having done from urine of pregnancy and in 1928 they reported on the effect of an acid extract of bovine anterior lobes in producing hypertrophy and vaginal canalization in immature rats. They suggested that the luteinizing principle was best obtained with alkaline extraction and the follicle-stimulating principle best removed by acid extraction; but at first they were inclined to believe that the luteinizing hormone and the growth factor might be the same substance. Shortly afterwards, fractionation of pituitary gonadotrophic extracts into follicle-stimulating hormone (FSH) and luteinizing hormone (LH) was reported by other workers, notably by Fevold and Hisaw, who showed more definitely that follicular stimulation and luteinization of the follicles were probably due to two

separate chemical substances. But with this Evans and Simpson were at first unable to agree since they were inclined to believe that the luteinizing hormone (LH) and the growth factor might be the same substance.

It is an interesting commentary that the spectacular response of the ovaries of the rat, which was obtained with fresh implants of the anterior lobe when Smith first used this method, could not have been obtained had any animal other than the mouse or rat been used for this investigation. Had the guinea-pig, rabbit, cat or dog been used, the result would have had a different course. The fortunate choice of an animal which responded spectacularly to implants and a gland which was active by this means opened one of the most active phases of biological and chemical investigations then being carried out in Evans's department.

The conception of separate follicle-stimulating and luteinizing hormones, as the names imply, arose from work on the female animal, but the lack of any essential qualitative difference of the hormone content of the pituitary glands of male and female suggested that the substances would have analogous functions in the male. The subsequent investigations of Fevold and Hisaw gave ample proof of this probibility when they showed in 1936 that in the immature male their FSH fraction caused only stimulation of the seminiferous tubules and the luteinizing fraction only stimulation of the interstitial cells, as shown by enlargement of the accessory organs. About the same time Evans and Simpson and their group (1936) reported that they had been able to separate from sheep pituitaries three fractions with specific effects on the ovaries and testes of hypophysectomized rats—the first, which they called interstititial cell-stimulating hormone (ICSH) stimulated the interstitial cells in both sexes; the second (LH) luteinized the walls of ovarian follicles; and, the third (FSH) stimulated follicles in the ovary and seminiferous tubules in the testes.

The idea of the existence of a specific ICSH, separable from LH, was elaborated by Evans and his colleagues in later papers (e.g. Evans, Simpson and Pencharz 1937; Simpson, Li and Evans 1942), but it gradually became accepted that LH and ICSH were identical. Chemical work on the pituitary gonadotrophins reached its climax when FSH was obtained in a physicochemical homogeneous state in 1949 by Li, Simpson and Evans. The use of separate FSH and LH has now become common-place and highly purified FSH and LH have been prepared by several groups of workers; a process which was greatly facilitated by the discovery of electrophoresis by Tiselius in 1937.

The intensive work of Evans and Simpson during the period 1927-1933, demonstrating a reciprocal relationship between the hypophysis and gonads, added more knowledge of the glandular interrelationships than with any of the other endocrine glands. Thus they were the first to point out in 1929 that the gonad-stimulating capacity of the anterior lobe of cryptorchid males was midway between that of the normal and castrated male. Their evidence was based in part on the more pronounced activity of the pituitary as a gonad stimulant after castration and experimental cryptorchism than pituitaries of normal males; in part also on their prior

demonstration of the effectiveness of their extracts of ox pituitaries and of extracts of pregnant mare's serum (PMSG) in permitting the pituitaryless animal to carry on germ cell production. They thus inferred that the pituitary-influencing factor from the testis was formed in the seminiferous tubules rather than in the interstitial tissue, a view which, after 40 years appears to be supported by evidence for distinct pathways of steroid metabolism in interstitial tissue and in sertoli cells of the rat testis. However, evidence for de novo synthesis of steroids by the tubules is still awaited.

Mammogenic hormone

The last three years of this period (1927-1933) witnessed as rapid a succession of significant events as had till then been seen in the endocrinology of lactation and in the functional relationship between the anterior lobe of the hypophysis and the pancreatic islets. And in this Evans and Simpson were to play a part. In 1929 the two investigators published another significant discovery. Working with aqueous alkaline extracts of the anterior hypophysis rich in the growth hormone, they observed that the mammary gland responded by marked proliferation. Upon continued injection, virgin rats were observed to exude milk from the glands when the latter were incised at autopsy. This experiment and a similar one, at essentially the same time by A. S. Parkes, working in London on rabbits, suggested that something in their pituitary extracts was responsible for the hypertrophy of the virginal glands. This gave a strong hint of yet another hormone of the anterior lobe, a hint confirmed in 1929-1933 by Stricker and Grueter of Strasbourg, the essence of whose experiments lay in their demonstration that Evans-type pituitary extract caused rabbits actually to secrete milk; by G. W. Corner at Rochester, N.Y., who proved that previous action of the corpora lutea is not required for this effect; by Oscar Riddle of the Carnegie Institution at Cold Spring Harbor, who isolated and almost completely purified the lactation hormone (now called prolactin) ; and by W. R. Lyons in Evans's laboratory, who completed the purification in 1937.

Stricker and Grueter used rabbits that had been exposed to the action o the corpora lutea of pseudo-pregnancy. On the tenth day extracts of the anterior pituitary were injected for four or five days. On the eighteenth of twentieth day the animals were killed. An abundant secretion of milk was observed in the gland. In order to determine whether the action of the pituitary was directly upon the mammary gland or through the interaction o the ovary, rabbits were ovariectomized on the tenth day of pseudo-pregnancy Following the injection of the extract for two or three days some milk was observed which became very abundant by the sixth to the tenth day. In a further case, the mammary glands were allowed to atrophy for three months after pseudo-pregnancy and ovariectomy. Upon injecting pituitary extras the mammary gland became active again and secreted milk. However, the secretion of milk was not stimulated unless the gland had been previously developed by pregnancy or pseudo-pregnancy. Later Grueter and Stricke: reported further success in stimulating lactation in rabbits, dogs, pigs an( cattle. They emphasized again that the gland must be previously developed in order for lactation to be stimulated but, in animals with developer glands, milk secretion could be stimulated even though lactation had cease(

for as long as six months previously. These experiments thus indicated that while extracts of the anterior lobe cause luteinization of the ovary an( retention of the corpora lutea, there is present also a hormone which is capable of directly stimulating the secretory activity of the mammary gland Stricker and Grueter were both pupils of Bouin, the one an obstetrician and the other a veterinarian, and W. R. Lyons has reminded us that the' acknowledged in one of their papers that Evans had sent the instruction for preparing the hypophysial extract used. In this connection it is of interest to recall that Evans and Simpson had been working with the rat; otherwise they would also have discovered a direct lactogenic effect of the same hormone that gave them an indirect mammogenic effect via the ovary.

By 1930, Corner had left Evans's department at Berkeley and was we] established at Rochester, N.Y. Working independently and using an alkalin extract of sheep pituitary prepared by Parke Davis and Company, he showed that abundant milk secretion could be induced in the mammary glands of young, adult ovariectomized rabbits (8 to 9 months old) which had never previously been pregnant or even pseudo-pregnant. Corner, therefore, concluded that the pituitary hormone caused proliferation of the mammary gland and simultaneous lactation, and that preparation by action of the corpus luteum was not necessary.

Following the claim by Corner that lactation was induced with anterior pituitary extracts in spayed mature virgin rabbits, Evans and Simpson in the following year injected spayed virgin rats with their alkaline extracts of beef anterior lobes for periods of 20 to 30 days. In no case was growth of the gland or lactation produced. To determine the early influence of the corpus luteum of pregnancy, groups of rats were bred and then spayed from 18 hours to 3-1/2 days after copulation. Rat hypophyses were then implanted on alternate days followed by autopsy at 10 days. Mammary ducts alone were present, showing further the necessity of the ovary. Evans and Simpson also reported the absence of mammary hyperplasia in male rats treated with their extracts and this they believed was also evidence of the necessity of ovarian mediation. These discordant results were later reconciled however, when, in 1933, Lyons and Catchpole, working in Evans's laboratory, and using their acid-acetone pituitary extracts devoid of FSH and ICSH (LH), induced milk secretion in non-ovulated oophorectomized New Zealand white rabbits only if they were six months old or over with ovaries that had been undergoing the follicular growth and atresia characteristic of sexually mature, virgin rabbits. Apparently such ovaries secrete enough oestrin and progestin from theca interna and interstitial tissue to induce the minimum of lobulo-alveolar growth necessary for secretory activation by mammotrophic hormone.

Those who were active in this field at that time must surely have recognized that Stricker and Grueter, under the tutelage of Bouin (himself a pupil of Prenant) who, almost two decades earlier, had shown the importance of the corpus luteum as a mammogen, had contributed an outstanding classic in mammary physiology and, indeed, in the wider field of endocrinology. The crude extracts used by Stricker and Grueter were, as we have already indicated, similar to those used by Evans and Long in

their growth hormone experiments; and would now be known to contain at least eight other anterior, intermediate and posterior lobe hormones.

Diabetogenic action of A.P. extracts

In the meantime clinical and experimental data had been accumulating, indicating a functional relationship between the anterior lobe of the hypophysis and the pancreatic islets. In 1931 Evans and Simpson showed that daily intraperitoneal injections of anterior pituitary growth hormone free from gonadotrophic substances into dogs for a period of about eight months induced growth changes in the skeleton and an increase in body weight as compared with littermate controls. In a male this was accompanied by polyphagia, polydypsia and polyuria. The animal developed marked skin infections and abscesses, became emaciated in spite of a large appetite, was easily exhausted and 'excreted great amounts of urine to which flies were attracted'. This led to investigation of the urine of the injected male for the presence of sugar. It was present in large amounts. Fasting blood sugar was also high (252 mg/100 ml, normal 100 mg). The animal was obviously failing and injections were stopped to prevent its death. Four months after cessation of treatment the urine still gave a positive Fehling test. The amount of sugar excreted had decreased and the urine volume was less. The anima was more active and had gained weight. A female, though responding markedly to growth hormone, never showed clinical or laboratory evidence of disturbance of carbohydrate metabolism. Evans wrote to his friend Bernardo Houssay, about his experiments before publishing them and the latter acknowledged this letter and Evans's priority in a paper he subsequently published in 1932, in which he and his team confirmed the Evan phenomenon and showed that Evans-type extracts aggravated the phlorizin diabetes in dogs [7]. When in 1933 Houssay discovered that an anima could survive the loss of its pancreas if its pituitary gland had previously bee] removed, Evans believed the explanation of diabetes in acromegaly was in sight.

The outstanding feature of this work on the pituitary hormones and in particular that on the growth hormone is that it represents, in parallel wit] the work on enzyme isolation contemporary with it, an early example of the systematic application of the methods of protein chemistry and of the related physico-chemical control procedures, to the analysis of a complex natural system. Essential to this work were, of course, the methods evolved for estimating each of the hormones by its characteristic effect. Of these methods perhaps the most useful are those for the bioassay of growth hormone: b the gain in weight of the 'plateaued' female rat; by the 10-day weight gain test in hypophysectomized weanling rats; and by the sensitive test dependin upon the response of the proximal epiphyseal plate of the tibia of young hypophysectomized rats to growth hormone. It is perhaps true as W.

Lyons has said 'that much of the work done anywhere since 1940 on the isolation and purification of growth hormone has had to resort eventual] to one or another of these excellent quantitative bioassays'.

While Evans, with his collaborators, was thus since 1921 engaged in the

characterization and isolation of the gonadotrophic and pituitary growl hormones, and in obtaining the earliest evidence for a mammotroph hormone, other investigators had recognized that two other organs, the thyroid and the adrenals, are also targets for the action of anterior pituitary hormones.

Thyroid-stimulating hormone (TSH)

Philip Smith's skilful ablation of the pituitary rudiment of the tadpole of Rana boylei, done in Evans's laboratory, as already mentioned, had revealed that in tadpoles so deprived the thyroid does not develop. Why Smith succeeded in performing hypophysectomy in the rat, a similar finding reinforced the suspicion that a thyrotrophic hormone of the anterior pituitary was waiting to be identified. Little more happened for a decade until Junkmann and Schoeller developed their method of bioassay and established the J.S. unit of thyroid-stimulating activity which was widely used for twenty years. Isolation studies began in 1931 with the work of Janssen and Lolser in Germany and were followed by those of many other workers in several American and European laboratories.

In their early experiments Evans and Long's good fortune was that they established specific endocrine effects (gigantism and sex disturbances) from parenteral dosage of mammals with beef anterior hypophysis, after failure in a long series of massive oral administration. This work was completed in May 1921, before the demonstration of a similar inefficiency of the pancreatic insular hormone by mouth, and on its completion Smith successfully demonstrated the effectiveness of oral replacement therapy in his pituitaryless frog tadpoles. It is interesting to note that the Evans-type hypophysial substance which Smith used replaced the principle lost by ablation of the epithelial hypophysis, since Evans, as already mentioned, was unable to increase growth with any amount of oral dosage in normal mammals. Evans explained the situation here as due to a different character in the digestive juice of the cold-blooded organism.

Adrenocorticotrophic Hormone (ACTH)

By 1921, there was already sufficient evidence for the existence of a centre or centres in the floor of the diencephalon from which are regulated temperature, metabolism (at least that of water and carbohydrates) and the functional states of some organs, e.g. the gonads, thyroid etc. In his Harvey Lecture, which was delivered in 1924 and published in 1925, and in which he summarized his own contributions to the study of the functions of the anterior pituitary, up to that time, Evans had this to say: 'It is difficult to imagine more consequential relations of any bit of nervous territory than that in the neighbourhood of the infundibulum—the funnel—in the quaint words of Crooke (1616)—which is between the sleepy arteries and conveys the thicker brain excrements to the kernel of phlegm or phlegmatic gland.' This attestation, in so far as it relates to the adrenals, was not long forthcoming, for within a few years of the publication of the Harvey Lecture several workers had observed deficient development of the cortex of the adrenal gland in hypophysectomized animals.

The existence of a trophic principle which might influence the activities of the adrenal cortex had been suspected since 1912 when G. Ascoli and T. Legnani had observed that one of the effects of hypophysectomy in the dog is a profound atrophy of the inner zones of the adrenal cortex. Several years later, in 1919, Simmonds confirmed this dependence when he noted that persons who had suffered accidental destruction of the pituitary had atrophic adrenals. It was Philip Smith, however, who again pioneered the scientific work which led to the demonstration that ACTH is a separate pituitary factor. Actual isolation of such an agent in crude form was first achieved by J. B. Collip and his associates in Toronto in 1933, and four years later H. D. Moon first showed that adrenal cortical growth was due to a pituitary factor separate from growth hormone by producing adrenal hyperplasia and somatic growth retardation simultaneously in castrate weanling rats.

In 1942 and 1943, Evans, together with Choh Hao Li and Miriam Simpson succeeded in preparing from sheep pituitaries highly purified active protein materials free from the activities of other pituitary hormones, thus clearly establishing the existence of the adrenocorticotropic hormone, the structure of which was determined by Li in 1954. At about the same time Evans and his group introduced two procedures, the adrenal repair test and the adrenal maintenance test for the assay of their material. In the first of these, in which female rats were employed, the criterion of repair was the reappearance of lipid droplets in the subglomerular sudanophilic zone of the hypophysectomized rat adrenal. The second method used 40-day-old male rats which were hypophysectomized and given injections of ACTH for 15 days; the end-point being an amount capable of maintaining the weight of the adrenal equal to that of a normal 40-day-old control.

At this point we may digress for a moment to call attention to two other facets of Evans's pituitary studies. In his early experiments with Long in 1921 in which many targets in addition to his 'hypophysis giants' were shown to respond to crude bovine anterior pituitary extracts, examination of the ovaries revealed a luteinizing, as well as what is now recognized as a luteotrophic effect and referred to by Evans as 'a special stimulation of lutean cell growth typical of pregnancy'. Finally, brief attention must be accorded to an, as yet, ill-understood but intriguing effect of pregnant mare's serum gonadotrophin on thymic function reported by Evans and Simpson in 1934. They showed that chronic treatment of male and female rats, whether mature or immature, with equine gonadotrophic hormone results in atrophy of the thymus. But when the testes or ovaries are removed, gonadotrophic treatment does not cause thymic atrophy. The testicular component involved in this reaction appears to be the interstitial tissue and not the germinal epithelium, as treatment with gonadotrophic hormones after destruction of the germinal tissue by procedures which leave the interstitial tissue and its dependent accessory organs intact (cryptorchidism and vitamin E-deficiency) leads to the same atrophic changes in the thymus as in normal males. Subsequently, ACTH was likewise shown to be effective in producing complete regression of the organ. However, the reduction of the thymus in animals receiving ACTH after double

oophorectomy seemed to throw doubt upon, but does not completely eliminate, ovarian participation.

Thus, by the mid-1930s the six hormonal products of the anterior lobe of the pituitary gland now generally recognized as distinctive substances had been isolated in various degrees of purity, namely those for growth (somatotrophic, STH) ; follicle stimulation (FSH) ; stimulation of lutein and interstitial cells (LH, ICSH) ; lactation (prolactin); stimulation of the thyroid gland (TSH); and stimulation of the adrenal gland (ACTH). These hormones have been very difficult to separate, to purify and to characterize chemically, for they are proteins and hence exceedingly complex in their molecular structure. Furthermore, they are effective in very small dosage and it is therefore difficult to know when a preparation of any one of them is free of contamination by another. As Evans and his associates attempted to identify them and distinguish their functional activity, their progress like that of other workers was slow and confusing. One well known American endocrinologist, Oscar Riddle, insisted for a long time that Evans's growth hormone was identical with prolactin. As Evans himself has said, he and his colleagues published again and again statements that they had 'purified' the follicle-stimulating hormone as indicated by tests available at the time, only to find out themselves or learn from others that with different tests or different dosages their 'pure' preparations still produced effects that must be ascribed to another of the anterior lobe endocrines. Even at the present writing, when some of the amino-acid chains constituting these potent proteins have been identified, one of Evans's former co-workers, C. H. Li attributes the growth effect and the mammotrophic effect to the same group of amino acids while another of the group, W. R. Lyons, disagrees.

Because of these perplexities, the biographer and historian find it difficult to chart the course of discovery in this area of research, and to assign credit to any one man or group of co-workers for one or another item in an ever-changing pattern of knowledge. We shall do ample justice to Herbert Evans when we say that for thirty years he led his able associates in productive research of each and all of the anterior pituitary hormones. When he first began to experiment with pituitary extracts, nothing was known about the endocrine activity of the anterior lobe of the gland except that in some vague way it exerted control over bodily growth and was somehow essential to the reproductive function. When he retired from active research, worldwide investigation had recognized six hormones, characterized their activities and to a large extent revealed their chemical structure. Evans was in some way involved in almost every aspect of this great advance.

The importance of Herbert Evans in the light of present day endocrinology and reproductive physiology lies as much in his pioneering work as in his ability to bring an imaginatively stimulating experimental mind to probe beyond the confines of a priori fact. It was a case of the man of genius tilting at windmills, of the precise mind, impatient to probe the hidden mysteries of life and the nature of truth.

## OOGENESIS AND MAMMALIAN CHROMOSOMES

Because of his practice—in his maturity—of always working with one or more collaborators, Evans not infrequently stepped aside to attack with one or another of them, problems not closely related to the pituitary endocrines. One of these ventures was with Olive Swezy, a research associate in the neighbouring department of zoology, several years his senior in age. They jointly published reports on two important topics. One of these was the old question, whether or not in mammals the formation of egg-cells (oocytes) from the germinal epithelium of the ovaries continues after birth of the female infant and on through adult life. After much debate it had been generally accepted, in accordance with Waldeyer's original doctrine, that all the oocytes in the ovaries of a sexually mature woman or other mammalian female are formed during the foetal period so that the individual begins her period of reproduction with a finite stock of oocytes which gradually become exhausted. The opposite conclusion of Evans and Swezy (1929, 1931) based largely on study of the rhesus monkey, that new oocytes are formed throughout life, and in phase with the reproductive cycle, has not been confirmed by subsequent workers carefully examining similar material. The confusion which led to their temporary abandonment of the Waldeyer hypothesis derives from three sources. First, from the fact that they regarded the epithelium which covers the mature ovary as a germinal epithelium (though John Beard had pointed out 30 years before that this was a misnomer), and from the fact that they had observed that the cells of this epithelium were frequently seen to be undergoing mitotic multiplication. Second, from the fact that at any given moment a very high proportion of the oocytes present in the ovary appeared to be undergoing degeneration. And third, from the fact that they had noticed that there was a distinct fluctuation in the number of larger-sized follicles according to the phases of the reproductive cycle.

Their other chief topic was the number of chromosomes in man, which Evans had first studied in 1918 and which was further extended and published in 1929 with Dr Swezy. For this study Evans personally obtained exceptionally fresh and well preserved material by attending, at San Quentin State Prison, the execution of criminals whose bodies were not to be claimed by relatives; Swezy did most of the counting from thin sections of the testes. The observed count of 48 published by Evans and Swezy was unfortunately incorrect; it is now known to be 2 more than the mean figure but within the normal range. In 1969, to a gathering of scientific friends, Evans explained that semi-detached portions of two chromosomes had been counted as separate units. This study stands as a further instance of highly productive research which Herbert Evans stimulated by directing attention to a problem which he did not actually solve. The work represented the best technical achievement until the smear method was introduced; and their camera lucida drawings showed the 'sex' chromatin quite distinct from the nucleolus in resting nuclei in male cells but not in the position found typical for females by Barr in 1959.

## THE OESTROUS CYCLE OF THE BITCH

Another more successful side-line that attracted Evans's attention at this time was a descriptive account of the canine oestrous cycle, published in 1930 as a joint

monograph with H. H. Cole. For this research Evans was himself prepared by a study of the early embryology of the dog, done while still in Baltimore, where by greasing the palms of dog-pound attendants he was permitted to mate bitches in heat at stated times before they were put in the gas chamber. A few carefully preserved jewel-like blastocysts thus obtained remained for years in vials on his shelves at Berkeley; he never published the embryological findings.

## PIONEER COLLECTOR OF BOOKS

Few of Herbert Evans's fellow-scientists knew that he was a pioneer collector of books in the history of science. His bibliophilic taste, fortunately for him, was kindled by his schoolmaster and throughout his life he retained the mania of the genuine collector, especially of the great classics in the medical sciences. His adoption of such an avocation, ordinarily far beyond the means of a professor and surpassed only by his dedication to the pursuit of his scientific researches, is easily understood in the light of his aspiration for cultural distinction, long hampered by the lack of a classical education. In the introduction to his catalogue *Exhibition of first editions of epochal achievements in the history of science*, published by the University of California Press in 1934, Evans justifies his zeal for the collection of first editions, which he pursued with an almost lustful passion, on the grounds that: 'It is only by consulting the first form of a scientific achievement that one can hope to observe the origin and change of ideas. But, more than this, it may be maintained that one cannot adequately understand any scientific subject without knowledge of the manner in which our present conceptions were established.' This quotation shows, of course, his familiarity with Clerk Maxwell's aphorism: 'Science must be studied as it has developed, that is, in its original nascent form ; only thus can we see the strange interlarding of new truth with surviving error.' In this sense then Evans is derivative of Clerk Maxwell; these are difficult considerations, however, and here is no place to try to grapple with them.

Although William Osler was in England during Evans's first two years at the Johns Hopkins, his influence and that of others, notably Harvey Cushing and Franklin Mall, had clearly begun to show itself in Evans's newly developed interest in books on the history of medicine, and the acquisition of a library. Throughout this and succeeding years books are constantly mentioned by him. As a young man in Baltimore he was already sufficiently interested in the history of anatomy to publish one or two brief reviews of new books in that field. As he matured, even if he did not read the Greek of Galen and the Latin of Vesalius, or the antique French of Ambroise Pare, he came to relish the sight and feel of the volumes in which the works of these heroes of science were enshrined. Herbert Evans combined in marked (and, one might add, unusual) degree a lore of the history of science with a profound interest in scientific theory and achievement. His urge to collect books could, however, not be indulged, for lack of the necessary money, until he was well established in his professorship and the family exchequer was strengthened by parental bequests.

Evans knew the worthies and their writings from Hippocrates down. On one

occasion while on a visit with one of us (E. C.A.) to the library of Professor F. J. Cole of Reading, a fellow collector and a man of generous enthusiasms who had amassed a formidable collection of books and manuscripts, many of them rare and unobtainable, Evans remarked as we stood in one of the rooms on the ground floor: 'One can easily see that this is the library of a great collector. I have always thought that if one only had the time to study and compare the books which a man buys and reads, one would more surely get the truth of him than in any other way. But alas, one never has the time'. The library was well arranged with high bookshelves filled with books, except for a vacant space here and there where a volume had been removed. Evans put back in its place the book which he had been holding in his hands, and without turning, he continued: 'Come and stand with me, doctor, for even a glance at the back of them tells one something'. The book he had replaced was *The private college of Amsterdam*, which is the rarest and least known of all the early literature on comparative anatomy. Cole had decided to print an exact copy of it.

Herbert Evans's remarkable career as a pioneer collector of first editions of books in the history of science, 'one of the chief cults of bibliomania', as he put it, has been described since his death by Jacob I. Zeitlin [10], the well known Los Angeles dealer in rare books and manuscripts. No one know more than Mr Zeitlin about this aspect of Evans's life and character, and it is knowledge indispensable to a biography of the man. For therein lies one o the main interests of the last forty years of his life. Evans began serious collecting about 1930. His earliest purchases were financed, it seems, by borrowing from his wife Anabel's patrimony. By 1934 his first collection of *Epochal achievements in the history of science* was sufficiently important to be exhibited at the Berkeley Faculty Club by the History of Science Club of the University of California. A small catalogue which Evans prepared for the exhibit shows that he had interested himself especially in books embodying notably individual discoveries, the formulation of scientific laws, and announce ments of important hypotheses which have been responsible either directly' or indirectly for the advancement of science. According to Zeitlin the catalogue was a pioneer effort to compile a selected list of the most significant books in the history of science, and although it has been followed by at leas two similar endeavours by others in 1955 and 1964, respectively, neither c them has had the influence of Evans's pioneer work. It is still a valuable guide for advanced collectors and dealers. Zeitlin considers it largely responsible for the great increase in American demand for books in the history of science during the past 35 years and the consequent increase c prices.

Evans did not keep this first collection very long. Domestic infelicities requiring reimbursement of Mrs Evans forced him to sell it. Almost at one he began another, of first editions in the sciences, accompanied by a collection of bibliographic reference books on the subject. This too was sold, to settle the estate of his wife, who died soon after their estrangement and divorce in 1932.

Somehow Evans found the means to continue collecting, periodically getting himself in debt and selling off the books. 'Each time he received payment for the latest

collection', says Zeitlin (through whose hands most of them passed) 'he would plunge into another passionate campaign by letter, cable, telephone and overnight drives or air flights to all parts of the world, to try to recapture the treasures he had parted with a few days before'. 'Thus', Zeitlin continues, 'he remained all his years a happy victim of what Aldous Huxley has called "the most agreeable vice".' Even in his last days he was engaged in forming what he hoped would be his finest and greatest collection. He had planned a book plate for it incorporating his favourite quotation:

Blessed is he who contemplates the ageless order of immortal nature,

how it is constituted and where and why.—Euripides

But alas this was not to be.

The history and present whereabouts of the seven successive scientific collections show how widely this obsessive urge has ultimately served American scholarship, for almost all these books, estimated to number more than 20 000, are now in the possession of universities or other scholarly owners. Mr Zeitlin has tentatively listed the medical and scientific collections as follows:

Collection Number 1. 1930 (?)

'Classics in the Medical Sciences'.

Purchased by Dr and Mrs James Waring, Finley L. McFarland and Mrs Dora Porter Mason. Presented to the Denver Medical Society, Denver, Colorado.

Collection Number 2. 1950.

'First Editions in the Sciences, together with a Reference Collection on the History and Bibliography of Science'.

Purchased from the conservator of the estate of Mrs Anabel Evans by Zeitlin & Ver Brugge and John Howell: Books on behalf of Lessing J. Rosenwald and presented by him to the Institute of Advanced Study, Princeton, New Jersey.

Collection Number 3. 1953.

'First Editions in the Sciences, together with a Reference Library on the History and Bibliography of Science'.

Purchased by Zeitlin & Ver Brugge. Described in several catalogues. Many of the outstanding items were acquired by the Burndy Library and by E. L. De Golyer for the Golyer Collection at the University of Oklahoma at Norman, Oklahoma.

Collection Number 4. 1957.

'First Editions in the Sciences'.

Purchased by Bernard M. Rosenthal and John Fleming for Louis Silver of Chicago and presented to the University of Chicago. Some duplicates and out-of-scope works were sold by John Fleming (one of these, Semmelweis, *Die Aetiologie, der Begriff and die Prophylaxis des Kindbettfiebers*, 1861, was again purchased for Evans—the second

time that this book had passed into his hands).

Collection Number 5. 1961.

'First Editions in the Sciences'.

Sold by Zeitlin & Ver Brugge and John Howell: Books, as agents for Dr Evans, to Samuel A. Barchas of Tucson, Arizona.

Collection Number 6. 1962.

'First Editions in the Sciences, together with a Collection on the History and Bibliography of Science'.

Sold by Zeitlin & Ver Brugge and John Howell: Books, as agents for Dr Evans to Lew D. Feldman, acting for the University of Texas, Austin,Texas. Collection Number 7. 1967.

'First Editions in the History of Science and a Collection on the History and Bibliography of Science'.

Purchased by John Howell: Books, San Francisco, and Zeitlin & Ver Brugge, Los Angeles, and dispersed in a number of catalogues of both firms, the major part of the collection now at the University of Utah, Salt Lake City, Utah.

In addition to the medical and scientific books, Evans formed at least two great collections of Western Americana, two collections of Japanese prints, one collection of the prints of Jacques Callot, and at least one miscellaneous library of important works in poetry, art and the humanities.

During scientific trips to Latin America, particularly to visit his friend, the distinguished physiologist, Bernardo Houssay in Buenos Aires, Herbert Evans became interested in Spanish Colonial church architecture and his collection of illustrations of these remarkable buildings could well form the basis for an important monograph. And we are told that his home was filled with works of art, many of them reflecting the sensitive interest he maintained in ecclesiastical iconography.

UNIVERSITY OF CALIFORNIA HISTORY OF SCIENCE DINNER CLUB

Any account of the life and work of Herbert McLean Evans would be pitifully incomplete unless due regard were paid to the part he played in the foundation of the History of Science Dinner Club. Professor V. F. Lenzen of the department of physics of the University of California and the only surviving member of the foundation fellows who knew Evans well has recorded this story [11], and the following account is based on it.

The University of California at Berkeley which had been founded in 1868 by scholars who believed in the value of the classical tradition in higher education, was fortunate in having as its president, in the early decades of the present century, the distinguished Greek scholar and historian of Alexander the Great, Benjamin Ide Wheeler. President Wheeler was an accomplished administrator, a considerable

philosopher, an educationist and a man of infinite capacity and charm. Under the creative and sensitive leadership of this talented scholar the University provided a friendly environment for historical studies. Already in the 1920's, a movement was under way which was destined to affect profoundly the attitude of the various faculties towards historical scholarship. At this time various departments of the University offered courses in the history of the special sciences, notably in mathematics, physics, chemistry and astronomy.

Evans himself successfully promoted the serious study of the history of science and of medicine in particular as respectable subjects. Brilliantly persuasive as a teacher he combined a remarkable width of knowledge with tremendous powers of exposition. Utilizing his own colour slides, facsimile illustrations and even his own film, he brought history to life for his students long before university audio-visual centres were thought of. Professor Lenzen has told us that: 'This interest on the part of science professors in the history of their subjects finally resulted in 1930 in the appointment of Professor Charles Singer of the University of London to give a series of lectures which ranged in subject from Aristotle as a man of science through the scientific works of Leonardo da Vinci to anatomy and art.' Three years later George Sarton was appointed Hitchcock Professor and he gave a series of lectures under the general title Medieval Science and Medieval Culture. These lectures were delivered between 10 January and 6 February, 1933. Continuing his narrative Lenzen writes: 'On 15 August, 1933, Dr Herbert M. Evans addressed a note to the following members of the faculty: Professor D. C. Beasedale (Chemistry), Dr D. C. Duncan (Mathematics), Professor C. A. Kofoid (Zoology), Professor V. F. Lenzen (Physics), Professor W. F. Meyer (Astronomy), Professor N. L. Taliaferro (Geology) and Professor W. A. Setchell (Botany). Dr Evans opened his note by the statement:

"A wholly remarkable interest has been taken in the history of science in the University of California. For a number of years various departments have offered at least a single course each in the history of the specific science covered by the department . . . . It has occurred to me that the members of our faculty who are actually giving courses in the history of particular sciences would gain immensely from occasional social contact and I am venturing to suggest a dinner club to meet once monthly."

On 5 September 1933, Evans sent out an invitation for the first meeting and The History of Science Dinner Club met in the O'Neill Room of the Faculty Club on Tuesday 12 September 1933, 'in order to organize'. The minutes of the Club record that: 'Toward the close of the gustatory part of the meeting, Dr Evans,' who served continuously as chairman and secretary until only a few years before his death, 'called for the "show of books" 'a tradition that was to continue. Amongst those who exhibited rare books on this first occasion was Evans himself. The second meeting was held on 10 October 1933. At this meeting there was established the practice of having a prepared paper read.

A characteristic aspect of the Club, we are told, was the completeness of the

minutes. This was what might be expected, since Evans, as secretary, was responsible for their compilation. A member who brought a book for exhibit and discussion was solicited by the chairman to prepare a written statement for incorporation in the minutes and the reader of a paper was always asked to offer an abstract for inclusion. The minutes have been preserved in the University Archives of the Bancroft Library, Berkeley campus. As the twenty-fifth anniversary of the founding of the Club approached, it was decided to publish a volume of essays. This volume under the title Men and moments in the history of science and edited by H. M. Evans (University of Washington Press) appeared in 1959. It was a tribute to Evans that about the time of his retirement from active leadership, the Club voted to name itself The Herbert M. Evans History of Science Dinner Club.

JOURNEYS ABROAD

During the years before World War I, Evans made seven study trips to Germany and it was then that he acquired a fine command of German. His linguistic equipment, while not perhaps profound, was unusually wide and practical. After his return to Berkeley from Baltimore in 1915, he went several times to Central and South America, there to visit his friend Bernardo Houssay. In 1946 when he was 64, Evans went to Paris to receive from the Sorbonne an honorary doctorate which his friend Professor R. Courrier had sponsored. Four years later he was back in Europe, lecturing in Edinburgh and Birmingham, where he also received an honorary degree. In April 1953 he returned to England to be admitted to the Royal Society, to whose Foreign Membership he had been elected in 1951. His last visit to Europe was in June 1962 to attend a symposium on vitamin E held in Zurich in his honour.

On his visits to England, he spent a good deal of time with his friends, Sir Charles Dodds, Professor G. W. Harris, F. H. A. Marshall, Sir Alan Parkes, Lord Todd, Professor F. G. Young, and Lord Zuckerman. Here the records of the past constantly engaged his attention. To the Hunterian Museum of the Royal College of Surgeons he returned again and again and to the Ciba Foundation where relics of John Hunter belonging to the Hunterian Society were housed.

Significant in the light of Evans's own scientific concern with reproduction is the interest aroused by these visits, for as he related to one of us (E.C.A.) the brothers John and William Hunter came to mean more to him after he had obtained a copy of The works of John Hunter FRS. Edited by James F. Palmer (1837). Evans admitted that he had read these volumes but had never studied them in detail, merely collecting whatever might serve his purposes. However, all this was stored away in a monstrous memory which retained everything—words, places, expressions—with the same fidelity.

The fact that John Hunter (1771) had successfully transplanted the testis of a cock into the belly of hens and roosters—long before Arnold Berthold (1849)—greatly intrigued Herbert Evans, as did Hunter's (1780) observation that when a cock was incompletely castrated the residual fragment underwent hypertrophy during the next

eight months—possibly the earliest experimental evidence for a gonadotrophic hormone. 'This thought kept pressing on me', Evans declared, 'because I could share another's experiences by putting myself in his place.' Evans also drew satisfaction from Hunter's experiment demonstrating the growth and increase of follicles capable of ovulation in a sow after one-sided ovariectomy, 'Because', as he put it, 'Hunter had anticipated by at least a century and a quarter the "law of follicular constancy" advanced by Lipschutz and his collaborators from 1923 onwards.' This law gave expression to the idea that the number of follicles ripened in a batch was characteristic of the species and, provided oocytes were available was independent of the amount of ovarian tissue. It implied, moreover, that the ovary, like the testis, was dependent on some limiting extragonadal stimulus. But, as Evans was quick to point out, it is difficult to concede that Hunter was aware that male sex characters are maintained by a blood-borne secretion of the testis; this was Arnold Berthold's fundamental contribution.

During his visits to Paris and to London Evans's time was not spent altogether in work, for he spoke of renowned actors and singers and dancers who contributed to his recreation. He delighted to roam the streets of these capital cities at night, looking in at the shops which he thought 'greatly superior to those of Baltimore and San Francisco'. He took especial pleasure in hunting for old books on the walls of the quais in Paris and at the small dealers in the Charing Cross Road in London, to whom he was especially fond of showing how superior were the anatomical illustrations in the works of some of the older writers. Another visit that intrigued him was one to Japan in 1954 where he was received in audience by the Emperor who presented him with an illuminated copy of one of his zoological treatises. This, Evans greatly treasured, and he took great delight in showing the book to friends.

Evans took particular satisfaction in another event, a visit to George Bernard Shaw, which coincided with his trip to London with Mrs Evans after receiving his doctorate from the University of Paris in December 1946. The visit itself Evans tells us 'had afforded welcome relaxation after the elaborate academic panoply of the Sorbonne', and had been arranged over lunch by Charles Dodds (later Sir Charles Dodds, Bt) through his friend O. Kyllman, Chief of Constable and Company, Shaw's publishers; and Evans loved to talk about it. To him it was a revelation to have a friend who had known, in the flesh, the remarkable old man—G. B. S. had already celebrated his 90th birthday. The luncheon took place at the Escargot restaurant in Soho and Dodds had invited Kyllman and Helen Waddell, the medieval scholar who wrote the very notable *Wandering Scholars* and much else, to meet the Evanses.

The circumstances are recorded in a little known booklet *A visit with GBS* written by Evans and his wife Dorothy. 'Our talk with Helen', they wrote, 'was of Rhabanus Maurus, Abbot of Fulda, but we did not fail to remark the soft-spoken, sensitive Kyllman, who sat in the corner and interjected sparkling remarks all that hour, some of them starting with "Now, Mr Shaw once said" etc., and finally he blurted out "Dr Dodds, we must take the Evanses out to Shaw, he will endure them as well as we have done, let me arrange it". We thought no further of the plan, but referred it to the

exceedingly good brandy with which Dodds ended his luncheon—as if he had not already opened a red Chateau twenty years old!'

Some days later, Dodds sent the following letter to Evans:

3rd January 1947

Dear Professor

Mr Kyllman has just rung me to say that Mr Shaw will be very pleased to see you and your wife on Monday afternoon.

Mr Kyllman will himself take you in a car to Ayot St Lawrence and bring you back. I have promised faithfully to deliver you to Constable's at 2.15 p.m.

I am so glad that he has been able to fix this.

With kind regards

Yours sincerely

E. C. DODDS

The meeting having been thus arranged the party set out on the afternoon of Monday 6 January. The snow was more than an inch deep, but as Evans has said: 'We did not mind, for as we passed through the quaint village of St Albans we glimpsed the fairyland setting for the Dickens Christmas we had hoped—and failed—to find in postwar London. It was about 3.50 before we were at G.B.S.'s hedge. For the last two miles I had been reading Shaw's own directions, "From London to Ayot St Lawrence by Road" (printed on the soft light green paper which G.B.S. affects). "O.K." had put a copy of these into the driver's pocket, but I returned them to my pocket for my scrap album.' It was not long before 'a nice little maid' showed the visitors in, and in a few minutes Shaw slipped quietly in to greet the party. When the visit was over, Evans wrote: 'He had taken an unmistakable liking to me and I to him. I did not climb a throne; neither did he.' And what Evans then saw and heard would the more clearly be photographed in his always retentive mind by the sentiment of valediction, at the end of the visit. 'He came over', Evans wrote, 'and asked me whether I would not come again. I replied that this would have to be on my next trip to England. "I don't know I myself will be about then," he said significantly. He insisted on showing us to the door.'

It is best to accept the account as true in essence if not in all detail; and then to consider how it both modifies and accords with our present view of Evans. What is certainly true is that both Dodds and Kyllman were embarrassed and disapproved its publication, knowing full well, as did Evans himself, how much Shaw disliked and even hated giving interviews for the 'press'.

The notes we are given of the visit, whether with purposeful or unpurposeful tactlessness, must be something of a disappointment, unless we seek some justification for the more decorous permanence of book-form they achieved. What then is the justification for publishing them as a book rather than as a magazine article? There is to

begin with the justification obvious to scholars: that being an account of an afternoon spent with an author universally ranked as the most distinguished in the England of his day-'the greatest playwright since Shakespeare', they contribute facts and opinions about contemporary literature. On the other hand, there may be no reason to doubt him when he says: 'When a scientist strays from his laboratory, he is "out of bounds", and the modern world of specialization knows full well that he is on holiday and not to be taken too seriously; but that these faithful workers should also have zest for acquaintance with other adventures of the human spirit is natural and should be forgiven them. Forgiveness will surely come if the worker with test tube, telescope, or microscope has been nurtured in a goodly company which zealously loves books (the Roxburgh Club of San Francisco)—books whether they merely entertain or instruct—books which either convey the dreams of man or at any rate tell us what that dreadful cerebral cortex of his is doing'.

In a prefatory note to the account of the visit to Shaw, Evans says that it was based on a diary kept by him while on an air trip to Europe, from 7 December 1946-13 January 1947, primarily to attend the December Seance Solenelle of the University of Paris. Evans was, of course a consummate diarist, and in the following autobiographical fragment, taken from an interview with Sir Alan Parkes, he tells an amusing story of the fate of one of his diaries: 'I made altogether in my life nine study trips to Europe, and I kept a diary and sent the diary carbon to my laboratory. When I got there I found they hadn't read it. And I said, how can you defend yourselves, gentlemen? And they said, "that was your diary."—Wasn't that clever? It is what a loving youngster would say: that was your diary. It made me sore as hell because I took great care.'

CHARACTER

As the story of Herbert Evans's life unfolds, one question constantly recurs; how did one man accomplish so much? His writings tell the tale; his published work was vast.

Evans belonged to that generation now passed, in which men still liked to think that they might know about everything, although they were perfectly well aware of the fact that they could not. He was interested in everything which was going on in biology, in embryology, endocrinology, physiology of reproduction, nutrition, genetics, the history of science and medicine and the collection of books. Nothing was too large for him, nothing too trivial, if it threw light upon the central question—the pursuit of truth and the biology of man.

Evans's contribution to knowledge was not more brilliant in one department than another; almost everything he did contributed to the basis of the great generalizations with which his name is associated. But the very bulk and thoroughness of the work has made complete appraisal extremely difficult, if not impossible. A near complete bibliography has been appended to this memoir and no attempt has been made to analyse in detail all aspects of his work.

For the same reason it is scarcely possible to separate personal achievements

from those of his pupils; what is quite certain is that the latter, with but few exceptions, are always the first to recognize the inspiration they received from Evans. His gift as man of action lay first of all with those of like mind ; he was quick to appreciate talent, and in his choice of collaborators and his unreserved encouragement and support of their work he was wise, far-sighted and effective. Evans's influence in this respect, like that of his teacher Mall was partly mediated through others; he managed to find and hold those whose talents complemented his own—people like Miriam Simpson and Wm R. Lyons—and these colleagues had their own share in the extraordinary spirit of enthusiasm and enterprise which pervaded his laboratory.

Evans has told us that he 'worked through his students and through ingenious suggestions thrown out by them', and 'all the credit for anything I ever did was due to the wonderful individuals who surrounded me'. But at the same time he was a stern task-master with his pupils, and his prescription of 'throwing them into the deep end', patterned after the well-known (apocryphal) formula for bathing the baby attributed to Mall by students . . . 'put her in the tub and let her work out her own techniques', though not without risk was effective.

Of his own work, Evans has said: 'our particular studies, proper as it is that they should have consumed us, represent but one face or facet in the glittering jewel called MEDICINE, in which, for symmetry, other facets are of course equally polished'. 'The brilliance of the gleam from that facet', as Dr Saunders put it [4], 'which he polished with such assiduity and dedication will long shine in the diadem of science and sparkle in the medicinal eye of the doctor'.

Evans's memory was encyclopaedic and he delighted to discuss any and all topics with his friends. It was, indeed, a natural temptation, for so few could supply so many as he. That he could think is as obvious as that Schubert could write melodies. He could also recall with details, as numerous as they were vivid, the experiences of the long past, and that this was a gift he liked to exercise is evinced by the strange reason he gave for a hastily designed summer trip to Germany and to Gottingen; 'to place a wreath at the foot of the statue of Wohler, and to have a look at Wohler's crystals ofurea with the date 1828 on the little tube'.

Herbert Evans had, as a rule, a strong sense of 'occasion'. A conversation, or even a salutation of his was a form of action, and often of action in a public sense; and this process seldom failed to communicate to the action which it created an appearance of affectation—for it was nothing more than the appearance. Dr Evans was tall and broad shouldered. The framework of a well-proportioned body supports a squared skull with delicately vaulted forehead and thin uncommunicative lips. Yet two clear blue eyes and a nose of ample size—evidences respectively of faith and energy—stand out upon this face with an aggressive and commanding presence. For faith and energy are the fundamental traits of this powerful, yet lonely man. Herbert Evans was not only a courageous man but a tenacious one. His mobile features expressed alert interest in people and things about him, mingled now and then with a quizzical glance or the

subtle reflection of an arrière-pensée that might have meant anything from mockery to disdain.

For Herbert Evans, dialogue existed at several degrees of strength. In friendly conversation he was gay, sometimes extravagantly enthusiastic. But he enjoyed good conversation, and when he found himself in company that he respected, he was a good listener. He liked especially to talk with intelligent women, who responded warmly to his deferential manner. With his students he liked it to be with a single person and, when otherwise, with a small number—by preference, his 'family' of young graduates. This is why, as mentioned earlier, he put heart and soul into teaching small groups; it declared the value he placed on dialogue and his zeal for entering into the minds of others. In more formal conversation and in talk about scientific matters or book-lore, though expressively courteous, he could not conceal an air of superiority of which he may not always have been conscious, evinced by allusions to facts or personalities beyond his hearer's acquaintance, introduced in such a way as to suggest that one really ought to know about them. The same compulsive urge to be recognized as a cultivated person caused him, in his writings, to employ a high and sometimes high-flown literary style. Nevertheless his writings combined great erudition with readability and showed him as a master of his craft.

Typical of Evans's attitude towards the industrious, talented and zealous student was the story he told, when addressing the medical history section of the newly formed University of California Medical School at Los Angeles, of one such (Elmer Belt) who contrived to enter the Anatomy Department after the doors were locked at 5.45 p.m. to continue his dissections at night, thus permitting extra time for his researches. He said that Benjamin Ide Wheeler had called him to his office, and told him that the campus police reported seeing a student enter an unlocked window of the anatomy building nightly. 'Did Dr Evans know this student? What did he intend to do about it ?' Said Dr Evans 'Were I not fearful of frightening the student away from such devotion to anatomy, I would call him before the class and bestow honours upon him.'

As would be expected of a man always expending his full energies at the highest level of individual talent, Evans would not busy himself with the organizational routines of the scientific profession. He frequently attended the annual meetings of the American Association of Anatomists, presenting the results of his research at the scientific sessions and heartily enjoying the sociability of these gatherings, but when he was president of the Association (1930-32) he left the routine business to be handled by the vice-President. Duty required him to take the chair at the executive session but he did not inform himself of the agenda and was quite unabashed when he had to be coached by the secretary sitting beside him on the platform.

Thirty years ago some of his colleagues said some damaging things about Evans's aggressiveness, and they spoke for a number of contemporary endocrinologists then and since that date. It did not take long for these passions to find unpleasant channels to express themselves. Soon suspicion was rife, and intelligence, dignity and

fair play took flight. No man could be entirely unaffected by such treatment and whilst Evans behaved with superb courage, he found this hard to sustain.

His critics were awed by his immense capacity, infuriated by his meddlesome energy, deeply distrustful of his restless ambition. They quarrelled with him and admired him, decried him and were charmed by him, hated or loved him—but never could they ignore him; even these critics agreed on his rare gifts. But with all his shortcomings he was, in the words of his lifelong friend, Bernardo Houssay, 'the biggest man and the most striking personality in Endocrinology in all America.' Indeed, as Chauncey D. Leake has suggested [12], no fewer than four of Evans's major discoveries might well have merited a Nobel prize.

No adverse judgement, however, can stand permanently against an important investigator. We ourselves change, given time; and the spirit of the age, to which we subtly conform, also undergoes changes. And so we turn from things that had once to be dismissed in order that we might give our individual attention to different things. It has seemed worthwhile indicating these shifts of opinion, to emphasize that there is nothing unusual in Herbert Evans's mellowness in his old age.

Herbert Evans was of the West, and his appreciation of the West was 'often expressed in walks in halcyon days in the country and companions sensed the powerful influence outward nature had upon his mood.' 'Dressed in rough clothing, always with the old style red cotton handkerchief about his neck, he was a charming companion in the woods, extraordinarily well informed in natural history and regional lore.' He was a keen botanist, and was much impressed by C. Hart Merriam's work. And when on one occasion he was reminded of this by Dr Simpson, he remarked: 'When I joined the Sierra Club I carried a plant press, and collected on the timberline. This gave me great zest and even now (he was then in his 85th year) I can recognize many of the landmarks.'

Herbert Evans had many staunch friends among his colleagues in the Department of Anatomy and the Institute of Experimental Biology at Berkeley. There were C. W. Asling, H. H. Cole, Wm O. Reinhardt, Wm R. Lyons, J. B. de C. M. Saunders, to mention a few, but there was no one over the years more loyal and devoted than Miriam E. Simpson, who had been with him in his early days and who had worked so closely on the pituitary. The unique partnership with Dr Simpson was to last for nearly 50 years. Another whom Evans greatly admired, and whose friendship and counsel were to take a high place in his regard, was Bernardo Houssay, brilliant investigator and Nobel laureate, who also became a Foreign Member of the Royal Society.

MARRIAGES

Herbert Evans's three marriages marked cardinal phases of his life. Anabel Tulloch, the bride of his student days, exhibited as much independence and impetuosity as he when in disregard of family pressure he boldly set out on his scientific career. This marriage long withstood severe domestic strain and many tribulations, but as shown by an episode narrated earlier in this memoir Anabel did not

willingly endure the stresses of marriage to a man so intensely dedicated to science. She was the mother of his first born and for many years was not only an unselfish wife, but a loyal admirer of the ambitious and, in some ways, somewhat lonely scholar she had married, blindly believing in him, when even she might justifiably have had doubts. The daughter born of this marriage, Marian McLean, was greatly loved by her father and deeply mourned when she died in young womanhood.

Evans's second wife, Margery E. Sadler, was a highly competent research worker in his laboratory, fully qualified to tolerate the exigencies of his scientific activity. They were married in 1932, when his career in endocrinological research was at its crest, but while life was active and interesting for Herbert, it was by no means without anxiety for Margery. A daughter of this marriage, Gail Bayne (Mrs Rolf La Forge) no less beloved than was her half-sister, resides at Mill Valley, California.

Herbert Evans's first marriage failed and ended in divorce as did his second; but one is tempted to speculate as to the effect it might have had on his character and work had either of these marriages been as permanent as his third. Perhaps his interest in people as such would have been enlarged. Perhaps the enfant terrible would have receded and he would have been better understood by his fellow scientists. His personal life would almost certainly have been enlarged and enriched in countless ways. He found a measure of compensation in his work, which absorbed him increasingly, and may have helped in tempering his emotional urge.

The wife of Evans's later years, Dorothy F. Atkinson, was at the time of their marriage in 1945 active director of the Department of English at Mills College, Oakland, California. The third Mrs Evans was prepared by her training and career to sympathize with his interest in the history of science and his zest for collecting books and prints. Her humanistic studies gave her, indeed, a gentle superiority over his less deeply rooted literary and artistic qualifications, and her mature years gave her confidence to smile at his exuberances. No doubt, also, he had mellowed domestically. She was a co-author with him of one of his less well-known publications *A visit with G.B.S.*, of which we have already spoken. They lived quietly and happily together in their Berkeley hillside home, amid books and objects of art, until her death in January 1969.

LECTURES

Appointment to numerous endowed lectureships in the United States, England and Scotland testify to the admiration of fellow scientists and their desire to have their students see and hear this investigator and discoverer. Brilliantly persuasive, his talent for lecturing without notes was unsurpassed for ease and brilliance, erudition and wit. As a teacher, he combined a remarkable breadth of knowledge with tremendous powers of expression. He knew his subject well and loved it, while the wealth of illustration, comparison, similes and witty allusions he used was unequalled. He brought history to life, hence his charm; you received information and you were charmed. To him Goethe's dictum, 'The history of the subject is the subject,' had real meaning.

1923-1924. The Harvey Society Lecture.

1925. Faculty Research Lecturer, University of California.

1931. Bacon Lecturer, University of Illinois.

1934. Herzstein Lecturer, Stanford University and University of California.

1937. Beaumont Lecturer, Wayne County Medical Society, Detroit.

1937. Jackson Lecturer, University of Minnesota.

1939. William Henry Welch Lecturer, Mount Sinai Hospital, New York.

1940. Jones Lecturer, University of Oregon.

1942. Messenger Lecturer, Cornell University.

1942. Mellon Lecturer, University of Pittsburgh.

1942. National Sigma Xi Lecturer.

1942. Guiteras Lecturer, American Urological Association, New York.

1943. Porter Lecturer, University of Kansas.

1946. Vanuxem Lecturer, Princeton University.

1947. Ludwig Hektoen Lecturer, Frank Billings Foundation, Institute of Medicine of Chicago.

1947. William E. Lower Lecturer, Cleveland Academy of Medicine.

1947. Eastman Memorial Lecturer, University of Rochester.

1949. Banting Memorial Lecturer, American Diabetes Association.

1950. William Withering Lecturer, University of Birmingham, England.

1950. MacArthur Lecturer, University of Edinburgh.

1954. Walker-Ames Lecturer, University of Washington.

1959-1960. Faculty Research Lecturer, University of California School of Medicine, Sar. Francisco.

HONOURS

Herbert Evans was the recipient of innumerable academic honours; veritable shower of doctorates from universities in the Old and New World besides his own Almae matres, California and Johns Hopkins, and membershii of academies, including the U.S. National Academy of Sciences and the Royal Society descended upon his ever receptive shoulders, more than ample to justify the choice of a career that he had made with filial concern in young manhood. But of the honours which came to him there is little doubt that he valued most his election to Foreign Membership of the Royal Society. On the day he signed the roll, he had come prepared to address the Society in

the false belief that this was a traditional custom required of the recipients of this honour.

Another English honour, which greatly heartened him in his declining years, was the award in his eighty-fifth year of the Marshall Medal of the Society for the Study of Fertility, struck in honour of F. H. A. Marshall of Christ's College, Cambridge, whom he greatly admired, and whose book, the first to be devoted to the physiology of reproduction, he considered a masterpiece.

National Honours

Member, U.S. National Academy of Sciences.

Fellow, American Academy of Arts and Sciences.

Member, American Association of Anatomists (President, 1930-1932). Member, American Physiological Society.

Member, Society for Experimental Biology and Medicine. Member, Phi Beta Kappa.

Member, History of Science Society.

Honorary Professorships

Chile Honorary Professor, Facultad de Biologia Y Ciencias Medicas, Universidad de Chile.

Ecuador Honorary Professor, Facultad de Ciencias Medicas, Universidad Central del Ecuador.

Medals and Prizes

1928. John Scott Medal.

1946. Gold Medal (first award) for Scientific Exhibit, American Medical Association, San Francisco.

1949. Banting Medal and Squibb Award, Association for the Study of Internal Secretions.

1949. Mickle Fellow, University of Toronto.

1952. Passano Award, Baltimore.

1959-1960. Fellow of the Center for Advanced Study, Wesleyan University. 1967. Marshall Medal of the Society for the Study of Fertility.

Honorary Degrees

1941 Chile Hon. M.D. Universidad Catolica de Chile.

1954 Ecuador Doctor Honoris Causa Universidad Central del Ecuador.

1946 FranceDoctor Honoris Causa University of Paris (Sorbonne).

1930 Germany Hon. M.D. Albert Ludwigs—Universität Freiburg i. Br.

1950 Great Britain Hon. Sc.D. University of Birmingham.

1941 Peru Doctor Honoris Causa Universidad Nacional de San Marcos de Lima.

1956 Switzerland Doctor es Sciences, Honoris Causa Université de Geneve.

1955 USA Hon. LL.D. University of California.

1957 Hon. Sc.D. Johns Hopkins University.

1960 Hon. Sc.D. University of Bridgeport.

Foreign Societies of which Herbert McLean Evans was Honorary, Foreign, or Corresponding Member

Argentine

Chile

France Germany

Great Britain Hungary Sweden

Honorary Foreign Member, Academia Nacional de Médicina de Buenos Aires.

Corresponding Member, Sociedad Argentina de Biologia.

Honorary Member, Sociedad Medica de Santiago (Chile).

Honorary Member, Sociedad de Biologia de Santiago de Chile.

Foreign Corresponding Member, Academie Nationale de Médecine, Paris. Member, Kaiserliche Leopoldinisch—Carolinische Deutche Akademie der Naturforscher.

Foreign Member, Royal Society of London.

Member, Societas Regia Medicorum Budapestinensis.

Foreign Member, Royal Swedish Academy of Sciences, Stockholm.

RETIREMENT

One mark of Herbert McLean Evans's greatness, if we are to do him justice, is that we should spend as much space on the years when his reputation was, comparatively speaking, in the eclipse as on the years of its rise and long ascendancy. But this is a task for those who knew him better, and who may consider that the picture drawn in this notice is too subdued in tone and that it does not revive the image and personality of an ambitious, intellectually proud man fighting his way with all necessary vigour through some of the most exciting years endocrinology has known.

With Evans's retirement from the Department of Anatomy and the Institute of Experimental Biology, in 1952, the adventurous chapter of his life seemed to close, but other chapters and other adventures awaited him. He was still an eager enquiring soul; looking ever for something new, always appearing to tilt at windmills, but out of each bout bringing a measure of practical success and hastening to new encounters.

His thought was not to rest, but to devote his time more continuously to lecturing, more especially on the history of medicine. He knew his subject well and loved it. He was accurate, punctual, precise and unvarying in patience over detail, while the wealth of illustration, comparison, and simile he used was unequalled.

Perhaps the hardest thing in Evans's early retirement was the fact that he had to be torn from his laboratory. He was constitutionally incapable of idleness, and he was assiduous in his attendance at the Medical School. He wrote. He gave lectures. He carried on immense correspondence with people all over the world. He liked nothing better than having his friends to visit him and was always the most delightful and gracious of hosts. He had too much courage, too much urgency, to sink into the state of grumbling lethargy that often dims the later days of unemployed professors, but all his duties were self-imposed. He was as restless of body as of mind. He went to Japan, to South America and to Europe. And he was still an innovator.

In 1969 he inaugurated a series of lectures on his favourite subject to the medical students at the University of California (San Francisco) and thereafter introduced a number of guest lecturers who spoke on current research topics in medicine. In his opening address of the series he began characteristically:

'Gentlemen, the history of medicine, in these days, is what has happened since breakfast.'

These lectures became immediately popular and showed the richness of his scholarship and his familiarity with a great variety of scientific topics. Few of his contemporary anatomists have been so well versed in medical historical literature as was Herbert Evans. He knew the worthies and their writings from Hippocrates down. Apparently he never again quite gained the heights reached in the heydey of his genius, but he still spoke acceptably and with much of his old brightness to a large company of appreciative students. The senior class voted him 'Best Teacher' in appreciation of these lectures. Though he had never been a professional teacher of the history of science, no one would have questioned that he had as much right as any professor in America to be considered a representative of philosophy. He had been, as we say, through the mill; few anatomists could rival his acquaintance with the literature of the philosophy of science.

As his bibliography shows, Evans was not idle in retirement. Between 1952 and 1964 he continued to teach histology to the freshman medical students and published a series of works—partly endocrinological, partly teratological and partly bibliographic. These show his continuing interest in the lines of studies established after he went to Berkeley. His last publications in the field of endocrinology were two chapters in Harris

and Donovan's The pituitary gland (1966). These were on 'The physiology and chemistry of adrenocorticotrophin' with Lowell L. Sparks and Jonathan S. Dixon, and on 'The physiology and chemistry of growth hormone' with J. H. Briggs and Jonathan S. Dixon. The editors had also asked Dr Evans for an introductory chapter on 'The history of the pituitary gland' but although he gathered photographs of many of his contemporaries who had helped to create that 'History', and although he worked sporadically on the text it remained unfinished, largely because of the overwhelming mass of new publications that had to be assessed and evaluated.

To the end of his life Herbert Evans continued to exhort and stimulate the young people about him. In his annual and welcoming address to the new class of medical students, only a few months before his 88th birthday, 'he joyfully expressed his lively sense of the importance and fun of discovery.' Shortly afterwards a severe stroke terminated Evans's intellectual activities and ended his hopes of amassing yet another distinguished collection of rare books. For the next nine months he lingered on—cared for by a faithful secretary of an earlier day, Mrs Helen Peters—and though confined to bed or to a wheel chair, he continued to see and chat enthusiastically with his family, his colleagues and numerous friends from many countries who never failed to visit him whenever they were in the Bay area. But that brilliant mind was beginning to give way. He would often sit silent, pondering, and it was hard to rouse him. But when he was roused, the old curiosity and the old fire returned, apparently unabated. He was worn out at last, and as he lay staring fixedly under his shaggy white eyebrows, only waiting to follow the vivid company, in which he had played so spectacular a part, on to the stage of history, what was passing behind those blank eyes? This we shall never know, but whatever he saw or did not see, one person must have been in the shadows his daughter, Gail Evans La Forge.

Herbert Evans died at his home on 6 March 1971. His passing removes one of the most singular and influential scholars in endocrinology, in the history of science and in the physiology of reproduction. He was a giant who bestrode the domain with singular authority, profound learning and a highly idiosyncratic mind. He was generally acknowledged as the foremost student of the pituitary—*Time* magazine once dubbed him 'The premier antepituitarian'. His death has also removed an almost legendary figure from the endocrine scene and with the recent deaths of Bernard Zondek, P. E. Smith, Harry van Dyke, Bernardo Houssay, Oscar Riddle, C. N. Long, Arne Tiselius, J. E. Markee, F. Allbright, S. J. Folley, G. W. Harris and Emil Witschi, this branch of study has suffered very severe losses. Notably brilliant researches on the largest possible scale stand as records of Evans's achievements. These are finished; but his influence always, extraordinary, is still active. Only those who have known him and worked with him or under him can realize the extent to which this is true. Chauncey D. Leake [13], a close colleague and friend of Herbert Evans for over forty years has told us that he 'was particularly fond of the subtle artistry of Euripedes (484-406 B.C.). His favourite Greek drama was The Bacchae; let the last chorus provide his epitaph:

There be many shapes of mystery,

And many things God makes to be

Past hope or fear

And the end men looked for cometh not,

And a path is there where no man thought.

So hath it fallen here.

In writing this memoir we have been greatly assisted by many of Professor Evans's friends. We are particularly grateful to Dr Wm R. Lyons for valuable bibliographic information and for the use of the bibliography prepared by him; to Professors Chauncey D. Leake, J. B. de C. M. Saunders, Wm R. Lyons and Alfred E. Wilhelmi for permission to use their admirable necrologies from which we have borrowed freely; to Sir Charles Dodds, Bt, M.V.O., F.R.S. for the loan of his copy of A visit with G.B.S.; to Sir Alan Parkes, C.B.E., F.R.S. for allowing us to use the original transcript of his interview with Professor Evans and for the loan of bound volumes of the latter's publications; to Dr J. S. Perry and Dr Robert O. Scow, for help with the revision of the text and correction of the proofs, and to Mr D. W. Butcher, Librarian at the A.R.C. Institute of Animal Physiology, Babraham, for his invaluable assistance in many ways. Finally, it is to be recorded with regret that this memoir has been written by E.C.A. and G.W.C. only because Professor Evans's closest scientific friend in England, Professor G. W. Harris, C.B.E., F.R.S., died before he could do more than collect a few notes upon which to base a memoir to be written by himself.

E. C. AMOROSO

G. W. CORNER

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