Arthur St George Joseph McCarthy Huggett, 1897-1968

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ARTHUR ST GEORGE JOSEPH McCARTHY HUGGETT

1897-1968

Elected F.R.S. 1958

Arthur St George Joseph McCarthy Huggett, known to all his friends as Hugo, was born in what is now North Kensington on 23 April 1897, the only son of Arthur Henry Richard Huggett and his wife Helen Mary. He had one younger sister. His father was a Lecturer in Botany at the Goldsmiths' College and came of Kent and Norfolk stock. His mother was a McCarthy from the west of Ireland and came from the landed gentry. Only one of his forebears is known to have achieved distinction in science or the public service, a great-grand-uncle who pioneered the overland camel route between the Mediterranean and the Red Sea, on the way to India before the Suez Canal was made. His mother was an intelligent and public-spirited woman who was 39 years old when she married. She had been educated in France and Germany and was a prolific reader, interested particularly in history and politics. In Ireland, before her marriage, she had been an active supporter of Home Rule and afterwards was an early member of the Suffragette movement, speaking several times a week at street-corner meetings. During the First World War, when the battle for women's suffrage had been largely won, she joined the Labour Party, a courageous act in those days for a woman in her position. She became a member of the Kingston Board of Guardians in 1918, being specially interested in the problem of unmarried mothers and their children. She was greatly concerned with the welfare of others and indifferent to her personal comfort. Her husband, though not always agreeing with her views, gave her support and sympathy in her undertakings. Theirs was a happy home and they both made great sacrifices, especially during the war years, to enable their son to complete his medical education. Hugo was brought up in this environment in the Roman Catholic faith, which he later formally renounced.

He was educated until he was 12 years of age by a governess. Then he went for three years to Wimbledon College and from that to the City of London School. At Wimbledon he records that he was fortunate in being able to combine science and mathematics with history and classics under two inspiring masters. At the City of London School he joined the Classical Upper Fourth and later the science side. He had no scholarships at school. He played soccer and was a cross-country runner, winning the open mile on one occasion. He obtained an open Entrance Scholarship to St Thomas's
Hospital Medical School which he entered in 1914, and two years later he was awarded a Musgrove Scholarship. He qualified M.R.C.S. and L.R.C.P. in 1918 after a shortened war-time course. Huggett records his indebtedness during this period to John Fairbairn, the Senior Obstetrician, and to John Mellanby, the Professor of Physiology. He describes the former as 'a man of extreme imagination, the initiator of ante-natal clinics, no scientist but well aware of the problems of obstetrics and of his own limitations. A rare Scots wit.' The latter he said 'was intensely shrewd, half-Yorkshire and half-Scot, possessor of a caustic, penetrating but never malicious wit; he thought of the human being as a biological organism and biology as a branch of science linked to physics and chemistry and that therefore accurate physical chemistry was essential for understanding man and his pathology. This as early as 1906.' It is evident that both these men had a lasting influence upon him, for he states 'these two focused one's interest on physiology of the foetus, placenta and of pregnancy. Both... were inspiring teachers but both had something more.' Huggett served for a time as Obstetric House Surgeon at St Thomas's Hospital, presumably under Fairbairn.

Having completed his minimum medical qualification Huggett was called up for military service in 1918 and served as a medical officer with the R.A.M.C. on the Archangel expedition. After his release from service in 1919, he returned to the Department of Physiology at St Thomas's, graduating in the University of London, B.Sc. with first-class honours in 1920 and M.B. and B.S. in 1921. During this period he was Demonstrator in Physiology and engaged in research with Mellanby. The award of a junior Beit Fellowship (1922-1925) enabled him to undertake independent research and he embarked on the first of the long series of studies of foetal physiology which were to be his dominant interest throughout life. He remained at St Thomas's until his appointment to a Lectureship in Physiology at Leeds under Professor B. A. McSwiney in 1930. So highly was he thought of there that the following year he was made Reader in Pharmacology with the responsibility for developing that subject within the Department of Physiology. During his stay in Leeds he continued his researches on foetal physiology and also collaborated with Professor F. M. Rowe of the Department of Colour Chemistry on the anticoagulant properties of azo dyes. His knowledge of these led to his visiting Sir Joseph Barcroft's group in Cambridge and to collaboration with them. He was appointed to the chair of Physiology at St Mary's Hospital Medical School and returned to London in 1935, remaining there until his retirement in 1964 when he was made Emeritus Professor in the University of London. From 1964 until his death on 21 July 1968, he was Consultant Physiologist at the Animal Diseases Research Association, Moredun, Edinburgh, but this was a period when his health was declining rapidly. While he was at the Moredun Institute he tried to encourage physiological work and continued with some of his own research, but it was the impact of his insight and enthusiasm upon his colleagues which was his most valuable contribution.
Arthur St George Joseph McCarthy Huggett

The degrees of Ph.D. (1925) and of D.Sc. (1930) were conferred upon him by the University of London. He was Still Memorial Lecturer of the British Paediatric Association in 1951, de Lee Lecturer of the University of Chicago in 1953, Claude Bernard Lecturer at the Sorbonne in 1955 and Purser Lecturer at Trinity College, Dublin, in 1956. He contributed to many International Conferences and Symposia in several parts of the world. He was elected a Fellow of the Royal Society in 1958, a Fellow of the Royal College of Obstetricians and Gynaecologists in 1960, an honour of which he was particularly proud, and a Fellow of the Royal Society of Edinburgh in 1965.

Huggett travelled widely, examining, lecturing, and taking part in conferences, and he obviously enjoyed it. He was fortunate in that the opportunity came relatively early in his career to act as an examiner for the University of London at Overseas Universities with the object of maintaining common standards of medical training. He visited Australia, India and Egypt in this way and, later Nigeria, Uganda and Jamaica. Invitations to lecture, as his work became known, or attendances at conferences took him to most of the countries of Europe, to the U.S.A., South America and to Canada. A sabbatical year in 1953-1954 was spent in the United States, mainly in Baltimore working at the Carnegie Institution of Washington Department of Embryology and as visiting lecturer at Johns Hopkins University. He visited the Faeroes to investigate foetal whales, and Madagascar in the hope of determining the type of carbohydrate metabolism of foetal lemurs. He was an inveterate attender at conferences and rarely resisted speaking, a congenial companion and a stern critic of the behaviour of any of his fellow countrymen which fell below the high standards he expected of them when guests overseas. He enjoyed entertaining all and sundry and as a host was generous to a fault.

He married Margaret Mary Head in 1923. She died in 1934, leaving a daughter and a son. In 1938 he married Esther Margaret Killick, Professor of Physiology at the Royal Free Hospital School of Medicine and they had two daughters. She died in 1960. He married Helen Kemp Porter, F.R.S., Professor of Plant Physiology at Imperial College, London, in 1962. She, his four children, and six grand-children by his eldest daughter survive him.

Huggett went to St Mary’s in 1935, soon after the new Medical School building had been completed, to an almost moribund and minute department that had been kept going by the herculean efforts of A. C. Frazer, an Assistant Lecturer and the only full-time member of the staff. Huggett brought with him J. R. Hancock, whom he had trained at Leeds, as Head Technician, a post he still occupies. His exceptional technical skill was a great asset, not only in these early stringent days, but later when he became a valuable member of the post-war research team. This small staff ran courses in physiology, including physiological chemistry and histology, and also in pharmacology, which Huggett’s teaching experience at Leeds rendered him
competent to undertake and which was probably a factor in his appointment to the chair. This heavy burden of teaching, falling on only two full-time members of staff, is now shared by three full departments as well as a sub-department. A measure of their success in those early days can be judged from a tribute by Professor A. D. M. Greenfield who had entered St Mary’s as a student only a term or two before Huggett’s arrival. He says: ‘It is therefore remarkable that I had, as a student, good, satisfying courses in these subjects and that Hugo somehow managed to take a personal interest in us and to give us much encouragement. For example, in addition to all the work for the University exams, he encouraged a few of us to sit for the Primary exam for the F.R.C.S., which at that time could be taken before the qualification in medicine, and he somehow fitted in teaching for this and enabled us to pass. And still more he started up an honours B.Sc. course in 1936, which was just the right moment for me personally, and which made considerable calls on his energies.’ A. C. Frazer went to Birmingham in 1942 and Huggett recalled Greenfield to take his place. So far as physiology was concerned the staff had not been increased in the interval, but the position had been somewhat relieved by the formation of an independent sub-department of Pharmacology under H. G. Stewart, who later became the Professor.

Although St Mary’s was one of the first hospitals in the country to have had full-time chairs of Medicine and of Surgery, Huggett found that the administration had little interest in the preclinical departments or in encouraging research within them, and was disinclined to staff or equip them properly. Small wonder that Huggett with his enthusiasm for research and his vision of the scientific basis of medicine came into conflict with the Dean within and without the school. He conducted a campaign for improvement in the number and in the conditions of the non-professorial and of the technical staffs and for more adequate equipment. When the chair of Medicine fell vacant he played an active part in securing the appointment to it in 1939 of G. W. Pickering (afterwards Sir George). He had little time to carry on with his own researches during these early years but he did all in his power to promote research and to encourage his students to pursue it. The publications that then appeared from his department, though few under his own name, bear witness to his efforts. He remained at St Mary’s during the war, apart from a brief period when the medical school was evacuated temporarily to Manchester, and took an active part in air-raid precaution duties. Teaching went on, but once again development of the kind of research group he dreamt of was postponed. At the conclusion of the war Pickering’s presence and a new Dean opened up the long-awaited opportunities. Many new appointments were made and Huggett found it possible to get his foetal research going on a more adequate scale with a regular team consisting of D. A. Nixon, H. Britton and D. P. Alexander, together with J. R. Hancock. He welcomed collaboration, ‘which did not have to be on his own main theme, but could be on any aspect that could be
reasonably accommodated within the programme. By this generous policy he soon assembled an array of a dozen or more people, who were linked to various aspects of the work, but who had a considerable measure of independence’ (A. D. M. Greenfield, personal communication). ‘In season and out of season Hugo would promote research and encourage students to do it. Cooper (Professor K. E. Cooper) and Kerslake (Dr D. McK. Kerslake), for example, showed that there was reflex vaso-dilatation to radiant skin heating, and did the first part of their work while still medical students and in Hugo’s department’ (K. W. Cross, personal communication).

On the more personal side I cannot do better than quote two of his colleagues again. Professor Greenfield writes: ‘Hugo was seen as a man of great tolerance; people felt that they could discuss any topic with him. He was a great encourager of his young people; the only drawback was that he backed us so strongly that some of us wondered whether we were worthy of such strong support, or even felt pretty sure that we were not. He was ready to engage in combat for us on any reasonable issue. He was a kind person, who had a deep understanding of the personal problems that some of his staff faced from time to time. Hugo and Pickering were certainly, in my view, the two people with great influence on development at St Mary’s in the 1940’s and early 1950’s.’ Professor Cross writes: ‘He was good at promoting the welfare of his junior colleagues. One felt on occasions that he thought that all his geese were swans but this, if it is a fault, is at least on the right side.’ And again: ‘I think it is correct to say that he “fathered” a disproportionately large number of professors of physiology and of medicine.’ Certainly he was proud, and justifiably so, of the number of his students and staff who achieved scientific distinction. On his retirement his colleagues presented him with a list of publications appearing from the Department of Physiology during his occupancy of the chair; it comprises 259 titles of which less than one-third bore his name and provides impressive evidence of his success in stimulating research in many branches of the subject.

Apart from service on many Medical School and University Committees he served for 16 years on the Physiological Sub-committee of the Flying Personnel Research Committee of the Ministry of Defence under the Chairmanship of Sir Bryan Matthews. He was President of the University of London Mountaineering Club, in which he took a great interest and was largely instrumental in their acquiring a club hut in Snowdonia which bears his name.

Huggett’s first published paper, in collaboration with John Mellanby, appeared in the *Journal of Physiology* in 1923 [1).* It dealt with the adrenalin and vagal types of apnoea in cats and rabbits. It was concluded that adrenalin causes apnoea by bringing about constriction of the arterioles of the respiratory centre. Adrenalin apnoea could be prevented by the

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* Numbers in square brackets refer to the serially numbered Bibliography at the end of this memoir, p. 360.
intravenous injection of ergotoxin. Vagal apnoea was found to be comparable to adrenalin apnoea except that it could not be annulled by ergotoxin. In a further paper it was shown that injection of adrenalin did not have any effect on a variety of cranial and of spinal reflexes associated with voluntary muscles. It was concluded that the hypotheses that adrenalin produces local vasoconstriction of the blood vessels of the bulb was improbable and that it must bring about its effects on respiration by specific action on the cells of the respiratory centre and on them alone. Thus the authors came near, but failed, to find the carotid sinus reflex, which was discovered in the same year by Hering. A characteristically frank comment of Huggett's left in a note on these papers reads: 'Missed completely the carotid sinus reflex.'

Another study at this time concerned the effect of respiratory obstruction on the output of the heart of the cat. It was conducted partly at Cambridge in 1922, evidently to learn from Barcroft his method of measuring cardiac output in the intact animal. The obstruction used was a resistance of 5 cm of water, it having been found that 7 cm was sufficient to result in asphyxia. Inspiratory obstruction increased both the minute- and stroke-volumes of the heart and the oxygen consumption but the oxygen utilization per ml of blood fell. Expiratory obstruction produced exactly opposite results, as did combined inspiratory and expiratory obstruction. The pulse rate showed little change and the circulatory rate consequently was proportional to the output per beat.

Having found that adrenalin has no effect on various reflexes, Mellanby and Huggett were dubious of Hunter and Royle's hypothesis that the plastic tonus of voluntary muscle is controlled by the sympathetic nervous system. Therefore, they extended their enquiries to the effects of the drugs known to stimulate or paralyse the nerve endings of the sympathetic, parasympathetic and somatic systems respectively on muscle tonus in the intact and decerebrate cat. They found that drugs affecting the sympathetic and parasympathetic systems had no effect on the plastic tonus of the decerebrate cat, but that curare, paralysing the somatic nerve endings, abolished rigidity. They concluded that voluntary muscle tonus, whether in the intact or decerebrate animal, is the result of somatic nerve impulses and not of sympathetic impulses.

Next Mellanby and Huggett turned their attention to the distribution in the intestine of the goat of secretin and to the form in which it is present. They found that it is absent from the gastric mucosa but present in large quantity in that of the proximal two-thirds of the small intestine and in relatively small quantity in the distal third. Thus it is present well behind the region on which the acid of the gastric chyme could act. It exists in a preformed state in the mucosa and hydrochloric acid is not necessary for its formation.

This paper concluded the early work published jointly with Mellanby and all of which appears to have arisen from established interests of the senior author. The award of a Beit Fellowship in 1922 freed Huggett to develop his own interests. He started to investigate the physiology of the foetus and
the first paper appeared under his own name in 1927 [8]. Thereafter all his publications relate to problems of foetal and placental physiology, with the exception of a series of studies on anticoagulants carried out between 1930 and 1934 while he was at Leeds. Although the earlier papers on foetal physiology precede these, it is convenient to consider his work on blood-clotting at this point, rather than to break the continuity of his main contribution for chronological considerations.

The anticoagulant action of certain bisazo dyes was observed in 1930 but no attempt had been made to explore their mode of action in this respect. Huggett undertook this problem. He described (with H. Silman, 1932 [14]) the anticoagulant effects of the dyes Chlorazol Sky Blue FF and Chicago Blue 6B, which had been observed to have this property, and showed that they inhibited the activation of thrombin by the thromboplastic substances. Next (with F. M. Rowe, 1933 [15 and 16]) he investigated this property of a number of azo-dyes with the object of finding ones which produced less discoloration of the blood, and found that many of them were anticoagulants, a property which appeared to depend on their chemical structure but not on their molecular weight. Impurities always present in the commercial preparations of the dyes modified their effects considerably. It was found that Chlorazol Fast Pink BKS was the most efficient of the dyes in vitro, was more efficient than the preparations of heparin then available and was not appreciably toxic. An isomer was even more effective as an anticoagulant but unfortunately was more toxic. The most effective anticoagulants were disazo direct dyes prepared from tetrazotized diamines coupled with aminonaphthol sulphonic acids. The effects of salts, NaCl and Na₂SO₄, which are the chief impurities in the dyes, on the anticoagulant action was examined also [20]. It was shown [19, 21] that the dyes inhibit both the thrombin and the thromboplastic substances without destroying them and use was made for the first time of the prothrombin time. The trypanocidal drug Bayer 205 (Suramin) was known to have anticoagulant properties and a chemical structure resembling the azo-dyes. Consequently Huggett (with S. F. Suffolk [23]) investigated the effects of these dyes on trypanosomes and found that they are excellent trypanocidal agents, only slightly less effective in this respect than Bayer 205 though somewhat more toxic.

In 1926 Huggett published a short note on 'Factors influencing the foetal respiratory centre' [7], his first incursion into the field of foetal physiology which thereafter was to become his main preoccupation. It was shown that the foetal respiratory centre responds to the same nerve stimuli as that of the adult but has a higher threshold of response, even after decerebration, thus showing that it is not due to cerebral inhibition. The following year a further paper [8] appeared dealing with 'Foetal blood-gas tensions and gas transfusion through the placenta of the goat', in which it was clearly shown, and has since been generally accepted, that the transmission of oxygen and carbon dioxide across the placenta is due to diffusion. It had been known for
many years that maternal asphyxiation can result in so lowering the maternal arterial oxygen content that oxygen from the foetal blood passes back through the placenta to the maternal blood. Huggett, reinvestigating this problem, introduced the method of differential tonometry for the direct comparison of gas tensions in different blood samples and showed by this means that maternal asphyxiation can so elevate the carbon dioxide tension of the maternal blood that that of the foetal blood in the umbilical vein exceeds that of the blood in the umbilical artery. Clearly the passage of carbon dioxide, like that of oxygen, across the placenta is reversible. He showed also that normally the CO₂ concentration in the foetal blood is greater than that in the maternal blood. The results were of a magnitude that could be accounted for by diffusion, but not by an active secretory mechanism. It followed also from the results that the foetal blood undergoes a 50 per cent mixing in the right heart. The standard dissociation curves for the foetus were unlike those for adult animals and indicated that CO₂ has a smaller effect on the oxygen dissociation curve of the foetus than it has on that of the mother, a point which excited Barcroft’s interest (1946, Barcroft, J., *Researches on pre-natal life*, p. 166. Oxford: Blackwell). Perhaps the greatest importance of these two papers from the historical viewpoint resides in the method employed. This was to carry out Caesarean section of a goat during late pregnancy submerged in a warm saline bath so that the exposed foetus remained submerged but still attached to the functioning placenta, thus rendering it possible to carry out a wide variety of experiments on both mother and foetus. The method of Caesarean section for investigating the functions of the living foetus had been practised by Zuntz and Preyer in 1877, but it was left to Huggett nearly 50 years later to revive it, for the first time in this country. It was to prove the beginning of a new era in the study of foetal physiology. It provided him with a technique which, with minor modifications, was to make possible his studies on foetal carbohydrate metabolism. It was adopted by Barcroft and was the means of enabling the great advances in foetal vascular and respiratory physiology to be achieved by the Cambridge School. Thus it was the start of two important lines of advance which, in their turn, have stimulated research in foetal physiology all over the world.

Further studies of foetal respiratory reflexes in the goat followed [10, 12]. It was shown that the foetal goat central nervous system is sufficiently developed 4 to 6 weeks before full term to respond to strong stimuli. Stimulation of a nerve which excites respiratory movements in the adult excites them also in the foetus, while those, such as vagal stimulation, which inhibit them in the adult do so also in the foetus. The response achieved by the premature foetus is irregular and laboured, lacking the regular adult rhythm, and a stronger afferent nerve stimulation is required to excite it. The response ceases soon after a period of stimulation but the interval of after-discharge is more prolonged the nearer full term is approached, and then the normal state of respiratory quiescence is resumed. Foetal apnoea is
facilitated by this high threshold of afferent stimulation, by such stimuli being subliminal in normal intra-uterine conditions and it is not due to cerebral inhibition.

The next paper dealing with the foetal blood volume and its oxygen capacity was published jointly with R. H. Elliott and F. G. Hall and is dated from the Physiological Laboratory, Cambridge, and the Department of Physiology, Leeds [18]. A note acknowledges Professor J. Barcroft’s ‘personal aid’. Blood volumes were measured by the dye method with chlorazol sky blue FF and the experiments were performed using Huggett’s method of Caesarean section in a saline bath. It may be inferred that his expertise in both these techniques was the reason for this collaboration. It was in or about 1932, when this research would have been in progress, that Barcroft adopted Huggett’s method of Caesarean section (see Obiary Notices of Fellows of the Royal Society, 6, 327). This paper is notable for providing the first measurements of the total volume of blood in the foetus and placenta together and for showing that it is nearly constant at about 9 per cent of the weight of the tissues throughout gestation, a quantity comparable to that of the adult. Since the weight of the placenta was shown to exceed that of the foetus for the first two-thirds of gestation, and thereafter to decline, while that of the foetus was increasing very rapidly, the distribution of the total volume between placenta and foetus varied. It was shown also that the oxygen capacity of the foetal blood rose throughout gestation, being about 13 vol. per cent from the 11th week onwards but appreciably lower at earlier foetal ages. Correspondingly the total oxygen capacity of the circulation was about 1 per cent of the combined weight of foetus and placenta after the 11th week. It was found also that the oxygen carrying capacity of the corpuscles was higher during the last third of gestation than earlier or than it is in the adult.

Subsequently, when at St Mary’s Hospital Medical School Huggett and some of his colleagues returned to the subject of foetal circulation [37, 38, 44], describing a method of measuring directly the rate of blood flow in the umbilical cord of the sheep, which had previously been estimated only indirectly. It was shown that between 60 and 143 days of gestation the flow ranged from 250 ml min \(^{-1}\) (kg foetal wt)\(^{-1}\) at the earlier ages to about 130 ml min \(^{-1}\) kg\(^{-1}\) at the later ages and that there was a relationship of the rate of flow to the percentage weight increase per day. This completed his contributions to foetal circulatory and respiratory physiology.

Much of Huggett’s work has been concerned with the carbohydrate metabolism of the foetus. He became interested in this subject early in his career and it remained a dominant interest to the end of his life. The first communication concerning the carbohydrate metabolism of the placenta and foetus was made to the Physiological Society in 1928 and the full account appeared the following year [9, 11]. It was known that glycogen is present in quantity in the maternal decidual tissue of the rabbit placenta and is maximal about the 21st day of gestation and that it is relatively constant in
comparison to the maternal liver glycogen. Huggett confirmed this constancy under a number of experimental conditions. He found that the placental glycogen is unaffected by carbohydrate feeding or by injection of glucose alone or with insulin, which raise the maternal liver glycogen. Depletion of the maternal liver glycogen with insulin treatment had no effect on the placental glycogen, though continued insulin treatment did result in a slight fall. Thyroid feeding did reduce the glycogen content of the placenta but not proportionately to the reduction in the maternal liver and muscle glycogen. Pyrexia induced by tetrahydro-β-naphthylamine or anaesthesia with ether and amytal decreased the placental glycogen. It was concluded that the glycogen of the maternal placental tissues of the rabbit provide a reserve for the foetus which the mother normally cannot draw upon except in extreme cases of disordered metabolism over a prolonged period. Examination of the products of autolysis of placental glycogen [17] showed that it yielded approximately two-thirds glucose and one-third polysaccharide, and only traces of lactic acid, showing that the metabolism was unlike that in muscle and that it is not used as a source of energy for the placenta itself. Experiments with ¹⁴C-labelled glucose injected intravenously into pregnant rabbits [77] showed that the placental glycogen is in a state of continuous exchange with the maternal blood glucose. The percentage of glycogen was much higher in the maternal decidual tissues of the placenta than in the foetal placental tissues, but the glycogen of the foetus and of the foetal placenta was labelled more rapidly than that of the maternal decidua. Later he demonstrated [97] that in the rabbit the maximum glycogen content of the placenta is attained at the time when the final rapid growth in weight of the foetus is beginning and that its subsequent sharp decline to full term is coincidental with this rapid growth phase. In the rat a similar time relationship was shown. Rats, mice, monkeys and man resemble the rabbit in having substantial quantities of glycogen in the placenta and these have been called glycogenic species to distinguish them from species lacking placental glycogen. In the rat the distribution of glycogen in the placenta between the maternal decidua and the foetal trophoblast is not altered or its concentration in the tissues increased or diminished by foetal death when this occurs under circumstances which permit the continued growth of the placenta [33, 35].

Many years later he had an opportunity of studying the carbohydrate metabolism of monkeys. While on a visit to Baltimore, in collaboration with colleagues at the Department of Embryology of the Carnegie Institution of Washington and at Johns Hopkins University he investigated the transmission of sugars across the placenta in monkeys and in women. An elegant technique of cannulating the interplacental artery of the rhesus monkey while the foetus was in utero and the amnion was intact was devised [70]. Using this technique the foetal blood could be sampled for periods of up to 5 hours. The maternal blood glucose levels approximated to normal human levels. The foetal blood glucose level was 100 mg per cent or less and was
usually a little less than the maternal, and the fructose level of the foetal blood was up to 6 mg per cent. Glucose injected intravenously into the mother appeared rapidly in the foetus, but was unaccompanied by any rise of blood fructose in either mother or foetus. Labelled glucose injected intravenously into the foetus in small quantities appeared rapidly in the maternal blood and this foetal maternal transport was unaffected by heavily loading the maternal circulation with glucose and the consequent large simultaneous maternal foetal transport. Labelled fructose given to the mother appeared rapidly in the foetal blood but there was some evidence of glucose competing with it for transport. Experiments were also carried out on women undergoing Caesarean section, cannulation of the umbilical vein enabling the foetal blood to be sampled for periods of up to 11 minutes before the foetus was removed. The results were in line with those obtained from the monkeys. Thus, the anthropoid placenta, unlike that of the sheep, does not form fructose from glucose when foetal hyperglycaemia is produced and the normal primate foetal blood sugar is glucose. Moreover, the passage of glucose from foetus to mother against the concentration gradient was such as to be consistent with an active transport system as was suggested from Huggett’s laboratory by Widdas to account for the kinetics of this phenomenon in sheep.

Although Claud Bernard in 1854 believed from its laevo-rotation that fructose was present in the amniotic fluid of the cow, and other workers subsequently claimed to find it in foetal fluids, it was not until 1946 that its presence was unequivocally demonstrated by Bacon and Bell in the blood of the foetal sheep. They showed that both glucose and fructose were present. This was an important landmark in our knowledge of the carbohydrate metabolism of the foetal ungulate and it stimulated much of Huggett’s subsequent work. Immediately he applied his method of Caesarean section of pregnant sheep in a saline bath to the study of foetal sugars. The first paper appearing in 1949 [46] dealing with the maternal and foetal bloods, and the amniotic and allantoic fluids at various stages of gestation from the 49th day to near term. No determinable amount of fructose was formed in the maternal blood, but the amount of fructose in the foetal fluids was substantial and tended to exceed the values for non-fructose reducing substances, most of which were assumed to be glucose. There was no correlation between the amounts of either fructose or non-fructose reducing substances in the amniotic or allantoic fluids with those in the foetal blood, but the values for both categories of carbohydrate in both foetal fluids tended to be higher than the foetal blood sugar values.

The next step was to determine the site of formation and origin of the foetal fructose. A similar experimental technique was used but with spinal anaesthesia of the ewe supplemented with intravenous pentothal, which was shown not to affect the blood sugar level. Using late foetuses which were viable and could be maintained in the bath breathing themselves with their mouth and nose above water after detachment from the placenta it was
possible to study the carbohydrate metabolism in both the detached foetus and in the placenta isolated from the foetus by pump transfusion; by using twin pregnancies one foetus could serve as control for the other. Thus a flexible and elegant experimental procedure was attained and used to good purpose. It was shown by these means [47, 56] that hyperglycaemia induced in the ewe by intravascular injection of glucose was followed rapidly by a parallel but smaller foetal hyperglycaemia and by a delayed but prolonged foetal hyperfructosaemia. The foetal blood glucose level never exceeds that of the mother, but the sum of the foetal glucose and fructose levels may do so, thus explaining the observation that total foetal blood sugar levels may exceed the maternal. Direct injection of glucose into the umbilical vessels resulted in a similar delayed but prolonged foetal hyperfructosaemia, but although there was accompanying rise in maternal blood glucose levels, showing that the placenta is permeable to glucose in both directions, no detectable quantities of fructose reached the maternal blood. Hyperglycaemia in a detached foetus did not result in hyperfructosaemia, the initial fructose level falling gradually, but perfusion of the placenta isolated from the foetus with hyperglycaemic blood resulted in hyperfructosaemia in the placental blood. This was a clear demonstration that the fructose was formed in the placenta and explained the rapid disappearance of fructose from the blood which is known to occur after birth. Fructose when injected into the maternal circulation was shown to reach the foetal circulation but more slowly than glucose. Thus the placenta of the sheep is permeable to fructose in only one direction, though freely permeable to glucose in both directions.

The use of $^{14}$C-labelled glucose [59, 75] confirmed that foetal fructose is formed from glucose, and that it is formed even when the blood glucose is at normal levels. The rate of formation of fructose is greater than can be accounted for by the rise in fructose concentration in the foetal blood when blood sugar levels are normal, showing that fructose is being utilized under these conditions at a rate of approximately 1 per cent per min. The rate of transfer of glucose from mother to foetus with maternal hyperglycaemia is over 70 mg/min, but there is an accompanying rapid transfer back across the placenta, resulting in a net transfer considerably less than that which might occur if the process were simply diffusion. By means of placental perfusion experiments in which the perfusion fluid either traversed the placenta only once and was then collected, or was recirculated through the placenta [61, 76] these results were confirmed and it was shown that under these conditions the rate of formation of fructose in the placenta is constant at 8 to 13 mg/min, irrespective both of the maternal and foetal blood sugar levels. Foetal hyperfructosaemia never occurs without foetal hyperglycaemia, but it does occur without maternal hyperglycaemia when the foetal hyperglycaemia is brought about by direct injection of glucose into the foetal circulation. Maternal glucose passes first into the foetal blood and is then converted by the placenta into fructose. Since the rate of formation of
fructose is so constant the foetal hyperfructosoaemia would appear to result from decreased utilization of fructose by the placenta or foetus in the presence of excess glucose, indicating preferential utilization of glucose.

Two findings of this earlier work were reinvestigated subsequently. The reducing sugars of the amniotic and allantoic fluids of the sheep had been determined as total reducing sugars and fructose, the non-fructose part having been assumed to be mainly glucose. Re-examination of these fluids [99], testing for both glucose and fructose as well as total reducing substances, showed that glucose was present only in very small quantities and that almost all the non-fructose reducing substances were other than glucose. It was suggested that as foetal urine contributes to these fluids the low glucose content may have been due in part to reabsorption in the renal tubules. Secondly, the estimation of the constant output of fructose by the perfused sheep placenta had been determined in preparations in which maternal, rather than foetal, blood containing initially little or no fructose had been used as perfusate. It had been suggested that the consequent subnormal concentration of fructose in the perfused blood resulted in an increased fructose production. This was tested by perfusing sheep placentae with blood of different fructose concentrations [105] and it was found that fructose production was suppressed by high fructose concentrations in the circulation.

The experiments with isotopically labelled glucose had shown that glucose was a principal, and possibly the only, precursor of the foetal fructose. The next step was to enquire if the conversion of glucose to fructose proceeded by the route already long established for many tissues, namely, phosphorylation of glucose by hexokinase followed by conversion to fructose-6-phosphate by isomerase and loss of phosphate by phosphatase action. Hexokinase seemed to be inadequate in quantity, and isomerase had not then been demonstrated, in sheep placenta and alkaline phosphatase though present, was less in quantity than in the placentae of species which have little or no fructose in the foetal blood. It had been suggested that the path might be that by which fructose is formed in the seminal vesicles, glucose $\rightarrow$ sorbitol $\rightarrow$ fructose by means of aldose reductase and sorbitol dehydrogenase and it had been shown that aldose reductase but not sorbitol dehydrogenase was present in the sheep placenta, that sorbitol was present in the foetal blood and sorbitol dehydrogenase was present in the foetal liver. It had been suggested on this basis that glucose was converted to sorbitol in the placenta and the sorbitol converted to fructose in the liver. It was confirmed [96] that the perfused foetal sheep liver can convert sorbitol to fructose, but that it could not convert glucose, galactose or inositol to fructose. Fructose is not metabolized in the foetal liver and little is metabolized until five days after birth. Huggett and his associates [106] also confirmed that D-sorbitol was indeed formed in the perfused sheep placenta, but that the concentrations observed were insufficient to provide for an adequate production of fructose by the liver. Using $^{14}$C-labelled glucose,
Fructose and sorbitol in the perfusate it was shown that glucose was both rapidly metabolized and readily transmitted to the maternal circulation. Ten to 20 per cent of the activity in the glucose administered appeared in fructose, but hexitol was also strongly labelled and in one case glycerol, although inositol was not labelled. The fructose and sorbitol were metabolized scarcely or not at all in the placenta and transmission to the maternal circulation was very small. On the basis of these results it was concluded that fructose was formed mainly or entirely from glucose in the placenta and that this might occur via sorbitol within the cells if these are impermeable to sorbitol. Huggett had shown in 1959 [97] that the maximum amount of fructose in the sheep conceptus coincides in time with the middle of the period of final rapid growth of the foetus, much as do the glycogen maxima in the rabbit and the rat. Evidently both fructose and glycogen, according to whether the species is fructogenic or glycogenic, are reserves not normally available to the mother, that are utilized more rapidly than they are produced during this period of foetal growth. It had been shown that the horse and the pig, as well as the ox, sheep and goat, were species in which fructose was the principal blood sugar, and that the whalebone whales also fell into this group, whereas all other species examined at that time had little or no fructose in the foetal blood. The phylogenetic implications of these findings intrigued Huggett and he set out to increase the number of species that could be assigned to one or other group. He defined fructogenic species as those in which the fructose concentration in the foetal blood exceeded 10 mg/100 ml and was even greater in the amniotic and allantoic fluids. They were further characterized, where it could be determined, by the conversion of intravenous glucose into fructose. He added to the list [94, 98] of fructogenic ungulates Père David’s deer, the kob antelope, the giraffe, both dromedary and bactrian camels, the llama, hippopotamus and rhinoceros, and to the Cetacea, both fin and sci among the whalebone whales, the pilot amongst the toothed whales. He also showed that the three-toed sloth amongst the edentates belonged to the glycogenic group. This evidence tended to support the derivation of the Cetacea from the same root stock as the Ungulata after this had diverged from the ancestral Carnivora. However, it was known that some glycogenic species, notably man and monkeys had smaller quantities of fructose in the foetal blood, although they had much glycogen in the placenta and converted glucose to glycogen rather than to fructose. He was interested to know to which group the lower Primates belonged and even visited Madagascar in the hope, which proved unsuccessful, of investigating this problem in the lemurs of that country. However, later, he had an opportunity of examining Galago [104] and found that it was essentially fructogenic. This finding, surprising from a phylogenetic viewpoint, led to the suggestion that fructogenesis might relate rather to placental structure since all those species in which it was known to occur had epitheliochorial or syndesmochorial placentae.
Huggett was deeply interested in problems of foetal growth. First, he explored the possibility that maternal pituitary growth hormone might affect the growth of the foetus (with Frazer and Wohlzogen [42]). Crude extract of anterior pituitary containing largely growth hormone, together with some gonadotropins, was injected daily into pregnant rats which were killed at full term. The foetuses of those injected only from the 10th day of gestation onwards were of normal weight at autopsy, but those injected from conception date were smaller, being the same weight as normal foetuses 4-5 days younger, probably because of delayed implantation induced by the gonadotropins. All the injected animals showed gains in maternal weight. It was concluded that growth hormone did not affect foetal growth, either because it did not traverse the placenta or else because the foetuses did not respond to it.

The supply of iron to foetal and newborn rats was examined by tracer experiments with $^{59}$Fe (with Widdes [49]). It was found that the young rat obtains most of its iron from the milk after birth and relatively little before birth, contrary to what was believed previously. Although the iron/weight ratio actually falls continuously during the last week of gestation and the first three weeks of lactation this is due to the growth increase exceeding that of total iron, which nevertheless in the three weeks after birth is double that of the three weeks of gestation. A paper appearing posthumously (Frazer and Huggett [107]), was intended as a test of Hammond's theory that tissues with the highest metabolic rates received priority in the supply of available nutrients. If this thesis held, then changes in the supply of nutrients during pregnancy should result in the increase or decrease being shared equally between the maternal and foetal tissues. Four groups of pregnant rats were used, one being fed at a level just sufficient for a non-pregnant adult (10 g/day), one at a still lower level (7 g/day), one was given pituitary growth hormone and, together with the controls, fed ad lib., the hormone treated group having an increased intake in consequence. It was found that whether the intake of food was lowered, normal or increased, the increase in the conceptus weight during the last half of pregnancy was related to the total maternal weight increase as:

$$y = \frac{x}{4} + 4.5n,$$

where $y$ = total conceptus weights at term, $x$ = total tissue increase over the last eleven days of pregnancy, and $n$ = the number of foetuses, when $x > 20$ g. This equation did not hold when $x < 20$ g, but $y$ never fell below 4.5 ($n + 1$). These results were considered to confirm Hammond's theory of the partition of nutrients.

The relation of foetal weight to age in sheep was examined for the purpose of checking the ages of foetuses used in his experiments (with W. F. Widdas, 1951 [57, 58]). It was found that the cube root of the weight was related linearly to age from the 50th day of gestation to full term. The extrapolation
of this line cuts the time axis. The relation can be represented by the expression \[ W(t-t_0) = a(t-t_0), \]
where \( t_0 \) is the interval between conception and the age at which the line cuts the axis, \( t \) is the age from conception and \( W \) is the weight. It was found that a similar relation held for those other species, mouse, rat, rabbit, guinea-pig, cow and man, for which data were available in the literature. The constant \( a \), which determines the slope of the line, was characteristic of each species, but \( t_0 \) bore some relation to the length of gestation as a fraction decreasing as gestation increased. Thus it is possible to make an approximate estimate of \( t_0 \), knowing the length of gestation, and hence if the birth weight is known, the value of \( a \) can be estimated with an error of probably not more than 15 per cent for species with short gestations and 10 per cent for those with long gestations. The value of \( a \) for all the primates from lemurs to anthropoids for which data were available was found to be remarkably close to that of man and was less than that for almost all other mammals. The value of \( a \) for the blue whale was the greatest, the rate of growth of the foetus being at least 10 times as fast as that of other mammals and 500 to 1000 times that of man. It was shown subsequently (with J. F. D. Frazer, 1959 [93]) that, unlike primates, the values of \( a \) in the Cetacea differ from species to species, so that birth size in them is determined largely by the growth rate, rather than the length of gestation; the opposite of that in the Primates, where the growth rate is constant but the length of gestation varies. The porpoise appears to have the slowest growth rate, slower even than that of man, so that the whales span the whole range of mammalian foetal growth rates [89, 90]. This work is often quoted in the literature and has provided those working on foetuses of unknown age with a convenient means of estimating the approximate age from the weight.

Much more extensive data obtained from the International Whaling Statistics covering most of the principal species of both whalebone and toothed whales have been considered in a posthumous paper (Frazer & Huggett [108]) using foetal lengths instead of the cube roots of weights. It was found that in both groups greater birthweights were attained by increased foetal growth rates rather than by longer gestation periods. The whalebone whales had the greatest growth rates and the shortest gestation periods of 10.5 ± 1.5 months, and in the rorquals the largest species actually had shorter gestation periods than the smaller species. The toothed whales had lower growth rates associated with longer gestation periods of 14 ± 2 months. It was suggested that as the whalebone whales tended to penetrate farthest into Arctic waters in search of their specialized crustacean food and then to migrate seasonally into warmer waters, gestation periods of less than 12 months were essential. The timing of pregnancy in them was such that early pregnancy coincided with maximum nutrition and accumulation of fat, whereas during late pregnancy the females stop feeding and lose body fat to the foetus when its growth is maximal. The larger toothed whales, feeding mainly on squids, live mainly in warmer waters and seasonal requirements are less exacting. Consequently the larger species tend to have
longer gestation periods with foetal growth rates not greatly exceeding those of the smaller species and very much less than those of the whalebone whales.

It was thought that the great size of whales rendered possible by the aquatic environment might account for the need for this wide variation in foetal growth rates. This supposition raised the question of whether similar variation in foetal growth rates occurred in any groups of land mammals. The original finding of similar foetal growth rates amongst related species of land mammals [57, 58] was based largely on related species that did not differ greatly in size. Accordingly a further study was made (Frazer & Huggett [109]) to determine if there was a correspondence in foetal growth rates for groups of land mammals within which there were relatively large size differences between related species, such as the Carnivora, Ungulata and the Rodentia when a wider range of species were considered. It was found that there were marked variations in growth rates under these circumstances amongst members of a particular order, sub-order or even genus of land mammals, although none attained the specific foetal growth rates found among the larger whales.

Huggett published also a number of short notes on technique, mainly on methods of determination of blood glucose levels. As well as his original contributions, he published many lectures and reviews on aspects of foetal physiology of which the most valuable are his articles in the British Medical Bulletin on ‘Some applications of prenatal nutrition to infant development’ [36] and ‘Carbohydrate metabolism in the placenta and foetus’ [97], his lecture on ‘The physiology of parturition’ [67], his contribution to a Cold Spring Harbor Symposium on ‘The transport of lipids and carbohydrates across the placenta’ [71] and his Solomon Theron De Lee lecture on ‘Growth, pregnancy and carbohydrate metabolism’ [73]. His review of the book Researches on prenatal life, published by Sir Joseph Barcroft just before he died, is a warm appreciation of that great man’s contribution to foetal physiology. Huggett contributed also, in collaboration with Sir John Hammond, a valuable chapter on the ‘Physiology of the placenta’ to the third edition of Marshall’s Physiology of reproduction [63].

There can be no doubt that Barcroft and Huggett, the one wholly and the other partly Irish, working simultaneously but essentially independently and on different aspects of foetal physiology, the one at Cambridge and the other in London, were largely responsible for the revival of interest in this subject. The great advances in this field that have been made during the last 40 years in this country, in the United States of America and in Europe can be traced to the stimulus which their work provided. Huggett’s part in this revival has tended to be overshadowed by that of Barcroft, who was far better placed for facilities and to attract recruits to his school. Yet Huggett’s contribution, with the resources available to him, was great, though the recognition he received during his lifetime was relatively meagre. His paper in 1927 on foetal respiratory exchange in the goat was the starting-point of this revival, though his major personal contribution was the long series of papers on the
carbohydrate metabolism of the placenta and foetus. He built up around himself at St Mary's a notable school whose members are continuing to extend our knowledge of various aspects of foetal life. His place in the history of foetal physiology is honourable and secure.

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The photograph is by Walter Bird.

F. W. R. Brambell

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