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Maternal blood glucose and the baby. The origins of the Hyperglycaemia and Pregnancy Outcome study

The Scott-Heron Lecture at the Royal Victoria Hospital – 17 January 2001

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It is a great honour to be asked to give the Scott-Heron Lecture at the Royal Victoria Hospital. The list of lecturers since the first in 1957 comprises a formidable catalogue of distinguished medical names from all over the world. I remember as a medical student hearing the first lecture, on Smallpox in Ireland, by Sir William McArthur who was renowned for his remarkable visual memory and who gave his talk without notes. Little did I think that I might find myself in the same position over 40 years later. I am particularly honoured to be only the fifth serving member of the Royal Victoria Hospital staff to be invited to give this lecture.

The topic, Hyperglycaemia and Adverse Pregnancy Outcome, (HAPO) represents the story of my research interests over those 40 years, which range across a number of clinical boundaries including endocrinology, medical obstetrics, nutritional paediatrics and a great deal of epidemiology. The lecture was endowed by the generosity of Dr Francis Hugh Scott who died in 1946. He had practised as a family doctor in the district dispensary in Saintfield, County Down, where he was the predecessor of the present Dr James McKelvey's father. Dr James McKelvey himself remembers as a small boy meeting Dr Scott and being very impressed by his large motor-car. Dr Scott lived in a house in the Main Street in Saintfield as a bachelor, with a maid and a chauffeur who drove the big white car. The house is still there in the Main Street; now painted a rather dark brown colour, just opposite the parish church (Fig. 1). Dr Scott had a distinguished undergraduate career, winning the Malcolm Exhibition at the Belfast Royal Hospital and the gold medal at the Ulster Hospital for Children and Women. He qualified in 1891 by passing the

Fig 1. Saintfield Main Street, December 2000.

Scottish Triple Conjoint Diploma which was often taken by Belfast medical students at that time as the trip to Dublin to sit the MB BCh BAO examination of the Royal University of Ireland was considered more difficult and passing less assured. Also the triple qualification, although not a University degree, looked most impressive on a professional plate – LRCPEd, LRCSEd, LRFPS Glas. After general practice for a while in the south of England he was appointed to the district dispensary in Saintfield and worked there for the rest of his professional career. When he died in 1946, he left a legacy of £3,000 to the Royal Victoria Hospital for educational purposes. By careful investment this legacy has increased considerably in value and is maintained in both a capital and a revenue account under the supervision of the Chairman of the Medical Staff Committee. Dr Scott was buried in his mother's family mausoleum in Killyleagh Churchyard, the Heron family being long established in County Down. One of the early Herons was a joint founder

of the Ulster Bank, and a major donation to this hospital by another Heron enabled the top floor of 'A' Block to be built when it was known as the Heron Clinic for private patients. Major donations and legacies from wealthy families are still made to this hospital, but not any longer to the general funds of the hospital and often these donations are earmarked for a particular disease or specialty. This has made the continued funding of the Royal Victoria Hospital Clinical Research Fellowships increasingly difficult over the past number of years as these Fellowships have been funded from the general undefined Trust Funds of the hospital, and with the recent fall in financial interest rates the funds available for Clinical Research Fellowships have become severely limited.

WHERE ARE WE COMING FROM?

The HAPO Hypothesis states that

"hyperglycaemia in pregnancy less severe than overt diabetes mellitus is associated with increased risk of adverse maternal, fetal and neonatal outcomes that is independently related to the degree of metabolic disturbance".

The story begins with Dr Heinrich Bennewitz in 1823 at the Charité Hospital in Berlin[1] who was responsible for the delivery of a 12 lb baby to a patient who had developed thirst and polyuria in her pregnancy (Fig. 2). There was no measurement of blood glucose at that time, but he was able to demonstrate the presence of large quantities of sugar in her urine by the simple expedient of boiling this up in a saucepan and producing a treacle-like substance which he carefully weighed. The outcome of the pregnancy was not good. The baby died because of obstruction during delivery because it was so large. Dr Bennewitz wrote the case up as his thesis for the degree of doctor of medicine at the University of Berlin, but no further documentation either of his career or of

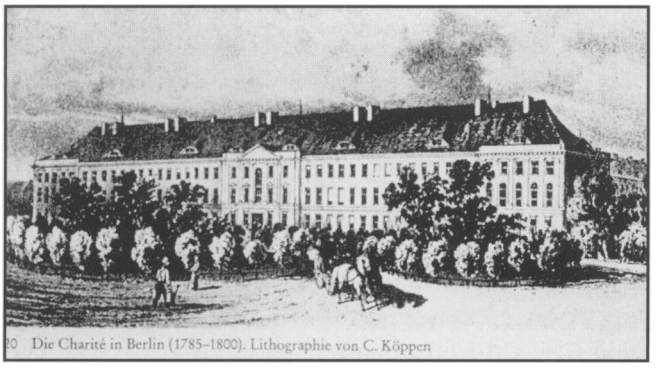

Fig 2. Charité Hospital, Berlin (1785-1800).

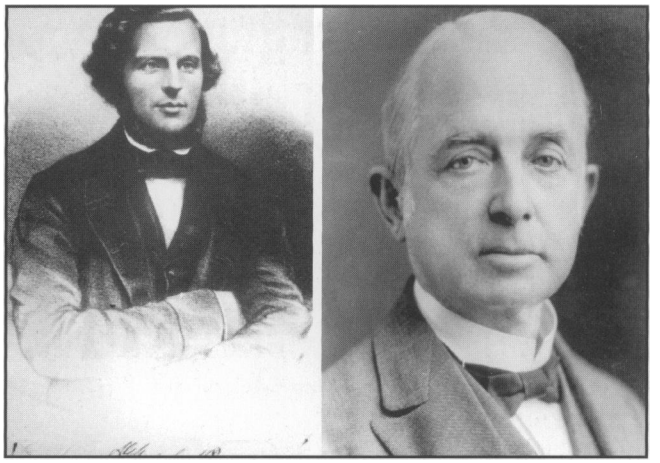

Fig 3. Dr Andrew Malcolm (1856)/Professor J A Lindsay (1923).

the future outcome of the mother has been found. The thesis, in Latin, was discovered in an archive in Germany in 1986, and was translated into English at the Department of Latin at the Queen's University of Belfast. Diabetes in those days was considered a relatively unusual diagnosis, and this was the first record of gestational diabetes.

Thirty years later, Dr Andrew Malcolm (Fig. 3), one of the brightest stars of the early Belfast Medical School, was in the process of writing a book which summarised his clinical lectures when he died suddenly of tuberculosis in 1856 at the age of 42. The book was published posthumously by his colleagues as "The interpretation of symptoms and signs".[2] In this he states "urine containing sugar is seen only in cases of diabetes . . . the characteristic taste of the urine is also an excellent test". Many years later, in 1923, the year that insulin first became available for clinical use, the academic interest in the diagnosis of diabetes in Belfast had changed somewhat. Professor James A Lindsay (Fig. 3) was more concerned in the possibility that the Belfast medical graduate might miss the diagnosis and pointed out a number of potential errors – "the urine may not be abundant, sugar may be temporarily absent, thirst and wasting may be unnoticed, the first symptoms may relate to eyes, skin or nervous system". Professor Lindsay's concern would not be inappropriate in the present era of clinical governance. He was well known to the medical students of his day for his small book "Medical axioms, aphorisms and clinical recommendations" which was published in 1923, and one of these aphorisms "for every mistake in medicine made by not knowing, there are ten mistakes made by not looking" is still very relevant

today.[3] There is a need for a Professor of Clinical Medicine to act as a focus for education as well as for research and it is everyone's hope at this time in the Belfast Medical School that a suitable person to fill that post will soon be identified.

Dr Jack Smyth was the first doctor in Belfast to specialise in diabetes mellitus. His background was originally in clinical biochemistry and this made it possible for him to obtain accurate blood glucose measurements through the clinical biochemical laboratory at this hospital.[4] In those days much of the clinical practice of physicians took place in their private consulting rooms and Dr Smyth lived at 23 University Square. I have found a letter from Dr Smyth to my father Dr Robert Hadden in Portadown dated 25 April 1944 giving an exact method of carrying out a 50 g oral glucose tolerance test at home. This shows that shared care for diabetes between family practice and hospital consulting practice was possible in those days, and it is also probable that this glucose tolerance test was actually carried out in early pregnancy on this particular patient. It was Dr Smyth who was responsible for encouraging his patient Sir George E Clark to leave a sum of £10,000 specifically to build a metabolic unit at the Royal Victoria Hospital. This unit was finally opened on 7 June 1957 by Professor Charles Best, one of the discoverers of insulin from Toronto (Fig. 4). The building was built by the old established firm of H & J Martin who are currently employed jointly in building the new Royal Victoria Hospital, which will open this year. It was then and probably still is the only purpose built unit for endocrinology and diabetes

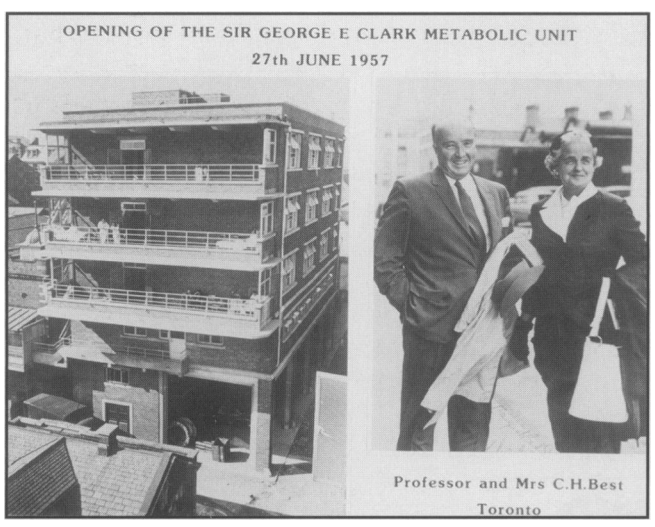

Fig 4. The opening of the Sir George E Clark Metabolic Unit, Royal Victoria Hospital – 27th June 1957.

in these islands containing the beds, the specialist and paramedical facilities, the education centre for diabetes and endocrinology, and the clinical and secretarial offices for the staff in the one building. Originally the metabolic outpatient clinics took place in this building but these were moved with the building of the new outpatient centre in 1967 to the other side of the hospital, which has always been an inconvenience for our medical and nursing staff as well as our patients. It has been my privilege to work in this building for the past 40 years. It opened while I was a medical student and it will close shortly before my retirement.[5]

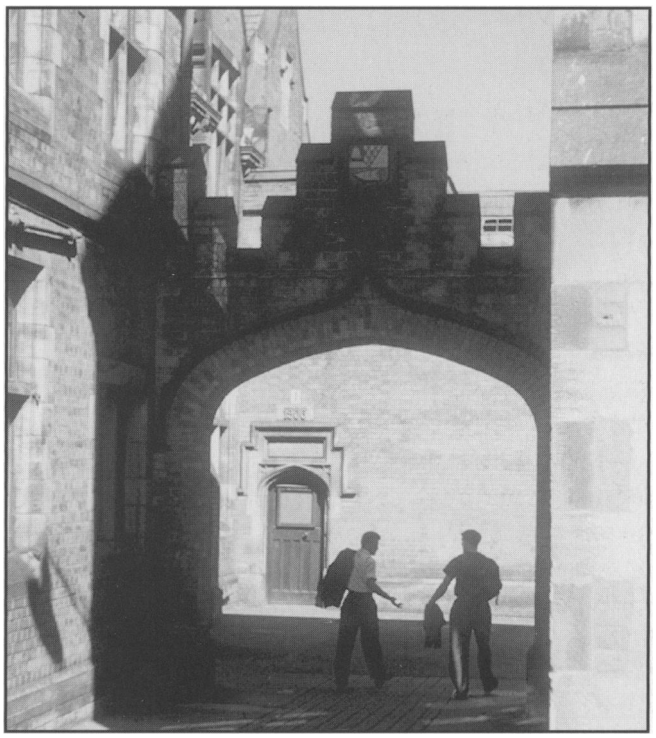

Fig 5. Biochemistry Department, the Queen's University of Belfast, 1956, seen through the archway (now replaced by the Administration Building).

Biochemistry in 1957 was taught entirely as an academic subject in the very small university department of biochemistry by Professor D C Harrison at the back of the quadrangle in the main campus of the university (Fig. 5). Theoretical biochemistry seemed distant and remote to most of us and the link between university and hospital was extremely tenuous.[6] Doctor Smyth was of the opinion that the only biochemical knowledge needed for a medical student was how to measure the blood glucose and the blood urea; he then added that the blood urea could be assessed by looking at the tongue – so we only learnt how to

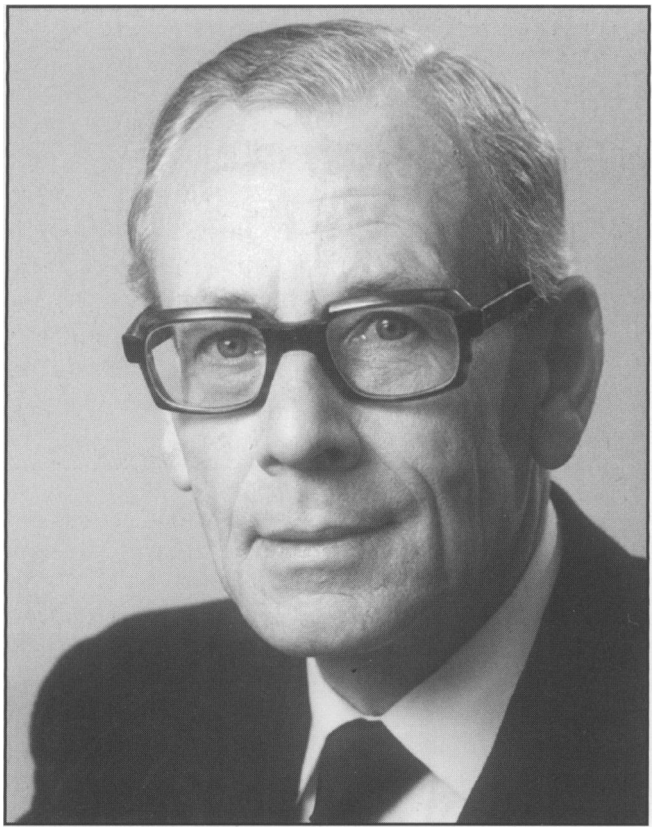

Fig 6. Professor D A D Montgomery.

measure blood glucose which was a tedious but exciting method involving Bunsen burners and test tubes, and various different coloured liquids. The ability for patients to self-monitor their own capillary blood glucose with a glucose oxidase strip has totally revolutionised the care of people with diabetes, in particular in pregnancy. In 1975, in the second edition of his textbook on Medical and Surgical Endocrinology, Professor DAD Montgomery stated "retrospective studies suggest there is an increased risk of perinatal death in children born to mothers who develop clinical diabetes later in life and that birth weights tend to be high. The characteristic features of the infant of the diabetic mother are well known. The baby is big for dates, owing mainly to excessive fat, but all organs, except the brain, are disproportionately large. The cause of the fetal "gigantism" is not known, but it may be that excess of glucose from the mother induces hyperplasia of the fetal islet cells, and this in turn causes fetal hyperinsulinism, excessive lipogenesis and neonatal hypoglycaemia. Effective control of the maternal blood sugar throughout pregnancy prevents these changes, and results in babies of average weight. An objection to this hypothesis is that many women with very mild diabetes, or those with potential diabetes and normal glucose tolerance, may have large babies years before their diabetes becomes manifest. The production of a large baby in a potential diabetic pregnancy may thus be genetically determined".[7] Professor Montgomery had established the academic basis of the metabolic unit which has continued to the present time, and he sends his apologies that he is unable to attend this lecture today (Fig. 6).

The knowledge that babies born to diabetic mothers could be either large or small had been identified by Dr Jorgen Pedersen in Copenhagen. He had been a physician interested in the outcome of pregnancy in the diabetic mother and wrote a famous book on this topic.[8] In this book is a photograph of two infants of diabetic women born on the same day at the Rijkshospital, Copenhagen (Fig. 7). One large fat baby weighing 4.7 kgs at 38 weeks gestation was born to a diabetic mother who had not attended the centre until two days before the baby was born. This mother's blood glucose was clearly much too high throughout the pregnancy. The other baby weighed only 2.05 kgs, born rather earlier at 36 weeks. The mother had attended regularly throughout the pregnancy but had more complicated diabetes with pre-eclampsia. Both large babies and small babies can happen in relation to diabetic pregnancy. These observations and others elsewhere sparked an ongoing interest in hyperglycaemia in pregnancy. In Belgium Dr J P Hoet, an obstetrician, had started doing 50 g

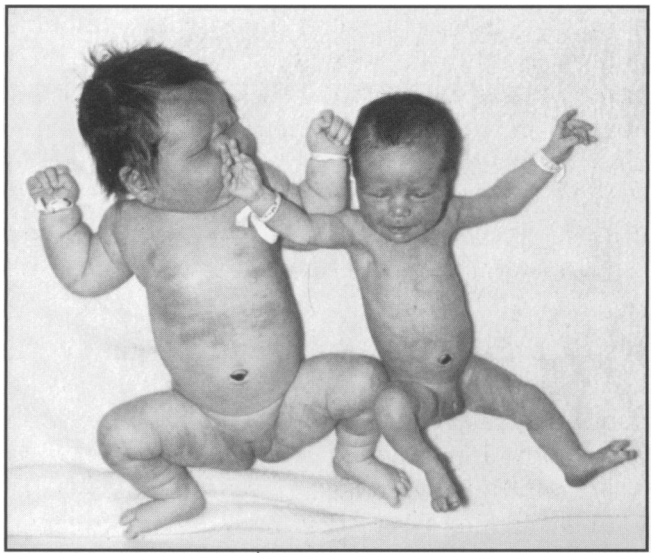

Fig 7. Two babies born to diabetic mothers in the Rijkshospital, Copenhagen, 1956 (reproduced from reference 8).

glucose tolerance tests in pregnancy after World War 2.[9] Following his visit to Boston, USA, a large prospective study of the effect of hyperglycaemia during pregnancy on the mother, and in particular on the chance of her developing permanent diabetes, was established by Dr John O'Sullivan at the Boston Lying-in Hospital and published in 1964.[10] This produced the major US criteria for the diagnosis of gestational diabetes which still stand to the present day, based on a 50 g glucose load for screening plus a second 100 g load for diagnosis. In Belfast, Dr Graham Harley and I had started glucose tolerance testing in pregnancy in 1962 as part of my MD thesis. My hypothesis at that time was that the big baby of the diabetic mother was in some way attributable to excess growth hormone secretion in response to hyperglycaemia in pregnancy. This was not a particularly robust hypothesis and I was never able to prove it, but I did learn a great deal about glucose tolerance tests in pregnancy, which interest has continued to the present day.[11]

I was awarded an RVH Research Fellowship of about £1,000 per annum (there were never more than two or three research fellows at the same time in those years). I was able to collect human pituitary glands from autopsies carried out by the Department of Pathology and to extract human pituitary growth hormone from them. Ultimately it was possible to obtain further human pituitary growth hormone from the combined UK collection of pituitaries and to use this for treatment of growth hormone deficient children with very encouraging results in over 40 cases. The possibility that even one of these human pituitary glands might have been carrying the then unrecognised Creutzfeld-Jakob disease prion did not become apparent until about 20 years later. I am glad to say that none of these patients treated in Belfast for growth hormone deficiency have thus far developed this fatal condition and they remain under counselling and long-term endocrine supervision.[12]

With this incomplete knowledge about growth hormone and its immunoassay, and some continued interest in glucose tolerance tests in pregnancy I proceeded to the Johns Hopkins Hospital, Baltimore, Maryland, USA, to work with Dr Samuel P Asper who was at that time the senior endocrinologist (Fig. 8). Dr and Mrs Asper were most kind to me and took me into their home for some time in much the same tradition as Dr and Mrs Osler had offered the latchkey of their

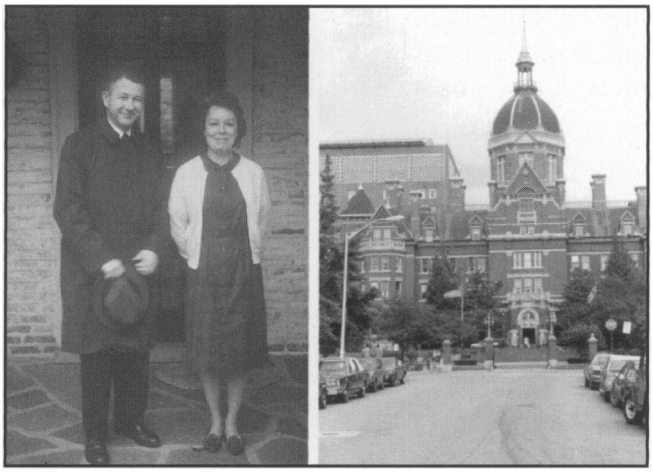

Fig 8. Dr and Mrs Samuel P Asper, Baltimore, 1964 and the Johns Hopkins Hospital, Baltimore, USA.

Baltimore house to the young Dr Harvey Cushing in 1920. Dr Asper was an expert in thyroid disorders and subsequently became Visiting Professor at the American University of Beirut in the Lebanon where he was in charge of the hospital during the civil strife and riots in that city. He gave the Scott-Heron Lecture at the Royal Victoria Hospital in 1977 and related his experiences in Beirut, which were much more alarming and dangerous than any of us had been exposed to during the Belfast troubles. While at the Johns Hopkins Hospital I was asked to attend a meeting for Fulbright Fellows to meet President John F Kennedy in the Rose Garden at the White House, shortly before his assassination. I remember President Kennedy's address to the visiting fellows. He most politely thanked us for coming to his country and for bringing our knowledge so

Fig 9. President John F Kennedy addressing Fulbright Fellows at the White House, Washington, USA, in September 1964 (DRH in the front row).

that they might benefit. I am sure we all felt that the knowledge was travelling in the reverse direction to our own benefit (Fig. 9).

At the Johns Hopkins Hospital I collaborated with Dr Thaddeus Prout who had developed an ingenious method of demonstrating binding proteins in normal human serum using radioiodinated hormones and jointly we demonstrated for the first time that there was a growth hormone binding protein in normal human serum. I presented this to the Annual Meeting of the Endocrine Society at Atlantic City, New Jersey, and met with considerable opposition from a member of the audience, who mounted the platform and pronounced that my work was wrong. I only found out later that this was Dr Solomon Berson who at that time with Dr Rosalyn Yalow had developed a radioimmunoassay for human growth hormone, which would have been under some theoretical suspicion if a growth hormone binding protein actually existed in normal human serum.[13] It has taken over 30 years for this argument to be resolved. It is now clear that growth hormone can be measured in normal human serum using an additional strongly binding gamma globulin antibody, but that there is also a less strongly bound normal serum binding protein. This was finally demonstrated by Dr Gerard Baumann at Northwestern University, Chicago in 1986.[14] It is interesting and perhaps salutory that as the Medline computerised database on the Internet does not extend backwards in time before 1966 no mention is currently made of the original discovery of the binding protein in 1964 (Fig. 10).

When I returned to Belfast I found that the original protocol for 50 g glucose tolerance tests in pregnancy had been continued under Dr Graham Harley's supervision at the Royal Maternity

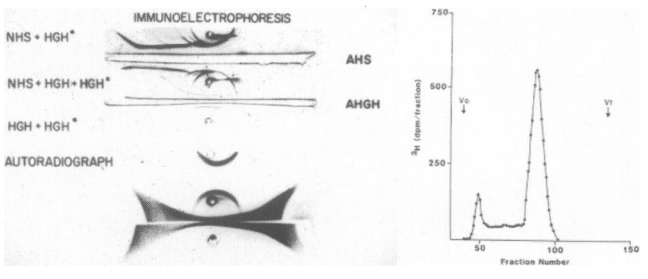

Fig 10. The growth hormone binding protein in human serum identified by radioimmuno-electrophoresis in 1964, and again by selective chromatography in 1986 (reproduced from references 13 and 14).

Hospital and soon there were a very large number of glucose tolerance tests which we analysed in many ways to assess the relation of maternal hyperglycaemia to the fetal result.[15] Several papers were published but the matter remained uncertain and we were not able to demonstrate strong relationships between the size of the baby and the maternal blood glucose. It eventually became clear that this is because the prevalence of gestational diabetes in Belfast is much less than in other parts of the world. Further developments of the glucose tolerance test including a standard breakfast test have been subsequently used but none have been predictive in Belfast in terms of outcome of the pregnancy.[16]

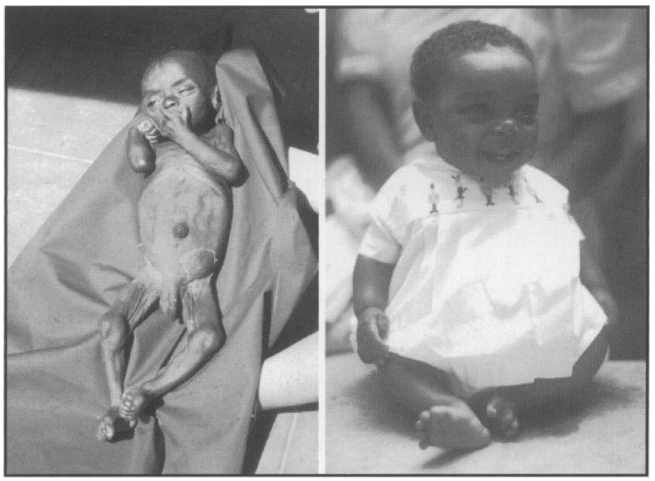

Fig 11. A severely malnourished marasmic infant at the MRC Infantile Malnutrition Research Unit, Kampala, Uganda – on admission and after refeeding (1966).

After a year or so back in Belfast I was met one morning on the RVH main corridor by the then Professor of Medicine, Professor G M Bull, who asked me what I was doing. I told him I was interested in hyperglycaemia in pregnancy and in hypoglycaemia in the infants of diabetic mothers. He replied that I should go at once to Uganda where the Medical Research Council were looking for a clinical investigator to study the hypoglycaemia that was thought to occur in the malnourished children with marasmus and kwashiorkor in that country. As Professor Bull was a member of the Tropical Medicine Board of the Medical Research Council it was a matter of only a few weeks before I found myself called for interview at Park Crescent in London, the headquarters of the Medical Research Council, and very rapidly dispatched to the Medical

Research Council Infantile Malnutrition Research Unit at Mulago Hospital, Makerere University, Kampala, Uganda. I have discussed my findings there elsewhere, suffice to say that there was evidence of insulin resistance in the protein deficient children with high serum insulin and low serum growth hormone levels which did relate to the degree of fat retention (Fig. 11). This was entirely related to their protein deficient diet, in the face of a relative sufficiency of carbohydrate coming from the banana staple in that country.[17, 18] The MRC unit in Kampala was technically under the control of Professor R A McCance, the Professor of Experimental Medicine in Cambridge at that time. He encouraged me to return to Cambridge bringing blood specimens for measurement of insulin and growth hormone with me from the babies. Professor McCance had been undertaking parallel experiments with a group of undernourished pigs at a farm outside Cambridge and the picture of the three pigs of the same age is now famous – one pig, very small, being severely energy restricted, one pig of medium size but pale, puffy and lethargic, having had sufficient carbohydrate but insufficient protein it its diet, and the third pig having had normal mash and having grown to normal size. These animal studies, which were backed up by further studies on smaller animals such as rats and guinea pigs, confirmed that nutritional status had a profound effect on growth in early life, and it is now clear that growth in the fetal period is equally dependent on a proper nutritional balance.[19, 20] At that time I was the senior registrar in endocrinology at the old Addenbrooke's Hospital in Cambridge. I think I had only one patient and most of my time was spent hearing about the Professor's pigs and other animal interests, to say nothing of his well known racing bicycle (Fig. 12).

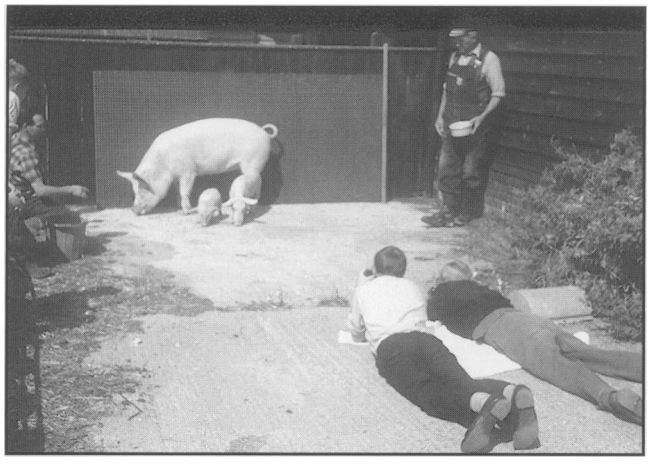

Fig 12. Professor R A McCance (lying on right) photographing three pigs aged one year old, the two smaller pigs having been undernourished to mimic marasmus and kwashiorkor (Cambridge 1965).

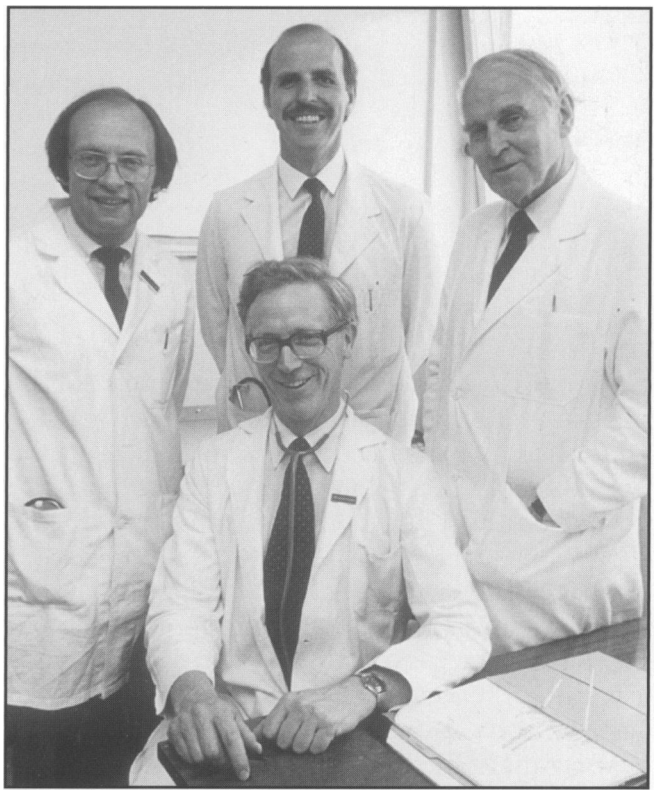

Fig 13. Dr A B Atkinson, Dr A L Kennedy, Dr J A Weaver and DRH in the Metabolic Outpatient Clinic (1983).

After Professor Montgomery's retirement in 1980, Dr Weaver and I were joined on the staff of the metabolic unit by Dr Laurence Kennedy and Dr Brew Atkinson (Fig. 13). At that time a main interest in the metabolic unit was the epidemiological study of patients with Type 2 diabetes. After a number of retrospective studies we had embarked on a prospective natural history study of the long-term survival of patients with this type of diabetes which became known as the Belfast Diet Study.[21, 22] This has achieved a considerable degree of international recognition by the demonstration that with careful and even rigorous dietetic advice and follow-up under the supervision of Miss Anne Wilson and her dietetic colleagues it was possible for a large group of newly diagnosed patients with Type 2 diabetes mellitus to be controlled by diet only (Fig. 14). The graph shows that after a period of weight loss over the first year the group of 172 patients

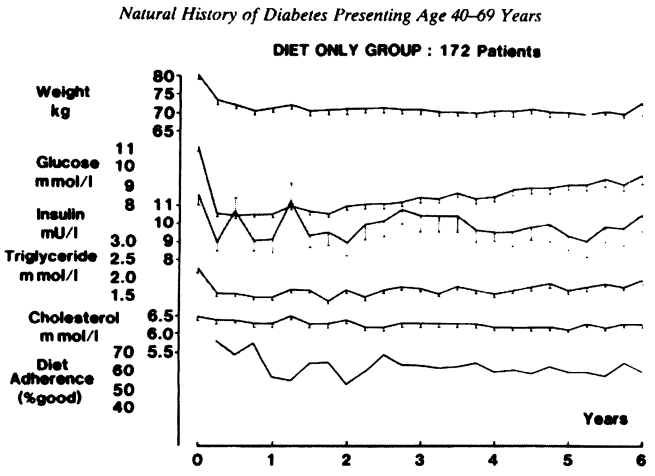

Fig 14. Six year analysis of the Belfast Diet Study (Reference 22).

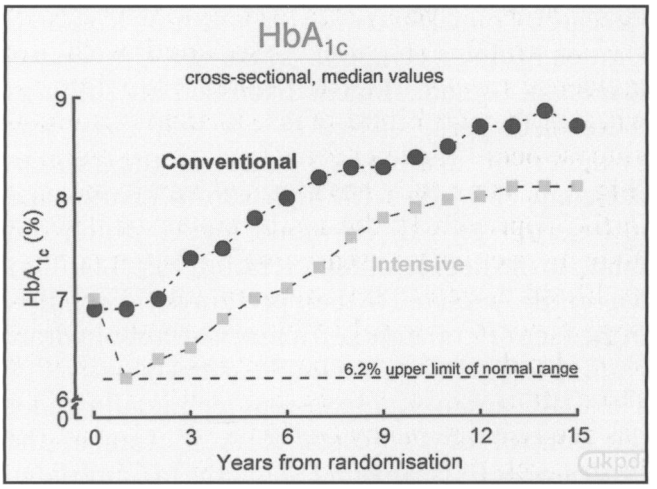

Fig 15. Fifteen year analysis of the UK Prospective Diabetes Study (Reference 24).

remained exactly the same average weight for the following six years. The fasting blood glucose which had fallen in the first three months from the initial diagnostic mean level of 11 mmols/l to about 8 mmols/l did not, however, show the same steady level of longterm control and there was a slow inexorable rise during the following years. There was no change in serum cholesterol and our simple measurement of dietary adherence also did not reveal any significant alteration. This study and its subsequent extension to 10 years has become known as "The Belfast Blood Glucose Phenomenon". The fasting plasma glucose in Type 2 diabetes mellitus treated on diet only rises steadily, in spite of good control of weight and good dietetic adherence, by 0.3 mmols/1 per year. This means that over 10 years it will rise by 3.0 mmols/1. Further studies in the Metabolic Unit suggested that this was largely due to the gradual failure of the beta cells of the pancreas although there is still reasonable debate that it is also due to increasing insulin resistance with the passage of time.[23]

After completing this study we joined the much larger United Kingdom Prospective Diabetes Study which had been initiated by Dr Robert Turner at Oxford. This study enrolled over 5,000 newly diagnosed Type 2 diabetic patients and followed their progress for 15 years. It subsequently became clear that these patients also showed the initial fall of blood glucose on intensive control but that there was a steady inexorable rise at about 0.3 mmol/1 per year over the next 15 years. This is demonstrated by the HbA1c data which shows that both on conventional and on intensive treatment this progressive rise in blood glucose took place [24] (Fig. 15). There is further evidence that this is due to a combination of both beta cell failure and insulin resistance. Sadly Dr Turner died in 1999 shortly after the important results of the study had been published.[24] We in Belfast recognise that 10% of the patients in this large study came from Belfast, both at the Royal Victoria Hospital and the Belfast City Hospital, and the further follow-up of the surviving patients will continue for some years to come. A further important outcome of the United Kingdom Prospective Diabetes Study was the recognition that blood pressure is just as important as blood glucose in the long-term survival of these patients. Both the updated mean systolic blood pressure and the

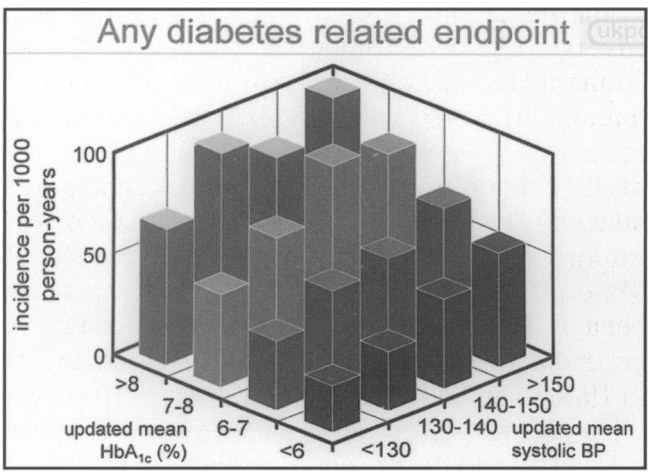

Fig 16. Relation of updated mean HbA1c and of updated mean systolic blood pressure to incidence of any diabetes related endpoint (Reference 25).

updated mean glycosylated haemoglobin (HbA1c) are separately stepwise associated with the incidence of any diabetes related endpoint, but when both high blood pressure and high blood glucose occur together the effects are cumulative (Fig. 16). This study has initiated a major change in the approach to the management of Type 2 diabetes, not only in searching for better control of blood glucose but also in clarifying the importance of control of blood pressure and of blood lipids. Further important research into the association of insulin resistance and hypertension has been carried out by Dr P M Bell and a number of research fellows at the Metabolic Unit using the glucose clamp technique. The United Kingdom Prospective Diabetes Study was one of the first in which nursing research played an important independent role and the pioneer work of Nurse Netta Webb and her nursing colleagues has been widely respected throughout the study.[25]

These studies in the genesis of insulin resistance and beta-cell failure in Type 2 diabetes were taking place at the same time as the ongoing studies of glucose tolerance in pregnancy. Dr Ralph Roberts at the Royal Maternity Hospital had initiated investigation of the association of insulin sensitivity with pregnancy induced hypertension, using a different "minimal model" technique for assessing insulin response to glucose stimulation and had suggested that pregnancy induced hypertension was in many ways analogous to pregnancy induced hyperglycaemia.[26] The close proximity of the Metabolic Unit to the Royal Maternity Hospital facilitated these studies, and provided a suitable background to the development of the hyperglycaemia and adverse pregnancy outcome concept. Professor Graham Harley had continued to encourage our interests in the obstetrical aspects of carbohydrate metabolism and his place as obstetrician in charge of diabetic pregnancy at the regional centre was taken by Dr A I Traub. The outstanding record of improvement in perinatal mortality at the Royal Maternity Hospital over the past 60 years has been internationally recognised, with a fall in perinatal mortality from over 30% of pregnancies in 1940 to about 6% in the year 2000.[27] However this still is greater than the overall hospital mortality, and the present day diabetic mother is still faced with a fourfold greater risk to her baby than a nondiabetic mother. Perinatal mortality over the past 10 years in the whole of Northern Ireland was 37/1000 for diabetic pregnancies compared to only 9/1000 overall.[28] It is our aim further to reduce this risk of pregnancy to the diabetic mother. A recent pregnancy outcome for a diabetic mother who had difficulty in obtaining good blood glucose control in early pregnancy will illustrate the point. Her baby was born with only two chambers in the heart, one ventricle and one atrium, but after cardiac surgery has survived to the age of five or more. He was also unfortunate enough to be affected by another complication of maternal hyperglycaemia known as sacral dysgenesis which meant that his sacrum and bladder did not develop properly at the right embryological time and he had to remain in nappies up to the age of four years (Fig. 17). Similar congenital abnormalities can be produced in experimental rats where the mother is exposed to a high blood sugar for a relatively short time in the early stages of pregnancy and there seems to be a window in time when the teratological effects of a high blood glucose are expressed.[29]

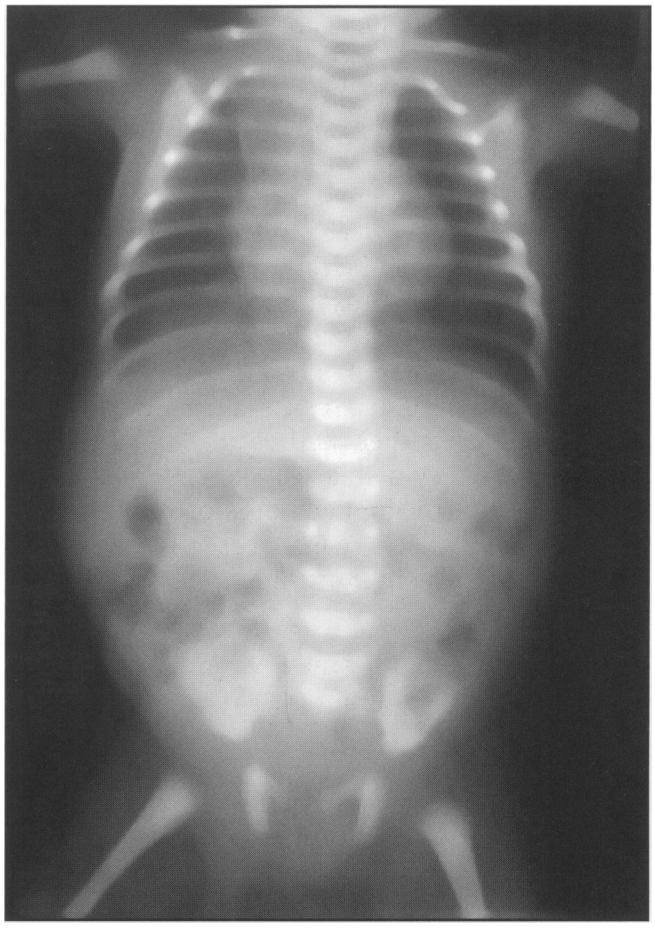

Fig 17. X-ray of new-born baby of Type I diabetic mother showing cardiomegaly due to congenital maldevelopment producing only one atrium and one ventricle, and also sacral dysgenesis.

WHERE ARE WE NOW?

The Pedersen hypothesis has now been amply established, with the demonstration that decreased maternal insulin sensitivity produces impaired maternal glucose metabolism resulting in maternal hyperglycaemia, which passes directly across the placenta to cause fetal hyperglycaemia; the fetus however is not diabetic and has normal pancreatic beta cells after 20 weeks and therefore is able to produce increased insulin in response to the high blood glucose (Fig. 18). This increased insulin in association with normal nutrition results in increased fetal fat deposition and macrosomia. This hypothesis has been proved to be true in a number of experimental models and is now widely accepted as the explanation for the occurrence of at least some cases of macrosomia in diabetic pregnancy. However, large babies continue to be born even when the blood glucose appears to be relatively normal.

The concept of gestational diabetes has now been defined as "glucose intolerance with onset or first recognition during pregnaney".[30] There is good evidence that the prevalence of gestational diabetes varies very considerably in different parts of the world with a 100-fold difference demonstrated in studies between Newcastle-on-Tyne and Belfast where the prevalence is low, and in cities like Los Angeles and San Antonio, USA, which are both close to the Mexican border and to which many Mexican-Latino mothers come during their pregnancy, where the prevalence is one in ten pregnancies or more.[31] The reasons for this enormous difference in the prevalence of gestational diabetes has not been fully explained, neither has the increasing incidence in different ethnic groups coming from different parts of the world to live in the same place, such as the increasing prevalence shown in studies in St Mary's Hospital, London, or in Melbourne, Australia over a relatively short time. There are a number of reasons why gestational diabetes is different in different parts of the world including different prevalences of Type 2 diabetes, different diagnostic criteria, different screening methods for hyperglycaemia in pregnancy and different genetic backgrounds in different ethnic groups. The reason for the apparently dramatic increase in prevalence over relatively short periods of time is widely thought to be related to changes in the food which is eaten amongst the population in rapidly developing countries. There is intriguing evidence that the prevalence of diabetes was very low in Ireland before the potato famine in 1840 but that there was a rapid increase associated with the increasing living standards of the general population following the famine, although that was associated with a change from the previous very healthy diet which had consisted of up to 10 pounds of potatoes and a pint of milk per day for a working man (90% of the energy carbohydrate, 5% protein and 5% fat).[32] Whether dietary changes explain all of the rise in gestational diabetes remains uncertain but it is undoubtedly a major public health problem in the developing as well as the developed world.[33, 34]

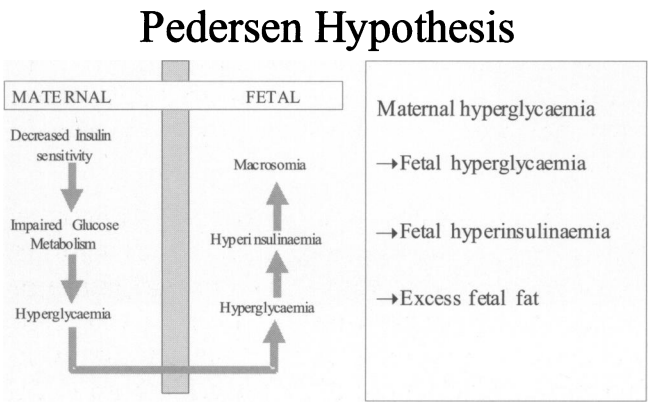

Fig 18. The Pedersen Hypothesis.

The careful studies of O'Sullivan in Boston have proved that gestational diabetes predicts subsequent Type 2 diabetes in the mother.[35] A further question, however, is whether gestational diabetes poses a risk to the baby. O'Sullivan's studies had suggested an increased perinatal mortality in babies born to mothers with gestational diabetes (6.4% versus 1.5% in a control group). His definition of gestational diabetes was related to the original 100g three hour glucose tolerance test which has long been used by American obstetricians.[36] More recent studies by the group at the US National Institute of Health in Phoenix, Arizona, studying the Pima Indians, showed similar results related to a 75 g glucose tolerance test which has been much more widely used in other parts of the world including Europe.[37, 38] In Australia the large experience of Beischer was conducted in relation to a 50 g oral glucose tolerance test which he had learnt to use when working as an obstetric registrar in Belfast in the late 1950's.[39] For many years the Australian continent continued to use the 50 g GTT. There were thus considerable difficulties in comparing the results from one country to another.

This difficulty and other concerns about the long-term outcome of the infants of gestationally diabetic mothers led a group of interested physicians, obstetricians and paediatricians to meet at the invitation of both the US National Institute of Child Health and Human Development and the US National Institute of Diabetes, Digestive and Kidney Diseases, at an international workshop on Adverse Perinatal Outcomes of Gestational Diabetes in 1992, at the National Institute of Health, Bethesda, Maryland, USA. At that meeting we determined to make a joint application for a study of the outcome of pregnancy in the milder hyperglycaemic mother, and this eventually developed into the HAPO hypothesis (Hyperglycaernia and Adverse Pregnancy Outcome). It was recognised that there was considerable controversy in the field, with concern that the results of blood glucose measurements were confounded by maternal obesity, increasing maternal age and maternal hypertension,[40,41] and also that there might be bias expressed by the care giver in relation to suspected but unproven risk associated with alleged hyperglycaemia that might still be within a normal range.[42,41,44] At the same time there was increasing concern from parts of the world where gestational diabetes was common that even lesser degrees of hyperglycaemia than those currently recognised as gestational diabetes were causing effects on the baby which were being passed on to the next generation. There was thus conflicting advice on the one hand to increase screening procedures and to lower diagnostic criteria and on the other hand to stop all efforts to identify maternal hyper-glycaemia unless more data on morbidity in the offspring of glucose intolerant mothers was available.[41,46]

At about that time the studies of Professor David Barker and his colleagues in Southampton University, which have become known as the Barker hypothesis, were being published. These studies initially comprised long-term retrospective follow-up of populations of babies born in several well described parts of England where it was possible to identify those same babies 50 or more years later. It was found that babies who were small at birth were very much more likely to have developed Type 2 diabetes and hypertension 50 or 60 years later and that the diabetes and hypertension were associated with insulin resistance.[47,48] The Barker hypothesis was that these small babies were due to placental

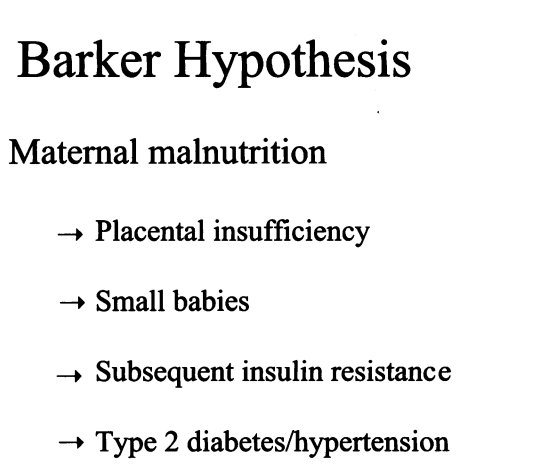

Fig 19. The Barker Hypothesis.

insufficiency related to some form of maternal malnutrition. This has led to a debate on the merits of the so-called "thrifty genotype" hypothesis and the "thrifty phenotype" hypothesis. The former had been proposed 30 years ago,[47] based on the concept that a hypothetical diabetes gene would endow an ability to survive in time of famine, as the blood glucose would be maintained for longer at a level to allow normal physiological function of muscle and brain, rather than suffering from hypoglycaemia. This idea had some credence in the unusually high recent prevalence of diabetes in some native American tribes who had survived in apparent good health without diabetes during successive generations of presumptive nutritional deficiency when they were actively defending their territory, only to show a dramatic increase in the incidence of diabetes when they became sedentary and were exposed to nutritional excess under a U.S. government settlement in the safety of an Indian Reservation. The thrifty phenotype hypothesis, on the other hand, emphasised that Type 2 diabetic adult had achieved a physiological adaptation involving insulin resistance in a number of metabolic processes, following on an early period of nutritional deficiency which could be both intrauterine and early postnatal: this adaptation led to obesity, hyperglycaemia, hyperlipidaemia and hypertension.[48]

The very extensive epidemiological database available on the Pima Indian population in Arizona, USA, allowed further investigation of these transgenerational effects. Dr David McCance and colleagues were able to show in that population where diabetes affects up to 50 per cent of adults, that there was a greater, prevalence of adult diabetes when the individuals

birth weight had been either smaller than average (less than 2.5 kg) or greater than average (more than 4.5 kg), than when birth weight was between these figures.[49] This "U-shaped" curve of diabetes prevalence held for adults aged 20-39, and led to a third concept of the "surviving small baby genotype". Was the small-for-dates baby which had been identified in the Barker hypothesis carrying a gene for diabetes or diabetes susceptibility which both accounted for its small size at birth and its later diabetes? This would not necessarily be the same pathophysiological process which accounted for the increased diabetes risk of the large-for-dates baby, where the previous Pedersen hypothesis seemed to give an adequate explanation (Fig. 20).

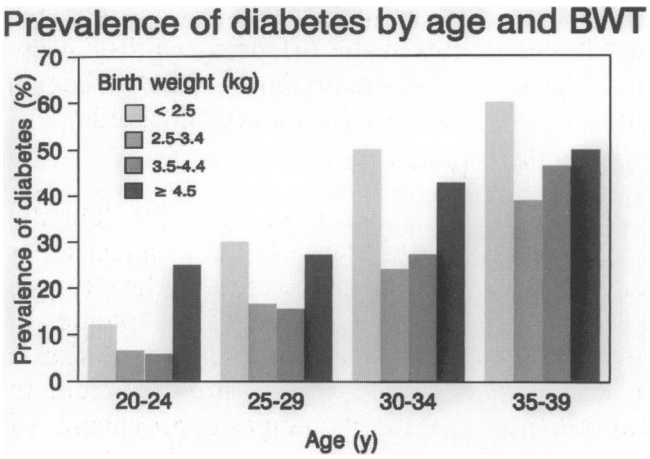

Fig 20. The "surviving small baby" genotype (reference 49). The diagrams show that the prevalence of diabetes in adults in four age groups from 20 to 35 years, each showed a U shaped curve with more becoming diabetic for birth weights less than 2.5 kg and more than 4.5 kg than for the intervening birth weights.

An extension of this third hypothesis was offered by Hattersley and Tooke[50] in an elegant demonstration of the birth weight distribution in a small number[58] of off-spring born to mothers known to have an unusual form of Type 2 diabetes due to a recognised genetic mutation affecting the glucokinase enzyme. When neither mother nor fetus had the mutation the birth weight was normal, as it was when both mother and baby were affected. When the mother was affected (and hyperglycaemic) but the baby was normal (did not have the mutation) the birth weight was high, presumably due to fetal hyperglycaemia leading to fetal hyperinsulinaemia as in the Pedersen hypothesis. When the mother was normal, but the baby had the defective glucokinase

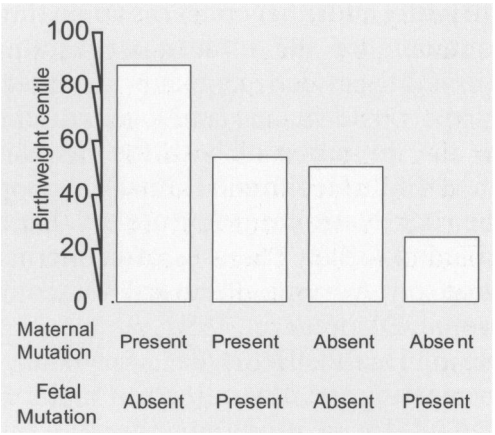

Figure 3: Birthweight centile distribution in 58 offspring of parents with glucokinase mutations according to maternal and fetal genotype

Fig 21. Birth weight centles in MODY families with glucokinase mutations, according to maternal and fetal genotype (Reference 50).

gene the birth weight was low, presumably because the developing fetus could not metabolise even the normal glucose available to it (Fig. 21). Hattersley has indicated the two alternative explanations for the association of small thin babies with insulin resistance, Type 2 diabetes and ischaemic heart disease - either an effect of poor intrauterine environment, or of a gene influencing insulin resistance. Each of these mechanisms would result in small thin babies, and each would account for insulin resistance which would ultimately lead to the long-term problems of the adult.

There had been careful studies of fetal pancreatic beta cell function in gestational diabetes in a number of centres, and there is no doubt that in this condition the fetal insulin is high enough to affect the outcome. Mean amniotic fluid insulin in 52 gestational diabetic pregnancies was 15.0 mU/l compared to 7.4 mU/l in 27 control pregnancies, and similar differences were found in umbilical cord c-peptide levels at birth.[51] There is also evidence that both childhood[52] and adult obesity[13] in the offspring is related to gestational diabetes in the mother.

These concepts have also been confirmed in studies of the development of adult diabetes in the next generation. The role of the intrauterine environment has been demonstrated in producing congenital susceptibility to Type 2 diabetes in the Pima Indians[54] and in adolescent offspring of gestational diabetic mothers in Chicago.[55]

The development of a large-for-dates or macrosomic baby related to increased maternal blood glucose has been recognised from the early studies of diabetes in pregnancy. More extensive epidemiological reports from the Pima Indians,[37] Italy[56] and the Latino population of Los Angeles[57] have confirmed this concept in mothers with gestational diabetes. There is also evidence that treatment of the mother with insulin during pregnancy will prevent this macrosomia. In an early randomised clinical trial of prophylactic insulin in 1966 O'Sullivan showed that whereas 13.1% of babies born to 306 gestational diabetic mothers weighed more than 9 lb at birth, compared to 3.7% of 324 control normoglycaemic mothers, administration of a standard dose of 10 units of isophane insulin in later pregnancy significantly reduced the number of babies weighing more than 9 lb to 4.3% of 305 pregnancies.[58] Subsequent clinical studies have supported this study, although there is still considerable uncertainty as to when and how best to use insulin in this situation.[59]

The present concept of transgenerational diabetes, which is related in part to intrauterine malnutrition and in part to overnutrition, with or without the expression of a gene promoting hyperglycaemia, and resulting in either a small baby or a large baby which has resistance to insulin action, is reasonably well accepted (Fig. 22). These theoretical concepts of the effects of carbohydrate intolerance on maternal fetal outcome will only be of public health importance if they represent an increasing problem even at lower levels of blood glucose than those currently diagnosed as gestational diabetes. The Toronto tri-hospital project (which used the standard North American 100 g OGTT) studied 3,600 women who were known not to have gestational diabetes and showed that even a relatively mild degree of increasing carbohydrate intolerance within the normal range was associated with macrosomia, pre-eclampsia, increased Caesarean section rate and a longer hospital stay.[61] The stage has thus been set for the HAPO study to investigate this matter by a larger study using a standardised 75 g glucose tolerance test in many parts of the world. This will allow further assessment of the relative roles of the Pedersen hypothesis of fetal overnutrition and the Barker hypothesis of fetal undernutrition on the subsequent development of insulin resistance in the baby, and the longerterm risks of diabetes and hypertension in the offspring as they grow up. The overall concept that "diabetes begets diabetes" is gradually becoming accepted.[61]

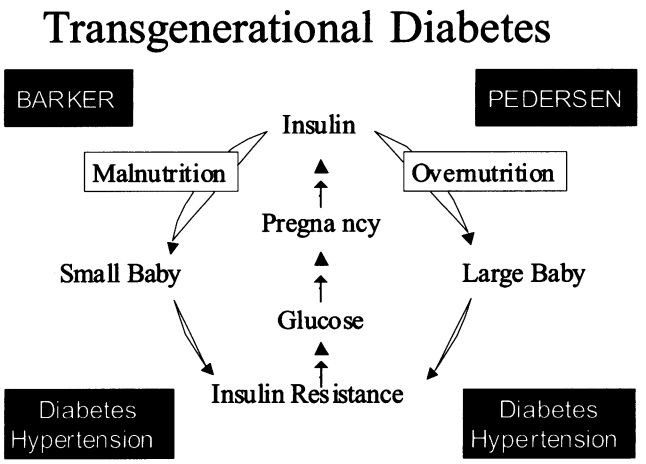

Fig 22. Transgenerational diabetes: the possible roles of under-nutrition and over-nutrition in producing a small or a large baby, related to insulin resistance and subsequent diabetes and hypertension.

WHERE ARE WE GOING?

Charles Darwin in his work in 1859 "On the origin of species by means of natural selection or the preservation of favoured races in the struggle for life" is generally accepted as the founder of the concept of genetics as the means of evolution.[62] Whether genetic mechanisms are sufficient to explain the rather rapid changes in prevalence of diabetes mellitus remains uncertain. The previous and largely discredited theories of Lamarck (1801) on the inheritance of acquired characteristics might be thought to be applicable to the transplacental passage of hyperglycaemia from mother to baby but that concept would not be sufficient to explain the famous problem of why the giraffe has a long neck.[63] Both the philosophical and practical aspects of mild disturbances in maternal carbohydrate tolerance were initially emphasised by Dr Norbert Freinkel, at that time in charge of the research group at Northwestern University, Chicago, and he would certainly have approved of the subsequent application for a major international grant to study this problem.[64] The first application was made by the Steering Committee in 1995 and after very considerable work and the utilisation of a very large amount of paper in many parts of the world, was finally successful at the third attempt in 1999. The organisational details of the study are now available on the Internet.[65] The Steering Committee met again in Chicago in 1999 to finalise the very detailed manual of

operations which has undergone further refinement with the passage of time. The total grants awarded to date include $8.8 million from the National Institutes of Health supplemented by $1.5 million from the American Diabetes Association and £102,000 from Diabetes UK. A smaller grant of 36,000 Ecu's had been awarded by the European Community for portions of the work judged to show the principle of subsidiaity within Europe but unfortunately even that small grant was withdrawn because of our failure to start the study within their strict time limit. We hope that some further generosity from the European Community will still be available.

The aim of the HAPO study is to examine glucose tolerance in a large multinational multi-cultural ethnically diverse cohort of women in the third trimester of pregnancy with medical caregivers "blinded" to blood glucose data (except when predefined criteria are met). There will be 16 centres with a common protocol and data collection, a uniform training of personnel and a central laboratory. This will derive internationally acceptable criteria for gestational diabetes mellitus. The field centres are at Bangkok, Barbados, Beersheba, Belfast, Bellflower (Los Angeles), Brisbane, Chicago, Cleveland, Hong Kong, Manchester (UK), Newcastle (Australia), Petah-Tiqva (Israel), Providence (USA), Singapore, Toronto and Utrecht. Other centres were considered by the Steering Committee and it was with considerable reluctance that we had to reduce to the final 16 in order to satisfy the very strict obstetrical criteria laid down by the US National Institutes of Health. This is not to say that the findings of the HAPO study will not be of equal importance in all parts of the world and in all obstetrical communities.

The central laboratory for the whole study will be at the Royal Victoria Hospital under the supervision of Professor Elizabeth Trimble, with blood samples from 25,000 women coming in over the next two years for measurement of glucose (Mr Selby Nesbitt and Mr Mike Smye), C-peptide and insulin (Mr Brian Sheridan and Mr Colin Burgess) and glycosylated haemoglobin (HbA1c) (Professor T Lappin and Miss Geraldine Savage). The laboratory has been inspected to a very high degree by the US National Institutes of Health and found to be satisfactory in every respect. There will be a very considerable amount of work to complete the measurement of all these samples within the time line. The clinical co-ordination centre and data interpretation centre will be at Northwestern University in Chicago and data from the central laboratory will be transferred instantaneously by e-mail to the computer suite in Chicago for statistical analysis.

An important ethical issue is the blinding of the obstetricians and midwives (caregivers) to the results of the glucose tolerance test, unless these exceeded those levels which are currently diagnostic of gestational diabetes. This is in order to provide unbiased information, without intervention following the GTT, on any relationship between the outcome of pregnancy and the maternal blood glucose. The whole study including this aspect is carefully explained to all mothers at time of enrolment and detailed informed consent is obtained by the HAPO midwives. We have already found very many mothers attending the Royal Maternity and Jubilee maternity service to be enthusiastic about joining this study and they show considerable interest in what happens, both to themselves and to the study as a whole.

The primary outcomes will be the occurrence of a Caesarean section, of fetal macrosomia or obesity measured by skin fold callipers, of neonatal hypoglycaemia measured one to two hours after birth by heel prick analysis, and of fetal hyperinsulinaemia measured by a cord blood C-peptide assay. Secondary outcomes will include neonatal polycythaemia, hyperbilirubinaemia, respiratory distress and the occurrence of shoulder dystocia or any birth injury. One initial study was necessary to document the effect of early feeding on the neonatal blood glucose level at one hour of age.[66] This has already been published indicating that early breast feeding as sometimes practised at the present time does not affect the baby's capillary blood glucose level between one to two hours, and is therefore acceptable if it is the wish of the mother within the study protocol. A number of other ancillary studies have now been approved by the Steering Committee. These include a further study of matemal blood pressure and insulin responses which will allow assessment of the role of insulin resistance in both pre-eclampsia and gestational hypertension in this large group of pregnancies. At the same time, and after specific informed consent, blood specimens from mother and baby will be kept for DNA analysis allowing further investigation of possible genetic determinants of Type 2 diabetes and of fetal weight. A specific study in the Asia and Pacific

region will investigate further possible causes of neonatal hypoglycaemia unrelated to hyperinsulinism. The Hong Kong group will undertake a study of maternal oxidative stress and its effect on fetal outcome. The Cleveland Ohio group hope to study a number of more detailed and more accurate markers of neonatal total body fat in relation to maternal nutrition. The Belfast group will study a number of factors including maternal thyroid status at the 28 week time of the oral glucose tolerance test, the genetic control of haemoglobin synthesis, maternal nutritional status by dietary questionnaire, and a more detailed genetic study including DNA sampling from the father as well as the mother and baby which should allow a more searching assessment of the fetal insulin genetic theories which have been discussed previously. The HAPO study has already commenced in most of the centres, after careful inspection and accreditation by the US National Institutes of Health to ensure consistent standards both of obstetrical practice and neonatal care. The considerable grant income associated with this study has had a beneficial effect on the research ratings of the endocrinological, biochemical and obstetrical groups at the Royal Group of Hospitals and also with the Queen's University of Belfast.

Charles Darwin stated "without hypothesis there is no useful observation". The HAPO hypothesis that hyperglycaemia in pregnancy less severe than overt diabetes mellitus is associated with increased risk of adverse maternal fetal and neonatal outcome that is independently related to the degree of metabolic disturbance remains to be proved, but we expect very considerable interest in the outcome of the study when it is finally published in the year 2004. There has traditionally been an interest in the birth of a big baby and concern at the birth of a small baby. The relation of both of these events to the consumption of 75 g of a glucose drink by the mother at 28 weeks gestation, and whether the mother's glucose levels are connected to the weight of the baby by a nutritional or by a genetic mechanism, or by both acting in concert, remains uncertain.

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