David Robert Hadden (1936–2014)

President of the Ulster Medical Society 1995–96

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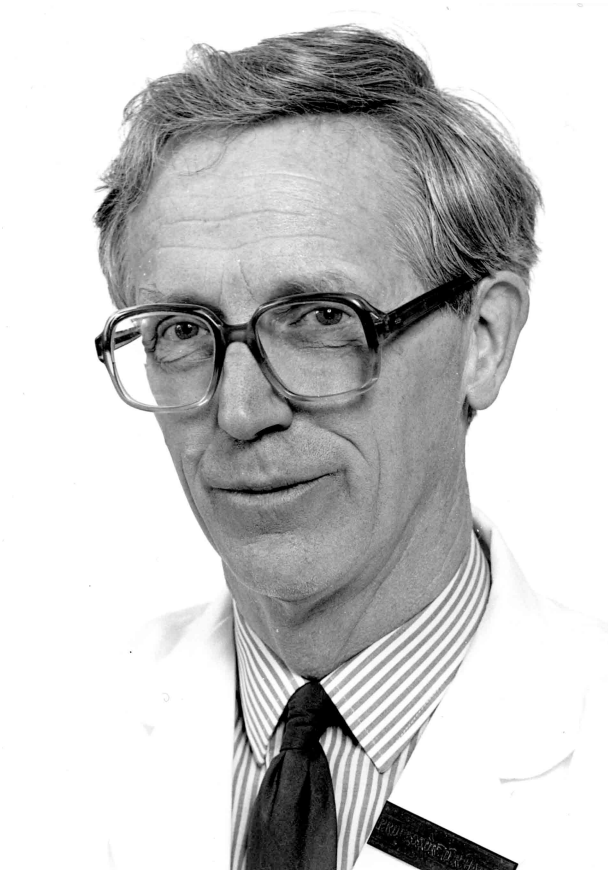
DISEASE ORIENTED MEDICINE—
THE METABOLIC MODEL

When you elected me to be your President for this year—an event which was initiated by a letter from the President before last—Professor Robin Shanks—I was certainly honoured, and challenged, but I made a mental note that I should be forward looking, and practical, and above all, medical in any remarks I would offer by way of a presidential address. Professor Philip Reilly delivered a thoughtful dissertion on the development of the branch of the practice of medicine which we now know and respect as general practice. He recalled how there was a tendency to lurch from one problem to another in the administrative arrangements, and to take shelter in any port in a storm: the present arrangements for the practice of primary care medicine, or family practice, are the outcome of much deliberation and foresight, and the overall respect and admiration for doctors in that most general of all medical disciplines at the present time is a compliment to the professional wisdom of the founding fellows of what became the Royal College of General Practitioners. They set a high standard, and the profession has followed their example.

The Ulster Medical Society is not heavily encumbered by a mission statement or a business ethic, and its constitution is more concerned with good organization than high sounding phrases about the practice of medicine in Ulster. But the 19 original founding fathers who met at a house in High Street in Belfast in September 1806 to establish the Belfast Medical Society—there may not have been any more than that in those days in Belfast where the population was only about 20,000—were concerned with meeting each other and continuing their medical education in the most practical way. The subsequent history of the Society, and of the development of Belfast medical and surgical practice, and of the Belfast Medical School, has been carefully documented. Professor Desmond Montgomery in his Presidential Address to the Society in 1975, 20 years ago—'The Ulster Medical Society—Quo Vadis?' the year we moved into our new



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rooms in the Whitla Medical Building—believed that we were coming to terms with the challenge of specialization, and adapting ourselves to the changing pattern of medicine. He saw the Society as fulfilling an integrative role for a divided profession, always striving to maintain the highest ideals of the art and practice of medicine. It is in that forward looking perspective that I hope to consider some of the challenges of medicine that lie ahead of us.

THE PAST

"'*Tis the sunset of life gives me mystical lore,*
And coming events cast their shadows before".
Thomas Campbell, 1777-1844
Lochiel's Warning.

Thomas Campbell was also the source of the one liner "'*Tis distance lends enchantment to the view*"—and we must guard at looking backward through tinted spectacles, either rosy or black: but it is reasonable to

see if the events which took place did in fact cast a shadow in time, and whether medical planning was ever successfully proactive rather than reactive.

It was my father, Dr Robert Evans Hadden, of Portadown, who talked to me about these matters: in the 1940s, when all sorts of things were happening, a far greater change in medical practice than is occurring now. It is interesting to realize that it was in the King's speech on VJ Day, 16 August 1945, that the first small reference to the National Health Service crept into a Government statement, carefully camouflaged between social security and industrial injury compensation. My father was a fellow of this Society, as was his father before him—the journey from the country into Belfast was always tedious for those who lived outside the centre: he was nevertheless a good attender, and found the Society an important source of continuing education. The Health Service committees at that time seemed to have just as much trouble as their counterparts today in trying to foresee the future: they frequently got it wrong, particularly with medical student numbers, and with the steady growth of specialization. He had given his Presidential Address in 1960 to the Northern Ireland Branch of the British Medical Association on the subject of poetry in medicine, with particular reference to 'The Testament of Beauty' by Dr Robert Bridges, Poet Laureate: perhaps it needs a Trinity College Dublin graduate to bring back the broader educational values which are stultified by our present highly specialized A level examinations and medical school entrance criteria.

General medical practice at that time had many problems, but in retrospect, I remember the happy times and we seemed to have good holidays, and the sun shone and the snow snowed and the frost froze at the appropriate seasons. Many doctors at that time were so fearful of, and so unhappy with the National Health Service that they advised their children to have nothing to do with it.

Those of us who persevered despite the doom and gloom did so with the support and encouragement, not of committees or books of rules, but of those elders and betters whom we knew and trusted. Perhaps it was always so.

Practical genetics is a fascinating discipline, and pedigrees of diseases can be traced through many generations. It is more difficult to be sure of diagnostic criteria in earlier cases such as the difficulty in establishing a retrospective diagnosis of porphyria in the case of George III's illness, even when the abnormal colour of the royal urine was recorded carefully by the otherwise incompetent (or perhaps more kindly expressed as inadequate) physicians of the day. This family tree [not illustrated] shows a condition which has recurred through five generations, and not all branches have been shown in full. In earlier generations it was rather intermittently expressed, and appeared to be sex linked to males. In later generations female cases occurred. Some early females married males who expressed the condition. This would fit a genetic explanation with a dominant transmission, but it is of course entirely an environmentally determined condition—at least the study and practice of medicine is thought to be such. The affected members of this pedigree probably all felt that they made the decision to study medicine of their own free will: Darwin and natural selection would not allow any genetic explanation, but Lamarck and his discredited theory of the inheritance of acquired characteristics would have recognised some possibility of the transgenerational passage of environmental factors. This latter concept, now dignified by the term 'imprinting' and the Barker hypothesis, may be allowed some respectability, and it has been further studied by Professor Joseph Hoet and his team in Belgium. Robert Bridges expressed the message succinctly and elegantly in his Testament of Beauty as an "*atomic mechanism with unlimited power to vary the offspring in character, by mutual inexhaustible interchange of transmitted genes*".

But would these early doctors have foreseen the problems ahead in 1840? Could the crisis of the Irish potato famine have been predicted? Dr David Hadden (third sibling of the second generation shown) studied medicine as an apprentice to his elder brother in Wexford, and took the examinations of the Apothecaries' Hall in Dublin in 1839: the rules of his apprenticeship make strange reading: the Medical Acts later in the 1840s abolished this method of becoming a doctor, and Dr Hadden himself clearly felt the need of a more established degree as he took the MRCS London and the MD Glasgow by examination in 1846, even though his dispensary practice in Skibbereen, Co Cork, was then in the centre of the worst area for the famine.

As an aside, the profession in Ireland was even then concerned with financial matters, and more urgently the alarming mortality among medical men themselves. Dr William Wilde presented a memorial to the Lord Lieutenant in 1847 signed by 1160 practitioners, "It is right to draw your Excellency's attention to the fact that statistical returns for upwards of twenty-five years exhibit a fearful mortality from fever among the medical men of this country and recent events have shown that from the same cause we have to deplore the loss of many of the best and most efficient practitioners who contacted typhus

fever in the discharge of their duties among the sick poor. We most strongly, but respectfully, protest against the… five shillings per day…offered by the Board of Health for the discharge of that onerous responsibility and dangerous duty". To which they received the reply that "the lordships of the treasury are of the opinion that the remuneration is as high, as under the circumstances of the case, as they should be justified in granting". The average income of a dispensary doctor at that time was about seventy pounds a year. Dr Hadden's response to all this is not recorded, but his patients must have felt strongly about it, for in 1860 they presented him with a service of silver and a purse of 200 sovereigns, which must have been of considerable benefit in his financial affairs.

The practice of medicine in Ireland was entirely empirical, whether by Dr David Hadden in dispensary practice in Skibbereen, or by the leaders of the profession like Graves and Corrigan in Dublin, or by the 19 worthy doctors in Belfast who founded this Society. "These are awful times—never did you see the like, what the end of them will be God only knows—let us watch and be sober": these premonitions are just as relevant today as they were when they were written to the first male member shown on the pedigree on the occasion of his marriage in 1808. Some of the medical members died young and their families had to emigrate to a new life in America, where they often did well—still in medicine. Some had less successful careers, and one at least even came to a bad end: one was a ship's doctor, Dr William Edward Hadden, my grandfather, who was shipwrecked on Rue Point, Rathlin Island in 1886 and that is why I am here in Ulster tonight. One of the American connection, Dr John Hadden, has become a distinguished expert in the immunopharmacology of cancer, and will address this Society on this topic. But none could have foretold two world wars, nor was their medical education appropriate to deal with the problems specifically due to war or famine. A study of the past, whether within a small family or as part of the larger community of doctors, does not identify any common theme of prescience, but always suggests that given a good education, perhaps particularly a good practical Irish medical education, North or South, the practising doctor can adapt to the problems that arise.

THE PRESENT:
"*Reading maketh a full man,*
Conference a ready man,
Writing an exact man"
Francis Bacon, 1561-1626

Reading, conferring and writing about a subject are all essential elements in the search for knowledge, and only by increased knowledge, properly applied, can treatment be improved. Specialization in medicine has come about in a number of different ways, which have led to rather different approaches by the groups of doctors involved (Table I).

TABLE I
A classification of types of medical practice

Age-related	Neonatal
	Paediatric
	Geriatric
Gender-related	Gynaecology
Organ-related	Ophthalmology
	Otology
	Cardiology
	Gastroenterology
	Psychiatry
Procedure-related	Anaesthetics
	Radiotherapy
	Chemotherapy
	Biochemistry
	Pathology
	Emergency medicine
Diagnosis-related	General medicine
	General surgery
	Family practice
Disease-related	Rheumatology
	Haematology
	Tuberculous diseases
	Ischaemic heart disease
	Endocrinology
	Diabetology

An age-related approach has led to neonatal, paediatric and geriatric medicine: children are special because they are small, even very tiny, and need smaller equipment and smaller doses of medicine. They also have parents who want to be part of the action. At the other end of the age range, elderly people have special problems of frailty and the difficulty of living alone—they also have carers, although these may not be their own relations. So these age-related specialities often focus on the broad spectrum of care without necessarily emphasising the detail of individual disease processes or what causes them.

Gender-related medicine is virtually confined to female reproduction, which involves obstetrics and gynaecology: the diseases that develop in women are important because of their effect on the reproductive process and its subsequent long-term effects. Recent trends include the investigation and management of impaired reproduction or infertility, which has taken

on the male component as well. The study of male genito-urinary medicine might in some ways be considered the male counterpart of gynaecology, and the long-term effects of sexually transmitted diseases may be of equal importance to the traditional problems of female reproduction.

Organ-related medicine is also easy to identify. The eye, the ear, the heart, the gut, are all clearly defined, with easily measured physiological functions. The mind is also an organ, though measurement is more difficult. Each of these organs can be the seat of different disease processes, so the specialist must be to some extent multidisciplinary although they will not get to the broader limits of the several disease processes with which they interface.

Procedure-related specialists include anaesthetists, radiologists, radiotherapists and chemotherapists—now becoming known as oncologists as their skills are confined to cancer therapy. The laboratory based specialities are also essentially procedure based, such as biochemistry with its complex measurements, and pathology with its histological examinations. These procedures allow a detailed knowledge of a number of specific aspects of disease processes, but still do not encompass the full spread of a particular pathological process.

Diagnosis is still the most important process in medical care and treatment, whether established in primary care as it frequently is, or uncovered after complex specialist investigations in hospital practice. Diagnosis-related medicine will include the present broad fields of general medicine and general surgery, and both of these relate closely to family practice and primary care medicine, although the present-day family doctor will have a major role in the prevention of disease, as much as or even more than in its diagnosis.

Disease-oriented medicine first appeared with the treatment of tuberculosis, and the success of that exercise, particularly the work of the Northern Ireland Tuberculosis Authority between 1946 and 1959, has been documented by H G Calwell and D H Craig in the booklet 'The White Plague in Ulster'—in 1946 twenty people were dying from tuberculosis each week, and by 1959 this had fallen to two per week and has continued to fall, though not unfortunately to disappear altogether.

There were several reasons for that success, not least the discovery of effective drugs: but tuberculosis remains a scourge in other countries and the great value of a focused and authoritarian approach to disease control must not be forgotten. I first realized I was practising disease-oriented medicine in 1960, when I became senior house officer to Dr Desmond Montgomery and Dr John Weaver in the Sir George E Clark Metabolic Unit at the Royal Victoria Hospital. This had been opened three years earlier, in 1957, by Professor Charles Best of Toronto, who was famous as one of the team who discovered insulin—now recognised to include Banting, Best, Collip and Macleod. It was then, and is now, one of the very few units specifically devoted to metabolic diseases—what has now come to be known as endocrinology and diabetes. The phrase 'metabolic' is rather specific to Northern Ireland, and comes from the biochemical background of Dr J A Smyth who was physician in charge of the biochemical department and had not had direct control of inpatient beds to treat the increasing number of patients referred to him with diabetes of all types. A large diabetes clinic for outpatients had grown up, since the first use of insulin in Belfast, but this was accommodated initially on a row of chairs outside the biochemistry laboratory and later in the basement of the original outpatient hall, now still the department of dietetics. When one of the Clark family of the Workman Clark shipyard left the then large sum of £10,000 to the Royal Victoria Hospital it was in recognition of the work done for diabetes over the years; the building was designed to incorporate outpatients in a carefully organised progressive consultation system with full time clerical, nursing and dietetic staff, and for 30 beds on two floors upstairs for inpatients.

No other hospital in the United Kingdom has a Metabolic Unit quite like ours, and we must cherish it and look after the concept whatever comes in the future. Our outpatients are now seen in the new general outpatient building which is much too far away; the regional endocrine laboratory was accommodated in the ground floor of the Metabolic Unit for twenty years but has now moved to the new Kelvin laboratory building. The space is now being reopened as the Diabetes/Endocrinology Day Centre, with facilities for diabetes nurse specialists, dietitians and dedicated patient education facilities. We will also have proper accommodation for the secretarial and clerical staff, and for the computerised diabetes and thyroid registers.

In 1960, endocrinology was the most exciting field in medicine, with new hormones and new diseases and new drugs to treat them being discovered each year. The pioneering work of Montgomery and Welbourn in bilateral adrenalectomy for Cushing's Syndrome had established Belfast as a centre for the new speciality, and when the facilities of the Metabolic Unit became available, with the biochemical expertise developed by D W Neill, the situation was ripe for rapid devel-

opment and all of us who were junior staff in those days benefited greatly. Cortisone had recently been discovered and the adrenal steroids made enormous therapeutic advances possible, although controlled double blind trials were certainly not undertaken and many misjudgements must have been made. It was perhaps Desmond Montgomery's insistence on long-term review of these Cushing's Syndrome patients, who were maintained on cortisone acetate and came to a special clinic which still exists, called the Adrenal Clinic, once a month, that started one line of disease oriented medicine. By following the patients it became clear that a few would develop excess ACTH secretion, and eventually succumb to a locally aggressive pituitary basophil tumour—the world knows this as Nelson's Syndrome, but we in Belfast know that it was first recognised by Montgomery and Gleadhill and their colleagues. Some of these early patients still survive 40 years later, and still come to the Adrenal Clinic: the natural history of a disease takes a lifetime to identify, and will involve the professional lifetimes of several medical attendants. Good records, and the passage of interest and enthusiasm from one doctor to the next, are necessary for long-term studies.

Thyroid disorders were probably the reason for the term 'metabolic'—special single rooms were built for measurement of basal metabolic rate, which was the only test for hyper- or hypothyroidism: the old BMR machine still exists but it was a poor and inaccurate measure. The duty of the senior house officer was to creep into the room early in the morning, with the patient sedated and the blinds down, and gently put in a large rubber mouthpiece and ask the patient to breathe normally into a canister of soda lime: not an easy thing to do even in a physiology laboratory, and certainly alarming first thing in the morning in a strange hospital. But it is surprising how good the results were, and even the subsequent development of radio-iodine neck uptakes and then accurate assays for serum thyroxine and TSH have not entirely removed the concept of measuring the end organ action of the thyroid hormone by some index of oxygen consumption.

Hypothyroidism had first been treated in Ireland in 1892 by Dr Thompson of Feeny, Co Londonderry, whose history was identified by the late Dr Mary Logan: hyperthyroidism proved a more difficult therapeutic task, and although subtotal thyroidectomy was surgically possible in the 1930s, even post-war it was still a formidable procedure. The development of antithyroid drugs and the introduction of therapeutic radio-iodine has made a cure of Grave's disease a much more straight-forward, and more certain, procedure. The long-term recall of many of these radio-iodine treated patients became unnecessary when the metabolic unit thyroid computer review service was introduced in the 1970s, and although many general practitioners are now sufficiently well organised to provide this service themselves, some patients still are pleased to feel they have contact with the Metabolic Unit, even if only by computer-generated letter.

The overall change in management of hyperthyroidism between 1970 and 1990 is shown in Table II. The great reduction in subtotal thyroidectomy and its replacement by radio-iodine means that a two-hour day procedure with only a few subsequent hospital reviews should be sufficient. The staff of the Metabolic Unit are registered for this radio-isotope administration, and the concept of disease oriented medicine means that we are still interested in the long-term outcome. In the early days we used smaller doses, but the tendency to relapse, with need for more hospital attendances pointed to the use of larger ablative doses, and when Dr Atkinson and Dr Kennedy returned from the USA in 1980, and brought this more radical approach, both Dr Weaver and I were happy to go along with it. Thyroid cancer management requires even larger doses and close co-operation with the endocrine surgeons—initially Mr Willoughby Wilson, and now Mr Colin Russell.

TABLE II
Hyperthyroidism in Northern Ireland. A therapeutic audit of the numbers of patients treated by three different methods over two six-year periods. (Based on data from Hadden D R, McDevitt D G,1974 and subsequent analysis.)

	1966-71	1986-91
Carbimazole (standardized treatment years)	3,127	2,739
Radio-iodine	633	1,063
Subtotal thyroidectomy	295	60
	4,055	3,862

It was Mr Russell's interest in thyroid cancer that has resulted in a long-term investigation of a widely distributed kinship of the MEN 2 syndrome (Multiple Endocrine Neoplasia type 2): members of this family have developed malignant medullary thyroid cancers, with or without adrenal phaeochromocytomas. The search for effective endocrine tumour markers—initially with serum calcitonin, and subsequently with the interest of Dr Patrick Morrison the demonstration of genetic markers on chromosome 10 has meant that members of these families can now be identified with a high degree of accuracy to be either at risk or not at risk of thyroid cancer. The family tree shows that the

genetic marker has been 100% accurate in known cases, but the problem of management of children in the next generation who are genetically positive but have absolutely no evidence of thyroid cancer, means that the skills and wisdom of the thyroid surgeon are still needed. The disease-oriented approach to these patients means that one team keeps in touch with all members of the family, so that consistent advice is given, although with most careful confidentiality between different branches of the family. Even in well integrated families there are personality difficulties, and it can be difficult and at times disappointing when people known to be at risk refuse to come for even simple treatments or tests. Pre-clinical diagnosis is not always popular, and this aspect of medicine in the future will tax our successors just as much as some of the tragedies of today.

My own interest in research in the Metabolic Unit started off at a very early stage in wondering why some babies born to diabetic mothers were so large. The theory of Dr Jorgen Pedersen in Copenhagen was that maternal hyperglycaemia caused fetal hyperglycaemia and subsequent endogenous fetal hyperinsulinism which caused fetal overgrowth: my somewhat naive concept was that the mother's growth hormone might also be too high, and account for the impaired maternal glucose tolerance in the first place.

With the enthusiastic support of Dr Graham Harley, and the encouragement of Dr Montgomery who had already set up their combined metabolic antenatal clinic with the intention of simplifying the clinical attendances of the diabetic mothers, we set off on an odyssey which still continues. Glucose tolerance tests in pregnancy have proved to be a never-ending search for international agreement, and have introduced me to the medical and political interactions of a number of countries round the world.

We hope that Belfast will be one of the central points and the laboratory for the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study, one of the largest cooperative international studies ever undertaken, on 25,000 normal pregnant women each of whom will have a glucose tolerance test, in 25 different countries, simply to sort out the ethnic and environmental differences. Once that is done, the disease-oriented approach will allow careful monitoring of what is most likely the real cause of the explosion of non-insulin dependent diabetes throughout the developing world. The transgenerational effect of maternal hyperglycaemia has been shown to affect the second and third generation in animal models, and to be responsible for both obesity and diabetes in the first generation in human studies. Whether the Barker hypothesis of maternal malnutrition as a cause of many of the ills of the offspring when they grow up will be confirmed is still uncertain, but there is major evidence to support the diabetes effect.

The road to measurement of maternal plasma growth hormone was long and difficult. I made my own human growth hormone from pituitary glands collected in the mortuary. I made antibodies to it in rabbits, and set up radio-immunoassays which largely did not work. I was fortunate to be able to go to the Johns Hopkins Hospital, Baltimore, USA, and work in the Endocrine Unit under Dr Sam Asper and Dr Thad Prout, who had also trained Dr Weaver before me. The endocrine link with the Johns Hopkins Hospital extends further back, to the time when the then Dr John Henry Biggart studied the neuropathology of the posterior pituitary in the 1930s.

The assay for growth hormone came with me, and diverged into studies as to why it did not work, which led to the first clear identification of a growth hormone binding protein. This was received with much disbelief by the originators of radio-immunoassay techniques in the USA, Berson and Yalow, but I was encouraged to find they spent the next two years repeating my work in order to try to disprove it, and even more to find the growth hormone binding protein rediscovered in Chicago by Dr Gerhard Baumann 22 years later. The pathophysiological role of this substance still remains unclear. Dr J K Nelson followed me in Baltimore, and ultimately a method of assaying growth hormone in serum was developed which has proved robust and consistent in clinical practice. It does not seem to be important as a cause of big babies.

After return to Belfast for a year, my metabolic story took a curious, but entirely logical turn when the opportunity arose, through the good offices of Professor Graham Bull and the Medical Research Council, to become a temporary member of the scientific staff and, in fact, the only qualified doctor at the MRC Infantile Malnutrition Research Unit in Kampala, Uganda. This was then a very famous unit, where most of the scientific work on malnutrition had been undertaken, with careful analysis of the differences between kwashiorkor and marasmus: there were close links with Professor R A McCance and Dr Elsie Widdowson, although they stayed most of the time safely at home in Cambridge. The question was whether growth hormone, and insulin, played any part in the endocrine response to malnutrition, and whether it might be possible to explain and hopefully prevent the sudden deaths that occurred during refeeding of these malnourished children.

David Robert Hadden

Uganda in 1965 was a delightful country: the Medical Research Council ran a first class research unit: the work went well and I learnt a lot of paediatrics and basic nutrition, which has left me with the life-long determination to improve the teaching of nutrition in our own medical schools. Even after a famine, a rapid increase in mortality from diabetes and the present day Northern Ireland epidemic of ischaemic heart disease which may well be entirely nutritionally based—there was no ischaemic heart disease in the African population of Uganda in 1965—there is still no formal teaching, or department of nutrition, at The Queen's University of Belfast.

On return to the Department of Experimental Medicine in Cambridge I was one of the last fellows to work under Professor R A McCance, the distinguished but eccentric professor who had been born and brought up in Woodburn House, Dunmurry. His early interest in the growth of babies has laid many of the foundations for the present interest in the relation of size at birth and subsequent disorders in adult life. Growth hormone and insulin were certainly affected by the malnourished state, and showed a pathophysiological adaptation: as might be expected, the best way to avoid serious events during recovery was to proceed slowly and not to give too much by way of either nutritional or hormonal supplements. These basic clinical concepts had been reinforced by the nutritional studies on pigs under McCance's supervision.

At the same time as these laboratory investigations there was much clinical interest in the use of growth hormone in helping short-statured children to grow more normally. Human pituitary glands had continued to be collected carefully at autopsy and stored, and were eventually pooled with similar collections at the MRC pituitary peptide laboratory in Cambridge. The Medical Research Council, and subsequently the Department of Health, drew up most stringent rules for deciding which children would be eligible for this rare and expensive therapy, which had to be given by daily injections, but which certainly worked and produced considerable growth spurts in growth hormone deficient children. I sat on these committees in London, and the constant problem in the 1970s was that there was not enough human pituitary growth hormone to satisfy the demand both from paediatric endocrinologists and from parents of the small children. When a child was accepted for treatment, the enthusiasm always overcame any reservations about possible long-term side effects from a hypothetical slow virus.

In 1985, the first case of Creutzfeldt-Jakob disease was recognised in a person who had received human pituitary growth hormone 20 years before. This is a rapidly fatal progressive dementia and ataxia: there have now been 15 cases among the 1,850 children who received the human growth hormone between 1960 and 1985. There have been none among the 40 children treated in Northern Ireland. No further treatment with this human product was given after May 1985, and it was fortuitous that genetically engineered biosynthetic growth hormone identical to the human molecule became available within six months of the withdrawal notice.

But these people are justifiably concerned about their future, and the ultimate outcome is not yet clear. Several of the Northern Ireland patients have become pregnant in the natural course of events, and no problems have arisen in the children. The benefit of the disease-oriented approach in the Metabolic Unit is that I am still able to look after these people, and keep in contact with them at least annually as far as possible. In Great Britain the greater separation between paediatrician and adult endocrinologist meant that most of the early growth hormone treated children who had grown up had stopped attending hospital, and it has proved remarkably difficult to contact some of them again, even in these circumstances.

Another angle on the disease-oriented approach to diabetes is the long-term review we know as the Belfast Diet Study. Those of you who refer diabetic patients to the Royal Victoria Hospital will know that we have a "we try harder" approach to reducing energy intake and advising sensible eating for non insulin dependent diabetes.

Belfast has a mild degree of fame on the international diabetes circuit for this approach, and specialists from other countries, especially the USA and Germany, will still stop and ask how we achieved such good results on diet alone? The answer they suggest is that there must be something special about the diabetic people in Belfast—perhaps our dietitians deserve the credit too.

But like all long-term studies, even where the patients live longer than the doctors, there is still a down side, and there is no doubt that the prevalence of death from myocardial infarction is still considerably higher in these patients after 10 years than in the population of Northern Ireland. This hospital-based diabetes study will become one of the markers for the future management of this disease in family practice, and the risks of this so-called mild disease must be fully understood by patient, nurse and doctor. The most recent analysis of the Belfast data shows a strong relationship between high blood glucose levels identified as a continuous variable

during the ten-year review period and either death from or the occurrence of a myocardial infarction. Macrovascular disease in non insulin dependent diabetes is the real problem.

There is not time to discuss a number of other disease-oriented concepts in endocrinology. Metabolic bone disease, from hyperparathyroidism to osteoporosis, is a slow moving but crucial problem which requires a long-term approach to assess results. The management of female hirsutism and the polycystic ovarian syndrome are still under investigation. And the problem of what happens to children with an inborn error of metabolism such as phenylketonuria, when they grow up, will be the subject of the next meeting of this Society.

In retrospect, considering these past 40 years in the present tense, we were a fortunate group of medical students. We arrived at a time when scientific medicine was taking a great leap forward and we were able to participate in that leap. We had a scientific education from the combined clinical course at Queen's University, and we were encouraged to carry out clinical research projects. So I have no problem in maintaining an optimistic stance as we try to look into the future.

THE FUTURE

"Say not the struggle naught availeth
The labour and the wounds are vain,
.....
In front the sun climbs slow, how slowly!
But westward, look, the land is bright! "
Arthur Hugh Clough 1819-1861

The future of disease-oriented medicine is to abolish the disease. This is certainly a possibility for all the endocrine and metabolic disorders, particularly those which have an autoimmune basis such as insulin dependent diabetes and both hyper- and hypothyroidism. All that is needed is a means of preventing the initiation, or of the progression, of the activity of the activated T-cell lymphocytes in the cascade of events which leads to the production of antibodies to the specific hormone, such as islet cell antibodies in diabetes. There are a number of studies in progress in this field, of which we are participating in one called ENDIT—a study of the effect of nicotamide in this process—jointly with Dr Dennis Carson at the Royal Belfast Hospital for Sick Children.

The identification of children at risk for insulin dependent diabetes because of the presence of islet cell antibodies, even though their blood glucose is completely normal, leads to a number of both ethical and management problems, as there is no clear way ahead at present. The most important fact is that not all these children will actually develop the disease, and in some way nature overcomes the incipient autoimmune process in some of them. That spontaneous cure is what we are looking for. The future management of diabetes may well be a complex matter of identification of the condition before it occurs, and some form of immune modulation to prevent the progression and encourage the remission of the process—all without the classical marker of a high blood glucose and the rather dramatic symptoms that used to go with it. This form of pro-active prevention will need a dedicated team, and an efficient process of identification, education and review—the concept of a diabetes prevention clinic, or even a computerised postal review process, is not yet with us. The experienced family doctor will recognise the difficulty of practising preventive medicine, even when the interaction is as simple as an inoculation to prevent diseases that used to be lethal.

These concepts should also be possible for the prevention, or at least the prevention of progression of the several diseases due to activation of a genetic process in a clone of cells in the anterior pituitary gland. Cushing's disease is due to the inappropriate activation of the gene for ACTH production in the anterior pituitary on chromosome 12: it is not a malignant tumour, but expresses itself because of the profound effect of the excess ACTH on the production of cortisol in the normal adrenal. Even if inactivation of the abnormal gene (without complete suppression of the normal ACTH producing basophil cell mechanisms) is not immediately possible, the concept of targeted radiotherapy or chemotherapy to the anterior pituitary using specific antibodies to the abnormal hormone producing cells is tantalizing, though still ineffective. The role of the neurosurgeon in the cure of Cushing's syndrome, so well practised in Belfast by Colin Gleadhill, Derek Gordon and Tom Fannin and John Grey is still necessary, but like the changing role of the thyroid surgeon, no operation is forever. The recognition by Professor Brew Atkinson that some patients with pituitary dependent Cushing's syndrome may be intermittent, or cyclical, indicates that there must be other as yet unrecognised processes involved in switching on and switching off the pituitary trophic hormones, which may lead to drugs with as striking an effect as that of bromocriptine in hyper-prolactinaemia.

In the absence of total prevention of the disease, our present aim is to prevent the complications. For diabetes this means returning the blood glucose to normal, and keeping it there. The discovery of insulin in 1921 produced the means to do this, and we are

still learning how to use this potent cure; the problem is that as the only potent drug which is self-administered by people with the disease, and which has such an unpleasant and potentially lethal side effect, it is human nature not to want to push the dose too close to the borderline between normoglycaemia and hypoglycaemia.

The late Dr Jack Smith was remembered by his patients for insisting that they kept their blood glucose normal, and for insisting that it was measured in the laboratory before he saw them—this early insistence is largely responsible for the overall better level of control of hyperglycaemia which can still be shown in comparisons between diabetic patients in Northern Ireland and those in less well organised places—for example in the South of England, where many diabetic people were rather left to their own devices with only occasional contact with a family doctor and only the unsatisfactory measurement of urine glucose as a yardstick of success.

Good organization is essential, and the record cards introduced by Professor Montgomery in 1958 are still the basis of management in the Royal Victoria Hospital and most others in Belfast: the computerised patient management system pioneered at the Royal, but developed jointly by the Northern Ireland Diabetes Group, will produce the means of auditing the success of this long-term and rather intensive form of preventive epidemiology. The development of measures of control of hyperglycaemia by identifying the amount of glucose stuck non-enzymatically on to the haemoglobin (by Dr Laurence Kennedy), or other protein molecules (by Dr Tim Lyons), has produced a much better long-term assessment. Dr Laurence Kennedy should get the credit for introducing this measurement into hospital practice in 1980, when he returned from the USA, and the early work in Belfast, including the demonstration by Dr David McCance that long-term prospective control of glycosylated haemoglobin will prevent the microvascular complications, was one of the first real proofs of the importance of good control. We always knew it to be so, but it had been very difficult to prove. Eventually the Diabetes Control and Complications Trial in the USA has confirmed the Belfast studies, by a prospective randomised trial. The evidence is available and our only problem is to deliver the goods.

Dr Patrick Bell had demonstrated that excellent control could be achieved by special insulin infusion pumps, and these were part of the very expensive DCCT study. In Europe, where we are rather in advance of US medicine in many ways at a pharmaceutical level, it was soon realized that the pen injectors would allow multiple insulin doses to be given with minimal inconvenience to the person with diabetes, and that these simple devices were much preferable to the expensive and more complicated pumps.

The Northern Ireland Committee of the British Diabetic Association, which is about to open an office in Belfast, and a number of Department of Health and Regional Board committees will help to organise the dream of achieving a disease-oriented diabetes treatment programme in which we can all take part—-general practitioner, diabetes physician, specialist nurses, dietitians, chiropodists, and people with diabetes.

The immediate future is therefore a process of facilitation of the delivery of a drug discovered over 70 years ago. The encouraging resurgence of interest in diabetes management in family practice, and the development of shared care and outreach clinics should assist this in the short term, and there is much work to be done by us all. If we are successful, our colleagues who have provided such important services in fixing up the ravages of persistent hyperglycaemia may be less heavily involved.

I have not had time to discuss the importance of these complications, but the ophthalmologists under Professor Archer and his team; the experts in end-stage kidney disease at the Renal Unit in the Belfast City Hospital who follow the recipes for success laid down by Professor Mary McGeown; the extraordinary vascular surgical repairs and when necessary the preventive amputation of digits undertaken by Mr Barros D'Sa and his colleagues; the preventive approach to foot ulceration with neurological measurements and the provision of practical footwear and foot care by skilled chiropodists; and the cardiological management of diabetes-related ischaemic heart disease which is now the ultimate killer in the great majority of our patients: all of these hard working and uncomplaining colleagues in our practice of disease-oriented diabetic medicine could and should be put out of business!

I have not referred to some of the present day problems of medical organization such as funding, or purchaser-provider splits, or priorities, or resource allocation, or even medical fees, because like the doctors who coped with the problems of fever and famine 150 years ago, the practice of medicine is always with us. Future developments will certainly change what we do, but both specialization and generalization will persist beyond the year 2000. The new building for the Royal Victoria Hospital, which will incorporate a new Metabolic Unit, will allow our team to continue to practise our form of disease oriented metabolic medicine. The next generation of

endocrinologists will still need the enthusiastic co-operation of colleagues in all branches of medicine, and from all parts of Northern Ireland. The next millennium is almost with us, and “the land is bright”.