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Banting Memorial Lecture 2021

Banting, banting, banter and bravado:

Convictions meet evidence in the scientific process

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Abstract (272 words)

This personal account presents some glimpses into the clinical research processes which have made radical changes to our understanding of disease and treatment, and some characteristics of researchers, drawn from history and personal experiences around obesity and type 2 diabetes.

Some summary messages emerge:

- The history of clinical diabetes research has shown how, perhaps through skilful leadership, combining very different personalities, skills and motivations can solve great challenges
- Type 2 diabetes is a primary nutritional disease, secondary to the disease-process of obesity, not a primary endocrine disease
- Type 2 diabetes is a manifestation of *the disease-process of obesity,* revealed by weight gain in people with underlying metabolic syndrome genetics/diathesis, mediated in large part at least by reversible ectopic fat accumulation impairing function of organs (liver, pancreas, brown adipose tissue)
- Treat overweight/obesity more seriously (defined as a *disease-process with multiple organ-specific complications* - not as a BMI state or cut-off)
- Discuss the complications and risks of T2D openly: remission is as important as for cancers
- Offer and support an optimal dietary weight-management programme as soon as possible from diagnosis, specifically aiming for remission
    - Warn against non-evidence-based programs that look similar or claim to have similar potential: we have fully evidence based programmes
    - Target sustained loss of >15kg for Europeans, (possibly less, eg >10kg for Asians?)
- Increase future research support to enhance long-term weight loss maintenance. Several approaches need consideration:
    - Personalise diet compositions (recognising there is no intrinsic advantage from different carbohydrate/fat content)
    - Novel diet strategies (eg 5:2, time-restricted, flexible diet compositions)
    - New Pharmaceutical agents as adjuncts to diet if necessary
    - Food supplements to increase endogenous GLP-1 secretion

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To deliver the Banting Memorial Lecture is a great honour. It provides an unusual opportunity to discuss an approach to clinical science through a personal story, in which I will reflect a little on Banting's own contributions.

Banting, Banting and banting

The discovery of insulin, exactly 100 years ago, was very remarkable for a huge number of reasons. Frederick Banting's entire research experience took up less than one year, before the seminal paper announcing the discovery was published in March 1922. Just a year after its publication, the Nobel Prize was awarded to Banting and John MacLeod. The term 'fast-tracking' had not been coined. This was development of global importance huge global importance. Academic and civil honours followed, statues were erected, and Banting's portrait appeared on postage stamps all over the world. That's a mark of fame few of us can imagine. The discovery was heralded as the cure for diabetes – job done. But where are we now, exactly 100 years on?

We shouldn't underestimate the importance of this discovery for Canada. Almost overnight, Banting became for Canada what Edmund Hilary was for New Zealand - a national male-caricature-hero of dimensions we would rank alongside Alexander Fleming, Alexander Bell, John Logie Baird, David Hume, William Wallace, Robert the Bruce and Sean Connery, all rolled into one.

The discovery of insulin has been documented many times. I have been guided by and refer to the provocative book by Michael Bliss, whom you many of us will remember from his attendances at Diabetes UK meetings (1). It, of course, contains the photograph, familiar to all diabetes specialists and many others, showing Banting, the medical student, Charles Best, with whom he shared his Nobel Prize, and the dog, Marjorie. Charles Best gave the very first Banting Memorial lecture, in London in 1947, six years after Banting's premature death in a military plane crash (2).

The story of Banting and his input into the discovery of insulin, as related in Bliss' book, brings to mind the 1986 Willendorf lecture given in Jerusalem by Jules Hirsch, another megalithic figure in obesity and metabolic research. In that lecture he traced the roles of contrasting personality styles, characterised as Mutts, Moles, and Mappers, in their approaches to clinical research. The mutt, or dog, sees a target, barks furiously, and goes for it on sight alone, without regard for anything on the way. It will crash through fences and do damage, all the way to reach that target. But may fail. The mole, in contrast, digs deep to reach the target, working quietly and scarcely seen, taking perhaps very much longer, but with great security and surety. The mapper is the first to see new territory, and makes sense of it to identify what the targets should be. We can all recognise those first two characteristics, perhaps within ourselves, and perhaps glimpse the role of a mapper. Jules Hirsch's message was that all these characteristics are often needed to make scientific progress. (3).

Frederick Banting completed his medical training in just four years, in order to go to the Western Front, where he was slightly wounded in his right arm. After the war, he returned home to London, Ontario and

tried to set up a solo surgical practice. He passed the necessary exams, however with experience limited to patching up soldiers and cutting a few things off, he lacked general surgical skills. And he certainly had no medical experience. Consequently, he had no patients, and he was forced to lecture to medical students for his living. Required to lecture about diabetes, he read up the accounts of Minkowski's work, some 30 years earlier, when it was shown that removing the pancreas would result in diabetes (4). It was well accepted that the pancreas must be making something other than just digestive enzymes, which was preventing diabetes, so this was not a new idea, but it had not been isolated. People were dying of diabetes, and Banting was probably angry at what he viewed as unacceptable delay because a former classmate and friend had developed type 1 diabetes.

In the middle of the night on 31st October 1920, Frederick Banting had a dream in his bedroom in London Ontario, which he recorded. He wrote:

"*Diabetus. Ligate pancreatic ducts of dog.*
Keep dogs alive till acini degenerate leaving islets.
Try to isolate the internal secretion of these to relieve glycosurea."
We notice that he spelled diabetes and glycosuria incorrectly. Diabetes was not his field - yet.

So convinced he was, by that dream, that less than a week later he marched up to the laboratory of John Macleod, the Scottish professor of Physiology in Toronto, and asked for a position to do his dream experiment. He started work exactly 100 years ago in April 1921. His initial meeting with MacLeod is not recorded, but there was a gulf of experience and understanding. Macleod was a very experienced scientist, with 15 years of experience looking for insulin. Banting's idea was not at all new, the name 'insuline' had been coined by a Belgian, Jean de Meyer, back in 1909 and independently by Sharpey-Schaffer in 1916 (5), when it became clear that the Islets of Langerhans were responsible. Macleod had probably actually already found it in fish, but he was something of a perfectionist, and wanted to be able to reproduce the discovery in animals before making any claims. A major clash of personalities soon emerged, as it became clear that Banting felt Macleod was being secretive, delaying the discovery that could save his diabetic class-mate and many others, and even aiming to claim the patent for insulin. Macleod was a stickler for reproducibility of experiments and wanted all the i's dotted. He was an archetypal presbyterian ex-pat Scot, who also took long holidays in his beautiful homeland. Banting was a brash non-conformist Canadian, who wanted 24-hour action and the flags flown for Canada.

Very soon, Macleod brought in a young medical student, Charles Best, to help Banting (or to keep him quiet), and also a very good biochemist, Collipp, from a local pharmaceutical company, to speed up the

measurement of glucose, which was a limiting step for his research at that time. The latter appointment inflamed Banting all the more, fearing that 'his' idea would be stolen by a drug company. A fist-fight ensued, with Banting famously laying out Collipp in the laboratory. Not the most auspicious approach to a Nobel Prize, but somehow this conjunction of conviction with evidence all worked.

Banting still believed that the past failure to extract a functional insulin was because of the digestive juices in the dissected pancreas. Collipp soon showed that this was not the explanation, but a different solvent extraction method was needed, but Banting took a lot of persuading. The number of Toronto's dogs sacrificed by Banting and Best's inexpert surgery in those few months was reckoned to be above 600, possibly well above that. A dog-catcher was paid $3 per dog, no questions asked. One, number 33, ('Marjorie') famously survived for 70 days without a pancreas, sustained by injections of crude pancreatic extractions from other dogs. The others all died miserably, usually of infections. For Banting, Marjorie and a handful of other survivors was the proof he needed, and without permission from Macleod or anyone else, he began to try injecting his pancreatic extracts into humans with diabetes.

The paper announcing the discovery of insulin was published in March 1922 in the Canadian Medical Association Journal (6). Significantly, the authorship did not include John Macleod, although experts have suggested that only MacLeod could have rescued Banting's writing to the level that could be presented as a paper. It described brief experiments, treating six patients (no ethical permissions of course) with a concentrated pancreatic extract containing the still-putative secretion of the pancreas. Two of those six patients showed signs of improvement in their biochemical and clinical signs of diabetes. Not a great statistical basis for the greatest medical discovery of all time, but with that paper in the bag, and headlines secure, Banting evidently agreed to the project's being transferred to Connaught Laboratories for commercialisation, with improved purification of the elusive pancreatic protein, and large-scale production soon followed.

The Nobel prize was awarded, with the dust barely settling, specifically to Banting and Macleod, but these two both took the unusual immediate step of sharing their prizes, Banting with Best, and Macleod with Collipp. All four wrote books about that extraordinary year, with very little common ground or agreement about what happened. John Macleod soon returned to Scotland, in relative obscurity, but not before he (the mole) and Frederick Banting (the mutt) agreed to sell the patent for insulin to the University of Toronto 'as a gift to mankind'.

This snapshot of clinical research in 1921-22, for which a debt is owed to Michael Bliss for his book, illustrates how both mutts and moles are needed to make great scientific advances, but would be

incomplete without mention of the dogs of Toronto. Their role, and that of the pigs and cattle which later provided the vast amount of pancreas needed to provide for people with diabetes world-wide, was vital. Much as one would always prefer to find research methods that do not harm animals, there was no credible alternative approach to discovering and then manufacturing insulin. Stray dogs and rescue dogs in Toronto have a very special place in diabetes history. They also feature prominently in an intriguing canine sci-fi novel (7).

Having established that insulin exists, it was soon purified and characterised biochemically and finally in 1969, after some 35 years of patient research, structurally – Nobel Prize laureat Dorothy Hodgkin herself delivered a Banting Memorial Lecture on the Structure of Insulin in 1972 (8). These are fascinating stories, but observations from its use in clinical practice over the next decade began to reveal different types of diabetes. It was a megalithic figure of diabetes research, Harold Himsworth, who first described two very different types of diabetes, depending on insulin sensitivity: insulin-sensitive diabetes which we now identify as type 1, and insulin-insensitive diabetes, which we now call type 2 diabetes (9). Intriguingly, commenting on Himsworth's scientific agility in his obituary, Edwin Gale drew an analogy from the classical fable, likening his devotion to diabetes (perhaps harshly) to the hedgehog who has only one strategy for life (to curl up and be prickly) as opposed to the wily fox or dog who darts from one to the next (10)

Importantly, Himsworth also showed in 1934 that non-insulin-sensitive (type 2) diabetes was better controlled with a high carbohydrate diet (11). This was a radical departure from the previously standard and ghastly 'Allen starvation treatment'. The idea that carbohydrate could be beneficial for type 2 diabetes was revolutionary, one in the eye for followers of William Banting, a distant ancestor of Frederick Banting, an English doctor who had a weight problem. He published a 'letter' in 1863, which related his weight-dependent symptoms, and described the improvements from his losing about 15kg on an extreme low-carbohydrate diet (12). He fuelled the naive belief that if sugar was coming out in the urine, the treatment should be to stop putting sugar (or by extension carbohydrate) into the mouth. The 'Banting Diet' became widely followed as a treatment for diabetes, its vestiges remain, and the word 'banting' remains a common term for dieting in the Swedish language. There are even Banting diets for dogs, which are phylogenetically better-suited than humans to low carbohydrate diets.

The BAT man arrives

The very first lecture I ever gave, as a newly appointed MRC Clinical Scientist in 1980 was about the history of diabetes diets, including William Banting, when I stood in at short notice for Jim Mann at a

British Council meeting in Cambridge. At that time, I was working on the brown adipose tissue of humans, as a possible mechanism for body-weight control, as well as dietary approaches for diabetes. That four-year interlude in a medical career of full-time research training was invaluable, sharing ideas and spending time with clever and ingenious people of every discipline, and experiencing the long agonies and occasional ecstasies of success within clinical research.

One line of inquiry took me into the eclectic field of phaeochromocytoma research, because animal work had shown that brown adipose tissue thermogenesis, through uncoupled oxidative phosphorylation, was stimulated by catecholamines. **Figure 1** shows omental and perirenal adipose tissue (internal sites of brown adipose tissue in infancy) from a young man who had died tragically in a road traffic accident. The histology is essentially the same as subcutaneous white fat. Very different multilocular histology, exactly like brown adipose tissue of experimental animals, and as seen in human infants, is found in the internal adipose tissue removed at surgery from patients with phaeochromocytomas. (13)

After purifying the 32kD uncoupling protein from isolated mitochondria, I was able to measure the uncoupling protein (now referred toas UCP-1), and to show that it is uniquely located in mitochondrial folds, using gold immune-staining. (14) Studies using oxygen electrode, and GDP-binding, demonstrated that human mitochondria which possess UCP-1 exhibit the uncoupled respiration needed for non-shivering thermogenesis, and for energy wastage to oppose weight gain and obesity. In most human adults, mitochondrial uncoupling protein content was very low, but slightly higher in infants and children who have greater need, and capacity, for thermogenesis. However, we showed extraordinarily high UCP-1 contents in the mitochondria from patients with phaeochromocytoma (**Figure 2**), similar to those in experimental animals. This was a highly thermodynamic tissue burning calories, causing patients to lose weight, and specifically relevant to my present story, to lose the volume of their abdominal fat (15).

The reduced intra-abdominal fat content, and weight loss, of people with phaeochromocytoma linked in my mind with the opposite situation in type 2 diabetes, where the intraabdominal fat compartment is expanded, and most obviously preferentially expanded with large lipid-filled cells, in people with type 2 diabetes who are not yet severely obese. This looked like tissue which, although derived from a site of brown adipose tissue in infancy, appears almost devoid of the features of thermogenic brown adipose tissue. I took this hypothesis into the clinical sphere, by putting people into a whole body calorimeter to examine the metabolic effect of mild cold exposure. Normal, healthy individuals all demonstrated an increase in metabolic rate overnight at 22° C, compared with thermoneutral 24 °C, indicating the expected rise with non-shivering thermogenesis. In contrast, obese type 2 diabetic patients all dropped their energy expenditures, and their core temperatures tended to fall at 22°. A single volunteer with obesity

and type 2 diabetes spent a night at 19°, an ambient temperature which many would find uncomfortably cool. She slept soundly, but core temperature fell more, and she showed an extraordinary 13% reduction in sleeping energy expenditure. People who were overweight but not diabetic showed intermediate responses to mild cold exposure (Table 1) (15)

These were small complicated clinical studies. They did not prove that brown adipose tissue thermogenesis was specifically absent in people with type 2 diabetes, but the findings are at least suggestive, and they resonate with several studies which have identified type 2 diabetes as a frequent feature among people who are admitted to hospitals with hypothermia (16). Additional support was published just a few weeks ago, in a paper from Phoenix Arizona which showed that people who tend to become overweight, with a 'thrifty phenotype' dropped their metabolic rate with the cold exposure. They used very similar experimental conditions and temperatures to what we used we used in Cambridge almost 40 years earlier, but they also showed with PET scanning that these individuals lacked the normal activation of brown adipose tissue thermogenesis which increases metabolic rate on cold exposure. (17)

The Great Waist Trail

The realisation that tissue volume is not necessarily an indicator of physiological function was part of my route into what we might now call the Great Waist Trail. I think it is now fully established that a big waist is bad for metabolic health outlook, whether or not there is a very large BMI. The evidence we used to derive and validate the waist circumference cut offs, for personal action >80 cm in women >94 cm in men, and for professional intervention at >88cm in women and >102cm in men, was purely observational, with highly pragmatic conclusions (18, 19). Another potentially shaky-science start, possibly with mutt characteristics rather than mole, but this work has been supported very consistently elsewhere, and those cut-offs have stood the test of time. It is important to recognise that they were originally developed as part of the work for the first SIGN guideline on obesity, published in 1996, as a simpler alternative to BMI for Health Promotion (20). They are used world-wide for this purpose (**Figure 3**).

It was unexpected to many that waist circumference should be a better predictor than BMI for future diabetes or heart disease, but with consistent evidence that this was the case, and that it was not necessary to adjust waist for height, our waist cut-offs became, and remain, the key diagnostic criteria for the metabolic syndrome (21). Why a large waist was a slightly better predictor of metabolic ill-health was not immediately clear. Several studies showed that waist circumference correlated with the intra-abdominal fat mass, measured by CT or MRI (22). Other studies were less conclusive. Part of the reason for that was that in larger people, and always with BMI >35, the abdomen descends towards the knees

without increasing, so its relationship with intra-abdominal fat mass is lost and BMI becomes a stronger predictor of risk.

This brings me to another great figure behind our understanding of what insulin does and what diabetes is, in Gerry Reaven - a very good friend of many of us in Diabetes UK and EASD, and great man for an argument and a drink. Gerry delivered the Banting Lecture in 1988, introducing what he called Syndrome X, briefly renamed Reaven's Syndrome, but now known as Metabolic Syndrome (23). In his Banting Memorial Lecture in 1990 (24) he expanded on the observations that type 2 diabetes, hypertension and dyslipidaemia commonly co-exist in overweight people, and together promote premature cardiovascular disease. Over half of all people with type 2 diabetes are also on treatment for hypertension, and this points to a common aetiological link behind the features of metabolic syndrome. The diagnostic criteria for metabolic syndrome (25) (**Table 2**) are set at levels which individually do not constitute a diagnosis, or a need for treatment. It is not the most powerful tool for predicting diabetes or cardiovascular events; instead, its importance is that all its components are preventable, and also reversible, by a single action - weight loss.

From our UK evidence, supported from other countries, it appeared that waist circumference was a really important factor driving the metabolic syndrome. Reaven was sceptical, because his data from US showed only a marginally more powerful relation with waist than BMI (26, 27). The reason for that was probably simply that in the US most people were more overweight, and so the influence of the intra-abdominal fat mass, and thus waist circumference, was obscured.

Initially misunderstood by cardiologists and others, the importance of Reaven's metabolic syndrome, for unravelling the mechanisms behind Himsworth's 'insulin-insensitive diabetes' and its clinical consequences, and as a signal for action to preserve health, is growing again. Understanding that the metabolic syndrome is reversible is a critical step which allows us to face up to the seriousness of type 2 diabetes.

Aiming to be DiRECT

Until recently type 2 diabetes was commonly known as 'maturity onset diabetes', and considered a permanent development with aging, indeed in some cultures as a sort of mark of seniority accompanying a paunch. It was treated with a brief general exhortation to eat better, or take some exercise, and then with glucose-lowering tablets. At the start of my career, the average age of diagnosis in UK was about 64 years(28). Few lived long enough to develop specific secondary complications, and we rather failed to recognise or act on the accelerated cardiovascular disease, other than to give more drugs with rather

modest absolute effect sizes (often misleadingly high relative risk reductions). Colossal amounts of research money have been spent to show tiny improvements in clinical outcomes from medications.

The reality was that people with type 2 diabetes were losing an average of 6 or 7 years of life, with painful and disabling complications (28). That remains the case now, but with an average BMI about 30 kg/m^2 and age 50-55 at diagnosis, the global obesity epidemic is driving more and more people into type 2 diabetes at ever younger ages (29). We don't often present survival data this way for diabetes, but from Swedish data, type 2 diabetes has a 50% 10-year survival (30). The prognosis from a diagnosis of type 2 diabetes is thus similar to many major cancers: breast cancer has an 80% 10-year survival (31), non-Hodgkins lymphoma a 60% 10-year survival (32). . Although not strictly comparable data, these conditions have similar associations with age. These are serious cancers, and virtually 100% of our patients would be willing to go through even a very painful and unpleasant treatment programme if that offers a remission. The treatment of type 2 diabetes should therefore be taken as seriously as a treatment of cancers, with the aim of a remission- freedom from evident disease for as long as possible. This means a shift in the way type 2 diabetes is perceived by doctors and other healthcare workers, and taking that message to our patients if they are not already demanding remission.

Thinking the unthinkable – is type 2 diabetes reversible?

The evidence base that type 2 diabetes is driven by weight gain is inescapable. The Nurses' Health Study is perhaps the most striking, with relative risks rising towards 100-fold as BMI reached 35kg/m^2: it is hard to argue that this is not a causal relationship. And I point out that body mass index of 22 is a place which is comfortable to be, and where you are very, very unlikely ever to develop type 2 diabetes (33). We have also known from a number of consistent trials that quite modest intentional weight loss, of the order of 8 kg and only partially maintained, is enough to halve the incidence of new type 2 diabetes in overweight people with pre-diabetes at baseline (34).

An early indication that we might get rid of the disease with weight loss came from our retrospective study in Aberdeen, where we looked at the life-expectancy of people with BMI >25kg/m2 and type 2 diabetes, according to whether they changed weight in the first 12 months after diagnosis. Here I must offer thanks and recognition to John Stowers, Aberdeen's enigmatic and eccentric first UK professor of diabetes, himself diagnosed with type 1 diabetes in his 20s. He lived his life on the knife-edge of hypoglycaemia, but had the vision (and support) to establish not just a diabetes clinic, but a *Diabetes and Dietetics Clinic* at Woolmanhill Hospital in Aberdeen. Until the 1980s every person diagnosed with diabetes of any kind across the North-East of Scotland attended that clinic, usually 4 times a year, and

they always saw a dietitian before the doctor at each visit. It turned out that the bullying by dietitians had a greater effect than the medications prescribed by doctors. **Figure 4** shows weight loss in the first year with a survival curve expressed as years of life lost, compared to the life-expectancy of people of the same age but without diabetes, living in Aberdeen at that time. All were followed from diagnosis until death. Those who lost no weight in the first year lost six or seven years of life-expectancy, but those who lost 15 kg, at the limit of the reliable data, had the same life expectancy as people who never had diabetes (28). This amount of intentional weight loss appeared able to eliminate the disease process that is shortening lives of people diagnosed with type 2 diabetes. These data did not demonstrate remission of diabetes, as now understood, and we did not attempt to document how medications were used, but bariatric surgeons have been telling us for years that their diabetic patient see great improvements and even remissions of the disease. **Figure 5** shows data from different studies using different bariatric operations in different places. They vary slightly, but remission rates at two years range from 60-85%. It should be noted these remissions after bariatric surgery are not permanent: two of these studies reported 10 years results, at which time the 2-year remission rate was halved, and at durations of 5-6 years the results are intermediate (35, 36, 37, 38).

Bariatric surgery is commonly aiming to achieve weight losses of 30-50 kg, with some inevitable adverse effects. But how much weight loss is necessary for remission of type 2 diabetes? The first ever randomised trial of bariatric surgery, reported by John Dixon's study in Melbourne, provides an answer. This was a small study of laparoscopic gastric band surgery, compared to usual diabetes clinic care. Overall, 73% of the patients randomised to receive surgery were in remission at two years. Their weight losses varied and a cut-off of >15kg (or >15% as they had an average weight of 100kg) captured 83% remissions (39).

To become no longer diabetic, not requiring medication, at two years is an attractive target for people with type 2 diabetes, and >15kg weight loss also seemed a target which many should be able to reach by non-surgical methods. That study provided key evidence behind the thinking that led to the Diabetes Remission Clinical Trial (DiRECT), funded by Diabetes UK to myself, and Roy Taylor, bringing together as Co-Principal Investigators two old friends with our research teams in Glasgow and Newcastle. The more recent background evidence was threefold. Roy Taylor and his colleagues in Newcastle, in the mechanistic short-term proof-of-concept Counterpoint Study, confirmed what John Dixon had found using surgery: 15 kilograms weight loss, achieved with a formula diet, normalized liver fat and patients were no longer diabetic- the beta cells had recovered (40). In Glasgow we ran a single-arm real-life intervention in routine primary care with a structured dietary weight management programme (which became

commercialised in a spin-out company from Robert Gordon University, called 'Counterweight Plus'), that achieved weight losses at 12 months of over 15kg for about 33%, and over 10kg for about 70% (41). Vitally, Sarah Finer, Paul Robb and colleagues, conducted a survey co-funded by Diabetes UK and the James Lind Alliance which revealed that people with type 2 diabetes wanted finding a way to get remissions of type 2 diabetes as their top priority for diabetes research (42).

DiRECT in practice.

DiRECT was set up as a cluster randomized trial in primary care across Scotland and the northeast of England. The practices agreed to provide care under current evidence-based guidelines (NICE in England or IGN in Scotland, whose contents are very similar), and to be randomised to control or to add the Counterweight-Plus diet programme, administered by a practice nurse or a local dietitian if one was routinely available: these practitioners received 2 days of training and then mentoring from Counterweight Specialist dietitians employed in our Universities as Research Associates for the study. After some very early hesitation over the somewhat radical protocol, we had a very high recruitment rate, at 28%, more than the usual 10% for recruitment from primary care into research trials, and had to stop recruitment after the target 280 was exceeded. With average age 54, BMI 35 HbA1c 59 mmol/mol, they were very typical of patients within six years of diagnosis, with mean duration diabetes duration three years. None were yet on insulin, as we felt it would complicate the study to ask GPs to adjust insulin doses with weight loss, but 20% came from more deprived areas where diabetes is more common and more difficult to manage (43).

The DiRECT intervention program had one or two interesting features. We asked patients, on day one, to stop all their anti-diabetes medications, and also all their antihypertensive and diuretic medications, because we did not want to cause hypoglycemia or postural hypotension with weight loss, and also because this is a big incentive to continue with the program patients. The first phase was nominally 12 weeks on a formula diet of 830kcal/day, to induce a weight loss of 15 kg if patients followed it fully. However, to retain as many participants as possible we introduced flexibility such that this could be extended up to 20 weeks with the formula diet, to accommodate individuals who had holidays or breaks for one reason or another (43).

Whilst weight loss was clearly vital, we started to prepare participants, reinforced at each visit, for the time when they would moving on to reintroduce meals with normal foods, over a period of about two months. That process, employing various behavioural change strategies, was intended to normalize new food and eating behaviours for long-term weight loss maintenance, using a diet, which was very similar to

that which is normal in the United Kingdom, so not high carbohydrate nor low in carbohydrates. Again, there was some flexibility here, allowing individuals to choose a higher or lower carbohydrate diets. Follow up, with continued low-intensity support, was for two years within he randomised trial but subsequently extended to five years.

DiRECT was the first study ever designed with remission as its primary outcome. It set a target effect size of greater than 20% at 12 months, and was powered to detect or reject that. That figure was based on guidance from public health experts, that a readmission rate of 20% at one year would be sufficient to demand a change in our management of type 2 diabetes. In the event, above our all our best expectations, the DiRECT intervention achieved a 46% re-admission rate at one year - way beyond what was considered to be a successful outcome (44)

At two years the figure remissions fell to 36%, entirely explained by weight regain in 15 patients, to a point within 10kg or their baseline weight (45). While that is disappointing, the converse is very exciting, that remissions were almost all completely sustained for the second year if the weight loss was maintained: with a weight loss of >15 kg maintained for two years, the remission rate remained at 82% at two years. Remission rates for lesser degrees of weight loss are also substantial and very well maintained for two years (**Figure 6**). (46).

Supporting the notion that the clinical features of metabolic syndrome are aetiologically linked to excess fat accumulation, the DiRECT intervention also showed quite dramatic falls in blood pressure, around about 10 mmHg on average, across the formula diet period while participants were losing weight. That applied to those not previously on antihypertensive medications, and also to those whose drugs were withdrawn at baseline, although about 30% did need to return onto some antihypertensive medication during that study phase, at a mean of 42 days (**Figure 7**). Importantly the study protocol did not lead to any worrying rises in blood pressure, and it avoided any serious postural hypotension (47).

Among the secondary outcomes in DiRECT, at two years, quality of life improved substantially – it is worth reflecting that a 10 or 15 kilograms weight loss really does improve quality of life: losing 5kg is hard work and rarely seems worth the effort of maintenance. The intervention group had lower HbA1c with fewer on drugs, and similarly lower blood pressure using less medication. For those in remission, QRISK (risk of a cardiac event in 10 years) was halved from 16% at baseline to 8% (mainly the effect on this index of not having diabetes, so unlikely to be a step-halving of risk). There were substantially lower NHS costs, with fewer drugs being prescribed, fewer consultations, and fewer serious adverse events - in fact statistically fewer in the second year, compared to the intervention group (48, 46).

Among the predictors of remission, and clearly far ahead of anything else, was weight loss at every stage in the trial. We found weak signals for greater likelihood of remission with male sex, better socioeconomic backgrounds, and of course, lower baseline HbA1c and receiving fewer glucose-lowering drugs. Importantly, baseline BMI was not a predictor of remission, nor fasting insulin. There are only very modest predictors, which allow us to conclude that remission is worthwhile as a target for everybody with early type 2 diabetes (46).

Mechanisms behind diabetes remission and relapse

As a vital component of DiRECT, Roy Taylor and his colleagues took a subset of DiRECT participants through a comprehensive programme of mechanistic studies. The big messages were firstly to confirm that type 2 diabetes is commonly accompanied by a very abnormal fatty liver, whose function is impaired Not all people currently classified at type 2 diabetes have exactly the same metabolic dysfunction, and many mechanisms are involved, but ectopic fat appears very important. There have been insufficient studies using MRI to be confident about its contribution as a cause of type 2 diabetes. Not all would be diagnosed as NAFLD, but with weight loss and remission in DiRECT, liver fat fell to normal levels, and VLDL export from the liver, also high at baseline, also fell to normal. Interestingly, we saw a rise in VLDL in those participants who relapsed back into diabetes at year-2 (49). That fall in VLDL with remission was associated with a reduction in the abnormally high fat content of the diabetic pancreas, and in a beautiful recent analysis, the MRI morphology of the pancreas is normalised with remission. The pancreas with type 2 diabetes is a poor sad thing. It has about half the tissue volume of a normal pancreas, and ragged appearance with high fractile dimension. With remission, the pancreas gradually filled out and became virtually indistinguishable from a normal pancreas at 24 months. This was accompanied by a doubling and normalization of the maximum insulin secretion capacity (50).

DiRECT has told us some important things about what happens when people with type 2 diabetes lose weight, and it has also provided evidence about what happens when diabetes-susceptible individuals regain weight and diabetes returns. A crude view of the epidemiology suggests that about 60% of all people do not have a predisposition to metabolic syndrome: if they gain weight, they may experience a modest increase in macro vascular disease, but most of them can gain weight and remain reasonably healthy from a metabolic perspective. However, about 40% of all people, or more in Asian populations, have that elusive predisposition, either genetic or epigenetic, which is revealed by developing metabolic syndrome phenotype by age 70 (51). When these 40% gain weight, at a certain point they will start putting fat into ectopic sites - liver, pancreas, heart, and possibly into sites of brown adipose tissue: these

individuals will develop the clinical features of metabolic syndrome and exaggerated risks of type 2 diabetes, hypertension and premature macrovascular disease. If brown adipose tissue becomes dysfunctional when lipid-replete, this may yet explain some of their aggravated weight problems (15).

Importantly, the DiRECT trial has shown that the *disease process of obesity*, which includes its metabolic complications, is reversible, at least in the early stages. Given their very serious health risks, we should give the opportunity to try to get a remission to all our patients with type 2 diabetes, using evidence-based methods.

The totality of the diabetes remission literature

To complete the picture, we have assembled all the published evidence on remissions of type 2 diabetes (**Table 3**). Two randomized controlled trials seeking remission of type 2 diabetes have now been completed. The second was DIADEM-1, using an almost identical design to DiRECT, carried out by Shahrad Taheri and colleagues in Qatar. They had an even greater weight loss and remission rate of 61% at 12 months, but also 12% remissions in the usual care arm (52). This probably related to enrolling patients with a shorter duration of diabetes, under two years since diagnosis, and there may have been greater confidence and enthusiasm for achieving substantial weight loss among the clinicians and participants after seeing the results from DiRECT. The massive US LookAhead trial, focussed mainly on physical fitness and with many participants with long durations of diabetes was not designed to look at remissions, but used meal replacements for weight control, and a post hoc analysis showed 8.6% weight loss of 12 months with 11% remissions (53). Reflecting current media interest, three studies have published on diabetes remissions with low carbohydrate diets. None of these are randomized controlled trials designed for this purpose. The commercial American Virta Health Organization got very good weight loss of 13%, with a very low carbohydrate ketogenic diet, but only 19% remissions at 12 months (54). That disappointing result was partly because they left a lot of the patients on glucose-lowering medications, so some of them might have had remissions. David Unwin published a remarkable study of his single primary care practice in England, advising a similar very low carbohydrate diet. He reported a remission rate of 12.5% over two years for his whole practice of 473 people with diabetes, which was 46% remissions among the 128 patients who persisted with the diet (55). A recent systematic review examined earlier publications on low carbohydrate diets in diabetes: it identified seven studies which reported weight losses, which were not significantly different from the high carbohydrate diets at 12 months. Only two trials reported data from which remissions could be calculated. The 4% remission rate at 12 months was again not different from high carbohydrate diets, although in the short term (6 months) there was a greater weight loss of 3.5kg and 16% remissions (56). These conclusions (57) are consistent

with the large high-quality meta-analyses which have found no differences between very low and higher carbohydrate diet advice for body weight, or for HbA1c, in trials of 12 months or more, and minimal differences, of no clinical value, to favour lower carbohydrate diets over 3-6 months (58). The lack of long-term effect in these trials, necessarily in free-living people whose degree of adherence is always variable and probably zero in some cases, does not exclude biological effects on blood glucose and other metabolic variables from extreme carbohydrate restriction and glycogen depletion, The older literature is also dogged by poor recording of medications and possible acute changes in energy balance which are not reflected by body weight change. More recent studies seeking remission of diabetes are more reliable, as they must document glucose-lowering medication

Reprise

Just as Frederick Banting's discovery of insulin was not a cure for type 1 diabetes, neither is substantial weight loss likely to be a permanent cure for type 2 diabetes, but life can be improved by both treatments. The message from the totality of the evidence on remission of type 2 diabetes is quite clear, that more weight loss that can be achieved and maintained up to 12 and 24 months, the greater readmission rate. Results are best early after diagnosis. Weight losses greater than 15-20kg, achieved with bariatric surgery, do not increase the remission rate, but remissions are more often achieved and may be better maintained at 5 or 10 years. A low carbohydrate diet approach in good hands can thus be effective for weight control and possibly remission of type 2 diabetes, if that is what the patient wants, but there is no useful intrinsic benefit in head-to head comparisons with higher carbohydrate diets. It is time for devotees of William Banting and of Harold Himsworth to shake and make up, and for researchers to accept this evidence and stop repeating these diet comparisons. The priority for the future are to make evidence-based dietary programmes, capable of sustaining weight losses >15 kg, more widely available, and to focus effort on the knotty problem of long-term weight loss maintenance.

While urging adherence to the evidence-based methods to get the best results, as a corollary to all this evidence, it is not necessary for everybody to use the relatively expensive formula diets and professional support programs to achieve weight losses and remissions of type 2 diabetes. The food-based Newcastle diet works well for those who find it attractive (59). It is also possible to design very acceptable diet programmes which are nutritionally complete and have similar calorie contents based on many traditional diets, including the porridge, lentil and fruit 'No Doubts Diet' in Scotland, and for Nepal a diet based on dahl and bhat in appropriate amounts. Quality prospective evidence is needed for their effectiveness.

In relating this very personal story I have echoed some great thinkers, and pointed out how the progress of science is rarely a simple linear accumulation of knowledge. Seemingly unrelated elements can come together to move on our understanding, timing is all-important, and some very different personality types can have massive influence in research. Frederick Banting came into research with immense bravado and very powerful convictions, and surprising disregard for authority for a recent soldier, but absolutely no scientific knowledge or understanding of research process. In many ways he was a disruptive menace, but Macleod saw value in his determination, and he made things happen in a big way. We can celebrate their shared humanity in making the patent for insulin a gift to mankind, and we should remember the dogs of Toronto who made all this possible. Banting wasn't much of a doctor either, and never really practiced. However, like many doctors he had other skills. He was a superb artist, and became one of Canada's greatest oil painters. His paintings, in a bold colourist style, are very striking. He travelled widely to paint, often by boat, producing very beautiful and evocative sea-board and mountain scenes (**Figure 8**) (60). His premature death in a plane crash in 1941 was a massive loss to Canada's creative arts, as well as its only Nobel Prize winner.

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Table 1 Sleeping metabolic rate at 22°C, compared with thermoneutral 24 °C, showing the expected normal rise with non-shivering thermogenesis in healthy non-obese individuals. In contrast, obese type 2 diabetic patients all dropped their energy expenditures, and their core temperatures tended to fall at 22°C. (14)

		Change vs thermoneutral 24°C	
		Core Temp	Sleeping EE
		(°C change)	(% change)
Non-obese (n=6)	22°C	-0.3°C	+ 3.8% *
Obese (n=4)	22°C	-0.4°C	- 2.0%
Obese T2D (n=5)	22°C	-0.6°C	- 4.1% * (p<0.05)
(n=1)	19°C	-0.7°C	- 13%

* At 22°C, all 6 normal weight rose, all 5 T2D fell

Table 2 Criteria for commonly co-existing components of Metabolic Syndrome. Waist circumference cut-offs were taken from Lean et al 1995. The IDF modification was proposed to offer greater power to identify risk of type 2 diabetes (16, 17, 19)

		(ATP III 2001) 3 or more of:	(IDF 2005) WC + 2 of:
Waist Circumference	**m**	**>102 cm (>40 ins)**	**>94 cms (37 ins)**
	f	**>88 cm (>35 ins)**	**>80 cms (32 ins)**
Fasting glucose		**>6.1 mmol/l**	**>5.6mmol/l**
Blood Pressure		**>130/85 mmHg**	
Triglycerides		**>1.7 mmol/l**	
HDL Cholesterol	**m**	**<1.0 mmol/l**	
	f	**<1.3 mmol/l**	

Table 3 Published data for remissions of type 2 diabetes using dietary methods (from Churuangsuk et al 2021 in press).

Interventions reporting T2D Remissions

Trials	Design	Sample size (ITT)	Test Diet	12m weight loss (kg)		12m T2D Remissions (%)	
				Interven-tion	Usual care	Interven-tion	Usual care
DIADEM-I (Qatar, 2020)	RCT	Intervention=70 Usual care=77	TDR/ Maintenance	-12.0 [a]	-4.0	**61%**	12%
DiRECT (UK, 2018)	RCT	Intervention=149 Usual care=149	TDR/ Maintenance	-10.0 [b]	-1.0	**46%**	4%
Virta Health (USA, 2018)	Non RCT	Intervention=262 Usual care=87	VLCD/Keto	-13.8 [a]	-0.2	**19%**	-
Unwin (England, 2020)	Practice audit	With T2D = 473 *Persisted with diet = 128*	VLCD/Keto	-	-	**12.5% (23m)** ***46%***	-
Goldenberg (2021)	Systematic review	12m remission: 2 RCTs n=126 12m weight loss: 7 RCTs n=499	Low/VLCD	-0.3 (NS) (vs control)	-	**4% (NS) (vs control)**	-
Look AHEAD (USA, 2012)	RCT	Intervention=2570 Usual care=2575	Meal replacements	-8.6% [b]	-0.7%	**11%**	-

TDR, total diet replacement;
Churuangsuk, Halls, Reynolds, Griffin, Combet, Lean. Unpublished systematic review, 2021

Trials	Design	Sample size (ITT)	Test Diet	12m weight loss (kg)		12m T2D Remissions (%)	
				Interven-tion	Usual care	Interven-tion	Usual care
DIADEM-I (Qatar, 2020)	RCT	Intervention=70 Usual care=77	Formula Total Diet Replacement + Maintenance	-12.0 [a]	-4.0	**61%**	12%
DiRECT (UK, 2018)	RCT	Intervention=149 Usual care=149	Formula Total Diet Replacement + Maintenance	-10.0 [b]	-1.0	**46%**	4%
Virta Health (USA, 2018)	Non RCT	Intervention=262 Usual care=87	Very Low Carbohydrate/ Ketogenic	-13.8 [a]	-0.2	**19%**	-
Unwin (England, 2020)	Practice audit	With T2D = 473 *Persisted with diet = 128*	Very Low Carbohydrate/ Ketogenic	-	-	**12.5% (23m)** *46%*	-
Goldenberg (2021)	Systematic review	12m remission: 2 RCTs n=126 12m weight loss: 7 RCTs n=499	Low/Very Low Carbohydrate	-0.3 (NS) (vs control)	-	**4% (NS) (vs control)**	-
Look AHEAD (USA, 2012)	RCT	Intervention=2570 Usual care=2575	Meal replacements	-8.6% [b]	-0.7%	**11%**	-

Figure 1 Omental and perirenal adipose tissue (internal sites of brown adipose tissue in infancy), lipid-replete from a young adult who died in a road traffic accident and showing multilocular brown adipose tissue characteristics in another with a phaeochromocytoma. (12, 14)

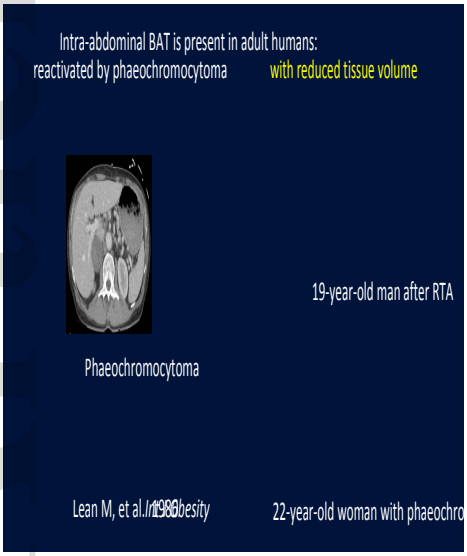

Figure 2 Uncoupling protein-1 contents of the mitochondria from omental and perirenal adipose tissue of human infants, children and adults, and patients with phaeochromocytoma. (redrawn from from 14)

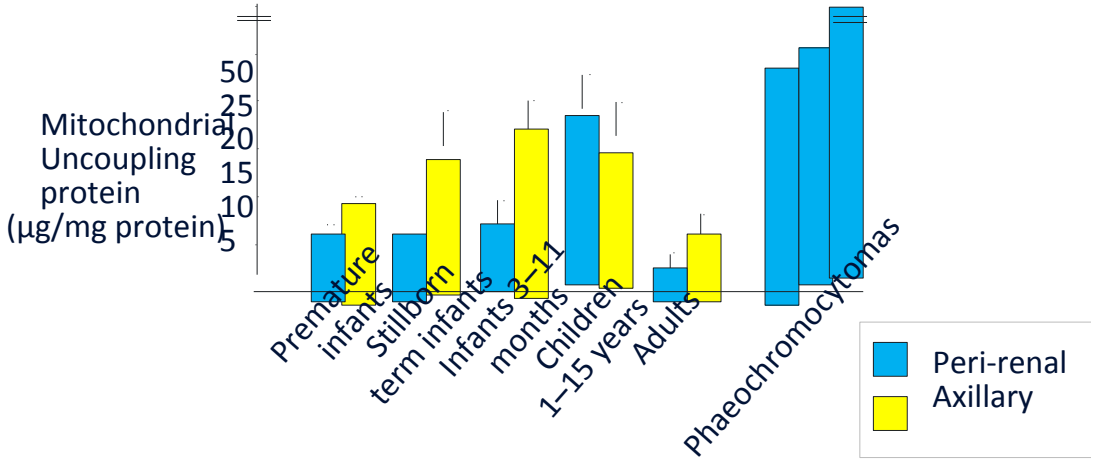

Figure 3 Diabetes UK campaign using waist circumference cut-offs for health promotion.

(we need a high definition version from Diabetes UK)

Figure 4 Survival curve of patients with type 2 diabetes and BMI>25lg/m^2, with average age at diagnosis of 64, according to weight change under dietitians' advice during the first year after diagnosis (adapted from Lean et al 1990).(26)

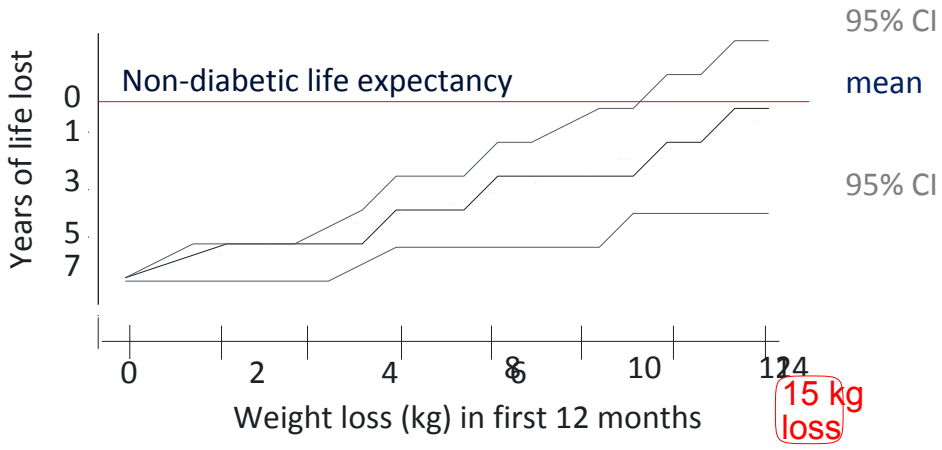

Figure 5 Remissions of type 2 diabetes at 2 years and longer following different bariatric procedures.(33, 34, 35, 36)

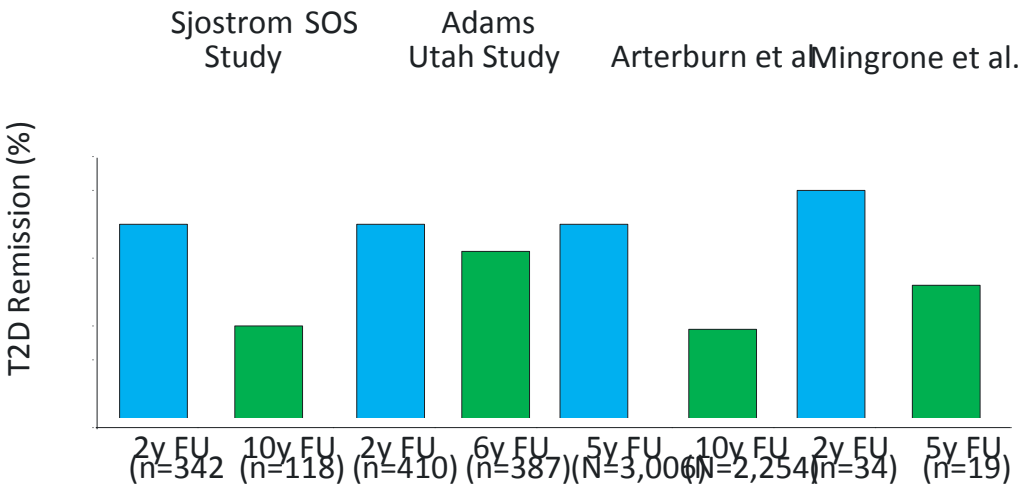

Figure 6 Remissions of type 2 diabetes at 1 and 2 years, according to the weight loss maintained (from Thom et al 2020)(44)

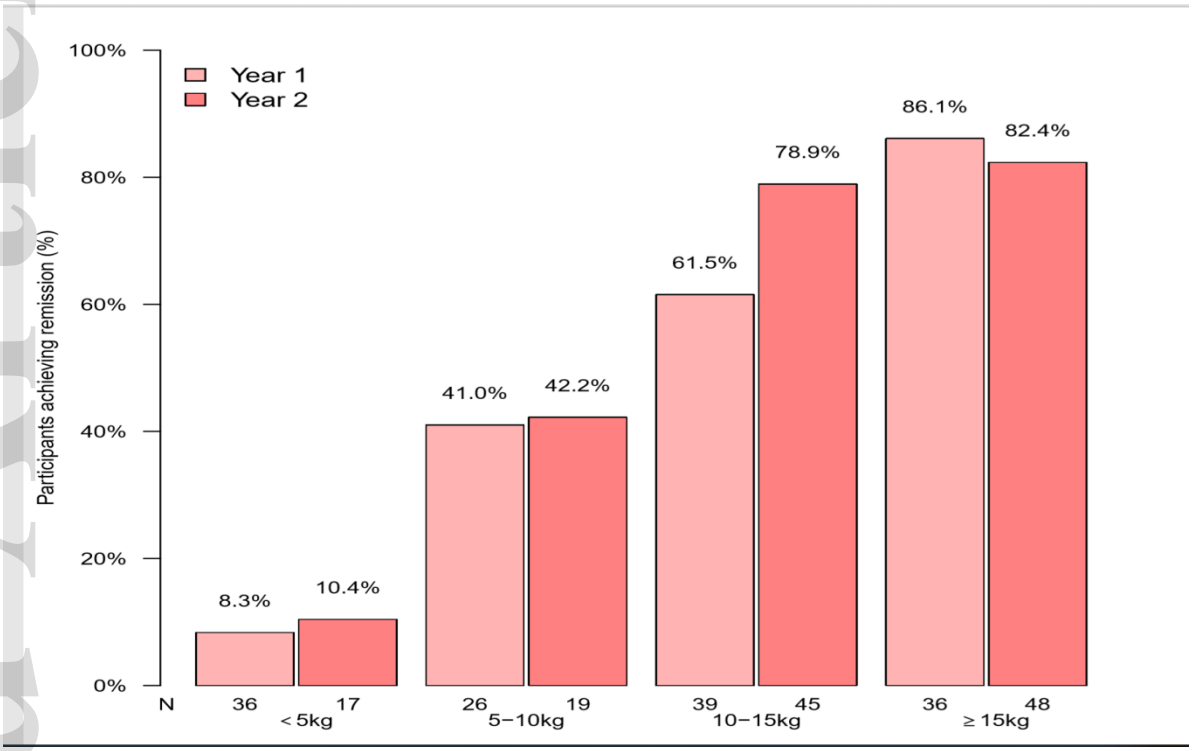

Figure 7 Blood pressure changes during weight loss induction using a nutritionally complete formula diet for 12-30 weeks (Leslie et al, in press Diabetologia).

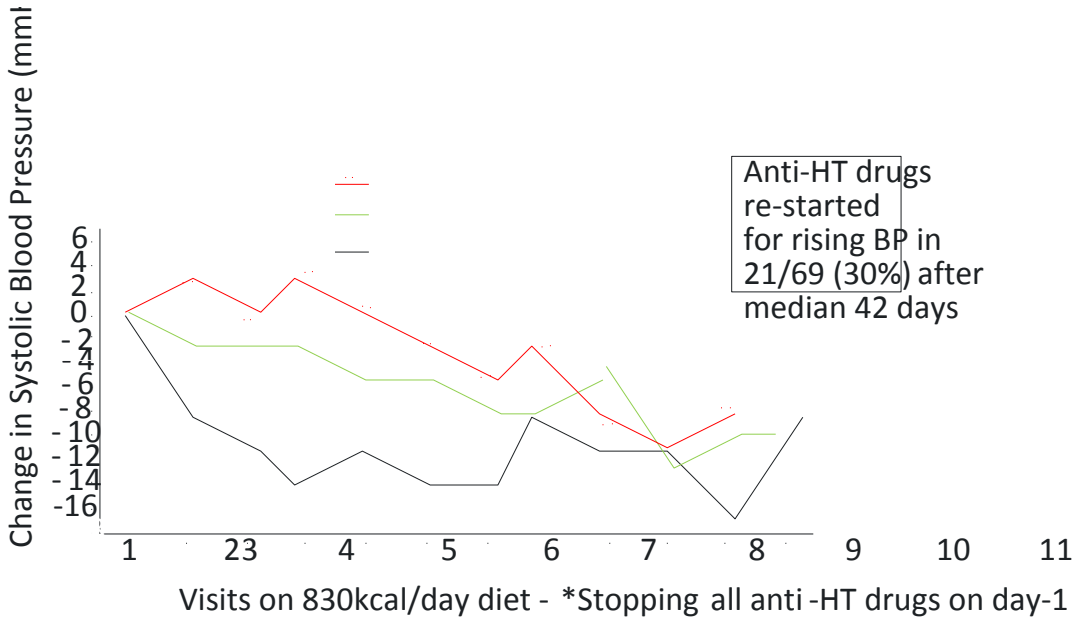

Figure 8 Paintings by Frederick Banting