



“Treasure Your Exceptions” – Studying Human Extreme Phenotypes to Illuminate Metabolic Health and Disease: The 2019 Banting Medal for Scientific Achievement Lecture

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The study of humans with genetic mutations which lead to a substantial disturbance of physiological processes has made a contribution to biomedical science that is disproportionate to the rarity of affected individuals. In this lecture, I discuss examples of where such studies have helped to illuminate two areas of human metabolism. First, the control of insulin sensitivity and its disruption in states of insulin resistance and second, the regulation of energy balance and its disturbances in obesity.

THE EXPLANATORY POWER OF HUMAN GENETICS

The Banting award celebrates a clinician-scientist who, together with his collaborators in Canada, made a seminal discovery in 1921 that was rapidly translated into a life-saving therapy for people with diabetes and recognized and honored at the highest international level. I would like to start by paying homage to two scientists whose seminal discoveries were, in contrast, made somewhat ahead of their time. Gregor Mendel, who discovered the particulate nature of inheritance, remained largely unrecognized during his lifetime. Archibald Garrod, a Regius Professor of Medicine in Oxford, was a quiet and modest man who was somewhat overshadowed by his more flamboyant contemporary William Osler. Garrod first identified Mendelian forms of human disease (1). But, importantly, he also recognized the contribution that medical genetics was likely to make to common disease. He foresaw that there were some diseases that ran in families but tended to

present later in adult life. As he expressed it, he “found it difficult to escape the conclusion that although these maladies were not congenital, their underlying causes were ‘inborn peculiarities’” (2). The importance of Mendel’s discoveries only began to become apparent to the wider scientific community at the beginning of the 20th century, some 20 years after his death. The prescience of Garrod’s insights from medical genetics became widely recognized only in the second half of the 20th century.

My own appreciation of the explanatory power of genetics developed when I started to undertake clinical research for the first time. Having encountered the common and frustrating problem of trying to establish the mechanistic link between two associated physiological variables, I realized that if one of those variables was in the sequence of genomic DNA, then the direction of causality could be readily ascribed. This was something of a revelation—at least to me.

Later, I began to understand that if the perturbation of a gene and an associated phenotype were both extreme, then one could obtain profound insights into the control of human physiology, irrespective of the rarity of the disorder. This became a guiding light for my scientific career. This concept was expressed elegantly by William Bateson (3), the Cambridge scientist who first brought Mendel’s work to public attention and coined the word “genetics” when he wrote “Treasure your exceptions: They are like the rough brickwork of a growing building which tells us there is more to come and shows where the next construction is to be.” The exceptions I will discuss in this lecture are of two types.

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Figure 1—Robert Turner (1938–1999). An exceptional physician-scientist.

Firstly, there are the exceptional patients that have been the cornerstone of much of the work that I have done over the past 30 years. But I also want to use this opportunity to thank the exceptional people that I have been fortunate enough to be associated with throughout my professional life.

Mentors and Inspirers

One such person was Robert Turner, founder and Director of the Diabetes Research Laboratories at the University of Oxford, who died in 1999, far too young (Fig. 1). I entered Robert's lab as a scientific ingénue. I wanted to be an endocrinologist, and Robert convinced me that insulin was the most interesting hormone. At that time it was widely considered that type 2 diabetes was primarily a disorder of insulin resistance, with pancreatic β -cell exhaustion being a late and secondary phenomenon.

Robert, David Matthews, and I studied first-degree relatives of people with type 2 diabetes. These relatives had only minimal disturbance of glucose tolerance. But they had clear quantitative and qualitative abnormalities of pancreatic β -cell secretory function at a time when they were not particularly insulin resistant (4,5). Later genome-wide association studies revealing the dominance of alleles affecting the islet in conferring predisposition to type 2 diabetes (6) have vindicated that earlier work.

Through the study of families with type 2 diabetes, I developed a growing interest in how the condition might be inherited. This was timely because Oxford, under the leadership of David Weatherall, was then pioneering the application of molecular genetics to medicine. I had

the good fortune to train in the lab of one of David's acolytes, Jim Wainscoat, and there I began to learn some molecular genetics. Although my initial attempts to find genes that caused type 2 diabetes were largely unsuccessful (7), they did lay the groundwork for later more fruitful gene hunts in the lab, including those undertaken when Andrew Hattersley was a fellow (8).

In 1989, I was awarded a Medical Research Council Traveling Fellowship and decided to go to Boston to open up my scientific horizons. I first went to Joel Habener's lab at the Massachusetts General Hospital, where I made some ineffectual attempts to clone the glucagon-like peptide 1 receptor before deciding that I was better suited to an environment closer to clinical questions. Jeff Flier kindly took me in at Beth Israel Hospital, and David Moller was given the impossible job of trying to turn me into a competent, bench scientist. While we made some progress using emerging genetic technologies (9), suffice it to say that just prior to my departure I was awarded the "Glowing Geiger Award" for generating the greatest number of radiation safety incidents during my 2 years in the laboratory.

It was, however, in Jeff's lab that I began to reflect more fully on the power of the extreme human phenotype. Brown and Goldstein, through their work on rare patients with early-onset atherosclerosis, had of course made their momentous discoveries regarding cholesterol homeostasis (10). In the 1970s, though, there had been a landmark paper closer to my own field in which Jeff Flier and Ron Kahn, working with Jesse Roth at the National Institutes of Health, had first described rare genetic and immunological disorders of insulin receptor signaling (11). Jeff had continued to pursue studies in patients with various rare phenotypes of extreme insulin resistance (12). He generously allowed me to use some related preliminary data in a grant application that I wrote to the Wellcome Trust to fund me to return to the U.K. to set up my independent lab. I returned, not to Oxford, but to Cambridge.

RESEARCH ON INSULIN RESISTANCE AND THE METABOLIC SYNDROME

Studies in Extreme Insulin Resistance

In Cambridge, Nick Hales, a pioneer of the study of insulin secretion, led the Department of Clinical Biochemistry. The department also housed Ken Siddle, a doyen of insulin receptor signaling, and John Hutton, an inspiring molecular endocrinologist. It was a superb environment in which a young clinician-scientist could build a fledgling career. The wonderful Anna Krook, now a professor at the Karolinska Institute, was my first research assistant and then my first PhD student and postdoctoral associate. We focused on studying patients with mutations in the insulin receptor. The work we did helped to clarify relationships between genotype, impact on signal transduction, and clinical phenotype (13–16). Anna demonstrated wisdom and maturity beyond her youth by effectively banning me

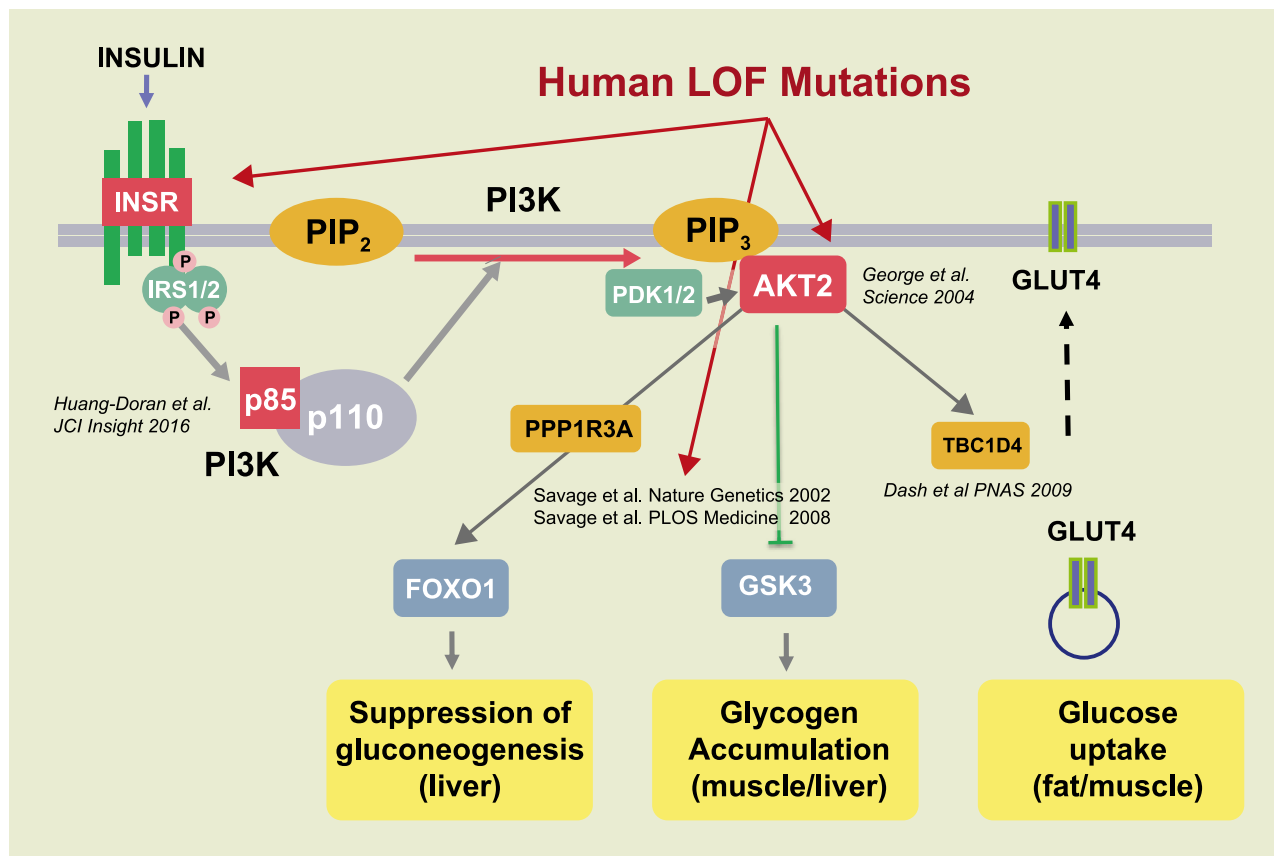


Figure 2—Loss-of-function (LOF) mutations in components of the insulin signaling pathway found in patients with syndromes characterized by severe insulin resistance. PI3K, phosphatidylinositol 3-kinase; PIP₂, phosphatidylinositol 4,5-bisphosphate; PIP₃, phosphatidylinositol (3,4,5)-trisphosphate.

from entering the lab area, due to the high risk that I would break something valuable.

We continued to amass a collection of patients with severe insulin resistance and in that cohort discovered a range of novel inherited disorders of postreceptor signaling (17–19) (Fig. 2). During that time, among a host of talented research fellows and collaborators were Robert Semple and David Savage, both now international authorities in syndromes of insulin resistance. We also discovered genetic disorders where aspects of postreceptor insulin signaling were pathologically enhanced. For example, we discovered a mutation in the Pleckstrin homology (PH) domain of AKT2. This caused it to bind phosphatidylinositol 4,5-bisphosphate rather than phosphatidylinositol (3,4,5)-trisphosphate. So, AKT2 is targeted to the plasma membrane, where it becomes active even in the absence of insulin. Children carrying this mutation had a syndrome of severe fasting hypoglycemia with undetectable circulating insulin (20). In later work, led by Robert Semple in collaboration with Les Biesecker at the National Institutes of Health, we found that somatic activating mutations in the catalytic subunit of phosphatidylinositol 3-kinase can result in syndromes of regional overgrowth (21).

Returning to insulin resistance syndromes, when we phenotyped patients who had defects in the early components of the insulin signaling pathway we found that they did not fully phenocopy those found in patients with typical “metabolic syndrome.” They had, as would be expected, high levels of insulin and an increased risk of diabetes. But they had no alterations in circulating levels of triglycerides or of HDL. To our surprise, many had high serum adiponectin and their levels of liver fat were frequently normal or even low (22–29) (Fig. 3). We concluded from these observations that it seemed unlikely that the mechanism of insulin resistance seen in common forms of metabolic syndrome or in type 2 diabetes would be explained by a defect in insulin signal transduction.

Lipodystrophy, a Model for the Metabolic Syndrome

However, there was one subset of patients with severe insulin resistance who did, in fact, exhibit all the features of common metabolic syndrome. That is the group of patients with lipodystrophy, a syndrome characterized by an impaired ability to generate healthy adipocytes or to make or retain triglyceride stores within fat cells.

Over the years, we discovered or contributed to the discovery of many of the genes which lead to human

	Impaired Insulin Signaling (IR, p85, TBC1D4)	Typical metabolic syndrome
Plasma Insulin	↑↑	↑
Diabetes Risk	↑	↑↑
Plasma Triglycerides	→	↑
Plasma HDL	→	↓
Serum Adiponectin	↑	↓
Liver Fat	→ ↓	↑

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Figure 3—Studies of the pathophysiology of insulin resistance syndrome indicate that patients with lipodystrophy share all the key features characteristic of common metabolic syndrome. In contrast, patients with primary disorders disrupting insulin signaling have only a subset of such features and do not have all the typical features of metabolic syndrome.

lipodystrophy (30), including PPAR γ (31,32), lamin A (33), and AKT2 (19). In recent years these efforts have been led by my colleague and former fellow David Savage. Ines Barroso has been a valued collaborator in many of these, and indeed other, studies.

Mutations in PLIN1 (34) and in CIDEC (35) are particularly notable, as they involve mutations in genes whose encoded proteins exist solely on the surface of the triglyceride droplet of the white adipocyte. Given their highly cell- and organelle-specific pattern of expression, it is remarkable that their disruption leads to severe illnesses characterized by every systemic feature of the metabolic syndrome.

In work on perilipin 1 (PLIN1) led by David Savage in Cambridge and Corinne Vigoroux in Paris, we have a beautiful example of where a rare extreme phenotype can really be very illuminating. The disorder results from heterozygous frameshift mutations that disrupt the C terminus of perilipin 1 and result in the coexpression of a wild-type and an elongated mutant form of perilipin in adipocytes (34). Carriers of such mutations, which disturb a gene only expressed in white adipose tissue, consistently suffer from partial lipodystrophy, insulin resistance, and dyslipidemia and frequently develop early-onset fatty liver disease and atherosclerosis.

Because the C-terminal part of PLIN1 is disrupted, CGI58, a molecule that normally binds securely at that site, is, instead, free to interact with the initiator of lipolysis, adipose triglyceride lipase or ATGL, bringing it in contact with its substrate at the surface of the fat droplet. Thus, irrespective of nutritional state there is a continuous condition of unregulated lipolysis and release of free fatty

acids. This alone appears to be sufficient to result in every feature of the metabolic syndrome. Individuals carrying this defect in perilipin 1 cannot transition normally from the healthy fed state to the overnight fasted state, when a series of coordinated phosphorylation events normally promote regulated lipolysis.

The Molecular Basis for Common Metabolic Syndrome

These findings led David and I to speculate on whether a similar adipocyte-based mechanism might underpin more common forms of the metabolic syndrome. To do that we talked to our colleagues Nick Wareham, Robert Scott, Claudia Langenberg, and Luca Lotta from the MRC Epidemiology Unit, one floor down from us in the Institute of Metabolic Science (IMS). We asked if they would be interested in using their powerful resources and skills to examine the population genetic substrate for a composite phenotype reflecting the “metabolic syndrome.” We decided to study individuals who were in the top centiles of a composite score reflecting high fasting insulin (adjusted for BMI), high fasting triglycerides, and low HDL cholesterol. In data from nearly 200,000 people, they found 53 single nucleotide variants that were associated with this composite trait at genome-wide levels of significance.

Reassuringly, in independent populations with either type 2 diabetes or coronary artery disease, the direction of the associations was as predicted. What was surprising is that when we looked in several independent populations for the association of these single nucleotide polymorphisms (SNPs) with different markers of adiposity, the metabolic syndrome risk SNPs were strongly associated with *lower*, not higher, body fat percentage, in examination

of regional body fat data from nearly 13,000 DEXA scans in relation to the genetic risk score. Strikingly, the risk score was very strongly associated with lower amounts of fat on legs, arms, and thighs and only very modestly associated with increased visceral fat (36).

Using bioinformatics tools, we attempted to discern which tissues and cells were most likely to be mediating the effects of these polymorphisms, based on the sites of expression of adjacent genes and the extent to which the SNPs influenced gene expression. The answer was very clear. The only sites with convincing evidence for enrichment were adipose tissue and adipocytes. It is worth emphasizing that these SNPs were discovered in a genome-wide hypothesis-free analysis. The adipose tissue spoke to us spontaneously; it was not forced to do so! When we manipulated the expression of a subset of the genes colocalized with the risk SNPs in adipocyte cell lines we found that many could influence fat accumulation (36).

In summary, the genetic architecture underlying the predisposition to “metabolic syndrome” points strongly to adipose tissue biology (see Table 1). A common finding in those genetically predisposed is an inability to expand safe adipose depots. This is probably more important than excessive storage of fat in visceral areas, an assertion supported by recent published analyses by Luca Lotta and colleagues (37). So, rather than diabetologists talking about people with a high waist-to-hip ratio, we should really be talking about those with a low hip-to-waist ratio!

Our current work in this area has now moved to the deeper characterization of functionally impactful mutations in specific genes that are associated with waist-to-hip ratio and metabolic syndrome (38). This work should lead to the identification and validation of target genes that could be pharmacologically manipulated to improve the health of adipose tissue depots and ameliorate insulin resistance and other aspects of the metabolic syndrome.

Whether we remain metabolically healthy or develop insulin resistance seems largely dependent on how we manage any imbalance between energy intake and energy

expenditure. This I illustrate as a bath with the tap left on and the plug left out (Fig. 4). So long as the “energy in” is balanced by the “energy out” with the bath able to store any excess energy, the bathroom floor remains pristinely dry, a simile for metabolic health. On the other hand, a large excess of intake over expenditure lead to an overflowing bath and a metabolically “soggy” bathroom carpet (we had such things in my youth!). Discussions about the adverse effects of obesity frequently focus rather simplistically on the relationship between energy input and output. The research I have just described suggests that we may not have paid enough attention to the fact that the size of the bath can vary greatly between individuals.

In brief, adipose storage capacity, something that is strongly genetically determined, has a major influence on whether positive energy imbalance can be handled safely by the body or instead results in the rerouting of nutrients to nonprofessional storage tissues such as liver and muscle, causing them to become insulin resistant.

RESEARCH IN MECHANISMS LEADING TO OBESITY

I will now switch to describing a body of work more related to the causes than to the consequences of obesity. My interest in pursuing research in this area was largely initiated by a single patient that I first saw in my weekly endocrine outpatient clinic, shortly after arriving in Cambridge. When I first met the patient, she was 35 years old and had been referred with recurrent severe reactive hypoglycemia. She had a history of severe childhood obesity including being admitted to hospital for a year at the age of 3 years for enforced caloric restriction. Additionally, she had a complex set of medical problems including hypogonadotropic hypogonadism, intestinal symptoms, and extreme fatigue. At that time I had been wondering whether some cases of reactive hypoglycemia might be due to an excess of proinsulin, given the fact that it retained significant bioactivity but had a much longer half-life than insulin. In work we did initially with Nick Hales and then with Ken Polonsky, we showed, remarkably, that this woman had not a single molecule of detectable insulin in her circulation. She was living entirely on unprocessed or partially processed proinsulin (39).

Not only was she not processing proinsulin normally, but also we gathered evidence that she was failing to normally process a number of other prohormones. A terrific trainee clinical biochemist, Robert Jackson, working largely in his spare time, and at that time with relatively primitive genetic tools, managed to clone our top candidate gene, PCSK1, and discover the compound heterozygous mutations in that gene responsible for her complex phenotype (40).

In December 1994, Friedman and colleagues (41) published the finding that the extreme obesity seen in the *ob/ob* mouse was explained by the lack of a newly discovered adipocyte hormone, which they called leptin, the normal

Table 1—Lessons from the study of genetics of human insulin resistance

- Disorders of insulin signaling only partially phenocopy common insulin resistance
- Monogenic lipodystrophies provide a more complete phenocopy
- Allelic variants underpinning common variation in fasting insulin, triglycerides, and HDL are dominated by genes with high expression in adipose tissue
- These findings are more consistent with the model of impaired adipose tissue expandability and lipotoxicity (cf Vidal-Puig) than with the view that inflammation is the major link between overnutrition and insulin resistance
- Large-scale population genetic studies are now pinpointing specific genes and helping to validate them as therapeutic targets

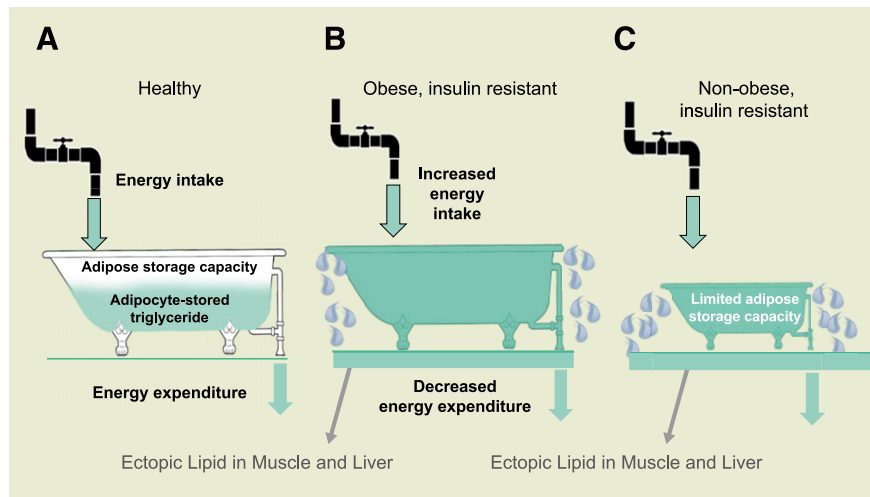


Figure 4—The “Soggy Bathroom Carpet” model of metabolic disease.

role of which was to inform the brain about the state of caloric stores in adipose tissue. Shortly after, probably because I had been speaking publicly about our work on PCSK1-related obesity, we were referred two British children, first cousins of consanguineous Pakistani origin, who had severe obesity and hyperphagia from a young age (Fig. 5). At that time, the genomic sequence for human leptin had not yet been cloned. But we thought we might at least

be able to examine its coding sequence by getting RNA from the tiny amounts of fat adherent to punch skin biopsies that the referring geneticist had obtained. Leptin mRNA of normal length was detectable in the children’s fat. We managed to get enough RNA to PCR and sequence the leptin cDNA. We obtained that rather murky sort sequence that one commonly saw back in the old days of radioactive label-based technology.

Unfortunately, the control lane did not work that day, so we did not have anything to compare it directly to. To compound matters, an accepted consensus sequence for human leptin had not yet been established. We could not see any obvious mutation in the children. As we had used up their RNA, we temporarily parked the project. Some 18 months later, Sadaf Farooqi joined the lab as a new research fellow. As her first experiment, I suggested that she use a recently available commercial leptin assay to measure leptin in the children’s stored plasma. She ran the assay, after which she reported that while plasma from control subjects seemed to give sensible values, she could not find any leptin in the plasma from the cousins. I said, “Well, you’re very new in the lab, so let’s run it again in case something went wrong.” She did that and again found no detectable leptin. So we went back to that original film, filed away in a drawer in the lab, and found, to our horror, that 18 months previously we had actually missed the fact that instead of the six Gs in a row here, that were expected in the normal sequence, in the cousins’ DNA there were actually only five. So, the children were carrying a frame-shift mutation encoding a premature stop codon. We confirmed this by more modern methods then available and demonstrated that the mutation resulted in a truncated protein that could not be secreted from transfected cells. So, we had established that leptin was necessary for the control of human body weight and this was not a phenomenon restricted to rodents (42).



Figure 5—Severe early-onset obesity resulting from congenital leptin deficiency in two first cousins, ages 8 and 2 years.

As reported at the time by Rudy Leibel (43), within a month our small lab had reported the first two specific genetic defects causing human obesity.

Sadaf Farooqi, with her characteristic energy and drive, convinced me that we should establish a much larger population of patients with severe early-onset obesity. At that time Giles Yeo, a terrific molecular biologist who had trained with Sydney Brenner, led our human molecular genetic efforts, and the magnificent Tony Coll, who came to research late in his clinical endocrine fellowship, courageously immersed himself in murine physiology and generously brought that expertise to the lab. I am delighted to say that these colleagues have all remained in Cambridge at the Wellcome-MRC Institute of Metabolic Science, where they are now all tenured academic faculty.

We and others around the world began to discover other single gene disorders that caused obesity (44–48). For example, simultaneously with Philippe Froguel's group (49) we described humans with obesity due to melanocortin 4 receptor deficiency (50). As the genetic discoveries mounted, it became clear that the vast majority of the genes that, when disrupted, caused obesity were expressed and primarily functioned in the brain, particularly the hypothalamus. Our institute's exciting work on new gene discovery in childhood obesity has continued, under Sadaf Farooqi's leadership, to the present day.

We did not stop at gene discovery. We recruited children carrying these mutations to our clinical research facility and measured food intake, energy expenditure, and other parameters. What became clear was that children who carried mutant copies of these genes were usually characterized by profound hyperphagia. At ad libitum meals, these children ate far in excess of their energy expenditure—and much more than their siblings who did not carry the mutations (51,52). Although some of these genetic defects did have some discernible effects on reducing energy expenditure, by far the biggest impact they had was on food intake. So, monogenic forms of obesity were more accurately described as inherited disorders of eating behavior rather than of metabolism (53).

It has been an enormous privilege to witness the dramatic clinical benefits of leptin therapy in children suffering from its congenital deficiency. We have learned a great deal from observing people undergoing this intervention, gaining new insights into leptin's roles in human immunology, endocrinology, and reproduction, and we are enormously grateful to them for their participation in ongoing studies (54,55). In experiments undertaken with our neuroscience colleagues that were uniquely possible in humans, we demonstrated the profound and rapid impact of leptin on the higher reward centers of the brain and their responses to visual images of food (56).

Metreleptin, which is the licensed pharmaceutical form of leptin, is dramatically effective in congenital leptin deficiency. It also has beneficial effects on the metabolic sequelae of severe forms of lipodystrophy. It is now

a licensed drug for both conditions. Why isn't it a blockbuster drug for obesity?

The explanation for that appears to be in the shape of the leptin dose response curve. Unlike many other hormones, leptin does not continue to have additional effects with administration of higher doses. In fact, while leptin is highly effective in suppressing food intake when severe deficiency states are corrected, it is much less effective when physiological levels are augmented. Jeff Flier and Rex Ahima in their landmark paper (57) described the critical role for acute reductions in circulating leptin in signaling the starved state to the brain. It is reasonable to speculate that leptin evolved principally as a signal of the transition between the starved and the adequately nourished state rather than as a signal to prevent obesity.

That said, ongoing work suggests there are likely to be patients with obesity, fatty liver disease, or hypogonadotropic hypogonadism where relative leptin deficiency might be playing a significant pathophysiological role. If such patients could be readily identified, then agonism of the leptin receptor, whether with metreleptin or other agents, might have broader therapeutic utility in the future.

GDF15: WORK IN PROGRESS

The final story I want to share with you today concerns another hormone that signals events occurring in the periphery to the brain. That hormone, called GDF15, sometimes referred to as MIC1, was discovered some 20 years ago by Sam Breit, a clinical immunologist in Sydney, Australia, as a transcript upregulated in activated macrophages (58).

It grabbed the attention of the metabolic community a few years later when Breit and collaborators showed that transgenic overexpression of GDF15 reduced body weight and food intake. They also showed that tumors that produce GDF15, when implanted into mice, cause cachexia. When the GDF15 was neutralized with an antibody, then weight loss was prevented (59). For many years the field did not progress far beyond those tantalizing observations because it proved extremely difficult to find a receptor for GDF15.

Fast-forward to some 18 months ago, when four different pharmaceutical companies all reported that the receptor for GDF15 was a heterodimer of a receptor called GFRAL with the tyrosine kinase Ret (60–63). All agreed that this heterodimer is only expressed in a small number of neurons in the hindbrain. The principal site of expression is the area postrema, a nucleus that is outside the blood-brain barrier and classically involved in the transmission of nauseating and other aversive signals.

So what clues do we have to the normal biology of GDF15? High levels of circulating GDF15 have been reported in a wide range of conditions, including disease states, toxin ingestion, and exposure to other environmental stressors. GDF15 is expressed at low levels in a broad range of cell types, with expression levels increasing in response to a wide variety of stressful stimuli (reviewed in 64).

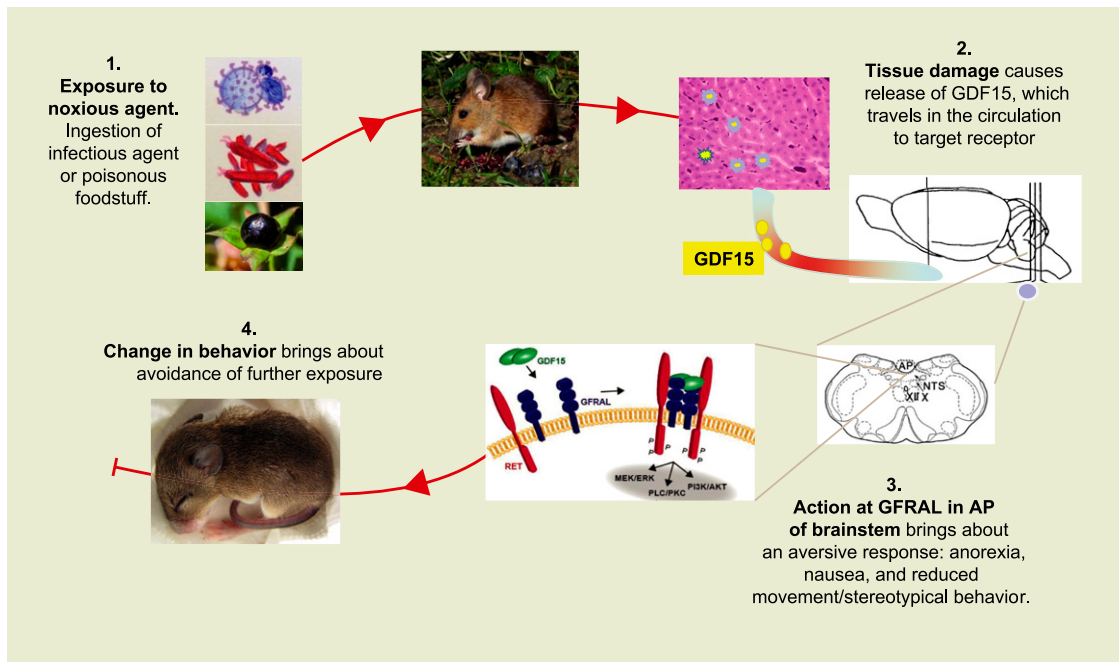


Figure 6—The physiological role of GDF15, a sentinel hormone signaling a range of somatic stresses to the brain. AP, area postrema; NTS, nucleus tractus solitarius; PI3K, phosphatidylinositol 3-kinase.

That led me to speculate, back in 2017, that GDF15 might be the endocrine arm of the cellular integrated stress response (65) (Fig. 6). The idea was that perhaps GDF15 had evolved to increase in the circulation of an animal that had ingested a noxious agent. By signaling through the area postrema, two types of responses might result. In the acute setting, the slowing of gastric emptying and vomiting in some species, and pica in others, could diminish continued exposure to the agent. The area postrema also transmits signals that help lay down memories of previous adverse exposures. So GDF15 might perhaps be involved in creating a memory that would encourage avoidance of that noxious substrate in the future. Over the last 18 months we have, with help of many collaborators, started to explore some of these questions.

In a recent study (66), we have reported the following: 1) GDF15 expression is increased by activation of the integrated stress response in a manner that requires the induction of the transcription factor CHOP; 2) in collaboration with Danna Breen and colleagues at Pfizer, we reported that it does indeed induce conditioned taste aversion/avoidance; 3) we showed that, unlike for example glucagon-like peptide 1 or leptin, GDF15 levels are not influenced by short- or medium-term caloric perturbations; 4) consistent with reports that mice lacking GDF15 are susceptible to gaining more weight than wild-type mice when fed a high-fat diet, we found that long-term high-fat feeding of mice results in increased levels of GDF15, coming largely from adipose tissue and from liver.

So, GDF15, unlike leptin, may actually contribute to a signal that limits indefinite positive energy balance in the face of high caloric availability. It is certainly worthy of further exploration as an antiobesity agent, likely in low dose combination with other moieties.

We have recently gone on to demonstrate that the effects of metformin to reduce body weight in humans and in mice appear to be largely attributable to its induction of GDF15 gene expression and elevation of circulating concentrations of GDF15 protein (67). In the absence of GDF15 action, metformin has no impact on body weight or adiposity in mice. Remarkably, metformin increases GDF15 expression principally in the lower parts of the gastrointestinal tract and the kidney and not significantly in the liver. While there are clearly effects of metformin to lower glucose and insulin that are independent of GDF15, our findings are consistent with recent (68) and earlier (69) work indicating that a substantial proportion of these effects of metformin are exerted at the level of the gut.

I described GDF15 to you as a sentinel hormone designed to respond to environmental toxins. This new work now suggests that a drug that we have used in millions of patients for more than half a century requires that sentinel to exert some of its beneficial effects. Of course, this intimate relationship between pharmacology and toxicology is nothing new. The Renaissance physician Paracelsus was perhaps the first to point out that it was only dosage that differentiates a poison from a useful medicine: “All things are poison, and nothing is without

poison, the dosage alone makes it so a thing is not a poison" (70).

Acknowledgments. In the long run, it's all about people: the mentors, colleagues, trainees, and collaborators we interact with; the patients and participants who work with us; and the family and friends who support us. In the course of this lecture, I have paid homage to my scientific mentors and to the many lab members and collaborators who have contributed directly to the work described. I would like to thank all members of the lab, past and present, for their dedication and skill. I am proud of its many alumni who have made successful careers elsewhere. In particular, I would like to mention Anna Krook, my first graduate student; Robert Semple, a more recent escapee, now a Professor at Edinburgh University; and John Prins, now Dean of the Medical School at Melbourne, who helped me to get through a very difficult time in the late 1990s. In addition to the former fellows who have stayed on and become independent principal investigators in the IMS, i.e., Tony Coll, Sadaf Farooqi (who this year was awarded the Outstanding Scientific Achievement Award of the American Diabetes Association, a Cambridge "double act" of which we are both immensely proud), David Savage, and Giles Yeo, our institute hosts many wonderful scientists. In particular, I would like to thank Krishna Chatterjee, FRS. We worked together in London in the early 1980s as medical residents, and in the late 1980s in Boston, where we were both postdoctoral fellows, we lived in the same apartment complex, after which we both moved to Cambridge, U.K. For nearly 40 years, Krish has been a constant source of wise counsel and scientific inspiration to me. Without the dedicated people who support us all in the Wellcome-MRC Institute of Metabolic Science, the work I described today would have been impossible. Maria Adams, our Director of Research Operations, and Chris Ford, our institute administrator, and their teams go so far beyond the call of duty. In nearly 25 years, I have only had two Personal Assistants. Without the dedication and skill of, first, Mun Flint and now Carole Smith, I could not have been relied upon to put one foot in front of the other. It has been an honor to share the Directorship of the IMS with Nick Wareham. It has been a privilege to work with Nick and his talented colleagues in our concerted attempt to cross the boundaries between epidemiology and mechanistic laboratory science. Without our funders, our numerous collaborators, the physicians who alert us to puzzling patients, and, of course, those patients and research participants themselves, none of what I have described would have been possible. Thanks also go to two leaders of the Cambridge School of Clinical Medicine who had key roles in the creation of the Wellcome-MRC Institute of Metabolic Science: to Keith Peters, who, as Regius Professor, the Cambridge equivalent of Dean, provided me with the crucial support needed for the fundraising, launch, and development of the institute, and to his successor Patrick Sissons, who supported me through good times and bad, and whom we lost all too soon in 2016. The ultimate thanks go to my family and friends, who have been unstinting sources of strength and support throughout my life.

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