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Early nutrition and diabetes mellitus

Nutrition during fetal life and infancy may be crucial to the development of diabetes mellitus

The pancreatic β cell mass in humans develops rapidly during gestation and infancy, increasing more than 130-fold between the 12th intrauterine week and the fifth postnatal month. In rats the number of β cells increases rapidly in the four to six days before birth, and the proliferative compartment—the proportion of β cells able to replicate—is thought to fall from 10% during fetal life to 3% in young adulthood. These observations suggest that the peak β cell mass may be determined early in life, even during gestation, and the factors that influence it are likely to be important in the development of diabetes.

Nutrition is the main determinant of the growth of β cells.[1] The factors that influence the size of the proliferative compartment are less clear, though in rats there are genetic differences. Hyperglycaemia during late pregnancy leads to hyperplasia of β cells in the neonate,[2] and malnutrition in growing rats leads to a permanent reduction of the β cell mass.[3] Human infants who are small for dates—a marker for poor intrauterine nutrition—have fewer β cells.[4] Freinkel likened the environment of later gestation to a culture medium and coined the expression "fuel mediated teratogenesis" for the longer range metabolic disturbance of middle life which he foresaw might result from the excess or deficiency of certain "culture" nutrients essential for normal fetal growth.[5] Two recent reports have focused on the part that early nutrition may play in the later development of diabetes.

In the first report Hales and Barker suggest that the factors determining early growth also influence the β cell mass in adulthood.[6] They hypothesise that impaired glucose tolerance and possibly type II diabetes may both result from poor nutrition early in life interacting adversely with abundant nutrition later on.[7] Obesity in later years leads to insulin resistance, and the functional β cell mass, programmed in leaner times, may then be unable to meet the rising demand for insulin. Hales and Barker cite two convincing lines of evidence. Studies of men in their 60s whose birth records were still available showed that low birth weight and low weight at 12 months were associated with glucose intolerance later in life. The degree of glucose intolerance for any given birth weight was influenced independently by body mass index in adulthood. Men with a low body mass index in later life were relatively protected against the susceptibility to glucose intolerance stemming from their low birth weights, while 17% of those of low birth weight but with a high body mass index later in life were frankly diabetic. The studies have been extended to show the same inverse relation between birth weight and glucose tolerance in young men aged 18-25.[8]

A report from Oxford in this issue confirms an inverse relation between glucose tolerance in later life and birth weight (p 302) but was unable to account for the marked impairment of β cell function in the type II diabetic subjects by low birth weight alone.[9] The authors conclude that additional genetic or environmental factors are likely to be necessary for the development of type II diabetes, consistent with the very high concordance rate for type II diabetes observed in monozygotic twins.

Insulin is packaged inside β cells as the precursor proinsulin, which is cleaved on secretion into C peptide and insulin. Small amounts of proinsulin and the fragment 32-33 split proinsulin are also released in health. Serum concentrations of both are raised in patients with type II diabetes, reflecting most probably a shift in the relation between demand for insulin and the capacity to produce it.[10] Whether the increased release of the precursor in type II diabetes is due primarily to a low β cell mass or to insulin resistance is unclear, but the serum concentration of 32-33 split proinsulin in the men reported on by Hales and Barker correlated inversely with their body weight at 12 months.[7]

The second report suggests that the autoimmune damage to islet cells responsible for type I (insulin dependent) diabetes may also have a nutritional basis which operates early in life—but a totally different one. Though the clinical presentation of type I diabetes peaks around puberty and sometimes occurs much later, highly sensitive assays for islet cell antibodies have suggested that everyone who develops type I diabetes is seropositive by the age of 5 years.[11] The implication is that the fuse for type I diabetes is lit early in life but may burn faster in some than in others.

Some years ago Western Samoans were found never to develop type I diabetes in their own environment but to do so when brought up in New Zealand. Exposure to cows' milk was the suspected trigger. An association between bottle feeding and type I diabetes has also been found in Finland.[12] Laboratory rodents that spontaneously develop autoimmune type I diabetes did so at a much lower frequency when fed a synthetic chow free of cows' milk protein,[13] and recently a peptide antigen called p69 was identified on rat insulinoma cells which cross reacts immunologically with a similar sequence present in bovine, but not human or rat, albumin.[14] Antibodies to bovine serum albumin were present in all patients with type I diabetes of new onset but in only 2·5% of

controls. Antibodies to the relevant peptide sequence in the bovine serum albumin also identified the p69 antigen from islets on immunoblots. Karjalainen and colleagues have hypothesised that one route to type I diabetes is through molecular mimicry between the islet antigen p69 and bovine serum albumin in cows' milk.[14] Early sensitisation to bovine serum albumin through bottle feeding in infancy leaves memory T cells which destroy β cells expressing p69. The p69 antigen is inducible by interferon γ released intermittently during childhood infections, so that the process of destruction of β cells is protracted, variable, and uncertain. Only a subset of the population—those with a genetic make up that was able to present the critical sequence of bovine serum albumin to the immune system—would be susceptible to the mimicry.

It therefore seems conceivable that susceptibility to both type I and type II diabetes is determined during gestation or infancy in response to nutrition, and research should respond with a new focus on early events. But the similarity between the two of an early influence of nutrition may not stop there. Diabetes results when the insulin reserve no longer meets demand. If the stress on β cells that leads to type II diabetes is a progressively increasing demand (insulin resistance), the stress that leads to type I diabetes is arguably a progressively diminishing reserve (insulitis). In either case the outcome is likely to be influenced by the peak β cell mass. Perhaps the genetic linkage that has recently been described between type I and type II diabetes[15] is a determinant of the β cell proliferative compartment and its response to early nutrition.

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1 Swenne I, Bone AJ, Howell SL, Hellerström C. Effects of glucose and amino acids on the biosynthesis of DNA and insulin in fetal rats maintained in tissue culture. *Diabetes* 1981;**29**: 686-92.
2 Van Assche FA, Aerts L, Holemans K, Danneels L. Fetal consequences of maternal diabetes. In: Anderani D, Bompiani G, Di Mario U, Faulk WP, Galluzzo A, eds. *Immunology of normal and diabetic pregnancy*. Chichester: Wiley, 1990:229-36.
3 Swenne I, Crace CJ, Milner RDG. Persistent impairment of insulin secretory response to glucose in adult rats after limited period of protein-calorie malnutrition early in life. *Diabetes* 1987;**36**: 454-8.
4 Van Assche FA, Aerts L. The fetal endocrine pancreas. *Contrib Gynaecol Obstet* 1979;5:44-57.
5 Freinkel N. Of pregnancy and progeny. *Diabetes* 1980;**29**:1023-39.
6 Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C, *et al.* Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991;**303**:1019-22.
7 Hales CN, Barker DJP. Type 2 (non-insulin dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992;**35**:595-601.
8 Robinson S, Walton RJ, Clark PM, Barker DJP, Hales CN, Osmond C. The relation of fetal growth to plasma glucose in young men. *Diabetologia* 1992;**35**:444-6.
9 Cook JTE, Levy JC, Page RCL, Shaw JAG, Hattersley AT, Turner RC. Association of low birth weight with β cell function in the adult first degree relatives of non-insulin dependent diabetic subjects. *BMJ* 1993;**306**:302-6.
10 Temple RC, Carrington CA, Lazio SD, Owens DR, Schneider AE, Sobey WJ, *et al.* Insulin deficiency in non-insulin dependent diabetes. *Lancet* 1989;**1**:293-5.
11 Pilcher CC, Dickens K, Elliott RB. ICA only develop in early childhood. Proceedings of the 11th International immunology diabetes workshop. *Diabetes Res Clin Pract* 1991;**14**(suppl 1):S82.
12 Virtanen SM, Rasanen L, Aro A, Lindstrom J, Sippola H, Lounamaa R, *et al.* Infant feeding in Finnish children less than seven years of age with newly diagnosed IDDM. *Diabetes Care* 1991;**14**:415-7.
13 Daneman D, Fishman L, Clarson C, Martin JM. Dietary triggers of insulin dependent diabetes in the BB rat. *Diabetes Res* 1987;5:93-7.
14 Karjalainen J, Martin JM, Knip M, Ilonen J, Robinson BH, Savilahti E, *et al.* Evidence for a BSA peptide as candidate trigger of type 1 diabetes. *N Engl J Med* 1992;**327**:302-7.
15 Rich SS, Panter SS, Goetz FC, Hedlund B, Barbos J. Shared genetic susceptibility of type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus: contributions of HLA and haptoglobin. *Diabetologia* 1991;**34**:350-5.

Improving medical education

Educators need to develop an open mind and a willingness to share

Stella Lowry's analysis of the problems affecting medical education (which ends this week, p 320[1]) holds for countries other than Britain. For example, we in the Netherlands are also struggling with medical curriculums overloaded with factual information, often of little clinical relevance, which risk turning our students into passive consumers, their creativity and curiosity stifled. We assume that competent doctors emerge at the end of an obstacle course of traditional examinations based on facts.

Little place exists in many of our curriculums for other important opportunities for learning, such as use of simulated patients and early clinical contact, or for developing skills in self directed learning and communication. As in Britain, changes in health care are only haphazardly incorporated into the educational programme.

If we all agree that change is required then why is it so difficult to implement? Two impediments come to mind. The first is the attitude of teachers. Typically, tradition weighs heavily on us: curriculums are organised and taught in the way that we have always done it. We have all gone through the same system (which seems not to have harmed us), and it is difficult to accept that current students should be taught differently. Interestingly, this attitude contrasts starkly with how people conduct their clinical practice or academic research. Here, a highly rational approach is the norm. In clinical practice we try to keep up with the scientific literature and adapt our actions accordingly. In academic research we submit our findings to rigorous peer review. Regrettably, this attitude does not extend to our educational activities.

The reward system in our universities is the second impediment to change. Just as examinations define students' academic success, so the academic success of university staff is defined by excellence outside education: higher status is mainly attained through outstanding research or excellence in clinical work rather than educational achievements. Spending too much time on education may actually endanger one's career as less time is available for more effective ways of achieving success. As long as this biased reward system persists, motivating teaching staff to improve the training of medical students will be difficult.

Starting from scratch has a certain attraction but is hardly an option in countries, such as Britain, which have long established medical schools. So how could change be achieved in existing medical schools? In her article Stella Lowry provides several examples. Firstly, we need to convince our colleagues that problems exist and that there are better ways of doing things. As well as persuasion, however, some external pressure, both from within and from outside schools, is needed to produce change. Some central control is required over medical education to ensure that rational decisions are being taken and that the quality of education is monitored.

Individual departments in most medical schools have nearly unrestricted autonomy as far as their teaching is concerned. We can therefore hardly expect change from individual departments: they lack an appreciation of the curriculum as a whole and are inherently inclined to defend their own interests.

Outside pressure is another indispensable force to achieve change. In Britain institutions like the General Medical Council and the King's Fund could provide it yet they apparently lack the power to enforce recommendations. On