Saturday 3 April 1999

BMJ

Ordeals for the fetal programming hypothesis

The hypothesis largely survives one ordeal but not another

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That antenatal experience could have dire consequences is ancient folklore. In 1921 Stockard gave scientific form to the idea in the "critical period" hypothesis: failure of a developing organism to progress from one stage of development to the next within preset time limits could lead to a permanent deficit. Since then several studies have addressed related hypotheses, though mostly in animals. From the 1950s human observational studies reported effects in later life of various exposures—for example, to radiation,[1–3] famine,[4] and viruses.[5] In a large number of more recent publications, Barker has elaborated the idea that fetal experience might "programme" cardiovascular health states in adult life. He has been ingenious in seeking out birth records of cohorts of a half century ago and more. Studies using such sources face some irreparable difficulties—for instance, incomplete samples and attrition on follow up with selective bias, inadequate as well as missing records, and the absence of data crucial for controlled analysis.

Some of these problems are being better resolved in later datasets assembled for long continued longitudinal studies. An analysis from one such birth cohort study in New Zealand appears in this week's issue.[6] This analysis also addresses a second—entirely reparable—problem previously discussed by one of us.[7] This is the observation that Barker's studies, fertile as they have been in stimulating life course studies, do not meet Galileo's crucial scientific requirement that a hypothesis should be subjected to an ordeal. In other words, science requires the framing of refutable questions.

The authors of this week's study have followed the editorial injunction and pursued some of the ordeals suggested. They report on systolic blood pressure at the ages of 9 and 18 in a cohort followed from birth. Losses at follow up were remarkably few, with missing data at a minimum and enough variables to control for confounding. For most important variables—exposures, outcomes, and covariates—standard measures were used. The hypothesis drawn from Barker is that undernutrition, manifest in slow growth and consequent low birth weight, programmes the fetus for high blood pressure in later life. The authors' refutable formulation is that low birth weight due to known and clearly specified antecedents—namely, twinning, maternal smoking, and maternal size—should result in raised systolic blood pressure.

The results for twinning and maternal height, the authors conclude, are in the main contrary to the hypothesis: the low birth weights of twins were associated with lower average systolic blood pressure and, conversely, the higher birth weights accompanying mother's height with higher pressure. Maternal smoking was associated with lower birth weight—an effect consistent with the hypothesis, but only on the assumption that the mechanism is indeed nutritional.

The authors rely on path analysis to elaborate these results. Path analysis is a clever way to organise causal thinking that is seldom seen in the medical literature. Invented in the 1920s by Sewall Wright,[8] a founder of population genetics, it was little used until in the 1960s it was revived in population genetics and became a vogue in the social sciences. To see how it works, take the underlying statistical method of multiple linear regression. Between a presumed antecedent variable x and a presumed outcome variable y one can obtain the result that a unit of x "accounts" for a given amount of change in y. When multiple variables serve as antecedents, the multiple linear regression method apportions the contributions of each of the many x's to the variance in the outcome y. In essence, path analysis assembles the variables usually seen in an unstructured form in multiple regression analysis into a structure of presumed causal paths between the variables. The variables thus form a set of presumed causal sequences, and are laid out in a path diagram for clarity.

Given such a presupposed causal model, path analysis allows one to estimate the relative strengths of relations between the variables in the model. This it does in two ways. One estimate expresses the variance of the key outcomes as a sum of all the components that are the presumed causal antecedents of those outcomes. A second estimate "decomposes" the correlations between variables—that is, distributes them—in terms of the model among their causal antecedents.

Each connection between the variables is assigned a path coefficient, (a value expressing how many standard deviation units the variables at the head of an arrow change in association with a one standard deviation change in the variable at the tail, other causes held fixed). The path coefficient corresponding to a multilink causal pathway between two variables is obtained by multiplying path coefficients along the links, and the overall correlation between two variables is the sum of the path coefficients over all such causal pathways, direct and indirect.[9]

The method has the advantage of prior commitment to hypotheses about the appropriate causal ordering of all the variables included. It follows that the presumed links between variables are thereby tested

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and can sometimes be refuted. If not refuted, they stand as compatible with the hypotheses, although not proved by such a result standing alone. In short, path analysis does not prove the validity of a causal model. Many such models can be fitted to the same data, and each will produce an associated path analysis. Path analysis quantifies, and thereby illuminates, sequences among variables which, for the purposes of the model, the analyst must already assume do in fact hold.

The caveat about proof is important because the language of the method invokes causality in speaking of "causal" paths and the like. This is especially the case in analyses using the simultaneously collected cross sectional data of surveys when, between many variables linked in the path model, even time order remains unascertainable and hypothetical. In the study by Williams et al,[6] however, the method is given greater cogency by the longitudinal design. Hence the time order of many path sequences is known and not assumed, with considerable advantage for causal inference.

In Williams et al's paper a modest negative correlation between birth weight and systolic blood pressure is compatible, though weakly, with the fetal programming hypothesis.[6] The path diagram shows this correlation to be composed of a larger, direct negative effect between these two variables, together with two positive indirect effects (through child's height and body mass index), and several joint antecedent causes of both birth weight and systolic pressure with positive contributions (in particular, twinning, maternal height, and maternal smoking).

The causal model in the diagram is complex. If correct, it suggests that the fetal origins hypothesis, if it is indeed represented by the direct, inverse effect of birth weight that lowers blood pressure, competes with other causal pathways with important, indirect, countervailing influences that raise blood pressure. In particular, if the low birth weights of twins are taken to be the result of impaired fetal nutrition, as the Barker formulation has generally done, the model falls on the side of refutation.

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Combined kidney and pancreatic transplantation

Ideal for patients with uncomplicated type 1 diabetes and chronic renal failure

Diabetes mellitus is the single most common cause of end stage renal failure in Western societies. Despite rigorous glycaemic control, dietary changes, exercise, and use of disease modifying drugs, some patients with diabetes, mostly but not exclusively those with type 1 disease, will develop renal failure requiring dialysis.[1] In the first five years after transplantation, kidney graft survival is similar in diabetic and non-diabetic populations,[2] but overall mortality in the diabetic group is three times that in non-diabetic transplant recipients.[3] Accelerated coronary atherosclerosis, sudden death related to autonomic neuropathy, and infection account for much of this excess mortality. Strict control of blood glucose with intensive insulin therapy reduces, but does not eliminate, these risks.[1] In the United States simultaneous kidney and pancreas transplantation is now regarded by many clinicians as the treatment of choice for uraemic diabetic patients in the absence of advanced coexisting vascular disease or after its correction.[4–5] Is it time for the rest of the world to follow suit?

Since 1980 nearly 9000 pancreatic transplants have been performed worldwide,[6] over two thirds of them in the United States; current trends suggest an annual rate exceeding 1500. In contrast, in the United Kingdom and elsewhere pancreatic transplantation has been viewed more critically. This concern has been fuelled by the high rate of surgical complications, with increased perioperative morbidity and mortality, and by the perceived risks associated with the requirement for increased immunosuppression to prevent organ rejection[7]: fewer than 200 patients have received pancreatic transplants in the United Kingdom.

The addition of a pancreatic transplant at the time of renal transplantation establishes a return to normal carbohydrate metabolism.[4 5] Quality of life is improved through the abolition of dietary restrictions, freedom from exogenous insulin and blood glucose monitoring, and removal of fear of hypoglycaemia. Combined kidney and pancreas transplantation produces patient and pancreatic graft survival rates of 92% and 79% at 1 year and 81% and 67% at 5 years, respectively—results comparable to cadaveric kidney transplantation in non-diabetic patients.[2–6] Most importantly, early results show that not only does patient survival improve by at least 10% at five years but that long term kidney graft survival is also better after combined organ grafting than after renal transplantation and continued exogenous insulin.[2–8] Moreover, when diabetic patients receive a kidney transplant histological changes of diabetic nephropathy recur within two years,[9] progressing to end stage disease after 10 years. Successful

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