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Twins and fetal programming of blood pressure

Questioning the role of genes and maternal nutrition

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The weight of evidence linking reduced size at birth to raised blood pressure is now substantial[1] and that for an increased risk of non-insulin dependent diabetes and coronary heart disease is increasingly convincing. Despite continuing scepticism,[2] initial concerns that these statistical associations were due to chance, artefact, or confounding by factors in later life have been largely resolved. Attention is now turning towards elucidating underlying mechanisms and the public health importance of the "fetal origins" hypothesis.

Over the past five years the biological plausibility that circumstances in utero can "program" the fetus, such that postnatal physiology and disease risk are altered, has been bolstered by evidence from animal models. Experimental manipulation of the environment of the fetus in utero, through modifying the maternal diet and other means, can undoubtedly have profound long term effects on structure and function.[3]

The direct relevance of these animal models to humans has not been adequately assessed, particularly with regard to maternal nutrition. Nevertheless, they provide an important counterpoint to the suggestion that genetic rather than environmental factors drive the association between impaired growth and later disease in humans.[4] More direct human evidence about the possibility of a purely genetic explanation can come from studies of twins. A particularly powerful design is to examine whether variation in size at birth within monozygotic twin pairs is associated with differences in later outcomes. This application of twin data, focusing on effects within twin pairs, is very different from studies that set out to compare blood pressure between twins and singletons.[5]

A recent Danish study found that in monozygotic twin pairs discordant for non-insulin dependent diabetes it was the diabetic member of the pair who tended to be the lightest at birth,[6] suggesting strongly that the inverse association between size at birth and non-insulin dependent diabetes cannot be entirely accounted for by common genetic factors. In this week's *BMJ* a similar approach is applied to blood pressure in 8 year old Australian twins by Dwyer et al (p 1325)[7] and to 50 year old female British twins by Poulter et al (p 1330).[8]

Consistent with the in utero programming hypothesis, but not with the genetic alternative, both studies found a tendency for the monozygotic twin who was lightest at birth to have the highest systolic blood pressure later in life. Moreover, the larger the difference in birth weight, the larger the difference in later blood pressure. These associations were not, however, statistically significant in either analysis. The British study was based on 167 monozygotic twin pairs,[8] whereas the Australian study had only 16 monozygotic twin pairs,[7] relatively few twin pairs showing substantial discordance in birth weight. Nevertheless, these results are intriguing, and further similar studies, with larger numbers of monozygotic twins, are needed to help resolve the role of genetic factors.

On the assumption that there are in utero programming effects, one of the key issues to be resolved is the role of maternal factors in driving them. This is central to the public health implications of this hypothesis. David Barker, who has pioneered the fetal origins hypothesis, emphasises the importance of improving maternal nutrition. Indeed, he suggests that the primary prevention of coronary heart disease and non-insulin dependent diabetes may ultimately depend on changing the body composition and diets of young women[9] because of their impact on the environment in utero. However, direct human evidence from epidemiological studies implicating maternal nutrition and diet is sparse and fragmentary.[10–12]

Twin studies can contribute to the debate about the role of maternal nutrition. Variation in fetal growth within twin pairs cannot be determined by differences in maternal diet in pregnancy or cumulative nutritional status as these factors are identical for each member of a twin pair. Interestingly, therefore, both Poulter et al and Dwyer et al report that when all multiple birth pairs—regardless of zygosity—are examined the lighter member of the pair tends to have the higher blood pressure. The extent of the difference in blood pressure is proportional to the difference in birth weight, this effect being statistically significant among the 492 twin pairs studied by Poulter et al[8] but not among the 55 multiple birth pairs studied by Dwyer et al.[7] What is particularly striking about these results is the magnitude of the effect. A recent systematic review found that in studies of singletons there was an average reduction in systolic blood pressure of around 2 mm Hg for every kg increase in birth weight in children and of 3 mm Hg in 50 year olds.[1] The effects within twin pairs reported in this week's *BMJ* are appreciably larger, both studies showing a reduction in systolic pressure of over 5 mm Hg per kg increase in birth weight.

This suggests that the causes of variations in fetal growth within twin pairs (which cannot include nutritional characteristics of the mother) are sufficient

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to exert a programming effect if—as seems likely—such an environmental mechanism exists. This in turn directs attention to the potential role of the fetal supply line, and placentation in particular, which is known to play an important part in determining variation in growth between twin pairs and also singletons.[13] The comparatively large effect seen in within pair analyses relative to singletons suggests that discordance in birth weight within multiple pregnancies may be more closely related to the underlying mechanisms of fetal programming than is birth weight variation between unrelated singletons.

These data from twin studies should encourage a more critical approach to the debate about the public health implications of the fetal origins hypothesis as well as to the underlying mechanism. Striving to improve the nutritional status of girls and young women is undoubtedly desirable. However, whether this holds the key to the primary prevention of coronary heart disease and non-insulin dependent diabetes is far from clear—even though the basic propositions of the fetal origins hypothesis look like they may well be correct.

David A Leon *reader in epidemiology*
London School of Hygiene and Tropical Medicine, London WC1E 7HT (d.leon@lshtm.ac.uk)

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Managing the clinical performance of doctors

A coherent response to an intractable problem

The last few years have seen a progression of "rogue doctors" and health care scandals through the media.[1] Now, unsurprisingly, we have a series of proposals that attempt to guarantee to patients that the doctors treating them are up to standard. Public confidence must be restored, or trust in the National Health Service will be destroyed. Three weeks ago the prime minister launched the Commission on Health Improvement (CHI), which will inspect health services in England and Wales and respond to services in trouble.[2] Two weeks ago the General Medical Council discussed its proposals for revalidation for every doctor in the United Kingdom.[3] Now the chief medical officer of England has issued his proposals on how poor clinical performance among doctors will be prevented, recognised, and dealt with.[4] The old system—based on an expectation that professionals would keep up to date and do something about poorly performing colleagues combined with some half hearted systems of self regulation—is dead.

Nobody can deny that there is a problem. "Bristol"—the case of poor performance in paediatric cardiothoracic services—heads the list and, I have argued, changed everything.[5] But there have been several other episodes, and chillingly the chief medical officer seems to accept there are more to come: "We expect that over the next three to five years, an increasing number of incidents will surface as local services begin to 'declare' longstanding problems that have not been addressed." Medicine—and not just in Britain[6 7]—has a culture of hiding errors and forgiving those who make them. This stems not only from professional tribalism and a feeling that "there but for the grace of God go I" but also from doctors knowing that they simply cannot do much of what patients want and even expect them to do.[8]

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England's chief medical officer, Liam Donaldson, knows about the culture of turning a blind eye because he has contributed to a book that enlarges on the theme.[7 9] He has also published a study in the *BMJ* showing that 6% of senior doctors in the NHS had a performance problem in a five year period.[10] Furthermore, he found himself caught up in a long running dispute in Gateshead that led to questions in parliament and a government inquiry—so he knows first hand the deficiencies in the present system.[11]

The report gives the impression that the government has considered the possibility of ending self regulation. It's not only for doctors that self regulation has been questioned. The press, for instance, does a poor job—but is unlikely to be reformed because it's much more important and threatening to politicians than doctors are. A government task force on better regulation has been looking at all forms of self regulation and has concluded that overall it does have some benefits.[12] But the chief medical officer's report qualifies its support for self regulation by saying that it will continue "if such arrangements can be modernised to offer patients appropriate protection." General Medical Council and royal colleges be warned.

Donaldson's main recommendation for preventing poor performance is appraisal for all doctors in the NHS. Appraisal may sound scary to those who have

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