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Relation of birth variables to death from cardiovascular disease

EDITOR—D J P Barker and colleagues’ study puts a further nail in the coffin of those who doubt that the intrauterine environment influences later health—in this instance, death from cardiovascular disease.1 A theme running through the Submission, and no doubt of substance in this case, is that maternal nutrition is primarily responsible for reduced prenatatal growth. Though there can be no doubting the importance of maternal malnutrition as a cause of reduced fetal growth in poor countries and the overwhelming importance of undernutrition in the early part of this century, where Barker and colleagues’ cohorts were born and brought up, there is no strong evidence of undernutrition now being responsible for restraining intrauterine growth in developed countries.

Maternal diet is only one of the many factors that can lead to fetal growth retardation. To begin to understand mechanisms that might link the environment of fetal life and infancy with later cardiovascular disease, it is necessary to understand how and why birthweight affects the risk of cardiovascular disease in adult life. BMJ 1993;306:422-6. (13 February.)


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Paradoxical pain

EDITOR—David Bowsher defines paradoxical pain as any pain that he believes does not respond to morphine.3 It is more generally understood as pain that is made worse rather than better by increasing doses of morphine. It has been reliably reported with large doses of intrathecal morphine and diphosphate and probably occurs occasionally with large daily doses of the same drug intravenously. Bowsher and his colleagues have made a good case for paradoxical pain being the result of a genetic inability to metabolise morphine to the potent morphine 6-glucuronide, leaving large quantities of morphine 3-glucuronide (a putative morphine antagonist or a non-specific cerebral stimulant, or both)9 unopposed. It is difficult, therefore, to understand why Bowsher has opted for an alternative definition.

It is also disturbing that he has used “overwhelming pain” as a synonym for paradoxical pain. Overwhelming pain is a term used to emphasise a consequent result of chronic unrelied severe cancer pain. It almost always responds to adequate amounts of morphine, coanalgesics if appropriate, and, usually, an axiolytic. A comparable situation is sometimes seen despite large doses of morphine when the patient experiences fears and anxiety. It has been addressed. Thus, in one case, a patient with inoperable cancer of the oesophagus was still in pain despite receiving 12 g of oral morphine a day when he was admitted to a hospice; a week later he was free of pain when taking 60 mg of morphine a day and 10 mg of diazepam at night. His seemingly morphine resistant nociceptive cancer pain responded to listening, explanation, and the setting of positive rehabilitation goals.

Nociceptive pain is also relatively resistant to morphine and other opioids when there is peripheral or central neural sensitisation. Sensitisation occurs in damaged tissue and the surrounding area and in areas subserved by either an injured peripheral nerve or an injured part of the central nervous system. Pain associated with inflammation is a typical example of peripheral sensitisation, hence the need to use a non-steroidal anti-inflammatory drug in most patients with painful soft tissue or bone metastases. Morphine alone is often inadequate, but there is nothing paradoxical about this. Central sensitisation may also occur in such cases as part of a secondary “wind up” phenomenon in the dorsal horn. Occasionally this can occur in the thalamus, and is associated with an N-methyl-D-aspartate receptor blocker such as ketamine.12 Central sensitisation in neuro-pathic pain is more complex and, as Bowsher points out, demands a range of alternative measures.1,12

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In 1967 Cicely Saunders described the concept of total pain, which encompasses the psychological, emotional, and spiritual turmoil of some patients with severe pain. Might this be what Bowsher refers to as overwhelming pain?1,3

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Editor—David Bowsher’s editorial oversimplifies a complex and contentious issue.1 Paradoxical pain may well exist but is neither well documented nor common; it does not account for the majority of cases of uncontrolled pain, and we are not aware of any evidence that it was an important factor in the care of the patient in the recent highly publicised court case.2

One hypothesis is that paradoxical pain is caused by abnormal metabolism of morphine is plausible but built on shaky foundations. The evidence in rats that morphine 3-glucuronide may antagonise the antinociceptive actions of morphine1 is unsubstantiated and is hard to explain given that morphine 3-glucuronide has a much lower binding affinity for opioid receptors than either morphine or the active metabolite, morphine 6-glucuronide.3 Furthermore, large interspecies variations exist not only in the metabolism of morphine but also in the distribution of opioid receptors.4 Thus animal data on this subject cannot, and should not, be extrapolated to humans and many questions remain.

Though recognition of this potential therapeutic problem is welcome, until the clinical importance of the morphine metabolites in humans is completely understood these rare cases of paradoxical pain will remain unexplained.

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Editor—The concept of paradoxical pain and its relation to morphine metabolites raises many questions.1 There are several conceptual errors inherent in this description. One of the most fundamental is that the pain syndromes as described should at any time actually respond to opioids. This makes the assumption that so-called paradoxical pain is nociceptive pain, with the second assumption that all nociceptive pain...