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 Southampton group's many studies on this topic is that maternal nutrition is primarily responsible for reduced prenatal growth. Though there can be no doubting the importance of maternal malnutrition as a cause of reduced fetal growth in poor countries and even perhaps in Preston, Sheffield, and Hertford 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 disease, influences other than maternal nutrition need to be considered—for example, Edwards *et al* have recently proposed that links between the fetal environment, adult hypertension, and low birth weight could be mediated through dysfunction of the placental barrier to maternal cortisol.[2]

D P DAVIES
J MATTHES

Department of Child Health,
University of Wales College of Medicine,
Cardiff CF4 4XN

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Paradoxical pain

EDITOR,—David Bowsher defines paradoxical pain as chronic nociceptive pain that does not respond to morphine.[1] 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 diamorphine and probably occurs occasionally with large daily doses of the same drugs 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,[2] leaving large quantities of morphine 3-glucuronide (a putative morphine antagonist or a non-specific cerebral stimulant, or both[3,4]) 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 common result of chronic unrelieved severe cancer pain.[5] It almost always responds to adequate amounts of morphine, coanalgesics if appropriate, and, usually, an anxiolytic. A comparable situation is sometimes seen despite large doses of morphine when the patient's anxieties and fears have not 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,[6] hence the need to use a non-steroidal anti-inflammatory drug in most patients with painful soft tissue and 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 requires specific correction—for example, with an *N*-methyl-D-aspartate receptor blocker such as ketamine.[7,8] Central sensitisation in neuropathic pain is possibly more complex and, as Bowsher points out, demands a range of alternative measures.[9,10]

ROBERT TWYCROSS

Sir Michael Sobell House,
Churchill Hospital,
Oxford OX3 7LJ

1 Bowsher D. Paradoxical pain. *BMJ* 1993;**306**:473-4. (20 February.)
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EDITOR,—Paradoxical pain is a new and confusing term that has been defined in different ways. David Bowsher decribes it as nociceptive pain that is not receptive (does he mean responsive?) to opioids.[1] Yet in an earlier publication, in which the term was first coined, he and his colleagues used it to describe "pain [which] ceases to be relieved *or is worsened* by further administration" of morphine or diamorphine (our italics).[2] We have not seen any patients whose physical pain has been made worse by morphine or diamorphine, nor are we aware of any good evidence that this occurs. More importantly, we fear that the suggestion that this may happen may deter some doctors from giving adequate doses of these drugs when they are properly indicated.

It is well recognised that opioid analgesics do not always relieve pain, and there are already several unsatisfactory ways in which such pain is described, including "opioid insensitive," "opioid non-responsive," and "opioid resistant." As we have written elsewhere, these terms have subtle differences in meaning, which are partly semantic but partly reflect different views.[3] The introduction of yet another term will add confusion. We believe that what has been described as paradoxical pain is what we would refer to as "opioid poorly responsive" pain and that opioid responsiveness is a continuum that may be influenced by any of a large number of factors related to the patient and the drug as well as the pain. The pharmacokinetics of morphine may provide at least part of the explanation, but there are too few data to justify the editorial's subheading (morphine 3-glucuronide does not, by the way, bind to opiate receptors).

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?

G W C HANKS
W M O'NEILL
M T FALLON

United Medical and Dental Schools,
Division of Oncology,
Department of Palliative Medicine,
St Thomas's Hospital,
London SE1 7EH

1 Bowsher D. Paradoxical pain. *BMJ* 1993;**306**:473-4. (20 February.)
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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]

The hypothesis 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 analgesic actions of morphine[3,4] 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 morphine metabolite, morphine 6-glucuronide.[5,6] Furthermore, large interspecies variations exist not only in the metabolism of morphine but also in the distribution of opioid receptors.[7,8] 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.

CAROL L DAVIS
ROSE TURNER

Palliative Care Unit,
Royal Marsden Hospital,
Sutton,
Surrey SM2 5PT

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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