Paradoxical pain

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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 study is that intrauterine issues and those at birth are not independent. Rather, there is a strong interaction between the two, and it is maternal nutrition that is primarily responsible for the observed later-day effects. As Barker and colleagues point out, life expectancy in developing countries has increased more rapidly than that in developed countries, and the environment influences a range of conditions in later life.

Maternal diet is 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, it is important to consider the possibility that maternal malnutrition can affect fetal growth and cause conditions later in life. The results indicate that low birth weight is associated with such conditions as chronic disease and mental retardation, and low birth weight is associated with higher death rates. Furthermore, large intercountry variations exist in the proportion of women who are malnourished.

The term maternal nutrition is often used to describe the relationship between the environment in which an organism lives and its health. It has been shown that maternal nutrition can affect the development of the fetus and can result in long-term effects on health. These effects can be observed in both the maternal and the offspring generations. For example, maternal malnutrition during pregnancy can result in small for gestational age newborns, which are at increased risk of developing chronic diseases such as hypertension, diabetes, and cancer later in life.

Barker and colleagues have found that maternal malnutrition during pregnancy can result in small for gestational age newborns, which are at increased risk of developing chronic diseases such as hypertension, diabetes, and cancer later in life. It has been shown that maternal nutrition can affect the development of the fetus and can result in long-term effects on health. These effects can be observed in both the maternal and the offspring generations. For example, maternal malnutrition during pregnancy can result in small for gestational age newborns, which are at increased risk of developing chronic diseases such as hypertension, diabetes, and cancer later in life.

This makes the assumption that called paradoxical pain is no longer valid. In fact, this pain is now called nociceptive pain, with the second assumption that all nociceptive pain is nociceptive at birth and is not influenced by later events.

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Editor—David Bowsher defines paradoxical pain as pain that is not caused by any lesion, or that is not responsive 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. When morphine and probably other opioids are given 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, rather than the morphine glucuronide, leaving large quantities of morphine 3-glucuronide (a putative morphine antagonist or a non-specific cerebral stimulant, or both) 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 consequence of chronic unrelied severe cancer pain. It almost always responds to adequate amounts of morphine, coanalgelsics if appropriate, and, usually, an anxiolytic. A comparable situation is sometimes seen despite large doses of morphine when the patient experiences severe anxiety and fears of death have 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 intact part of the central nervous system. Pain associated with inflammation is a typical example of peripheral sensitisation, whereas pain associated with a N-methyl-D-aspartate receptor blocker such as ketamine is central sensitisation in neuro-pathic pain is more complex and, as Bowsher points out, demands a range of alternative measures. 1,2

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Paradoxical pain

EDITOR—Paradoxical pain is a new and confusing term that has been defined in different ways. David Bowsher describes 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 that was worse or was worsened by further administration of morphine or diamorphine (our italics). We have not seen any patients whose physical pain has been made worse by morphine or diamorphine, nor are we aware of any 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 antiresponsive” and “opioid resistant.” As we have written elsewhere, these terms have subtle differences in meaning, which are partly semantic but partly reflect different views. 2 The introduction of yet another term will add confusion. We believe the term “paradoxical pain” that 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 a number of factors related to the patient and 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).

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Reference