

## Microbes and the brain

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"Many authors assure us that mental alienation is epidemic. It is certain that there are years when, independently of moral causes, insanity seems suddenly to extend to a great number of individuals"

Esquirol, 1845

The roles of nature and nurture as determinants of human behaviour have been grist for philosophers for millennia. For much of the twentieth century infectious diseases captured the popular imagination with the hope that vaccines and antibiotics would provide cures not only for diseases clearly due to microbes such as poliomyelitis, rabies, and syphilis, but also for chronic brain disorders of unknown pathogenesis such as multiple sclerosis, depression, and schizophrenia. Proponents of infectious bases for these disorders have cited such evidence as discordance for disease in monozygotic twins (schizophrenia), increased prevalence with distance from the equator (schizophrenia and multiple sclerosis), and preponderance of second-trimester maternal exposure to respiratory tract infections, particularly influenza (autism, schizophrenia).

More recently, we became enamoured with the notion that panaceas will arise through genome projects. Frustration with the ability to move beyond simple allelic associations to genetic causation has led to models based on interactions of genes. Although such models are plausible, it is reasonable to reintroduce the environment into the equation. As with most complex dialectics, the answers are likely to be found in synthesis: susceptibility genes coupled with environmental factors such as infectious agents, toxins, and psychosocial stressors.

Most people would agree that if the relationship between any microbial agents and schizophrenia, affective disorders, or multiple sclerosis were elementary, the influence of such environmental factors on disease expression should already be apparent. A number of scenarios have been proposed to explain the difficulties in apprehending specific microbes through routine strategies for pathogen detection: low-level persistence in neural tissues, "hit-and-run" mechanisms, or indirect effects of pathogens through mechanisms such as molecular mimicry, where immune responses to an agent cross-react with normal host tissues to cause disease. Alternatively,

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environmental factors might also be inappropriately dismissed in cases where a wide variety of pathogens, neurotoxins, or general stressors induce nonspecific damage through elaboration of cellular or soluble immune mediators that lead to a final common pathway resulting in immediate or delayed brain dysfunction.

The advent of molecular tools for detecting microbial footprints, such as subtractive cloning, polymerase chain reaction, and in-situ hybridisation, and also of methods for defining targets of immune responses, has rekindled interest in the search for a role of pathogens in



Van Gogh: infected with microbes?

Frida's Genealogy Museum, Netherlands/Bridgeman Art Library, London/New York

idiopathic brain disorders. Examples include proposed linkages between multiple sclerosis and human herpes virus 6 or retroviruses, Alzheimer's disease and herpes simplex virus 1 in patients having the type 4 allele of the apolipoprotein E gene, neuropsychiatric disorders (major depression, bipolar disorder, schizophrenia, or chronic fatigue syndrome) and Bornaviruses, and paediatric obsessive-compulsive disorder and streptococci. Although intriguing, none of these relationships is established either as causative or as associative; however, each remains open and controversial despite ongoing investigation. Indeed, clinical trials are in progress for antimicrobial treatment of some of these disorders based on what many would consider to be only

preliminary data. It is clear that neither Koch's postulates nor an updated facsimile inclusive of molecular technology will serve us here. The new era of microbial neuropathogenesis will require teams of diagnosticians, microbiologists, immunologists, geneticists, developmental neurobiologists, and epidemiologists who appreciate the complexity of host:microbe interactions and their implications for brain dysfunction.

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## Preterm birth and pre-eclampsia—bad news and good news

James M Roberts, Kristine Y Lain

Our understanding and treatment of preterm labour and pre-eclampsia, the two major causes of perinatal mortality, morbidity, and long-range neurological disability, are improving. None the less, there is bad news as well as good news. The rate of preterm birth has not changed in the past 20 years despite efforts by obstetricians and their patients. Attempts to identify pregnancies at risk by demographic and epidemiological factors have been unsuccessful. After a huge financial investment, it is now established that ambulatory contraction monitoring increases the diagnosis of preterm labour but does not reduce preterm births. Many women have been treated with drugs in an attempt to inhibit uterine contractions. This strategy has also not reduced preterm births. Despite these pessimistic observations, there has been progress.

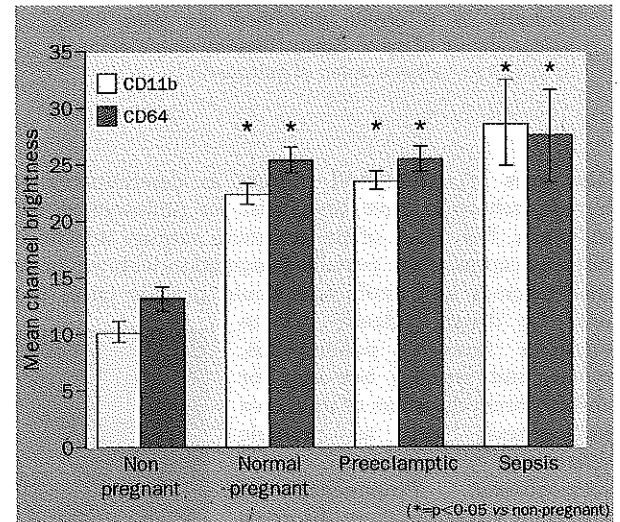
A breakthrough is the recognition that not all preterm births are a result of the same cause, and that their pathophysiology is rarely just the early onset of term labour. Subclinical infection is present in the amniotic fluid, placenta, and membranes of many babies delivered after premature labour, but this is not the case for infants delivered early for medical indications. This raises hope that if these pregnancies could be recognised, treatment could perhaps ameliorate the infection, thus reducing preterm births. Current investigations search for this diagnosis by examining markers of vaginal infections as indicators of intrauterine infection. Studies suggest that cytokines and basement membrane components may also be useful markers. In a large observational study of 3000 low-risk women, one such marker identified 60% of babies delivered before 28 weeks' gestation.

The same study assessed potential clinical markers and provided further evidence that preterm labour is multifactorial. Cervical length was an independent marker of preterm birth. As the length of the cervix, determined sonographically at 24 to 26 weeks' gestation, decreased, the risk of preterm birth increased. At the 10th centile for length, the risk increased seven fold. Finally, in another study, increased oestriol in saliva appeared to be a predictor of preterm birth occurring primarily after 32 weeks' gestation. Thus, perhaps at least three causes—subclinical infection, mechanical cervical factors, and hormonal effects—are involved in preterm births.

Pre-eclampsia has met with similar successes and failures. It is now clear that aspirin will not prevent pre-eclampsia in a way that is clinically useful. Contrary to early studies and meta-analyses, several studies indicated that aspirin did not prevent pre-eclampsia in women at either low or high risk for the disorder. When the studies were viewed in total, however, there did seem to be a small effect. Thus, although aspirin did not seem to be the right choice, if our understanding of pre-eclampsia reaches a stage where a more appropriate treatment

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Inflammatory markers (mean [SEM]) on monocytes

strategy is identified, early treatment, before clinically evident pre-eclampsia, could be effective.

Information continues to accumulate indicating that maternal constitutional factors contribute to pre-eclampsia. For example, abnormalities of homocysteine metabolism and thrombophilic disorders are associated with pre-eclampsia. Many of these factors are also risk factors for cardiovascular disease in later life. If the risk persists beyond pregnancy, why does pre-eclampsia abate with delivery (and cardiovascular morbidity arise decades later)? The finding that normal pregnancy is associated with activation of the inflammatory response and that this response maybe worse in pre-eclampsia may provide an answer (figure). The sensitisation of many systems, including the vascular endothelium, could make the effects of insults which would ordinarily take years to be manifest be expressed during pregnancy and resolve with delivery.

For both pre-eclampsia and preterm labour there is optimism that solutions are at hand. Several clinical trials are in progress, testing treatment strategies directed at the causes of preterm birth. For pre-eclampsia the hope is as real, but the clinical implications are less immediate. Research on the entire pathophysiology of the disorder rather than simply pregnancy-induced hypertension will provide directions for clinical trials in the future.

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