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MEETING REPORT

In this report Dr. Hanson and his colleagues describe some of the major observations and conclusions presented at the Second World Congress on Fetal Origins of Adult Disease. The abstracts of that meeting were published as a supplement to the June 2003 issue of Pediatric Research. The fetal origin of adult disease is a new, exciting and often controversial concept that is of importance for our understanding of human development.

Report on the 2nd World Congress on Fetal Origins of Adult Disease, Brighton, U.K., June 7–10, 2003

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ABSTRACT

In 1989, reports suggested that the fetal environment, as reflected in birth size, was related to the risk of noncommunicable diseases in adult life. This association was first described for coronary heart disease but rapidly extended to include type 2 diabetes, osteoporosis, and metabolic and endocrine homeostasis. This led to the development of the fetal origins of adult disease paradigm, which resulted in a refocusing of research effort over the next 10 y to consider the lifelong consequences of perinatal influences on chronic diseases. Previously, perinatal influences had largely been seen in terms of teratogenic effects or acute birth injury rather than whether trajectories and responses made during early development had lifelong consequences. Indeed, in developmental biology, it is widely recognized that adaptive plastic responses during early development often have consequences for function in later adulthood. Although the relative importance of this newly recognized set of phenomena to the burden of human disease has been controversial, the research precipitated by those early observations has confirmed their robustness and started to provide a mechanistic basis to this biology. Two world congresses have been held to review progress in this research. Both have been characterized by a unique multidisciplinary attendance ranging from molecular, experimental, and developmental biologists to epidemiologists and health economists. **(*Pediatr Res* 55: 894–897, 2004)**

The 1st World Congress on Fetal Origins of Adult Disease (FOAD) was held in Mumbai, India, in February 2001. From the outset, researchers in India have recognized the likely global importance of the concept of developmental origins of adult disease. In developing societies, type-2 diabetes and coronary heart disease are reaching epidemic proportions and epidemiologic data have strongly supported a role for the FOAD phenomenon in the genesis of this epidemic. The 2nd World Congress was held in Brighton, U.K., in June 2003.

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More than 80 invited speakers participated and 325 posters were displayed, about twice as many as the 1st World Congress. Abstracts are published in *Pediatric Research* [volume 53(6), part 2]. The Congress demonstrated the enormous interest in this area.

What were the major themes to emerge from the 2nd World Congress? A central feature was consolidation of the importance of the FOAD concept in its wider context of gene–environment interactions extending from conception into childhood, and possibly even involving the oocyte before conception (1). Critics of the FOAD concept had focused largely on the magnitude of the birth weight–hypertension association, and there was agreement that such a view missed the point. Attention has shifted from birth weight *per se* to patterns of growth before and after birth, for which birth weight is known to be a very poor proxy, and from markers of disease, such as blood pressure, to the underlying mechanisms of disease themselves. Moreover, where in Mumbai it was not yet clear whether animal models would provide robust support for the phenomenon, there now emerged a considerable degree of consistency in these, largely due to stronger methodology and a focus on early gestation challenges as the most worthy of current investigation.

As noted before in this journal (2), reduced birth weight is not a prerequisite for evidence of fetal adaptive responses, especially those occurring in response to challenges in early gestation. This distinction was underlined at the Congress to permit separation of pathophysiological processes operating in growth-restricted (intrauterine growth-restricted, small-for-gestational-age) fetuses from those physiologic adaptive responses occurring in normal fetuses or those subject to physiologic constraints. Discussion of the latter included the effects of parity (3), twinning (4), and maternal age (5). These processes, which account for part of the normal spectrum of human and animal phenotypic variability, can be included under the heading of maternal constraint (6). One mechanistic basis for such a process has been described in rodents and involves allele-specific imprinting of the type-2 IGF receptor gene (this being a growth suppressor, acting as a clearance receptor for IGF-2 peptide) *versus* the paternally imprinted *Igf-2* gene (7). The mechanism for such imprinting involves DNA methylation, and there is now evidence that during prenatal development this process may be altered by changes in methyl-group availability arising from variations in maternal nutrition (8). The need for folate and glycine is underscored by their ability to rectify cardiovascular effects of a low-protein diet in pregnancy on the offspring in rats (9, 10). New data on the role of epigenetic processes in placental growth and function were presented (7), and extended to provide a model in which placental growth may play a key role in the early growth trajectory of the conceptus, but aspects of placental function may be fine-tuned in later gestation in relation to fetal nutrient demand (11).

Such epigenetic processes are evident in the embryo, and experiments in pregnant rats fed a low-protein diet solely during the preimplantation phase of development have shown that this produces hypertensive offspring (12). New evidence indicates that a maternal low-protein diet produces changes in *H19* gene expression in the embryo (13), altering its relationship to the expression of *Igf-2*. How the effect is transmitted to the embryo is not known, but concentrations of IGF-1 and insulin alter cell allocation between the inner cell mass and trophectoderm in the mouse embryo *in vitro* (14). In addition, data were presented that, during embryonic development, elevated maternal plasma homocysteine levels can alter mitochondrial DNA copy number in the offspring (15).

Observations of environmental effects on embryo genes are important for several reasons. First, they give insight into potential mechanisms that may be universal features of mammalian development. Epigenetic effects could, for example, explain consequences of periconceptional nutrient restriction in sheep on later outcome in the offspring (16, 17). Second, they raise concerns about the longer-term consequences of assisted reproduction technologies in humans, especially *in vitro* fertilization. Professor Lord Winston aired these issues in his plenary lecture at the close of the Congress. Thirdly, new research is examining the possibility that developmental exposure to environmental agents such as phytoestrogens and pesticides might alter epigenetic processes and influence health in postnatal life (18, 19), and indeed it is hypothesized that interactions between nutrients and chemical exposures could have long-term consequences (20).

The focus of many of the papers at the Congress was on underlying mechanisms and, in this regard, the animal models of programming show considerable commonality. Epigenetic processes, including changes in DNA methylation, may be determined not only during the early embryonic period alluded to above, but even during the early postnatal period. Here, long-term effects of maternal-infant interactions on the behavior of the offspring result from altered methylation of the NGFI-A binding site in the promoter for the glucocorticoid receptor 1_7 isoform (21). This example of an epigenetic basis for environmental programming is of particular interest as it occurs in a nonimprinted gene.

As anticipated, a good deal of discussion at the Congress was devoted to the epidemic of obesity in children and young adults in both developed and developing countries, and the inevitable consequences in terms of developing metabolic syndrome and type 2 diabetes. The global health implications of these are obvious, and new data from New Delhi highlight the scale of the problem; in a group of 30-y-old adults, the incidence of overweight is 45% and that of impaired glucose tolerance and type 2 diabetes exceeds 15% (22). An encouraging facet to emerge from these otherwise daunting data is the realization that the growth trajectories of children and adolescents (especially the time they take to achieve "adiposity rebound") differ between those prone to develop aspects of the metabolic syndrome and those who will remain healthy. This offers the prospect of early identification of those at risk (perhaps coupled with measurement of predisease markers such as disordered vascular endothelial function) and, thus, intervention to prevent the progression to disease in these individuals. Pragmatic information on the early characterization of those at risk is needed by the makers of health policy and will certainly be required if pharma- and nutraceutical companies are to become involved in interventions. The im-

portance of a developmental perspective on the global epidemic of obesity cannot be overemphasized.

Until recently, it had been assumed that obesity was the consequence of lifestyle after birth. Clues that there may be a prenatal component came from follow-up studies of the Dutch famine (23) and evidence supporting this has now emerged from studies of Indian neonates (24). Studies in rats make it clear that prenatal undernutrition programs not only postnatal cardiovascular dysfunction but also obesity, elevated plasma leptin concentration, glucose intolerance, and even reduced activity levels and dietary preferences (25, 26). Similarities were reported for sheep experiments, in which placental restriction by carunclectomy was associated with adiposity and increased insulin sensitivity during postnatal life (27). If such processes occur in humans, then it may be that postnatal interventions will be too late to reduce the risk of the metabolic syndrome, and the efficacy may be disappointing.

A further complication is mounting evidence that in populations in which maternal stunting and underweight are common, such as in India, relative fetal adiposity and its complications may be observed at relatively low birth weights at or below the mean birth weight in westernized communities (24). In such populations, interventions to improve fetal growth may not be appropriate without prior measures to produce a commensurate increase in maternal size.

At the time of the 1st Congress, it was hoped that the 2nd World Congress would provide the forum for detailed discussion of intervention strategies. Much attention has been given to the use of micronutrients, particularly folate, to improve birth weight (28). However, a note of caution was sounded about folate fortification of foodstuffs. Animal data show that although dietary folate supplementation prevents some of the adverse effects of a low-protein diet in pregnancy, it may also have unexpected adverse effects on the offspring (9). Moreover, preliminary data from a cohort of pregnancies in India also suggest that greater clarity is needed before new recommendations can be made about folate intakes (Fall CHD *et al.*, unpublished experiments). In other areas of health promotion, examples of interventions that have exacerbated the problem were rehearsed (29). Although it has become routine to refer to health education or social marketing as the panacea, the point was made that education at the individual level may not achieve the desired result unless specifically targeted to at-risk groups, or, better still, backed by legislation and societal changes (30). With adolescents, particularly girls, it is important to stress the immediate benefits to the individuals themselves of a balanced diet and regular exercise. Referring to the consequences of comprehensive deprivation, Professor Amartya Sen discussed the broader issues of improving the health of women in developing societies, and in deprived sections of the population in developed societies. Improving women's health benefits not only women, but also their families and descendants, and the economy as a whole. Women's nutrition is becoming a pressing issue as accumulating experimental evidence indicates that adaptive responses made by females before they are born can be transmitted to their children. The effects of environmental and dietary influences operating in one generation may be expressed in grandchildren and further generations.

The consequences and implications of prenatal responses on function in later life were placed in a wider evolutionary biology context at the Congress (6, 31). Adaptive responses can cause permanent changes in structure and function and may have multiple pathways to their induction. The responses have predictive value to the offspring; if the postnatal environment is similar to that predicted, the adaptive responses confer a survival advantage, which operates before the end of the reproductive phase. If the postnatal environment is dissimilar to that predicted, then such predictive adaptive responses lead to increased risk of disease. It is proposed that predictive adaptive responses have been selected and preserved by evolution as they protect genetic diversity in a species and enable the maximum number of a species to survive a transient environmental change.

The Congress concluded with a presentation by Her Royal Highness, The Princess Anne, Patron of the Congress. In her considered and highly supportive address, Her Royal Highness stressed the importance of FOAD research for global health and the need for an integrative approach to solving the problems. In particular, she stressed the problems of nutritional and other transitions in populations adapted to poor diets and harsh environments over many generations. She concluded by presenting a silver salver to Professor David Barker, FRS, in recognition of his pioneering—and continuing—work in this field.

The enthusiasm and commitment to a multidisciplinary approach to further our understanding of fetal health and chronic disease was evident at the Congress. The field has shifted from phenomenology to mechanistic biology and its translation. Accordingly, delegates agreed to the formation of a learned society, the International Society for the Developmental Origins of Health and Disease (DOHaD). This name recognizes the broader scope of the developmental cues, expanding from the oocyte to the infant, and the wide span of health outcomes associated with programming. Membership already extends from evolutionary biologists to clinical epidemiologists. The Society intends to cover the full spectrum of activities of a learned society. The 3rd World Congress will be held under this rubric in September 2005 in Toronto.

The International DOHaD Society may be contacted at www.dohadsoc.org. Membership application forms may be obtained from the Web site or through Mrs. Bronwen Parnall, DOHaD Society, Level F (887), Princess Anne Hospital, Coxford Road, Southampton, SO16 5YA, U.K., or e-mail: admin@dohadsoc.org. Annual subscriptions are set at US$50. The foundation chair is Professor P.D. Gluckman; secretary, Professor M. Hanson; and treasurer, Professor C. Cooper.

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Johnson Nutritionals, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Pharmacia, Unilever Research Ltd., World Health Organization, and Wyeth Nutrition.

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ERRATUM

In the Letter to the Editor by Zimmermann et al. (Pediatr Res 54:554–555, 2003) there is an error in the listing of authors. The corrected listing of authors appears below. The authors regret this error.

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