century, the physiology of the mature animal is but the tip of the iceberg and a reflection of time and biological memory.

References


Commentary: The global relevance of ‘biological Freudianism’

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While a stick is green, thou canst bend it as thou listest. When it is dry; fire alone can make it straight.

Saadi, 13th century Persian poet

For centuries, it has been recognized that during limited ontogenetic periods, subtle environmental influences can alter the course of human development and thereby affect an individual throughout life. As Dubos pointed out in his 1966 article, such ‘early influences’ have most commonly been recognized to affect human behaviour. A huge body of work from the past 40 years, however, illustrates convincingly that in addition to conditioning behaviour, early environmental influences on developmental pathways help shape individual anatomy, physiology, metabolism, and gene expression. Dubos proposed that this area of research might develop into a new science called ‘biological Freudianism’. Considering the various connotations now associated with the term ‘Freudian’, it is probably a good thing that Dubos’ proposed terminology never caught on. Rather, the term ‘programming’ proposed by Alan Lucas is now widely associated with persistent structural or functional changes caused by a broad range of early environmental influences. Waterland and Garza more recently proposed the term ‘metabolic imprinting’ to encompass a subset of adaptive responses resulting specifically from early nutritional influences. Recognizing the extensive contributions of David Barker, and his popularization of the concept that a majority of adult disease originates in utero it is not uncommon for scientists to refer to the ‘Barker Hypothesis’. As illustrated by the above quote by Saadi, however, as well as this historical article by Dubos, the idea that early environmental influences are important to shaping human development and health is certainly not new. What is relatively new is our increasing...
ability to quantify the magnitude of these phenomena in human epidemiologic studies and probe the underlying mechanisms in sophisticated animal models.

From a historical perspective, it is worth noting that René Dubos developed his interest in ‘biological Freudianism’ in the latter part of his remarkable career. Born in France in 1901, Dubos received his PhD in microbiology in the US and spent most of his career at Rockefeller University in New York City. His interest in environmental influences on bacterial populations evolved into a passionate fascination with the interactions between humans and their environment. A prolific author, he wrote numerous books including the Pulitzer Prize winning *So Human an Animal* (1968). As perhaps his most widely-recognizable claim to fame, he is credited with coining the omnipresent bumper-sticker slogan ‘Think Globally, Act Locally’. When he died in 1982 he left behind a scientific and philosophical legacy that will have a lasting influence for years to come.

Dubos’ focus in his 1966 article was to describe animal models his lab developed for the study of ‘sociomedical problems’ recognized in human populations. Foremost among these, he identified the trend in the US towards earlier maturation of children, and proposed that this trend may be largely attributable to environmental influences during early life. Recent data indicate that maturation age has continued to decline since the 1960s. Much more alarming, however, has been the explosive epidemic of childhood obesity that has occurred over this period, especially in the US.7 Consistent with Dubos’ conjecture, it has been postulated that this increase in childhood obesity is partly due to environmental influences operating early in development.8,9

Whereas animal models demonstrate clearly that subtle environmental influences during early development can make a major impact on gene expression, metabolism, and various chronic-disease phenotypes in adulthood,3 the physiological relevance of such phenomena in humans continues to be hotly debated. Owing to progress in information technology and analytical approaches over the last several decades, human epidemiologic studies now often include sophisticated analyses of data from huge samples of individuals. Nonetheless, the overall complexity of quantifying persistent effects of early environmental influences in human populations inevitably potentiates confounding, selection biases, and inconsistencies within and between studies.10 Hence, Dubos’ statement that ‘the complexity of the interplay between man and his total environment has handicapped the epidemiologic and clinical study of such sociomedical problems’1 remains true today. In contrast to the large number of human epidemiologic studies in this field, there has been a dearth of robust clinical intervention studies examining the long-term consequences of early nutrition. The noteworthy exception is Alan Lucas’ prospective study of preterm infants who were randomized to receive different infant formulas or banked breast milk during the first few weeks of life.11

Dubos’ animal models1 focused entirely on the early post-natal period as an important ‘critical window’ for environmental influences on development. He recognized that the dramatic environmental transition at birth stimulates many important developmental processes, and the specific nature of the early post-natal environment may therefore have lifelong effects. Dubos probably would have argued against the overly restrictive terminology of the ‘foetal origins hypothesis’,4 because his animal models demonstrate that environmental influences on development are not limited strictly to foetal life. Accordingly, the International Society that was originally founded to foster research into the ‘Fetal Origins of Adult Disease’ (FOAD) recently broadened its name (and focus) to the Developmental Origins of Health and Disease (DOHaD).

Dubos noted that even genetically identical newborn mice can follow widely divergent growth trajectories, and that these differences are apparent within a few days of birth. He randomized and redistributed newborn mice to foster dams, and discovered that the ‘nursing effectiveness’ of the mother, not innate differences amongst individual pups, largely determines growth rate during the suckling period. An elegant study from Michael Meaney’s group12 recently provided an important extension of this finding by demonstrating that overall caregiving behaviour (licking, grooming, and nursing) varies dramatically amongst individual inbred rodent mothers. Moreover, during the first few days of post-natal life these differences in maternal caregiving affect permanently the offspring’s stress responsivity, apparently by a mechanism involving altered DNA methylation of the glucocorticoid receptor gene in the hippocampus.12

Dubos described his studies in which female mice were placed on various experimental diets during lactation. After weaning, all pups received free access to the same diet. In one experiment, animals exposed to a standard natural rodent diet were compared to those whose mothers were fed a semi-synthetic (casein–cornstarch) diet during the suckling period. Weight gain of the casein–cornstarch diet group lagged behind that of the other group at weaning and, although the differential diet exposure was limited to the suckling period, this body weight difference persisted throughout adulthood. Dubos showed that the ‘critical window’ for this effect was limited to the first five days after birth; when dams were started on the synthetic diet after this time their pups followed the same growth trajectory as pups suckled by dams fed the standard diet throughout lactation.

It is difficult to gauge the impact Dubos’ early diet studies made in terms of stimulating research in the area. Certainly, many subsequent studies have examined persistent influences of early post-natal diet. The lack of details on the experimental diets Dubos used, however, would complicate efforts to reproduce and extend his results. By comparison, a far more generalized model by which to study persistent effects of early post-natal nutritional status was reported years earlier by Widdowson and McCance.13 They randomized the offspring of several litters of rats born on the same day, and redistributed them to foster mothers in either small or large litters, causing early post-natal over-nutrition or under-nutrition, respectively. Even though all pups were provided free access to the same diet after weaning, animals from large litters remained smaller than those from small litters. The studies of Widdowson and McCance were the first to demonstrate a ‘critical window’ for early post-natal nutritional influences on growth,13 and their rodent litter size model has been employed to study the persistent effects of early post-natal nutritional sufficiency on body composition,14,15 lipid metabolism,14–16 insulin axis function,14,15,17 and endocrine pancreas gene expression.17
It was perhaps merely a ‘Freudian slip’ that, in the context of his work, Dubos failed to acknowledge the seminal contributions of Widdowson and McCance.

While recognizing it would be ‘desirable’ to understand the specific biological mechanisms by which early environment affects development, Dubos asserted that his aim was not to discuss mechanisms, but rather to illustrate that animal models can be used to study ‘biomedical aspects of social situations’. Of course, controlled studies in animal models can lend biological plausibility to putative causal pathways inferred from human epidemiologic studies. Without a detailed understanding of underlying mechanisms, however, we cannot be confident that specific animal systems are appropriate models for the phenomena we seek to understand. Directly after disavowing himself of an interest in underlying mechanisms, Dubos suggested that the study of animal models ‘should help in the formulation of social programs’ for the control of obscure socio-medical problems. Thankfully, very few social programs have been implemented based solely on the findings of animal model studies.

The best way to make progress in unraveling the developmental origins of health and disease is to employ animal models to develop a very detailed understanding of how environmental signals influence mammalian development. Such advances will enable the formulation of very specific hypotheses that can most readily be tested in humans. There is an urgent need to obtain this information. Whereas most of the human epidemiologic data in support of the ‘developmental origins hypothesis’ is based on populations in industrialized nations, there is a growing concern that the epidemiologic transition currently underway in many developing countries will render multiple generations of people ill-adapted to their ‘improving’ circumstances, leading to a global pandemic of diet-related chronic disease. Dubos was optimistic in challenging mankind to ‘improve the lot of man on earth by manipulating the environmental factors that shape his nature and condition his destiny’. Now is the time for us to take his challenge seriously.

References


