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The Borderland of Teratology and Developmental Psychology

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Abstract: Despite the emerging signs of deterioration of human reproductive performance in high developed countries, the general incidence figures of birth defects do not change. An acceptable explanation has been found in the specific feature of dose-response relationships in teratology characterized by transformations of embryotoxicity end points (i.e. altered growth, structural abnormality, functional deficiency, and death of the developing organism) along the dose scale. Considering the probable nature of individual exposures under different environmental conditions we coin a hypothesis that the incidence of inborn structural and functional defects acquires a character of a dose-dependent quasi-continuous variable which invades more and more the functional sphere and ultimately concerns even the highest brain functions. In this way the frontiers of developmental toxicology and developmental psychology may be fuzzy and future investigations may bring both disciplines into an intimate and fruitful contact.

Introduction

In his famous book, the Informatorium on "The School of Infancy", Comenius some three and half centuries ago considered prenatal development and harmonious biological maturing as basic conditions influencing the learning abilities of children (Langmeier 1992). Even recent studies often find an association of minor physical anomalies with poorer intellectual function and manifestation of premorbid conditions in psychiatric patients (O'Callagan et al. 1995). Also the transformation of organic brain deficits into mental disorders appears to be extensively studied (Gaedt 1995). All these events speak in favour of the idea of a close proximity of structural and "pure" functional deficiency. In the present article we coin a hypothesis that the incidence of inborn structural and functional defects acquires a character of dose-dependent quasi-continuous variable which invades more and more the functional sphere and may concern ultimately even the highest brain functions.

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The Incidence of Structural Defects

The steep technical deployment of the 20th century leaves fingerprints upon human reproduction. Stress and global pollution from thousands of chemicals, a 100-fold increase in the generation of electric power per capita accompanied by mass non-ionizing irradiations, degradation of biorhythms and natural physical stereotypes – this all is reflected in the quantitative and qualitative deterioration of man's sperm and in the increasing frequency of poor pregnancy outcome. In spite of this, the incidence of classical birth defects has remained essentially unchanged – even since the time when this apparent curiosity was recognized and pointed out by Joseph Warkany (1981). One to 3% of the defects are regularly recorded at birth and 5–7% of others become diagnosed several years after (Kučera 1989).

Dose-response in Teratology

It has been generally accepted that the explanation of the above mentioned discrepancy is to be searched for in an unusual dose-response relationships in teratology. While the typical log-logistic model of the dose-response curve is valid for developmental toxicology, if, and only if, all the embryotoxicity manifestations (i.e. intrauterine growth retardation (IUGR), malformation and death of the conceptus) are summed up, the occurrence of malformed embryos along the dose axis follows a biphasic bell-shaped course (Peterka et al. 1986). This means that the individual end points examined at birth depend basically upon level of exposure. A very high exposure results in early embryonic loss, whereas a lower one may result in a congenital anomaly observed at birth (Sellevan et al. 1987). Thus, the probability of delivering a normal healthy baby which at present is estimated between 30–50% of all successful conceptions (Palmer 1985; Wilcox 1983; Baird et al. 1986) and, conversely, the occurrence of poor pregnancy outcome of any kind is mostly dependent on the accidental exposure to embryotoxic factors.

Embryotoxic Potential of the Environment

As mentioned in the introduction, the embryotoxic potential of the environment is constituted by many different and interacting factors, and any pregnant woman is at risk of exposure to one or more embryotoxic agents of different intensity present in meals, ambient air, water, remedies, infection and the whole socioeconomic sphere. As derived from the experience with personal monitoring devices, the individual exposure levels appear extremely variable (Binková 1996, personal communication). It means that a woman can meet an embryotoxic impulse of high intensity even in the environment of low embryotoxic potential and, on the contrary, the conceptus may escape any harm under a generally dangerous situation. Only the probability differs (see Fig. 1).

The Importance of Being Hit at the Appropriate Moment

It is well known, since the time of Schwalbe (1906) and Stockard (1921) that any particular defect can be induced only within a limited interval called the morphogenetic critical period. The critical period for structural defects occupies in

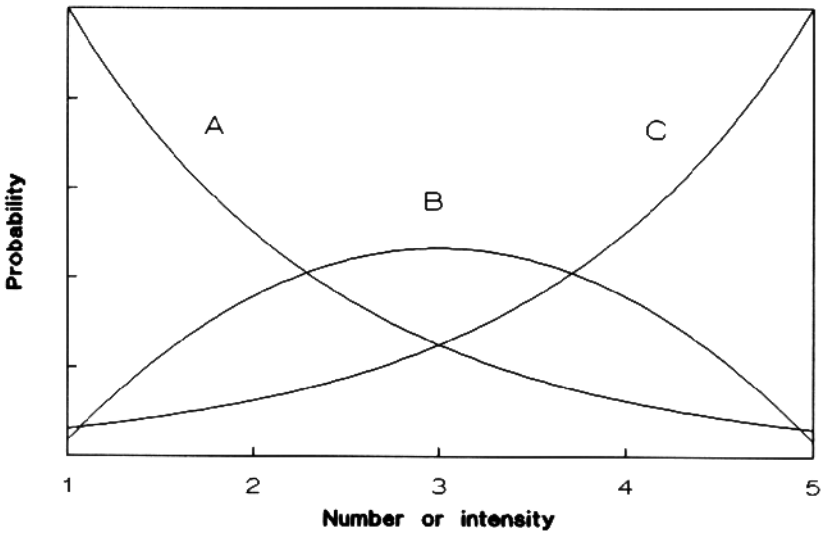

Fig. 1. A hypothetical probability of exposure to embryotoxic impulses in three different situations. A: low embryotoxic potential, B: moderate embryotoxic potential, C: high embryotoxic potential of the environment. Abscissa: number or intensity of impulses.

humans the first 8 weeks of development. Within this time interval we can discern particular critical periods of different morphogenetic systems, that partially overlap, beginning with neurulation and terminating with the formation of external genitalia. After week 8, in course of the fetal and perinatal periods, the embryotoxicants were demonstrated to induce IUGR, functional and behavioral defects, and transplacental carcinogenesis. Consequently, it is extremely important when the exposure to a deleterious agent occurs.

The Importance of Being Hit by a Proper Impulse

However, the type of end point depends apparently, not only upon when the gravid female meets an impulse, but also upon its intensity. Severe impulses kill the embryo in a short time, less intensive interfere with morphogenesis and weak interventions slow the growth rate. This scaling is however pretty relative. A rule of thumb tells us that the younger the embryo, the more prone to death. Generally, it is true, but exceptions exist with substances of receptor-mediated teratogenesis (Jelínek et al. 1983). At any rate, the impulse which appears moderate to an embryo at a certain developmental stage, may condemn to death its younger mates and, apparently, makes no harm to the same embryo in more advanced developmental stages.

Transformations of Embryotoxicity Phenomena and a Dose-dependent Shift of Malformation Spectra

It must be kept in mind that, at any moment the prenatal human population is constituted by conceptuses in different developmental stages and their distribution is similar to the actual curve of prenatal loss (see Fig. 2). Taking into account the

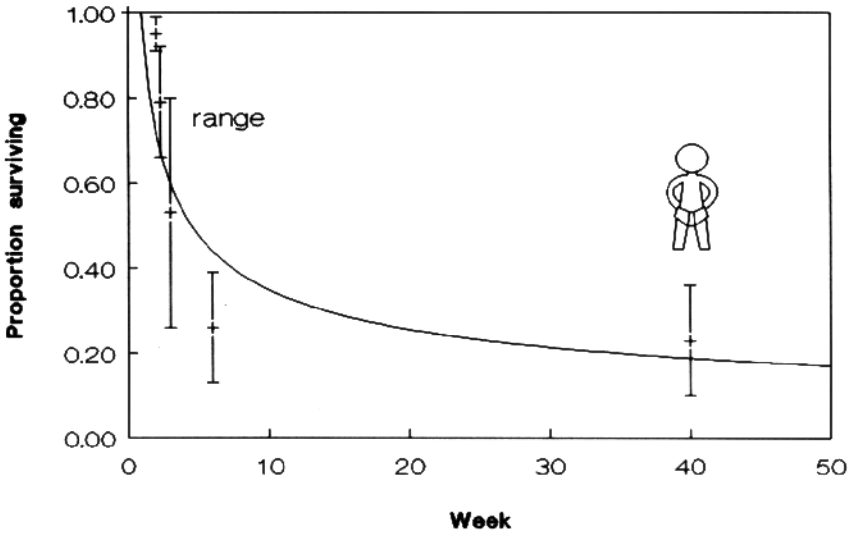

Fig. 2. Human reproductive loss (modified following Baird et al. (1986)). The course of reproductive loss in the course of pregnancy represents simultaneously the distribution of developmental stages of conceptuses exposed at any moment to embryotoxic impulses. The range depicts spread of data in the literature.

probability of being exposed to an embryotoxic impulse of appropriate intensity in differently polluted environments, we will easily come to the conclusion that changes in embryotoxic potential induce changes in proportion of developmental toxicity end points. The more severe the situation, the more embryos will be killed, first in early developmental stages, then in later critical morphogenetic periods and, ultimately at the end of the 8th week. The probable nature of exposure will, of course, allow survival to a certain number of intact embryos, however the impact zone will shift to the right affecting individuals in more and more advanced developmental stages. Provided that the deterioration of the environment continues, the trends occurring at the population level will appear as follows:

1. Increasing reproduction loss and the number of intercourses necessary for childbirth.
2. Decreasing number of malformations of the early critical period (e.g. neural tube defects) replaced by
3. Increasing incidence of malformations of late critical periods (e.g. hypospadias)
4. General decline of gross structural defects replaced by
5. Increasing functional and neurobehavioural abnormalities leading to
6. Deterioration of population performance, resistance and adaptability.

Some of these secular trends, well documented in a number of experimental studies (Rychter and Jelínek 1978; Jelínek 1985, 1988; Bednář 1986) become supported by human studies (Kučera 1989). Just to mention one single study: the recent prevalence rate of behavioural problems based on clinical diagnosis nears 23% in children between 2.5–5 years of age even in low polluted areas (Pavuluri et al. 1995). It has always been difficult to bring evidence of a slow progrediating change

in the human population, however the developmental sequences and principles of teratogenesis are common to any species. Our hypothesis is based upon nothing more.

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