CAUSES OF BIRTH DEFECTS: LESSONS FROM HISTORY

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ABSTRACT Environmental causes of birth defects have increasingly been recognized since the mid-20th century. The teratogenic effects of maternal infections such as rubella and therapeutic drugs such as thalidomide were first reported by alert clinicians. Among clinicians and researchers who have contributed significantly to our knowledge of these environmental causes, Norman Gregg was a Sydney ophthalmologist whose seminal study in 1941 identified maternal rubella as a cause of birth defects. The teratogenic effects of thalidomide were first noted in 1961 by William McBride, a Sydney obstetrician, and independently confirmed by Widukind Lenz, a German pediatrician. Marsh Edwards, an Australian veterinary scientist, showed experimentally that maternal hyperthermia caused birth defects in various animal species. While it is likely that alert individual clinicians or researchers will continue to signal the first clues about new environmental causes of birth defects, especially therapeutic drugs, it is now usually teams of laboratory researchers and epidemiologists who are more likely to provide definitive evidence of these new teratogens.

Key Words: Birth defects, environmental causes, history

INTRODUCTION

As members of the Australian Birth Defects Society, we are delighted to congratulate our colleagues in Japan who are celebrating the 50th anniversary of the Japanese Teratology Society, a notable landmark event in their studies of birth defects. I am pleased to extend warm personal greetings from Emeritus Professor Marshall Edwards at the University of Sydney who actively collaborated with Professor Kohei Shiota at Kyoto University in studies of maternal hyperthermia.

After taking note of definitions of teratology and teratogens, some important milestones regarding causes of birth defects are described. These examples give a mainly Australian perspective of environmental causes. The diverse professional disciplines of those recognizing new patterns and causes of birth defects are emphasized as is the role of alert clinicians and researchers who made causal observations. Serendipity or ‘natural experiments’ may also stimulate research of possible causes.

By the early 1940s, the genetic causes of some birth defects were recognized and experimental studies in rats and other animals had demonstrated that some vitamin deficiencies and various chemicals could also cause birth defects (Warkany 1971). It was speculated that environmental agents might be teratogenic and viruses and other infective agents were known to cross the placenta, sometimes causing fetal infections. The teratogenic effect of maternal rubella was first described in 1941 but it was some years before this became widely known.

When the Japanese Teratology Society was formed 50 years ago, relatively little was known about proven environmental causes of birth defects. The recognition that thalidomide was a potent human teratogen soon came in 1961 and maternal hyperthermia was first reported as a teratogen in animal species in 1963. Fetal alcohol syndrome was reported in 1973.

Fifty years ago, the number of human chromosomes had just been shown to be 46 and the chromosomal abnormalities in infants and children with specific patterns of multiple malformations were soon to be reported.

DEFINITIONS OF TERATOLOGY, TERATOGENS AND CONGENITAL MALFORMATIONS

Teratology is the science dealing with monstrosities, or congenital malformations (Warkany 1971). Or, put another way, it is the branch of medicine and of developmental biology which deals with congenital malformations (Shorter Oxford English Dictionary 2007).

A teratogen is an agent that causes or produces congenital malformations. Although applied chiefly to environmental causes (drugs, chemicals and viruses), abnormal genes and chromosomal abnormalities can also be teratogenic (Warkany 1971). Alternatively, a teratogen is described as an agent or factor which causes malformation of a developing embryo (Shorter Oxford English Dictionary 2007).

Congenital malformations are structural defects present at birth (Warkany 1971).

MINAMATA DISEASE

This largely forgotten environmental disaster occurred in the late 1950s when methylmercury was discharged from the chemical factory at Minamata into the Yatsushiro (or Shiranui) Sea in southwest Kyushu in the Kumamoto prefecture of Japan.

This methylmercury contaminant accumulated in fish and shellfish. Those who ate contaminated fish over a prolonged period developed the neurological symptoms and signs of Minamata disease. While methylmercury is not regarded as a teratogen in the conventional sense as it did not cause structural birth defects, children whose mothers had eaten excessive amounts of contaminated fish during pregnancy had neurological defects from early in life. Many of the children later shown to have congenital Minamata disease were often mistakenly diagnosed as having cerebral palsy. The clinical characteristics of congenital Minamata disease
consisted of severe mental retardation, abnormal reflexes, cerebellar signs, epilepsy, many other neurological abnormalities and physical handicaps (Harada and Smith 1975; National Institute for Minamata Disease 2010).

The major neurological birth defects of Minamata disease in affected adults and children are starkly illustrated in many published black-and-white photographs (Smith and Smith 1975).

### CHROMOSOMAL ABNORMALITIES AND CONGENITAL MALFORMATION SYNDROMES

Joe Hin Tjio (1919–2001) was a cytogeneticist who is renowned because he was the first person to recognize the normal number of human chromosomes. This major event occurred in December 1955 at the Institute of Genetics of the University of Lund in Sweden, where Tjio was a visiting scientist. Tjio was born to Chinese parents in Java, Dutch East Indies, and educated in Dutch colonial schools. He trained in agronomy and did research on potato breeding. Then, funded by a Netherlands fellowship for study in Europe, he worked in plant breeding in Denmark, Spain and Sweden, and subsequently in plant chromosome research in Spain, and in Sweden with Albert Levan (Gartler 2006).

Albert Levan (1905–1998) was a Swedish botanist and geneticist who specialized in plant cytology. In later work, he studied chromosome structure of cancer cells and errors in plant cells due to chemical or radioactive elements (Gartler 2006).

Within just a few years of Tjio and Levan establishing that there were normally 46 human chromosomes (Tjio and Levan 1956), further laboratory analysis of infants, children and adults with congenital malformations and other features in later life rapidly showed various chromosomal abnormality syndromes. These included Down syndrome, first described in 1866 (Down 1866), and shown to be due to chromosomal abnormality (trisomy 21) in 1959. Among other syndromes proven to have chromosomal abnormalities in that period were: Turner syndrome, first described in 1938, chromosomes (45,XO) in 1959; Klinefelter syndrome, described in 1942, chromosomes (47,XXY) in 1959; Edwards syndrome, described and chromosomes (trisomy 18) in 1960; Patau syndrome, described and chromosomes (trisomy 13) in 1960; triploidy, described and chromosomes (69,XXY or 69,XXX) in 1960; 47,XXY, described and chromosomes in 1961; and Cri-du-chat syndrome, described and chromosomes (5p deletion) in 1963 (Jones 2006).

The association between advanced maternal age and Down syndrome was shown by Shuttleworth, an honorary consulting physician at the Royal Albert Institution in Lancaster, United Kingdom (Shuttleworth 1909).

Other congenital malformation syndromes were described in the decades from 1900 to the mid-20th century. These syndromes included Treacher Collins (1900), Apert (1906), Crouzon (1912), Cornelia de Lange (1933), Ellis-van Creveld (1940), Russell-Silver (1953 and 1954), and Beckwith Wiedemann (1964 and 1969) (Jones 2006).

### MATERNAL RUBELLA AND BIRTH DEFECTS

In his seminal article, the Sydney ophthalmologist, Norman Gregg, described an increase in the number of infants with cataracts in his personal practice and clinical features of atypical congenital cataracts, congenital heart defects, and infants who were small-for-gestational age. He noted “...features of what might almost be regarded as a mild epidemic”; that “...cataracts, usually bilateral, were obvious from birth as dense white opacities completely occupying the pupillary area”; and that babies were “of small size, ill nourished and difficult to feed” (Gregg 1941). Gregg reported on 78 infants from his own practice and from colleagues in other Australian states. He found a history of maternal rubella in early pregnancy in 68 of the 78 infants, but there was no history of maternal rubella among other healthy young babies seen by Gregg during a 5-month period. A family history of cataracts was present in only one of 78 infants. They had a high mortality; 15 of 78 infants died in early life.

As infants with congenital rubella grew older, other birth defects – notably deafness, retinitis, mental retardation, and dental defects – were soon noted in other Australian studies (Swan 1944; Swan et al. 1944; Burgess 1991).

The rubella epidemic occurred during the latter part of 1940 and early months of 1941. It was an unusually susceptible population: except for an epidemic in 1937, no major epidemic had occurred for more than a decade. There was enhanced spread of disease in military camps and through general community (Leading article 1941).

To account for the lack of previous reports of birth defects associated with maternal rubella, it was suggested that the rubella virus causing the 1940–1941 epidemic was more virulent than usual. This hypothesis was refuted by later studies of census data from Australia, New Zealand and other countries linking births of deaf people with known rubella epidemics as far back as 1899 (Lancaster 1951; Lancaster 1954; Lancaster and Pickering 1952).

In studies to 60 years of age from children from Gregg’s initial cohort, an increased prevalence of diabetes, thyroid disorders, early menopause and osteoporosis has been found among survivors (Forrest et al. 2002).

Soon after the rubella virus was isolated in 1962 (Weller and Neva 1962; Parkman et al. 1962), there was a major epidemic of rubella in the United States in 1963–1965, resulting in more than 20 000 infants being born with birth defects due to maternal rubella and leading to the effects being named the congenital rubella syndrome (Cooper and Alford 2001). This epidemic led to the eventually successful search for rubella vaccines (Hilleman et al. 1969; Meyer et al. 1969; Plotkin et al. 1969; Prinzie et al. 1969). Effective vaccination programs have given hope of eliminating rubella and congenital rubella syndrome in the United States (Plotkin 2006; Reef and Coci 2006; Reef et al. 2006).

Norman McAlister Gregg (1892–1966) was born in Sydney and educated at Homebush Grammar School and Sydney Grammar School. He graduated with first-class honours in medicine at the University of Sydney in 1915, having been President of the Undergraduates Association and a director of the University Union. He excelled in many sports, gaining University blues and representing his state of New South Wales in cricket and tennis; he was also a member of the University baseball and swimming teams. After his university days and service in the First World War, where he was awarded the Military Cross for gallantry, Gregg was a keen golfer and became Captain and later President of the prestigious Royal Sydney Golf Club (Lancaster 1992; Lancaster 2007).

After training in England as an ophthalmologist, he was appointed as an ophthalmic surgeon at Royal Prince Alfred Hospital and the Royal Alexandra Hospital for Children in Sydney. He was lecturer in Diseases of the Eye at the University of Sydney from 1940 to 1951, President of the Ophthalmological Society of Australia in 1944–1945, and President, Board of Management, Royal Alexandra Hospital for Children (1959–1966).

For his work on congenital rubella, Gregg received numerous national and international awards, including the Charles Mickle...
Fellowship from the University of Toronto in 1951. He was knighted in the British and Australian honours system in 1953.

The concept that maternal viral infections might harm the fetus was not novel, but Gregg mounted strong evidence for the causal link. His findings had a major impact on development of the fledgling science of teratology, gave impetus to isolation of the rubella virus in 1962, and later stimulated development of vaccines to prevent congenital rubella.

THALIDOMIDE

Thalidomide (DL-alpha-phthalimidoglutarimide) was first used in 1956 for treating influenza, then as a sedative, and subsequently for nausea and vomiting in pregnancy. It was marketed under various trade names in different countries: Contergan, Distaval, Kevadon, Asnaival, Tensival, Valgis, Valgraine. Following recognition of its teratogenic effects, the drug was withdrawn worldwide in 1961 or 1962. However, in recent years it has been reintroduced to treat many new conditions, including human immunodeficiency virus infections, skin conditions, multiple myeloma, other cancers, such as malignant melanoma and prostate cancer, and some neurodegenerative diseases.

The classic thalidomide embryopathy (sometimes known as fetal thalidomide syndrome) shows a pattern of major malformations, variably consisting of phocomelia or amelia, anotia and other ear abnormalities, congenital heart defects, duodenal atresia, aplasia of thumbs, and triphalangism.

Infants with birth defects born after maternal use of thalidomide were first reported independently by McBride in Sydney (McBride 1961) and Lenz in Hamburg (Lenz 1961; Lenz 1962). It was soon shown that the sensitive period occurred between 27 and 40 days after conception (Lenz and Knapp 1962).

Widukind Lenz (1919–1995) was born in Eichenau, Germany. His father, Fritz Lenz, was a professor of human genetics. After studying medicine in Tubingen, Berlin and Prague (1937–1943), Lenz held positions in the Paediatrics Department, University of Hamburg, and later was chair in Human Genetics (1961). He subsequently became Professor and Director at the Institute for Human Genetics in Munster (1965–1984) (Opitz and Wiedemann 1996).

William McBride AO was born in Sydney in 1927. He graduated in medicine from the University of Sydney in 1950, and completed his doctoral medical degree in 1962. He was in clinical practice as an obstetrician and gynaecologist at Crown Street Women’s Hospital and other hospitals in Sydney. For his work on thalidomide, McBride was awarded the Gold Medal of the Institut de la Vie in France, leading to his establishing Foundation 41 in Sydney.

Many theories have been put forward to suggest teratogenic mechanisms for thalidomide. Based on radiological studies of infants born with thalidomide embryopathy, Janet McCredie, a Sydney radiologist, proposed her theory that thalidomide damaged the developing neural crest to account for the spectrum of congenital malformations (McCredie 1974; McCredie 2007).

In Japan, where several hundred births occurred after maternal exposure to thalidomide, a register of patients with thalidomide embryopathy identified hearing impairments and other defects among teenagers and young adults (Kida 1987; Kida 1988).

In the aftermath of the thalidomide disaster, there were major changes in the use of therapeutic drugs in pregnancy. Legislation resulted in more effective regulation of these drugs. Testing of drugs in pregnant experimental animals became mandatory. Many countries eventually developed national or regional systems to monitor the occurrence of birth defects. Many families with children born after maternal thalidomide received compensation. There was a new impetus to the fledgling science of teratology.

MATERNAL HYPERTHERMIA

A ‘natural experiment’ in a temporary colony of guinea-pigs in an iron shed at Camden on the outskirts of western Sydney stimulated experimental studies of the role of hyperthermia as a teratogen. In the spring months of 1963, the region experienced an unseasonably high temperature of 42–43°C for several days. In pregnant guinea-pigs, spontaneous abortions were more frequent than usual and multiple limb contractures (arthrogryposis) were noted in fetuses. These findings led to research in other species, giving particular emphasis to characterizing the timing and duration of elevated maternal temperature in pregnancy leading to birth defects (Edwards 2006).

Experimental studies in mice in Japan confirmed the association between maternal heat stress and neural tube defects, embryonic and fetal death, and skeletal malformations. This study led to hypotheses about the mechanisms of hyperthermia teratogenesis (Shiota 1988).

There have been relatively few studies of the association between maternal hyperthermia in human pregnancy and spontaneous abortion and birth defects. The hypothesis that maternal febrile illness could cause neural tube defects was tested in Japan using human embryo data. Maternal hyperthermia was found to be more likely for some types of neural tube defects when compared with normal controls and other birth defects, supporting the causal hypothesis (Shiota 1982).

When the core maternal temperature is raised at least 2°C above normal, and depending on its timing and duration, the possibility of birth defects needs to be considered. In avoidable situations, such as hot tub or spa use during early pregnancy, it is recommended that pregnant women, or those liable to become pregnant, should limit their exposure to temperatures above 39°C (Chambers 2006).

Research on the teratogenic effects of maternal hyperthermia was initiated by Marshall Edwards. He was born in Sydney in 1928, educated at North Sydney Boys’ High School and Hurstave Agricultural High School, and then graduated in veterinary science at the University of Sydney. He was later Professor of Veterinary Clinical Sciences and Dean of Veterinary Science at the University of Sydney (Graham 2005). He now enjoys an active retirement on a cattle farm west of Sydney!

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Whether birth defects are due to maternal infections, therapeutic drugs or maternal hyperthermia, these examples of environmental causes of birth defects share some common features. Sometimes serendipitous ‘natural experiments’ may arise in human or animal populations. It then depends on alert clinicians and researchers, who are well trained and have ‘prepared minds’, to take advantage of these situations and test causal hypotheses.

The recognition of specific patterns of birth defects may be important in indicating a possible new teratogen. Irrespective of who makes an initial observation associating a possible environmental cause with one or more types of birth defects, the clinician or researcher then has the responsibility to assess the validity of such claims.

As shown here by the diverse professional careers of those who have made significant contributions to our knowledge of the causes of birth defects, the recognition and understanding of causes of birth defects have made significant contributions to our knowledge of the causes of birth defects.
REFERENCES
