These figures are similar to the prevalence of congenital anophthalmia. In Britain, reporting of live births and microphthalmia was 0-4 and 0-3/10,000 live births respectively. These figures are similar to the prevalence of congenital anophthalmia and microphthalmia at birth in England and Wales for 1981-5 and 1986-90 was 0-4 and 0-3/10,000 live births respectively. The discrepancy between registries may be partly due to underreporting in Britain, differing case definitions, and overestimation of prevalence in centres with a particular interest in ocular abnormalities.

Data showing trends over time are less affected by underreporting. Since 1971, two years after benomyl was licensed in Britain, no increase in the reported prevalence of anophthalmia and microphthalmia has occurred: the reported prevalence for England and Wales was 0-4, 0-5, and 0-4/10,000 live births in 1971-5, 1976-80, and 1981-5 respectively. Over the past 10 years the use of benomyl has fallen, but use of its metabolite, carbendazim, which also causes malformations in rats, has increased nearly 1000-fold since 1965 (M R Thomas, Ministry of Agriculture, Fisheries, and Food, personal communication). These data suggest that benomyl and carbendazim are unlikely to be major causes of anophthalmia or severe microphthalmia in humans.

A French population based study of 78 cases during 1979-88 found no trends with time or space-time clusters. The largest cluster reported by the Observer comprised nine cases born in north Lincolnshire over 12 years. No details of the proportion with anophthalmia or microphthalmia was presented. "Clusters" identified retrospectively, without a prior hypothesis and without predefined geographical, temporal, and diagnostic boundaries, require cautious statistical treatment. Cases within the cluster may not be causally related: the cluster may be due to chance or manipulation of boundaries.

Paternal exposure to chemicals before conception

Some children may be at risk

The dangers to children of maternal exposure to a variety of chemicals and drugs is now well established. Interest in this area may be traced back to the discovery in the 1960s that giving thalidomide to women during the first trimester of pregnancy caused severe limb reductions in their offspring. No similar dramatic discovery has been made of an effect of paternal exposure to drugs or environmental chemicals.

Over the past two decades, however, evidence has been accumulating that exposure of men to xenobiotics can impair their fertility and adversely affect their progeny. Such adverse outcomes may include pregnancy loss, malformations evident at birth, and problems that are detected only later in life, such as behavioural abnormalities and cancer. We focus here on the risks associated with paternal exposure to chemicals; we will not discuss the extensive literature dealing with the effects of paternal exposure to radiation.

Future research should be designed to benefit those at risk, and studies of clustering may not achieve this. Clustering could be consistent with fetal exposure to pesticides, pestiviruses, or other environmental agents; genetic susceptibility to specific environmental agents; or even a genetic cause if affected family members lived in the same area. Conversely, the absence of clustering would not provide evidence against an association with a specific environmental factor, particularly if exposure to that factor is widespread.

Future epidemiological studies on anophthalmia and microphthalmia should include the detailed ophthalmological and dysmorphological assessment of affected patients and their families to define cases accurately and identify those of known cause. Such assessment would also provide the opportunity to investigate chromosomal and genetic factors, with potential benefits for genetic counselling and antenatal diagnosis.

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RUTH GILBERT
Lecturer in epidemiology
Department of Epidemiology and Biostatistics, Institute of Child Health, London WC1N 1EH

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anencephaly, with painters having the highest risk. Other paternal occupations that have been associated with an increased risk of having a liveborn child with a birth defect include firemen, janitors, forestry and logging workers, printers, and plywood mill workers. An increased risk of stillbirth, preterm delivery, or of delivery of an infant who is small for gestational age was associated with paternal employment as artists or in the textile industries. Though in most studies the chemical exposures for each occupational group were not identified, in two studies where exposure was measured a significant increase in the risk of spontaneous abortion was found in women whose husbands had increased blood lead or urine mercury concentrations before conception. 7,8 Estimates of how much paternal occupational exposure increases the risk of an adverse effect on the progeny vary from 1-5 to 5 times depending on the profession and the defect. Conversely, many jobs either have no adverse effects or improve the outcome. 2,5 Despite this, certain paternal occupational exposures, including exposure to fuel combustion products, organic solvents, and metals such as lead and mercury are consistently associated with significantly increased rates of abnormal outcomes. The possibility that “lifestyle” exposures of the father to cigarette smoke, alcohol, cocaine, and other agents that may have adverse effects should also be addressed. Although no definite evidence exists that paternal smoking or alcohol consumption causes birth defects, paternal smoking has been associated with low birth weight and increased perinatal mortality in several studies. 9,10 Therapeutic drug exposures are more readily documented, and there is information on actual doses. Several studies have examined the consequences of treatment of the father with cytotoxic drugs. Treatment with these is often associated with impaired fertility, either transient or permanent. Children fathered by these men are no more likely to be malformed than other children. 11-13 No definite conclusion can as yet be drawn on the effects of cytotoxic drugs because the numbers of patients are too low to detect anything less than a relatively high increased risk. The role of paternal occupational exposure in childhood cancer has attracted much attention. One of the most studied associations is that between exposure to motor vehicle exhaust fumes or the products of combustion engines and childhood leukemia. 14 Another established association is that of Wilms’s tumour in the children of vehicle mechanics, autobody repairmen, and welders. 13,14 It is noteworthy that the paternal occupations for which an increased risk of childhood cancer has been identified overlap with those for which there is evidence of an increased incidence of birth defects. The inherent limitations to most epidemiological and clinical studies include an inability to identify the specific chemicals and to control for multiple exposures and the time of exposure. Well controlled animal studies avoid these difficulties. Overwhelming experimental evidence exists showing that paternal exposure to specific environmental or therapeutic agents results in a higher incidence of adversely affected progeny. Many environmental chemicals (for example, lead and dibromochloropropane) and drugs (for example, cyclophosphamide) have been shown to do this. Drugs or environmental chemicals to which the male is exposed may be present in his seminal fluid and thus may directly affect the ovulated egg, fertilisation, or embryonic development. Alternatively, drugs or other chemicals may adversely affect the fetus by “functionally” altering male germ cells. The adverse effects that have been observed include loss before and after implantation (spontaneous abortions), physical malformations evident at birth, behavioural alterations, and a higher incidence of cancer. Furthermore, the germ cell line of the progeny may also be affected. An example of the model drug used to show the risks of paternal exposure to procarbazine and cyclophosphamide.

Chromosomal abnormalities of cyclophosphamide given to the male rat do not significantly affect his fertility and yet produce dramatic adverse effects on his progeny. These effects are dose related and depend on the length of the treatment, reflecting the effects of the drug at different stages of spermatogenesis and sperm maturation. The range of effects on progeny spans an increase in early embryo loss and malformations, growth retardation, and behavioural abnormalities. 16-18 Furthermore, the surviving, apparently normal, progeny of males treated with cyclophosphamide produce litters with an increased incidence of embryo deaths and malformations. 19 Interestingly, in this animal model the effects on progeny may be reversed readily by stopping treatment with the drug. 20 The exact molecular mechanisms underlying these effects remain a mystery.

It is thus apparent from epidemiological studies that paternal exposures to some chemicals result in abnormal progeny. There is a need for more extensive epidemiological studies and thorough monitoring by governmental agencies of chemicals that may be implicated. It is also apparent that animal models have been developed that are both accurate and sensitive in assessing male mediated adverse effects on progeny. These models have, however, been used mainly to test mutagens. Information derived from the studies of occupational exposure must now lead to research to identify the site(s) of action of these agents. Meanwhile, men occupationally exposed to certain chemicals should be made aware of their increased risks. They should be counselled to avoid certain chemical exposures before their partners conceive.

BERNARD ROBAIRE
Professor

BARBARA F HALES
Professor

Department of Pharmacology and Therapeutics, McGill University, Montreal, QC, Canada H3G 1Y6
