MONITORING FOR CONGENITAL MALFORMATIONS

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Prior to 1960, few reports paid attention to associations between congenital malformations (CMs) and environmental agents (81). Monitoring—routine determination of the occurrence of CMs for the purpose of detecting trends and clusters—was performed in only a few localities. The thalidomide disaster of 1959–1961 rapidly stimulated the development of such systems. Between 1963 and 1976, birth defects monitoring started nationwide in seven countries (12, 21, 29, 36, 45, 117a, 128, 145) and in parts of 12 others (34), including the United States (27, 110, 121, 122). In 1974, the International Clearinghouse for Birth Defects Monitoring was created (34, 86); by 1982, 22 programs, collecting data from 26 countries, were participating (63).

During the 1970s, problems of toxic waste dumps and accidents such as those at Three Mile Island and Seveso raised concern about the possible teratogenicity of environmental agents other than drugs. Between 1981 and 1985, 11 states in the US passed laws either requiring reporting or giving state agencies access to medical records (L. Edmonds, Centers for Disease Control, personal communication; 44). Many of these laws specifically mention environmental hazards and permit the establishment of “registers” in which the identity of those with CMs is recorded, thereby facilitating follow-up investigation. In 1979, the EUROCAT project was started to establish registers of CMs within each country in the European Economic Community (93, 144). Identification of births with CMs is not a required feature of monitoring, but it is of registers.
A few monitoring systems, such as the one conducted by the Centers for Disease Control (CDC) in Metropolitan Atlanta (27), also record names. Issues of confidentiality and privacy do not arise in monitoring *per se* and are not considered here in assessing systems.

Monitoring systems have described upward trends in the incidence of patent ductus arteriosus, ventricular septal defects (4, 92), hypospadias (23), renal agenesis (61), gastroschisis (62, 71), and congenital hip dislocation (145), as well as a downward trend for neural tube defects (83, 150). Greater than expected changes in maternal age-specific rates of Down syndrome have also been noted (58, 61, 63). No associations with etiologic agents have been demonstrated. Improvements in diagnostic techniques, correlations with autopsy rates, and, in the case of Down syndrome in infants of older pregnant women, prenatal diagnosis and induced abortion provide partial explanations.

Short-lived increased incidences or localized clusters have also been observed. A sharp increase in reduction deformities of the femur reported from the Rhone-Alpes program (61) seems to have subsided spontaneously (62); it was not seen elsewhere. Data in the CDC’s Birth Defects Monitoring Program suggested higher rates of central nervous system defects in some counties with vinyl chloride industrial plants. Further study failed to establish an association with parental exposure (26). Data from US monitoring systems were used to correlate sales of spray adhesives with birth defect rates; no correlation was found (32b). Other studies also failed to confirm an association reported earlier (cited in 114). Monitoring has also failed to reveal that birth defect rates were higher in counties with nuclear power or reprocessing plants (122).

In only one instance has a monitoring system contributed to demonstrating the teratogenicity of a new drug. The Rhone-Alpes program reported a higher than expected proportion of open spina bifida cases in the offspring of women with epilepsy; nine of the ten women had taken valproic acid (13). A number of other reports followed (38, 100a, 124, 138).

In view of this sparse yield, the value of monitoring systems can be questioned. Did other changes in the wake of the thalidomide tragedy prevent subsequent disasters of such magnitude? Are the existing systems capable of detecting weaker associations? If not, what are the reasons? Are there other adverse reproductive outcomes that should be measured on a population-wide basis, perhaps by other methods? These are the questions that we attempt to answer.

**RESPONSES TO THE THALIDOMIDE TRAGEDY**

Between 1959 and 1961 approximately 7000 cases of reduced or absent limbs (phocomelia), sometimes with gastro-intestinal and cardiac malformations, followed maternal use of thalidomide in the first trimester of pregnancy (96).
This tragedy sensitized manufacturers, governments, professionals, and the public to the problem of birth defects, as well as the possible teratogenicity of drugs.

**Increased Awareness of Congenital Malformations and Teratogenicity**

Stimulated in part by the thalidomide tragedy (141, p. 22), the teratogenic effects of drugs already in use came under close scrutiny. The teratogenicity in humans of antithyroid medications, folic acid antagonists, androgenic hormones, coumarin anticoagulants, synthetic estrogens, and vitamin A have been established (76, 91, 129). Ototoxic antibiotics, cancer chemotherapeutic agents, some anticonvulsants, lithium carbonate, and D-penicillamine are probably teratogenic in humans (125).

Other agents consumed by pregnant women for many years have only recently been studied for teratogenicity. Maternal ingestion of alcohol early in pregnancy leads to multiple problems in the offspring, including microcephaly and mental retardation. Teratogenicity of cigarette smoking has not been clearly established, but low birth weight does result (45, 89, 142).

Teratogenicity of maternal rubella infections was established in 1941, and more recently cytomegalovirus and **toxoplasma gondii** have been demonstrated to cause CMs; the teratogenicity of other infectious agents has not been unequivocally established (76).

A number of reviews considering possible associations between CMs and exposures resulting from occupations, industrial agents, or pollutants have appeared recently (76, 85, 86, 90, 100, 111). Methyl mercury is clearly teratogenic (see reviews) and exposure to organic solvents may be (48). The catalog compiled by Shepard (133) should be consulted for the evidence for teratogenicity of specific agents. Despite the advances, the causes of most malformations remain unknown (76).

The public and physicians have been alerted to possibilities of harm from environmental exposure, and both patients and practicing physicians have instigated studies of harmful effects (111). It was a single case report of an association between maternal valproic acid treatment and spina bifida that "prompted" the monitoring system to describe its cases (125). Studies in Sweden and Germany indicate that drug consumption during pregnancy has decreased in recent years (129).

**Government and Industry Response**

Ten days after Lenz (97) communicated his findings of an association between intrauterine exposure to thalidomide and phocomelia to the German manufacturer, the drug was withdrawn. The British manufacturer followed suit a day later (137a). Other countries were slower to act (118).

Lenz subsequently commented that the original animal and clinical reports
on thalidomide were on such a "low level" that in his opinion they "should not have been accepted for publication by the editor of a medical journal who should be aware of his responsibilities" (96).

In the United States, where the drug had not been approved for marketing, the tragedy played a key role in the passage of the 1962 amendments to the Food, Drug, and Cosmetic Act. The amendments for the first time gave the Food and Drug Administration (FDA) jurisdiction over the testing of all new drugs before they were approved for marketing, as well as the authority to remove drugs that were unsafe (139, pp. 120–26). In 1966 it issued "Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use," which described procedures for testing the teratogenicity of new drugs prior to human use (149).

The investigational requirements, as well as those for labeling of drugs approved for marketing, have recently been described by Kelsey (78). She also points out that once a drug is approved for marketing, the manufacturer must make periodic reports to the FDA of all accounts of adverse reactions it receives. In addition, the FDA Drug Bulletin, which is mailed to more than one million health professionals, includes a form for reporting adverse drug effects. These latter mechanisms were responsible for the prompt reporting of spontaneous abortions and CMs in association with the use of isotretinoin within one year following its marketing in the United States as an oral agent for treating acne in 1982 (127). These cases occurred despite the warning of teratogenicity in the package insert. With only 21 infants with CMs reported from throughout the United States by 1984 (91), the human teratogenicity of isotretinoin could not have been detected so promptly by birth defects monitoring. Other countries have also adopted more stringent drug testing regulations (139, 149).

Thus, through regulation, the chances that new drugs with the teratogenic potential of thalidomide will reach the market have been reduced; even if they should reach the market, post-marketing requirements reduce the likelihood of another major epidemic.

BIRTH DEFECTS MONITORING SYSTEMS

Rapid reporting, inclusiveness of CMs, and complete coverage of the population are criteria against which to measure monitoring systems. Unfortunately, all three cannot be completely satisfied simultaneously.

Criteria for Monitoring CMs for Environmental Hazards

TIMING Almost one and a half years elapsed between the first births of infants with phocomelia and awareness that an epidemic was at hand (97, 98, 137a). In this period, at least 153 affected infants had been born (98). Once the epidemic
was recognized, less than six months elapsed before the etiological agent was identified. Kallen & Winberg (73) estimated that had the Swedish system been in place in 1960, it would have sounded an alarm about thalidomide after the first seven infants had been born with the syndrome over a four-month period.

Early recognition requires prompt reporting of CMs to the monitoring agency, as well as rapid analysis of the data by the agency. To accomplish this, many systems limit reporting to CMs detectable in the first seven to ten days after birth (12, 27, 62, 107, 128, 135b). Less published information is available on the maximum time allowed to transmit this information to the monitoring agency. It is usually between two and six months after birth (12, 27, 29, 107). Once the agency receives the information, rapid analysis is also important. In the CDC’s Atlanta program the data are analyzed each month (27), in Sweden every two months (29), and in Italy by three months (107). An early age of cutoff is not without its problems. Some CMs do not become manifest in the first week. In actuality, CMs that are not diagnosed prior to discharge, which may be as early as 24 or 48 hours, will not be reported. In Sweden, only 61% of CMs that were ultimately detected were reported by six months of age (29). A large prospective study in the United States found that about twice as many severe CMs were detected by one year as by six days, and about four times as many by five years. The investigators point out that their finding of an association between “moderate” CMs, particularly strabismus, and smoking depended on ascertainment after one year of age (19). In the US Collaborative Perinatal Project, only 37.4% of all malformations present at one-year were detected at birth (116). Many of the new laws in the United States set one year as the cutoff point for reporting.

Another problem with early reporting is that the diagnosis of certain CMs cannot be made with certainty. To reduce this problem, some systems insist that only definitely diagnosed CMs be reported; others permit the report to be amended. Nevertheless, false positives may be retained. A study in Birmingham, UK found an overall false positive rate of reporting to the national program of 17% (87).

INCLUSIVENESS OF CMs In many systems, physicians or hospitals are asked to report all CMs. Some systems request a written description and drawings or photographs. Coding is generally left up to the staff of the monitoring system. The code must be specific enough to distinguish within categories of defects. Kallen et al (72) point out that the epidemic of thalidomide embryopathy might have been missed by monitoring systems that simply coded the limb defects as “skeletal malformations.”

Sentinel defects The new monitoring laws in Maryland, Washington, and West Virginia emphasize reporting of 12 “sentinel” defects that are usually
detectable within the first week after birth (anencephaly, spina bifida, hydrocephaly, cleft lip or palate, esophageal atresia, rectal and anal atresia, hypospadias, reduction deformities of upper or lower limb, congenital hip dislocation, and Down syndrome). Although all CMs are reported to the systems participating in the International Clearinghouse, only the sentinel defects are routinely forwarded to the Clearinghouse. In New Zealand, although all CMs are reported, only the sentinel defects are monitored (35, 36). The National Center for Health Statistics is considering including a short list of CMs on the standard birth certificates, which can be checked off when present (S. Ventura, personal communication). This might facilitate collection of data on the occurrence of at least the CMs on the checklists among all US births. Currently, no data on CMs is reported to the National Center for Health Statistics on the computer tapes it receives from most states.

Despite the practical arguments for limiting the CMs reported, especially when detection is limited to the period of newborn hospitalization, the possibility exists that exposure to a new environmental teratogen would result in other CMs. Thus, at the other extreme, arguments can be made for monitoring minor CMs.

**Minor CMs** These include antimongoloid palpebral slant, ocular hypertelorism, preauricular pits, simian creases, and hallucal or mammillary (e.g. supernumerary nipples) abnormalities. Two arguments can be made for monitoring them:

1. Minor CMs, which can be detected in the newborn period, may indicate the presence of major CMs that will not be manifest until later. In Hungary, 11,508 neonates were carefully examined and scored for the presence of the above minor abnormalities. The only minor CMs that appeared significantly associated with later-diagnosed, hidden major defects were ocular hypertelorism and mamillary abnormality. However, the scoring was such that infants with these abnormalities may also have had intrauterine growth retardation, a positive family history of CMs or other adverse pregnancy outcome, or other minor abnormalities. Their predictive value as isolated findings cannot be determined from the report (Table V, 109).

2. Minor CMs could signal the presence of environmental exposures. In a study of children of epileptic mothers, Rating et al (123) found that mothers exposed to antiepileptic drugs in utero \( n = 84 \) had significantly more minor CMs than those of epileptic mothers receiving no anticonvulsants or than epileptic fathers. In a study of over 7000 births, Holmes et al (49) did not find an increase of minor CMs in 39 infants exposed to phenytoin in utero. The power of the study was adequate to detect an increase as large as that reported by Rating.
With immense difficulties in standardizing the reporting of minor CMs, and of training physicians and other health providers to look for and recognize them, the equivocal findings suggest the need for more investigation of the value of monitoring minor CMs before any recommendation for including them can be made.

**Stillbirths** The inclusion of CMs in stillbirths in monitoring has been debated (22, 55, 56). Although stillbirths have higher rates of CMs than live births (22, 55, 135b), they constitute no more than 1% of all births (22, 59, p. 9). Moreover, they are neither consistently autopsied nor reported. Without autopsy, internal manifestations in a stillbirth will be missed. Finally, states and countries differ in their definitions of fetal deaths. Some base it on gestational age (e.g. deaths after 20 or 28 weeks); others on weight (e.g. fetuses over 500 or 1000 g) (55).

The programs participating in the International Clearinghouse differ in their definitions and whether or not they count stillbirths (63). For anencephaly, hydrocephaly, and spina bifida, these differences make comparisons of rates difficult to interpret. In Budapest, for instance, the rate of anencephaly in stillbirths is over 200 times higher than live births; consequently the rate in total (still plus live) births is 6.5 times higher than in live births. Hydrocephaly is 49 times higher in still than live births and the rate in total births is 3.5 times higher than in live births. For spina bifida cystica, a two-fold difference in rates was found. The rates for other CMs are not altered much by the inclusion or exclusion of still births (calculated from Table 1, Ref. 22).

Despite their relatively small number, the larger rate of at least some abnormalities in stillborns makes them valuable for monitoring, provided that all fetal deaths are autopsied and reported to the monitoring system. We agree with Hook’s suggestion (55) that fetal deaths should be reported separately from live births.

**Multiple CMs** There is general agreement that when a CM appears with others, each CM should not be reported as an isolated occurrence (22, 56, 70). A CM that appears as part of a syndrome may have different causes than when it appears alone (82, 83). If monitoring agencies simply record occurrences of a CM, without regard to whether it was part of a syndrome, they may miss syndromes that may be the only evidence of the introduction of a teratogen into the environment.

**POPULATION BASE** The reporting of all affected births within the geographical area will provide the most rapid indication of a change in rate of occurrence. In a few systems (63), reports are obtained only from certain hospitals. Bias will be introduced if the hospitals’ births are not representative of all births in the
area (70, 99). For instance, an association between a CM and some new pesticide, or other agent used in agriculture, might be missed if urban hospitals are the source of data. If hospitals to which high risk pregnancies or sick newborns are referred are over-represented, bias will result because of the association of these complications with CMs. In some systems, hospitals are selected because of interest of physicians. Although this does not resolve the bias problem (and may contribute to it), it may improve diagnosis and reporting. In the International Clearinghouse, however, CM rates do not differ between hospital-based and population-based systems (70).

Methods for Obtaining Information

Since births must be recorded in most countries, the birth certificate is the source of information on CMs in a number of systems. In many places, however, the birth certificate may not require sufficient detail. It also may be filed before the infant is carefully examined. Moreover, there is frequently a time lag before data processing (121). To circumvent these problems, some monitoring systems are either special forms or hospital discharge records. In Atlanta (121), personnel of the monitoring program review the hospital records. The laws in California and Arizona also provide for this method. A few systems use more than one of these sources, and others as well, such as chromosome laboratories and genetics, cardiac, and other specialty clinics. When multiple sources are used, identifiers are needed so that the same infant is not counted more than once. Multiple sources improve completeness, but they also extend the time before all sources can report.

Studies have compared the completeness of different modes of reporting. In Birmingham, UK, substantially more CMs were reported to the local system, which used the birth certificate and other sources, than were reported to the national system, which depended entirely on a special notification form. The differences were present even when reports to both systems were limited to the first week after birth (87). A study from northern Ireland found that only 60.7% of neural tube defects, ascertained from multiple sources, were in the national system (117a). In Sweden, reporting of CMs on the medical birth record was started in 1973; a special report of congenital malformations was required beginning in 1964. A comparison of the two systems in 1973–1974 indicated that neither had complete ascertainment of CMs; only 64% of ten types of CMs were reported to both, while 13% were reported only on the special form and 22% only on the birth record. Some specific defects were better ascertained by the special form, others by the birth record (29). The authors suggested that the introduction of the second system may have reduced reporting to the first. Deficiencies of reporting on birth certificates in a number of states in the US have also been described (122). Down syndrome appeared as a CM on birth certificates of less than 40% of infants determined to have the abnormality by chromosome analysis in California (43), New York (57), and Ohio (60).
Detecting Significant Rate Changes

Monitoring systems usually conduct periodic analyses [e.g. every month in the Atlanta system (27)] of incoming data. One of three statistical methods that depend on rate changes are used to detect significant increases: the Poisson distribution, CUSUM, or sets techniques. Alternatively, cluster analysis can be performed (16, 17).

THE POISSON DISTRIBUTION  The number of newly registered cases of a specific CM is periodically tested against an expected number derived from a baseline rate, usually obtained from previous monitoring periods, and the number of births in the current period. This expected number is assumed to be a Poisson variable. An alarm is signaled if the observed number exceeds a critical value, usually 2.4 standard deviations above the expected number. The method relies on the assumption that most CMs are quite rare. It is used by several monitoring systems, including the Centers for Disease Control systems in the US (27).

CUMULATIVE SUM (CUSUM) TECHNIQUE  A constant value, computed using baseline rates from earlier periods, is subtracted from the observed number of cases in a defined time period (e.g. one month). With only random fluctuations, positive and negative differences will be observed around an expected value of 0. If the sum of the differences for successive periods exceeds an upper limit, computed on the basis of baseline rates, an alarm is signaled. This procedure has been shown to be very efficient in reducing the time interval until detection of a true increase, and may cause fewer alarms than the other methods (10, 16). It requires the use of computers, which may limit its applicability. The CUSUM technique is used in the UK monitoring system (145).

SETS METHOD  The time interval between births of consecutive infants with a specific CM born in individual hospitals or in the area as a whole is measured (18). An alarm is signaled when the time interval between cases is less than that calculated on the basis of known incidence data. The technique is simple to apply and is as efficient as the Poisson distribution in signaling alarms. Once the critical interval is established, monitoring can be performed each time a new case is reported. The other techniques require an accumulation of cases over a defined time before analysis.

CLUSTER ANALYSIS  For these methods (88, 105, 146), information is not usually required on the size of population monitored or the rate of malformation. For example, Knox’s method (88) tests for space-time clustering by classification of all possible case pairs on the basis of geographical distance between each member of a pair and the interval between their respective occurrences. Care must be taken that the space vector is chosen, not on the basis
of the mothers' residences at birth, but during the critical period of their respective pregnancies. The time vector should be based on estimated times of conception rather than birth (28). The method was applied to determine possible clusters of cleft lip and palate (88), neural tube defects (140), and Down syndrome (94), all with negative results.

PROBLEMS IN MONITORING

False Alarms (Type I Error)

False alarms present a common problem in birth defects monitoring. These type I errors are inevitable when a large number of statistical tests are performed; the expected number of alarms due to chance alone are quite large (27). This problem may be reduced by ranking the increases on the basis of their $p$-values or the ratio of observed-to-expected numbers of cases. Alternatively, the Bonferroni technique can be used to alter the significance level for rejection of the null hypothesis by dividing the critical $p$-value by the number of comparisons carried out. However, the stringency of this method could lead to missing true effects (99).

The problem of disentangling a true increase in the occurrence of a CM from a false alarm has been addressed by several authors (17, 27, 70, 120). When faced with an increase, several possibilities must be considered in addition to type I errors before investigating a true increase. First, changes in number of births registered, or CMs reported or ascertained, have to be considered. For example, the increase in the incidence of preauricular tags in the Swedish birth defects registry between 1965 and 1972 probably was due to increased reporting (74). Second, an apparent increase may be due to changing demographic factors, or changes in fertility (70). For example, because Down syndrome is highly dependent on maternal age, a change in the maternal age distribution will result in a change in the overall incidence of Down syndrome (2).

Investigation of a true increase usually requires follow-up studies. Before undertaking them, biologic plausibility, as well as attempts to eliminate the factors discussed above, should be considered. For example, an increase in the number of cases with a specific combination of defects is more likely due to a common exposure when embryological development of the various affected organs is consistent with a single exposure and when geographic aggregation and time clustering of cases is noted than when these conditions are not satisfied.

Statistical Power (Type II Error)

Failure to detect genuine increases in the occurrence of CMs (type II error) has recently received attention (72). An epidemic may go unnoticed regardless of the statistical methods used. Important factors that influence detection are the
frequency of the malformation, the size of the population monitored, the relative risk of the exposure, and the proportion of the at risk population (parents) exposed at the critical time.

Table 1 shows the minimal ratio of observed to expected cases that would signal an alarm (alpha = .05, beta = .20) in populations of defined size for defects of varying baseline frequency. For a relatively common malformation, such as cleft lip, with an incidence of about .001, an observed:expected ratio of less than 1.3 would be overlooked if 75,000 infants are monitored. If only 10,000 are monitored, only ratios of 2 or more would signal an alarm. Still higher ratios are needed to signal an alarm for less common defects. Of the 22 systems that belong to the International Clearinghouse, six monitor between 25,000 and 50,000 births per year, and seven between 50,000 and 100,000 (62). They would be incapable of detecting ratios of less than two for CMs with baseline frequencies of less than .0001.

Table 2 shows the number of cases of a CM of specified baseline frequency (.001) that would be observed in a population of specified size (50,000) when varying proportions of the population are exposed to teratogens of varying relative risk. With relative risks of 3 or less the epidemic will be missed if less than 10% of the population at risk is exposed to the teratogen. Although the relative risk conferred by thalidomide was over 100 (95), the relative risks of other teratogens are much lower. For instance, the relative risk of hydantoins for the most commonly found abnormality associated with it (distal digital hypoplasia) is only 7.3 (95% confidence intervals = 2.5 – 21.5) (calculated from Ref. 80a). Exposures of more than 10% of the at risk population to proven

<table>
<thead>
<tr>
<th>Number of births</th>
<th>Frequency of malformation</th>
<th>Expected number of cases</th>
<th>Observed number of cases needed to signal increase</th>
<th>Minimal ratio of observed to expected cases</th>
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<tbody>
<tr>
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<td>.00001</td>
<td>0.1</td>
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<td>30.0</td>
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*Based on Poisson distribution for α = .05 (one-sided) and β = .20.*
teratogens are unusual. Only about 2% of pregnant women were exposed to thalidomide (95), and fewer than 0.1% to isotretinoin (E. Lammer, personal communication). It seems likely, therefore, that weak teratogens to which only a small fraction of the at-risk population are exposed will be missed by monitoring (M. Khoury and N. Holtzman, in preparation).

In using monitoring systems, one cannot be confident that all cases classified under one diagnostic rubric are clinically homogeneous. Poor reporting, excessive inclusiveness of the code used, or failure to distinguish single from multiple abnormalities will result in heterogeneity and a consequent loss in statistical power. For instance, neural tube defects that occur singly probably have different etiologies than those that occur in conjunction with other malformations in the same infant (multiples) (83, 84). If they are lumped together in monitoring, the detectability of a teratogen that causes an increase in multiples, which account for about 20% of all cases, is likely to be lessened (M. Khoury, N. Holtzman, in preparation).

Statistical power is of paramount importance in follow-up studies as well as in monitoring. Investigators mounting case-control studies of birth defects are increasingly using larger sample sizes to attain adequate power to detect risk factor differences. In the recently completed study of the possible teratogenic risk of service in Vietnam and agent orange exposure, information was obtained on past military service and exposure to agent orange on the fathers of about 4000 babies with CMs and the fathers of about 2500 normal infants. The study was designed to yield a 70 to 90% chance of detecting a relative risk of 1.2 for all defects. However, the power to detect increased risks for specific defects was much smaller. The very few significant associations that were found among the many sought could well be due to chance (30).

Table 2  Effect of proportion of population exposed to a teratogen, and relative risk on number of cases observed

<table>
<thead>
<tr>
<th>Proportion of population exposed to the teratogen</th>
<th>Relative risk of teratogen</th>
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<tbody>
<tr>
<td></td>
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<td>1.0</td>
<td>63</td>
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*aBased on Poisson distribution for an expected number of cases = 50 (e.g. if 50,000 births are monitored and the baseline frequency of the defect is .001). For α = .05 (one-sided) and β = .20, detectable teratogens are those that give 70 or more observed cases.

*bSignificant increase [α = .05 (one-sided) and β = .20].
Variations in Susceptibility; Genetic-Environmental Interactions

With the exception of thalidomide it is unlikely that most teratogens cause birth defects or other adverse outcomes in the offspring of all parents exposed to teratogenic doses at critical times. Environmental factors including nutrition and exposure to other agents undoubtedly influence susceptibility to the harmful effects of a specific agent. Although genetic differences in susceptibility have been known for years in animals (37), only recently have genetically determined factors been identified in humans.

Manchester and his colleagues (103, 104) found that women who smoked in pregnancy and had high placental monooxygenase activity were significantly less likely to have infants with CMs than smokers with low activity. One explanation is that the organs of fetuses who have inherited an allele for high activity of the enzyme in their placentas are protected from the teratogenic effects of cigarette smoke. If this effect is confirmed it may explain why studies have failed to find an association between smoking and CMs; they did not take differences in susceptibility into account.

Strickler et al (136) presented evidence that an inherited deficiency in the ability to detoxify arene oxide metabolites of phenytoins explains the occurrence of major CMs in offspring of mothers receiving these anticonvulsants during pregnancy. Fourteen of 24 children exposed in vitro had at least one major CM. Twelve of the 14 with major CMs had detoxification defects ($p = .002$, Fisher’s exact). For each subject with a defect, one parent also had evidence of the same defect. Use of this test should make it possible to tease apart the roles of maternal epilepsy and phenytoin anticonvulsants in the etiology of CMs.

Recent recombinant DNA (5) and chromosome morphology studies (66) suggest the presence of genetic factors that increase the likelihood of the common, non-dysjunction type of Down syndrome. The ability to document the presence of predisposing genetic factors, increasingly possible with recombinant DNA technology (52), will enhance the ability to detect potential teratogens. If the genetic factor is incapable of causing the CM by itself, the relative risk of a CM following parental exposure to a potential teratogen will be higher when a genetic predisposition is present than when it is absent. Higher relative risks require a smaller increase in the number of infants with the resultant CMs in order to detect a significant effect.

Perhaps the failure of most efforts to detect associations between environmental agents results from the model imposed by our ignorance of the complexities of etiology. In essence, the model assumes that single agents, after adjusting for non-interacting confounding factors that can be measured, are capable of causing CMs. The likelihood of genetic-environmental interactions...
has been ignored, largely because of the seeming impossibility at getting at the genetic factors. As the examples cited above indicate, this is no longer the case.

**Obtaining Information on Exposures**

Obtaining information on exposures is not an inherent feature of monitoring, and programs differ markedly in the extent to which they do so. This information can be obtained at the ecological level by determining whether differences in incidence rates in time or geographical area have been accompanied by differences in exposure to specific environmental agents (26, 114). More direct evidence can be obtained at the individual level, but many difficulties arise. Evidence of exposure that is collected prior to the birth of the infant with a CM avoids problems of bias, but may be sparse, or difficult for monitoring systems to obtain. Evidence collected afterwards requires contact with the mother, something that is not possible in all monitoring systems. Access to the parents, or at least to other records pertaining to them, is possible through registers, if parents consent. When information on exposure is available, controls are needed to determine the magnitude of risk of CM conferred by the exposure.

**COLLECTION OF INFORMATION OBTAINED PRIOR TO DIAGNOSIS OF THE CM**

Information in the mother’s prenatal record can be transcribed to the notification form used for monitoring (either the birth certificate or the special form). In Finland, the maternity record is included with the notification (46). Birth certificates in most states (44) and countries do not contain information about occupation of both parents. In general, special forms ask for more information about exposures, but to simplify reporting not much is requested. In addition to occupational and residential information, data regarding exposure to drugs, cigarettes, alcohol and non–work-related chemicals would be helpful. Frequently, the information is easier to obtain directly from the mother rather than the records.

**Record linkage**

The monitoring agency itself can tap into information about the mother’s exposures provided that the report it receives contains adequate identifiers on the mother. This can be a unique identifying number, or her name. If she is married, her maiden name should be included as well. In systems using special notification forms, inclusion of the name of the infant, or a unique identifier used on all the infant’s records, permits linkage to the mother through the birth certificate, provided the monitoring agency has access to it. Registers and a few other systems obtain infant identifiers (7, 12, 13a, 29, 36, 135b), but linkage to mothers’ records is not always possible.

In addition to the mother’s medical records, linkage permits the use of central repositories of prescriptions (67, 134) to determine drug intake before and during pregnancy. Such data does not, however, demonstrate that the drug was
taken, or with what regularity. An association between spermicide use prior to pregnancy and CMs (68) that was derived by using prescription records as the source of data has been criticized on this score (14).

Acheson (1) has proposed the creation of registers of women who have worked in industry during pregnancy. Linkage with them would permit the monitoring agency to determine occupational exposures of mothers of infants with CMs. In Maryland, the names of all employers of both parents for the year preceding the birth of the CM infant are required on the notification form. The state also maintains a toxic substances registry containing this information. The two systems are linked (N. Holtzman, unpublished).

Occupational and other information relevant to exposures can be obtained from the census (1, 11). In Norway, a study of CMs occurring between 10 months before and 38 months after the 1970 census was able to link 98.8% of all births to the census data. The study found a small but significant relative risk of CMs in first borns of mothers who worked, adjusted for age, educational level, and residence. The highest relative risks were found for nurses and technicians (11). Census data has the disadvantage of providing information only at the time of the census.

COLLECTION OF INFORMATION OBTAINED AFTER DIAGNOSIS OF THE CM In some systems, information is collected from the mother prior to her discharge from the hospital. This may be by direct interview or abstracting information from the infant’s medical record. In a few others, the mothers of at least some CM infants receive questionnaires, and may be interviewed after their infants are discharged from hospital (35, 121, 128). In northeast France (Bas-Rhin, including Strasbourg), every family of an infant with a CM has a genetic study as well as genetic counseling (135b).

When a cluster is observed, interviews may be the only means of establishing a possible exposure. Mothers of affected infants do not always recall exposures. This was evident in attempts to establish exposures in the epidemic of phocomelia that was eventually traced to thalidomide; many mothers, as well as their physicians, denied use of the drug (135, 137a). Sometimes it was necessary to inquire about stressful episodes early in pregnancy that might have led to use of the drug before a positive response was forthcoming (96, 137a). Once thalidomide was suspected, the outcomes of 13 pregnancies still in progress, in which the mother had used the drug during the critical time, were determined prospectively. All 13 infants were affected, thus providing strong support for the hypothesis formulated from the retrospective data.

CASE-CONTROL STUDIES A number of systems request the reporting of control infants to the monitoring agency for the birth of each infant with a CM, or at least for infants with certain categories of CMs (15, 121, 128, 135b).
Frequently, this is the previous or next birth, although other restrictions may be used as well, for instance residence (128). Information on exposures is then collected by the same methods on both case and control families. The laws in Maryland and Washington also permit the collection of controls. Analysis of case-control studies is beyond the scope of this review, but brief consideration of bias and confounding are in order.

**Bias** Participation in case-control studies will be voluntary, even when both groups have been identified by monitoring. Once an exposure is suspected, it is possible that women of affected offspring who have been exposed to the agent are more likely to participate than nonexposed (100).

In reviewing an earlier study, Lippman & Mackenzie (101) point out that while postdelivery information obtained from mothers is inconsistent with that obtained in midpregnancy—thus raising the question of reliability of recall—the inconsistency was not different for mothers of dead or malformed children than for mothers of healthy children. They plan to study this matter further. Sometimes it is possible to verify the information provided by the mother. The early reports of an association between in utero X-ray exposure and childhood cancer were criticized because of possible recall bias. The same results were obtained, however, when the mothers' pregnancy records were used to establish exposure (99). Situations of underreporting by mothers of affected children may also arise. For instance, guilt about an exposure such as alcohol ingestion may lead to denial (99).

**Confounding** Before CMs are attributed to maternal drug exposure, consideration must be given to the reason that the drug was used. The role of anticonvulsant drugs in causing CMs has been disputed (33, 79, 80); the underlying disease, as is the case for diabetes (20), may be responsible, as well as differences in genetic susceptibility, as discussed above. It has been suggested that factors responsible for reducing fertility (23) or increasing the chance of spontaneous abortion (106), rather than drugs used to overcome these problems, are responsible for harmful outcomes, including CMs.

Problems of confounding are not unique to retrospectively collected information. In Finland, an association between influenza and CMs was found using the maternity records. In this matched pair study, the records of mothers of affected infants also showed increased analgesic use. The authors concluded, “We cannot see how (the two factors) can be distinguished in an epidemiologic study” (128). Human randomized trials to test teratogenicity are obviously out of the question. Sometimes, as Doll has pointed out, removal of a suspected agent “as an experiment in prevention . . . is not a bad last resort. . . . Proof in the strict logical sense may not have been obtained but does this matter if the disease has disappeared?” (quote in full in Ref. 99).
ARE CONGENITAL MALFORMATIONS THE BEST MEASURE OF TERATOGENICITY?

Congenital malformations in liveborns or stillborns constitute a small proportion of all of the possible adverse outcomes of teratogenic agents. Infertility, spontaneous abortions, intrauterine growth retardation, low birth weight, altered sex ratio at birth, developmental disabilities, childhood cancer, and late onset diseases that result from new mutations are others. A number of studies have shown correlations between one or more of these factors and CMs (90, 128, 131, 133, 135b, 152). A chromosome abnormality in the sperm of men exposed to 1,2-dibromo-3-chloropropane (DBCP), which might result in certain CMs in surviving fetuses, was postulated to selectively cause fetal death of male offspring (39). In addition to impairing male fertility, DBCP has been associated with a significant excess of female livebirths among the offspring of exposed males; spontaneous abortions may also be elevated (39). Smoking has also been associated with impaired fertility, as well as spontaneous abortions (discussed further below), low birth weight (8, 142), and strabismus (19).

The ability of environmental agents to cause more than one adverse outcome is biologically plausible. The specific outcome could depend on the time of parental exposure, the dose, and other environmental and genetic factors (75, 122, 126). The structural and functional properties of the agent, which influence its reactivity (e.g. as a mutagen) or its ability to compete with or bind to endogenous molecules, or alter its chemical reactivity (e.g. mutagenicity) (108), will also influence the specific effect. Exposure to agents very early in pregnancy, when many cells are still totipotent, usually has an “all or none” effect, resulting in early loss of the embryo or complete repair (90). Mutagens that reach germ cells in prospective parents could lead to chromosome abnormalities in the offspring; if they “hit” certain somatic cells of the fetus during the stage of organogenesis, malformations might result; at a later stage, childhood cancers could result (90). Genetic factors in the parents, which could be transmitted to the fetus, could predispose to these events. Kellogg (77) suggests that prenatal exposure of the fetus to drugs that bind to central nervous system receptors may not be expressed until childhood or later.

There are a number of objections to using these other outcomes as indicators of the introduction of teratogens into the environment. Those that do not occur until some time after birth will be further removed from the time of the exposure, so that more individuals will be exposed until a causative agent is incriminated. Moreover, determining exposures will be more difficult. Outcomes such as developmental delay, low birth weight, and infants small for their gestational age are known to be influenced by many factors in addition to potential teratogens. In the remainder of this section we consider the use of early postconceptional outcomes—spontaneous and induced abortions—for monitoring.
Monitoring of Spontaneous Abortions

SPONTANEOUS ABORTION RATES  With the use of human chorionic gonadotropin (hCG) assays, the occurrence of fertilization can be determined accurately by 14 days after ovulation. Consequently, the survival of fertilized ova in apparently healthy young women wishing to conceive can be followed. Using this technique, or direct examination of fertilized ova, clinically unrecognized pregnancy loss has been reported in between 32 and 55% of all conceptions (25, 148, 152). A lower estimate of 8% was reported by Whittaker et al (147). In the two most recent studies (25, 147), recognized spontaneous abortions occurred in 12% of all conceptions. Over 90% of all fetal loss occurs before 20 weeks of gestation (148). This may represent a loss of over 60% of all conceptions, and certainly no lower than 20%.

Theoretically, a sample of fecund women could be followed by hCG assays or recording menstrual irregularities. Those in whom fertilization occurred could be followed to determine outcomes. Deviations from baseline rates of spontaneous abortions could be determined by the methods already described. Because of the high spontaneous abortion rate, the numbers needed to detect a significant increase would be much lower than those shown in Tables 1 and 2 (148).

PATHOLOGICAL OUTCOMES  Judging from the high proportion of pathology in spontaneously aborted embryos and fetuses, abortion is not truly “spontaneous” but a powerful selection mechanism against serious malformations. Zakharov (152) has summarized the rates of chromosome abnormalities in human spontaneous abortions found by different investigators. In spontaneous abortions occurring at 8 to 15 weeks, an interval during which most abortions would be recognized by the woman, approximately half of all abortuses have chromosome abnormalities. From a review of surveys of chromosome abnormalities in live births, Hook (54) estimated that only 0.6% had any cytogenetic abnormality. Considering that at least 20% of all conceptions abort before 20 weeks, the use of chromosome abnormalities is statistically much more powerful than chromosome monitoring of newborns (50) or than birth defects monitoring. Most of the chromosome abnormalities observed in abortuses are lethal; a few of them, particularly trisomies of certain chromosomes, and monosomy of the x chromosome, are seen occasionally in liveborns, but occur more frequently in spontaneous abortuses (42, 64).

Not all chromosome abnormalities will reflect recent exposure of one of the parents to a potential teratogen. The majority of trisomies, the most frequent chromosome abnormalities found in abortuses (64), originate in the first meiotic division of the ovum, which takes place in the fetal ovary. Others, such as triploidy, which are never observed in liveborns, may have more recent origins (54).
The Central Laboratory for Human Embryology at the University of Washington reported the pathological findings in a relatively unselected series of 748 spontaneous abortuses received from the Group Health Cooperative of Puget Sound. Only about 5% of material of gestational age less than two months could be considered "normal." The rate of neural tube defects in their study (13.4/1000 abortuses) was at least 10 times higher than the rate in newborns; the rate of Turner's syndrome (5.4/1000) was 100 times higher (31). This is consistent with the high rate of the x-chromosome monosomy in chromosome studies of abortuses (41, 69). Among chromosomally normal abortuses, Jacobs (64) noted that as many as 40% were reported to have ABO incompatibilities, a much higher proportion than in newborns.

Thus, certain chromosome abnormalities, other malformations, and ABO incompatibility have much higher rates in conceptuses who do not survive the early months of pregnancy than in those that do. The factors that are responsible for the survival of some with a specific defect, and the fetal loss of others, is unknown. Experimental studies indicate that some teratogens cause an increase in embryonic or early fetal death and an increase in CMs in liveborns (75). If this is so, then the introduction of a teratogen could much more profoundly increase spontaneous abortions than CMs in liveborns. Consequently, by monitoring only liveborns, a greater time would elapse before the effect would be detected than if abortions were monitored as well; a greater number would need to be monitored to detect an effect.

For other teratogens the relationship between spontaneous abortions and CMs in liveborns or stillborns is inverse, at least in animal studies (75). Roberts & Lowe (126) found that women who delivered in the districts of South Wales that had high rates of neural tube defects had lower abortion rates than in the districts with low rates of this defect. They concluded, "the environmental factors at work in South Wales are not directly teratogenic but in some way change the uterine environment so that more abnormal fetuses remain in the uterus until the twenty-eighth week of pregnancy." If their hypothesis is correct, then vitamins may reduce the occurrence of neural tube defects in live and stillborns by increasing spontaneous abortions. Data in a recent report (130) showing the effectiveness of periconceptional vitamins in women who previously had babies with neural tube defects suggest that spontaneous abortions occur with greater frequency in women who are fully supplemented with vitamins than in women who are unsupplemented.

Ayme & Lippman (5a, 6) presented data to support their hypothesis that the greater risk of having liveborns with Down syndrome as maternal age increases could be due to an inverse relation of spontaneous abortion of affected fetuses with maternal age. Hassold & Jacobs (42) have summarized the data and arguments against the hypothesis, concluding that the increase in liveborns with Down syndrome in older women "is almost certainly due to factors acting at or before conception, not subsequent to it."
In view of the possibility of an inverse relationship between abortuses and CMs in liveborns, it is not necessarily the case that monitoring of abortuses will increase statistical power of detection of teratogens that have adverse outcomes on liveborns. It would be a mistake to abandon monitoring of CMs in liveborns (and stillborns) in favor of abortion monitoring. However, useful information about etiology, and, perhaps, an earlier warning of teratogenicity when there is a direct relationship between abortions and CMs, can be gained by monitoring both events, keeping the results separate.

Several of the same problems already addressed for CMs would be even greater in abortion monitoring. Inclusion of abortions below the gestational age at which most abortions reach medical attention could bias the results and make it impossible to establish rates (50, 59, 118). (The use of hCG testing of a random sample of fecund women in order to detect pregnancies is one way around this.) In countries in which abortion is illegal or not readily available, the inclusion of induced abortions would cause problems. If, in addition to rates, fetal CMs or chromosome abnormalities were sought, careful physical examination, autopsy, and karyotyping would be needed. Poor preservation of abortion material and scarcity of resources (including fetal pathologists) could make this difficult. In view of the dependence of chromosome abnormalities on gestational age, age-specific rates would be appropriate. Bias in determining antecedent exposures also enters in the study of abortions, although the time since antecedent events is less than with CMs in liveborns. Bias would not enter into studies in which exposures in the parents of one type of abortus were compared to those in another type, e.g. chromosomal compared to other abnormalities (142). Other factors known to influence spontaneous abortion, such as maternal age and smoking (142), could confound associations with environmental agents.

Monitoring of spontaneous abortions has been most extensively conducted in New York by the group at Columbia University. Warburton (142) reviewed the findings of this group and others. Independent associations between cigarette smoking and alcohol consumption during pregnancy and abortion of chromosomally normal embryos have been established. For smoking, a dose-response relationship with abortion was observed. Smoking prior to pregnancy increases the risk of trisomy in older pregnant women. In other studies cited by Warburton, maternal and paternal irradiation histories have been associated with chromosomally abnormal abortions. The effect of occupational exposures on abortion has been reviewed by Lindbohm et al (100).

**Monitoring of Induced Abortions**

Over one quarter of all recognized pregnancies were terminated by induced abortion in the United States in 1982 (47). As might be expected, the frequency of chromosome abnormalities and CMs in induced abortuses is higher than in
liveborns (137, 143); some fetuses electively aborted would have spontaneously aborted at a later time. Thus, for certain abnormalities monitoring of certain abortions could provide more statistical power and a shorter lag time than monitoring CMs in liveborns.

In addition to the problems discussed above for spontaneous abortions, the use of induced abortions has still others. They do not represent a random sample of all pregnancies, and consequently of potential exposures. The ability to examine fetal material will depend on the method used or the place of abortion; in the US in 1982, 82% of abortions were performed in nonhospital facilities (47). Tanimura (137) has summarized the relative merits of monitoring spontaneous and induced abortions and newborns.

The growing use of induced abortion following prenatal diagnosis of chromosomal or other CMs, particularly neural tube defects, must be taken into consideration in monitoring. The sharp decline in liveborns with Down syndrome in some countries in women over 35 years, noted by the International Clearinghouse in its 1982 report (63), was attributed to prenatal diagnosis and elective termination. The use of maternal serum alpha-fetoprotein to screen for neural tube defects at 16–18 weeks gestation, followed often by termination when the diagnosis is confirmed, could contribute to the decline in liveborns with these conditions. Considerable power would be lost by not including fetuses electively aborted as a result of adverse prenatal diagnosis. As some of those discovered by prenatal diagnosis would not survive to term (53), fetuses with chromosome abnormalities detected prenatally should be counted separately from liveborns (55).

Prenatal diagnosis will become more important with technological discoveries. Ultrasound makes it possible to detect some structural abnormalities early enough to permit pregnancy termination (51). The introduction of chorionic villus sampling (65, 113), which can be performed as early as the ninth week of gestation, may increase the use of prenatal diagnosis (51). Foreseeably, prenatal diagnosis on fetal cells in the maternal circulation, which would be without risk to the fetus, and the use of recombinant DNA techniques to detect alterations in chromosome number much more inexpensively than current methods could permit detection of this large class of chromosome abnormalities in all pregnancies (52). This would be a powerful monitoring tool.

PROSPECTIVE MONITORING

In view of incompleteness and possible bias when information on exposures is collected after the occurrence of a CM, prospective collection is an attractive alternative. The use of hCG assays to follow pregnancy outcomes from shortly after conception in exposed versus unexposed women is mentioned above. Two innovations in health care in recent years make other forms of prospective
monitoring feasible: health maintenance organizations (HMOs) and computerization of medical records.

HMOs often provide care to women before, during, and after their pregnancies, possibly to their mates, and to their offspring as well. Frequently, they computerize records and have the capability of linking those of different family members to each other as well as to prescription records. At least three organizations that have been providing prepaid care for many years have used their record systems to examine associations between prospectively collected maternal characteristics and pregnancy outcomes (19, 68, 131, 132). Although fewer than 10% of the population is currently enrolled in HMOs, the proportion is expected to grow rapidly (135a), making them a more representative source of information for monitoring. The quality and completeness of information on exposures, particularly occupational ones, in HMOs remains to be established.

Individuals could carry with them information about their exposures as well as pertinent medical information. In Canada, parents are given a Child Health Record that contains information on major illnesses and malformations. Its purpose is to enhance communication between parents and health professionals by providing continuity of records (9). Laser scanning permits the storage of extensive information on small cards that individuals could carry. Such cards could be updated to contain information on occupational, drug, and other exposures. The card would be the property of the individual, who would know what it contained and could decide when to provide others with access to it.

Other types of prospective studies have been reported, but they are of a special nature and do not lend themselves to continuous monitoring of CMs. In the US, the Collaborative Perinatal Project systematically and carefully followed about 56,000 pregnant women from the first months of their pregnancies, and their offspring, in order to relate “events which affect parents before and during pregnancy to the outcome of pregnancy” (116). Several studies on prenatal factors associated with CMs have emanated from the Project (19a, 19b, 40, 102, 115, 116). A follow-up study determined chromosome abnormalities when the study group was 7 or 8 years old and related their occurrence to prospectively recorded antenatal factors. More than 20% of mothers of children with de novo chromosome abnormalities had received abdominal and pelvic X rays in the year prior to conception, compared to only 6% of the entire study group (102).

Studies in which women with specific diseases are enrolled prior to pregnancy in order to determine factors influencing the occurrence of CMs have been described. A recent prospective study failed to clarify the relation between maternal epilepsy and anticonvulsant therapy during pregnancy on the one hand and CMs on the other (80, 33). A prospective study on the outcome of diabetic pregnancies is currently in progress (112).

Pregnancy outcomes have also been determined following known in-
trauterine exposures to potential teratogens as a result of environmental disasters (111). Microcephaly and mental retardation occurred with increased frequency in children exposed early in gestation to the atomic bomb explosions at Hiroshima and Nagasaki. Studies of children who were born more than nine months after the explosions have so far failed to reveal evidence of increased mutation rates, although such effects cannot be excluded (117). A birth defects registry established after the accidental release of dioxin at Seveso, in which intrauterine exposures could be established, did not show an increase in CMs. A peak of spontaneous abortions occurred six to nine months after the accident (32).

SUMMARY AND CONCLUSIONS

Many countries instituted birth defects monitoring systems in the wake of the thalidomide tragedy. Having these systems in place will shorten the time before an alarm is signaled, should a teratogen of the potency of thalidomide be introduced. However, with stronger laws and regulations for testing drugs for adverse reproductive outcomes, a tragedy on the scale of thalidomide from ingestion of prescribed drugs by pregnant women is unlikely. Prospective parents could be exposed at the critical times to new physical, infectious, or nondrug chemical agents teratogenically as potent as thalidomide. (Teratogenic agents whose widespread use antedates monitoring will not cause rate changes or clusters detectable by monitoring.) What seems more likely is that the introduction of "weakly" teratogenic agents, or the inadvertent use of new drugs that are teratogenic, like isotretinoin, will be responsible for increases in birth defects. In neither of these situations are large numbers of cases likely to accumulate in short periods of time, particularly in the relatively small catchment areas (fewer than 50 to 100,000 births per year) of many monitoring programs. In addition to having to cope with this problem of rare outcomes, many monitoring systems have not been able to obtain complete ascertainment of CMs, at least not from single, rapidly reporting sources.

Two remedies to these inadequacies are possible:

1. Expand the catchment area. All births in the US, for instance, could be monitored if information on specific CMs was included on birth certificates, which were then transmitted to a central agency that could analyse the data rapidly. Alternatively, if different monitoring systems had comparable methods of ascertainment and diagnostic classifications, their data could be pooled with greater reliability than is currently possible.

2. CMs in newborns are only one indicator of teratogenicity. At least 20% of all conceptions end in spontaneous abortions. A much higher proportion of abortuses have chromosome abnormalities, congenital malformations, or both, than newborns. The time necessary for such outcomes to manifest after the
introduction of a new teratogen could be considerably shorter than the time before significant increases of CMs occurred in liveborns and stillborns. Monitoring the spontaneous abortion rate or chromosomal and other abnormalities in abortuses would be an important adjunct to monitoring newborns. However, since some teratogens may only cause CMs in newborns, the current approach to monitoring should not be abandoned. Moreover, the problems of ascertainment encountered in monitoring newborns are greater still in monitoring abortuses.

Monitoring systems are inadequate on an additional count. They seldom receive much information on exposures to potential teratogens. Although more could be included in reporting, two other solutions should be considered. The first involves linkage with records of the parents that gives more information of exposures. These might be medical, prescription, or work records. The adequacy or even the existence of such records is problematic. With increased enrollment in HMOs and computerization of records, this type of prospective monitoring is not inconceivable in the future. If these records could be linked by code numbers, identity need never be disclosed. The second solution requires identifying infants with CMs so parents can be interviewed about past exposures. Controls would also have to be identified for more definitive studies. Aside from problems of bias in collecting information of exposures retrospectively, consent to release of names and confidentiality if they are released are issues that must be faced.

The proportion of infant deaths due to CMs is increasing. In the US, CMs are the leading cause of infant mortality (3, 119). CMs result in substantial impairments for many of those who survive (24). The causes of most of them remain unknown. Evidence that individuals differ in their susceptibility to harm from environmental exposures is slowly accumulating. Appreciation of the complex etiology of CMs may well lead to better epidemiologic and molecular approaches to their prevention.

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