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DIVISION OF NONCOMMUNICABLE DISEASES

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REPORT OF THE JOINT WHO/ICBDMS CONSULTATION ON
MONITORING CONGENITAL MALFORMATIONS AND MUTATIONS

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1. INTRODUCTION

This meeting was organized jointly by the World Health Organization and the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) to discuss the significance of congenital malformations as a health problem and to illustrate approaches to identify possible environmental causes of congenital malformations and human mutations. All participants unanimously remarked that there was an increasing awareness of congenital anomalies as a global health problem, and so it was important that existing international experiences were analyzed to improve knowledge worldwide.

The following subjects were presented individually and followed by discussion on selected topics only.

2. MONITORING AND DRUG TERATOGENS

Case History of the Detection of a Teratogen (Dr E. Robert). The question of teratogenic effects of antiepileptic drugs was raised for the first time within the Clearinghouse in March 1981. A meeting of the Epidemiology Committee in Lund was held at this time. The report of this meeting stated, among other topics, that "it might be profitable for the Clearinghouse to organize studies of teratogenic effects of drugs, particularly in cases of infrequently used, but nevertheless medically important drugs. Some of the antiepileptic drugs were mentioned as examples". This proposal was accepted during the General Session of the Lausanne Annual Meeting (1981). A questionnaire related to the feasibility of a joint survey was then circulated among all members in April 1982. The result of the inquiry was discussed at the following Annual Meeting, in London (September 1982), revealing that five programmes seemed to be able to participate in a cohort study on antiepileptic drugs. At that moment, the participants in the meeting were informed of an observed unusual rate of valproic acid in utero exposure in the Rhone-Alpes programme among infants with spina bifida. Once the question of an association was raised, the role of the Clearinghouse was of importance for: underlining the interest of the observation; disseminating information globally through programme directors in 20 countries; and, providing methodological support of experienced epidemiologists, in order to make a correct data interpretation.

In an ideal world, where birth defects registries with 100% ascertainment would be available to the population at large, and where all the data would be available, the association would probably have been created much earlier. As it has recently been stated, the detection of valproic acid teratogenicity raised from an unusual set of circumstances in the Rhone-Alpes region, due to the following reasons: a high prescription rate of valproic acid (28% of epileptic women of childbearing age); the existence of a birth defects registry; a special interest for spina bifida in the registry; and, a questionnaire with a routine question on epilepsy; the status of Clearinghouse member of the registry, without which perhaps the cases would have remained stored in a computer.

The importance of belonging to a nongovernmental organization when investigating such clusters was stressed during discussion which followed, since there are no constraints of drug companies nor of governmental policies.

Epidemiology of Congenital Hazards (Professor F.W. Rosa). The FDA's interests in congenital hazard information exchange, and specific exposure questions (vitamin A congeners, antiepileptics, viral treatments and immunizations, lithium, prostaglandin inhibitors, benzodiazepines, imidazoles) were briefly presented. The FDA's interests are not limited to drug exposures, since it also has bureaus for biologics, foods, veterinary medicine, devices and radiologic health.

The limitations for basic monitoring of temporal and geographic birth defect frequencies were recently well reviewed by Khoury and Holtzman (American Journal of Epidemiology 1987; 126(1): 136-143). Although it is only possible to demonstrate few known human hazards (iodine deficiency, methyl mercury, and certain viruses) to date, the

potential remains for detecting as yet unanticipated major disasters. Exposure identification is ultimately essential for identifying an exposure hazard. Some monitoring systems routinely collect limited exposure information, and others employ registered defects for case control exposure follow-up of selected questions. Temporal and geographic definitions of exposures have been weak. Even where exposures are both high frequency and high relative risk (practically never for drugs, and rarely for other hazards), time is required to assemble sufficient exposed outcomes to show impact on monitoring systems. Outcome data on cohorts of exposures, or isolated case reports of suspected congenital hazards, offer the only potential for early detection.

Maternal or neonatal serologic tests are an additional index for detecting congenital hazards. These are already routinely collected for syphilis, PKU, and thyroid, and in selected studies for AIDS, hepatitis B, HTLV 1, antiepileptics and lead.

Additional reproductive outcomes including spontaneous abortions, intrauterine growth retardation, subsequent development, and neoplasms are related to birth defect registry objectives.

Discussion centred on the quality of prescription information and ascertainment of dosage actually taken, plus the effect on prescribing practice if an association is established between a suspected agent and a specific malformation.

The Clearinghouse and Drug Teratogenesis (Dr B. Källén). A joint study on the effect of anticonvulsant use in monotherapy and birth defects was originally suggested for two reasons: the large data banks of the Clearinghouse should be suitable to study rare exposure of this type; and, the absence of a definite end result made a case-control approach less suitable and the study could test the ability of the Clearinghouse members to identify cohorts of women exposed to a specific type of agent. The result of this study⁽¹⁾ indicated that actually few programmes could submit this type of information, but material consisting of data from three countries (France, Italy and Sweden) could be collected. Information on 577 infants born of epileptic women treated with anticonvulsants in monotherapy was provided and the possible difference in effects studied. Two results appeared. The total rate of severe malformation was lower than usually seen in infants born of epileptic women (the majority of which are treated with polytherapy), and no definite difference in teratogenic potential could be seen. There was, however, a difference in the effect on baby dimensions indicating a more pronounced small-for-date-ness after carbamazepine exposure than after other drugs.

The small size of the cohort made it a blunt instrument for studies of teratogenesis. A second effort was made to compare the possible teratogenic specificity of various anticonvulsants using the following technique. Data were collected from six programmes that could and wanted to submit information on malformed infants born to women with epilepsy and using anticonvulsant drugs - a total of 253 infants. A search was then made for a heterogeneity between drug usage and malformation type after stratification for programme and mono/polytherapy. The association between valproic acid and spina bifida was verified but it was mainly based on data from the France RAA programme. Another association between phenobarbitone, especially in polytherapy, and facial clefts was found, and a possible association between carbamazepine and spina bifida.

The Clearinghouse material can offer special advantages from various points of view: the large numbers which can be obtained, and the fact that therapeutic traditions vary between different countries which helps to break strong associations between specific drugs and specific conditions. The latter is at present utilized in a joint study directed at the possible association between progestational agents used during pregnancy and the origin of hypospadias where the unique aspect is that different populations with very different usage of hormone therapy can be compared, assuming that the indications for hormonal therapy (early pregnancy bleeding, previous miscarriage, etc) is probably similar in the population.

This is an aspect of the Clearinghouse activity which could probably be much expanded and could even lead to an ongoing drug - malformation surveillance which may be more sensitive in the detection of new teratogenic drugs than any system effective at present. But in order to achieve this, substantial funding would be needed.

It was clear from discussion which followed that in the analysis presented it had not been possible to postulate the proportion of different types of epilepsy occurring within different countries and hence to adjust for the different indications of the medications. Minor cases, such as dysmorphias, had not been included in the analysis as they had been thought biased. However, the result would not have been significantly changed by their inclusion. The second study described was an original use of statistics. Differences in drug use between various participating countries were probably not due to differences in types of epilepsy. It was postulated that the distribution of cases of different types of epilepsy was the same among the different countries; variations were in the drug prescription habits.

3. MONITORING ENVIRONMENTAL TERATOGENS, CHROMOSOMAL ABNORMALITIES AND MUTATIONS

Monitoring Environmental Teratogens, Chromosomal Abnormalities and Mutations (L.B. Knudsen). This study analyzed the material collected by the Clearinghouse on Down's Syndrome. The quarterly monitoring is made according to two age groups (<35 and >35). Large variations exist between baselines in different countries. One explanation could be that some programmes still use baselines data collected before the period of expansion of prenatal diagnosis practice. The annual monitoring includes an analysis based on maternal age distribution into five-year classes. An analysis is also made of induced abortion after prenatal diagnosis, and on the cytogenetic type of cases: difference is made between free trisomies and translocations. The study described is based on a large data set, already published in the Clearinghouse Annual Reports.

The purpose of the trial is to evaluate the ascertainment of cases of Down's Syndrome in the different programmes, and the impact of prenatal diagnosis during the last few years. The Swedish annual data, which are based on a multisource ascertainment, were considered as an estimation of the true age-specific baseline rate for Down's Syndrome, which is postulated not to have geographical variations. The data were collected before the prenatal diagnosis technique became more widespread. Annual data from different programmes of the Clearinghouse were then compared with the Swedish data for the evaluation of ascertainment and impact of induced abortion on age-specific rates of Down's Syndrome.

It was stressed that during the past few years, the changes observed in the maternal age distribution within some programmes have played a major role in the differences observed in incidence rates. It was noted that rates of chromosomal abnormalities were unlikely to change rapidly and therefore quarterly monitoring of these abnormalities might be considered unnecessary. The final diagnosis is often reported much later than three months after the birth of the child. Different maternal age distributions have more impact on the rates than differences between countries in the use of prenatal diagnostic techniques. The ethnic distribution of a population could also affect the maternal age distribution.

Monitoring for Environmental Teratogens and Mutagens (Dr P. Lancaster). Environmental agents account for only a small proportion of proven causes of congenital malformations in humans. Nevertheless, pregnant women may be at risk from exposure to a wide variety of chemicals and to other environmental agents such as infections and ionizing radiation. With their large pool of malformed cases and sometimes information about parental exposure to potential teratogens and mutagens, birth defects monitoring programmes are well placed to investigate these environmental causes. Joint studies conducted within the Clearinghouse have the advantage of exploring possible casual relationships in situations of diverse exposure.

Parental exposures to chemicals may occur in many ways - by occupational exposure; by the use of household chemicals such as cleaning agents and insect sprays; by air pollution

and contamination of water and soil; and, by the ingestion of substances in food. Compared to therapeutic drugs, these environmental chemicals pose much greater problems in measuring accurately the timing and dose of exposure.

Monitoring programmes that record data on the occupations of parents, either by linkage of occupational and birth defects registers or by recording such information on malformed cases and controls, may provide initial clues to possible casual relationships. Alternatively, the role of environmental agents as teratogens or mutagens may be suggested by temporal or geographical clustering of birth defects, by reported associations between birth defects and exposures to chemicals, or by concerns about environmental health issues. Indirect measures of exposure, such as the area of residence or occupation will frequently be required in studies of environmental causes. As proven teratogens usually cause specific types of birth defects, accurate diagnosis of fetuses and infants with single and multiple malformations is essential in these studies.

While the risks of exposure to chemicals and other environmental agents will usually be less than those of ingested drugs, chemicals may not always receive the same rigorous evaluation as drugs. Birth defects monitoring programmes have an important role in assessing the possible teratogenicity and mutagenicity of these environmental agents.

Mutagenic and Teratogenic Effects of Radiation (Professor C. Stoll). Prior to the blastocyst stage, the embryo has resistance to the teratogenic and growth-retarding effects of radiation and the greatest degree of sensitivity to the lethal effects of irradiation. During early organogenesis, the embryo is very sensitive to the growth-retarding, teratogenic and lethal effects of irradiation.

In humans the effects of radiation on the developing embryo and fetus are growth retardation and central nervous system anomalies such as microcephaly, with or without mental retardation, and eye malformations (microphthalmia, cataracts, retinal degeneration, optic atrophy and strabismus). Neurophysiological and behavioural changes are difficult to evaluate (no changes seem to occur for exposures less than 250 mGy). Induction of childhood malignancy is controversial. In humans, two factors are important - the time of exposure and the dose of in utero irradiation.

Mutagenic effects can be studied by determination of the frequency and mutation rate of chromosomal structural abnormalities or by the surveillance of sentinel phenotypes and protein variants.

Recently, evidence of increased somatic cell mutations at the glycophorin A (GPA) locus in atomic bomb survivors was produced with demonstration of a loss of gene expression at the polymorphic GPA locus. Significant linear relations between variant frequency and radiation exposure were observed for three different variant cell phenotypes. This supports a mutational origin for variant cells.

Swedish Studies after Chernobyl (Dr B. Källén). Before starting any study on the possible effects of the Chernobyl accident on reproductive outcomes, it was postulated in Sweden that: the actual measured radiation doses cannot cause teratogenic effects; it is theoretically possible that mutagenic effects could have occurred in germ cells; studies on malformations based on pregnancy cohorts must be conducted to meet public demands; and, the radiation doses following the Chernobyl accident, or other consequences of it, could have had other effects such as preterm delivery low birthweight, perinatal death, spontaneous abortion or induced abortion.

The exposure rates were different in various parts of Sweden, so the country was divided into four categories according to the levels of exposure to Ce^{137} . The study might be criticized because one can argue that effects might or might not have followed local exposure levels, as contaminated food was disseminated all over the country. The preliminary results showed that the Chernobyl accident had had no significant effect on the resultant births. The only positive finding in Sweden is an increased rate of induced abortions in 1986, resulting in a 5% decrease in the birth rate. This was not due to the

direct effect of low-dose radiation but to misinformation or misunderstanding of information by the population.

Consequences of the Chernobyl Accident on the Incidence of Legally Induced Abortions in Denmark in 1986 (L.B. Knudsen). In Denmark, each woman has a right to a legally induced abortion if it can be performed before the end of the 12th week of gestation. All abortions are performed in public hospitals free of charge, as all inhabitants in Denmark are covered by a health insurance financed through a general tax payment. For each abortion, a notification form that contains information about the woman (personal identification and residential area) and the operation is sent to the National Board of Health. Based on these forms, annual statistics are published.

The final database of births and spontaneous abortions during 1986 not being available in time for the meeting, only the effect of Chernobyl on the incidence of legally induced abortions could be described and evaluated. The number of legally induced abortions in 1986 was 20,067, about the same as in 1985 where it was 19,919. Even if the total increase is less than 1%, there is a great variation between counties, ranging from an increase of 7% to a decrease of 12% in numbers. Of the counties with an increasing number, two had an increase of more than 20% in the three months period following the Chernobyl accident. These counties are situated in the Southern part of Jylland (West Denmark), exactly in the area of Denmark where the most fall-out was registered after the Chernobyl accident. This fact was well-known among the public and received significant press coverage.

The results thus indicate that a certain number of women chose to interrupt their pregnancy by a legally induced abortion, due to uncertainty about the consequences of the fall-out.

First Evaluation of the Reported Frequency of Chromosomal Anomalies in 18 EUROCAT Registries from 1 January 1986 to 31 March 1987 (Professor P. de Wals). In January 1987, a cluster of 10 cases of trisomy 21 was reported in births in West-Berlin, 9 months after the radioactive contamination resulting from the Chernobyl accident. Chromosomal anomaly syndromes (n=758) recorded from January 1986 to March 1987 in induced abortions, live and stillbirths (n=474,229) in 18 EUROCAT Registries were reviewed. In no registry, a significant cluster was observed in the period January-March 1987. Analysis of frequency rates by month of conception did not indicate any increase after 1 May 1986. Comparing cases conceived before 1 May 1986, with those conceived later, there was no significant variation in the ratio free trisomy 21/translocation 21, in the ratio trisomy 21/other trisomies, nor in the sex and age distributions.

Under-registration of cases in some registries and incomplete information on karyotypes affects the sensitivity of analysis. Larger and more accurate studies including monogenic dominant mutation syndromes are needed for a proper evaluation of the genetic impact of the Chernobyl accident in the population of Europe.

Studies in Hungary after Chernobyl (Dr A. Czeizel). The hypothesis that low dose radiations had had a teratogenic or mutagenic effect was tested. Findings showed no increase in the rate of malformed infants.

The monthly distribution of different adverse pregnancy outcomes was evaluated in Hungary after the Chernobyl accident: induced abortions, fetal deaths, low birthweight infants (under 2500g), isolated congenital anomalies, identified multiple congenital anomaly pairs of unidentified multiple congenital anomalies. Only a somewhat higher than expected rate of low birthweight newborn infants was detected in May and June 1986; this may have been due to premature labour caused by the result maternal psychosocial anxiety.

Discussion resulted in a general feeling in favour of collaborative studies on the possible effects of the Chernobyl accident within the ICBMS. Norway was planning to undertake a similar study to that conducted in Sweden; exposure doses were awaited. No significant increase in malformation rates had been observed in Finland. A number of special studies were underway in the USSR. The findings from these studies were awaited

with interest. There was no measurable increase of induced abortions in Hungary comparable to what was observed in Sweden and Denmark. This is due to Hungarian law which severely limits induced abortions. There were fears that media coverage may have heightened public anxiety about pregnancy outcomes after the Chernobyl accident. In some countries, meetings with journalists could result in more accurate media coverage. Presenting negative findings in reputable journals could also counter the previous impressions given by the media.

Genes, Maternal Resistance, and Birth Defects (Dr J. Kucera). Resistance is the ability of an organism to neutralize action of certain noxa and thus, to maintain functional balance of an individual. The resistance (joint terms "intolerance" and/or "sensitivity") may be inherited or acquired, transient or permanent. Maternal resistance against embryotoxicants is a particular form of resistance.

Inter and intra population differences in the level of teratogenesis indicate distinct resistances in both populations (e.g., some polygenic traits, enzymopathies) and individuals (e.g., contergan embryopathy). Sufficient knowledge on what causes these is not yet available in order to introduce methods of prevention of teratogenesis. The preconceptional prevention tries to increase resistance against factors causing orificial clefts and/or CNS dysraphic defects, but the results leave much to be desired. The term "maternal resistance" does not express appropriately this phenomenon: not only mother but also the product of conception - carrying a half of the father's genome - plays a role in normal embryonal development. The indirect evidence for participation of the fetus is the secondary sex ratio of phenotypes malformed in different organs and/or systems.

We cannot make use of genes/markers mapped in chromosomes to date, no loci were identified as a factor preserving safe morphogenesis. Therefore, protective regime starting in the 1st segment of reproduction and continuing in early pregnancy must be based on elements like high-nutrition-standard, stop-infection and special case for diabetics, epileptics, asthmatics and women employed in risk occupations. This seems to be the only way how to raise the resistance contra failure of fetal development.

It is an opportunity for both ICBDMs and WHO to conduct a study, the model of which - with several data from abroad and from the CSSR - is ready for discussion. One such collaborative study could investigate malformations in twins.

4. EXAMPLES OF PROGRAMMES AND STRATEGIES FOR COLLECTING DATA IN DEVELOPING COUNTRIES

A Methodological Approach Suitable for Developing Countries (Professor E. Castilla). After running the ECLAMC for over 20 years, a set of characteristics typical of the underdeveloped world can be identified. However, the long survival of the ECLAMC suggests that most of those drawbacks can be overcome. The following are the main problems we have encountered, each of them linked with the way we found to deal with it.

(a) High infant mortality rates result in birth defects having a negligible importance in public health. This is illustrated in the table below. This is dealt with by running the programme as a research project, not as a public health system.

Infant Mortality Rate in Different Parts of Latin America in 1986

<u>Country</u>	<u>Infant Mortality Rate per 1.000 live births</u>	<u>Component Due To birth defects</u>
Cuba	13	1st cause
Argentina	35	2nd cause
Brazil	70	4th cause

(b) Low resources available, mainly in health and education, non-profitable political investments in the short run (there is no long run reality in underdevelopment) - run a cheap programme; the strongest argument in favour of monitoring birth defects lies in its low cost;

- (c) Political and institutional instability. Therefore work directly with people instead of doing it with institutions even if people are often moving too. It is important to keep a monitoring system independent of institutions therefore build up a hospital-based study over a network of perinatologists, not over a network of hospitals;
- (d) Poor hospital records. Therefore construct a full data base including data about risk factors, and full descriptions of birth defects: remember there are no valuable hospital records where to call if needed;
- (e) Poor health and vital statistics. Therefore register and store your own denominators: number of births classified by main characteristics; maternal and paternal age; sex; parity; birthweight; gestation;
- (f) Poor communications because of long distances and different languages. Therefore trust the mail, simple old air-mail, and meet personally with all people involved in the study as frequent as possible depending upon distances;
- (g) Physicians and other health officers frequently are professionally frustrated. Therefore pay them intellectually for the job they do daily; let them participate in all decisions; feedback with clinical data, not with boring epidemiological data;
- (h) Miscellaneous cultural vices: i.e., people do not answer letters - respect those cultural "values"; do not work against them; and,
- (i) Health authorities are not interested in your work, and if a new teratogen comes to be found you will never convince your government to withdraw that teratogen from the market.

In short, the model recommended here is that of an economical research project working over a hospital-based sample, with a clinical-epidemiological approach, with case-control data about a large set of risk factors, based on the voluntary participation of the persons actually involved in examining the newborn babies and recording their data. Make the programme simple, and join the Clearinghouse.

Dr Mutchinick commented on the presented approach. Poor medical education in public health; physicians not being used to count and register observations; poor communication of communicable diseases and no communication of congenital malformations leads to nonexistent or unreliable vital and public health statistics. Priorities of malnutrition, fertility control and infant disease together with low levels of funding for public health results in lack of central support for a Registry of congenital malformations. Therefore, he agreed that a cheap and independent research programme run by few people was required.

A Large National Programme in a Western Country - USA (Dr J.D. Erickson). The Birth Defects Monitoring Programme (BDMP) is a national surveillance programme in which researchers monitor and analyze hospital discharge data on newborns for birth defects and other newborn conditions. The BDMP was initiated at the Centres for Disease Control (CDC) in December 1974. The BDMP currently is comprised of two separate data bases, derived from information sent by participating hospitals to their respective health-data processing system.

The two systems are the Commission on Professional and Hospital Activities (CPHA) and McDonnell Health Information System (MDHIS). Each of these health data processing systems operate in a similar manner. Discharge abstracts are coded by hospital medical records department and submitted regularly to each system for processing. The major difference between the two systems is the exclusion of stillbirths from the MDHIS. Some 161 defect categories are analyzed to identify increase or unusual trends. The CPHA data is available from 1970 through 1985, over 800,000 births were monitored in 1985 or 22% of the US births. The MDHIS data are available for the year 1982 to 1985. Five hundred thousand newborn discharges in 1985 or about 12% of the US births. The data are reviewed four times a year,

and defects are usually reported three to six months after an affected infant's birth. Although this data source is not population-based and not a random sample of US births, it nevertheless represents the largest single set of uniformly collected and coded discharge data on birth defects among newborns in the USA.

The BDMP functions primarily as an early warning system. However, it can be useful also for correlating incidence patterns with such trends as the temporal and geographic distribution of drugs, chemicals and other possible human teratogens.

Dr Erickson offered practical advice as to the ideal components of a monitoring system. These included: comparable numerator and denominator data; a written description of defects; central coding; the use of multiple ascertainment sources; personal identifiers; regular monitoring; analytical studies; and, regular reports to people contributing to the monitoring system. In epidemiology terms the USA is underdeveloped since the inclusion of many of these components in their programmes would not be possible. The best population would usually be population-based but this would depend on what was practical and would be governed by the purposes of the surveillance programme.

The purpose of surveillance is a question which should be addressed regularly: the purpose of surveillance is to detect a new teratogen; a population-based programme is theoretically preferable but not always possible; denominator and numerator data must be comparable; notifications should be made by a surveillance staff in each hospital; they should be made as a written description of the newborn; the coding should be made centrally; it is preferable to have a multisource ascertainment; personal identifiers are highly suitable, much better than names, which often change. Otherwise it is impossible to make an analytical study without long procedures; monitoring, i.e., data analysis should be regular; training is often required for the surveillance staff; more than just collecting data, conducting analytical studies is important; and, regular reports should be sent to people filling the notification forms.

The problem of personal identifiers was solved a long time ago in the Nordic countries, but there are now some mediatic campaigns against it. As suppressing these identifiers would be a clear regression from a scientific point of view, the question was raised whether the Clearinghouse could do something through the media to underline the importance of identifiers for conducting epidemiological studies.

A National Birth Defects Monitoring Programme in the People's Republic of China

(Dr Kunze Xiao). The Chinese Birth Defects Monitoring Programme (CBDMP) was set up in May 1986 with the support from the Ministry of Public Health of the People's Republic of China. The CBDMP is a hospital-based case-control monitoring programme with the participation of 945 hospitals from all the 21 provinces, three metropolis and five autonomous regions. The development and organization of this nationwide programme lasted a period of five years. This is because China is a country with a large population, a vast territory and has multiple nationalities; it would be too difficult to organize a nationwide birth defects monitoring programme within a short period of time.

Research started in December 1981 in seven hospitals in the Chengdu area of the Province of Sichuan. From 1982 to 1983, 18,158 perinatals in the Chengdu area were monitored by volunteer paediatricians, obstetricians, medical geneticists, pathologists and other specialists. The preliminary result of this work won the support of the Sichuan Health Bureau. A provincial Birth Defects Monitoring Programme (SBDMP) was set up in December 1983, which covered 100 hospitals from all 18 cities, prefectures and autonomous regions of the Province of Sichuan. By the end of 1984, a total of 55,653 perinatals were monitored in these 100 hospitals, and during this study a tier monitoring system was formed.

The publication of the birth defects monitoring in the Chengdu area and in the Province of Sichuan drew the attention of colleagues in other provinces. For example, in Guangdong, Guangxi, Jiangsu, Shanxi, Guizhou, etc, colleagues started birth defects monitoring using ours or a similar method and investigative forms. They sent their data and information to

the SBDMF and expected the development of a cooperative network, and since then there has been good communication and cooperation.

In brief, experience has been as follows: work began in a small area with several hospitals and the result of the pilot study was publicized; the scope of monitoring was expanded gradually from city level to provincial level and then to the national level; this process enabled the development of cooperative work and communication with colleagues in multiple-disciplines from more cities, more provinces and finally extending coverage of the whole country; and, efforts were made to win over the support of health authorities at all levels.

In the meantime, suggestions and proposals have been submitted requesting that birth defects should be taken as a priority health problem in China and that a nationwide birth defects monitoring programme would ensure implementation of the same method of data collection, data management and data analysis, and thus the accuracy, reliability, comparability and generalizability could be attained.

In the discussion which followed, it was noted that the Chinese experience is a good example of the organization of a monitoring system in a very large country. It was hoped that an atlas of birth defects would be available from the Chinese programme which would be mainly composed of pictures, with an educational objective.

5. FURTHER COLLABORATION BETWEEN WHO AND ICBDMs AND RECOMMENDATIONS

It is reasonable to continue birth defects monitoring, training programmes in monitoring and epidemiology, international studies of birth defects, communication between WHO interest groups and ICBDMs, and a supplement on birth defects for ICD 10. There had already been some collaboration on the latter aspect. In particular, subjects for collaborative studies could include the incidence of major congenital malformations, chromosomal abnormalities and conditions detected by neonatal screening programmes, the impact of prenatal diagnosis on the incidence of malformations at birth, the incidence of malformations in different ethnic and geographic groups, and the contribution of birth defects to perinatal and infant mortality.

Other areas for collaborative work could include work with ICBDMs assistance in the preparation of educational material and joint publications on practical guidelines on the prevention and detection of birth defects. This could include methods for diagnosis and indications for prenatal diagnosis. The benefits of such collaboration could be more widespread monitoring activities, better recognition of the prevention of abnormalities through prenatal diagnosis, leads for future studies into the causes of particular malformations, standardized definitions and classifications, regional WHO collaborating centres, and specific tasks for an International Centre for Birth Defects.

Some points focussed on the relationship between ICBDMs and WHO in developing countries. As infant mortality reduces, congenital abnormalities become a proportionately larger problem. There would be a need for some restructuring of health care facilities, and the inform health establishments in developing countries that congenital malformations could become a primary problem into the 21st Century.

Another area for collaborative work was the training of those wishing to develop monitoring programmes. As societies become more industrialized, it is more likely that chemical and radioactivity problems will occur; the ICBDMs has a large group of members ready, willing and able to provide assistance in dealing with such problems. It was hoped that communication could be fostered between ICBDMs members and the regional units and Member States of WHO.

It was emphasized that considering the existing collaboration between the Clearinghouse and WHO, WHO could provide the necessary channels for an international body dealing with health; could facilitate transnational communication and official national contact; and,

could disseminate information and provide authoritative and hierarchical paths to bring recommendations into action. It was stressed that WHO was not required merely for financial support. The ICBDS could provide expertise, suitable data, training and education facilities, and could produce manuals and reports to help members.

Therefore, areas for possible collaborative action were outlined as follows:

- worldwide investigations determining the incidence of malformations at birth, assessing the contribution of mortality and evaluating the impact of prenatal diagnosis.
- developing new methodology in defining rates, establishing baselines, recording observations, comparing observed and expected numbers and in monitoring multiple malformations.
- classification of malformed infants at ICD level or more specific levels, of multiple malformed infants, and delineations of syndromes.
- transferring appropriate technology to other countries through training and education (including printed publications).
- training and education, possibly through WHO fellowships.
- providing a task force for teratogenic emergencies, a team (comprising: chief of mission, epidemiologist, statistician, clinical dismorphologist, photographer) always prepared to depart, provided jointly by WHO and ICBDS; and,
- publications with WHO assistance with printing and dissemination of the results.

General discussion welcomed the positive presentations and the wealth of ideas for effective collaboration between the ICBDS and WHO.

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7. REFERENCES

(1) Bertollini, R.; Kallen, B.; Mastroiacovo, P., and Robert, E. "Anticonvulsant Drugs
in Monotherapy. Effect on the Fetus". Europ. J. Epidemiol 3:164. 1987.

ANNEX 1

FREE PAPERS

Paper 1 - Dr E. Robert, France

A Cluster of Esophageal Atresias in the Rhone-Alpes-Alvergne Programme

Abstract: The birth defects monitoring system working in the Rhone-Alpes region of France has detected a cluster of isolated forms of esophageal atresia during 1984 (27 observed, 14 expected). A special study revealed that the high observed rate was partly due to seven cases (1 expected) of affected infants born in a small area of the region. Personal interviews of parents of these seven cases were made, centring the questions on maternal environmental conditions during the first trimester of pregnancy. These interviews failed to demonstrate the existence of any common risk factor, leading to the conclusion that either the cluster was just random, or the interviewers asked the wrong questions.

Discussion: Similar increases had been recorded in the report of the first quarter of 1984 by the Spanish and South American programmes but they did not persist. The Mexican programme noticed such a cluster in the fourth quarter of 1985, involving mainly cases already included in the reporting of multiple malformations. The Italian programme reported a similar cluster in the third quarter of 1986. Clusters are frequently observed among the programmes, and investigations into these usually result in negative findings. The question of when and how other programme directors follow up clusters was discussed.

Paper 2 - Dr P. Lancaster, Australia

Congenital Malformations and Chromosomal Abnormalities After In Vitro Fertilization

Abstract: Although experimental studies in various animal species have not shown increased risks of congenital malformations after in vitro fertilization, several factors may possibly increase such risks in human pregnancies. These include the more advanced ages of both parents, the underlying cause of infertility and its treatment (e.g., drugs such as clomiphene), the IVF procedures, and the higher proportion of multiple births due to the placement of more than one fertilized ovum.

The register of IVF pregnancies in Australia and New Zealand obtains data on the outcome of these pregnancies from all IVF units. Between 1979 and 1985 there were 26 fetuses and infants with congenital malformations or chromosomal abnormalities among 1,138 births, an incidence of 2.3%. This was slightly higher than the population incidence of 1.5% but the method of ascertainment of cases was not the same. No unusual pattern of congenital malformations was noted, but hypospadias occurred in two infants after maternal treatment with progesterone in the luteal phase of pregnancy. In three cases, the pregnancy was terminated after prenatal diagnosis of fetal abnormalities. In one of these cases, osteogenesis imperfecta was diagnosed after the use of a frozen embryo.

In a case-control study in which each case was matched with four normal infants from the same fertilization cohort, no major differences in the causes of infertility and management of the pregnancies were observed between the two groups.

Discussion: The observed slight excess of chromosomal abnormalities had not been due to possible parental balanced anomalies because all the couples had had an infertility screening including karyotype. The different types of generalized skeletal anomalies observed in this sample were felt to be of interest for study. The results of the study seemed to show that, from a clinical point of view, amniocentesis was not indicated for monitoring pregnancies after IVF.

The results presented had been based upon live births following IVF; it was agreed that supplementary information on aborted fetuses would be of interest. In general, the parental socio economic group was higher than in the general population, due in part to the cost per IVF cycle. Dr Lancaster was not aware of any routine use of preconception vitamins prior to IVF treatment.

Paper 3 - Dr P. Merlob, Dr A. Stoupel, Israel

Fetal Growth and Incidence of Selected Major Malformations in Extreme Periods of Solar Activity in the 21-22 Solar Cycles

Abstract: The possible influence of sun activity on fetal growth was evaluated using the standard anthropometric measurements (weight and length) of neonates born in two extreme periods of solar activity. 1,171 infants born in the maximal solar activity of 21 cycle (1979-1980) were compared with 1,277 neonates born in the lowest sun activity period (last four months 1986). The decrease in mean birth weight and length during the second period (end 1986) was statistically significant for the total newborn population and males, but not for the females. This unexpected decrease in fetal growth cannot be explained by the influence of other known potential growth retarding factors. Our data suggest that there might be a correlation between sun activity and fetal growth but further investigations are needed in order to explain this time-related biological phenomenon.

The possible influence of sun activity on the incidence of selected major malformations was evaluated using the data reported by the Israel Congenital Malformations Monitoring System to the International Clearinghouse. The total number of 17 selected major malformations and their rates per 10,000 births were determined for each year in the period 1978-1986 for the Beilinson Medical Centre and for all four hospitals in the Israel Programme. There might be a good correlation between sun activity and trends in the incidence of selected major malformations. Therefore, the future reports on secular trends in the incidence of congenital malformations should take into account this possible influence of sun activity.

Discussion: There had also been a comparison of comparable data from different ICBDMS programmes. This had shown a maximum major malformations rate for different years in different geographical areas. These data suggested a possible association with solar activity but the limitations of this analysis were emphasized. No explanation was proposed for the sex difference in the results.

Paper 4 - L.B. Knudsen and F. Mac, National Board of Health, Copenhagen, Denmark.

Comparison of birth prevalence of selected congenital malformations in Denmark in two Registries: The Medical Birth Registry on Congenital Malformations.

Abstract: Since 1963 the midwives in Denmark have had the obligation to notify congenital malformations to the National Board of Health. In 1968, a Medical Birth Registry was established, based on notification forms completed by midwives, including notification of malformations.

A new Registry of Congenital Malformations was set up as of 1 January 1983, based on notifications from doctors in hospitals, covering all malformations diagnosed within a child's first year of life.

The Medical Birth Registry has been a member of the Clearinghouse since 1980. The quarterly reporting from the beginning of 1986 and the data for the Annual Report of 1985 has been based on the Registry of Congenital Malformations.

Since the new registration started, several steps have been taken to improve the registration. One example is that for all births since 1 January 1985, there has been a continuous follow-up of infants notified to the Medical Birth Registry as having a malformation, but not known in the Registry of Congenital Malformations, which has improved the coverage of the new Registry.

For this paper a special evaluation of ascertainment of those malformations, selected for the quarterly reporting in the Clearinghouse has been performed.

Results will be presented to show which kind of malformations are reported equally in both systems and where the largest improvement of the coverage can be seen in the new system.

Discussion: Omphalocele had been better ascertained with the new Registry. Almost no cases of esophageal atresia had been known to the Medical Birth Registry but many had been notified to the new Registry of Congenital Malformations. Other differences in reporting practice, although apparent, had not been as large as cleft lip and palate. This experience was felt to be a good example of data validity improvement. Similar dual source comparisons in Sweden, Norway and Belgium were described. It was noted that the use of several sources was the best way to improve data quality. In Denmark the baseline was currently based on 1983-84 data, but they were now considering changing so as to be based on data from the improved ascertainment. No systematic comparison of diagnosis had been made, but comparisons had been made in some cases.

Paper 5 - Professor G.I. Laziuk, USSR

Birth defects monitoring systems in Byelorussian SSR

Abstract: There are two types of birth defects monitoring systems in Byelorussia: the system registering congenital malformations (CM) in the perinatal period; and, that registering CMs in the embryonic period.

(a) The system of perinatal genetic monitoring has existed since 1979, is a state programme, approved by the Ministry of Public Health, and compulsory for all delivery units established in the Byelorussian Republic. Approximately 170,000 births per year are monitored. The listed CMs below were diagnosed in infants during the perinatal period by using this system, and which are registered irrespective of whether an infant is alive or stillborn:

- spina bifida (and occipital encephalocele)
- cleft lip and/or palate
- polydactyly
- limb reduction defects
- esophageal atresia (stenosis)
- atresia (stenosis) ani
- Down's syndrome
- hypospadias
- all types of multiple malformations

Following the birth of an infant with any of the CMs mentioned above, a special registration card is completed at the hospital where delivery has taken place and sent to the monitoring centre. The card is filled in by a neonatologist (if an infant is discharged or transferred to another institution) or by a pathologist (if an infant dies within the first seven days of life or is still-born).

The card is normally sent to the monitoring centre no later than 10 days after the birth of the infant. The registration cards are then checked for accuracy and in due time are controlled by the staff of the monitoring centre who regularly visit the medical institutions in the Republic.

As our studies have shown, about 12% of all nonclassified CM combinations are due to dominant mutations, and the contribution of multiple CMs resulting from sporadic dominant mutations is essential. In this respect, the increase of only multiple CM incidence may be indicative of the growing dominant mutability.

It is quite natural that the ascertainment of a complex as "multiple" CMs involves a lot of difficulties, since the notion of multiplicity itself is evaluated by various

investigators ambiguously, either by the number of anomalies (2 and more or 3 and more), or by the spectrum (what can be regarded as CM). Unification of the approaches, particularly via the WHO system, might be of great value and would allow multiple CMs to be used more in surveillance systems for mutation process and environmental factors.

The baseline figures of the main nosologic entities are fairly consistent with the incidence of these anomalies in the regions adjoining Byelorussia (the incidence of the neural tube defect is 0.76:1,000, the incidence of cleft lip/palate is 0.95:1,000, the incidence of polydactyly is 0.55:1,000, and limb reduction defects are 0.2:1,000). The surveillance period shows a decreased incidence of Down's syndrome and multiple malformations. The decline of multiple CMs may be ascribed both to decreased mean paternal age (and consequently, to a decrease of multiple CM incidence due to dominant mutations) and to urbanization, break down of isolates, an increase of the proportion of international marriages, decreased possibility for realization of recessive genes. The decrease in Down's syndrome incidence may be explained by a lower maternal age. More than twice lower the proportion of mothers older than 38, who gave birth to Down's syndrome children was observed in 1985-1986 as compared with 1980-1981. In view of this it should be clearly realized that the effectiveness of the prenatal diagnosis based on the age criterion will be lower.

As regards most of the other registered forms, no significant changes in the malformation incidence were noted during the surveillance period.

(b) The monitoring system of embryonic malformations includes random examination of induced abortions in the population of Minsk (about 3,000 women per year). This monitoring is not a state system and has been carried out by staff at the monitoring centre since 1980. All anomalies found in induced abortions at gestational age of 12 weeks are registered.

As compared with the monitoring of perinatally diagnosed malformations, the monitoring of registering malformations in abortions has some advantages and disadvantages. The main advantages are as follows:

- A higher malformation occurrence (our studies showed 55:1,000, whereas the total incidence of model forms of the anomalies, diagnosed in the perinatal period was 7:1,000),
- An unambiguous evaluation of malformations, because they are examined by quite a limited number of highly trained experts.
- The major disadvantages (laborious work and small samples) do not reduce the significance of this monitoring.

Paper 6 - Lie, Rolv Terje, Norway

The Development of a New Statistical Basis for the Epidemiologic Surveillance of Congenital Malformations in Norway

Abstract: The notification of births to the Medical Birth Registry in Norway was made compulsory by law in 1967. Adverse delivery outcomes are monitored through selected groups of congenital malformation, low birthweight, and perinatal mortality. A statistically based epidemiologic surveillance of congenital malformations has been run since the early 1970's. The shortcomings of this routine and the needs for methodological changes are discussed on the basis of experience over almost 15 years. An outline of the principles of a new system is given below.

In Norway, methods of surveillance had remained almost unchanged since the system began in 1971. Shewhard Charts (based on a binomial model) were used with baselines derived from 1967-71 data. The new system would probably be based on IBM technology and the surveillance technique used would depend on the level of ascertainment of the particular malformation and the stability of the observed malformation rate.

Discussion: It was recognized that the paper presented the strategy all Programmes would ideally wish to follow. However, no list of specific malformations could be exhaustive; all malformations would need to be monitored. A number of alarms triggered by the Norwegian data were thought to be due to the dated baselines. Baselines derived from more recent data had not yet been tried.

Paper 7 - Dr A. Czeizel, Hungary

Preliminary Results of Trials of Periconceptional Multivitamin Use

Abstract: There is a debate about the effectiveness of periconceptional multivitamin supplementation in reducing the recurrence risk for neural tube defects (NTDs). Hungary takes part in two projects. First, the British Medical Research Council's Vitamin Study is a double blind trial using four different types of capsules (mineral, as placebo, mineral and multivitamin) in women having previous offspring affected by NTD. Thus the purpose is to evaluate the effectiveness of periconceptional multivitamin and/or folic acid supplement in reducing the recurrence risk for NTD. Second, the Hungarian Optimal Family Planning Programme supported by WHO also involves a double blind trial using placebo and multivitamin (Elevit Pronatal Roche) including folic acid in women without previous unsuccessful pregnancy outcomes. Thus, the aim of this Programme, among others, is to study the effectiveness of periconceptional multivitamin supplementation in reducing the first occurrence of NTD. So far over 1,000 pregnancies have ended in birth. The preliminary results of these projects will be summarized.

Discussion: These trials followed earlier trials by Smithells et al and by Laurence et al which had been criticized due to selection bias and the small sample respectively. One major problem with analyzing the preliminary Hungarian results was the small number of pregnancy outcomes on which they were based (1,282 outcomes). In addition, the preliminary findings in the UK are not applicable to the remainder of Europe where the etiology might be different.

There was also discussion concerning compliance in the Hungarian trials. Blood and urine samples were taken at three month intervals and interviews were conducted so there was a high degree of confidence in the compliance data.

Paper 8 - Professor C. Stoll, France

Congenital Heart Disease in 78,967 Consecutive Pregnancies

Abstract: Congenital heart defect (CHD) is at present the most frequent of all congenital anomalies. During the 1979-84 period, 22% of babies notified to our Registry of Congenital Anomalies had a defect of the cardiovascular system. The overall prevalence rate (per 10,000 births) of CHD was 67.9. The prevalence rate of CHD among newborn and voluntary interrupted pregnancies was increasing. This increase was the consequence of better ascertainment due to the use of modern diagnostic techniques such as echography. If the data of 1982 to 1984 are pooled and considered separately, the prevalence rate (per 10,000 births) was 24.4 for ventricular septal defect, 6.1 for patent ductus arteriosus, 5.3 for coarctation of aorta, 4.2 for atrial septal defect, 3.8 for single ventricle, 3.4 for transposition of great arteries and 2.7 for tetralogy of Fallot.

Prenatal diagnosis by routine examination was scarcely done.

A diagnosis was made during the first week of life in 87.9% of the cases; 42.3% of the children with CHD had extra-cardiac anomalies, 24.9% had 3 anomalies and 13.9% had four anomalies. About half of the extra-cardiac anomalies were musculo-skeletal and gastro-intestinal defects. The sex ratio was 1.13, 46.1% of the women were pregnant for the first time, 28.3% had one previous pregnancy. More conceptions occurred in the summer than in the winter. The mean maternal and paternal ages were, respectively, 26 and 28. 20.04% of mothers worked during pregnancy. No peculiar genetic factors were noted. Length, head circumference and weight at birth were not significantly different from the control group. The length of gestation was less than 37 weeks in 20.25% of the cases, and 43% of the mothers smoked (control 50.6%).

Discussion: Complex heart defects had been classified according to the most important lesion with respect to the survival of the child. This was often a difficult decision. No proved congenital rubella syndrome had been found. All cases had been confirmed using diagnostic techniques such as echocardiography. No space time clustering had been found. It had not been possible to investigate possible associations with patterns of maternal alcohol intake. A few cases of Epstein disease had been registered in the Strasbourg registry. None of these had been exposed in utero to lithium.

Paper 9 - Dr L.A. Friesleben, Dr J.F. Cordero, Dr J.D. Erickson, USA

High Rates of Craniosynostosis in the State of Colorado

Abstract: For the past few years, we have been working with the State of Colorado to evaluate an apparently high rate of craniosynostosis. From 1978-1985 about 12.5 babies per 10,000 births have had surgery for this defect in Colorado, as compared to about 2.5 in metropolitan Atlanta. The study questions were:

- (a) Is the difference between rates due to differences in diagnostic criteria?
- (b) Are there differences in referral patterns?
- (c) Are there differences in sutural locations?

The cases were distributed into four classes: normal, sagittal, coronal and multiple. The surgery rates in Colorado were higher for all sutures, but markedly higher for cases with multiple suture involvement. In 1986, a meeting of neurosurgeons, radiologists, and dysmorphologists was held to discuss these findings. Since the majority of surgery for craniosynostosis is done by one neurosurgeon in Atlanta and one neurosurgical group in Colorado, it was decided to obtain radiographic records from the two practices and to have them blindly evaluated for evidence of craniosynostosis. The evaluations were done by the Colorado and Atlanta neurosurgeons, and also by an independent radiologist. Some, if not all, of the differences in craniosynostosis rates between Atlanta and Colorado can be attributed to differences in diagnostic approach. Regional variations of this magnitude are quite common in any surgical field in the USA.

Discussion: Cases secondary to surgical treatment for hydrocephalus had been removed from the analysis. Almost all the cases had been diagnosed during the first year of life but not necessarily during the neonatal period. Virtually all the operations had taken place before the infant's first birthday.

A slide was presented showing comparative rates of craniosynostosis in Sweden since 1967. An increased rate of craniosynostosis was observed in Sweden, comparable to that observed in Colorado. The incidence rate was between 0.5 and 1.5 per 10,000 births. These results were preliminary and a more precise analysis was underway. The experience of Atlanta and Colorado was of interest for comparison with, and interpretation of, the Swedish data.

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