

*The following study was made to evaluate the reliability of retrospective studies dealing with environmental causes of malformations. It is a significant contribution to epidemiologic methodology and presents unique data.*

## **PROSPECTIVE VERSUS RETROSPECTIVE APPROACH IN THE SEARCH FOR ENVIRONMENTAL CAUSES OF MALFORMATIONS**

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SOME years ago, Harold F. Dorn<sup>1</sup> made the following statement in his Cutter Lecture when discussing studies on the etiology of human diseases: "How else but by observation upon man himself can one hope to find clues to the etiology of his diseases?" Recent experiences have repeatedly demonstrated the truth of this statement with regard to the environmental causes of congenital malformations: the important information gained from experimental teratology cannot as such be applied to human fetuses and, therefore, parallel epidemiological studies have to be performed in human populations. Here, as elsewhere, two main approaches are available: a retrospective study, where information is collected after delivery when the outcome of the pregnancy is known, and a prospective one, where data are recorded during the course of the pregnancy.

The more popular of these has long been the retrospective investigation, where information regarding large numbers of malformed children can be obtained from hospital records or vital statistics and, therefore, impressive series can easily be collected. Although the limitations and fallacies of this approach

are evident, few prospective studies have been performed because of the slowness and laboriousness of such analyses.<sup>2-7</sup> The present report deals with a comparative study in which the same mothers were interviewed during and after pregnancy (prospective and retrospective), and the replies compared individually.

### **Material and Methods**

The prospective study was performed between November 1, 1963, and May 31, 1965, in the province of Keski-Suomi (population about 250,000) in Finland.<sup>8</sup> All pregnant women attending the maternity welfare centers prior to or during the fifth month of pregnancy were carefully interviewed by midwives trained by the authors and the replies entered on a form. The interview was always performed during the fifth month and the information obtained in this way covered 73 per cent of the expectant mothers of the province. (The rest had either already visited the welfare centers and did not return or they made their first visit subsequently—all these were omitted from the study.)

The whole series, consisting of 3,674

gravidae were then followed through their pregnancies and all abortions, stillbirths, neonatal deaths and congenital malformations were recorded and examined by a physician. In the entire material, 108 abortions, stillbirths, and neonatal deaths (2.9 per cent) and 103 malformations (2.8 per cent) were recorded. The mothers involved in these pathological cases were reinterviewed after delivery, using the same form and the very same method of interviewing. The second interview was always performed by the same midwife, who had already seen the mother during the fifth month, but who was no longer in possession of the results of the first examination.

Of the 211 mothers of dead or malformed children, 203 were reached for the retrospective interview. In addition, an identical control group was investigated, consisting of mothers of healthy children born next to the pathological one and attending the same maternity welfare center. These mothers, too, were already included in the prospective study.

For the final comparative study, two paragraphs of the form were chosen, namely, the occurrence of nonchronic diseases during early pregnancy and the drug consumption of the mothers during the first five months of pregnancy. Both were recorded as to their nature and date, the latter to the nearest month. In all cases the replies were compared with the records of the maternity welfare center, where all earlier observations and therapeutic measures should have been recorded by the physician and midwives. In addition, physicians' prescriptions were collected in all positive cases and if the mother had been hospitalized, the hospital records were carefully perused.

## Results

### Prospective Study

In the final series of 203 mothers of healthy children and an equal number of

pathological cases, 77 gave a positive prospective reply regarding nonchronic diseases and 369 as to consumption of drugs. When these replies were compared with the information available from other sources (see Methods), altogether 12 cases of inaccuracy or error were found, all regarding drug consumption. On the other hand, when the individual replies for the different drugs or categories of drugs were compared point by point, 36 of the total of 420 positive replies proved to be incorrect (Figure 1). Thus, these two observations clearly indicate that the incorrect replies come mainly from mothers who took several drugs during early pregnancy. Altogether, however, these results show that the prospective interview gave fairly reliable results when compared with the maternity welfare center and hospital records.

### Retrospective Study

The results of the retrospective interview of the 406 mothers are individually compared with the prospective information in Table 1. It might be argued, as a working hypothesis, that mothers of dead or abnormal children would have a tendency to "find an excuse" for their misfortune, and, therefore, would more easily remember an exposure to abnormal environmental conditions during early pregnancy. However, statistical analysis of the results given in the table did not reveal any significant difference in the percentage of unidentical replies between the pathological and normal groups. In both groups the percentage was very high, and in addition to missing or discrepant data, a great number of positive replies without a prospective history were detected.

Since no statistical difference could be shown between the two groups, it seemed justifiable to combine them for further analysis. The larger and in several respects more interesting group of mothers was that of drug consumers—reference

can be made to the abundant literature on drug teratogenicity in human populations, most of which is based on retrospective studies.<sup>9,10</sup> In Figure 1, all positive replies regarding each drug or group of drugs have been individually analyzed and the prospective and retrospective replies compared.

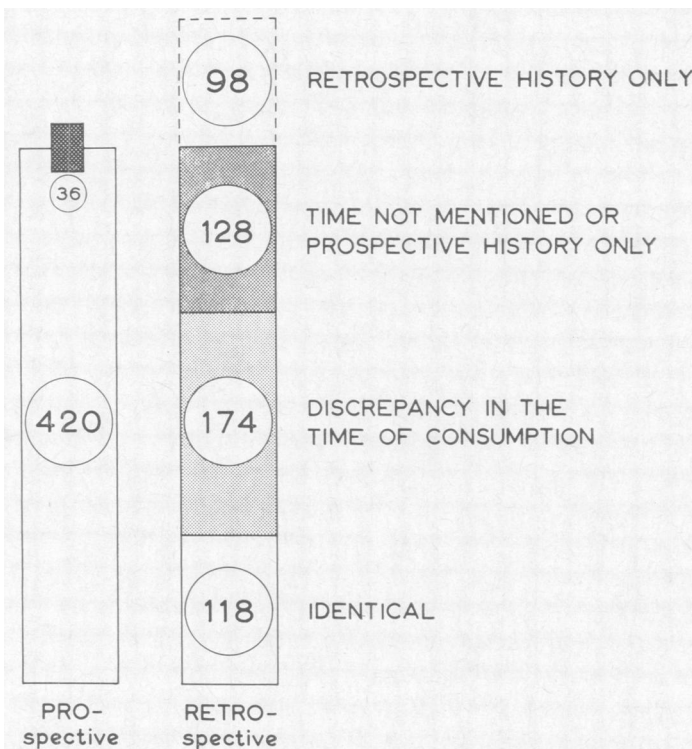
#### Time Factor

Finally, the time factor was analyzed. Owing to various retarding factors (slow communication, extended hospital examinations, deaths and autopsies during the observation period, and the like), the retrospective interview was, in many cases, delayed until several months after

delivery. Consequently, the material offered a possibility to analyze whether a time factor possibly affected the results. Although the groups were rather small, some idea can be gained from the results indicated in Table 2. Accordingly, the time factor plays an insignificant role as to the reliability or unreliability of a retrospective study—at least in the limits of a year.

#### Discussion

In the present study, the mothers' memory after delivery has been tested with regard to two criteria—the non-chronic diseases occurring during early



**Figure 1—Drug consumption during pregnancy according to a prospective interview and distribution of the replies of the same mothers when interviewed after delivery. The dark bar in the results of the prospective study indicates the number of replies showing discrepancy with the information collected from other sources (maternity welfare center records, prescriptions, etc.).**

**Table 1—The number of mothers giving positive replies in the different groups in the prospective study and the corresponding number of identical replies in the retrospective interview of the same mothers**

	Normal child formations (203 mothers)	Deaths and malformations (203 mothers)
Diseases reported in the <i>prospective study</i>	34	43
Identical replies in the <i>retrospective study</i>	1	7
Additional retrospective information ("false-positive?")	11	15
Positive drug consumption in the <i>prospective study</i>	182	187
Identical replies in the <i>retrospective study</i>	33	23
Additional retrospective information ("false-positive?")	41	57

pregnancy and the consumption of drugs during that period. The reference point, the result of the prospective interview, proved to be fairly reliable when compared with information collected from other sources. On the contrary, the retrospective replies proved to be extremely unreliable: only a small proportion of the diseases and drugs during early pregnancy were mentioned at the interview some months after delivery. In addition, a great amount of "new," obviously incorrect information was collected in the retrospective investigation.

On the basis of the data presented, it could be calculated that roughly 25 per cent of the information collected prospectively appeared as identical replies in the retrospective study. On the other hand, approximately two-thirds of the positive replies in the latter had no identical prospective history and should

be considered incorrect or at least very doubtful. The most probable explanation for the great number of "false-positive" replies is that the mothers remember the diseases and drugs of late pregnancy and erroneously refer them to an earlier period (significant from the point of view of teratogenesis). Therefore, it can be concluded that the retrospective approach to the problem of environmental factors in human maldevelopment is relatively unreliable and such studies might explain some of the rather contradictory findings reported recently in the literature. (The reader is referred, for example, to the lively discussions on the teratogenicity of meclozine.<sup>11-14</sup>)

The data presented do not throw any light on the factors underlying the great discrepancy between prospective and retrospective "memory." They indicate, however, that the outcome of the pregnancy and the condition of the child born do not play a major role, nor does the time of the retrospective study (within a year). The observations simply indicate that a mother, having once undergone pregnancy, loses interest in it during the period immediately after delivery. This seems to be especially true

**Table 2—The percentage of nonidentical replies in the prospective and retrospective interview regarding the consumption of drugs during pregnancy. The mothers were interviewed during different postdelivery months. (The replies of five mothers interviewed from 16 to 21 months after delivery are omitted from this table.)**

Postdelivery month of interview	Number of mothers interviewed	Nonidentical replies (percentage)
I-III	224	80
IV-VI	52	79
VII-IX	68	90
X-XV	57	86

in regard to exposure to abnormal conditions during the "sensitive period" of the recent pregnancy. Therefore, the laborious prospective approach is preferable when the causal relationships between environmental factors and malformations in human populations are explored.

### Summary

In order to evaluate the reliability of retrospective studies in the search for environmental causes of malformations, the following study was made: A retrospective interview was performed with mothers of 203 dead or malformed children and a control group of the same size and the replies were compared with those obtained in a prospective study of the same mothers made in the fifth month of pregnancy. The comparison dealt with information on the occurrence of nonchronic diseases and the consumption of drugs during early pregnancy. The results indicated that only about 25 per cent of the prospectively collected information was accurately elicited in the retrospective study. In addition, the results showed that two-thirds of the positive replies in the retrospective study could not be confirmed from the prospective interview or information collected from other sources.

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