Monitoring the Human Abortus for Developmental Defects

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Clefts of the lip and palate are excellent examples of human birth defects whose embryological origins continue to be explained through reliance on classical textbook accounts. Although reasonable for the day in which the texts were written, these accounts, it now appears, were based on data from samples of questionable size and specimen documentation. With recent changes in national attitudes on therapeutic abortion, the climate is now opportune for a systematic collection and study of human abortuses, therapeutic and spontaneous, aimed at providing some retrospective account of what may have gone on in a given abortus at the time of onset of a defect. Such an approach allows the reconstruction of a developmental picture on a documented background, including information on the sex, weight, size, race, and age of the abortus as well as family history and history of the pregnancy. This permits going beyond the classical accounts of malformations which usually relate developmental status with only age and/or size and which are usually limited to a description of an "average" picture.

A program of monitoring human abortuses has purposes and functions which are different from programs of fetal surveillance. The latter are designed to assess the fetus during pregnancy with the principal purpose of offering therapy or abortion when defects are detected. An abortus-monitoring program can provide detailed developmental information against a background of many pertinent variables, as mentioned above. Also, monitoring abortuses could prove valuable in the early detection of new teratogens in the environment through the prompt detection of unsuspected defects in a population not ordinarily subjected to intensive examination. It also could prove valuable in alerting physicians to population exposure to mutagenic agents, such as chemical and ionizing radiations.

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As Miller and Poland (*1*) pointed out the closing of the time lag between the initiating events of anomalous development and the time the results of those events are observed is an essential of a surveillance program. The use of observations made on term infants means not only that many defects will not be seen but that between the initiating event and the time of observation there is an interval of seven to nine months during which memory for events has become clouded. Furthermore, the monitoring of abortuses reduces the time interval between the occurrence of an event which may be of etiologic significance and the time at which it is recognized. In this respect, it is acknowledged that the perspectives gained from an abortus-monitoring program will be decidedly biased toward the abnormal, but we regard this as no reason to forego such surveillance.

Program Objectives

Monitoring human abortuses is most profitably undertaken as a cooperative venture involving basic and clinical scientists actively interested in normal and abnormal development. With this in mind, the University of Michigan Medical Center has established the Teratology Unit as its monitoring unit. The general aim of the unit is to evaluate the early and/or abnormal products of pregnancy by centralizing, and coordinating the efforts of investigators with expertise in the diagnosis and study of human growth and maldevelopment. More specific aims include: (1) identifying atypical developmental pathways with respect to their detailed morphology, potential pathogenesis and etiology, (2) gaining a more substantive insight into the normal events and characteristics of human prenatal development, (3) evaluating the status of the embryo and fetus in light of the clinical histories of the pregnancy and family, (4) determining the cause of death, and (5) providing a service to the referring physician by communicating findings, particularly as information to be used in genetic counseling and family planning.

Development and Organization of Program

One of the first hurdles in establishing an abortus-monitoring program is to establish an administrative procedure that cuts across but is compatible with the administrations of several clinical and basic science departments. The support of each department is vital to the efficient functioning of the program. When we set up the Teratology Unit, the chairmen of the participating departments were visited, the plans were discussed and advice was sought. Discussions were also held with the appropriate staff at hospitals outside the Ann Arbor area. These initial discussions served several purposes, such as securing departmental support, both in manpower and financing, and helping to refine the goals and procedures of the Unit in light of the available facilities and talents. In operational terms, it was agreed from the outset that all faculty investigators, from whatever department, who were concerned with the study of human embryonic and

fetal materials would be involved in the evaluations of abortuses and share with others the specific data generated by their individual investigations. The Teratology Unit serves as a central repository for these data and maintains a dossier for each specimen.

The University of Michigan Teratology Unit represents a logical blend of several developmental biology research programs, chiefly in the Departments of Anatomy, Pediatrics, Human Genetics, Obstetrics, Radiology, and Pathology. The co-directors represent the basic and clinical sciences, and principal investigators are from the departments listed above. In addition, input is made by scientists from our Center for Human Growth and Development, and individual investigators from other medical school departments and subsections participate occasionally. Collaborative arrangements have been made with the medical center's Antenatal Diagnostic (amniocentesis) Unit and Neonatal Intensive Care Unit to provide detailed anatomic evaluations of abortuses and selected infants dying in the perinatal period and to coordinate such other studies on these specimens as may be indicated. Prior to the establishment of this program investigators from many areas obtained fetal/embryonic tissues either through time-consuming personal contacts or most often by chance. The Teratology Unit now serves both as an abortus-monitoring service and a centralized collecting service from which materials are disseminated to multiple investigators.

Methods of Collection

Abortuses of any age or condition can be submitted for evaluation by a physician. In fact, our Teratology Unit encourages the submission of all human embryos and fetuses, whether "normal" or abnormal, along with any available family history and medical data on the pregnancy. In addition, the Unit evaluates a number of stillbirths and infants dying in the neonatal period and it cooperates with the Department of Pathology in the examination of infants and children dying with major malformations. In Michigan, the consent of the parents is legally required for the submission of any fetus estimated to be twenty weeks of gestational age or older. The consent form clearly authorizes eventual disposal, by cremation and burial, of the specimen through the Department of Anatomy, without charge to the parents.

Specimens received by the monitoring unit are processed quickly according to the condition of the specimen. Fresh and unfixed specimens obviously allow the greatest number of alternative pathways of developmental analysis. These specimens are generally received from local hospitals, within 15 minutes of our laboratory. Receipt of fresh specimens by the laboratory requires the active participation of the Unit's investigators. On notification of the actual or impending availability of a fresh specimen, one of the Unit's investigators goes directly to the delivery or operating room area to collect the specimen. This is especially important when

valuable material, such as therapeutic abortion of an embryo by hysterotomy, is involved. Arrangements to have one of us on-call, 24 hours a day, to the delivery/operating room have served to demonstrate the seriousness and credibility of the Unit's program. As a rule all specimens, fresh or not, are collected by a unit investigator and this provides an opportunity to advertise the work of the Unit and encourage submission of more specimens. By placing the burden of specimen collection on the monitoring unit, the only imposition on the already-busy delivery/operating room staff is usually a telephone call for which phone numbers are clearly posted.

The Teratology Unit urges that all specimens be sent to it regardless of the specimen's condition. This eliminates the need for delivery/operating room personnel to decide whether or not we can make use of a specimen, and ensures our receiving as much material as possible.

Embryos and fetuses mailed to the Unit are fixed in 10% formalin. Practicing physicians in Michigan who are interested in this program of monitoring human abortuses are urged to contact either of the Teratology Unit's two directors (ARB or MB) at the University of Michigan Medical School. A registry of contributing physicians is maintained, and they are provided with the necessary mailing materials.

One important aspect of a centralized abortus-monitoring program is documentation of the abortus' history. This information can come directly from the contributing physician or, in the case of our own hospitals, from direct examination of the mother's medical records by the Unit's physicians. Information gathered includes patient identification data, contributing physician, hospital, estimation of the abortus' age based on the date of the last normal menstrual period, date and time of delivery, problems during pregnancy, course and nature of labor, and family history, including the outcome of previous pregnancies. More detailed information can be obtained when it is needed.

Examination Procedures

Every specimen received is examined immediately by a member of the Unit. The specimen is identified, documented, and given an immediate, external examination including somatic measurements when possible. These measurements are weight, crown-rump and crown-heel lengths, foot length and other selected measurements of body proportions. Radiologic examination of fetuses may be done at this time or may be deferred to a more convenient time. The pathway that a specimen follows after the initial examination depends chiefly on whether the specimen is fresh or fixed, macerated or nonmacerated, and the immediate need for fetal tissues for investigative work. The determination of specimen quality and freshness is critical to much of the work done by our collaborating investigators. The criteria established by Shepard and co-workers (*2*) are as reasonable as any and are used by us to grade each abortus: *Grade I*—the

heart is beating or from gross inspection the material is expected to have prophase mitotic figures; *Grade II*—material without discoloration or collapse of the body cavities; *Grade III*—all material with distorted or discolored limbs, collapsed body cavities, and/or peeling of the skin.

Samples from specimens with fresh and viable tissues, may be removed for cytogenetic studies, biochemical/hormonal assay, and other studies and uses requiring fresh tissues. With grade I and II specimens, an autopsy is usually performed promptly, combining a detailed search for morphologic abnormalities with acquisition of data on normal organ growth. All tissues and organs not used in fresh-tissue studies are fixed for histologic study and/or storage for later retrieval and study. The autopsies are performed by a unit physician, and the findings are documented photographically when appropriate.

Our experience is that most fetuses that are spontaneously aborted and all that are aborted medically show some degree of maceration, often pronounced. Macerated specimens should and can be evaluated if care is taken to try to distinguish between malformation and distortion produced by autolysis. Our procedure is to fix macerated fetuses in formalin after the initial examination but before dissection. In most instances the degree of maceration prevents histologic examination of the tissues, but most gross anatomic malformations should be detectable.

Embryos received by the Unit are generally added to the extensive collection of serially-sectioned material maintained by the University of Michigan as the Patten Human Embryology Research Collection. This collection is open to the entire University community for the investigation of early human morphogenesis.

Feedback to Contributing Physicians

Contributing physicians can expect to receive a preliminary report citing gross observations made on the specimen soon after it is received by the Unit. This report includes not only the results of the external examination and autopsy but also an evaluation of growth and commentary on any serious discrepancies between fetal development and the stated gestational age. A more detailed report, based on gross, histologic, and investigative observations, follows the preliminary report when appropriate. It is our practice, in our hospitals, to have a copy of these reports filed in the mother's medical record so the information is readily available for genetic counseling and family planning purposes. For patients outside our hospitals, all communication is carried out through the referring physician.

Summary

It is our observation that there is a serious lack of objective data in many aspects of human developmental anatomy. This information is necessary to understand better the beginnings and correlates of such leading birth defects as clefts of the lip and palate. It is suggested that appropriate

research teams, capitalizing on recent technical advances and attitude changes regarding abortion, should begin to monitor systematically the products of all interrupted pregnancies. This report discusses our experiences and procedures in establishing an abortus-monitoring unit in a medical center setting. The organization and operation of our program depend heavily on the prevailing circumstances at our medical center, and are not intended to be regarded as the ultimate model. Instead, our experiences in this venture and those reported by other groups engaged in similar tasks have convinced us of the practicality and usefulness of such programs. We are certain that abortus-monitoring programs could and should be established at other medical centers and be tailored to local energies, facilities, and capabilities.

References

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