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Congenital Anomalies, 1960

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Congenital anomalies always will be present in the human race. They are an integral part of every living species. That they need to be present to the extent to which they are now found is by no means a foregone conclusion. Some methods are presently at hand to decrease the frequency of certain anomalies, while other factors, if uncontrolled, will cause a theoretical increase. The apparently relentless increase of population throughout the world will result in more anomalous children who will need diagnosis, treatment and care, but it is not a necessary corollary that the rate of mutations will also increase.

What is the present incidence of congenital anomalies? The answer to this question involves so many factors that no true answer is possible. What is meant by "congenital anomalies"? The derivation of the word "congenital" suggests that its use be confined to the time of generation or fertilization of the egg. This interpretation places great stress on genetic factors and little on environment, except for the biochemical and physical environment of the oocyte, spermatozoa, and fallopian tubes. Common usage dictates that the term "congenital" refers to "the time of birth." What is meant by "anomaly"? A dictionary definition, which represents the opinion of a cross-section of intelligent people, suggests "a departure from the normal." Thus, a caput succedaneum, or a fractured clavicle, at birth, is, strictly speaking, a congenital anomaly. The term "malformation" denotes a morphological anomaly and in this decade is too limited. Although chromosomal aberrations would now be included under this morphological term, the biochemical anomalies of enzyme systems, hemoglobin chains, haptoglobins and other proteins would necessarily be omitted.

At what period of life is the incidence figure desired? Almost nothing is known in human beings, as to the survival of every fertilized egg. The data of Hertig and Rock[1] are the best at present regarding the recovery of the product of conception after a known date of possible fertilization. Their figure of 30 per cent, for successful recovery of embryos two weeks after coitus in women undergoing hysterectomy, agrees well with other mammalian data. In another 30 per cent, the zygote or early embryo was apparently not viable. Abortion specimens should be examined with at least the same care as that expended on autopsies of neonatal deaths. The published data for morphological anomalies accompanying stillbirths of viable age or weight

seem quite low: 10.1 per cent according to Potter.[2] No published investigation has been made of biochemical or chromosomal anomalies in human stillbirths, a fertile field for research.

The series of almost 6000 infants and children reported by McIntosh *et al*[3] in 1954 affords the first clue to incidence of morphological anomalies found in an urban American population. They report that 43.2 per cent of the anomalies evident after six years of follow-up visits were diagnosed at birth. By the end of the first year, a total of 97.3 per cent of malformations had been diagnosed. In the study of Wallace *et al*,[4] their data show that 84 per cent of the anomalies occurring in 629 children who had died with congenital malformations, were diagnosed by the end of the first year. Many more studies of this type are needed, with the denominator population clearly defined.

For what population is the incidence of congenital anomalies being described? In Japan, Neel and Schull[5] ran into difficulties in determining the effect of acute radiation from the Hiroshima and Nagasaki experience because the baseline incidence of congenital anomalies in the Japanese people was unknown. They were surprised to find that this incidence in their control group was distinctly higher than in the United States. Careful epidemiological investigations by Penrose,[6] Stevenson,[7] Record and Edwards[8] and others in Great Britain and Ireland seem to indicate an especially high incidence of anencephaly in Ireland and of congenital dislocation of the hips in Birmingham. In another British study, the biochemical anomaly resulting in phenylketonuria has been found to stem from grandparents born in Ireland.[9] There are no data for the vast majority of population groups.

What degree of anomaly should be included? The slightly webbed toes of the Dionne quintuplets were of no significance to them but are singularly important to the geneticist. This leads to other questions. For whom or what discipline is the incidence figure requested? What time in an individual's life is being considered? How serious an effect is produced by the anomaly? What is the source of information regarding incidence?

The anatomic classifications of anomalies have long been existent and have been useful to a certain degree. Below are listed many other factors to be considered in classifying anomalies and relating them to estimates of incidence:

Effect of Anomaly
- Fatal
- Seriously disabling
- Moderately disabling
- Of little consequence
- Of no consequence

Time in Life of Individual
- 1st trimester of pregnancy
  - zygote
  - embryo
  - fetus
- 2nd trimester of pregnancy
- 3rd trimester of pregnancy
- Neonatal period (0-28 days)
- Infancy (28 days to 1 year)
- Childhood (1 year to 12 years)
- Adolescence (12 to 18 years)
- Adulthood (18 years and older)

Observer
- Patient
- Relatives of patient
- General practitioner
- Medical specialist
  - General surgeon
  - Gynecologist
  - Metabolic specialist
  - Neurologist
  - Obstetrician
  - Pathologist
  - Pediatric internist
  - Pediatric surgeon
  - Physiatrist
  - Psychiatrist
  - Plastic surgeon
  - Public health officer
- Anatomist
- Biochemist
- Dental specialist
- Geneticist
- Government organizations
  - National Office of Vital Statistics
  - U. S. Public Health Service
  - War Department
- Psychologist
- Public Health nurse
- Rehabilitation workers
- Social service workers
- Statisticians
- Veterinary specialist
- Voluntary health organizations

Source of Information

Autopsy
Clinical record
Hospital
Outpatient clinic
Private practice record
Patient
Patient's family
et cetera

Available incidence figures indicate that severely disabling anomalies which are often fatal are present in 0.9 to 3.1 per cent of live births,[10, 11] that there is approximately a 7.0 per cent incidence of anomalies of significance to the pediatrician in the first six years of life,[3] and if minor dermal, dental and skeletal anomalies are included, almost half the population have anomalies.

The causes for congenital anomalies are much more elusive than figures for incidence. The extremely complicated interrelation of genetics and environment impatiently awaits further interest, and further skills of able people with a background in genetics, medicine, epidemiology, biochemistry, radiobiology and even unnamed specialties. With present knowledge, it has been suggested that genetic influence is mainly responsible for congenital anomalies in 20 per cent of patients.[12] As suggested by Runner,[13] every anomaly involves a "genetically permissive" individual, and an environment which is "permissive." There can be no complete separation of environmental and genetic effects. Neel[12] has indicated that another 10 per cent or so of congenital anomalies in human beings are related to antenatal viral infections of the mother.

There is definite evidence of effects of rubella infection especially in the first eight weeks of pregnancy, which results in cataracts, deafness, or congenital heart lesions in the infant, depending on the week of infection. There is some evidence for fetal death following poliomyelitis in early pregnancy, but none to date for the production of congenital anomalies. Mumps also is under suspicion as being related to the production of human malformations. Data on the effect of the influenza virus are conflicting. While it is logical to associate viremia in the mother with adverse effects on the fetus, it is possible that toxic by-products of virus infection may be responsible for anomalies, even without proven viremia. At any rate, it is most likely that anomalies resulting from virus infection of the mother during early pregnancy are not heritable, and should be classified as environmental effects, with no stigma of possible future anomalies in siblings, nor in the next generation.

There is a remainder of 70 per cent of congenital anomalies for which a proper cause is not known. Chromosome aberrations and enzyme deficiencies may account for another ten per cent, but such investigations are only recently under way.

What can be done about serious anomalies found at birth, today? The first line of attack is to expect them, in certain conditions. A thorough prenatal history should reveal the presence of anomalies in previous pregnancies, while in many instances, such as viral infections early during the previous pregnancy, these anomalies have no known relation to an abnormal second pregnancy; other anomalies do have a small, but definite relation to their occurrence in subsequent pregnancies. Their chance of doing so depends on the type of inheritance, if it is known, *i.e.*, dominant, sex-linked recessive gene.[14] Although nothing definitive can be done for these conditions in the immediate postnatal period, a somewhat guarded prognosis on the part of the obstetrician and pediatrician before delivery may spare the parents the shock of a second abnormal pregnancy. A few conditions which are operable at birth have been reported in more than one child, *i.e.*, tracheoesophageal fistula. The pediatrician, knowing of a previous anomaly in the family, will look especially for the anomaly in the next child, and institute proper therapy promptly. There is on record[15] a report of a woman, who herself had a congenital heart lesion of the cyanotic type, and who had had two anencephalic children. Surgical repair of her heart lesion resulted in normal oxygenation. Her next child was entirely nor-

mal. Although not conclusive, this report fits in with experimental data of Ingalls and others.[16]

If polyhydramnios is present in the mother, anomalous children also should be expected. The high association of this condition with anomalies in the offspring has been known for years. Estimates of the association range from 4 to 59.5 per cent.[17, 18] The anomalies which are found, following pregnancy with polyhydramnios are associated with interruption of the normal circulation of amniotic fluid during the last trimester. A variable, but appreciable amount of amniotic fluid is actively swallowed by the fetus, absorbed from its upper intestinal tract, and returned to the placenta by the mesenteric and umbilical circulation. Any interruption of this flow may lead to polyhydramnios. Several deficiencies in the central nervous system have been cited by Prindle as a cause.[19] All infants with anencephaly involving a functionally absent medulla are delivered from mothers having polyhydramnios, while the mothers of those with an occipital bone, or remnants thereof, which have a minimally functioning medulla do not have polyhydramnios since the fetus can swallow amniotic fluid. Many of the mothers of infants with tracheo-esophageal fistula and esophageal atresia have polyhydramnios.[20] Indeed, the diameter of the fistula can be predicted from this symptom. All mothers of infants with complete intestinal obstruction, whether from atresia, volvulus, constriction by an annular pancreas, or peritoneal bands have polyhydramnios. One mother of an infant who had suffered antepartum perforation of the ileum with tremendous hydroperitoneum had polyhydramnios.[21] It is indeed true that in many cases of polyhydramnios, anomalies are not found in the infants at birth, but they are often missed because of inadequate examination. In pediatric teaching, emphasis should be placed on the importance of questioning whether there was excessive amniotic fluid in the mother, when a newborn child is admitted as an emergency, or an excessive gain of weight (over 25 pounds). If the mother is not available, the father accompanying the child often knows the correct answer, or better yet, a conversation with the obstetrician will reveal polyhydramnios in the mother before delivery. Thus, the diagnosis of the anomaly in the infant can quickly be narrowed to those in which reparative surgery will be lifesaving.

The second line of attack is to examine all newborn infants routinely in the first fifteen minutes for anomalies. Aside from the obvious gross malformations, many hidden anomalies can be diagnosed with nothing more than a stethoscope, a flashlight or laryngoscope and a catheter, by an inquisitive physician or nurse. The catheter is used to rule out choanal, esophageal, anal, and rectal atresia, and to measure the contents of the stomach. Over 25 cc should suggest partial or complete intestinal obstruction. Observation for appearance of bowel sounds, and rectal swab examination for squamous cells should lead to a definitive diagnosis. The stethosocpe is used to rule out the presence of diaphragmatic hernia, which causes a shift of the heart sounds away from the hernia, and absent respiratory sounds over the site of the hernia. The light is used to rule out cleft palate due to bony or soft tissue defects.

Surgery, as soon as the infant has recovered from the normal birth asphyxia, and possible additional antenatal asphyxia, is indicated in the following conditions: tracheo-esophageal atresia, perforation of the stomach, intestinal obstruction, anorectal atresia, omphalocoele, and diaphragmatic hernia.

Auscultation of the various heart sounds will not yield diagnostic information unless their site of maximum intensity is distinctly misplaced. Murmurs and abnormal sounds are not diagnostic. Angiocardiography and phonocardiography from within the paracardial blood vessels may give useful information, but at the present, these are technics demanding highly trained personnel. It is now known that there may be a flow of blood in either direction, or

both, for some days or weeks after birth through the ductus, without abnormality. Persistence of flow may be associated with other cardiac lesions. In some, maintenance of flow through the ductus is lifesaving. Ligation is fatal. A pediatric cardiorespiratory team is the best hope for this group of patients.

In a few newborn infants, surgery is imperative to prevent death. Tracheostomy for complete laryngeal stenosis or for choanal atresia is occasionally indicated. The latter condition may be treated successfully by inserting an infant pharyngeal airway, or pulling the tongue away from the posterior pharyngeal wall with a suture through the midline near the tip. Operations on the bony atresia itself are being developed.[22]

A third line of attack is presented by exciting new diagnostic opportunities during the first week of life. These are concerned with biochemical abnormalities. The mental deficiency accompanying phenylketonuria can be completely prevented by early diagnosis and appropriate therapy. The same is true for galactosemia. Rh incompatibility is the anomaly of blood groups most widely recognized and treated, but many others exist. Abnormal amounts of fetal hemoglobin, abnormal hemoglobin chains, abnormal haptoglobins and other serum proteins can be diagnosed by new methods of protein analysis. Routine blood grouping of the infant for the common ABO groups may point out incompatibilities with the parents so that kernicterus may be avoided by exchange transfusion, or even newer therapeutic methods.

Practical human genetics is in its infancy. The mapping of gene loci on human chromosomes is just beginning, while in mouse chromosomes, it is far advanced. The discovery of three polymorphic loci on human chromosomes may lead to unexpected diagnoses and thus appropriate treatment: (1) The Lutheran blood group and the ABO secretor loci, (2) the Rh locus and that for elliptocytosis, and (3) the ABO locus and that for the nail-patella syndrome, in which the finger and toenails are variously deformed, the patellae are abnormal, the iliac crest shows unusually bony growth and the radius and ulna are frequently fused at the proximal end.[23]

In the last four years, technics to determine chromosome abnormalities have been developed. Over 35 different conditions have already been identified in human beings. Many of these involve diagnosis of sex. It is not surprising that human populations appear to have as many intersex variations as other mammals. A smear of the buccal mucosa, suitably stained, can be used to identify the presence or absence of sex chromatin, or the diagnosis of double sex chromatin. Tissue cultures of minute samples of skin or bone marrow can be harvested, and the infant's karyotype defined in detail. Certain entities are already apparent. All mongols have chromatin material equivalent to 47 chromosomes. However, not all persons with 47 chromosomes are mongols. In general, individuals with any number of chromosomes other than the usual 46, are not normal. Most are mentally deficient.

What are the prospects for the future? To date, there is no suggestion as to what can be done about abnormal chromosomes. It is not known whether the extra chromosome in mongolism contains normal nucleic acid, or an abnormal type. Most individuals with such abnormal chromosomes are not fertile, but the record of seven marriages involving one or both partners who were mongols shows that 50 per cent of the offspring were mongols.[24] Cytologists at present are advancing knowledge of heredity by surgery of the cell, micrurgy. In lower forms of life, nuclei are being transplanted from one cell to another. The next step will be to transplant or delete chromosomes and observe the effect on the organism. Following this, anatomy and chemistry of genes and gene particles will have been defined, and their transplantation may be effected.

For several years, mammalian eggs after fertilization have been transferred to foster mothers (rabbits) and the rela-

tive effect of heredity and environment noted.[25] Many more such experiments in many species are needed to properly interpret the results.

Only recently, it has been reported[26] that it is possible to distinguish from each other spermatozoa which carry the male, and those which carry the female chromosomes. So far, it has not been possible to separate these two types of spermatozoa, but such a time is not far off.

All these seemingly unrelated experiments have a bearing on human abnormalities. Even more, the development of a true social conscience among human beings, and a real desire to improve future generations, is within our reach *now*.[27] The few, well-proven genetically determined diseases of serious consequence should not be permitted the chance for transmission. First cousins should not consider reproduction unless their genetic history is marked by absence of expression of delterious genes. Young married women should not have elective x-rays for diagnosis in the pelvic regions, except in the first two weeks after menstruation, for the very early embryo is especially sensitive to radiation. Young married males, who have had accidental doses of radiation to their testes, should not consider attempts at fertilization for at least two months. Recovery of spermatozoa from radiation damage occupies about that period of time, but at least it is known that spermatozoa can recover from such an assault.

Although chemotherapeutic control of viral infections has been relatively unsuccessful thus far, there is considerable chance for success along this line. Possibly, the intentional exposure of young women of high school age to various viruses may lead to diminution of such infections during early pregnancy.

There is a new awakening of interest in the future of human beings. There is thought as to the improvement in their mental and physical attributes. Means are at hand to diagnose and study deficiencies in these attributes. Many more persons trained in these special methods, and able to discover new methods are needed. Ten years from now, many of the current problems will be solved and new and different problems will present themselves, only to be met by better-trained, more experienced investigators. Pessimism is impermissible.

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