In the operating room or intensive care unit, we tend to take for granted the dependable quality of the fluids we administer to our patients. If the label on the bottle reads Baxter-Travenol, we know we have an extra margin of safety. It is a pleasure to thank them publicly for providing anesthesiologists with this peace of mind, a commodity often in short supply in the operating room. We thank them also for less tangible contributions, such as their support of lectureships and symposia.

I have been permitted to select a topic only remotely related to anesthesiology, though less so in pediatric surgery, in which the large majority of your patients have birth defects. There is little likelihood that this number of patients will decrease. Rather, it will almost surely increase. In a recent study at Johns Hopkins, the children of parents who themselves were operated on for congenital heart disease have been followed. Whereas the estimate of this condition in the general population was 0.3 per cent, those children who had one parent with a history of successful heart surgery in childhood had congenital heart lesions at the rate of 1.8 per cent, a six-fold increase. There was no apparent relationship between the type of heart defect in the parent and in the child.

In this particular category of congenital anomalies, the eternal, nagging problem of classification comes up. I personally think that the diagnosis patent ductus arteriosus should always be separated clearly from other cardiac diagnoses. It is not a developmental defect, unless accompanied by an aneurysm of the ductus, but a physiologic defect. Its continued patency is not the result of hereditary factors, nor of environmental effects before birth, but, in all probability, of environmental effects after birth.
Importance of Pharmacogenetics — Also related more closely to anesthesiology is the specialty of pharmacogenetics. Errors in the construction of protein molecules are as much birth defects as cleft lip or palate, which themselves probably occur because of molecular mistakes. After Garrod's prescient work at the turn of the last century, the saga of pseudocholinesterase aberration started pharmacogenetics on its merry way. Understanding of the relationship of barbiturates to acute porphyria followed shortly thereafter. G-G-PD deficiency was quickly identified as being related to primaquine sensitivity, intolerance to certain sulfa drugs and fava beans — even to the smoke arising from burning bean pods. A delightful essay by Louis Lasagna. “The Diseases Drugs Cause,” in the Summer, 1964, issue of Perspectives in Biology and Medicine is highly recommended. I think it likely that most drug reactions will be found due to some enzymatic quirk, often heritable in nature.

Back in 1960, shortly after I joined the research staff of the National Foundation-March of Dimes, I was coaxed by Dr. Edwin Gold to write an article, “Congenital Anomalies, 1960.” Its rereading gives me cause for both optimism and pessimism. At that time, the proposed structure of the DNA molecule had been before the public for 6 years, and for 4 years it was known that human cells contained 46 chromosomes, not 48. At scientific meetings, there was hot discussion about the transcription of the hereditary message via RNA to the formation of proteins. Was it a triplet or doublet code? Was it degenerate? Were there nonsense triplets? Was ribosomal RNA specific? These particular questions have all been answered.

It is a triplet code; it is degenerate; all amino acids are cycled by two or more triplets. There are no nonsense triplets. All 64 possible combinations of the four purine or pyrimidine bases have been assigned to specific amino acids or to “start” or “stop” positions in the reading of the DNA code. Ribosomal RNA is not specific. Even E. coli ribosomes can be made to make hemoglobin if fed the right RNA message. But, as expected, new questions have arisen in geometric proportions.

Jacob and Monod gave birth to a theory of genetic control involving regulator genes, repressors and derepressors, operator and structural genes, derived from their work with bacteria. It is a brilliant theory, which has given a great impetus to research in this field. Whether or not it applies to mammalian cells remains to be proven. Whitehouse recently has divided living organisms into two major divisions, “... a chromosomal kingdom, in which the DNA is not associated with basic protein and no nuclear membrane encloses the DNA (bacteria and blue-green algae),” while all the rest is “... a chromosomal kingdom in which the DNA is associated with basic protein and a nuclear membrane encloses the DNP except during cell division.” There is much discussion about extra-nuclear DNA, found in mitochondria, with a different nucleotide coding than chromosomal DNA.

The elusive hereditary particles of Mendel, named “genes” by Johannsen over 40 years later, have finally been translated into chemical terms. “It is estimated that a gene consists of about 1000 nucleotide pairs. The smallest known organism, the virus X174, which has a single helical DNA molecule,
has five genes or 5000 nucleotide pairs. The lambda virus has 50 genes, T2 phage 20,000 and Drosophila 500,000 genes on eight chromosomes, only 0.1 per cent of which have been mapped. In human beings with 46 chromosomes, no gene locus has definitely been mapped though a number of linkage groups have been discovered.

In 1960, I mentioned some 35 different human conditions in which chromosomal abnormalities had been identified. This number is now well over 100 and, in fact, is limited only by methods of chromosome study. The commonly used techniques of counting the total number of chromosomes, arranging them in order by size and ratio of short and long arms, and their ingestion of tritiated thymidine by autoradiography, are responsible for the increase in positive diagnoses but leave much to be desired. New techniques are needed to study human chromosomes, especially in meiosis. Electron microscopic photographs of the synaptical protein in meiotic chromosomes of corn (Mea zea) give hope that this technique will pay off with mammalian chromosome studies. Does one chromosome have one DNA molecule, or does it have many? There is evidence on both sides. Is the repressor substance indeed a histone, though nonspecific itself, attached to a specific repressor RNA?

Chromosome "Breaks" — Chromosome "breaks" are much under discussion, prompted by their discovery in leukocytes of people using LSD, and their offspring as well. The offspring, though only a small group are under study, seem to be doing well, without birth defects or learning disabilities. In the leukocytes of children recovering from rubella infection, chromosome breaks are frequently found. In fact, in 3 to 6 per cent of controls, such breaks are found. Are they really "breaks"? Tjio thinks not, if they are aligned. One strand of the DNA chain, though presently invisible, is probably intact and can reproduce the other strand without difficulty, as has been known for some time in the case of radiation effect on chromosomes. Only occasionally do inversions, translocations, or deletions occur. Chromosome breaks in leukocytes have been reported after the use of many common drugs, such as caffeine, aspirin, and tranquilizers, but as far as the genetic implications are concerned, chromosome breaks in meiotic cells must be studied. To date, only streptonigrin has been identified as a drug which causes meiotic chromosomal breaks in human oocytes.

It comes as no real surprise that the chromosome complement of fetal cells in a quarter to a half of successful cultures from spontaneous abortion specimens have been found to be abnormal. Trisomies of all seven autosomal groups have been found, as well as several triploid and tetraploid fetuses. It is a surprise that the most common sex chromosome aberration in abortion specimens is the deletion of one sex chromosome, a condition which is often compatible with life and even normal mentality. It is obvious in genetic counseling that it is important to obtain an accurate history of spontaneous abortions. Whenever possible, such specimens should be examined for chromosome analysis. Only about half of attempted cultures are presently successful, probably because of contamination and delay in reaching a cytogenetics laboratory.

Problems of Mongolism — Those working especially with sex chromosomes report an estimated incidence of sex chromosome anomalies to be as high as one in 200 births, or 0.5 per cent. Living but abnormal children have been identified with chromosomal errors in groups A, B, D, E, and G. Only one child has been found with a missing autosome, from group G. Trisomy of pair 21 is the most common error, estimated to occur once in 600 births (mongolism). The causes for this nondisjunction are probably multiple. Heredity plays only a very minor role, if any, unlike its role in families with a translocated 21 chromosome.

It has been noted from Australian evidence that mongolism occurs in neighborhoods and in epidemics. It is suggested that the births of mongoloid infants regularly follow — about 9 months later — epidemics of infectious hepatitis, as a result of maternal infection early in pregnancy or possibly just before conception. Four other studies in other parts of the world do not corroborate this idea. By 1959, a definite answer should be found, for there is at present an unusual amount of infectious hepatitis in the State of Victoria, Australia.

Another clue to the causes of mongolism has received reinforcement. In 1960, it was reported from Canada that the mothers of mongoloid children had a history of x-ray exposure to the abdomen before conception four and one-half times greater than their neighborhood controls. Such an experience was not found in the followup of women and
their infants exposed to the atom bombs in Hiroshima and Nagasaki. Recently a much larger series of families was examined in Baltimore in which it was found that fluoroscopy and radiotherapy were present seven and one-half times as often in mothers of mongoloid children. Also, there was a hint of evidence that a greater percentage of the fathers had been in radar work in military service. The obvious preventive measure suggested by these findings is to protect, whenever possible, the future germ cells from the effects of x-ray at any age, both in intrauterine and extruterine life for males and up to the age of genetic death in women.

Another theory for the cause of mongolism is related to the sexual habits of married couples. It is well known that mongoloid children are born much more often to women nearing the end of their reproductive life. A woman of 25 has about 1:2500 chance of giving birth to such a baby. At age 40, these odds are nearer 1:40 or 1:50. (On the hopeful side, a woman of 40 has a 98 per cent chance of not having a mongoloid baby). Studies of reproductive biology in mammals all agree that the sooner an egg is fertilized after ovulation, the better the quality of the product. The quality of the mammalian egg and possibly the sperm, too, begins to deteriorate after 24 to 36 hours and, by 48 hours, fertilization is not possible. Ideally, the egg should be received in an environment of fresh, capacitated sperm. A study of the habits of long-married couples shows that the frequency of intercourse, on the average, declines with the length of marriage. Prophylactic measures, if conception is truly desired, are obvious. One important question which has not yet been answered, either in human beings or subhuman primates, is “when is ovulation?” Hopefully, future research will hold the answer.

**Teratogenic Drugs** — Thalidomide is the most teratogenic drug ever discovered. Its availability to women of reproductive age has very properly been made impossible. There is no real evidence why women beyond menopausal age and men should not have access to it as a tranquilizer or sedative, but the unhappy habit of Americans of sharing prescriptions with one another indicates that the decision to remove it from the market was correct. The only other group of drugs which have been demonstrated to be occasionally teratogenic are the progestins, frequently given to mothers with bleeding in the first trimester. Over 200 instances of masculinization of the female fetus have been reported. Fortunately, the changes in the external genitalia can be corrected by plastic surgery. A new concern has arisen recently about the use of these hormones and related steroids. There are rumbles on both sides of the Atlantic that the steroids used for certain pregnancy tests may be teratogenic. Likewise, a break in the prescribed routine of taking contraceptive pills may result in abnormality if pregnancy occurs during the break.

The present prescription for a better-quality baby with respect to steroids is to stay faithfully with the routine prescribed for contraceptive pills; when conception is desired, to stay off the pills entirely, have intercourse every 24 hours from the 10th to 25th day after the beginning of the last menstrual period, and avoid pregnancy tests which involve the use of ingested or injected steroids.

There are very few prospective data about the habits of American women and their exposure to environmental teratogens. One teratologist considers that the teratogenic period in human pregnancy is the first 40 days, another suggests that it is 60 days. Originally, in the large Perinatal Study of the National Institute for Neurological Diseases and Blindness, it was intended that women would be admitted to the Study only if they were in the eighth week of pregnancy or earlier. Now that 60,000 couples are under study, it is found that fewer than one third entered in the first 3 months of pregnancy, or 90 days. There are almost no data about the first 40 to 60 days following conception.

Two other studies, one in New York City and one in Oakland, California, are in progress, but only prescription drugs are entered for analysis. It seems imperative to enlist a group of women who are planning to have children in a prospective study which will involve daily reporting of a number of parameters. Such a study is being planned by The National Foundation, which will be extended to a large group of couples if found to be feasible.

**Congenital Anomalies Not Remote from Anesthesiology Interests** — This subject of congenital anomalies is not so remote from anesthesiology in still another respect. No longer are birth defects thought of as conditions which are present and diagnosed only at birth. In over 57 per cent of the babies,
the condition is diagnosed long after the usual 48 hours after birth, when a birth certificate must be filed. Between 85 and 95 per cent of significant birth defects are diagnosed by the end of the first year of life. In the broader view of this field, many birth defects are "expressed" in adolescents and adults, many of whom come under your care. A recent paper surprisingly reported the occurrence of congenital pyloric stenosis in a man of 40 who had had gastrointestinal symptoms all his life.

Diabetes is probably the most common biochemical defect in man. One in four of us has one gene for diabetes, while one in 20 has two genes — one for each parent — and if we live long enough, we shall have this genetic defect expressed. Yet, this condition is a most complex one. Recent techniques show that juvenile diabetes is quite different from the middle-aged type. A true deficiency of insulin production seems to be present in the former, while hyperinsulinism may exist in the older age group. The anesthetic management may be quite different in these two types of diabetes.

Congenital cerebral aneurysm is the most common diagnosis in strokes occurring in young people. Polycystic kidneys and other urologic abnormalities, such as those produced by vascular aberrations, are frequent in adults. Intestinal obstruction from a variety of gastrointestinal anomalies, colonic polyposis, and diverticula are all evidences of late expression of hereditary conditions. The classic book, "The Mendelian Inheritance of Man," now in its second edition, catalogs 1487 inherited traits, many of which you are already treating as anesthesiologists.

Fortunately, there are many advances on the therapeutic front. Augmenting the State Crippled Children's Clinics, 100 Birth Defects Centers have been established by The National Foundation-March of Dimes, where specialists in many disciplines are concentrated. The associated medical specialties are represented in full force: physical therapists, medical social workers, occupational therapists, and clinical psychologists. Medical students and nurses are exposed to this interdisciplinary approach. The individual patient and his family are offered all these services at one visit. This great number of patients offers an opportunity to set up birth defects registries, special genetic and environmental studies, and a comparison of therapeutic measures.

This review has touched only on the high spots in the field of human birth defects. No mention has been made of what has been learned from the recent rubella epidemic. Its occurrence has led to the identification of the virus, positive identification of antibodies and, shortly, to the production of an effective vaccine which will protect that 10 to 15 per cent of young women still susceptible to infection from the rubella virus.

Neither has mention been made of the imminent eradication of erythroblastosis due to the Rh factor. Some 5000 deaths annually of liveborn infants, let alone many thousands of stillborn infants, will soon be averted by administration of a special vaccine to Rh-negative women with Rh-positive husbands at the time of the first delivery.

Many dozens of other immunologic defects, most of them fatal to the child who inherits them, are under study. Recently, two conferences on immunology have been held at Sanibel Island in Florida, sponsored by the United States Public Health Service and The National Foundation-March of Dimes.

You, as anesthesiologists, will, I am sure, keep abreast of the literature especially dealing with inborn errors of metabolism. You have my sympathy when you are called upon to determine someone "legally dead" for cardiac transplant. I trust your efforts to change the legal usage of "death" from cardiac arrest to neurologic arrest will be successful in the near future.

May I assure you of my continuing interest and great optimism in new developments in anesthesiology.