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INTERFERENCE WITH ORGANOGENESIS AND FETAL DEVELOPMENT

Hulda E. Thelander, M. D.

From the Child Development Center, Childrens Hospital, San Francisco, California, and the Department of Anatomy, University of California Medical Center, San Francisco, California

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H.E.Thelander M.D.

ABSTRACT

After years of clinical service to handicapped children, an overview of possible causes of congenital anomalies, seemed timely. It lead off with a review of the epidemiology of birth defects throughout the world and then continued with a study of known and assumed causes. These include genetic syndromes due to dominant and recessive genes and the possibility that some abnormal genes may be expressed only under certain adverse conditions. What else protects others? The age of the mother is associated with mongolism, but it seemed pertinent to also review evidence that the age of the father may be significant. In other species the aging of the ova and sperm has been incrimenated. Nutrition, contrary to popular opinion at present, does not seem to play a role in congenital anomalies although important to the well being of the mother and the weight of the infant as well as to the frequency of complications during delivery. Intrauterine accidents may occur, usually associated with abnormalities of the umbilical cord or in connection with multiple births. Immunity and rejection as in Rh incompatability is an intriguing subject that needs further study. The hazards of radiation, at present frequently aired, does not seem to be that dangerous to our health; there is no evidence that diagnostic X*Ray poses a hazard and even the exposure to the atomic Bomb in Japan, did not seem to increase the birth of defective infants except in pregnant women who were close ebough to the area to sustain visible lesions themselves. Infections have not been found to be as common a cause as feared after the German Measles discovery. Toxoplasmosis, cytomegalic inclusion disease and syphilis are injurious to the fetus but they are relatively rare conditions . The thalidamide tragedy resulted in extensive study of drugs and toxins, but again, with the possible exception of aminopterin, results indicate that most drugs are tolerated by the fetus. Extrapolation from animals to man, especially concerning the brain and intelligence, must be very gaurded. The human cortex is rather unique and evolution has provided exceptional protection for it.

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PREFACE

At the Child Development Center, San Francisco, the histories of children with handicaps were probed relentlessly for over 20 years in an attempt to discover the etiology. From this search, a number of histories emerged in which certain events became suspect. When more leisure came my way, I explored problems of this nature in greater depth, for those hidden bits of information which, when amassed and combined with other experiences, can give new clues. The trips to the moon were made possible not through new discoveries but by piecing together known information and applying it!

I selected the following areas for scrutiny:

Epidemiology - to determine the occurrence of birth defects in different countries in different races and in different times.

Genetics - a field which has been and is burgeoning rapidly. Dominant and recessive transmissions of defects are well documented, but subtler abnormalities require continuing investigation. Since all humans carry a number of defective genes, under what circumstances are they most apt to be expressed?

Aging of Parents and of the Ova and Sperm: There is an increased incidence of Down's syndrome in the older mother, and there are hints that paternal age may also be a deterrent to normal progeny. Does aging of the ova or sperm occur in humans? Are there "sick" ova and sperm?

Nutrition: While maternal nutrition has become a popular topic and there are frequent references to the role of malnutrition in congenital anomalies and in mental retardation, others are skeptical.

Intrauterine Accidents: Strangulation by the umbilical cord has been suspected in some infants. Could this and other intrauterine accidents account for some anomalies?

Immunity and Rejection: Transplantation of organs has accelerated research in the field of immunity and rejection of foreign tissues. What protects the fetus from rejection by the mother? Can it occur?

Teratogenesis: Atomic radiation as well as the use of diagnostic x-ray also raises the possibility of radiation as a cause of birth defects. The rubella epidemic in Australia and the thalidomide tragedy in Europe focused attention on the role of infection, drugs and toxins. What protects us? Why didn't all mothers exposed to thalidomide or to rubella produce defective progeny?

Multiple Births: In the Child Development Center the incidence of defects in one or both twins seemed unduly high, so that the hazards associated with multiple births seemed timely for review.

Dermatoglyphics and the Occult: What is the significance of stigmata, dermatoglyphics, head size and other minor abnormalities?

Rewards and perils of extrapolation from animals to man: Are we cautious enough or sometimes too cautious in our interpretation of research on animals as it applies to man?

EPIDEMIOLOGY

A glance through the literature on birth defects is sufficient for one to apprehend the tremendous difficulties which can be encountered in trying to make a meaningful survey of the size and complexity of the problem throughout the world. Two studies were conducted almost simultaneously on the worldwide occurrence of birth defects: by Stevenson et al (1966) for the World Health Organization (WHO) and by W. P. Kennedy (1967). In addition, an intensive study of pregnancy wastage was conducted by Bierman (1963) and staff in Kauai, Hawaii, who not only had a follow-up after 2 years, but again at 10 years (Werner et al, 1971) and made further contributions on the recording of these defects on birth records.

Table I lists the countries or areas covered in the two major reports. Both comment on the difficulties of obtaining uniform interpretation of defects.

The WHO study was completed between 1961 and 1964, and included 24 hospitals in 16 countries, 421,781 pregnancies comprising 416,695 single births, 5,022 sets of twins, 65 sets of triplets and 1 set of quadruplets. The ratio of multiple births to single births followed Hellin's Law of 1895, i.e., single:twins approximately that of twins:triplets and triplets:quadruplets--1.24, 1.26, 1.59, respectively. In single births, the summed frequency of all major malformations was 12.7/1,000 total births; the stillbirth rate was 24.2/1,000, and the death rate in hospitals was 16/1,000. The crude frequency of all malformations was a mean of 12.7/1,000 with a range from 3.1 to 22/5/1,000 (1.5 to 2 times as many were expected to be discovered by 5 years of age).

TABLE I

Population Studies in Various Countries and Areas of the World

World Health Organization

Australia - 2
Brazil, Sao Paolo
Chile, Santiago
Colombia, Bogota, Medellin
Czechoslovakia, 6 hospitals
Hong Kong
India, Bombay, Calcutta
Malaysia, Kuala Lumpur, Singapore
Mexico, 2 hospitals
North Ireland, Belfast
Panama City
Philippines, Manila
South Africa, Cape Town, Pretoria, Johannesburg
Spain, Madrid
United Arab Republic, Alexandria
Yugoslavia, Zagreb, Ljubyana

National Foundation (Kennedy)

Britain alone
Europe, less Germany
Germany
USA and Canada
Other countries

Bierman

Hawaii

The report cited mongolism (Down's syndrome) as the most common defect, with possibly a million affected in the world. Neural tube defects contributed the next largest number of permanent handicaps and pregnancy wastage. Congenital heart disease (6%), talipes (21%) and congenital hip dislocation (2%) accounted for almost 30% of all malformations; when these are excluded, there was less variation from Center to Center--a variation as great as 6 to 54%.

The WHO report also noted that some Centers recorded under "major" defects such conditions as phimosis and tongue-tie, although at times, classification was reportedly difficult, e.g., between umbilical hernia and exomphalos. (Should a skin blemish be considered major if it results in severe emotional disturbance?)

Another concern was the cut-off point in the age of the fetus. The incidence of anomalies in abortuses is high; if these are included, the incidence rises. In the WHO study the cut-off date was the 28th week of pregnancy. However, the upper cut-off point is also important; anomalies of the kidneys, heart, or even of the gut may not be apparent until some time after birth, and may go unrecognized for years or be discovered only at autopsy.

Kennedy defines epidemiology as "the study of the distribution and determinants of disease prevalence". He repeats the definition of Wacker (1963) as being a "realistic one", e.g., "any gross developmental defect apparent on inspection at the time of birth or within the first few weeks of life." Wacker's study involved 296 cases which occurred in a 10-year

period at Mt. Sinai Hospital in Chicago.

Technological advances have made it possible to detect metabolic abnormalities early, such as phenylketonuria (PKU) but defects of internal organs may not be discovered until much later, when disease symptoms call for x-ray and/or other studies of the organs. Minor congenital anomalies may be the antecedents or precursors of later diseases, or indicators of a genetic defect that may be more fully expressed in descendents.

Kennedy observed that often the data are reported as "significant anomalies", "major malformations", "live births only","single births only", "birth weights over 500 grams", etc. Other inconsistencies occur when reports are made on branchial sinuses, but do not mention the ears. In countries where home deliveries are common, defects may not even be reported; furthermore, the pathological pregnancies are most apt to be hospitalized, so that the figures for anomalies become increased on hospital records over those of the population at large.

Kennedy's review was published in 1967, and covered 20 million births (Table II). The extensive Tables in this report show a variation in incidence of malformations from 0.27 to 9.41%. The low figure is from Austria and represents only the major cases or, as reported, "...visible without special examination"; the high figure is from an intensive study in San Francisco by Yerushalmy (1965) on 7,447 single white births. The Kennedy study concluded that not less than 2% of all births have some degree of anomaly.

Table II

TABLE II

Total % of Malformations by Region*

Area	% malformations
Britain and Eire	1.55
Europe, excluding Germany	0.77
Germany	0.98
United States and Canada	1.24
Other countries	1.24

* Kennedy, 1967

Regardless of the limitations and difficulties of these studies, the authors illuminated several facets of importance for future work, such as the inconsistencies of diagnostic criteria, the irregularities of reporting, the importance of follow-up studies, and the need for more detailed knowledge of prior histories--including abortions, stillbirths, etc.

Bierman's series (1963) covered between 2,000 and 3,000 births, with an intensive study of 1,922 single live births, with a follow-up study after 2 years, and again after 10 years (Werner et al, 1971). Bierman found that of 10 easily recognized abnormalities, only 4 were recorded on birth certificates and only 8 on the hospital chart. Bierman used 3 categories: minor abnormalities or defects which were very slight and required no therapy and would not affect development, defects that were easily remedied and had no sequelae, and long term defects (3.5% in her series).

Davis and Potter (1957) reported on lethal cases only, and found an incidence of 6.73% for stillbirths and liveborn; their study included all malformations. Another high figure was that of McIntosh et al in New York (1954), e.g., 7.26% for liveborn, stillborn and neonatal deaths; Wulf et al (1966) from Vermont reported 13.40% for 1,775 cases in a 12-year follow-up.

In all studies, birth certificates yielded the least information; hospital records gave better information but varied markedly from one hospital to another. In those Centers in which studies were being conducted, recording was much better than in others. Kennedy noted that in some the figure for anomalies ran as low as

0.15%, in others it was 1.26%, and where research was being conducted it might rise to 4.5% (this figure compares more nearly with Bierman's, although hers was in a select group and might be expected to be somewhat lower than average).

At certain times in history there has been an increase in a particular type or in the number of defects in a certain locale. Such an example is found in the increase in the number of cases of phocomelia on the European continent (Lejeune, 1970), which was later discovered to be due to the use of thalidomide by pregnant women; another occurrence was after an epidemic of rubella in Australia (Gregg, 1942). Many years prior to this, the Danes had noted that the importation curve for pyramidon was similar to the increase of aplastic anemia in the country, and suggested a relationship (personal communication). After these tragedies, Public Health personnel were more alert to these coincidences and urged more conscientious reporting of birth defects.

Racial variations: The WHO report also emphasizes the large contribution of neural tube defects to pregnancy wastage and/or permanent crippling; in some areas, they account for half the deaths due to congenital anomalies. Anencephalus is relatively uncommon in people of African origin; in Pretoria, the incidence in Bantu mothers is 0.5/1,000, with a similar low incidence suggested from East and West Africa. Kampala reports an incidence of only 0.41/1,000. In contrast, anencephaly in Indian mothers of Bombay is high; the incidence is also high in Fiji, where one half the population is Indian--for native Fijians it is only

0.33/1,000 but that of the Indians is 1.2/1,000. In Singapore, the figure is 6.5/1,000 for Sikhs and only 0.77/1,000 for all births. In Punjab, where the Sikhs originate, the ratio is 3.96/1,000 to 2.12/1,000 among the Hindus. Belfast and Alexandria also have a high incidence of anencephaly and neural tube defects.

Hydrocephalus, and hydrocephalus with spina bifida, are lower in incidence than anencephaly--0.87/1,000, with less variation in the different countries. The incidence is highest in Belfast (2.87/1,000) and in Alexandria (2.57/1,000). In 2 Melbourne hospitals, the figures were 1.96 and 1.89/1,000.

In contrast, the incidence of polydactylism, syndactylism and other hand anomalies is high among Africans. Abnormalities of fingers is about twice as common as of toes, with variations from a mere dimple to extra complete digits. The incidence of this anomaly is also high among the Chinese. In Hong Kong, it is 91/1,000 and, in a survey in Singapore, 19 of 20 cases had Chinese mothers. In Pretoria the incidence was 4.39/1,000--all in Bantus; in Sao Paolo, Brazil, among a population with a high African contribution, it was 2.63/1,000. As can be observed, when neural tube defects and polydactylism are omitted from the statistics, the variation in different populations of other defects is not very great.

Bierman's study in Hawaii involved a population representing Japanese, Caucasians, Filipinos, Hawaiians and mixed Hawaiian-Chinese, in that order of frequency. The study emphasized the increase in numbers of defects found in follow-up studies--in ear canal anomalies and other less conspicuous defects

only 5 of 21 were recorded on birth certificates, private physicians had added 37, and the special follow-up examination brought 75 more to light. The study also noted that cases of mental retardation not associated with gross structural defects were often detected late--in part determined by the degree of retardation, and the experience of parents. Some anomalies escape identification until the children enter school. Subtle abnormalities, such as dyslexia, apraxia, etc., likewise usually escape detection until the school period. A careful history of the pregnancy, ethnic background, and family traits help to alert the physician to the child at risk.

Consanguinity: Much has been written about the influence of consanguinity on birth defects. Consanguinous marriages have been relatively frequent in Japan and after the atomic bomb explosion several studies of birth defects in the Japanese population were made by Neel et al (1953). This work was sponsored by the Atomic Bomb Casualty Commission, Field Agency of the National Academy of Science, National Research Council of the United States, and the National Institute of Health of Japan. Consanguinous marriages did not differ significantly from non-consanguinous with respect to economic level, but they did differ with regard to maternal age, parity, paternal age and the frequency of therapeutic abortions. Inbreeding increased the frequency of malformations; also, the defects were often multiple and complex, without necessarily representing any known "syndrome". No effect on sex ratio was noted. In the major cities, consanguinous marriages were less frequent than formerly.

Schull (1958) in his study of consanguinity in the Japanese population, found similar results. There appeared to be no deleterious effects on fertility or pregnancy wastage prior to birth, but the infants carried to term showed a higher incidence of major birth defects, and infant mortality was higher.

A study by Slatis et al (1958) on consanguinous marriages in the Chicago area in the United States likewise found a greater frequency of abnormalities and a higher death rate in their progeny.

This brief review of the epidemiology of birth defects in various parts of the world, among various races of mankind and in consanguinous relationships, points up the importance of ethnic histories in determining the causes of abnormalities in the human species. The cliche that the cause of defects is unknown is due largely to faulty methods in taking medical histories. The outcome may seem inevitable when the problem is approached from the point of view that something went wrong with organogenesis during early embryonal life or during fetal development, or at the time of delivery, or if the genetic background showed evidence of abnormalities. A more basic question may arise: what protects the fetus under similar conditions in other pregnancies?

In the United States, particularly with its heterogeneous population and marriages of diverse races, such as blacks with whites, blacks with American Indians or Filipinos, it is important and also interesting to study the ethnic background of peoples.

It is estimated that the American Negro is 22% white. A visitor from South Africa recently commented that the Blacks in America resembled the whites except for a darker shade of skin and did not look like their African kin. The history of a child with spina bifida revealed a Welsh heritage on both the maternal and paternal sides of the family. Thus, the ethnic background is important.

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GENETICS

Some 24,000 genes on the various loci of the chromosomes determine the basic inheritance of humans (Snyder, 1955). Interest and understanding of this ultramicroscopic world has been greatly enhanced by the perfection of the technics of tissue culture and visualization by the electronmicroscope. The report of Lejeune et al (1959) of 47 chromosomes in individuals with Down's syndrome spurred research in the field, the momentum of which has not yet abated. The book, "Human Afflictions and Chromosomal Aberrations" by Turpin and Lejeune (1969), with its 71 pages of references, attests to the importance of this breakthrough in our knowledge of inheritance.

It is presumed that all humans have a number of defective genes. The critical site of these, their expressivity, their penetration, as well as their numbers,constitute the blue print for individual design. The pattern may be altered, however, by the intrusion of deterrent agents during the period of organogenesis. Diseases due to dominant and also to first degree recessive genes have and continue to be studied in many medical centers. Less expressive genes are more difficult to elucidate, but careful histories, with the full cooperation of family members, usually reveal the interaction of heredity and environmental agents in the production of defects.

Although the acceptance of the handicapped and retarded has changed dramatically the past 15 years, there still exists the tendency to de-emphasize the occurrence of a defective

child in the family background, or else to rationalize it on the basis of perinatal accidents that might have been prevented. The constant and nagging question brought up in these studies is: "What protects some individuals under like conditions?"

Why did 80 per cent of mothers who took thalidomide during the critical period of organogenesis have normal babies? Why did many fetuses exposed to rubella during the same critical period escape its consequences? Scientists like to equate cause and effect but the human embryo, although remarkably well protected during organogenesis, is a fabulously intricate organism. The marvel is that so many proceed to normal development under seemingly extreme and adverse conditions.

As we go down the scale of animal life the wastage increases, as observed in insects, fish, rats, guinea pigs and even in primates. Therefore, the protection of the human embryo must reside in the genes. An interesting study might be the application of our knowledge in genetics and body chemistry, especially in enzymology (by electrophoresis), to gerontology. Past history reveals that in all ages, in all cultures, and under all types of adverse conditions well functioning individuals can survive to extreme old age: Titian continued to paint at age 99; in more recent times, Winston Churchill lived to 91, Herbert Hoover and Albert Schweitzer both to 90 years. Every country has reported authenticated centenarians.

In animal husbandry (National Academy of Science Report #1685), economics has dictated the necessity for great care in selection and breeding for specific ends, e.g., for milk, etc.

It is tempting to extrapolate from studies of animals to man. Although many clues may be suggested by them, it is also revealing and disconcerting to find extreme variations even between different breeds of the same species. Homo sapiens is unique in that he has the most significant development of faculties needed to evolve an intricate mechanism of protection and survival, such as judgment, discrimination and creativity.

An example of such protection is found in the studies of the role of nutrition. Although poor nutrition has a detrimental effect on the growth of the fetus in the latter part of pregnancy, studies have failed to reveal a teratogenic effect on the embryo. The starving mother seems capable of extracting the necessities for the early differentiation of the embryo which is not afforded in smaller animals. Even after birth, mother's milk gives protection to the young; when such feeding is discontinued, nutritional diseases (such as kwashiorkor) can develop quickly. Of special importance to man is the survival of the central nervous system which may, like the kidneys, be endowed with a sufficient surplus of cells to meet the contingency of starvation, except in extreme cases.

The mystery in human reproduction probably lies in the phenomenon of protection against maldevelopment, not in its occasional occurrence. Only the magic of billions of years of evolution can explain it. If we could view the species more objectively and train our young to view reproduction with greater awe and reverence, evolution might be helped instead of deterred

in the continuing process.

In taking a patient history it is important to establish good rapport with the family members and to have a genuine interest in their welfare. When such a relationship exists, it is remarkable what information can come to light. The study of the First Arch syndrome and cleft lip and palate are examples of how the interplay of heredity and environment can be revealed in the history of the production of anomalies.

First Arch Syndrome: At the Child Development Center at Children's Hospital in San Francisco, we observed 4 children with variations of the First Arch Syndrome--2 of them had the characteristic pattern of involvement of the ear (with only remnants of the pinna) and the mandible (with marked asymmetry of the face), but no other bodily anomalies. One child had only ear involvement with unilateral deafness, the other had mandibular involvement without the ear anomaly. The children with the mandibular deformity were referred to Dr. Egil Harvold for therapy, who later asked me to review his series of cases. A brief summary of the findings follows.

Though the past and pregnancy histories of the families were not always well-recalled after the lapse of years, and sources of information were different, of the 16 cases seen in the clinic, 9 were males and 7 females, ranging in age from 8 to 27 years. All were born in the United States, except for 1 boy who was born of American parents residing in Europe at the time. The ethnic representation is found in Table III.

Table III

TABLE III

ETHNIC REPRESENTATION OF CASES WITH FIRST ARCH SYNDROME

Caucasian	11
Scotch-English	
Armenian	
French	
Spanish	
Portuguese	
American Indian	4
Japanese-American-Indian	1
Total No. Cases	16

Two of the children were illegitimate; 1 was in a foster home; 1 young man was in the military service; and the rest were in their own homes. One was an only child, but the rest came from families with 1 to 7 siblings. One was a twin (the twin was normal). Mothers' ages at the time of birth of the affected children varied from 17 to 34 years, with most in their 20's (this would tend to eliminate late maternal age as a pertinent factor). The fathers' ages ranged from 23 to 40 years (age as a factor could also be eliminated on the paternal side).

The Rh factor seemed very unreliable in the history, but a negative Rh probably would have been remembered, especially in families with more than 1 child. Half of the fathers and half of the mothers thought they were Rh-positive.

The pregnancy histories were not well remembered either and, on first questioning, were usually described as "not unusual".

In my experience, mothers tended to be rather stoical about their pregnancies, taking considerable pathology for granted as being a part of them. When direct and pointed questions were asked, however, they revealed such pertinent facts as severe vomiting during the first trimester, for which an unknown medication was given; severe viral disease; pneumonia during the first 8 weeks of pregnancy and an x-ray at the time, without recollection of whether drugs were given; cortisone for a skin condition, which was discontinued as soon as pregnancy was known; ingestion of preludin for reducing; "pills" for

reducing, without knowing the content; heavy smoking; emotional upset during the entire pregnancy by the mother of an illegitimate child.

The deliveries were not remarkable. The twin in the group weighed 4 pounds and only one other child had a somewhat low birth weight (5 pounds 7 ounces); one weighed 10 pounds.

In contrast to the above normalcy, the past-pregnancy histories were rather startling: 6 had miscarriages (1 had 2); 2 had stillbirths. Two families had a history of twins in the family background--one on both sides of the family.

Family histories also revealed other pertinent information. On the maternal side there was a report of an uncle and a cousin with club feet; on the paternal side, an uncle with a cleft palate, an aunt with a branchial cleft, and 2 other histories of branchial cysts. In one family there was a nephew with mental retardation and another with epilepsy. In the families with other syndromes, 3 of 7 brothers had bone defects.

Associated defects were not common! Hearing loss in the affected ear was usual but was part of the total pathology in the fully expressed syndrome. One child had a cleft palate; 1 had a large pigmented mole over a large part of the arm; 1 had had surgery for strabismus; 2 wore glasses. All had intelligence quotients within the normal range, although 2 were borderline. In only 2, the mandibular deformity was part of the bony deformity manifest elsewhere in the body, which had been diagnosed as "pseudoarthrosis".

The First Arch Syndrome appears to have a genetic basis. The pregnancy histories, aside from the proband, showed a high incidence of abortions, miscarriages and stillbirths. The incidence of anomalies in the family histories was also high and their expression may have been favored by the events of pregnancy in some cases.

Cleft Lip and Palate in the United States--a special study: In 1963, the Dental Health Center of the U.S.Public Health Service began its study of cleft lip and palate at its headquarters in the Presidio of San Francisco, with Sylvia Hay as Director. A preliminary study of live births recorded in 4 States between 1956 and 1960 was published in 1964 (Greene et al), which included 4,451 babies with cleft lip and palate, with a matched control group. After this preliminary work, a larger study was conducted in 29 States, with 2 cities enlisted. While birth certificates did not record all birth deformities, even when these were as evident as clefts, the records nevertheless offered a large number of cases for study at minimal cost and many items not well documented previously could now be analyzed.

In addition, the inaccuracies of birth records could be studied by utilizing hospital records, death certificates and Crippled Childrens' Services (CCS) records (since many of these children had medical repair under CCS programs). The pathological condition of cleft lip and palate was divided into 3 categories: cleft lip and cleft palate, cleft lip alone, and cleft palate alone (which was recognized as a separate entity with epidemiological characteristics which differed from the other two). At the cut-off date in July 1964, there were 18,234 records of

malformed babies and 19,654 controls available for study, representing 1,965,400 live births. Available data included race, age of parents, sex of the babies, seasonal and regional variations, birth weight, length of gestation, parity and occupation of the father. These factors were all analyzed.

There was a racial variation--approximately 85% of the malformed babies and the controls were born to white mothers, but 93% with clefts were born to white mothers. In contrast, only 45% of the babies with polydactyly were white, following the pattern reported in the worldwide studies.

More clefts of the lip occurred in males, but more clefts of the palate only were in females. Cleft palate by itself, in male and female, was associated with other defects--most often with a syndrome, e.g., Pierre Robin. Combined types were mostly in males.

In the 4-State study of Hay (1967), there was a relationship between both maternal and paternal age in all types of clefts, except cleft lip only. Other studies with clefts and with other malformations (notably mongolism) revealed a significant relationship between advancing maternal age and mongolism. There was also a relationship between clefts and paternal age, when the maternal age was kept constant (see LeGros, 1964 on teratospermia and Penrose (1955) on parental age and mutations).

There were 1.2 malformations of all kinds per malformed baby. Babies born with clefts showed the following incidence of accompanying defects: total clefts 16.5%, cleft lip alone

8.2%, cleft lip and palate 13.9%, and cleft palate alone 27.3%. The following defects were reported with the greatest frequency: defects of the eyes (anophthalmus, microphthalmus, congenital cataracts), micrognathia, choanal atresia and other nasal deformities. Most defects involved the head. When cleft palate was found as a part of a syndrome, other anomalies appeared more frequently.

A more intensive study of types was reported by Mackeprang and Hay (1971) who studied the distribution of deaths by cause. Of 347 deaths in children with clefts, 19% were attributed to congenital heart disease. Information from both birth and death certificates showed that 492 (27%) born with a cleft had associated congenital heart disease. Children born with isolated cleft palate or Pierre Robin syndrome had the highest death rates. There was a higher death rate for females than males for clefts involving the lip, and a higher rate for males with isolated clefts and the Pierre Robin syndrome. Females had a higher death rate associated with congenital heart disease than males with all types, except the Pierre Robin syndrome.

While the studies on regional variation are not yet completed, preliminary findings show an East-West gradient. It is proposed that, at least for non-whites, this may be due to ethnic differences--in the East there is a higher proportion of blacks and in the West a higher proportion of Orientals. A variation would thus be expected, since clefts are infrequent in blacks and common in Orientals.

The first reports do not indicate any seasonal variation. CCS from 26 States reported a total of 1,039 children born with clefts in 1963; of these, 231 were not reported on birth certificates (22% under-reporting). Isolated cleft palate was least well-reported. Conversely, 77.8% of CCS cases were reported on the birth certificates--combined cleft lip and palate 75.8%, and cleft palate alone 65.5%. The over-all unadjusted rate of clefts was 105/100,000 live births, with a range from 64 to 186; the over-all adjusted rate was 128/100,000 live births.

At a meeting in Bethesda, Maryland, to review the question of genetics in the inheritance of cleft lip and palate, attended by 14 experts in the field, Fraser (1970) reported the following:

Multiple factors are often involved: single mutant genes, chromosomal aberrations and environmental agents. There are 50 recognized syndromes, each one rare, which include cleft lip and/or palate; 60% of these are manifestations of mutant genes (14 autosomal dominant, 13 autosomal recessive, 3 X-linked); 40% do not seem to be familial. While specific environmental agents are not often implicated, cleft lip or palate occurred occasionally with both thalidomide and with rubella. Chromosomal aberrations were found with Trisomy D and E and in XXXXY. It is estimated that less than 3% represent a syndrome. It is recognized that isolated cleft palate is different from cleft lip alone or from cleft lip with cleft palate. Family frequencies differ and there is a sex difference.

There is less involvement among blacks, with a higher incidence in caucasians and Orientals. Males are more often affected than females but in cleft palate alone more females are involved. The cleft lip is involved in two-thirds of the cases, with bilateral cleft lip the palate is involved in 86%; and with unilateral cleft lip 68% have a cleft palate.

Environmental factors seem to have no relationship, nor do social class, season or age.

The relationship between population frequency and relatives is more like some other conditions, notably pyloric stenosis, situs inversus and atrial defects. There is a rapid decrease in frequency, with a decreasing degree of relationship--half, half, and one-eighth for first and second degree relationship. The drop in frequency between first and second degree relationship is greater than between second and third degree. (The risk for relatives versus population incidence needs further study.) There is a higher incidence in both of monozygotic twins but more data are required. If the defect in twins is not of the same degree, the twins are often listed as non-identical. The risk of recurrence is greatly increased after two affected children and varies with the sex of the proband. First degree relatives have a higher risk if the proband is a female, whether for both cleft lip and palate or cleft palate alone. This risk varies also with the severity of the defect in proband. Increased frequency of microforms in relatives is significant. These are hard to

define but include bifid uvula, vocal incompetence, suggestion of cleft lip, asymmetry, etc.

Developmental instability, other anomalies, stigmata, and asymmetries, were often found. The timing of events as to failure of meeting and fusion of tissues seems to vary in different individuals. Consanguinity appears to be a factor but more data are needed. Maternal pathology may include such factors as threatened abortion, severe vomiting, bleeding, toxemia, etc.

Future studies might profitably be directed toward understanding developmental variations and thresholds. An important stage occurs when palatal shelves become horizontal above the tongue and reach each other. Some factors which may contribute to this movement are head width, tongue size, tongue mobility, reduced mandible size, shelf width. The parents of these children have been noted to have large bizygotic distances, flat maxillae, thinner upper lip, etc.

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PARENTAL AGE AND CONGENITAL ANOMALIES

The reproductive period of women is limited. It is generally assumed, and studies tend to confirm this, that within this span there is an optimum time for pregnancy with an increase in problems at both ends of the spectrum. The length of the reproductive period varies considerably in different individuals, and statistics indicate that the duration may have changed even in the last decades.

Tanner (1962) presents a graph of the age of menarche
Fig.1 (Fig. 1) in different countries. In Norway in 1840, apparently the earliest record, the age was 17 years; in the United States, in 1900, it occurred between 14 and 15 years. In the tropical climates menarche starts earlier, but the trend in all countries seems to have stabilized downward in the past 10 to 15 years. This has been credited to temperature changes and to improved nutrition. Recent studies (Behrman and Hsia, 1969) on the effect of light on the metabolism of bilirubin raise the question of the possible effect of both heat and light in the northern climates (with easy availability and cheap lighting with electricity). Even technology deserves some praise in this century with its severe critics!

The time of onset of menarche varies considerably, even now. In the study of about 200 teenage pregnancies at Children's Hospital in San Francisco (John Piel ~~et al~~ & Weber et al, unpublished), the
Table IV stated age of onset varied from 7 to 16 years. Fifteen gave

TABLE IV. AGE OF MENARCHE and TIME OF PREGNANCY.

Age in Years	No. Cases	Interval Yrs.	No. Cases.
7	I	1	6
8	0	2	17
9	I	3	26
10	16	4	44
11	31	5	48
12	57	6	42
13	44		
14	22		
15	8		
16	2		

Mean 12.3

Webb, Gilbert, A., Briggs, Catherine, and Brown, Richard C.: A Comprohensive Adolescent Maternity Program in a Community Hospital. American Journal of Obstetrics and Gynecology. Vol. 113, No. 4, pp. 511-523, June 15, 1972.

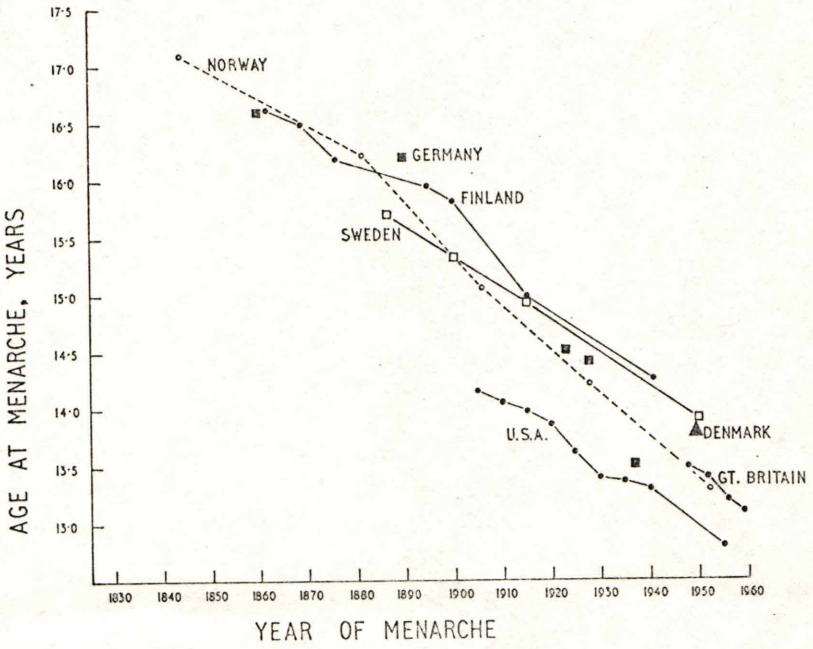

FIG. 31. Secular trend in age at menarche 1830-1960. Sources of data as follows:
Finland: 1862-1915, hospital patients Helsinki, from Malmio (1919) and Vara (1943); 1941, medical practice and health visitor inquiries, all Finland, age at interrogation 17 to 27 only, from Simell (1952).
Sweden: 1886-1915 hospital patients, Lund and Stockholm, from Essen-Möller (quoted in Lenner, 1944), Lundh (1925), Samuelson (1942) and Lenner (1944) (hospital data of last two pooled for value at 1915); 1950, schoolchildren, estimated from data of Romanus (1952).
Norway: 1844-81, from Backman (1948); 1907 Oslo hospital patients, from Skerlj (1939); 1928-52 Oslo schoolchildren, data of Schiötz (1930), and Kiil (1953) fitted by probits.
Germany: 1860-1928 hospital patients various towns, successively from Schlichting (1880), Heyn (1920) and Schaeffer (1908) pooled, Risopoulos (1936), Scheibner (1938); 1937, schoolchildren S.W. Germany, probits fitted to data of Ley (1938). See also values reported in Backman (1948) and Wallau (1952).
Great Britain: 1948-60 schoolchildren, probits, successively S. England, from Wilson & Sutherland (1950b), Edinburgh from Provis & Ellis (1955), Bristol from Wofinden & Smallwood (1958), London from Scott (1961).
U.S.A.: 1905-40 University of South Carolina entrants, from Mills (1950), 1960 estimated, see text.
Denmark: 1950, Copenhagen schoolchildren, probits, from Bojlén, Rasch & Weis-Bentzon (1954).
Values are plotted at year in which the average menarche took place, i.e. in 'recollected-age' data if average menarche of 40-year-olds interrogated in 1900 was 15 years, this is plotted at 1875. This places old data on same age scale as modern probit data. Where age of interrogation is not recorded an estimated amount has been subtracted according to nature of population studied (primiparae, etc.). Grouping errors have been corrected where necessary (i.e. '13-year-olds' centred at 13·5 years, not 13, as in some of older literature).

the age as 10 years, and 2 as 16 years. Tanner states that probably the first one or two years of menarche are anovulatory; however, in the above study 6 pregnancies occurred during the first year of onset, and 17 in the second year. Since the study included girls 18 and 19 years of age, it can be assumed that many of these were biologically mature. The youngest mother was aged 13 years; 12 were 14 years of age. Dodge (1964) stated that the youngest in her experience was 9-1/2 years old, probably the youngest recorded in the United States at the time.

In 1939 the world was startled by the report from Lima, Peru, of the birth of a normal infant to a child 5 years of age. Lina Medina, the mother, was born September 23, 1933, the eighth child in a family of 9 children--her birth record was verified by the physician. Her parents said she had menstruated since the age of 8 months. On May 14, 1939, she gave birth to a male infant by cesarean section, weighing about 6 pounds. He was named Gerardo, and the case was reported in Presse Medicale by Edmundo Escomel (1939).

In 1947, William Krehen reported his follow-up story on this case in LIFE magazine on December 15, 1947. According to him, some American promoters wanted the mother and child to appear at the World Fair in New York that year, but Dr. Lozado objected and the President of the Republic cancelled the deal. This angered the father, and the mother and child were returned to their home in the highlands above Peru. The story had a picture of the boy at 9 years of age, apparently well and normal,

who thought his mother was his sister. Lina, shown in a picture with her classmates, was described as a short squat girl, somewhat gloomy, seeming younger than her 14 years, who plays with Gerardo as her brother. The Government had ordered a criminal investigation of the case but the parents objected, believing it to be an "Act of Providence".

On November 7, 1971, the San Francisco Sunday papers carried a story of a 9-year old girl in Lima, Peru, who gave birth to a healthy boy weighing 7 pounds.

The upper age limit of motherhood is less well documented. The McWhirters' "Guinness Book of World Records" assigns it to Mrs. Ruth Alice Kistler and has a picture of mother and daughter. The mother was born June 11, 1899 and gave birth to Susan in Glendale, California, on October 18, 1956, when she was 57 years and 129 days. The same source reports that, according to Albanian records, 5,500/million newborns have been born to mothers 50 years of age or more. My personal experience is limited to one mother who was 50 years of age when her child was born.

Obstetricians believe there has been an advancement in the age of the climacteric also, and Tanner (1962) states that as the menarche occurs earlier, menopause is later, thus lengthening the total period of fertility.

There is a general impression that congenital anomalies occur more frequently in younger as well as older mothers. Mongolism is well documented in older mothers but other anomalies

have not been as carefully studied. In my experience, other types of defects are also common. Interestingly, I have seen some very bright children of older mothers and have often wondered if the children also tended to be at the extremes, i.e., either retarded or bright.

The increased frequency of congenital anomalies in young mothers is less definite, but pathology associated with the perinatal period is increased; the children tend to be of low birth weight, prematurity is more common, and toxemia of pregnancy is increased. There are also more problems associated with delivery. The rapid growth spurt of adolescence tends to unbalance hormonal homeostasis; nutrition is not optimum, and the teenager is socially and mentally immature for the problems of pregnancy. If this is added to illegitimacy, poverty and low mentality, the problems are multiplied.

Information regarding paternal aspects is hard to come by. In the study made at Children's Hospital, San Francisco, there were 2 fathers aged 15 years, and 11 aged 16 years. The symposium on adolescent pregnancies (edited by Wallace, 1971) discusses the reaction of the young father to his illegitimate child, a problem to which very little attention or concern has been shown. Are the young men totally indifferent about their role? They often are forced into marriage to "give the child a name", a situation which frequently ends in divorce (Pannor, 1971). In some countries, notably Sweden, the father is made

equally responsible for the support of the child and the responsibility for collecting the funds rests with the government and not with the mother as in the United States. Though I have encountered a few instances in my practice of pediatrics where the mother deserted the family and the father assumed full responsibility for the care of the children, this is very rare. I even knew one young man who, when faced with the situation of an illegitimate pregnancy, insisted on marriage--even though the girl objected, because he wanted his child.

The extremes of male fertility are less definite, since neither the menarche nor the climacteric of the female are present. Fathers of 70 years are not rare.

Studies of fertility and sterility (MacLeod, 1971) indicate equal frequency in the sexes. Low fertility and birth defects are associated. Several authors have raised the question of the role of the father in birth defects of progeny. Greene et al (1964) stated: "In mongolism, for example, it is the older mothers, regardless of the age of the fathers, who contribute to the difference in the distribution. On the other hand, it is the father's age, regardless of the age of the mother, which apparently is of significance among cleft lip and palate combined." Penrose (1955) noted that paternal age correlated with achondroplasia in the progeny, and Eichenwald (1968) raised another question: "If we assume that a virus can cause damage to chromosomes, shouldn't we also be studying the father of a defective child to determine whether he had a viral illness

just prior to the initiation of pregnancy--perhaps the chromosomes in a significant proportion of sperm were altered by the illness--wouldn't it be just as logical to assume that it is paternal, rather than maternal disease that is causing the problem?" Braden (1959)discussed non-genetic defects of the gametes in the etiology of prenatal mortality and traced some of this to poor semen quality in the husbands. Other studies pertinent to male infertility have been made by Javier et al (1971); Woolf (1963); Sherman (1964); Bishop (1964); Ansbacher (1971).

LeGros (1964) reported 6 patients and referred to 6 earlier cases in which abnormal spermatozoa were associated with defective progeny. In these 12 marriages there were 19 pregnancies, with the birth of 3 normal girls, 5 spontaneous abortions, and 11 stillborn males. One man had been married to 3 women, each of whom had borne a defective child. In 1 instances, 82% of the spermatozoa were abnormal. On the other hand, Milham and Gittelsohn (1965) question any relationship of paternal age to fetal anomalies.

My interest in the possibility of the paternal role in teratogenesis was caused by the following case. In 1954 a very defective infant girl was born to a family with 2 normal children, aged 4 and 2-1/2 years. Both the maternal and paternal family histories revealed high fertility, several healthy offspring and no previous history of birth defects. The maternal age was 32; she was para I, gravida III, Rh-positive. The pregnancy had been normal. A study of events

in the preceding year revealed that the father had mumps with orchitis some weeks before conception. The infant died at the age of 5 weeks. At autopsy, microcephaly, anophthalmia, dextrocardia, septal defect, polydactyly, near-atresia of the esophagus, and retrosacrococcygeal teratoma were noted. The family had a normal child later. Since mumps with orchitis is often followed by sterility, it seemed a logical conclusion in this case to attribute the unusual teratogenesis to the paternal disease.

The possibility of congenital anomalies resulting from fertilization of aged ova and sperm has been discussed by Lanman (1968). He cites Jahnel (1938) who suggested that congenital malformations were a potential hazard of frozen sperm, stating: "It is remarkable how little attention has been paid to this obvious problem." In reviewing articles which deal with therapy for infertility and sterility, there is seldom any follow-up on the progeny.

An observation we made at the Child Development Center may have some bearing on this problem. The incidence of a defective child with the first pregnancy of a second marriage seemed unduly common. It was not associated with age, as several of the families had subsequent normal children. Lanman's studies (1968) on aging ova and sperm come closest to providing an answer to this. When a defective child is born and the etiology is obscure, both parents should be studied.

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NUTRITION

The Child Development Center at Children's Hospital in San Francisco was started in 1952, not long after World War II. Some of the children were from refugee and escapee families of the occupied territories or concentration camps. This raised the question of the possible role of starvation or malnutrition in birth defects.

Holland which was occupied from 1940 to 1945 suffered great deprivation, the severest starvation period being the 6 or 7 months prior to liberation in May 1945. Following this, a team of physicians headed by Clement A. Smith (1947) made a study of conditions in some of the major cities in that country, where the lack of food had been greater in urban than in rural areas. In 2 cities, Rotterdam and the Hague, approximately 50% of women became amenorrheic and were presumably sterile and the birth weight of many children decreased. After the restoration of food, not only did birth weights rise but there was a virtual baby boom. The greatest total weight gain of the fetus occurred during the last third of pregnancy, so that the starvation of the first months of pregnancy was not as devastating to the fetus as the latter months.

The study of the occurrence of malformations was inconclusive. Of 224 infants examined, 7 were deformed--an incidence of 3.1%, which is not unduly high. No specific type of anomaly could be attributed to malnutrition per se since many other factors

were involved--cold, crowding, harassment, fear and abuse--in this tragic and traumatic situation. This degree of starvation in such a large population has seldom existed for so long a period of time.

In 1971, according to World Medical Reports (1971), Stein studied the military inductees from Holland born during the famine period of 1944-1946. When intelligence tests were scored on them, there was no greater prevalence of severe or mild retardation among those exposed to famine than in the control group. The conclusion was that either a high order of protection was afforded the fetus, or the fetus in the face of starvation had a tremendous resilience.

Although infant mortality is high and nutritional diseases are rampant in many areas of the world, the effect of malnutrition on fertility is not as apparent in these areas as it was in Holland. Contraception is now being introduced on a large scale in many countries where malnutrition and over-population coexist.

The epidemiological studies of congenital anomalies reveal no marked variation in different areas of the world, which again tends to indicate that malnutrition is not a major factor in congenital malformations of the human young.

Selective malnutrition as a cause of deficiency diseases was recognized long before specific agents were discovered, e.g., scurvy, rickets and Beri-Beri. The lack of other elements, such as iodine, iron, copper, zinc and magnesium may produce disease. Maternal ingestion of oral progestogens, androgens

and estrogens have produced masculinization and advanced bone age in the infant (Grumbach and Ducharme, 1960; Bongiovanni and McPadden, 1960), and fertility pills have been implicated in multiple births up to 9 in number (Glass and Vaidya, 1970).

Since man does not lend himself readily to controlled experimentation, most studies on nutrition have been conducted on animals and, at times, there may be a tendency to extrapolate these findings to man. However, at the Ross Conference on Nutrition in 1970 (Silverman,chairman), it was pointed out that studies on smaller animals--such as rats, mice and guinea pigs--cannot be extrapolated to humans. In guinea pigs, a litter of 4 may account for 50% of the weight of the pregnant female animal; the ratio in humans is very different, e.g., in a mother who weighs 140 pounds and produces an infant weighing 7 pounds, the ratio would be 20:1.

There has been some emphasis on the effect of malnutrition on brain growth and mental retardation (Stock and Smythe, 1967). Winick and Rosso (1969) studied children in Chile for the amount of DNA and RNA. In 10 brains from apparently normal Chilean children who had met accidental death, the DNA and RNA content was normal and equal to that found in well-nourished children in the United States. In 9 infants who died of severe malnutrition during the first year of life, there was proportional reduction in weight and protein, as well as in RNA and DNA content. Three infants who weighed less than 2,000 grams at birth were the most severely affected, having a 60% reduction in DNA content.

These findings or their significance to intelligence has been challenged by several recent authors.

In my private practice, the two smallest surviving prematures included a boy weighing (at his low point) 733 grams and a girl weighing 790 grams. When tested inhigh school, the boy had an intelligence quotient of 165; the girl graduated from college and, last year, announced her marriage. The girl's early progress was uneventful for a premature of that size; on the other hand, the boy had a very stormy time before he gained his momentum, and had a residual mild hemiplegia. These two children did not have optimum nutrition during a critical period of brain development.

Although the incidence of both bodily defects and mental retardation is high in prematures, and nutrition may be a contributing factor, caution must be exercised in attributing mental retardation to malnutrition alone. Again, it is especially inappropriate to extrapolate the findings in small animals or for that matter of any animals to humans, and vice versa, whose brain size and cognitive development is rather different. It may be that the human brain, like the kidney, has a surplus of cells for an emergency. We can do very well with only one kidney, and children have not done too badly after hemispherectomy. (Has any human reached his inherent potential?). Wharton (1970) notes that the relation between maternal nutrition and neonatal well-being is indirect and starvation or famine strikes more at fertility than organogenesis.

Cheek (1971) has questioned the contention that early poor school performance is due to brain deficiency. He attributes it, rather, to hunger and fatigue because when properly fed, the performance of such children rises. This same view was put forth by Latham and Cobos (1971). Daniel et al (1971) in their study on folate-deficient adolescent girls, found that in 163 pregnant girls less than 16 years of age the incidence of infant prematurity was almost identical with a control group. None of the folate-deficient group had bleeding during pregnancy, abruptio placentae, or malformed infants. The dietary intake was less than 50% of the recommended allowance in 90.4% of the patients, and 50% took less than 10% of the recommended folate.

From the Bush country of Ghana comes the report of Buff (1971): "There is a great need for health education. It is hard to break custom. Until they're two years old and walking about, children pull on their mothers' wrinkled breasts. Many of the children don't survive just for that reason. The breast milk of their anemic, undernourished mothers doesn't supply the needs of growing children from 6 months to 2 years old. But the village women (even some nurses) can't seem to realize this. On the other hand, if a mother doesn't put the breast in her child's mouth when he is crying, what can she give him? Nothing! At certain times of the year--around the end of the dry season (March-May) there's just no food to eat."

Complications at delivery are more frequent in malnourished mothers, even when the infant is not large (Burke et al, 1943-44).

In this connection I was interested in Mrs. Maillard's comments (personal communication) about her experience in raising sheep. When she first started her ranch, she took care of the lambs and lambing but left the feeding and general care to the ranch hands. When she experienced many complications and lamb deaths, she decided to take over the entire care of the flock herself. After establishing a good feeding regime and providing tender-loving-care to the flock, she had a marked decrease in problems, even in the presentations at delivery (I wonder if any studies have been made comparing the nutrition of mothers with abnormal presentations at birth with those who have normal presentations).

It is extremely difficult, therefore, to evaluate the role of nutrition in congenital anomalies as well as in physical and mental development; it is intertwined with numerous other factors. Human development must be considered in relation to phylogeny. As the only species with higher cognitive powers, selection on the basis of conserving these assets must have occurred through the millenia.

The early history of the fertilized human ovum is not well documented. In some primates, apparently the fluid of the duct and the uterus, in preparation for implantation, supplies nourishment. The embryo is minute. During this stage, fluid and glucose may play a greater role than protein. At 28 days it is estimated that the embryo is 5 mm; even at 12 weeks it is only 56 mm and weighs 14 gm. Organogenesis, therefore, takes place at a stage when the embryo is very small and may not utilize much protein.

While the incidence of both birth defects and mental retardation is high in prematures, this cannot be attributed to malnutrition per se. Prematurity itself is anomalous and, in many instances, probably should be considered as a delayed abortion. The incidence of anomalies in aborted fetuses is high, as in prematures. Defective infants, even when born at term, are smaller than normal and find adjustment to postnatal life difficult; the mortality is high and those that survive are often retarded. Mental retardation in prematures must be considered in this perspective. In contrast to this type of premature, infants born prematurely due to mechanical causes, such as an incompetent cervix or in multiple births, even though very small, usually pose no feeding problem, thrive, and often attain average weight by a year.

Not all organs of the body are apparently equally vulnerable nor are they at the same developmental stage at the same time. The growth curves are described in Gray's Anatomy, citing mostly the work of Scammon. Human development, including the growth of the central nervous system has been discussed also by Dodgson (1961), Cheek (1968), Glass in the text by Scheide and deVellis (1971), and by Graham and Adrianzen (1971).

Obesity also appears to interfere with normal delivery. Malnutrition is not limited to the poor countries nor to the poor of the prosperous countries. Obese people often eat a diet high in fats and carbohydrates and neglect protein foods. A teenager, who may elect to lunch on potato chips and coca cola at the corner eatery instead of the meat sandwich provided by her mother, may be malnourished in the midst of plenty. Food

fads pose another problem and are not determined by either economics or intelligence. It can be popularized by Nobel laureates or commune hippies--note how Vitamin C sales have increased! And, they often say if one vitamin is good, why not add others? The drug salesmen won't discourage this thinking either. It is amazing how many people who participate on talk-programs on television practice some type of food faddism--organic foods, huge doses of vitamins, meatless diets, etc. Majumder (1972) elaborates very well on this subject.

A few years ago a child was brought to me from a town in Northern California because of failure to gain. At 15 months of age, he weighed 13 pounds and was barely able to sit up. His history revealed that the family had joined a religious sect that called for a diet without meat or any animal products, including milk and eggs, which had been maintained for almost two years. They also brought another child, about 7 years of age, from whose growth figures, as maintained in his "baby-book", I was able to plot his growth curve and to show his failure to gain after the onset of the new diet. It was a most dramatic illustration of the effect of diet on growth. After spending almost 2 hours with the family and demonstrating the effects on their children of this type of diet, the father asked if there wasn't any food without animal products that they could use! I wrote to the Public Health Department of the town in which they lived, only to hear that this sect involved a considerable number of people in the area who, so far, had resisted change.

In one of the local day care centers, the teachers expressed concern over the diets of some of the children who belonged to a Hindu sect that also forbade meat in the diet.

All too often instruction in nutrition is minimal, and this situation requires correction.

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INTRAUTERINE ACCIDENTS

Fifteen to 20% of infants are born with the umbilical cord coiled around the neck one or more times, the highest number reported being 8 times. Although specimens, such as the one shown by Potter (1961) and in Fig. 2, indicate that fetal strangulation may be lethal, the opinion of obstetricians and pediatricians is that survival without sequelae is the usual outcome. However, when one probes the histories of abnormal children, it is impossible to escape the implication that cord strangulation is either the sole etiology or a contributing factor to brain injury in an occasional child. It is interesting that in folklore (Newman 1969) around the world, cord strangulation plays a prominent role, being attributed to numerous and varied acts of the mother.

Fig.2

In our hospital, when the cases with a history of definite distress due to cord strangulation were reviewed, 8 were selected; of these, some had the cord around the arm, leg or body and did not fit the study of strangulation per se. Others suffered from anoxia secondary to separation of the placenta due to a short cord and coiling. In 2 cases the pathology seemed to be due solely to the strangulation; their histories follow:

Fig.2 Lethal cord strangulation. Strangulation is not the only cord accident. Potter's (1971) case shows almost-amputation of an arm from cord entanglement. Others have reported twin fatalities from entanglement and still others have attributed limb deformities from intrauterine accidents. A very short cord may cause separation of the placenta. Cords with knots have also been recorded.

Case 1. D.R. (a female child born June 25, 1957, of normal healthy parents--the second child with a normal sibling) was delivered 15 days prior to the estimated due date, weighing 4 lb. 15 oz. The cord was wrapped tightly around the neck 4 times, her face was highly suffused, and there were scattered petechiae over the face, neck and scalp. The rest of the physical examination revealed no pathology. In the newborn nursery, the nurses described her as having a curious "no-voice" cry.

She was first seen by me at 11 weeks, at which time her weight was 9 lb. 2 oz, height 24 inches, head circumference 15 inches, and chest 14-1/2 inches. Except for her small size and her peculiar hoarse-sounding cry, there were no abnormalities. She was seen again at 9-1/2 months, at which time her weight was 17 lb. 7 oz.

She was an extremely quiet child, but responded with smiles to play. Again, the curious quality to her voice was noted. At 2 years of age her weight was 25-1/4 lb, height 35-1/2 inches; she had started walking at 14 months. Her father described her as having two voices--a very feeble hoarse voice at times, and at others a high, squeaky one. She was referred for a laryngeal examination and was reported to have some webbing of the vocal cords which was corrected, but with no improvement of her vocal quality.

This child had 3 developmental evaluations. In the first, she fell within the normal range; in her second at 19 months, her score was barely normal; in the last one at 29 months, her performance was erratic and scattered, with only one success for her age, and her communication was mostly with gestures.

Case 2. B.T. was born on April 27, 1950, and her mother had been told that she almost strangled to death. She was placed in oxygen for several hours, but was dismissed with the mother. At 1 year of age the mother became concerned about her development. The child did not walk until she was 2-1/2

> years old and never developed any speech. She was first seen in our Center at age 5 years and presented a curious picture. She was well developed and nourished, and had no such stigmata as simian lines or minor congenital anomalies. Her head was kept tilted to the right in a curiously cocked position, but there was no fixed torticollis. She was friendly, recognized people, but used no speech. She comprehended verbal commands. An electroencephalogram was described as within normal limits for her age. An eye examination revealed some hyperopia. The neurological examination, except for the lack of speech, was negative. The psychological evaluation placed her at the middle grade defective level. At 7 years of age she was admitted to a class of aphasics and was reported to be communicating with some "bird-like" sounds, always rising in pitch at the end. She understood the spoken word when kept at her level of intelligence but would never participate in any speech activities no matter how simple the games were kept and, when challenged, would withdraw. She never defended herself or her toys. She was placed in a school for the retarded.

Near-strangulation by the umbilical cord poses some intriguing problems in body dynamics. The factors that influence the outcome are 1) the unique quality of the umbilical cord to resist obstruction; 2) the ability of the heart to keep up the necessary pressure to maintain the circulation and body homeostasis; 3) the effect of the strangulation on the local tissues of the neck, blood supply, nerves and trachea; and 4) the effect of strangulation on the central nervous system. Other factors may also play a role in the outcome: the size and sturdiness of the infant, the duration of the restriction and probably, most important, the ability of the cord to maintain some blood flow between contractions, and the prompt resolution of the dilemma by the attending physician.

Table V

Table V summarizes the studies from the literature (Earn, 1959; and Shui and Eastman, 1957), and includes a local study by Dr. Stangl (unpublished data), in which he noted signs of distress in the infant. In the analysis of 415 cases, 331 showed no respiratory or circulatory difficulties nor any abnormalities during the neonatal course. In 84 infants, signs of distress ranged from "slow to cry" to more severe problems, either during delivery or in the neonatal period.

In a recent study, Arto-Medrano (1970) discussed the influence of the cord around the neck on fetal acid-base balance. He noted that since the blood pressure in the umbilical vessels is higher than that in the superficial vessels of the neck, a moderate degree of compression, sufficient to impair circulation through the neck vessels, would not affect umbilical circulation. A moderately tight cord around the neck would impair cephalic venous blood flow and only a very tight cord would compromise umbilical circulation and produce systemic hypoxia. In most cases studied, the tightness of the cord was enough to provoke a cephalic circulatory stasis, but not enough to impair umbilical circulation. The degree of compression varied--it increased with contractions and decreased with relaxation. The intense pressure of the blood when the cord was cut under circumstances of strangulation was noted. The criteria for distress were: a slow heart before delivery, meconium-stained fluid before or at the time of delivery. In the group which showed no distress at birth, only 13.5%

TABLE V

SUMMARY OF CASES OF CORD LOOPINGS AT BIRTH

Authors:	Earn	Shui	Stangl
Total No. Cases	5,676	1,007	2,677
Looping:			
No. Cases	1,272 (23%)	(20%)	420 (15.7%)
Number loops:			
1	1,103		(85.4%)
2	133		
3	31	2	(12.3%)
4	4		(0.4%)
8	1		
Over 3 loops:			
loose			331
tight			84

were recorded as having the cord under tension, whereas in the group that showed evidence of distress 25% of the cords were described as under tension.

We also reviewed the findings in cases of strangulation by other means than the umbilical cord. Kecht (1957) reviewed 3 cases of attempted suicide by strangulation in adults; 2 showed temporary palsy of the pharyngeal nerves(but recovered after 2 months; one showed a retrograde amnesia unilateral laryngeal palsy with anesthesia, later hyperesthesia of the larynx, and improvement after 2 months).

The conclusion seems justified that cord strangulation is not always benign. Although sequelae are relatively rare, the following may occur: fetal death, mental retardation, various mixed encephalopathies, or laryngeal pathology resulting in interference with normal speech development and torticollis. These unexpected events emphasize the importance of monitoring labor, for there is no other means by which the drama being enacted in utero can be detected.

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IMMUNITY AND REJECTION

In the histories of children with defects at the Child Development Center in San Francisco, the number of mothers in the Rh-negative group seemed far too high to be of no significance (these children had not suffered from erythroblastosis). In 1967, therefore, I made a study of the deliveries and the infant morbidity and mortality for the year 1966 at Children's Hospital, San Francisco. Of 1901 deliveries, 164 infants were listed in the morbidity and mortality book; in the total series, the percentage of Rh-negative mothers was 11.5%, but in the infants with non-specific pathology (Table VI) the percentage of Rh-negative mothers was between 20 and 25%.

Table VI

Yannet and Lieberman (1945), in a study of 280 cases of middle-to-low grade mental retardation in an institution, found that 157 belonged to well recognized etiological groups; 123 were undifferentiated, 70 of whom belonged to the A-B groupings. They felt that isoimmunization was of etiological importance, although Book et al (1969) apparently disagreed with these findings. This question should be relatively easy to clarify. Many newborn nurseries now have a neonatologist in charge and the Rh and ABO factors are usually known in all mothers; this information should be part of the physician's records even if not in the hospital notes.

The phenomenon of non-rejection of the fetus, half of which is foreign tissue to the mother, has received a great

TABLE VI

Maternal Status of 164 Defective Children

Rh-positive	120
Rh-negative erythroblastotic - 4	30
Rh not recorded	14
Total	164

deal of attention. Three possibilities for the safety of the fetus have been suggested by Lanman et al (1962): 1) the fetus may be antigenically immature; 2) the immunological capacities of the mother may be altered during pregnancy; or 3) the physical separation of fetus and mother by an intact placenta and by separate circulations may prevent homograft rejection of the fetus.

The mammalian mother can and does respond immunologically to her fetus, and trophoblast and fetal lymphocytes may gain access to the maternal circulation. Maternal responses include circulating antibodies and hormonal influences which may alter receptivity of grafts and influence maternal-fetal immunological interaction. Lanman (1965) states: "There are, however, in human infants a few clinical syndromes of poorly defined etiology where homologous disease might be implicated and could profitably be sought; these are spontaneous abortions, failure to thrive, and chronic diarrhea..Evidence of naturally occurring runt disease in mammals is scanty, but a search for such a syndrome in certain clinical syndromes of poorly defined etiology appears warranted."

Our interest and suspicion were also aroused at the frequent occurrence of birth defects in one of discordant twins, suggesting the possibility of transfer of cells between twins and thus setting up an adverse reaction.

Immunity and rejection are also of great concern in organ transplant and have led to intensive study of cellular immunity in other than blood cells. Hematologists have attempted to transplant bone marrow in patients with aplastic anemia and in certain leukemias. To prevent rejection, massive irradiation has been given prior to the infusion of the marrow. The best results have been obtained with identical twins as donors (Mills et al, 1964); however, if the pathology is not accidental (as in poisoning), the twins may be subject to the same disease.

Mathe et al (1965) reported a 26-year old physician in the third phase of lymphatic leukemia (after massive radiation) who was given bone marrow from six members of the family. Restoration of the bone marrow began 2 weeks after infusion and his condition continued to improve. One year later, when he was still in remission, he succumbed to herpes virus infection and meningoencephalitis. At autopsy, there was no evidence of leukemic infiltration, but there were multiple foci, suggesting chronic graft-vs-host activity. Only the cells of one donor, a brother, had taken successfully.

Donors for kidneys, as for bone marrow, are more readily available, since man is supplied with two and can spare one for a brother or relative. Considerable work on this has been done at the University of California-San Francisco Medical Center and there are survivals for as long as 10 years. Since heart transplants call for prompt removal of the heart after death, this has created problems and controversy over the definition of death. However, all studies have undoubtedly increased

our understanding of cellular immunity and the phenomenon of rejection.

There was great revulsion expressed in this country when the Russians reported use of cadaver blood for transfusions. On a visit to Russia in 1958, I observed that regulations for collecting it were strict. It had to be taken within 6 hours of death, only from "sudden death" cases, accidents, coronary cases, etc., then grouped, the Rh and bilirubin determined, and cultures made (3 successive cultures at daily intervals). The blood was held until the autopsy (gross and microscopic) had been completed. Surgical technic was used during withdrawal. A cannula was placed in the jugular artery, the patient placed in the Trendelenburg position and the blood collected by gravity. The 3 or 4 liters obtained were not kept more than a month. We were told that 95% of blood for transfusion in Moscow was obtained this way; other cities were not doing it at that time because of technical difficulties.

Another type of rejection may occur before fertilization takes place. In the studies of Glass and Vaidya (1970) on sterility and infertility, active normal sperm was destroyed before fertilization could take place. Some injured sperm may fertilize but produce an abnormal or defective fetus. Anyone who has conducted mortality and morbidity reviews of newborns is aware of the frequent occurrence of defective infants in families of low fertility or periods of sterility. It is unfortunate and inexcusable for those working in this

field to fail to report on the offspring after treatment of fertility problems; too often they merely record that pregnancy occurred, without comment on the condition of the infant.

The subject of immunity and rejection has now expanded to involve a great many specialities: hematology, obstetrics, pediatrics, gynecology, surgery, genitourinary and teratology.

Answers to queries on INTERFERENCE WITH ORGANOGENESIS- Thelander

1) Page 28 - Table IV was mailed to you on the 4th.

2) Pictures of hand and face deformities? Might be included in the Chapter on Dermatoglyphics and the Occult.

3) In the above context, they probably do not need legends, but if you think they should then the heading, Deformities of Head and Face" is appropriate. I think the pictures help to explain the popularity of some occult beliefs in the past. If faces are used, block out the eyes.

4) Abstract already sent, hopefully it arrived!!

5) Yes. I think " Birth Defects" is preferable for Table I.

6) Yes. It will clarify the statement if the sentence is changed to read, " He repeats the defination of Birth Defects by Wacker" ETC.

7) The name is Bierman and there are two papers reviewed as noted in the Bibliography,- one in 1964 and one in 1963. Maybe the article should note it as (1963 and 1964). I will leave that to your judgement.

8) no Contradiction but maybe it would be clearer if altered to read, "stillborn and neonatal deaths" Stillborn refers to deaths in-utero and neonatal to deaths of liveborn infants during the neonatal period.

9) There are two references to Bierman,- 1963 and 1964. Please note spelling.

10) There are two Cheekk references,- 1968 and 1971. See page 46.

11) Lets leave out the name Mrs. Mailliard and simply say"a friends comment".

12) Page 47, ref., 12, the word is Faith,- Fad, Faith or Fact.

13) Table V: under Sui, before 20%. He gave only the Percent.

14) Page 56 was all fouled up and I am ashamed that I did not spot it. That was my favorite study. This Bibliography should read as follows:

Book,J.A. Incompatability and Mental Deficiency. Amer. J. Human Genetics. I:66-78. 1969.

Lanman, Jonathan T., Dinerstein, Jenny, Fikrig, Senih. Homograft Immunity in Pregnancy: Lack of Harm to the Fetus from Sensitization of the Mother. New York Acad. Science Annals. Vol. 99.Article 3,pp 706-716. 1962.

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Mathe, G., Amiel, J.L., Schwarzenberg, L. Catten, A. Successful Allogenic Bone-Marrow Transplantation in Man: Chimerism, Induced Tolerance and Possible Anti-Leukemic Effect. Blood. Vol. 25. No. 2. pp 170-196. 1965.

Mills, Stephen D., Kyle, Robert A., Hallenbeck, George A., Pease, Gertrude L., Cree, Ian C. Bone Marrow Transplant. JAMA. 188: 1041. 1964.

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Glass, Robert, H., Vaidya, Rama A. Sperm Agglutinating Anti-bodies in Infertile Women. Fertility and Sterility. Vol. 21. No.9. pp657-661 1970
This should of course be in Alphabetical order. It appears on Page 57 last Par. second line.

15) Brady, J.P.. Williams, H.C. Magnesium Intoxication in a Premature Infant. Pediatrics 40: pp 100-103. 1967.(This reference is in my copy.)

16) I gave you the sad story of my inability to locate the original letters of my Siamese Twins.

Typeing is such agony for me that please excuse mistakes. Under 14 above, I have another reference that probably should be included, namely:

Thelander, H.E. Defective Newborns. Clinical Pediatrics. Vol.8. No. 8. pp 457. 1969.

Thelander might be inserted in the first or second line page 54 as this was the work reported.

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RADIATION

In the early 20's at the University of Minnesota, Dr. Richard Scammon investigated the then prevalent theory that sudden death in infancy was due to an enlarged thymus gland. By studying the thymus in deaths due to known accidental causes, he concluded that the thymus decreased in size rapidly with infection and with any prolonged illness and that the large thymus usually found in the sudden death syndrome was of normal size. When I came to San Francisco for my internship it was routine practice to x-ray or fluoroscope all infants for the size of the thymus and, if visible by x-ray, to give radiation therapy. Several pediatricians as well as other physicians used fluoroscopy machines in their offices to examine children routinely. I do not recall when this routine was abandoned, but when the children's Tumor Board was organized at Children's Hospital in San Francisco, I made some attempt to correlate cancer in childhood with previous thymic x-ray studies and treatment.

One mother who had a child with Down's syndrome brought her own "baby book", kept by her mother, in which it was recorded that she had had x-ray therapy for an enlarged thymus. I wrote a "Letter to the Editor" of a pediatric journal asking for similar records from others, but had no response. Curiously few mothers remembered whether or not the child had had such exposure, and I could draw no conclusions. Later, some one in the cancer field told me that he thought thyroid malignancies

were sometimes associated with thymic radiation.

For many years, shoe salesmen used fluoroscopy machines to see the fit of the foot to the shoe. In 1967, when the American College of Radiology convened in Los Angeles they discussed the topic: "Genetically significant dose to the U.S. population from diagnostic medical roentgenology." This subject is covered by Goodwin et al (1970).

Several warning events signaled the need to investigate the hazards of radiation. Miller (1956) reported that radiologists developed leukemia 9 times more often than other physicians and some suffered delayed but severe burns of the hands. Finally, the atomic bomb explosions during World War II alerted the profession to the necessity of controlling all types of irradiation.

In his book on congenital anomalies, Murphy (1947) noted that pelvic radiation in diagnostic doses during pregnancy does not influence the growth of the offspring and has no effect on the individual. On the other hand, therapeutic radiation to the pelvic area during pregnancy had caused a high incidence of malformations (of 75 children, 38 were abnormal--10% might have been due to other causes, and most defects involved the nervous system).

Russell and Russell (1952) undertook a careful study of radiation hazards on the developing fetus in mice and other small animals to determine the critical stages of embryonic growth during which irradiation produced specific anomalies.

Although the growth of the human embryo is much slower, they noted that similar critical periods exist, as in animals, even though at longer intervals. The anomalies were a direct effect on the fetus and not mediated through the mother. The critical periods probably were susceptible in humans also. The authors specifically state that 'probably' must precede any extrapolation of results from animals to man until proven. The comparable active periods in humans would probably be 2 to 16 weeks.

Rugh (1958), who carried out similar experiments, reached the same conclusions. He plotted the sequence of organogenesis in mice and rats with those in the human embryo and found them basically the same, although slower in human. Every irradiation-produced anomaly in the human fetus was experimentally produced in mouse and rat embryos, and at a comparable state of development; the effect on the embryo was direct and not mediated through the mother.

The radiation tolerance of the human ovum after insemination but before implantation is not known. The most sensitive period of the human embryo is probably about 18 to 38 days, when rapid differentiation is taking place. After this, higher levels of exposure are necessary. Microcephaly is the most common anomaly after fetal irradiation and an increase in leukemia may also ensue.

Brown et al (1967) found that the estimated medical x-ray

visit rate during pregnancy was 26/100 women, significantly less than that of all women between the ages of 15 and 40 years in the general population. Approximately 21% took place during the first trimester, 25% in the second trimester, and 54% in the third trimester when practically all x-rays were abdominal and related to the pregnancy. Chest and other x-rays were more evenly distributed in the other periods. They emphasized that about two-thirds of the women who bear children can be expected to have at least one more child during their lifetimes and the effect of exposure of ovaries to radiation is unknown. The visits for x-ray were generally lower in the Northeast and South (24/100) than in the North Central and Western States (30/100). The rate was also higher in the metropolitan than in the rural areas. The subject is covered very well in a symposium on the late effects of radiation in which Brent (1970) devotes a chapter to the effects of radiation on the fetus.

The effect of atomic bombs on the people of Japan has been studied by many scientists, particularly geneticists from Japan as well as from many other countries. In reviewing their work there is surprisingly little evidence of an increase in congenital anomalies. Neel et al (1953) and Neel (1966) emphasize the difficulties encountered in Japan in these surveys because of the history of consanguinity and its role in birth defects in that country. This was further complicated because of the work of Christian missionaries over many years to counteract such marriages, thus making it difficult to have a good control group. The amount of critical material was small and

the results questionable on the frequency of malformations, sex ratio, stillbirths and birth weight.

Plummer (1952) reported on 205 children at the age of 4-1/2 years from Hiroshima whose mothers were in the first trimester of pregnancy at the time of the blast who had definite evidence of injury; such as burns, epilation, purpura, vomiting, fever, diarrhea and bleeding of the oropharyngeal area. Of the 205 children studied, there were 28 anomalies: microcephaly and mental retardation in 6, mongolism in 2, hydrocephaly in 4, congenital heart in 3, hydrocele in 2, and 7 children had all other types. Anomalies in 7 of 11 occurred in mothers who were within 1200 meters from the epicenter of the blast.

Neel (1966) in the Russell Lecture reviews the subject rather extensively and again points out the great difficulty in analyzing the findings. He made the following statements: 1) the doses of radiation received by the survivors of Hiroshima and Nagasaki were not large by the standards of experimental genetics; 2) the experimentalist can manipulate his material to bring out genetic effects that are impossible with human beings. By 1953, Neel at al had collected data on 71,280 births in the two cities, but only 9,686 of these births were to parents one or both of whom had received substantial amounts of irradiation. They found no apparent relationship between the irradiation experience of the parents and the frequency of stillbirths, birthweight, or congenital malformations. The early studies raised a question about the sex ratio but this, too, was ruled out by subsequent studies.

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INFECTION

The report by Gregg (1942) of an increase in birth defects following an epidemic of rubella in Australia stimulated tremendous interest in the role of infection in teratology.

When poliomyelitis was prevalent in California, the Communicable Disease Divisions of Children's Hospital of San Francisco treated a large number of victims of this infection. In the early years of the epidemics, mostly the young children were affected and, hence, the original name--infantile paralysis; later, many more young adults were the victims and it was particularly severe in pregnant women. When contracted during the first trimester, practically all women aborted. The virus was never cultured from embryos which were sent to the Virus Laboratories. However, this was accomplished later in Eastern United States; at least one instance is mentioned in "Viral Etiology of Congenital Malformations" (Benirschke, 1968). Early abortions may have been due to maternal illness, which often was accompanied with high fever and marked toxicity. When the disease occurred after the first trimester, there was no evidence of injury to the fetus. One child who was delivered at term, while the mother was still in the acute phase of polio, had a febrile illness. We diagnosed this as polio but recovery was without paralysis and the virus was not isolated, so it was a presumptive diagnosis. One mother spent the last 5 months

of her pregnancy in the respirator and delivered a set of normal twins who at the age of 4 or 5 years were developing normally in spite of their unique experience.

One mother, admitted near term with a fulminating pneumococcal meningitis, died within 24 hours, but a live infant was delivered by postmortem cesarean. This child appeared to be developing normally at 2 years of age. A search of the literature at the time revealed few other cases of postmortem delivery. One newborn with pneumococcal meningitis recovered with antibiotic therapy but suffered severe brain injury, with microcephaly and mental retardation (Thelander and Goebel, 1949). Another mother had chickenpox about 2 weeks before delivery; her infant was born with evidence of the disease--benign circular skin markings rather evenly distributed over the body involving only the top layer of the skin and no scarring.

The 1967 symposium sponsored by Health, Education and Welfare and National Institutes of Health on the subject of "Viral Etiology of Congenital Malformations" (Kurt Benirschke, chairman) with 12 participants and 10 topics discussed this in considerable detail. This is such a comprehensive review of the subject that we can only seek out any new material since its publication in 1968. The conference stressed that birth defects could not be separated from the spectrum of intrauterine death, spontaneous abortion, premature labor or perinatal death. The viral infections mentioned included influenza, herpes

simplex, mumps, varicella-zoster (chickenpox, shingles), measles, rubella, and such less common infections as toxoplasmosis, cytomegalic inclusion disease and congenital syphilis (which disappeared for many years but is in danger of recurring as a result of changed cultural patterns). The other viruses had created no great concern until the report of Gregg (1942).

Toxoplasmosis, cytomegalic inclusion disease and congenital syphilis are rarely seen in private practice. The rare and unusual diseases tend to find their way to University departments, both Pediatrics and Pathology; the interest they create may give students a false impression of their incidence and importance. In our 50 years of pediatric practice in a hospital with a large newborn nursery, a contagious disease division and a large pediatric department, I can recall only 1 case of cytomegalic inclusion disease and 2 of toxoplasmosis. In the early years of practice, infants with congenital syphilis appeared at the rate of 1 or 2 a year, although the incidence undoubtedly was higher in hospitals which served the slum areas, now designated as ghettos.

The usual route for infections to reach the fetus is through the placenta; however, bacterial and other non-viral organisms--particularly enteric organisms--can find their way up the vagina and infect the fetus. Disease is most apt to occur if the membranes have been ruptured for any length of time before delivery.

A still unsolved question is the age at which immunological competence is achieved in the fetus. When immunization procedures were developed,the infant was believed to be immune-incompetent until 8 or 9 months of age and immunization was delayed until that time, but now it is started much earlier. There is considerable variation in competence as well as the time of its establishment; some children are deficient for long periods of time and others lose their immunity readily (see discussion of vaccinia). It is speculated that some viruses live in symbiosis with the fetus during the stage of incompetence and, hence, may not produce any defects in development, others can cause abortions, and still others may cause necrosis of some cells (which are repaired but with alteration in the developmental pattern). As noted with chickenpox, an infant can recover from the disease without any evidence of injury, but I have found no studies on the permanency of immunity in such children, although it would seem logical to expect such immunity. Chickenpox produces very lasting immunity; I do not recall seeing a second attack, but I have seen 2 patients with second attacks of measles, a disease that usually gives permanent immunity.

In private practice and during smallpox scares, the possibility of vaccinating a pregnant mother has arisen. Tondury et al (1969) cite 10 reports of vaccinia of the fetus following vaccination of mothers, and adds 2 more (with excellent pictures). The vaccinations were done when the conceptus was between 1 and 24 weeks. In 1, the mother was vaccinated between 4 and 14 days after conception and had an acute febrile reaction to the

vaccination; the fetus showed a generalized vaccinia eruption. In the second infant reported with varicella, the mother was vaccinated between 3 and 24 days. In 9 of the other reported cases, the fetus showed skin lesions and necrotic foci in various internal organs, but no malformations were present. The virus was isolated. The lesions resembled those observed in smallpox. The authors suggest that vaccination should be strictly avoided during pregnancy.

In a visit to China shortly after I had graduated from medical school, a smallpox scare in Peking resulted in the vaccination of all the personnel--75 Westerners and 109 Chinese. The physicians at the Institute did the vaccinating and decided to study the results. Seven of the 75 Westerners had typical primary takes, and gave the following histories: 3 had true primary takes (1 baby 6 months old); 1 child 2 years but not previously vaccinated; and 1 adult not previously vaccinated; 1 had no take since early childhood, although revaccinated several times in the interim; 1 had been vaccinated 6 years previously, and 3 vaccinations since then had been unsuccessful; 1 had been vaccinated 7 years previously with a good take, and had been revaccinated before leaving the States, without a take: 1 had a good take in childhood, another 7 years later, and 1 at the time of the scare, making a third typical take. Four other people who had been vaccinated successfully a few months earlier gave the history of having been vaccinated before leaving the States but with no take. Of the rest, 9

had 2 takes 10 to 15 years apart; 2 had 3 takes about 7 years apart; 1 had had 4 takes 4 years apart; and 3 showed scars of several takes! We concluded that 75 (20%) showed definite loss of immunity and 3 (4%) showed extremely rapid loss of immunity.

At this same time Dr. Lennox, of the Rockefeller Institute in Peking, in a study of the health of Westerners in China, received reports of 111 cases of smallpox, with 28 deaths. In 51 of these 111, there were histories of vaccination: 36 had never been successfully vaccinated, 15 had been successfully vaccinated. Of the nonfatal cases, 21 had never been vaccinated, 12 had been vaccinated once, and 3 had been vaccinated twice. Of the 15 cases of post-vaccinal smallpox, 1 had had a successful take 4 years earlier and 2 had a history of successful vaccination 1 year previously. Ten (approximately 9%) of the vaccinated Chinese had typical takes; 1 of the men had extensive scars. This experience gave me a wholesome respect for smallpox and I am not very enthusiastic about the present abolition of vaccination.

From the incidence of virological diseases in pregnancy (Table VII), very few had mumps or chickenpox in the first trimester. In the 45 mumps cases, the few anomalies were no more or different from the controls (there were no cardiac anomalies). There was considerable doubt cast on the theory that mumps during pregnancy predisposes to endocardial fibroelastosis, nor have the results of 10 collaborative studies

TABLE VII

INCIDENCE OF VIRUS DISEASE IN 30,059 PREGNANCIES*

Of 5% who had one or more viral infections of the major "flu-like" diseases:	
359	had herpes simplex
45	mumps
11	rubeola
34	rubella
33	varicella

* White, L.R. in Benirschke (1968).

been impressive. It was suggested that no such elaborate and expensive studies be initiated in the future, that smaller in-depth studies would be preferable.

Ataxia in cats was considered a congenital anomaly until it was found to be caused by a virus that infected only the cerebellum. This type of predilection varies from animal to animal and presumably also in man, thus making extrapolation from animal to man hazardous. The attenuated viruses, as in polio vaccine, may produce a modified disease in susceptible contacts. There are also resemblances between viruses and anti-metabolites. Particularly appealing comments in the seminars on the viral etiology of congenital malformations (Benirschke, 1968) included:

"I think one can make a living at scavenging good articles that have been overlooked." (Miller)

"Not being an expert, I can talk freely and think freely, unburdened by knowledge." (Axelrod)

"In summary, it would appear that as far as can be determined at the present moment, viral infections contribute only a small proportion of congenitally malformed children, that the majority of the other etiological factors remain unknown." (Eichenwald)

And what protects the fetus? Why did some mothers with rubella have normal infants?

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DRUGS AND TOXINS

Thalidomide created as great a flurry in the field of drugs as rubella did among virologists. Meester (1964) stated that prior to the thalidomide episode there was only one general review (Baker, 1960) on the effects of drugs on the fetus. Since then, thalidomide remains as unique in its field as rubella. We are a hardy species! Even thalidomide produced deformities in infants in only 20% of the mothers who had ingested it. What protected the other 80%?

Both Lucey (1960) and Apgar (1964) summarized the effect of drugs on the fetus--not only the teratogenic effects but also reversible conditions and toxic injuries. Thalidomide and aminopterin (Warkany et al, 1959; Shaw and Steinbach, 1968) appear to produce gross anomalies of the human fetus. Many endocrine preparations pass the placental barrier and affect the glandular systems. Progesterone, androgens and estrogens have caused masculinization and advanced bone age (Grumbach and Ducharme, 1960; Kalter and Warkany, 1959; Bongiovanni and McPadden, 1960). Cortisone has been implicated as a possible cause in cleft lip and palate. Other drugs prescribed for specific diseases in the mother have produced similar effects but were exaggerated in the infant. Iodine lack in the mother has caused enlargement of the infant thyroid. I have observed the gland of an infant so large that it interfered with delivery, due to inability to flex the neck. Dicumerol, and even the

salicylates, have caused excessive bleeding of the newborn infant and have sometimes resulted in death.

Even antibiotics are not benign. In animals, streptomycin can cause nerve deafness and, although it has not been proven that it does so in the human, its use has been abandoned in nurseries. Tetracycline can cause discoloration of the teeth and its use has been restricted. When chloramphenicol was found to produce the "grey" syndrome in infants it, too, was discontinued. The sulfonamides have been implicated in kernicterus.

Addiction in the mother has been known to cause death of the fetus or addiction in the newborn, which often--in spite of vigorous treatment, results in death (Schneck, 1958). The increased use of psychodelic drugs has been of great concern and the questions posed are still largely unanswered; even the possible effect of LSD breakage has not been settled. For several years the Public Health authorities have maintained that smoking mothers have smaller babies than non-smokers, but a recent editorial argues that other characteristics of smoking mothers, and not smoking per se, are the causative factors. Many smoking women who attempt to stop the habit, return to it when they find themselves gaining weight--apparently they are tempted to reach for a snack instead of a cigarette.

Usually, drugs taken during pregnancy imply illness, so that the effect of the drug on the fetus must be weighed against the effect of maternal disease. Some of the conditions for which medications are indicated are hyperemesis,diabetes

hypo-or hyperthyroidism, epilepsy, schizophrenia, and addiction. In the histories of children with defects , the incidence of hereditary disease inthe family and poor health of the mother was very high. As Monie (1963) has pointed out, the fetus has three environs: the immediate intrauterine, the maternal, and the external environment. From my experience as a child on the farm, I recall that the farmer selects good seed, plants it in good soil, and hopes for a favorable climate. If all is well, he gets a good yield. We are a part of evolution!

Even vitamins are not benign. When these were first introduced many mothers felt that if a little is good, more might be better. As a result, pediatricians began to report ill effects from hypervitaminosis (Yaffe and Filer, 1971)--Vitamins A, D and K have caused problems. What large doses of vitamin C may cause are unknown. Nora et al (1967) listed ten potential teratogens in 240 pregnancies (Table VIII). Table VIII

The drug business should be under the same ethical code as medicine. There should be no advertising and over-the-counter drugs should be prohibited from TV and Radio advertising. Drug research, like other medical research, should be conducted in the regular medical research centers and not by pharmacuetical firms.

Brady and Williams (1967) reported a case of magnesium intoxication in a pregnant woman, with a near-loss of her infant. The woman had been given magnesium sulphate, both intravenously and intramuscularly, for rapidly rising blood pressure. The infant delivered one-half hour later was flaccid, apneic and cyanotic, required a respirator and, finally, a replacement transfusion, but survived. Respiratory paralysis was reversed immediately on lowering the magnesium level by the exchange transfusion.

TABLE VIII

POTENTIAL TERATOGENS IN 240 PREGNANCIES

Potential teratogen	first trimester		second trimester	
	No.	%	No.	%
Acute illness	28	12	129	54
Analgesics	28	12	155	65
Antibiotics	29	12	101	42
Antihistamines	41	17	62	26
Antiemetics	36	15	38	16
Appetite suppressants	31	13	65	27
Insecticides	50	21	125	52
Radiation	29	12	72	30
Tranquilizers	22	9.2	51	21
Vitamins	156	65	214	89

Lead, copper, zinc and mercury have all been implicated in toxic symptoms in infants. A December 1971 Bulletin from the FDA warns against the use of hexachlorophene for bathing babies. Some staff members wondered if they dared use a soap that contained the product!

The effect of folic acid and other vitamin deficiencies on fetal rats (Nelson etal 1952; Monie et al, 1957; Chamberlain, 1970) have been of interest to me. Many years ago at Childrens Hospital, San Francisco, several infants with convulsions were traced to the lack of folic acid in a new commercial baby formula highly advertised as the equivalent of breast milk.

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MULTIPLE BIRTHS

Twins: In our study at the Child Development Center, San Francisco, an impressive number of twins had defects. They were observed in monozygotic, dizygotic, in both twins, in one, and in one with a history of death of the other. There is always fear of bias in reporting; even a private practice conducted simultaneously is not reliable as a control because that soon becomes weighted because of referrals by colleagues and selection for consultation by parents.

A study of twins from birth records at Children's Hospital between the years 1950 to 1961 may not be representative, for even the names of hospitals in San Francisco reveal segregation by ethnic background--Chinese, French, Jewish; religious--Catholic, Presbyterian, Jewish; or private or public-supported--County, University, Shriners; and even by sex--Women and Children's Hospital; and formerly an elite hospital--Dante. This segregation was not motivated by prejudice but by compassion for the sick--actually there is and was no discrimination in admissions.

From the birth records from 1950 to 1961 (Thelander et al, 1961), 302 multiple pregnancies resulted in 607 babies, with 3 sets of triplets, 45 stillbirths (23 male, 18 female, and no record of sex in 4), with fatal cases representing 7.4%. The sex representation of those alive was: both girls-106; both boys-100; mixed-92. The congenital anomalies are recorded in Table IX. Trauma at birth included fractures (skull in 1; humerus 1;

Table IX

Table IX.

Congenital anomalies recorded in the series:

	Male	Female	Total.
Diphragmatic hernia and dextra cardia	1	0	1
Congenital heart disease	2	2	4
Postural feet deformities	2	6	8
Spina bifida	0	1	1
Funnel chest	1	0	1
Macroglossia	1	0	1
Undescended testicles	1	0	1
Hemangiomas	0	3	3
Total	8	12	20

clavicle 1); limb injury; brachial plexus, etc., in 3; 2 were slightly jaundiced and 2 required replacement transfusions. Varying degrees of respiratory distress were noted: in A, or first-born, 47 (female 20, male 27); in B, or second-born, 77 (female 39; male 38).

Hay and Wehrung (1970), in their national survey of malformations made a special study of multiple births, found that from 96,000 live birth certificates checked for congenital anomalies, 2,000 twins were born. When these were analyzed to observe differences in like-sex, unlike-sex, and single births, they noted a higher incidence of anencephaly, hydrocephaly, and congenital heart disease in twins from like-sexed pairs compared with single births. Postural foot defects were higher in all twins than in single births. Down's syndrome was lower in twins from both like and unlike sexed pairs than in single births, with a particularly low incidence in like-sexed pairs. They suggested that placental anastomosis might play an important role in malformations; monozygosity, with a high loss of fetuses, could also account for the low incidence of mongolism in the series.

In Hendricks' careful analysis (1966) of twin births over a period of 9 years ending December 1964 in one hospital, 438 women delivered multiple infants. The incidence was higher among women of high parity, those in the fourth decade, and those who had previously borne twins. There was a high perinatal mortality and a high incidence of congenital malformations, attributed to biological rather than obstetrical

hazards. The incidence of congenital malformations in this series was 1/90 births. There were 360 multiparae, with a total of 1074 pregnancies prior to the twin births. Growth was found to slow as term approached: at 32-1/2 weeks, the weight was about the same as singleton term babies; at 34-1/2 weeks it exceeded 4,000 grams, and at term it reached 5,500 grams or approached 60% more than single births. In 210 cases, the first-born twin was the larger; in 306 cases the second was the larger, and in 14 the weights were equal. The perinatal mortality was high--twice as high on the Clinic service as in the private practice group; mortality rose inversely to size.

The anomalies in all the births was 3.3%. In 379 twin pregnancies, 7 of the first twins died, with the second surviving; in 15 instances, the first twin survived and the second died. The figures were all coded by the same person and the same standards were used throughout the study. There were 4 (18.2%) placental and cord anomalies in 22 sets of twins; 2 of these had mono-amniotic twinning and 2 had a probably fetus-fetus transfusion syndrome. In one set, the weights were 2,820 vs 840 gm macerated fetus. Of 44 infants in 22 selected pregnancies, 16 (36.4%) had fetal anomalies. The anomalies included cleft lip and palate, central nervous system anomalies, congenital heart, and hernia. Complications in 17 of the mothers (77.3%) included rheumatic heart disease, hypertension, tuberculosis, thyrotoxicosis, sickle cell anemia,

splenectomy, fibrocystic disease or poor reproductive history.

Hendricks concluded that the longer the twins remain in the uterus, the better the prognosis, depending in part on space. The smaller the twins, the more apt they are to die or have anomalies. The formula for reproductive failure is the triad of underweight, malformation and death. Primary failure is due to the type of pregnancy rather than to the birth process or the medical care. The only possible improvement visualized by Hendricks was early diagnosis and an attempt to prolong pregnancy by rest--best provided by homemakers rather than by prolonged hospitalization, and even though less glamorous than "heavily instrumental electronically oriented research". The final conclusion was that the human species was not designed to carry more than one-offspring at a time with any degree of biological grace!

Conjoined twins are even more rare. The only set in our series was of the thoracopagus type, born April 11, 1962, weighing 8 lb 6 oz, and successfully separated by Dr. Peter deVries (1967) at 6 weeks of age. Careful preliminary examinations had determined that their systems were intact and separate, with the liver as the only possible joint organ. At the time of surgery, the liver extended across the attachment but there was a line of differentiation along which the separation was made. The children are now 9 years of age, and of normal intelligence and are in appropriate grades in school. They are dependent on each other and, as the father said,

"inseparable"; for this reason, the school authorities have placed them in different groups.

The first developmental tests on these girls were made at 7 months of age. A's intelligence quotient was 105. She was described as independent, accepted objects presented by the examiners, and did not look to her mother for reassurance. She persistently reached for objects with her left hand but transferred them readily. The examiner who had previously examined B also noted that she was a little more alert and responsive. B had an intelligence quotient of 96 and was described by the examiner and the mother as being somewhat more shy and irritable than her sister. She was also the smaller of the two. In contrast to her sister, she reached for objects with her right hand and tended to keep her left closed. She did, however, pass objects from one to the other.

At Christmas, 1970, separate letters from the two girls were well composed and well written. I was intrigued by the difference in handwriting, and was pleased in reviewing the first psychological evaluation to find that there was a tendency of one to reach with her left and the other with her right hand. When I asked the mother about their handedness, she assured me they both were right-handed. This family is Chinese; the children may have been influenced to develop the use of

the right in preference to the left hand. We found this was done in Mexico to such an extent that a left-handed child was only rarely observed; when seen, it was explained that the child used it so stubbornly that they were unable to change the handedness.

Out of curiosity I had an amateur hand-writing enthusiast look at the twins' letters. Her interpretation, knowing nothing about the girls was: "A has an integrated personality, careful, interested in intellectual-type activity, tends to stay with a task with good attention span. B is more immature, less concentrated and a freer personality. In general, both appear to have "normal type" handwriting, with A possibly indicating higher scholastic achievement."

Very few people are completely symmetrical in their development. Interesting photographs have been made with the use of the two halves of the face, reproducing a picture as it would look if both sides were alike but in which facial features are usually quite different from the original. Could the difference in identical twins represent this type of variation? In our twins, who underwent extensive surgery at an early age, environmental factors should be considered as possible causes for the variation between the two. These twins have been discussed by deVries (1967) (with very good pictures) in an article which covers their history, embryology, obstetrical and clinical management and reports of other cases born in the United States.

Another publication, the Metropolitan Atlanta Congenital Malformations Surveillance Program (1971), reports 4 cases of conjoined twins born during a 3-year period. The reported incidence varied from 1/50,000 to 1/165,000, with the expected rate, therefore, of 2 and 0.6. All 4 cases were born between 1970 and January 1971, representing a sacropagus, 2 xiphogagus, and 1 craniopagus; 3 occurred in whites and 1 in a mulatto; 2 were stillborn and 2 liveborn. A careful investigation revealed no common cause. The conceptions occurred in June, September, January and March; the births in March, June, August and January. The families were interviewed for study of genetics, exposure to radiation, toxins during pregnancy, family diseases, consanguinity, occupational hazards and illness during pregnancy. The only element of consanguinity was present in second cousins in 1 case, and increased fetal wastage in another--with 5 previous pregnancies of which 2 ended in abortion. The sacropagus pair were successfully separated and are doing well. Of the xiphogagus twins, 1 died during and 1 after the operation; the other 2 were stillborn. This article states that 90% are stillborn and 73% are of the thoracopagus variety. In other species, both hyper- and hypothermia apparently have been factors in producing conjoined offspring.

Pediatric News, December 1970, reported identical twins with allergic differences. In our series, there were 2 identical girl twins, 1 born with a missing femur (the lower leg was attached to the hip). Also in our series were children,

1 of twin sets, with unexplained anomalies which made me wonder about chimeras occurring from fusion of circulations. The hospital pathologist studied the blood of the parents and of 6 children for all known groupings, without finding any evidence of chimerism. Since then, a British report (Brent, 1970) described 6 human blood chimeras in dizygotic twins. The blood groups showed that each twin had some directly inherited red cells, and the rest were acquired as grafts in utero from the opposite twin. The first case was a female blood donor who had 2 types of blood--61% of the red cells belonged to group O and 39% to group A. It was assumed that the genetic red cells were group O and that the A cells were descendents from her twin brother due to migration from him in the embryonic stage. The other cases were similar. Female drumstick-like projections on the nuclei of the male twin showed that ancestral white cells must have been grafted from the female twin to the male twin.

Turpin and Lejeune (1969) describe twins which they called heterokaryotic monozygotes. One set had a normal XY male and a Turner's XO syndrome; the other had a normal diplo-21 male and a mongoloid triplo-21 male. Both were monozygotic on good evidence; this contention was reinforced when it was found that reciprocal grafts between the boy and girl in the first set behaved like autografts.

Another problem encountered in twins was that of transplacental blood shunts (Becker and Glass, 1963; Shorland, 1971). In several instances, 1 twin had been exsanguinated. Unless

the condition is recognized promptly, death can ensue.

Although these accounts sound as if twinning is a problem, the percentage who survive and function well is very high. I have known two sets of twins who were both well known doctors; one of my closest friends in medicine is a twin, her brother is an engineer. The hazards must be kept in perspective.

Triplet births or more: During my years of practice, I recall only 3 sets of triplets (Thelander et al, 1961), whose total weight in one pregnancy was 21 pounds! All were girls; all were normal and all survived. In another set there were 2 boys and 1 girl; and in the third, 2 girls and 1 boy. Two sets were white and 1 set black. I saw no sole survivor in triple births; and no quadruplets or quintuplets. However, more quintuplet births have been recorded in recent years, usually attributed to hormones for infertility.

In the McWhirter "Guinness' Book of World Records", the following information is recorded on multiple births:

Octuplets: 4 males and 4 females were born on March 10, 1967 in Mexico City to a 26-year old mother. They weighed a total of 9 lb 10 oz, and all died within 14 hours. There have been 4 unconfirmed reports of octuplets in Mexico in 1921; in China in 1934; in Tientsin China in 1947; and in Argentina in 1953.

Septuplets: 4 confirmed births since 1900-Sweden in 1964; Brussels in 1966; Boston in 1966; Ethiopia in 1969.

Quintuplets: The Dionne quintuplets remain the most famous group. Emilie died in 1954 at the age of 20 years; Cecile and Annette are married; Marie died in March 1970. These

quints were born May 28, 1934, and their total weight was 12 lb 6 oz.

A set of triplets born in Australia had an aggregate weight of 23 pounds and, in 1968, triplets born in Iran weighed 26 pounds 6 ounces. Tan et al (1971) from Singapore report on conjoined twins in a triple pregnancy--the conjoined twins died but the single one survived. They reviewed the literature and reported similar cases--a total of 9 occurring in 1939, 1941,1943, 1948,1956,1958,1962 and the present one in 1972. One was reported from India, the present one from China, and the rest were all caucasians. The ages of the mothers varied from 19 to 41 years, with most in their twenties; the gravida varied from 1 to 4. Hydramnios was reported in 4 cases; the umbilical vessels and the placentae were described and discussed. Only 2 of the pregnancies reached term; 1 set survived, but there was no follow-up. The majority were thoracopagus. The diagnosis was seldom made in advance, even when x-rays were taken.

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DERMATOGLYPHICS AND THE OCCULT?

When Director of the Child Development Center, I frequently told students that I was a palmist and phrenologist and that all I needed to add to my accomplishments was a knowledge of astrology. In the last few years, astrology has become a part of the concern of youth and is popular even among many adult groups (Rowley, 1971). My sedate accountant, when working on my income tax asked me my zodiac sign. When he guessed wrong, he shrugged and said, "Of course, I don't believe in it."

Interest in mysticism and the occult has burgeoned to such an extent that John Godwin, the Australian journalist, when writing on "Occult America" (1971), commented: "I had to put most of my critical faculties into cold storage for the duration." Peter Rowley says that adherents to new and unconventional religions have increased in 10 years from 100,000 to 2.5 million. San Franciscans surely still remember the late Bishop Pike's involvement with extrasensory perception, and psychiatrists have added sensitivity training and postural language to their armamentarium; a recent book (1971) by Ashley Montagu is entitled, "Touching: The Human Significance of the Skin". Does hypnosis and acupuncture belong in this same category? Will we revert to a belief in prenatal "markings"?

Although phrenology has not enjoyed the renaissance that "palmistry" has under its new name, the size and shape of the head is important in diagnosis of anomalies. Anthropometric studies reveal a correlation between head size and intelligence,

when due allowance is made for such pathological conditions as hydrocephalus. The head measurements of the children with low intelligence in the Development Center, San Francisco, fell below the lowest of the standard norm (Pryor and Thelander, 1968). Size is not the only significant finding. Many defective children have peculiar heads. Synostosis of the sutures can cause marked abnormalities, depending on which sutures are closed. Asymmetries are common. Exaggerated flattening of the occiput or marked narrowing of the frontal region is frequent.

Fingerprinting is an accepted practice. Few Americans escape being fingerprinted at some time or another. For many years, all newborns had footprints taken, though I cannot recall when the practice was discontinued. The hands of mongoloid children, especially the palmar markings--of which the simian line is a relatively common feature--have been observed for many years. However, it is only within the past 10 or 15 years that dermatoglyphics have aroused much interest.

According to Cummins and Midlo (1961), the volar pads appear about the sixth week of development. At the close of the second month, when the fetus is about 2.5 cm, the digits become elongated and separate. The pads of the palms and fingers appear as localized bulges; in the next 4 weeks these pads become more rounded and distinct. Then, around the 13th week, when the fetus is approximately 7 cm in length, the

elevations are reduced and flattened, particularly in the thenar and hypothenar areas, and the palms become depressed. The ridges appear between the third and fourth months, but are not elevated on the skin surfaces until about 4-1/2 months. The whorls, loops and arches become distinct on the fingers first and, later, on the soles of the feet.

Many authors call attention to the occurrence of minor but suggestive malformations in parents, siblings or more remote relatives of the handicapped proband, such as widely-spaced eyes in the relatives of individuals with cleft palate, skin dimples or ear tabs in relatives of children with the First Arch syndrome. Two children in my practice had bilateral simian lines, but were highly intelligent and normal in all respects. One family had no more children and adopted a child; in the other, the mother aborted a couple of pregnancies after the first child and had no more. Because it is difficult to follow families long enough to determine later events, one resorts to animal experimentation then worries about extrapolation.

A recent book by Elbualy and Schindeler (1971) covers all facets of dermatoglyphics.

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EXTRAPOLATION: REWARDS AND PERILS

It is an advantage for a child to be reared on a farm, especially on a small farm with diversified activities. If the family also speaks a foreign language and lives in a northern climate with four seasons, the input can be very great. The child's acquaintance with animals ranges from the domestic (chickens, pigs, sheep, cattle and horses) to wild (which may include rabbits, gophers, the wolf through its howls on winter evenings, the beavers in their dams across the spring stream, crows who caw and doves that coo; even the skunk smell will become familiar). When he reaches for a downy yellow chick in the presence of its mother, he will learn quickly of the female's fury when her young are threatened--a rather consistent trait in man and animals. (Does the crowing of the male mean that fathers tend to be 'cocky'?) But when the newborn colt struggles to stand up on his long spindly legs and immediately knows where to find nourishment, the contrast between the foal and the helpless human infant is startling.

Young immigrant farmers perhaps did not have time to collect a library, but reading the Bible and Pilgrim's Progress from cover to cover in Swedish may not have been a bad way to learn about man's aggressive tendencies or aspirations.

From my library shelves I have refreshed my memory on several books pertaining to animals. "Rascal" is a delightful book by Sterling North (1963) about a lad's adventures with a

pet racoon. He, too, marvelled that one so young and without a mother to teach him, knew exactly how to catch minnows.

"King Solomon's Ring" (1952) by the great naturalist, Konrad Lorenz is a delightful book about his menagerie of small animals, especially birds--both domestic and wild. In general, birds attach themselves to the first living creature that contacts them, man or feathered friend, but not the mallard which runs away and huddles in a corner. But, when a farmyard duck hatches out the mallards, they accept her as readily as if she had been their own kind. Lorenz concluded that the secret was in the call note. What the duck had in common with the mallard was that the progenitor of the farmyard duck was the mallard. Lorenz' other book "On Aggression" (1963) deals more with 'territory' and its defence by animals, also with the 'pecking order' and the acquisition of weapons in man. In the author's own words, it carries a warning: "I am convinced that in the near future very many men--indeed, perhaps the majority of mankind--will regard as obvious and banal truth all that I have written in this book about intraspecific aggression and the dangers which its perversions entail for humanity." Its serious purpose robs it of the naive charm of "King Solomon's Ring." In "African Genesis" (1961), Robert Ardrey refers frequently to the work of Lorenz. His conclusions obviously have been influenced by Lorenz' studies, as well as by much other work in the preceding 20 to 30 years.

The delightful "Man and Dolphin" (1961) by John C. Lilly takes us into the world of the sea. A few years ago, when I visited Lilly's laboratory on St. Thomas Island, he was experimenting with communication with dolphins. The intelligence and the dolphin's friendship with man is legendary. Although originally many of the tales about them were regarded as myths, in more recent times many of the stories have been verified and dolphins now are utilized by navy personnel. Dolphins, whales, porpoises and even seals have many characteristics in common, but there is considerable difference in their ability to learn or to be trained by men.

Emily Hahn describes the different primate centers in the United States and the types of work being done in them--from Yerkes in Orange Park to the Center at Davis. She details the efforts to teach apes to talk--one was able to say 'mama', 'papa', 'cup'. Their lack of ability to speak is attributed to the anatomy of the larynx and pharynx. (I wonder if their anatomy has been compared with that of the talking parrot.) When all efforts to make monkeys talk had failed, it was concluded that the ape was a chimpanzee and not a child. On generalizations, Hahn makes the following comment: "...on primates there are as many systems of family, mating and dominance as there are primate species. Which must we accept as the shining example of domestic peace and happiness--the promiscuous chimpanzee, the easy going gorilla, or the monogamous gibbon?"

In "The New Knowledge of Dog Behavior" (1963), Pfaffenberger who was then Vice-President of Guide Dogs for the Blind, described the painstaking studies of dog traits and the critical learning periods. It takes at least 10 years of meticulous selection for desirable traits and elimination of failures in each litter in order to get a breed that is reliable. Traits are inherited independently of each other. The animal can fail in his training if only one trait is missing. No wonder it is rewarding, he says: "to get a great individual or, better still, a great dominant strain".

A friend who has had considerable experience with raising Siamese cats relates that when they were first introduced to England and then to the United States, they were large animals, clannish, and banded together to avoid other kinds of felines. Breeders tried to breed out the undesirable characteristics, and produced a cat with other undesirable traits. As the body and head became longer, the animal was sometimes born with receding chin, narrow forehead, cleft palate, and low intelligence. Cryptorchid males were sterile if the condition was bilateral; the inherited unilateral trait with inbreeding was apt to appear in the offspring as bilateral, with sterility in the male (humans with bilateral cryptorchidism are also sterile). With inbreeding, many other undesirable congenital anomalies also appeared, such as atresia, extrophy, and high mortality.

The National Academy of Science Report #1685, "Prenatal and Postnatal Mortality in Cattle" (1968) is another informative study, with the subject of calf losses divided into genetic, nutritional and those aspects due to disease. The methods used to breed out undesirable traits or to preserve desirable ones are interesting. Infections appear to play a much greater role in animal fetal wastage than in man. Very few epizootic diseases are transmissible to man, and each species of animal appears to have his own parasites. When I was first in practice, both human and bovine tuberculin tests were done on children, but this has since been abandoned. Even psychiatrists (Harlow et al 1971) have found it expedient to subject monkeys to surrogate mothers, periods of isolation, immobilization and depression in order to learn more about human psychopathology.

The smaller animals used for experimental purposes have not been mentioned, but the farther down the scale one goes the more care must be practiced in extrapolating from animal to man. The study of all living things has contributed to knowledge of our own species--Mendel to genetics and Darwin to evolution, are merely two examples. In mathematics "things equal to the same thing are equal to each other", but in the animal kingdom no two beings are ever alike. The subtle variations between individuals of the same species puts the biologist on constant guard in interpreting or applying results observed in studies of one animal to that of another species. There are many iatrogenic conditions in man to illustrate the tragic results which have ensued from such extrapolations. On

the other hand, medical science owes much of its progress to observations on lower animals and undoubtedly much could be learned from closer working relations and sharing of experiences with scientists in animal husbandry.

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REFLECTIONS

The study of human development, the environment in which it takes place, comparison with other species, the significance of stigmata and even the folklore surrounding it, is an awesome task. It is difficult to view one's own species with objectivity, and one's own finality prevents one from following individuals over an indefinite period of time. Pedigrees, statistics and extrapolation from animal observations have definite limitations, and there is not even an ideal model of human design for comparison.

As science progresses, more is learned about structure and function of the body, including the ultramicroscopic organiation of cells. Electrophoresis has made it possible to analyze enzymes, hormones and gamma globulins. It should be possible to establish profiles of these that could be used as indicators of health and disease. Nerenberg (1969), former pathologist at Children's Hospital, San Francisco, already has done this to a degree (by electrophoresis of a small amount of blood), elements that are known precursors of pathology can be detected and Cheek (1968) has moved a long way toward a total understanding of human structure and function.

Other unknowns and uncertainties of development could be clarified by the joint efforts of several specialties. One of these is the phenomenon of immunity and rejection. The

possible relation of this to blood incompatibilities could and should be investigated further in newborn nurseries and in institutions for the handicapped.

Fertility studies have sometimes shown inactivation of the sperm; the role of this type of rejection in the production of anomalies should be clarified. There are few studies on the role of pathological sperm in congenital anomalies. Sperm freezing, artificial insemination and vasectomy with later repair are practiced without careful or long-term followup of results. It is not enough to look only for the immediate gross defects, there must also be concern for the future health, life span and mental functioning of the progeny. Since infertility and sterility appear with equal frequency in the sexes, successful treatment must include a study of the resultant progeny for defects, especially mental retardation.

The association of the aging process and congenital anomalies needs further investigation, and should include both parents as well as both extremes of the fertility period--youth as well as senility. There is evidence also that the age of the ova and sperm, regardless of the age of the individual, may be a factor. Does the ova age? Or, is it the unfavorable environment of the elderly mother that predisposes to anomalies in the progeny?

We did not recognize that the fetus was vulnerable until thalidomide and rubella shocked us out of our smugness.

However, the aftershock resulted in everything being suspect--drugs, toxins, infection, and even emotions. This review has placed those dangers in perspective for me.

The embryo seems remarkably well protected; only a relatively few things apparently harm it. To date, rubella remains unique among infections and, except for thalidomide and aminopterin, the embryo seems capable of handling most drugs effectively. With the marked variation in drug toxicity between species, all drugs should remain suspect until proven safe. Emotions run so high regarding radiation that, for the present, the fetus is probably to be considered relatively safe from it.

The latter part of pregnancy puts the greatest strain on both the mother and fetus. In this phase, nutrition becomes important in order for the mother to carry the infant to term, with successful delivery, and without such dire consequences as toxemia, premature delivery, small-for-age infant, or pathological delivery. There is no conclusive evidence that malnutrition in humans produces congenital anomalies; even its role in mental retardation needs much further investigation. Sylvia Hoag (personal communication) has indicated that blood cells seem to have the capacity to extract from the most deprived mother the necessary ingredients to survive; under these circumstances even the fetus seems to develop at the expense of the mother. Phylogeny has probably looked out for the species!

Genetics has opened up a vast field for research. Since all humans carry a number of defective genes, the role of all extraneous factors is probably to enhance the expressivity and

the penetration of those which are defective. The question of nature versus nurture has surfaced again, with emphasis on the role of poverty, malnutrition, working mothers, one-parent families and deprivation as the major cause of poor performance of the young. The impression conveyed through the literature and especially the news media, is that if we fed them and loved them, geniuses would sprout all about us. This concept is bound to be doomed. Early stimulation may help an individual to more nearly reach his inherent potential, but it probably cannot alter the ceiling of that potential.

It is even possible that excessive stimulation in early infancy and childhood may be detrimental. The young child may need a slower pace while undergoing rapid physical growth in order to avoid exhaustion of motivation and creativity. What happens to the child who never has a chance to anticipate, wish for or yearn for things?

The study of nursery schools and day care centers prompted my suggestion that students, like faculty, should have sabbaticals. Apparently others have felt this need, too, as suggested in a recent Sunday supplement of the San Francisco Examiner-Chronicle in its article, "New Course at Davis--Dropping Out".

The improvement of gene pools in humans has been left entirely to chance. In the past, in order to preserve royal lines, kings, queens and emperors usually selected royal mates

for their progeny, but in so doing some inheritable diseases plagued the families--notably hemophilia. Parent-planned marriages have been practiced in many cultures, usually for reasons of wealth or prestige, not for racial improvement.

One possible study occurs to me. The selection of medical students in the United States is done with considerable care from a large pool of applicants and for traits such as intelligence, motivation and ideals. There have been sufficient marriages of medical women to medical men to make a study of their progeny feasible. Although such a study would not meet all scientific criteria, it might prove to be of interest.

Another possibility is an improvement in health education in the schools. Children are now sophisticated enough to be given information regarding human development at an age when curiosity is high and sexuality low.

Siblings of a handicapped child have asked me about the heredity of a condition if they should marry. Even couples who have handicaps in the family ask for birth control information because they want to marry, but want to adopt children instead of taking a chance of passing on an undesirable trait.

Many people are gravely concerned with the publicity given to "genetic engineering". Scientists realize the difficulties inherent in this field. Any major accomplishments are remote, if at all possible, but readers and listeners who are aware of the fulfillment of many tales from science fiction or

the "Brave New World" are worried and frightened by the idea.

Invasion of the pregnant uterus by amniocentesis and abortion causes grave concern among other groups (Fairweather and Walker, 1964; Queenan and Adams, 1964; Misenhimer, 1966). Are we destroying the normal fetus with good potential, while the careless, indifferent, and those of low mentality continue to reproduce? There is evidence already that young girls who have abortions and later have an abnormal child suffer severe depression and guilt. We will not know the full psychiatric impact of present practices for another couple of decades.

The beginning awareness of peoples all over the world who are still living in primitive conditions may have a tremendous impact on civilization as it is known at present. On one of my travels "down-under" (Australia), I asked a physician on the tour, "What will the world be like 100 years from now?" His reply was: "It won't be white." The integration of all races and ethnic groups in one FAMILY OF MAN is not going to be a smooth process. We may be in for a stormy century.

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Lecture given to Freshmen Med. Students later used by the Recreation Center

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Fleishhacker Pool Building
Great Highway near Sloat Boulevard
San Francisco, California 94132

FAMILY REACTION TO BIRTH DEFECTS

By H. E. Thelander, M.D.
August 23, 1971

The birth of a defective infant is a traumatic experience for a family. It is especially so for the mother. She has borne the baby for nine months with certain hopes and expectations. She therefore not only mourns for the child she had anticipated but she feels she is a failure. She may be concerned about her husband's reaction, her own family's disappointment and her in-laws. She wonders what she might have done wrong or what she may have left undone. She may have feelings of guilt because she took drugs, smoked pot or she may have had an elective abortion in the past that now haunts her.

The incidence of defective infants, as Dr. Tooley noted, is high. No matter what specialty you may choose, you are certain to be involved at some time. Although the brunt falls on the obstetrician, the pediatrician or the family physician, the plastic surgeon will start repair on a hare-lip before the infant leaves the nursery; the orthopedist puts casts on club feet equally early, the ophthamologist may be called for suspected cataracts, the otologist for possible deafness if the mother was exposed to German measles; even the internist will be consulted by the parents to see if they have some defect or inheritable disease.

Should the mother be told about the defect immediately? Should she be shown the child? A bilateral hare-lip and cleft palate, for

instance, can be very shocking to look at. It looks like a big hole where the face should be. Mental retardation is one of the defects that worries parents the most. If the infant is a mongol, Down's syndrome, do you tell the parents immediately? Most mothers are awake when the child is born. Her usual first question is, "Is he OK?" - if he isn't, how do you handle the situation? I suggest that you discuss these things now in seminars and on rounds to clarify your own reactions and get rid of your hang-ups if you have any.

I can give you some examples from my own experience. A decade or two ago, it was customary for the doctor to say to the parents of a mongol, "This child is defective, put him away, don't let the mother see it. Try again, better luck next time." One mother said she had followed this advice. But after three or four years she decided to go to Sonoma and see her child. He was a little mongol up and playing with the rest, gentle and happy. It was a great relief for her. She had pictured him as some sort of monster not fit to be seen. Another mother with a family of seven children had a mongol. Upon the advice of her physician, nurses, priest and family members, the child was placed in a foster home. After three or four months, that home folded and another place had to be found. The parents then decided to have a family council and abide by the decision of the children. The teen age daughter's reaction was, "How do I know that I wont have one some day? Let's take care of him ourselves." This was done and when the mother told me about it she said for the first time since his birth, the family was happy.

Some defects are discovered only after the infant is in the nursery. This may be true of bowel atresia, congenital heart; urinary obstruction and many others. Mothers are very intuitive. At the

Pediatric meeting in October, a film was shown of a taped recording of an interview with a mother who had been exposed to measles during her pregnancy. At the time of delivery no gross defects were noted. The next morning she said she heard the nurses bringing the babies to the rooms up and down the hall but no one came to her room. Then she heard two nurses say something about a blind baby and immediately she knew it was hers. When her doctor finally came in and told her the baby had cataracts, she was greatly relieved for she had imagined all sorts of terrible things. When I first started practice, a girl who had been a volunteer in my clinic, asked me if I would care for her baby when it arrived. When I was called, I found a beautiful little boy but when I put my stethoscope to the chest there was a loud heart murmur. I called the obstetrician and he said, "Don't tell Dorothy, I want to tell her first." I then called her husband and he also said, "Don't tell Dorothy, I want to be there." So I went in to see Dorothy and said "Congratulations, you have a beautiful boy." She looked up at me and said, "Has he a heart murmur?" Of course my walls came tumbling down. I said, "What made you ask?" She said, "I don't know." The moral of course is to tell a mother about the defect when <u>you</u> know it. It is also important to keep your lines of communication open with other doctors involved. It can be very embarassing for an obstetrician to find a mother in tears and she tells him what is wrong with the baby. Do unto others!

It is well to remember also that when you break the news to the mother she hears very little of what you tell her. It is important that you make frequent calls and give her time to ask questions. This is a time when you stand by and give support. She may have fears that she does not know how to express. One mother was afraid

the child's condition might cause sudden death. She might find him lifeless some morning. But she also feared that if she asked, the doctor might interpret it that she hoped this would happen. When you are in doubt about the mother's question, ask her one in turn. This gives you a little time to think and also she may reveal some thoughts that had not even occurred to you. I recall one instance when a mother brought her child in with a bladder infection. She seemed unduly concerned and I seemed unable to find the cause. After considerable conversation she said, "It isn't cancer, is it?" This was so remote it had never occurred to me.

I used this question method a great deal in a third type of situation, in the slightly or even moderately retarded child without other defects. The condition may not be detected until the child is several years old, sometimes not until he starts kintergarten or even first grade. This can be a very shattering blow to the family. Suppose a six year old comes up with an IQ of 70, and the mother comes to you for the results of the test. I had the mother tell me first. I might say, "How do you see this youngster? How does he compare with the other children in the family or in the neighborhood?" Unless the mother is very young or naive she will give you a very accurate estimate. If she describes her six year old as performing like a four year old, you can say, "That's what the test shows, too." If she wants a figure, you can say, "Two-thirds of his actual age, or about 60%." Again, it is very important that you stand by her. Have her come back as often as she likes but always make a definite appointment in addition, for if you do not, she is very apt to interpret it that you do not want to see him. A retarded or handicapped child is entitled to the same kind of routine care that is given to any child. His immunizations, routine physical examinations, and any other

treatment that may be indicated.

The great majority of parents with a retarded child adjust to the situation and make plans accordingly. Fortunately, communities have improved a great deal over the past ten or fifteen years, and there are many more facilities for these children. This has been accomplished largely due to the efforts of parents. Almost every major chronic disease entity has its own organization: muscular dystrophy, cerebral palsy, hemophiliac, etc, ad infinitum.

Occasionally you encounter a parent who does not adjust or who adapts to the situation in a peculiar manner. One father who married late wanted a son and heir. Their only child was mongoloid. I saw the child and mother for several years until the boy was five or six years old and the mother said her husband still insisted the child was normal and would be all right. I don't know the end to that story. One day a young couple came into see me with a very severely handicapped child of ten months. As they came into the room the mother looked very beligerent and said, "You are going to say my child as Cerebral Palsy. Well, she does not!" We had the mother watch us give the child some physiotherapy hoping that giving her a chance to talk to several people on the staff and other mothers attending the facility, she might make some kind of adjustment. The last I heard of that family was that the man had obtained a divorce and the mother and child had returned to Europe. This was a war marriage for one of our GIs. Another mother with an equally handicapped child accepted the fact of the handicap but projected onto this child all the hopes and desires she had for a normal child. She would tell us how much the child enjoyed operas, tell us about her favorite arias and a lot of other totally unrealist things that this severely defective child could not possibly comprehend as she

was a severe microcephalic.

In summary, be honest with your patients, tell the family the truth in as far as you know it, stand by and listen and give support. Get rid of any hang-ups you may have regarding the handicapped and retarded, and treat them as human beings, too.

The birth of a defective child is a very traumatic experience for a mother. She needs help and counseling. A child with major defects also undergoes unusual experiences immediately after birth. He has extensive studies and often needs surgery. He may be kept in the hospital several weeks. A defective or handicapped child who may need love and stimulation the most gets less than the normal child. The normal infant is loved, fondled, and caressed; the mother talks to him and plays with him. The mother who is sad and upset may have to be reminded to give her child this same type of stimulation. The early (during newborn period) stimulation of the handicapped child has been given the least attention.

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Great Highway near Sloat Boulevard
San Francisco, California 94132

THE NEEDS OF HANDICAPPED CHILDREN: RECREATION

By H. E. Thelander, M.D.

Infancy.

The child born with a major birth defect such as Hare-lip and Cleft Palate, Down's syndrome (Mongolism), or Hydrocephalus, experiences an infancy and early childhood that is very different from that of the normal wanted and anticipated newborn. He is deprived of the stimulations usually provided by the mother, such as feeding, cuddling, caressing, being talked to, smiled at and played with. The defective child, in contrast, is often hospitalized for weeks and sometimes months; he may be confined to an oxygen tent, he is usually subjected to many diagnostic procedures some of which may be painful and others fatiguing - such as X-rays, spinal taps, pneumo-encephalograms, biopsy or intravenous punctures by inexperienced house staff. Even his feedings may be traumatic. The child with a cleft palate has a great problem swallowing; infants with atresiae may need feeding by colostomy for months, sometimes for years or permanently. Still others must be given all their nourishment by the intravenous route. Sucking is such a basic newborn reflex that even deprivation of satisfying this instinct is an abnormal experience. Many defects require early surgery; hare-lips are often repaired during the first few weeks of life, atresias are emergencies that need prompt attention, and even cardiac surgery may have to be done during the newborn period. This means an anesthetic

in addition to the trauma of surgery and the post-operative pain and discomfort. It may mean weeks of hospitalization.

Superimposed on all of this is the grief of the parents, especially the mother - although in some cultures, if the defect is in a boy, the father may experience a unique and profound grief. The birth of a defective child is a traumatic experience. The mother feels she has failed, she wonders what she did wrong, she worries about the reaction of her husband, of his family, of her own parents and family. She may recall some events of the past - an elective abortion, smoking pot, or even thoughts she had harbored. She may even consider this as "punishment" for these deeds or thoughts. Most of all she grieves for the normal child she had hoped for and anticipated. It takes a long time for a family to adjust to the birth of a defective child.

Often forgotten is the impact of this grief on the child. What is it like to have a mother's tearful face greeting him instead of smiles and caresses? The handicapped even more than the normal needs love, tenderness, caressing and smiles. Unfortunately, the grief often leads to feelings of guilt and over-compensation later, thus again depriving the child of active stimulation toward self-confidence and independence when he is ready to profit from it.

Individuals working with the handicapped need to bear in mind these various reactions within the family and attempt to relieve anxieties and guide the family to more realistic approaches.

Questions and Answers

Bacterial Endocarditis Prophylaxis in Persons With Mitral Insufficiency and Normal Valves

Q Is antibiotic prophylaxis for subacute bacterial endocarditis indicated in the following group of patients: those without structural abnormalities of the cardiac valve but with mitral valve regurgitation related to papillary muscle dysfunction or ventricular dilation secondary to congestive heart failure?

DENNIS J. BAUMAN, MD
Salt Lake City

This inquiry was referred to a cardiologist (Dr Harrison) and an infectious disease specialist (Dr Hoppes).

A There is no final scientific answer to your question. Extrapolating from existing principles relating to the pathophysiological mechanisms necessary for bacterial invasion of either the endocardium or valvular structures in subacute endocarditis, antibiotic prophylaxis in this group of patients would be recommended. Mitral regurgitation can produce damage to the endothelium or to valvular structures. Platelet aggregation would then permit an appropriate nidus for bacterial invasion from the bacteremia that occurs during dental work or minor surgery, or with instrumentation, and suggests a need for antibiotic coverage to such patients. Standard prophylaxis as recommended by the American Heart Association should be given to such patients, in my opinion. While there can be no definitive answer to the question raised, I believe the prudent physician would administer antibiotics in this situation.

DONALD C. HARRISON, MD
Stanford University Medical Center
Stanford, Calif

A Your question is impossible to answer with certainty. Although antibiotic prophylaxis during procedures that are likely to cause transient bacteremia is a generally accepted practice in patients with valvular heart disease, there has never been a controlled study to prove this prevents endocarditis. The true risk of endocarditis in these patients is not known but is probably low. It has been estimated that proof of efficacy of antibiotic prophylaxis would require a carefully controlled study of 5,000 to 10,000 subjects,[1] and the ethics of withholding prophylaxis from certain patients might be questioned.

If the question of prophylaxis for patients with known valvular abnormalities is unanswered, the situation is even less clear with respect to patients who have no structural abnormality of the cardiac valves. Endocarditis can occur on presumably normal heart valves, especially with virulent organisms. Degenerative changes in the endocardium such as calcification and the formation of atheromatous plaques may predispose to endocardial infection. Endocarditis has been reported in association with the following circumstances: calcification of the mitral anulus fibrosis; mitral valve prolapse syndrome; as a complication of myocardial infarction in areas of mural thrombus overlying the infarcted myocardium; at the site of ventricular septal perforation; and in the presence of papillary muscle dysfunction.[2,3]

Even in the face of normal valve leaflets, hemodynamic changes, with flow of blood from a high-pressure zone to a low-pressure zone resulting in a jet effect and turbulence, may lead to endothelial damage and deposition of platelet-fibrin thrombi into which organisms might be implanted. This effect may be lessened in the situation of severe congestive heart failure because of the decreased pressure gradient involved.[4]

In summary, there is no hard evidence to support the use of prophylactic antibiotics in preventing endocarditis even in the presence of known structural abnormalities of cardiac valves. However, since it is generally accepted as reasonable medical practice, the hemodynamic abnormalities that exist in the situation of papillary muscle dysfunction and ventricular dilation secondary to congestive heart failure might just as reasonably call for antibiotic prophylaxis when an audible murmur is present.

Drugs of choice and dosages for the common procedures associated with a transient bacteremia have been recently reviewed in an American Heart Association monograph.[5]

WILLIAM L. HOPPES, MD
Northeastern Ohio Universities
College of Medicine
Canton

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Prophylactic Antibiotic Treatment in Surgery

Q A patient received intravenous antibiotic treatment 24 hours before surgery. During the operation the surgeon noticed a hole in his glove and ordered an additional gram of the drug for the patient. Was this a rational decision?

MD, Panama

A With certain surgical procedures in selected patients, the administration of an appropriate antibiotic in the perioperative period may lessen the risks of postoperative wound infection. The rationale for use of prophylactic antimicrobial drugs is protection during the operation and in the immediate postoperative period when bacterial contamination of the wound is most likely to occur. To be effective, an antimicrobial drug that is active against the potential pathogens should be administered by an appropriate route in sufficient dosage to achieve adequate concentrations in the wound at the time that bacterial contamination is likely to occur. Experimental studies have shown that administration of an antimicrobial drug should be initiated one to two hours before the operation to achieve adequate concentrations in the incision. It is preferable to administer the drug by the systemic route and for no more than 24 to 48 hours postoperatively; more prolonged administration does not appear to be protective and may encourage the development of infections due to resistant organisms.

Every letter must contain the writer's name and address, but these will be omitted on request. Submitted questions are published as space permits and at the discretion of the editor. All inquiries receive a direct mail reply.

In the example cited, if an effective antimicrobial drug was being administered in sufficient dosage by the intravenous route during the specified perioperative period, there would be no demanding reason to administer an additional dose of the drug.

MARTIN C. MCHENRY, MD, MS
Cleveland Clinic Foundation
Cleveland

Episodic Fever of 15 Years' Duration

Q For the past 15 years a 68-year-old woman of Norwegian descent has had febrile episodes approximately four weeks apart, lasting three to four days, that range between 37.5 to 38.3 °C. The first day of the episode frequently is accompanied by syncope. Cold sores appear on her lips during the episodes. About a week after the fever subsides, there is a marked increase of a clear nasal discharge, which continues until the start of the next episode. During this time she also has severe vaginal itching and a thin mucoid discharge. Results of extensive tests were all within normal limits. These have included the following: complete blood cell count; urinalyses; sinus x-ray films; 12-factor automated chemical analysis profiles; febrile agglutinins; urine porphobilinogens; antinuclear antibody; serum protein electrophoresis; lupus erythematosus clot; and various cultures. What are your suggestions for further diagnosis and treatment?

DONALD S. MATTSON, MD
Willmar, Minn

A I do not know precisely what this patient has except that it is not a life-threatening situation. I have never seen a patient with fever of unknown origin of this duration who has turned out to have serious disease.

The symptoms suggest that despite the normal sinus x-ray films, the patient probably has some form of sinusitis that is accompanied by an element of obstruction. When the outflow from the nasal sinuses is obstructed, secretions accumulate and she has fever. When the sinuses drain, the fever disappears.

An outside possibility is CSF rhinorrhea. However, we do not know if there is a history of head trauma. Moreover, CSF rhinorrhea without an occasional bout of meningitis is unusual, and if that condition were present, the fever should appear at the time of the nasal discharge rather than afterward.

It is not clear whether the patient received antibiotic therapy during the bouts of fever. A therapeutic trial with a drug such as erythromycin that would be active against most organisms present in sinusitis might be useful diagnostically if the fever responds.

I cannot connect the vaginal itching with the fever.

In summary, the only additional examination I would suggest is a thorough ear, nose, and throat evaluation in addition to the routine sinus films.

ROBERT G. PETERSDORF, MD
Harvard Medical School
Boston

A The 15-year duration of the recurrent febrile episodes and the absence of other abnormalities make it most unlikely that the episodes are a manifestation of a serious underlying disease such as lymphoma, vasculitis-collagen disorder, or infectious disease. However, brucellosis and tuberculosis should be excluded by means of an agglutination test and a tuberculin skin test. A serology test for malaria is sometimes helpful in atypical cases.

Most likely the patient has "periodic fever." Although colchicine prophylaxis, one tablet (0.6 mg) twice a day for an indefinite period, has been recommended for patients with familial Mediterranean fever, it has helped also to prevent the febrile spells of periodic fever in some of our patients. We do not know the cause of either disease, and there may be an overlap between the two syndromes.

PAUL E. HERMANS, MD
Mayo Clinic
Rochester, Minn

Prune Belly Syndrome

Q The smaller of twins weighed 1,568 g at birth and was found to have prune belly syndrome. The urinary tract was normal and the rectus abdominis muscle appeared normal, but the baby lacked abdominal musculature at the flanks, causing bulging of visible bowel loops at the flanks only. What precautions are advisable in the care of this child? Are there devices, or perhaps surgery, to improve cosmetic appearance?

B. J. BERESFORD, MD
Council Bluffs, Iowa

A The prune belly syndrome consists of absence of most of the musculature of the abdomen, urinary tract abnormalities, and cryptorchidism. It afflicts about one male in 40,000 live births and only rarely has been reported in females. It seems likely that the developmental anomaly that results in the prune belly syndrome in males usually causes fetal death in females. The syndrome is not known to be hereditary, and discordance in twins has been reported.

This baby is unusual in that the urinary tract is normal. The minimum abnormality ordinarily found in prune belly syndrome is tortuosity of the ureters, which is due to the lack of muscular support. Only rarely is this the only abnormality seen on intravenous pyelography. Much more commonly one or both of the kidneys are abnormally small and dysgenic, and hydronephrosis or reflux or both are often present. The middle and lower ureters particularly may be extremely dilated and tortuous. The bladder is often very large and thickened with an urachal diverticulum, and there is residual urine after voiding, predisposing to urinary tract infection even when obstruction or reflux is absent. Surgical correction can be complex, but ureteral straightening, to some degree, and reimplantation into the bladder are often required.

Thus, this baby has the least severe form of the prune belly or metanephretic dysplasia spectrum. The lack of abdominal musculature makes the internal abdominal organs more susceptible to injury, and participation in contact sports is not advised. The cosmetic appearance of the abdominal wall improves considerably though gradually with growth, and the abdomen becomes flattened and more normal in appearance with time. Clothed appearance may be improved by wearing an elastic abdominal binder, but surgical efforts to remove the redundant abdominal wall have not been successful. Although we advise such children not to participate in contact sports, they are not otherwise restricted, and they are encouraged to undertake other types of exercise, such as swimming.

LOWELL R. KING, MD
Northwestern University Medical School
Chicago

Shuttle fatality: Sloppy operations

On March 19, barely three weeks before the maiden launching of the space shuttle, a group of technicians at launchpad 39A in Florida's Kennedy Space Center entered the shuttle's aft compartment to conduct a test. Unbeknownst to them, the compartment was filled with nitrogen gas instead of breathable air. Two members of the team — John G. Bjornstad and Forrest G. Cole — died of oxygen deprivation; three more were rendered unconscious. Other than the three astronauts killed in a 1967 Apollo groundtest fire, Bjornstad and Cole were the only people ever to die from an accident aboard a U. S. spacecraft.

Now the National Aeronautics and Space Administration has issued its official report on the resulting investigation, revealing the cause to be not any hardware malfunction, but a string of communications breakdowns, improperly followed procedures and inadequate safety checks.

The fatal sequence of events began when a March 16 document detailing the test activities omitted mention of the fact that the newly added test (a check for a nitrogen-gas leak) would be conducted with nitrogen still in the compartment. The failure to point out a hazardous environment meant that the document was not processed through either NASA or contractor safety personnel. The omission was repeated in a briefing the next day, and the document survived an approval process by various officials without being questioned. One consequence of the perpetuated oversight was that the sign at the entrance ramp to the shuttle compartment provided no safety warning that could have alerted the technicians. Confusion continued when one of the suffocating men managed to call for help — safety officials did not report the accident for 2½ minutes, an ambulance was delayed at the launch complex gate and a fire alarm was inexplicably ordered on.

The investigating committee's 400-page report contains 19 pages of findings, observations and recommendations for use throughout NASA to prevent similar mishaps, from reinforced chains of command to tighter procedures and better signs. □

Project sunbean: Plant gene transfer

From French bean seed to sunflower, via a crown gall bacterium, is a strange route for a gene. But it is the first step in experiments at the University of Wisconsin applying genetic engineering to crop improvement. John D. Kemp and Timothy Hall report they have used crown gall bacteria to transfer the gene of a major seed storage protein, called phaseolin. The bacteria, carrying the bean gene, cause crown galls on the sunflower. The scientists have named these tumors, transferred into tissue culture, "sunbean." They find that the gene is stable in the sunflower cells and produces the messenger RNA that directs synthesis of phaseolin. But so far the protein itself has not been detected.

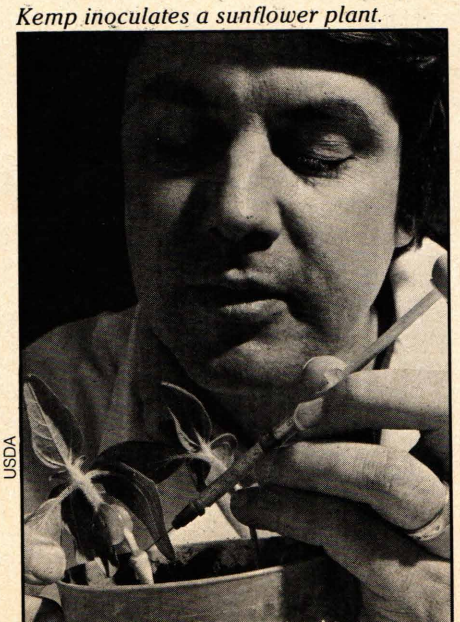
"This breakthrough achievement opens a whole new era in plant genetics. It is the first step toward the day when scientists will be able to increase the nutritive value of plants, to make plants resistant to disease and environmental stresses, and to make them capable of fixing nitrogen from the air," says John R. Block, Secretary of the U. S. Department of Agriculture.

The technique of using crown gall bacteria, or agrobacteria, to introduce genes into plant cells (SN: 7/15/78, p. 45) is employed in many laboratories, and a wide variety of genes have been so transferred. In one case there is preliminary evidence that the gene directs protein synthesis in the infected cells growing in culture. A recent report from a St. Louis group (SN: 4/25/81, p. 270), however, was premature. The scientists there transferred the gene for a yeast enzyme but are still searching for the enzyme in the resultant tumor.

In addition to modifying their methods to promote synthesis of phaseolin in the sunflower gall tissue culture, the Wisconsin scientists hope to regenerate a normal sunflower plant from the tumor cells. A group in West Germany and Belgium has already grown tumor-free tobacco plants from the plant cells infected with a modified agrobacterium. A gene introduced by the bacterium is transmitted as a simple genetic trait when the regenerated plants reproduce. But nobody has yet reported a regenerated plant that demonstrably synthesizes the protein of a foreign gene.

Discovering the effect of the bean gene on a sunflower plant is a quest that may be long and difficult. Therefore, Kemp sees the venture not in terms of immediate rewards, but as "laying the groundwork for 21st century agriculture." □

Kemp inoculates a sunflower plant.



USDA

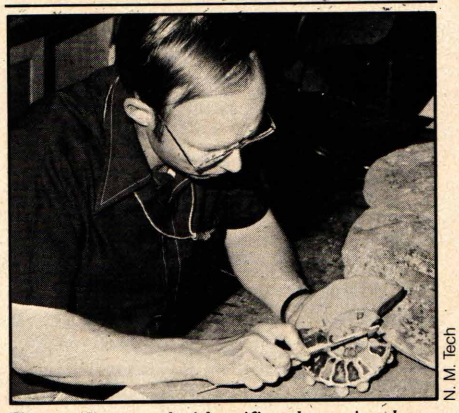
Nuclear safety at DOE is criticized

The Department of Energy nuclear-reactor program "appears deeply flawed when it comes to safety," charged Congressman Edward Markey (D-Mass.) this week in a sharp, seven-page letter to DOE Secretary James Edwards. Markey "urged" DOE to work with the Nuclear Regulatory Commission in reviewing its most serious safety problems and to frame an interagency agreement with NRC, giving the latter "a meaningful safety oversight role."

Despite claims by DOE officials (after the Three Mile Island nuclear accident) that the agency's facilities — including 80 DOE-owned reactors — would match or surpass the safety of commercial facilities, a recent internal DOE report shows that the agency has instead lagged behind the commercial industry in upgrading the training of its plant operators and in instituting lessons learned from the TMI accident. That report, completed under the direction of DOE's principal deputy assistant secretary for nuclear energy, John Crawford, particularly criticized DOE's management of reactor safety and notes "a number of serious deficiencies."

Although DOE has an 80-page "action plan" detailing efforts to upgrade its nuclear safety, Markey told Edwards he was disappointed that DOE had ignored or drastically limited implementation of recommendations contained in Crawford's March report. □

The angle, the age, the oil



N. M. Tech

The coiling angle identifies the animal, which indicates the age and origin of the rock in which it was fossilized, which indicates the potential for finding petroleum. Paleontologist Stephen Hook (above) of the New Mexico Bureau of Mines and Mineral Resources and mathematician Allen Gutjahr of New Mexico Tech worked out equations to determine coiling angles and developed formulae to identify and separate the hundreds-of-millions-of-years-old fossils. This procedure, they say, eliminates much of the subjectivity traditionally involved in identifying these animals and their ages.

BEHAVIOR

Ignorance is paranoia

The paranoid thoughts and behavior that sometimes arise following a hearing loss in an elderly person have been well documented (SN: 11/2/74, p. 280), but the triggers of the paranoia have not been clear. By using hypnosis to induce a temporary hearing loss in healthy college students, psychologists reporting in the June 26 SCIENCE suggest that a lack of awareness of the deafness and the pressures of social situations may push frustrations and anger to paranoia.

Philip G. Zimbardo and Susan M. Andersen of Stanford University, and Loren G. Kabat of the State University of New York at Stony Brook divided 18 easily hypnotized male students into three groups. The test group was given a posthypnotic suggestion of partial deafness without knowledge of the source. One control group was given the same suggestion, but was told to remember how the deafness was induced. The second control group was given a compulsion to scratch an itchy ear, in order to see whether merely carrying out a posthypnotic suggestion with amnesia might irritate subjects enough to induce paranoid behavior. Each subject was then encouraged to cooperate on several tasks with two confederates (students who had full knowledge of the experiment and had not been hypnotized).

"As predicted, the experience of being partially deaf, without being aware of its source, created significant changes in cognitive, emotional and behavioral functioning," the authors report. In addition to scoring significantly higher than controls on several scales used in judging chronic paranoia, subjects in the "deafness-without-awareness" group used significantly more evaluative language (e.g. right and wrong, good and bad) during the experiment, a hallmark of paranoia.

Despite the artificiality of the laboratory test, analogous predicaments occur in daily life, the authors insist. "People's hearing does deteriorate without their realizing it," they say. "Indeed, the onset of deafness among the elderly is sometimes actively denied because recognizing a hearing deficit may be tantamount to acknowledging a greater defect—old age."

Barbiturates and fetal brain cells

What happens to the fetus when a pregnant woman takes barbiturates? While little is known about the consequences in humans, the drugs directly affect the brains of unborn mice, producing long-term behavioral defects, according to investigators from the Hebrew University-Hadassah Medical School.

The research team, headed by Joseph Yanai of the Department of Anatomy and Embryology, found that barbiturates given to pregnant mice kill some developing brain cells in the fetus and damage many that survive. Because the drugs pass into the milk of the lactating mother, the neonate remains vulnerable to the damage as long as it nurses. Those mice exposed to barbiturates perinatally also show an increased susceptibility to barbiturates and alcohol addiction later in life, the researchers say.

These findings could have implications for humans, because barbiturates, a class of drugs that has fallen from favor as a remedy for insomnia (SN: 2/25/78, p. 119), have been given to women late in pregnancy to prevent neonatal jaundice. They are also sometimes administered to epileptic mothers to inhibit seizures and are given to their newborns as treatment for neonatal convulsions. Because of the drugs' therapeutic value, the researchers are now working to pinpoint the mechanisms of damage, hoping to prevent harm to the newborn without hampering drug effectiveness. "We are following up initial findings that barbiturates depress hormone levels, which may be one source of the brain cell damage and a clue to its prevention," says Rachelle H. B. Fishman, of the Albert Einstein College of Medicine in New York, who recently joined the group.

ASTRONOMY

Dietrick E. Thomsen reports from Calgary, Alta., Canada, at the meeting of the American Astronomical Society

Investigating QSO fuzz

Are quasars aka QSO's (that is, quasi-stellar objects) somehow related to the centers of galaxies? This question, still without a final answer, was raised shortly after the first quasars were discovered. Quasars are compact, like galactic centers, and, also like certain active galactic centers, they radiate large amounts of energy from this condensed volume. Quasars might be centers that had never developed galaxies or whose galaxies were invisible for one reason or another.

The discovery of "fuzz" or extended luminosity around several quasars in recent years has heightened the importance of the question. At the meeting J. B. Hutchings of the Dominion Astronomical Observatory in Victoria, B.C., Canada, reported a study of quasar fuzz done by himself, David Crampton of the DAO and Bruce Campbell of the Canada-France-Hawaii Telescope, located on Mauna Kea in Hawaii. They used the prime focus camera of the CFHT to make images of about 25 quasars with redshifts below 0.3 (that is, quasars fairly near to the earth).

Extended luminosity could be distinguished around all of them. The images were good enough to permit the observers to draw profiles of the fall-off of brightness from the centers outward and brightness contours around the centers. It turns out that the brightness profiles for images taken in blue light have a different shape from those in red. The significance of this has not yet been figured out.

In both colors the contour lines have cusps or points at various places. Connecting corresponding cusps from one contour line to the next draws a series of lines curving outward from the center that are shaped like the arms of a spiral galaxy. This geometry is highly suggestive, but what it means exactly is for the moment unclear.

A planetary nebula may be forming

Knowledge of the evolution of stars depends on being able to observe large numbers of them, some of them at each important stage along the path or paths of development. The times involved are too long to follow a single star along. Inevitably there are gaps in a picture drawn this way.

The possible filling of one of those gaps by a star called GL 618 was reported by Sun Kwok and Paul Feldman of the Herzberg Institute of Astrophysics of the National Research Council of Canada. On the basis of studies of this star's radio emission that they did at the Algonquin Radio Observatory in Ontario and the Very Large Array in New Mexico, they believe GL 618 is on the point of ejecting a planetary nebula, as had been proposed by Ben Zuckerman of the University of Maryland.

Theorists believe that this stage is part of the end of the line for old red giant stars. (The sun is expected to become one some day.) At such a moment the star ejects its atmosphere to form a nebula revolving around it and collapses its core to a small, hot white dwarf.

A flare taken with a flair

Most changes in stars come very slowly, but some varieties happen very fast. Flares, for example. Astronomers are always trying to catch flare stars flaring. It can take luck. Bernard M. Haisch of the Lockheed Palo Alto Research Laboratory reported a very complete observation of an X-ray flare on the nearest star to us, Proxima Centauri, that he and Jeffrey Linsky of the Joint Institute for Laboratory Astrophysics at Boulder, Colo., managed to catch simultaneously with the late Einstein Observatory satellite and the International Ultraviolet Explorer. At its peak the flare was 35 times brighter than the star's corona as a whole, and a peak temperature of 20 million degrees was calculated.

The Y Chromosome and Primary Sexual Differentiation

Renée Bernstein, MB, BCh

• **The mammalian Y chromosome plays a dominant role in initiating fetal testicular differentiation. Testicular differentiating genes on the Y chromosome can be serologically detected as H-Y antigen. The correlation of numerical and structural abnormalities of the X and Y chromosomes, combined with H-Y antigen reactivity, gonadal histology, and phenotype, has contributed to mapping the locus of these genes on the Y chromosome and has elucidated some of the mechanisms responsible for anomalous primary sexual differentiation. The causes for failure of gonadal differentiation despite the presence of a Y chromosome or for testicular differentiation in the absence of a detectable Y are discussed. Evidence is presented for genes on the X chromosome that regulate the activity of testicular differentiating genes on the Y chromosome.**

(*JAMA* 1981;245:1953-1956)

SEXUAL dimorphism is a prerequisite for sexual reproduction in higher organisms. This differentiation in mammals is achieved by a series of complex sequential developmental steps ranging from the basic genetic or chromosomal sex to the highest levels of psychosocial sexual behavior (Fig 1). The present review confines itself to the mechanisms initiating and regulating the *primary* basic step in this pathway, namely, the differentiation of the indifferent fetal gonads, which in turn will determine *secondary* sexual development mediated through the hormones secreted by the differentiated fetal testis or ovary.

The role of the sex chromosomes in determining the differentiation of fetal gonads and phenotypic sex is well known. The mammalian Y chromosome is associated with testicular differentiation and "maleness," whereas in the absence of the Y, the phenotype is female.[1] Yet, less than ten years ago Alfred Jost,[2] who has contributed so much to our understanding of the role of the fetal testis and its hormones in male determination, stated that "the processes which impose testicular organization on the gonadal primordium at an early developmental stage still are unknown."

Immunologic evidence for testicular differentiating genes on the Y chromosome has been provided in recent years by the serological detection of a weak sex-specific histocompatibility antigen, the H-Y antigen. This cell surface component is found in the heterogametic (XY) sex of all vertebrates examined and is capable of directly mediating testicular differentiation of the indifferent fetal gonad in mammals; H-Y antigen is present wherever mammalian testicular differentiation has occurred, irrespective of karyotype or phenotype, as reviewed by Wachtel and Ohno.[3] The H-Y antigen reactivity is therefore a remarkably useful diagnostic marker for testicular differentiating genes.

The many instances of gonadal sex at variance with the chromosomal sex[4] are obvious contradictions to the accepted tenets of primary mammalian sexual differentiation. How does one explain the female with a male chromosomal pattern and, conversely, the male with female sex chromosomes, or the hermaphrodite with the genitalia and gonads of both sexes but the sex chromosomes of only one sex?

The study of numerical and structural abnormalities of the sex chromosomes, correlated with H-Y antigen studies, gonadal history, and phenotypic expression in patients with anomalous sexual development, has elucidated the etiology of some of these enigmas in primary sexual differentiation[5] (Table), and the aim of this review is to acquaint the general reader with the present knowledge on this subject.

DOMINANCE OF THE Y CHROMOSOME IN SEX DETERMINATION

Investigation of patients with numerical sex chromosome abnormalities has shown that the male-determining genes on the Y chromosome are obviously extremely potent in inducing testicular differentiation. Patients with a sex chromosome constitution ranging from XXY (Klinefelter's syndrome) to XXXXY always show testicular differentiation (albeit dysgenetic), and their male phenotype is unequivocal despite all the additional X chromosomes.[6] As might be predicted, these patients are H-Y antigen positive, while males possessing an extra Y chromosome (the XYY male) have been shown to have excess amounts of H-Y antigen.[7]

In the absence of a Y chromosome, fetal ovarian differentiation ensues, even if only one X chromosome is present. Mice with a 39,X karyotype are normal fertile females,[8] but in humans[9,10] and other primates such as the baboon,[11] two functionally intact X chromosomes are necessary for survival of the oocyte and maintenance of normal ovarian architecture. Human 45,X fetuses have perfectly normal ovaries with primordial folli-

From the Department of Human Genetics, School of Pathology, the South African Institute for Medical Research and University of the Witwatersrand, Johannesburg, South Africa.

Reprint requests to Department of Human Genetics, University of the Witwatersrand, PO Box 1038, Johannesburg 2000, South Africa (Dr Bernstein).

Clinical Advisory Board: Robert G. Petersdorf, MD, Boston; Helen M. Ranney, MD, San Diego; Philip Leder, MD, Bethesda, Md; Bert W. O'Malley, MD, Houston.

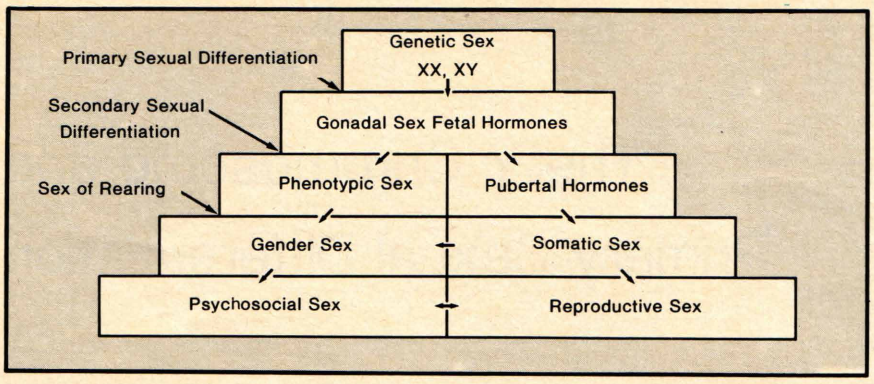


Fig 1.—Levels of mammalian sexual differentiation.

Anomalies in Primary Sexual Differentiation

	Y Chromosome	H-Y Antigen	Gonads	Phenotype
Normal male mammal	+	+	Testes	Male
Yp^- or i(Yq)	+ (Abnormal structure)	− or ±	Streak gonads	Female
XO/XY mosaicism (asymmetrical or mixed gonadal dysgenesis)	− or ± or +	− or ± or +	Streak/ dysgenetic testis	Variable
Pure XY gonadal dysgenesis	+	− or +	Streak gonads	Infertile female
Aberrant Xp Y female wood lemmings	+	−	Ovaries	Fertile female
Human Xp^+Y siblings	+	−	Dysgenetic ovaries	Female with multiple congenital abnormalities
XX male	−	+	Dysgenetic testes	Infertile male
XX true hermaphrodite	−	+	Ovary + testis	Ambiguous

cles, but ovarian regression begins in utero, and streak gonads are the rule by the time of birth.[9]

XY GONADAL DYSGENESIS

If the Y chromosome plays such a dominant role in testicular differentiation, why does it occasionally fail to induce testes, resulting in a phenotypic female with streak gonads? Several causes for XY gonadal dysgenesis have now been identified.

Structural Abnormalities of the Y Chromosome

The first prerequisite for testicular differentiation is a functionally intact Y chromosome. Correlation of phenotype, gonadal histology, H-Y antigen activity, and structural abnormalities of the Y chromosome indicate that there are several copies of testicular differentiating genes pericentrically located on the Y, the majority of these gene copies being localized to the Y short arm.[12] Loss of Yp will, therefore, result in deletion of a critical number of H-Y gene copies. For instance, patients with an isochromosome of the long arm of the Y chromosome, ie, duplication of the long arm and deletion of the short arm [46,Xi(Yq)], are H-Y negative phenotypic females.[12,13] One such female investigated by us had a mosaic karyotype, 45,X/46,Xi(Yq); she had the somatic features of Turner's syndrome and streak gonads, but one of the streaks showed histological evidence of primitive testicular tissue with early tubular formation. A Y-autosome translocation with loss of Yp was associated with a female phenotype, gonadal dysgenesis, and gonadoblastoma.[14] On the other hand, a patient with an isochromosome of Yp and mosaicism for a 45,X cell-line, 45,X/46,Xi(Yp), had testes with ambiguous external genitalia and was strongly H-Y antigen positive.[13]

Loss of the Y Chromosome

Gonadal dysgenesis despite a morphologically normal Y chromosome may be due to loss of the Y from some of the person's cells, ie, XO/XY mosaicism. The degree of gonadal differentiation and phenotypic ambiguity will depend on the proportion of XY cells in different tissues, especially the germ cell-line, and findings may range from females with pure gonadal dysgenesis to males with asymmetric or mixed gonadal dysgenesis, with a unilateral streak gonad and varying degrees of contralateral testicular differentiation and genital ambiguity. The variable expression of 45,X/46,XY moscaicism is illustrated by the following two cases we investigated.

The first patient was a 17-year-old girl with classic features of Turner's syndrome. She had bilateral streak gonads with no histological evidence of testicular differentiation. To our surprise, her peripheral blood karyotype was 46,XY, with only 2.5% of 122 cells showing a 45,X constitution, but 30% of 100 skin cells showed loss of the Y. Her Y chromosome was morphologically normal.

The second patient, aged 1 year, had ambiguous external genitalia. A dysgenetic testis was palpable in the left inguinal canal, and the right testis was replaced by a streak gonad. The phallus was small but erectile, and it was decided to rear the infant as a male. Blood metaphases showed 21% 45,X cells, the streak gonad 94% 45,X cells, and the dysgenetic testis 54% 45,X cells.

Factors Determining H-Y Antigen Expression

In the majority of females with XY gonadal dysgenesis, there is, however, no evidence of an undetected 45,X cell-line or a structural abnormality of the Y chromosome. These patients never show any of the somatic stigmata of Turner's syndrome. In fact, many patients are taller than average, whereas females with Turner's syndrome are characteristically shorter than average, and, unlike the streak gonads of 45,X females, the streaks of females with XY gonadal dysgenesis may show histological evidence of primitive testicular differentiation, and there is a tendency for malignant transformation to occur.[6] Several familial cases of XY gonadal dysgenesis have been documented, and the pedigrees were consistent with either an X-linked recessive or male-limited dominant mode of inheritance, leading to the hypothesis that other genes not on the Y may exert a regulatory effect on the testis-determining genes of the Y chromosome.[15] A curious phenomenon observed in wood lemmings (*Myopus*

schisticolor) has provided circumstantial evidence for this regulatory concept. Nearly one half of female wood lemmings have a male (XY) karyotype inherited as an X-linked trait, yet they have normal ovaries and are normal fertile females.[16] These XY females are H-Y negative[17] and were shown to have an aberrant X short arm.[18]

Investigation of a family with an X-chromosome anomaly[10] has shown a situation in man analogous to the wood lemming. The mentally retarded female proband and an electively aborted female fetus had severe multiple congenital abnormalities, female internal genitalia, and ovarian gonadal differentiation despite the presence of a normal Y chromosome. The fetal ovaries were normal, but findings from autopsy examination of the proband at five years, showed degeneration of both ovaries to bilateral streak gonads. They both possessed an abnormal X chromosome with duplication of the distal portion of Xp, karyotype 46,dup(X) (p21→pter) Y. The Y chromosome was morphologically normal, but both proband and fetus were H-Y antigen negative. Thus, in the functional absence of the testis-determining portion of the Y, the gonads of human XY embryos resemble their XO counterparts with respect to ovarian differentiation and subsequent regression. The abnormal X chromosome was maternally derived, the phenotypically normal mother and grandmother, as well as a normal female sibling, having a karyotype 46,X dup(X) (p21→pter); the abnormal X chromosome was nonrandomly inactivated in these latter persons. It is therefore postulated that H-Y antigen expression was suppressed in proband and fetus because of duplication of a regulator gene (or genes) on the X chromosome. If X-linked regulatory genes normally prevent excess production of H-Y antigen, duplication of these genes may reduce production of H-Y below the critical threshold required for testicular differentiation. Alternatively, abnormality of Xp may exert a position effect interfering with regulatory genes on the X chromosome that normally activate H-Y antigen production.

The H-Y antigen reactivity in males with XY gonadal dysgenesis has varied. Some cases are H-Y antigen negative,[19] a finding in keeping with the suppression of H-Y gene expression by regulatory genes on the X, but others are H-Y antigen positive.[20]

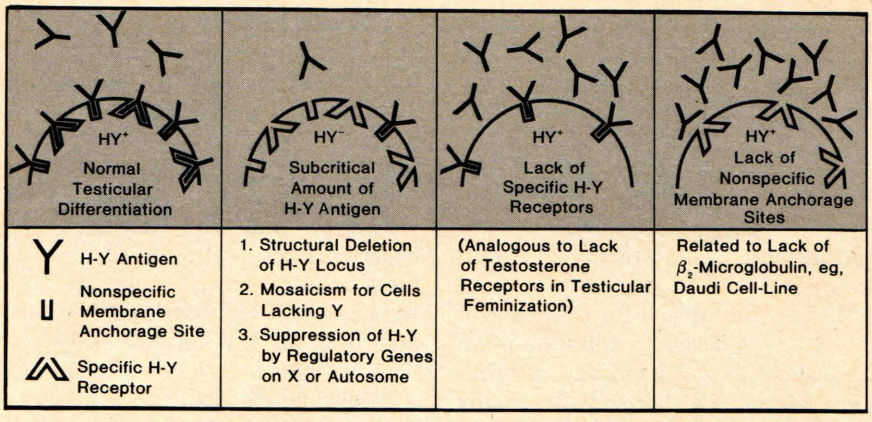


Fig 2.—Etiology of XY gonadal dysgenesis (modified from Wachtel[5]).

A female baboon with 42,XY gonadal dysgenesis[11] was found to be strongly H-Y antigen positive (Stephen S. Wachtel, PhD, written communication, May 21, 1979). This introduces an apparent paradox, because it was previously stated that H-Y antigen positivity is associated with testicular differentiation, but immunologic studies indicate that H-Y antigen can function only if bound by nonspecific membrane anchorage sites[21] to specific receptors on the cell surface of primordial gonadal cells.[22] The concept of a specific receptor deficiency for H-Y antigen is analogous to the testosterone receptor deficiency responsible for the XY female with testicular feminizing syndrome evolving after testicular differentiation has occurred.[6]

Thus, in summary, nonmosaic XY gonadal dysgenesis may result from (1) structural deletion of H-Y genes on Yp, (2) suppression of H-Y antigen activity by mutation of regulatory genes on the X chromosome (or autosomes), (3) lack of specific H-Y antigen receptor sites on the primordial fetal gonad, or (4) lack of nonspecific membrane anchorage sites (Fig 2). The former two mechanisms would be associated with H-Y antigen serological negativity, whereas the latter two modes would show H-Y antigen positivity.

Gonadal Agenesis Associated With Generalized Dysmorphogenesis

In some instances of XY phenotypic females, the indifferent primordial gonad fails to develop altogether as part of a generalized dysmorphogenesis because of an early defect in mesodermal development. This may be due to severely unbalanced autosomal chromosome abnormalities or to the teratogenic effects of an environmental agent acting on the embryo during the early critical stages of organogenesis (three to eight weeks in humans) as is found in its most extreme form in the mermaid anomaly or sirenomelia. The association of XY gonadal dysgenesis with campomelic dysplasia (possibly an autosomal recessive disorder) is at present an unexplained finding.[23]

THE ORIGIN OF XX MALES AND XX TRUE HERMAPHRODITES

The phenotypic male with testes and a female chromosomal constitution—the XX male—has been an enigma since first described in 1964.[24] At least three theories have been proposed to explain this condition:

1. XX males develop from zygotes that originally had a Y chromosome that was subsequently lost, giving rise to mosaicism with the XX cell-line predominating. A Y-containing cell-line has, however, been detected in only a minority of the XX males described.[25]

2. Ferguson-Smith[26] proposed that XX males may arise because of a meiotic X;Y genetic interchange, with translocation of male-determining genes on to the X chromosome. The known end-to-end meiotic association of the X and Y chromosomes by their short arms[27] and anomalous Xg blood-group segregation in XX males[28] favor this hypothesis. The identification of two phenotypic males (one of whom is clinically a typical XX male) with a cytologically identifiable X;Y translocation[29,30] is further circumstantial evidence that morphologically unidentifiable X-Y interchanges may occur. Evans et al[31] demonstrated a

cytological disparity between homologous X short arms in eight of 12 XX males, and Y-specific DNA (unrelated to H-Y antigen) was detected in one of three of these patients tested. These data imply that in at least 70% of XX males, maleness is a consequence of the inheritance of a paternal meiotic X-Y interchange product.[31]

3. The third theory for the origin of XX males is based on mutation of an autosomal gene causing masculinization of an XX fetus. Autosomally determined sex reversal is dominantly transmitted in Sxr XX mice[32] and recessively in polled goats[33] and possibly in man.[34] In all instances, affected individuals tested for H-Y antigen reactivity are H-Y positive.[35,36] Wachtel et al[37] have postulated that autosomal translocation of a critical or subcritical number of H-Y gene copies could explain both dominant and recessive modes of inheritance.

True hermaphroditism is the most common cause of intersexuality in the negroids of southern Africa. Van Niekerk[38] reviewed 278 previously described cases of true hermaphroditism and reported on a further 24 negroid cases investigated by him. The majority of these true hermaphrodites (21 of 24 patients) had an XX karyotype, and this has been our experience as well; all of our 25 histologically proved cases of true hermaphroditism have been negroids, and they all had an XX karyotype with no detectable mosaicism for an XY cell-line. The XX true hermaphrodites tested are H-Y antigen positive.[35] It is thus possible that translocation of a subcritical number of testicular differentiating genes on to an X chromosome or autosome could be responsible for at least some cases of H-Y antigen-positive XX true hermaphrodites, if the number of translocated H-Y genes are sufficient to induce testicular differentiation, but below the critical level required to inhibit ovarian differentiation. The XX male syndrome and XX true hermaphroditism may thus represent a varying spectrum of the same etiologic event.[39] In one case of 46,XX true hermaphroditism, cells from the testicular portion of an ovotestis were H-Y positive, whereas cells from the ovarian portion were H-Y negative, indicating that the ovotestis arose from $H\text{-}Y^{+}/H\text{-}Y^{-}$ mosaic primordial gonadal tissue.[40] This $H\text{-}Y^{+}/H\text{-}Y^{-}$ mosaicism is analogous to the mosaic XY/XX mosaicism one would expect to find in true hermaphroditism.

In conclusion, failure of primary testicular differentiation despite the presence of a Y chromosome and, conversely, the presence of testes in the absence of a Y is multifactorially determined, and the elucidation of these factors has provided an insight into the normal pathways determining fetal gonadal differentiation. Furthermore, the principle of an organogenesis directed molecule that binds to its specific organ receptor site may have wider application to fetal organogenesis as a whole.

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Hazards of Oral Anticoagulants During Pregnancy

Roger E. Stevenson, MD; O. Marion Burton, MD; Gerald J. Ferlauto, MD; Harold A. Taylor, PhD

• **Prenatal exposure to oral anticoagulants during pregnancy may result in defective fetal development or life-threatening hemorrhage. Fetal exposure during the first eight weeks of pregnancy may cause abnormal development of the facial structures, hypoplastic digits, stippled epiphyses, and mental retardation. Midtrimester exposure may result in optic atrophy, faulty brain growth, and developmental retardation. Third-trimester exposure may produce fetal anticoagulation, predisposing the infant to life-threatening hemorrhage in the perinatal period. Anticoagulation with heparin sodium does not provide a clearly safe alternative, since this therapy has been associated with excessive fetal loss.**

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ANTICOAGULANTS that act as vitamin K antagonists pose a substantial hazard to the unborn infant in both embryonic and fetal periods of gestation. These compounds readily cross the placenta, disrupting normal development and causing a state of anticoagulation secondary to deficiency of vitamin-K-dependent factors. Prenatal exposure to these compounds during the first eight weeks of pregnancy has been associated with a characteristic pattern of abnormal development, including midface and nasal hypoplasia, optic atrophy, hypoplasia of the digits, stippled epiphyses, and mental impairment.[1-6] Anticoagulation following the period of embryonic development may lead to fetal death, presumably from hemorrhage, and predisposes the infant to hemorrhage during the course of labor and delivery.[7-12] Preliminary reports suggest that exposure during the second and third trimester may also lead to growth, developmental, and visual impairments.[7,13-14] The seriousness of the hazards of these compounds should call into question the use of oral anticoagulants at any time during the course of pregnancy.

First-Trimester Exposure

Use of oral anticoagulants early in pregnancy may lead to the so-called warfarin embryopathy syndrome, the features of which are exemplified in the following case.

From the Greenwood Genetic Center, Greenwood, SC (Drs Stevenson and Taylor); The Family Practice Center, Anderson, SC (Dr Burton); and Department of Pediatrics, Greenville General Hospital, Greenville, SC (Dr Ferlauto).

Reprint requests to 1020 Spring St at Ellenberg, Greenwood, SC 29646 (Dr Stevenson).

Report of a Case

A female infant born at our hospital after a 31-week gestation weighed 1,049 g and had a head circumference of 29 cm and a length of 37.5 cm. The mother, a 23-year-old primagravida, had rheumatic heart disease at age 12 years and underwent tricuspid and mitral valve replacement one year before becoming pregnant. She took 5 mg of warfarin sodium each night for anticoagulation. Approximately one month before delivery, she experienced hematuria and hemarthrosis of the right knee. At that time, the prothrombin time was prolonged to 42 s.

At birth the infant's head appeared disproportionately large, but the anterior fontanel was flat. The optic discs were pale. The nose appeared underdeveloped, with absence of the nasal bridge and hypoplasia of the ala nasi (Fig 1). The nares were small and directed anteriorly. The palate was intact, and the mandible was small. There was a mild pectus carinatum deformity, and findings of the cardiovascular examination were normal. Severe respiratory distress with cyanosis, retractions, acidosis, depressed muscle tone, poor suck, absent Moro response, and absent deep-tendon reflexes marked the initial hours after delivery.

Mechanical ventilation was required during the first day of life. Following extubation for two days, there was an exacerbation of intercostal retractions and acidosis, necessitating placement of a nasopharyngeal airway tube for one week. Roentgenographic examination showed stippling of the lateral vertebral epiphyses, proximal femoral epiphyses, and tarsal bones (Fig 2). Urine amino acid determinations showed gross elevation of hydroxyproline and glycine levels at age 17 weeks. Repeated analysis at age 16 months showed normal amino acid levels.

At age 16 months, the child's length was 67 cm (less than the third percentile); head size, 47 cm (50th percentile); and weight, 6.8 kg (less than the third percentile). Ophthalmologic examination showed bilateral optic atrophy. There were four deciduous teeth present. Her facial features remained much the same, although the midface hypoplasia did not appear as severe. Dermatoglyphic patterns included five whorls and five ulnar loops. She could not sit alone, pull herself to standing, or use a thumb-finger grasp. In reaching for objects, some searching movement was

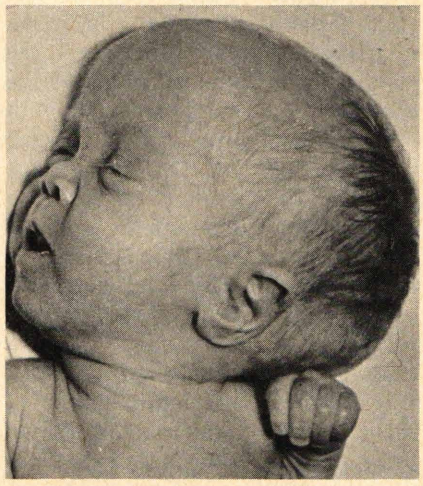

Fig 1.—Patient at age 1 month showing disproportionately large head and underdevelopment of nose and midface.

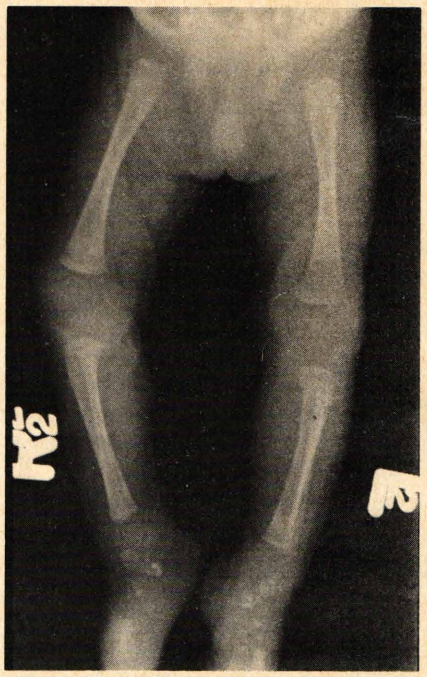

Fig 2.—Lower extremities of patient showing stippling of proximal femurs and tarsal bones.

Features Noted in 15 Infants Exposed to Oral Anticoagulants During First Trimester of Gestation*	
Early delivery	10/15†
Polyhydramnios	3/5
Prenatal growth retardation	4/14
Respiratory distress	10/11
Hypotonia	3/3
Postnatal growth retardation	1/3
Blindness	1/5
Delayed development	2/7
Mental retardation	2/6
Seizures	1/2
Death in infancy	4/15
Midface hypoplasia	9/9
Nasal hypoplasia	15/15
Optic atrophy	3/10
Low-set or malformed pinnae	1/1
Cardiac defect	1/3
Short extremities	5/7
Epiphyseal stippling	10/12
Calcification of thyroid tracheal or laryngeal cartilages	4/14

*In individual cases, hydrocephaly, encephalocele, cataracts, microphthalmos, single umbilical artery, limb asymmetry, joint contractures, dislocation of hips, simian lines, scoliosis, and hemangiomata have been noted.

†Denominator indicates the number of reports in which specific mention of the feature is made.

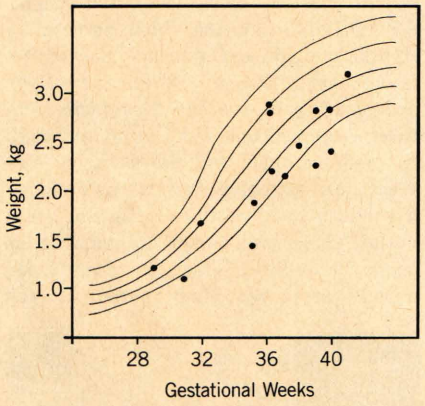

Fig 3.—Birth weight of 15 infants with prenatal warfarin syndrome. Five infants have weights at or above 50th percentile, and five have weights at or below tenth percentile.

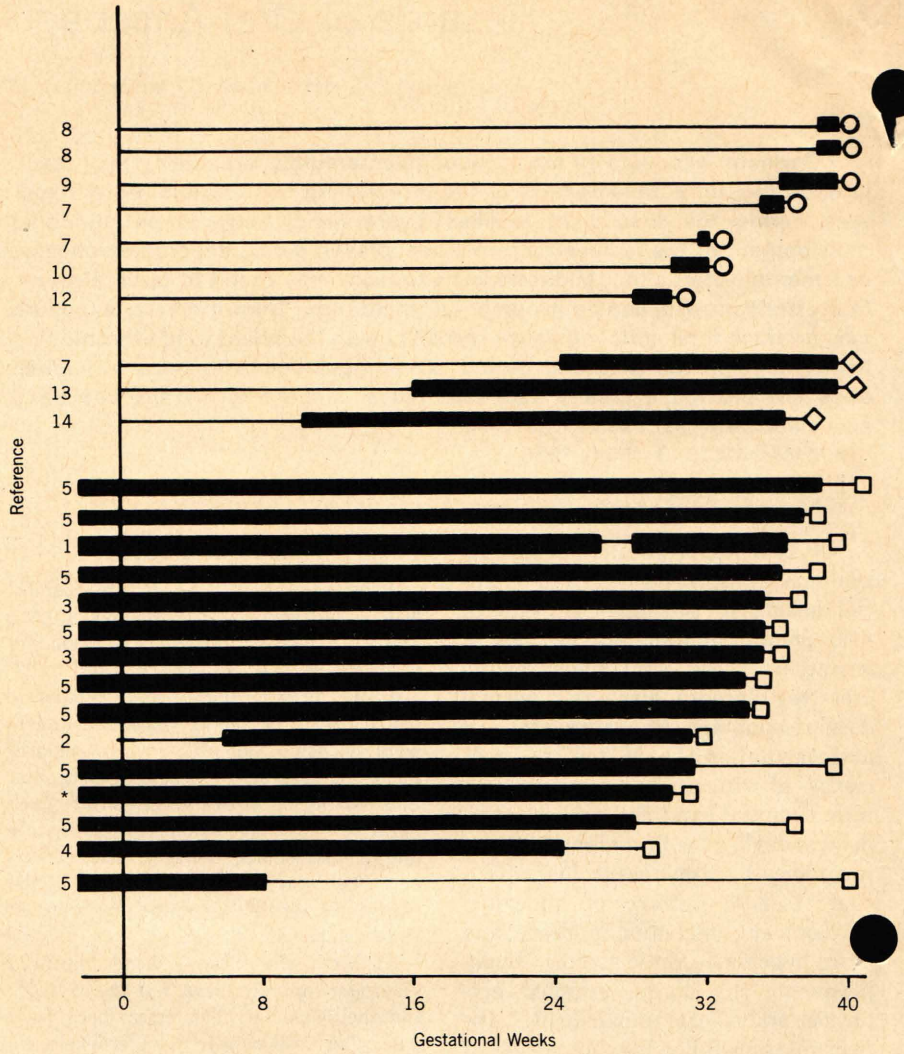

Fig 4.—Relationship of time of warfarin use during pregnancy (heavy bar) and outcome: square indicates prenatal warfarin syndrome; diamond, impaired mental development, growth, and vision; and circle, intrauterine or perinatal hemorrhage. Asterisk indicates patient described in present report.

apparent. Language skills were age-appropriate. Roentgenographic examination showed incorporation of most of the previously noted stippling in normal-appearing bone. Residual stippling could be seen in the distal calcaneus and the second cuneiform. The hyoid and the thyroid cartilages were calcified.

The features noted in previously reported cases of the warfarin embryopathy syndrome are given in the Table.[1-6] The most consistent features are premature delivery, respiratory distress secondary to small nasal airway or prematurity, midface hypoplasia, nasal hypoplasia, and widespread stippling of the bony epiphyses. Skeletal features have been noted in an infant exposed during only the first eight gestational weeks[5] and in an infant with exposure beginning in the sixth gestational week.[2] More serious complications, optic atrophy with blindness and delayed development, occur in one fourth of the infants. Evidence that growth failure is a component of the syndrome, however, must be considered tenuous at this point. The prenatal and postnatal growth pattern falls within the normal range as a general rule, although there are certain exceptions to this (Fig 3). Moreover, the contribution of the underlying maternal disease to some growth impairment in the fetus cannot as yet be dismissed.

The pathogenic mechanism by which the abnormalities in the warfarin embryopathy syndrome arise is not yet understood. Although microhemorrhages during intrauterine life have been suggested as a possible basis, one may more easily envision recurrence of this rather specific pattern of abnormal features as the direct result of vitamin K deficiency or oral anticoagulant exposure. Barr and Burdi[6] have presented limited pathological evidence suggesting that focal hemorrhage is not responsible for the abnormalities in the warfarin embryopathy syndrome. They could find no hemosiderin deposits in areas of disordered chondrogenesis in an affected 17-week fetus.

Second-Trimester Exposure

During the period following [illegible] phological development, maternal use

of oral anticoagulants may cause fetal anticoagulation, predisposing to the hazard of intrauterine or parturitional hemorrhage (Fig 4). Limited experience suggests that prenatal exposure beginning in the second trimester may impair mental development, growth, and vision as well.[7,13,14]

Quenneville and associates[7] reported the occurrence of optic atrophy, microcephaly, and cerebral agenesis in an infant exposed from the 24th week until term. Sherman and Hall[13] described an infant whose mother took warfarin during the last six months of pregnancy.[13] The infant had notable microcephaly, bifrontal narrowing, hypotonia, delayed development, and possible blindness. The epiphyses showed no stippling. A case of an infant with similar features (microcephaly, bifrontal narrowing, mental retardation, and blindness) has been reported by Carson and Reid.[14] The mother had received warfarin from weeks 12 through 36 of the pregnancy as treatment of deep venous thrombosis.

Third-Trimester Exposure

Vitamin K antagonists in doses adequate to anticoagulate the blood of mothers (prothrombin time in the range of 25 to 35 s) reach the fetus and may simultaneously anticoagulate fetal blood. Intrauterine hemorrhage may occur despite maintenance of the maternal prothrombin time within the stated safe range. The literature now contains several cases that attest to this unfortunate consequence of maternal therapy (Fig 4).[7-12]

Gordon and Dean[8] described twins born at term to a woman treated with ethyl biscoumacetate throughout the 38th week of pregnancy for deep femoral thrombosis. The prothrombin time was never greater than 35 s, nor was the prothrombin index less than 40%. The twins were born at term, one week after discontinuing anticoagulant therapy. The first infant was stillborn, with autopsy findings of intracranial, pericardial, testicular, and gastrointestinal hemorrhage. Twin 2 had neuromuscular depression at birth and, during the first day, experienced cutaneous and umbilical cord hemorrhages. Examination of ventricular fluid at age 3 days showed the presence of old blood. Subsequently hydrocephaly developed in the infant, and the infant failed to thrive, dying at age 35 days.

In a case described by von Sydow,[9] the mother received warfarin during the final month of pregnancy. The infant was anticoagulated at birth and experienced extensive cutaneous hemorrhages within a few hours. Signs of hydrocephalus, presumed to be the residual effect of intracranial hemorrhage, became apparent at age 3 weeks.

Additional cases of fetal or neonatal death associated with oral anticoagulant use during the third trimester are shown in Fig 4. Placental hemorrhage may have contributed to fetal death in the cases reported by Mahairas and Weingold,[10] Quenneville et al[7] (case 3), and Palacious-Macedo et al[11] (case 2).

Comment

Prenatal exposure to oral anticoagulants may result in abnormalities of both structure and function. No period of pregnancy can be considered safe for the use of these agents. Use early in pregnancy may lead to the warfarin embryopathy syndrome. During the period following morphological development, the fetus is predisposed to the hazards of intrauterine or parturitional hemorrhage because of fetal anticoagulation. During this period the fetus may suffer CNS or ocular damage as well.

No precise figure for the risk of perinatal hemorrhage or malformation in infants exposed prenatally to oral anticoagulants can be given. Several larger series reporting on the use of oral anticoagulants during pregnancy suggest that most infants will suffer no adverse consequences of their in utero exposure.[15-16] However, those infants who are affected have serious and, in some cases, fatal consequences. Published studies suggest the risk of perinatal hemorrhage from second- and third-trimester exposure to be 5% to 10% and the risk of malformations from first-trimester exposure to be 15% to 25%.[5,7,10-11,15-16]

The possibility of serious sequelae from oral anticoagulant exposure dictates caution in their use at any time during pregnancy. Heparin has not been associated with fetal anticoagulation or anomalous development and theoretically should be considered the anticoagulant of choice during pregnancy.

In practice, heparin has not been shown clearly to be a safe alternative anticoagulant. Pregnancies in which heparin has been used have had excessive maternal deaths, fetal loss, and premature delivery, results that may be related to the drug or to the maternal disorder requiring anticoagulation.[17] Heparin use entails the additional inconvenience and complications of parenteral administration.

Women requiring anticoagulation should be informed both of the potential for defective fetal development when the oral anticoagulants are used during pregnancy and of the threat to successful completion of pregnancy when any anticoagulant is used.

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Clinical Note

Acute Myocardial Infarction in Idiopathic Hypertrophic Subaortic Stenosis

M. R. Sasidharan Nair, MD; Wolf F. C. Duvernoy, MD; Eldred G. Zobl, MD

ANGINA pectoris, syncope, sudden death, and ECG changes simulating acute myocardial infarction are all well-recognized features of idiopathic hypertrophic subaortic stenosis (IHSS).[1,2] Acute myocardial infarction associated with coronary artery disease has been described in patients with IHSS.[3] Acute myocardial infarction occurring in young patients with IHSS in the presence of normal coronary arteries, verified by either arteriography or necropsy, has been described only rarely.[4-6]

For editorial comment see p 1554.

Report of a Case

A 19-year-old man was seen in the emergency room of Providence Hospital, Southfield, Mich, complaining of palpitations and severe crushing retrosternal chest pain starting suddenly after shoveling snow on Jan 27, 1978. Idiopathic hypertrophic subaortic stenosis had been diagnosed in this patient in June 1973. An echocardiogram in May 1977 showed asymmetric septal hypertrophy with a septal thickness of 18 to 20 mm and left ventricular wall thickness of 8 mm, giving a ratio of 2.25 to 2.5, and marked systolic anterior motion of the mitral valve (Fig 1). The patient's father was also known to have IHSS. In July 1976, the patient began to have anginal pain, exertional dyspnea, and palpitations that responded well to propranolol hydrochloride, 80 mg daily in divided doses. On examination, he appeared acutely ill. His pulse was irregularly irregular at a rate of 180 beats per minute. His blood pressure was 140/90 mm Hg. The neck veins were flat and the lungs clear. A grade 3/6 systolic ejection murmur was heard best at the lower left sternal border; it increased in intensity during the Valsalva maneuver and decreased with straight leg raising. The ECG at the time of admission showed atrial fibrillation with rapid ventricular response and marked lateral ST segment depression (Fig 2). His symptoms improved and the ventricular rate slowed after he was given 2 mg of propranolol hydrochloride intravenously (IV). A 40-mg dose of the drug was then given every six hours. On the following day, the rhythm reverted to sinus. The ECG subsequently showed left ventricular hypertrophy similar to that seen in previous recordings and

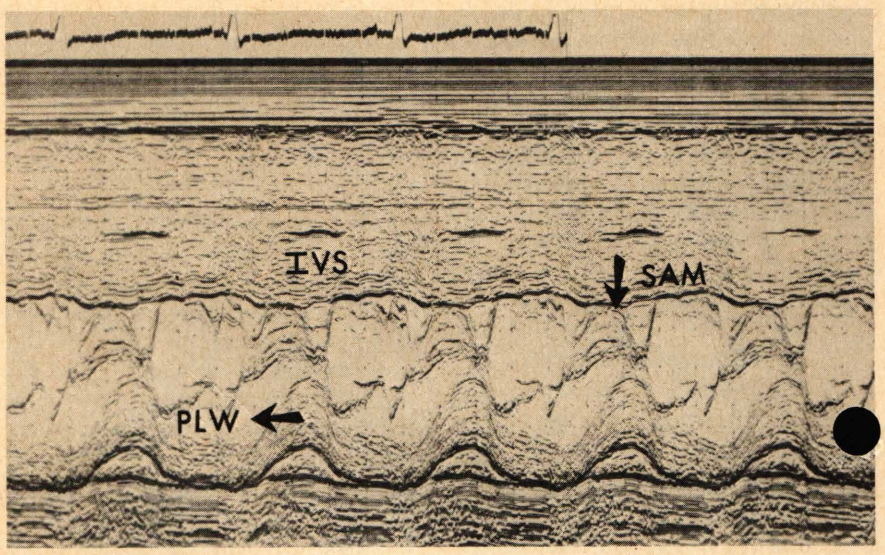


Fig 1.—Echocardiogram shows typical features of idiopathic hypertrophic subaortic stenosis. IVS indicates interventricular septum; PLW, posterior left ventricular wall; SAM, systolic anterior movement of the mitral valve leaflet.

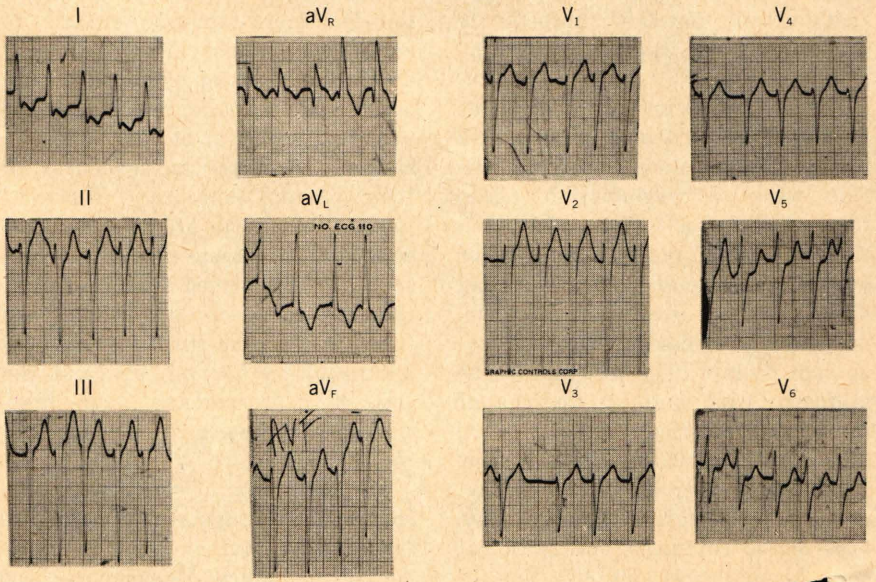


Fig 2.—Initial ECG shows atrial fibrillation with rapid ventricular response, left ventricular hypertrophy, and lateral wall ST depression.

From the Section of Cardiology, Providence Hospital, Southfield, Mich, and Wayne State University, Detroit.

Reprint requests to 22250 Providence Dr, Suite 704, Southfield, MI 48075 (Dr Duvernoy).

Hayes resigns in 'SERI'-ous shakeup

One of solar energy's sunniest and most visible advocates is about to be eclipsed, at least in terms of federal influence. Denis Hayes, director of the Solar Energy Research Institute since September 1979, has been asked by the Midwest Research Institute to step down from his post. MRI, which operates the federal facility for the Department of Energy, is said to be seeking someone with more research and laboratory experience since SERI is expected to take on a more laboratory-oriented role in the future.

But rumors and undertones attending the announcement also suggest MRI's role may be little more than that of a puppet whose strings are pulled from Washington. The Reagan administration is more than rumored to be plotting changes in the laboratory's intended mission and size. Most important, Hayes's ideology — that solar energy is not only a technology for the future, but also one capable of contributing mightily today — does not mesh with Ronald Reagan's conservative solar posture. And that ideological conflict is one explanation being offered to explain why DOE attempted, unsuccessfully, to withhold publication of a SERI study (SN: 5/2/81, p. 276) suggesting that stronger commitments to solar energy and to conservation would improve the economy.

SERI has come under fire repeatedly in the past 10 months for not being "effectively integrated into the federal solar program" nor coordinated adequately with activities of regional solar-energy centers. Consistent with that, administration budget carvers have drastically whittled down SERI's proposed funding for the coming fiscal year, and deferred indefinitely plans for a permanent SERI facility until conflicts over its size and mission are resolved. □

Only weak links: Bendectin, defects

Two reports in the June 12 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION may soften the blows responsible for Bendectin's black eye. Bendectin, a widely prescribed drug for treating the nausea and vomiting of pregnancy, is the subject of about 60 lawsuits charging that it causes birth defects. (SN: 12/27/81, p. 395; 6/13/81, p. 376). But both recently published JAMA studies concluded there is no significant link between the controversial drug and birth deformities.

One of the studies — reported by José F. Cordero and colleagues of the Centers for Disease Control in Atlanta, Ga. — involved determining whether mothers of 1,231 infants born with birth defects between 1968 and 1978 were exposed to Bendectin. In this analysis, Cordero and co-workers found weak associations between Bendectin exposure and cases of amniotic bands (a type of limb reduction), esophageal atresia (absence of the normal esophageal opening) and encephalocele (protrusion of the brain through a gap in the skull). But the three weak associations "do not establish a causal relationship between Bendectin and the birth defect categories we studied," Cordero and colleagues conclude. In a similar study — conducted by Allen A. Mitchell of Harvard Medical School in Boston and colleagues — researchers conclude that Bendectin exposure does not appreciably increase the risk of oral clefts or selected cardiac defects.

In both the Harvard and CDC studies, researchers compared incidence of Bendectin exposure in each birth defect category with that in a control group composed of birth defects other than the one being evaluated. This study design was employed to control for maternal-recall bias — the "greater tendency of women who have had an abnormal child to review events that occurred during pregnancy."

But does using infants with other defects as the comparison group preclude finding any associations should Bendectin uniformly increase the risk of all birth defects studied? "While theoretically possible, we believe the existence of such a teratogen would be unlikely," Cordero explains. "Known human and animal teratogens cause specific birth defects or patterns of birth defects; they do not uniformly increase the rate of all birth defects." □

Solar Max rescue

The possibility of repairing the ailing Solar Maximum Mission spacecraft in orbit during one of the space shuttle's three remaining test flights (SN: 5/23/81, p. 324) has been ruled out by NASA. Built with modular, plug-in components specially designed for easy replacement, "Solar Max" was launched Feb. 14, 1980, but suffered a malfunction in its attitude-control system after nine months aloft. Space agency engineers who have studied the problem believe that the faulty module could be replaced by use of a repair system flown aboard the shuttle, but the three flights remaining before the shuttle goes on full — and busy — operational status are taken up not only with checking out the vehicle itself but with two groups of scientific experiments and a classified Defense Department project. As for trying the rescue on a later flight (it would have to take place before Solar Max burns up on atmospheric reentry in 1984), NASA Associate Administrator for Space Transportation Operations Stanley Weiss calls it only a "remote possibility" that "doesn't have priority." □

Half an abortion in a case of twins

What is to be done when amniocentesis shows that one twin has a major congenital defect and the other twin is normal? In the June 18 NEW ENGLAND JOURNAL OF MEDICINE Thomas K. Kerenyi and Usha Chitkara report what they call "selective birth" of only the normal twin.

A procedure carried out last year at Mt. Sinai School of Medicine in New York destroyed the defective fetus in a pair of fraternal twins by drawing blood from its heart. The normal twin was born four months later and is now reported healthy at more than seven months of age. This is the first reported case of "selective termination" of an abnormal twin fetus in the United States. There has been one successful case in Sweden and an unsuccessful case in Denmark in which both twins were aborted after attempted cardiac puncture. In another recent case, in which only one twin had a major malformation, the parents opted for abortion of both twins. In three cases in which the pregnancies went to term, one abnormal twin was stillborn, one died days after birth and one with Down's syndrome survived.

Down's syndrome and fraternal twinning are both common in pregnancies of women nearing the age of forty. "The highest frequency of dizygotic twins occurs between the ages of 37 and 40," Kerenyi and Chitkara point out. "Therefore, with the increasing use of genetic amniocentesis, one may expect to be faced with the possibility of detecting Down's syndrome in one twin but not in the other."

In the recent New York case, the mother was 40 years old, childless and had had infertility problems. According to Kerenyi and Chitkara, "The mother desperately wanted to have the normal child but could not face the burden of caring for an abnormal child for the rest of her life." She was told about the Swedish success and requested a similar procedure. "If it had been refused, she would have chosen to abort both fetuses," the physicians report. They obtained confirmation from a court of law of the parents' right to consent to the operation on behalf of the normal fetus who was put at some risk.

The most serious problem in such procedures is distinguishing between the normal and defective fetuses. In the New York case, Kerenyi and Chitkara were "reasonably certain" that the twins' relative positions in the womb had not changed in the several weeks after the amniocentesis. The correct selection could not be verified until three days after the blood removal, when the fetus was already dead. The physicians did not consider the death of one fetus likely to harm the other because normal pregnancies have been observed following the natural death *in utero* of one fetus of a multiple gestation. □

On June 17 Fredrickson wrote to Richard S. Schweiker, Secretary of Health and Human Services, of his decision to resign. "I take this step with great ambivalence, for NIH is in the very marrow of my bones. I very much appreciated your immediate invitation to continue in my post upon your taking office as Secretary...." Schweiker responded that it was "with profound regret" that he learned of Fredrickson's decision.

After leaving NIH, Fredrickson plans to spend a period as a visiting scholar at the National Academy of Sciences "to sort out options," he told SCIENCE NEWS. There he expects to get involved with issues of support for scientific research and of institutional stability.

Asked whether times were getting rougher for NIH, Fredrickson replied, "No, I see no period of chaos. All public institutions are traveling through choppy water. But I have no fears for NIH."

Fredrickson looks back "with some pride" on his period as NIH director. "It was a very exciting six years. We could find and create solutions for most of our problems," he says. "We never felt anything was insoluble."

Among the problems Fredrickson faced was "everything associated with the recombinant DNA guidelines." That issue took up approximately half his time in his first years as director. He now describes the guidelines as the first restrictive code for biological research, a balance of scientific imperatives and public interest achieved without restrictive law.

Defining the boundaries of NIH responsibility was another issue Fredrickson addressed. "They were very ragged when I came," he says. He was concerned about protecting scientists' objectivity, while at the same time having them take appropriate responsibility. To meet this goal, NIH has instituted technical consensus exercises as a discussion process in which scientists, doctors, patients and others evaluate new medical technologies.

Fredrickson sees a need, in order to "make practical success out of biology," to cope with problems at the rough interface of university, government and industry, where it is necessary to take a complex scientific area and get all the people to work together. He says that this was possible in a "bureaucratic tour de force" for the issue of biological effects of radiation. "I find that very satisfying. It was even tougher than recombinant DNA."

Finally, Fredrickson is pleased to have been able to "anticipate the austerity likely to come." For example, recent budgets stabilized the funding of biomedical research to 5,000 new and competing grants. "This," he says, "makes a big difference to the confidence of people who take up biomedical research."

So far there is no word on whom Fredrickson's successor may be. Fredrickson says, "I just hope it's a good person, it's a very nice big job, and important." □

Gene-splice vaccine for foot-and-mouth

It's the first vaccine to be produced with recombinant-DNA technology, and it could lead to "annual savings of billions of dollars and an increase in the world's supply of meat," says Department of Agriculture Secretary John R. Block. The vaccine, which is being produced in genetically engineered bacteria, consists of a single protein of the coat of the virus that causes foot-and-mouth disease. Tests conducted during the past eight weeks have shown it to be effective against that disease.

Foot-and-mouth is a severe, highly contagious disease that affects more than 30 species of animals, including cattle, sheep and pigs. It causes blisters on the mouth, nose and feet — weakening animals and reducing their agricultural value. Foot-and-mouth disease is an especially serious problem in Asia, Africa, Latin America and southern Europe. Strict importation screening and quarantine procedures have prevented outbreaks of the disease in the United States since 1929.

Seven types of the virus, and 65 subtypes, are implicated in the disease; animals immune to one type are still susceptible to the others. And although there are no treatments for foot-and-mouth, there have been vaccines that protect against it. The vaccine currently in use contains killed or attenuated virus matched to the existing disease in an area. An estimated 500 million doses are used annually, making it the most widely used antiviral vaccine. This vaccine, however, is difficult to use in developing countries because it must be refrigerated. In addition, incomplete attenuation of virus has resulted in outbreaks of foot-and-mouth disease among vaccinated animals.

In contrast, explains Block, "The vaccine produced by the new recombinant DNA technology is safe and effective. It cannot produce the disease in vaccinated animals because only a segment of the virus is used, not the whole virus. Also, the vaccine produced with the new technology can be stored for long periods of time without refrigeration. It is economical to produce, and greater quantities can be produced at a time than was possible under previous methods of production."

The new vaccine is a result of collaboration between scientists of Genentech, Inc., a South San Francisco genetic engineering company, and the U.S. Department of Agriculture. The team was led by Howard L. Bachrach, who had previously demonstrated that a single protein, called VP_3, of the four on the foot-and-mouth disease virus surface, produces immunity in animals without causing infections (SN: 2/19/77, p. 120). The work was carried out on Plum Island, off the tip of Long Island in New York, because federal law prohibits the keeping of intact foot-and-mouth disease virus on the U.S. mainland.

The USDA announcement follows a recent report that German scientists have spliced genes into bacteria to produce a surface protein of the foot-and-mouth disease virus (SN: 3/7/81, p. 150). The German and U.S. teams produced different viral surface proteins (VP_1 and VP_3, respectively), and the USDA-Genentech group reported a higher yield — more than a million molecules of viral protein per bacterial cell compared with only 1,000 molecules per cell reported by the German group. The new vaccine protects against only one common type of the virus, but work toward a more general vaccine is underway.

The business agreement between Genentech and the USDA involved no money. Genentech holds patent rights and the right to license the manufacture of the vaccine, but the USDA retains the right to use the vaccine without paying royalties any time it is needed in this country. Genentech plans to manufacture and sell the vaccine, which it estimates to have a $200 million annual market, under an agreement with the fertilizer manufacturer, International Minerals of Northbrook, Ill. Commercial production is expected to begin in the mid 1980s. □

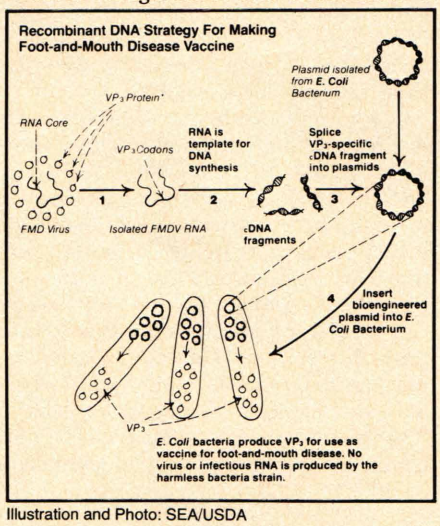
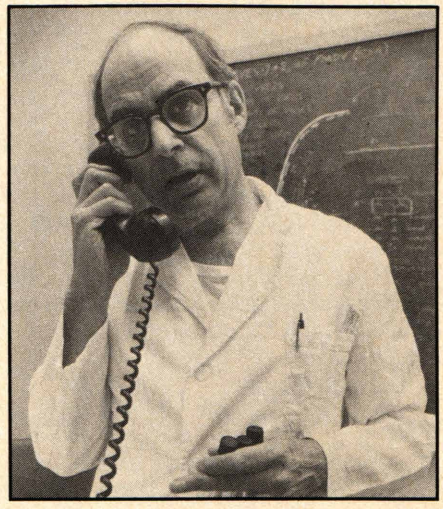


Illustration and Photo: SEA/USDA

Howard Bachrach



EVOLUTION: RETURN OF THE EMBRYO

BY JULIE ANN MILLER

A chicken and egg question confronted the group of 50 biologists who recently met in Berlin. Have the forces of biological evolution determined the patterns of an organism's development? Or have the available patterns of development shaped evolution?

The correct answer, of course, is: Both of the above. But in a week of intensive meetings, filled with argument, far-flung examples and occasional insights, the scientists could only begin to map out the interactions between evolution and development and attempt to discover how extensive those interactions might be.

Drawing parallels between development and evolution was much in vogue a century ago — as captured in the tongue-twisting slogan still memorized by students, "Ontogeny recapitulates phylogeny." But interest shifted away from development in the period following the widespread acceptance of Darwin's theory of evolution. To scientists who viewed an adult organism as a set of optimized parts comprising the best possible design, development was irrelevant, explains Stephen J. Gould of Harvard's Museum of Comparative Zoology.

Now, a rebirth of interest in embryology has occurred among biologists who think about evolution, and many of them are beginning to believe once again that important clues to the evolution of a living organism lie in its development. While scientists are not readopting the exact rule that a developing organism works its way through ancestral forms, biologists armed with new analytic methods are resurrecting the spirit underlying the ontogeny-phylogeny motto.

The philosophical shift that has renewed interest in embryology is a concern for large and relatively sudden changes that take place in evolution. Darwin and his followers occasionally admitted that major, discontinuous changes occur, but the emphasis was squarely on natural selection among small changes and thus gradual evolution. Now many scientists believe that a species spends most of its existence in a steady state; the small changes are generally fluctuations that don't build into a trend. And the major changes, which can create a new species, all crowd into a relatively short period. Then the discontinuous change creates a "hopeful monster," which can adapt to a now mode of life.

"Both modes of evolution occur in nature; there is a full continuum from gradual to punctuated," says Tony Hoffman, a paleontologist from Warsaw. While most of the scientists at the meeting agreed, each holds a strong opinion about which end of the spectrum is the most important, and that opinion influences his or her choice of research topic.

"Embryology is now mainline biology again," says Gould, who was one of the originators of the evolutionary model called "punctuated equilibrium." Focus on sudden change in evolution provokes interest in biological development for several reasons. One is that changes in an organism's development can be envisioned as a mechanism by which a small genetic change can be amplified into a major difference in the adult. A small genetic change that delays or enhances pigmentation early in development of a moth, for example, can cause large differences in the color pattern of the fully grown caterpillar. Delayed metamorphosis may be the origin of the axolotl, which reproduces in a form resembling a salamander tadpole. And prolonged brain growth may be the major difference between monkey and human brain size.

Antonio Garcia-Bellido of the Universidad Autonoma in Spain described extensive experiments on mutant fruit flies in which the alteration of a gene carries dramatic developmental effects. These flies, called homeotic mutants, have one part of the body transformed into another. One mutant has a middle leg in place of the outer part of the antenna. Another mutant has two middle thorax segments and no hind thorax segment, so it has a second pair of wings in the place of balancing organs. Although these flies are fascinating examples of a complex shape change resulting from a simple genetic change, Garcia-Bellido points out that there is no direct evidence for such a change in any organism's evolution.

Another aspect of evolution that may be influenced by development is the observed limits on characteristics. There are no six-legged vertebrates, for example. "Nature is not chaos, neither is it a boundless continuum of forms," says Pere Alberch of Harvard's Museum of Comparative Zoology. "There are discrete classes of forms that can be recognized and organized in a hierarchical manner (for example, vertebrates, mammals, rodents, house mice)."

The "empty spaces" between discrete classes can be explained in several ways. They might be structures eliminated by natural selection, or they might be body characteristics that simply cannot be produced by the available processes of development. One argument against natural selection being the sole cause of limits, for instance, involves the shells of ocean mollusks. Their color patterns are limited even though they spend their entire lives buried in the sand, and thus the shell pattern should not influence their survival.

Other things that limit the characteristics were also suggested. Mimi Koehl of the University of California at Berkeley points out that physical laws constrain the size, shape and possible forms of behavior of an organism. Biomechanics often produces an alternative explanation for trends that could generate speculation about natural selection or development.

A purely mathematical treatment of patterns of gene expression, presented by Stuart Kauffman of the University of Pennsylvania, demonstrated the capacity of a large system to settle into distinct patterns. A gene system with 10,000 genes has $10^{3,000}$ possible combinations. Given certain simple assumptions about the rules of regulatory interactions, the system spontaneously confines itself to about 100 different patterns of gene activities. Kauffman suggests that these represent the approximately 100 cell types in a complex organism. "Many properties of an organism may be trivial, such as the small number of cell types and their stability," Kauffman says. "These are powerful, deep underlying constraints that do not need natural selection."

Gould summarizes eloquently: "The common lesson in all this states that organisms are not pieces of putty, infinitely moldable by infinitessimal degrees in any direction, but are, rather, complex and resilient structures endowed with innumerable constraints and opportunities based upon inheritance and architecture."

Convincing examples of constraints and opportunities were difficult to come by. In part, the scientists were frustrated by the limited understanding of how an organism develops. Something determines symmetry early in development; something instructs cells where to move, how often to divide, what characteristics to express and when to die. But the details have not been spelled out.

One evolutionary opportunity now being analyzed was described by Michael Katz of Brown University. There have been few "quantal jumps" in the evolution of the nervous system, he says, but there is one on which neuroanatomists agree. The corpus collosum, the bundle of nerve fibers that connects the two halves of the brain, is found only in placental mammals. "The corpus collosum is really something new," Katz says.

Exactly what is new about the corpus collosum is not the number of nerve cells or the number of nerve fibers, called

since the Giant Fell

Federal investigators uncovered evidence in 1975 that the then commercial chemical-testing goliath Industrial Bio-Test Laboratories (IBT) was doctoring data. IBT's questionable test results continue to haunt the government.

BY LINDA GARMON

Joseph Calandra, Moreno Keplinger, Paul Wright and James Plank are the most recent reminders of a fallen giant. The four — indicted June 22 by a federal grand jury in Chicago on counts of giving false documents to the government and mail and wire fraud — are former employees of Industrial Bio-Test Laboratories Inc., of Northbrook, Ill.

In its heyday, IBT was one of the largest of some 200 independent labs that test the safety of new drugs, cosmetics, pesticides, plastics and food additives. In 1975, however, a U.S. Food and Drug Administration official fortuitously (the official apparently pulled an IBT file by mistake when checking a potential problem with another laboratory) discovered "serious deficiencies" in one of that lab's studies. More spot checks of IBT's data revealed, for example, a feeding study that IBT reported lasted 24 months but that actually was terminated after 18 months and reports of the use of live test animals after they had been reported killed in earlier experiments. So in a letter to pesticide manufacturers for which IBT had tested products, U.S. Environmental Protection Agency officials warned that IBT's records showed evidence of haphazard research and data that had been doctored to obscure potential harmful effects of chemicals. The giant had been slain.

But its ghosts — the more than 4,000 IBT health effect studies that supported the registration of 123 pesticides and the establishment of 160 pesticide tolerances (maximum permissible residue levels) — continue to haunt the government. According to the latest EPA estimates, nearly 1,800 of those tests must be reviewed — a task that has been divided between EPA and the Canadian government. Thus far, the inspectors have found that 100 percent of the chronic rodent tests and the majority of most other types of IBT tests reviewed are invalid (see chart A).

If most of the IBT tests for a particular pesticide are deemed invalid, then reviewers must search the literature for other health effect studies of that chemical. (To date, only 40 chemicals have been reassessed in this manner; see chart B.) If important tests still are lacking, then the information base for the pesticide is said to suffer from "major data gaps," and EPA — under the authority of the Federal Insecticide, Fungicide and Rodenticide Act — can request the pesticide manufacturers to fill in those gaps. During this case-by-case review, or EPA's "Data Call-In" program, all chemicals involved in the IBT case remain on the market.

EPA's method of handling the IBT case has met with criticism. Since evidence has amassed that IBT produced bogus data on a large scale, says Paul Merrell of the Northwest Coalition for Alternatives to Pesticides in Eugene, Ore., EPA should not bear the cost of case-by-case examinations. Instead, "Wholesale rejection of IBT data and withdrawal of pesticide registrations for products involved would seem to be more in line with EPA's mandate from Congress," he says. EPA officials, on the other hand, explain that under current law, once a pesticide is registered, EPA must bear the burden of proof that a substance can cause adverse health effects. Still, says Merrell, if his recommendation is impractical, it is only "because of industry's influence in the nation's capital."

Merrell also recommends changing the U.S. patent laws. "Strangely enough," he says, "our nation's patent laws are probably the largest single cause of chemical health and safety data falsification." Developers of new chemicals have 17 years to fully test and reap profits from their inventions before competitors can share their market. "A more rational approach might be legislation which would allow the chemical industry a liberal grace period in which to study effects of their chemical inventions before the patent clock begins ticking," Merrell says.

Financial connections between laboratories and chemical companies and financial corner-cutting also probably encourage commercial data falsification, Merrell says. "The problem doesn't end with studies performed by the IBT."

Indeed, results of an EPA audit from 1977 to 1979 of 70 pesticide-testing laboratories — obtained in response to a Freedom of Information Act request — seem to indicate that IBT was not alone in conducting haphazard research. For example, as long as a 99-day lag between times of test animal sacrifice and necropsy (without proper tissue preservation) was noted in bioassays Gulf South Research Institute of New Iberia, La., had conducted for the National Cancer Institute. At Harris Laboratory, Inc., in Lincoln, Neb., "rats listed as 'dead' were also listed as having been mated during the same time frame"; at Howard University College of Medicine in Washington, D.C., there were "autopsy records ... for several animals which were still alive." And studies performed by Biosafety Research Laboratory in Branchville, N.J., were invalidated by EPA auditors "on the basis of unclear dose determination and lack of proper animal examinations." Such examples are strewn throughout the EPA report.

But EPA employee Diana Horne — former head of the EPA auditing lab program — says the audit report reflected not an epidemic of IBT-like research, but rather the state-of-the-art of toxicological testing years ago. Since then, she says, techniques have improved and most of those laboratories audited now comply with EPA's Good Laboratory Practice regulations. "We think that IBT was a particularly bad situation and that it was not really the norm," says another EPA employee. "We assume that IBT was the worst case." □

In chronic studies animals are fed a test chemical for 2 years; subacute, 7 to 30 days, acute, once. Cholinesterase studies involve measuring a nerve-transmission chemical concentration in test animals.

CHART A

INVALID IBT STUDIES—UPDATE

	JUNE '80	DEC. '80	JUNE '81	# INVALID/TOTALREVIEWED
Chronic Rodent	100%	100%	100%	34/34
Carcinogenicity	94%	94%	94%	17/18
Teratology	76%	75%	78%	42/54
Reproduction	73%	79%	76%	22/29
Chronic Dog	64%	53%	62%	13/21
Subacute	59%	68%	74%	99/134
Neurotoxicity	50%	64%	61%	11/18
Mutagenicity	48%	44%	48%	13/27
Cholinesterase	46%	58%	67%	20/30
Fish & Wildlife	42%	75%	76%	123/162
Acutes	29%	32%	32%	156/481
Residue	—	42%	29%	15/51

CHART B

Status of Regulatory Reassessment Phase of IBT Review

Forty-nine chemicals have completed this phase. They fall into the following categories.

1. IBT review is complete and all studies are valid for: Alanap*, Carbaryl*, Chlorpyrifos*, Dyanap*, Pencap E*, Pencap M*, Fire Prep 1000, Harvade*, FloMo, System E, Sumitol and Pyrethrin*.
2. Metolachlor, 4-Aminopyridine and Terrazole already had been reassessed.
3. Completed because no registration is now in effect: Hinosan, Cycle, Butam, Cypromid, Ethiolate*, Chlorobromuron, Chloroprophylate, Fluorodifen, Metabromuron*, Methylene bis propionate, Malonoben, Dantoin, Heptachlor Epoxide, Potassium Azide, CGA 12223, Potassium Hexafluoro Arsenate, Binapacryl*.
4. Major data gaps have been identified for: Bux, Cobex, Disyston*, Sencor* and Cyanurates.
5. No major data gaps exist as a result of invalid IBT studies for: Brodifacoum, DSMA, Iodine, Merphos, MCPA, Nalco 247, Oxadiazon, Nemagon, Sectrol, Methomyl, Avenge and 2,4-D.

*Chemicals reviewed by Canada.