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TERATOLOGY

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DEFINITION

Teratology has been defined as "that division of embryology and pathology which deals with abnormal development and congenital malformations" (1) or alternatively as "the study of monstrosities or abnormal formations in animals or plants" (2). Both definitions are incomplete. Considering the first definition, teratology is not limited to embryology and pathology but incorporates a diversity of biological specialties, all of which contribute to the basic knowledge required in the study of abnormal development and congenital malformations. The second definition omits the basic premise of teratology—i.e., it is not related to the time at which the malformations arise. For example, this definition could cover the study of tumors, galls, and a variety of other abnormalities which are not considered to be teratological in origin. Kalter (3) has discussed the definition of the term "teratology", which he defines as the study of monstrosities (i.e. an abnormality of growth) (2). Again, this definition fails to pinpoint the period at which the growth abnormalities occur. However, the subsequent discussion makes it clear that Kalter was considering only congenital malformations.

For the purposes of this article, teratology may be defined as a study of the effects of intrinsic or extrinsic factors related to permanent structural or functional abnormalities arising during the period of embryonic development.

HISTORY

From the time that man has been capable of leaving any records, monsters resulting from biological malformations appear to have been of considerable interest. Thus, in early cave paintings, monsters are not infrequently portrayed. Recent painters have also utilized congenitally-malformed models (e.g., the painting of a phocomelic infant by Goya in the Louvre, Paris).

Early attempts to explain congenital malformations followed two basic premises—either they were of prophetic significance (a belief held by the Babylonians), or they were manifestations of the "Wrath of God".

In 1573 Paré (4) listed 13 possible causes of congenital malformations involving, among other things, various religious and astrological theories.

These included mental impressions of the mother, mixing of gametes, heredity, and mechanical effects (e.g. small uterus, blows on the womb, etc.). The idea that maternal mental impressions could influence development had been postulated some time earlier. Hippocrates (5) is attributed with saving the life of a princess who bore a colored child, which he attributed to mental impression created by a picture of a Moor located near her bed. The mixing of gametes was also a well-established theory in ancient times and was seriously challenged by Aristotle (6) on the grounds that different species had different gestation times, and gametes were, therefore, unlikely to be compatible. Scientifically, both of these theories are considered to be invalid today. However, in primitive communities, and in some country areas in Europe, it is still not uncommon to hear of a birthmark, shaped like an animal, explained by the statement, "Your mother must have been frightened by a . . . ." In this connection it is of interest to note that maternal emotional disturbances have been implicated as possible teratogens (Warkany & Kalter 7). In relation to the "mixing of gametes"theory, as recently as 1965 newspapers reported the execution of a mother and child in Iraq after a family trial; the execution was justified on the grounds that, since the baby had a well-developed tail, the mother must have indulged in obscene practises with a monkey!!

Another theory listed by Paré, the possibility that mechanical effects could result in malformed offspring, was discounted (Adams 8) or minimized (Willis 9, Morrison 10) until comparatively recently. However, Browne (11) has postulated that malposition, increased spatial pressure, increased hydrostatic pressure, or membranous perforation during gestation could account for certain malformed conditions at birth. Experimental evidence is still lacking to prove these hypotheses, but until data are available to confirm or refute them, the possibility that mechanical effects can result in malformations should not be disregarded.

In 1651 Harvey (12) advanced the theory that the arrest of embryonic growth in specific parts of the embryo may account for certain abnormalities. For example, he postulated that harelip and cleft palate could be due to lack of fusion of "facial buds". [Today it is known that delay in palatal shelf closure does result in cleft palate in some instances (Trasler & Fraser 13)]. Some thirty years later, however, theoretical teratology suffered a set-back because of the "pre-existence of germs" theory advanced by Swammerdam; according to this theory, the germ is a preformed miniature of the adult to which it progresses by simple growth (14). This was finally discounted in 1759 by Wolff (15) who advanced the epignetic theory involving transformation of the embryo by a process of cellular build-up. It was not until 1827 that mammalian ova were recognized as such (Baer 16) despite the earlier prediction of their existence (Leeuwenhoek 17). Fertilization of the ovum by the sperm was not observed until 1877 (Hertwig 18).

The groundwork for present-day teratology was laid by Etienne and Isidore Geoffrey Saint Hilaire (19, 20) who not only coined the term teratology, but also described and classified most known abnormalities. Isidore St.

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Hilaire (20) also reported the first attempts to induce malformations experimentally, using the developing hen egg as the test organism; these attempts were unsuccessful.

The first major work on experimental induction of developmental abnormalities in homeothermic animals, again using hen eggs, was reported by Dareste in 1891 (21). Heat, cold, shaking, and anoxia were the teratogenic agents used. Thus, Dareste provided the first proof that extrinsic factors could cause abnormal embryonic development. He also showed that the earlier stages of development were the most susceptible to teratogenic activity —an idea that seems to have been realized long before teratology became a science in its own right (4).

In mammals, the first report of induction of congenital malformations attributable to extrinsic factors is a single observation in 1921 (Zilva et al 22) who fed a pregnant sow a diet deficient in the "fat soluble factor". The progeny exhibited four offspring with rudimentary limbs. It was not until 1929 (Goldstein & Murphy 23) that X-rays were proved to affect embryonic development; chemically-induced teratogenesis was not finally accepted until 1935 (24), when Hale unequivocally proved that anophthalmia could be induced in piglets born to mothers fed a vitamin A deficient diet throughout pregnancy. Further deficiency studies (25–28) followed in the 1940s, but it was not until 1948 that nitrogen mustard (Haskin 29) and trypan blue (Gillman et al 30) were implicated as positive chemical teratogens. *Rubella* had been identified as a teratogen in 1941 (Gregg 31).

Interest in teratology continued to increase during the 1950s when considerable work was published on the effects of intrinsic (32–38) and extrinsic (39–46) factors on the developing embryo. Then in 1961, McBride (47), followed shortly afterwards by Lenz (48), implicated thalidomide as the causative agent of various congenital malformations. This provided a tremendous impetus to teratological investigations, which continues to the present day.

Fundamental Problems in Teratology

In any experimental investigation, as in any biological science, a primary consideration in teratology is the choice of a suitable experimental animal. Species ranging from Protozoa (Moriber et al 49) to Primates (Hendrickx et al 50; Courtney & Valerio 51; Kraus et al 52, Delahunt & Lassen 53) have been utilized. Unfortunately no other experimental animal parallels the teratogenic response observed in humans (Karnofsky 54). Thus, man must be the ultimate test species. Sullivan (55) pointed out that had thalidomide been tested in 20 to 30 pregnant females prior to therapeutic abortions, the several hundred malformed children born as a result of thalidomide usage could have been avoided. However, the counter-argument advanced by Robson (56) is that, in the case of a mild teratogen, several thousand women would have to be exposed to the drug in order to detect an increase over the normal background level of human "spontaneous" malformations.

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Since moral and social factors, outside the province of this article, prevent the use of human subjects in teratological studies, laboratory animals are presently utilized in such investigations. In selecting the species to be used in any particular study, a number of requirements must be considered. In addition to the normal criteria of availability, ease of maintenance in the laboratory, economics, etc., animal species used in teratological investigations should have a fairly short gestation period; a known estrus cycle; an easily determinable time of conception; high fertility in captivity; a large litter; a known embryological development; a stable genetic background; and pups sufficiently large to permit easy macroscopic examination of soft tissues, but small enough to permit easy maceration for skeletal examinations. These criteria are probably best met by the rat, the rabbit, the hamster, and the mouse. Also dogs, pigs, and monkeys frequently are employed.

If the metabolism of the compound is known in man and animals, the animal of choice would be that which metabolized the compound under study in a similar fashion to that observed in man. When metabolic data are not available, it has become fashionable in recent years to utilize species which are in close phylogenetic proximity to man (i.e., the nonhuman primates). Several studies on such species have been performed (51; Axelrod 57; Wilson & Fradkin 58; Wilson & Gavin 59). Recently, Wilson et al (60) have indicated that it is relatively easy to breed Rhesus monkey under laboratory conditions. In addition, these authors point out that embryonic development, and metabolic parameters (where comparative data are available), are similar to those in man. However, information on nonhuman primates, with their obvious disadvantages [168 day gestation period, 28 day estrus cycle (61), single (or rarely twin) offspring, and difficulty of determining time of onset of pregnancy], is still too limited to permit a definitive statement regarding the appropriateness of this species for extrapolation of experimental data to man.

No discussion of choice of species for teratogenic investigations would be complete without reference to the hen egg. While the hen egg does have the advantages of ease of accessibility to the developing embryo, short incubation time (21 days), convenient fetal size, and known genetic background, there are also a number of disadvantages. Thus age, diet, and strain of the maternal hen can all affect the results of tests on eggs (Adams 62). Storage temperature and the interval between laying and incubation can affect fertility (Landauer 63). Time of onset of development following the initiation of incubation is variable, and vulnerability to changes in external environment is high (21; Lindsey & Moodie, 64; Leighton et al 65). Physical properties of the test material (possibly due to the absence of gut wall and placental barriers) have a major effect upon results (Walker 66; Williamson et al 67). Despite these disadvantages, the chick embryo does have some place in teratological experimentation since the ease of access to the embryo permits studies on morphological and physiological disturbances early during development (Grabowski 68; Khera 69). As a test system for

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assessing potential human hazard from teratogenic compounds, the chick embryo can only at best be a coarse screening organism.

Five basic factors have been stated to determine teratogenesis in mammals: susceptibility of the species, nature of the agent, access of the agent to the embryo, level and duration of dosage, and developmental stage of the embryo at the time of treatment (Wilson 70).

Species susceptibility.—Species, strain, and individual susceptibility to teratogenic agents differ considerably (Grauwiler 71; Milic 72; Kalter 73; Joneja & Ungthavorn 74). This would, of course, be anticipated to some extent since the genetic constitution of an organism determines its response to environmental factors. In addition, interspecies and interstrain differences in the mechanisms of absorption and metabolism (Goldstein, Pinsky & Fraser 75; Kalter & Warkany 76), also under genetic control, play a part in determining the response to a teratogen. These aspects will be considered further in the section dealing with genetic aspects, below.

Nature of the agent.—To define the nature of a teratogen is an impossible task at the present state of our knowledge. A wide variety of physical agents: temperature (Munro & Barnett 77), X-irradiation (Jacobson 78), maternal stress (Peters & Strahburg 79), hypoxia (Werthemann & Reiniger 80), maternal age (Jaworska 81), maternal weight (Dagg, Schlager & Doerr 82), nutritional effects (Kalter 83), chemical agents (55, 83), and viruses (Brown 84) can influence or induce teratogenic effects. No structure-activity relationships or clear cut relationships to other biological effects (e.g. cancer-induction) have yet been proven.

Access of the agent to the embryo.—The site of action of a teratogen may be either indirect or direct. In the former case, the teratogen may affect maternal physiology, resulting in changes in the uterine environment, or alternatively may act upon the yolk sac, or placenta, resulting in deprivation of essential compounds required at specific development stages. Direct action involves the teratogenic agent acting within the developing embryo.

Even where the embryo is directly available (e.g. as in the hen egg), the degree of teratogenic (or embryotoxic) response can be influenced by the route of administration (Clegg 85). In the mammal the problem is considerably more complex. In addition to the route of administration, the suspending agent (Mauer 86), the production of metabolites (Wynn & Blake 87), the effect of the placenta (Robson & Sullivan 88), the rate of maternal metabolism (Wilson 89) and excretion (Lloyd, Beck & Griffiths 90) can all affect the access of the agent to its site of action. In this connection, the identification of metabolites and determination of their physical properties are of considerable importance to an understanding of the access of the teratogenic agent to its site of action. Despite several intensive investigations of thalidomide (91; Fabro et al 92; Faigle et al 93), the identity of the

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actual teratogenic agent is still uncertain. Access of the agent to its site of action may also account for intralitter variability in embryonic susceptibility to teratogens (88); however, genetic factors must not be overlooked in this context.

Level & duration of dosage.—As in most toxicological considerations, teratogenic activity is governed by a dose-effect relationship. The range of doses that induce teratogenic effects has been termed the "teratogenic zone" (Wilson 94). The teratogenic zone is postulated to exist for all compounds, provided the maternal toxicity is less than the fetal toxicity of the compound. Lower doses cause no effects, and higher doses will result in foetal death. Fortunately, in the majority of cases this zone is extremely narrow, i.e., at the critical point a small increase in dose will cause a large increase in foetal mortality. In the case of those compounds in which a large increase in dose only slightly increases the fetal mortality (e.g. thalidomide, where a tenfold dose increase results in about a twofold increase in embryotoxicity), the teratogenic zone is considerably larger and it is such compounds that are usually termed teratogenic (West 202).

Duration of dosage is equally important in investigating the mechanism of action of a teratogen, an instantaneous dose at a specific time in pregnancy would be ideal, so that critical developmental stages could be studied individually. While this is possible in the case of x-irradiation (Kalter 95), maternal physiology prevents such an ideal situation when chemical teratogens are under study. Even so, studies based upon a single dose can be useful in determing the period of greatest embryonic susceptibility.

Since the majority of teratogenic studies have been orientated toward safety determinations, repeated dosing during pregnancy (i.e. chronic exposure) has been used frequently. However, such procedures can be misleading, because microsomal enzyme stimulation prior to the onset of the susceptible period of development may result in a reduced maternal blood level of the teratogen (due to increased rate of metabolic activity) and a resultant false negative (King, Weaver & Narrod 96). On the other hand, increased teratogenic activity may also be observed following chronic treatment; this may be due to pathological damage resulting in reduced metabolic activity (89) or cumulation of the test material.

Development stage of the embryo.—The fact that the stage of embryonic development is critical to induction of teratogenic effects appears to have been realized for a considerable time (4). Prior to implantation the embryo is generally resistant to teratogenic effects. This may be due to the totipotency of the embryonic cells at this early stage of development. A number of exceptions to the general statement are known (89; Smith, 97; Roux 98; Brent 99; Lutwac-Mann, Hay & New 100) mostly involving teratogens which are known to, or are likely to be capable of, interfering with nucleic acid synthesis (70).

The period of embryonic development most susceptible to teratogenic ac-

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tivity is that commencing with the formation of the germ-layers (which approximately coincides with the time of implantation), and continuing throughout the period of organogenesis, at which time protein synthesis is at a maximum. Maximum sensitivity is frequently noted shortly after the onset of this period (Russell 101; Nelson et al 102; Ingalls & Curley 103), possibly because several complex embryological events occur at about this time. Similarly, induction has occurred (Rawles 104; Ebert et al 105), and the cells have lost their totipotent nature. This results in an interesting situation in that teratogenic action on the chemically differentiated cells (i.e. those that have undergone induction) can result in malformations in organs not actually present at the time of insult (Murphy 106; Wilson, Jordan & Brent 107). The variability in the time of susceptibility of the various organs and organ systems can be partially explained by differences known to exist in the time of onset of embryological development, and differences in the rate of this development. The critical periods for inducing various malformations by a number of teratogens in mice have been listed in an excellent review of teratogenesis in this species by Dagg (108).

As differentiation and organogenesis proceed, the developing young become progressively less susceptible to teratogenic activity; by the time the foetal stage is attained, production of deformities is limited to those parts of the body in which disturbances in growth, movement, or maturation can cause maldevelopment [e.g. the palate, cerebellum, and certain urogenital and cardiovascular structures (83)].

Genetic Aspects of Teratology

In man, some 10–15% of congenital abnormalities are known to be of genetic origin, and it is generally accepted that only some 2% can be attributed to environmental causes. It is highly probable that the remaining 83–88% are related to genetic or chromosomal aberrations (Cohlan 109).

Genetic influence can induce teratogenic abnormalities in one of two ways—either by direct action resulting in a change in the normal developmental pattern, or by interaction with the environment. The latter aspect will be considered under the heading of interactions in teratology.

Malformations attributable to genetic factors may be due to either chromosomal abnormalities, or activity of the gene(s) per se.

Chromosomal effects.—In the case of congenital abnormalities that are chromosomal in origin, multiple incidence of chromosomes is frequently involved. Multiple incidence of autosomes has also been shown to be the commonest chromosomal aberration noted in spontaneously aborted human specimens (Inhorn 110). Probably the best known example of a congenital malformation induced by chromosomal aberrations is Down's syndrome, or mongolism, which by definition involves the presence of excess material from chromosome No. 21. Down's syndrome was reviewed in 1966 (Penrose & Smith 111) and 1967 (Wolstenholme & Porter 112) since which time a number of papers have been published (Rosecrans 113; MacGillivray 114;

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Naeye 115), the most recent (Stoller 116) being on the possibility of virus-chromosome interaction as a cause of Down's syndrome (in addition to other congenital abnormalities). Other autosomal chromosome imbalances provide the subject for comprehensive reviews by Nusbacher & Hirschhorn (117) and by Polani (118).

A large variety of abnormal chromosome patterns have been observed in relation to the sex chromosomes (Court-Brown et al 119), but with the exception of Turners syndrome (associated with XO females), and Klinefelters syndrome (associated with XXY XXXY, XXXYY males), abnormalities are rare. The apparent lack of effect of sex chromosomes has been hypothetically explained by Lyon (120), who has further supported the original hypothesis in a detailed review in 1966 (121).

Before considering gene activity in relation to congenital malformations, it should be noted that chromosome abnormalities induced by teratogenic chemicals during embryonic development were mainly nonspecific and non-persistent, apparently occurring only in the first division after treatment (Soukup, Takacs & Warkany 122). Thus, chromosome damage induced during development is unlikely to affect the embryo except in relation to cell death [a known mechanism of teratogenic activity (Menkes, Sandor & Ilies 123)]. This however, remains to be proven.

Gene effects.—Turning now to the gene per se, a number of individual gene mutations are known to affect embryonic development, resulting in congenital malformations (Berry 124; Gruneberg 125). In certain cases (Gruneberg 126; Lulu, Corcoran & Andre 127; Konyukhov & Vakhrusheva 128) single gene mutations can lead to multiple malformations, which further confuses the situation. In addition, the heterozygous or homozygous presence of the gene can also materially affect the degree of incidence, and severity, of the malformation. For detailed data on these aspects of mutation, the reader is referred to Fraser (129) or Kalter (83). Fraser (129) has also discussed the polyfactorial action of genes, which probably accounts for the majority of malformations resulting from gene action.

Interactions in Teratology

For convenience, interactions in teratology can be considered in three major groups: interactions between genes, which has already been mentioned; interaction between genes and environmental stimuli; and interactions between chemical teratogens.

In the cases of interaction between genes and environmental stimuli, a small number of examples involving individual genes is known for the homozygous conditions (e.g. the relationship between the recessive mouse gene "pallid", and manganese (Erway, Hurley & Fraser 130), and the heterozygous conditions (e.g. the response of heterozygous "luxoid" mice to nonteratogenic doses of 5-fluorouracil (Dagg 131; Forsthoefel 132). However, the majority of such interactions are multigenic, and probably explain a large number of the strain differences in response to teratogens (82).

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Multiple interactions involving maternal diet, maternal weight, dose of teratogen, and strain of treated animal have indicated that gene-environment interactions can be extremely complex (Dagg 133). This and other studies (Beck 134; 37; 75) indicate that not only the embryonic genotype is involved in induction of congenital malformations, but in addition the maternal genotype can also exert a considerable influence. For further details relating to the interplay of intrinsic and extrinsic factors in teratology, the reader is referred to Kalter (135).

In the case of nongenetic interactions between teratogens, four possibilities for interactions have been postulated to exist (Runner 136), interference, no effects, additive effects, and potentiation.

"Interference" is the situation where the teratogenicity of the administered combination is less than either of the substances acting alone [e.g. the interaction of 6-aminonicotinamide, and nicotinamide in the mouse (Pinsky & Fraser 137)]. "No effect" is the situation where the combined effect of two teratogens acting simultaneously results in an incidence of abnormalities similar to that which would be anticipated from the action of the more potent teratogen acting alone [e.g. reduced dietary intake and iodoacetate, both mouse teratogens, administered simultaneously result in an incidence of abnormalities similar to that anticipated from reduced dietary intake alone (Runner & Dagg 138)]. An "additive effect" is where the incidence of abnormalities is equal to the sum of the total incidence of abnormalities produced when each of the teratogens involved is acting alone [e.g. hypoxia and methyl salicylate (Bertone & Monie 139)]. "Potentiation" occurs where the total abnormalities induced by the combined teratogens exceed the sum of the abnormalities induced by their individual activities [e.g. fasting and cortisone (Miller 140; Kalter 141) vitamin A and thiouracil (Woollam & Millen 142)]. The problem of potentiation deserves further consideration, since a compound normally not teratogenic in a species may potentiate the activity of a known teratogenic agent present at a level which may be below the threshold dose for that species [e.g. cortisone, not normally teratogenic in rats, potentiates X-irradiation defect incidence (Woollam & Millen 143); immobilization (again normally not teratogenic in rat) potentiates Vitamin A teratogenicity (Hartel & Hartel 144)]. Wilson has coined the term "proteratogens" for nonteratogenic agents that can potentiate the activity of a teratogen, and also for known teratogens below their threshold dose. While all the examples cited above involve known teratogens in one species or another, it can be envisaged that a compound that is not a known teratogen in any species could act as a proteratogen. Similarly it can be postulated that a combination of two or more nonteratogenic proteratogens could result in teratogenic activity. Such a mechanism could possibly explain presently unaccountable human malformations.

Finally, it must be noted that even the degree of interaction between two teratogens is subject to genetic influences, as expressed in differing responses in different strains of the same species (Shoji, Kohno & Ohzu 145).

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Mechanism of Action of Teratogens

Despite intensive studies on a number of teratogens [Trypan blue (Beck & Lloyd 146), oxygen deficiency (Grabowski 147), vitamin A (83), X-irradiation (83), hypoglycin (Persaud 148), thalidomide (149)] relatively little is known about mechanisms of action of teratogens.

Wilson (150) has tentatively suggested a list of possible causes of teratogenesis which include genetic mechanisms (mutation), chromosomal aberrations (mitotic non-disjunction, mitotic accidents, etc.), mitotic interference (mitotic spindle disruption, chromosomal stickiness), abnormal nucleic acid metabolism (interference with DNA integrity or replication, interference with RNA synthesis etc.), infection (virus or parasitic invasion of embryonic cells), enzyme inhibition, nutritional deficiency or excess at critical developmental stages, endocrine imbalance, water-electrolyte imbalance, mechanical factors (localized disturbances of haemodynamics, hydrodynamics, morphogenetic movement, etc.), immunological phenomena, or interference with placental transfer. The majority of these possible causes can be exemplified from the literature (83), but the final mechanism by which they induce malformations remains to be elucidated. Thus, considering abnormal nucleic acid metabolism the 5-fluorinated pyrimidines affect both RNA, and DNA synthesis. They are incorporated into RNA, and inhibit DNA formation by inhibiting thymidylate synthesis which catalyses the methylation of deoxyuridylic acid to form thymidylic acid (Murphy 151). Hydroxyurea also inhibits DNA, either directly, or via its conversion from ribonucleotides (151). With both compounds, inhibition of the formation of DNA is postulated to be the cause of the induction of the malformations, the period of sensitivity to the teratogens, and the variation in response to multiple dosing differ for hydroxyurea, and the 5-fluorinated pyrimidines, when the presumed basic cause of the teratogenic activity is the same in both cases. Possibly polygenetic control of the teratogenicity of each separate compound provides some explanation, but again, mechanisms of polygenetic control themselves are generally not known. Thus it is apparent that mechanisms of action of teratogens must probably be considered as individual problems and that no general hypothesis can be stated at present. Considerable further work will be required by future teratologists to elucidate the multiple problems involved in this complex area.

Teratogenesis in Man

Attempts have been made to assess the overall incidence of congenital malformations in human offspring (Halevi 152; Simpkiss & Lowe 153; De Porte & Parkhurst 154; Marden, Smith & McDonald 155; McIntosh et al 156; Miller 157; Colla, Trompeo & Tanferna 158). The reported incidence varies from 0.74% (Hendricks 159) to 16.3% (Carter 160), depending on the location under consideration, the ethnological group (Chung, Myrianthopoulos & Yoshizaki 161; Altemus & Ferguson 162) and the socioeconomic status (162).

Accurate assessment of the incidence of human congenital malformations is further complicated by the lack of criteria for assessment of what shall be considered to be a malformation, and by the lack of uniform examination procedures (Efron 163). Seasonal variability in the incidence of malformations further complicates analysis of the available data (Czeizel & Elik 164). However, a reasonable assessment seems to indicate that 2–3% of newborn live children show one or more significant malformations; by one year of age, this figure is doubled due to the detection of malformations not manifest at birth (Warkany & Kalter 165).

Malformations of genetic origin.—As has been stated previously (109) the majority of congenital malformations are of genetic origin, and a considerable literature exists relating to human congenital malformations induced by genetic or chromosomal aberrations. Fraser (166, 167), and Stevenson (168) have described a number of human malformations related to the presence of dominant genes (e.g. achondroplasia, craniofacial dystosis, lobster-claw defects of hands and feet, aracnodactyly, etc.) and recessive genes (e.g. conditions of hydrocephalus, some forms of infantile polycystic kidney etc.). Similarly, several other conditions believed to be genetic in origin because of the increased incidence of occurrence in certain families (e.g. anencephaly, cleft palate, clubfoot, etc.) are probably polygenetic in origin. Mention should also be made of the numerous congenital metabolic errors, which are frequently of genetic origin (169–172).

Chromosomal abnormalities in man have already been discussed (110–121), although specific autosomal chromosome abnormalities have not been related to specific syndromes. For detailed data on such relationships and for detailed descriptions of abnormalities resulting from gene activity, reference should be made to the collections of papers published from the First Conference on Clinical Delineation of Birth Defects (173).

Malformations and Nutrition.—Although considerable animal experimentation has been performed in relation to embryonic development and excess or deficiency of various vitamins, minerals, amino-acids, proteins, lipids, carbohydrates, etc. (Giroud 174) which cause congenital malformations, only three or possibly four cases have been identified in which nutritional factors resulted in human malformations. Thus vitamin D deficiency induces embryonic rickets just as readily as it does in the post-natal animal (although this is really a pathological effect). Abnormally high doses of vitamin D during pregnancy have also been suggested to cause abnormal skull calcification. Second, in recent publications (Robertson 175, Hadjimarkes 176) the possibility of selenium teratogenicity in man has been suggested.

Iodine, which affects the developing thyroid, and may cause brain damage in cases of deficiency (Lotmar 177) or excess (Black 178) is the only dietary element which has been definitely proved to affect the human embryo.

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Before leaving nutritional factors, two accidental contaminants of foodstuffs should be mentioned. Both lead (Angle & McIntire 179) and mercury (Matsumoto, Koya & Takeuchi 180), in excess, have been implicated in causing fetal neurological damage.

Maternal Infections.—Although Tönbury (181) has stated that ***in theory,*** every virus can be a teratogenic agent, very few viral agents have been shown to be teratogenic. In man, Rubella and cyclomegalic inclusion disease (salivary gland fever), are both proven teratogens. In the case of Rubella, a very considerable literature exists. The reader is referred to two review articles (Sever 182, Desmond et al 183). Similarly Hanshaw (184) has recently written a comprehensive article on congenital cytomegalovirus infections.

Various other viral infections have been suspected of teratogenic activity. In the case of influenza, increased malformation rates have been reported following epidemics (Saxén et al 185; Baron, Michiels & Rochas 186). However conflicting studies (Sayegh 187, Hewitt 188) indicate that influenza has no effect on the outcome of pregnancies. The Coxsackie viruses (Group B) can infect the embryo and a relationship has been suggested between subclinical infections and congenital heart disease (Fruhling et al 189). This is still not proven. Poliomyelitis is also known to infect the fetus (Schaeffer, Fox & Li 190) but there is little evidence of teratogenic potential, although brain damage has been suggested. The ECHO viruses (Kleinman et al 191) mumps (Katz 192), measles (Hill et al 193) smallpox (Dixon 194), & varicella (193), have also been considered as possible teratogens, but no definite conclusions can be drawn at present.

The only other infection known to cause teratogenic effects in man is Toxoplasma, a protozoan infection (Feldman 195). No bacterial infections have been shown to induce teratogenic effects to date, but the possibility that a bacterial toxin could be teratogenic cannot be ignored.

X-irradiation.—Since 1929, X-irradiation has been known to induct congenital malformations (23). A very considerable literature exists, the most recent review article being that of Jackson (78). Attention is also drawn to the paper by Tabuchi et al (196), and Russell (197).

Drugs.—A number of review articles have been published (Underwood, Iturrian & Cadwallader 198; Chaube & Murphy 199; Sutherland & Light 200; Lenz 201) on teratogenic effects of drugs on the human fetus. Space limitations do not permit further discussion in this article.

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