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Genetic counseling is an integral part of the physician's management of patients with presumptive or confirmed hereditary diseases. It is an art and science involving not only the use of technical genetic knowledge and precise medical diagnosis, but also accurate dissemination of genetic information in a tactful, empathetic manner. For optimum success the physician may request services from a variety of paramedical resources to insure maximum assistance for the counselee and his family in coping with a genetic problem.

Medical genetic knowledge has been accrued from many branches of genetics: population genetics, biochemical genetics, cytogenetics, immunogenetics, etc. Increased knowledge concerning birth defects, biostatistics, and computer science has also contributed to this field. All are constantly being made available to the genetic counselor. Figure 1 illustrates the various branches of genetics which have developed rapidly during the last several decades, all of which have provided valuable information to the genetic counselor.

A "tree of genetic counseling" presents thoughts on genetics from antiquity in its roots and trunk and more modern contributions up to but not including the most recent work in genetics and genetic counseling, branching out above (Fig. 2). Only a few of many interesting contributions to genetic counseling from antiquity will be discussed below. This will be followed by a brief discussion of some of the present problems in genetic counseling and a look into the future.

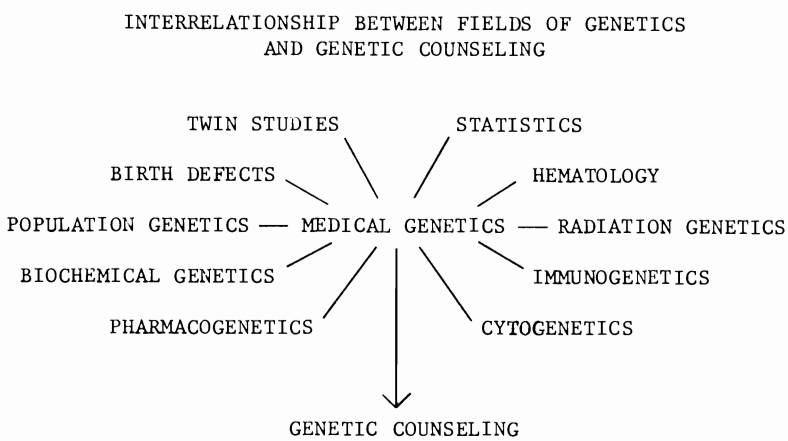

Figure 1 Various branches of genetics and medicine which provide valuable information to the genetic counselor.

Gout:

The history of gout extends back at least 7000 years. In 1907, two archaeologists discovered a large mass in the great toe of the skeleton of an elderly man in a cemetery in upper Egypt. Urates were identified in this mass by chemical analysis (Smith and Jones, 1910).

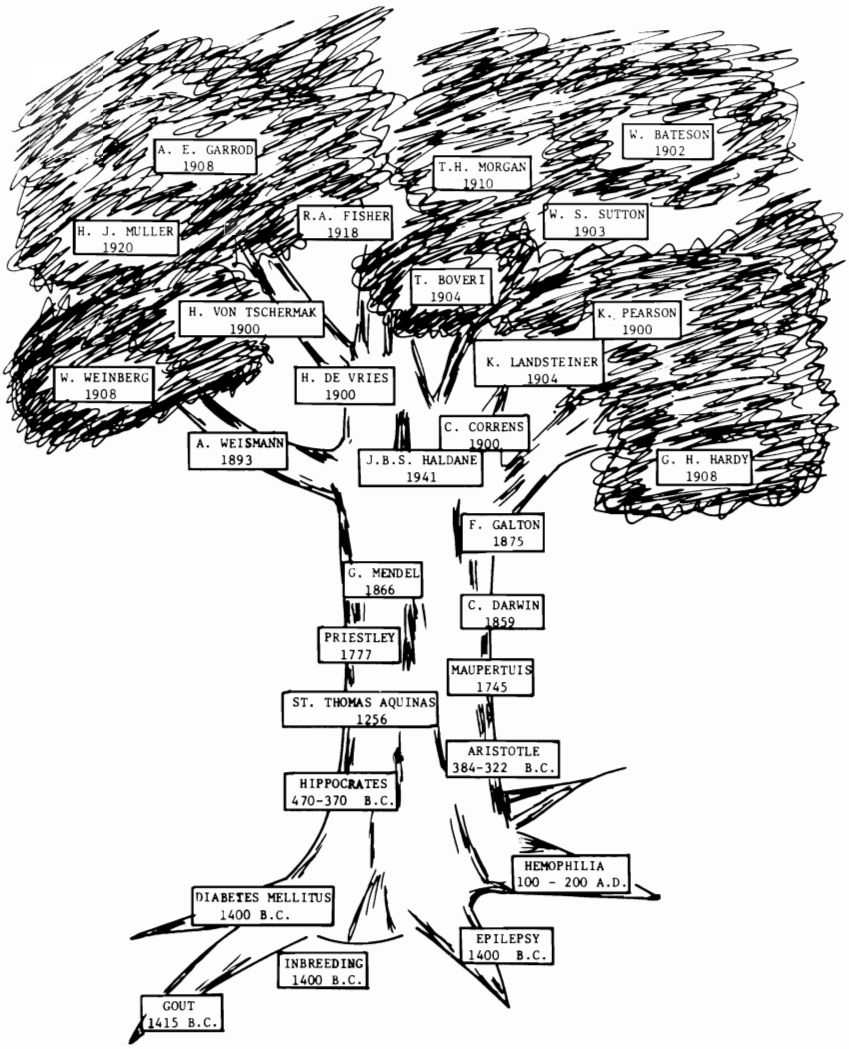

Figure 2 A "tree" of genetic counseling giving the names of persons (and writings) from antiquity to the present who have contributed to our knowledge of genetic counseling.

Later, references are made to gout in the writings of the Old Testament. In Exodus (29:20) hereditary factors were noted as follows: "Take of the blood (of a sacrificial ram) and put it upon the 't' nooch ozen' (ear lobe) of Aaron's right ear and that of his sons and upon the 'bohen' (middle joint) of their right hand and upon the 'bohen' of their right foot." (Brim, 1936). These anatomical sites are precisely those where gout occurs.

Again, in II Chronicles, (16:12) "King Asa . . . was diseased in his feet, until his disease was exceedingly great; yet in his disease, he sought not to the Lord, but to his physicians. And Asa slept with his father and died in the one and fortieth year of his reign." (Talbott, 1957).

Hippocrates, a native of Cos in Greece, who lived from 460-370 B.C., spoke of the "unwalkable disease". He noted the following: "Eunuchs do not take the gout, nor become bald. A woman does not take the gout unless her menses be stopped. A young man does not take the gout until he indulges in coition." (Adams, 1952).

Concerning the inheritance of gout and other conditions, he wrote: "For if a phlegmatic person be born of a phlegmatic, and a bilious of a bilious, and a phthisical of a phthisical, and one having a spleen disease of another having a disease of the spleen, what is to hinder it from happening that where the father and mother were subject to this disease, certain of their offspring should be so affected also?" (Adams, 1952).

Galen, the physician, was a native of Pergamum in Asia Minor and lived from about 130-200 A.D. He distinguished gout as a separate entity, a new form of podagra (arthritis) that was inheritable and related to luxurious eating and drinking (Hormell, 1940).

Archibald Garrod, an English physician, wrote a treatise on Gout in 1876. At that time, he noted that the "ancestral trait was almost 80%." Later, however, in considering various inborn errors of metabolism, he wrote: "It is still uncertain how far the accumulation of uric acid in the blood and the deposition of sodium biurate in the tissues which are characteristic features of gout, are actually due to derangement of metabolism as distinct from a mere excretory defect."

The liability to develop gout is often "inherited" but he thought that since the disease was not congenital, (present at birth) then the disease itself was *not* inherited. (Garrod, 1909).

More recently, Dr. John H. Talbott, former editor of the *J.A.M.A.* commented on hereditary factors in gout stating that "the greater the interest of the physician in pursuing the family history of gout, the higher the percentage of positive family histories." (Talbott, 1957). In other words, if a perfunctory medical history is taken, one is not likely to elicit a detailed genetic history from his patient.

Finally, in 1954, another investigator, W. S. Hoffman, and many others

noted that there is a familial tendency for hyperuricemia in gout and that gout is due to an inborn error of metabolism of uric acid.

Today, gout is recognized as an hereditary disease. Treatment is similar to that of the past, one being colchicum, which is derived from the crocus flower and saffron herbs. Allopurinol is the drug of choice at the present time, though benemid and colchicine are also used.

Hemophilia: (a sex-linked hereditary deficiency disease)

In the Talmud, (that part which was written between 100 and 200 A.D.) hemophilia was considered an hereditary disease. Circumcision was forbidden in families of bleeders (Brim, 1936). An early account of genetic counseling for this disease is found in the following quotation from the Talmud; "If she circumcised her first child and he died (as a result of bleeding from the operation), and a second one also died (similarly), she must not circumcise her third child." Much later, Rabbinic responsa differed only in interpretation of the number of repetitive events, i.e., deaths following circumcision, which would confirm a pattern and thus remove the deaths from merely a chance occurrence.

Hemophilia was one of the first diseases in which the etiology was found to be a defect on a single X chromosome. It was first recognized as an inherited hemorrhagic disease by Otto in 1803, but it was not until 1911 that it was completely established as a clinical entity. At that time Bulloch and Fildes presented pedigrees of approximately 600 families with hemophilia (editorial, 1962).

Epilepsy:

Hippocrates wrote about epilepsy and other convulsive diseases all of which had been given the label of the "sacred disease". Hippocrates, however, believed that epilepsy was no more sacred than any other disease known to man at that time. He wrote: "This disease seems to me to be no more divine than others; it has its nature such as other diseases have, and a cause whence it originates, and its nature and cause are divine only just as much as all others are, and it is curable no less than the others, unless when, from length of time, it is confirmed, and has become stronger than the remedies applied. Its origin is hereditary, like that of other diseases." (Adams, 1952).

Hippocrates gave the first recorded description of epilepsy in children (Schmidt, 1959). "At about the first or second century C. E. (Common Error or A.D.) the Talmud considered epilepsy as an hereditary disease and forbade marriage to one suffering from it; it was considered unhealthy for the community." (Jeb. 64b.)

And in the old testament (Gen. 17:3) "Abraham suffered from an attack of epilepsy, which did not again manifest itself after he was circumcised." (Brim, 1936).

Diabetes Mellitus:

Diabetes mellitus was known in the time of Leviticus (about 1400 B.C.). Even in modern times this disease is sometimes referred to as a "Jewish sickness" (Brim, 1936). In Lev. 26: 26-29, diabetes is described as a "destructive disease which will be prevalent among you, which will be due to a breaking down of your resistance to Schever Matteh Lechem (carbohydrates). The appetite will become so great that ten women will be required to bake bread upon one oven. You will eat without being satiated. Your bread will be delivered to you by weighing upon a scale" (Brim, 1936). It was described not only as a hereditary disease, but also that it would "eat up the flesh of your children" – a description of juvenile diabetes.

Although it is now quite clear that diabetes mellitus is an inherited disease, the mechanism(s) of the inheritance are still not clear-cut. The genetic counselor must emphasize that preventive medicine for relatives at risk for this disease should consist of weight control, and avoidance of smoking and alcohol. Regularity in health maintenance examinations should be stressed for early detection, followed by careful medical management once the disease is diagnosed (Lynch, 1969).

Teratology: (Birth Defects)

Aristotle, a native of Greece, lived from 384-322 B.C. In his works he considered problems of Life and Death, both spiritual and physical. We can date the beginnings of the science of Teratology to his writings: "There is violent death, and again natural death, and the former occurs when the cause of death is external, the latter when it is internal, and involved from the beginning in the constitution of the organ, and not an affection from a foreign source" (Ross, 1952).

In 1745, Maupertuis wrote about inheritance factors in polydactyly and discussed particulate inheritance.

Even before the rediscovery of Mendel's work on the genetics of peas in 1900, a French artist, Edward Munch, was made aware of genetic factors in disease (A.M.A., 1970). He wanted to paint "life as it is" and visited a hospital in Paris with a physician friend. There "a woman in tears showed them her naked child who had inherited a fatal illness from his father" (Fig. 3).

Since that time a great deal of information has been added to our knowledge of birth defects. Now we have a procedure known as amniocentesis by which means a sample of amniotic fluid can be analyzed for cytologic, immunologic, and biochemical abnormalities, thus permitting the diagnosis of certain genetic defects before the birth of a child.

This leads us to some considerations of the future in genetics and genetic counseling. These are the implications involved in what is now called genetic engineering. An example of genetic engineering is as follows: We are

Figure 3 Copy of a painting entitled "The Inheritance" by Edward Munch. (Reproduced with permission of the editor of *J.A.M.A.*)

conducting a genetic study of a family with an heriditary form of emphysema in which family members who have the condition (are homozygous for it) have a deficiency of a specific enzyme, known as alpha-1 antitrypsin. (Fig. 4)

By means of serum electrophoresis which records the amount of alpha-1 globulin present in the serum, other family members may be found to be heterozygotes (one normal gene; one defective gene). This disease was first described in 1963 by Laurell and Eriksson. Since the publication of their findings, this type of emphysema has been found to be less rare than at first considered. So far, a specific type of genetic engineering or a factor to make up for the deficient enzyme has not been found for this condition, but investigations in search for such a factor are being carried out in several research units in the .United States. Possibly the solution may come in the form of a virus.

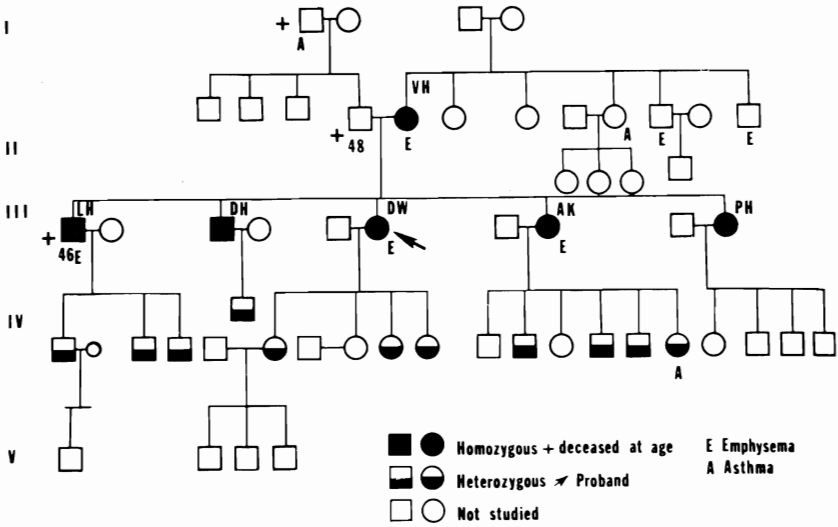

Figure 4 A pedigree of a family with alpha-1 antitrypsin deficiency, causing emphysema.

We know, for instance that the Shope virus carries information concerning the synthesis of phenylalanine hydroxylase, the enzyme that is missing in phenylketonuria, a disorder characterized by mental deficiency due to an excess of phenylalanine in the system causing a toxic effect on the brain. The obvious implication is that by correcting for this enzyme deficiency by means of the Shope virus, the disease could be effectively controlled.

Xeroderma pigmentosum is a disease which has recently been characterized by a deficiency in a nuclease that excises pyrimidine dimers in DNA. Patients with this deficiency ultimately develop cancer of the skin. We

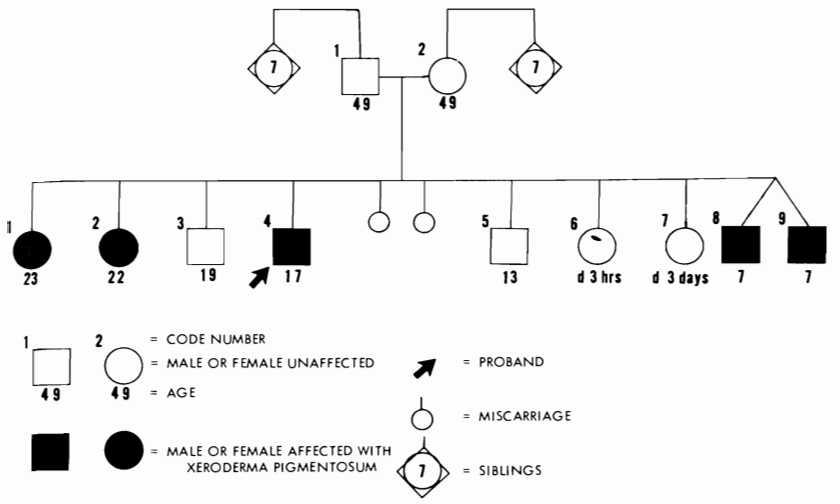

Figure 5 A pedigree of a family with xeroderma pigmentosum.

have studied a family with xeroderma pigmentosum in whom 5 of 7 siblings were affected, though this disease is inherited as an autosomal recessive (Fig. 5). It is hoped that, in time, a virus will be found which can carry information which will then induce the synthesis of this deficient enzyme and restore the normal mechanisms which protect against sunlight exposure. Thus, we might have a means of eliminating the high incidence of cancer of the skin in these patients, cancer which, as we mentioned, is thought to be related causally to sunlight exposure.

Theoretically, there may be a specific genetic deficiency disease related to each individual enzyme in the metabolic pathways in the body. Thus, it is also conceivable that a specific virus may be able to carry a message which would be capable of transmitting information which could effect the synthesis of each specific enzyme deficiency.

One might wonder why genetic engineering of this type is introduced in the subject of genetic counseling. The point is that this may well be the very future of so-called applied genetic counseling. It is obvious that one must first identify a family, assemble a pedigree to determine those who are at risk for a specific disease, and then secure the cooperation of the family in order to initiate a genetic study. In this case, when the genetic team obtains a complete medical and genetic history of a family with a specific hereditary disease, they may then direct family members to biochemists, virologists, and other medical specialists, who, through "genetic engineering," could select viruses which might alter or counteract the clinical manifestations of the genetic disease in affected family members.

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