

GENETIC STUDIES OF THE AMISH

Background and Potentialities

VICTOR A. MCKUSICK, JOHN A. HOSTETLER,¹ AND JANICE A. EGELAND²

*Division of Medical Genetics, Department of Medicine, The Johns Hopkins University
School of Medicine and Hospital*

Received for publication March 26, 1964

A description of the Amish (1, 2). Because of their unusual socio-religious tenets and practices, the Old Order Amish are widely known. They eschew personal adornment and follow closely prescribed habits of dress. They resist technologic advances, specifically using the horse and carriage for transportation and using mainly horse-drawn agricultural equipment. Electricity and telephones are not permitted in the home. Most Amish are farmers. Private enterprise with mutual assistance characterizes the Amish economic system. Many Amish, especially in Lancaster County, Pa., are prosperous and a few are fairly wealthy.

Some Amish are trilingual, speaking English, German and "Dutch" (a German dialect of Palatine origin) and all are bilingual. Religious services, conducted in German and "Dutch," are held in the several homes (or barns) in rotation. Amish religious beliefs are based on literal interpretations of the Bible. A strong system of sanctions, including excommunication and shunning (*Meidung*), helps maintain the group. As Anabaptists, the Amish oppose infant baptism. Reception into church membership by baptism is practiced at an age of decision on the part of an individual, usually in the late teens. Footwashing, a symbol of humility and service, is a characteristic part of the Amish communion service held twice a year. No formally educated clergy exists. Bishops, preachers, and deacons, chosen from the laity, are responsible for religious aspects and, indeed, most aspects of community life.

The Amish do not want their children educated beyond grade school. They also resist consolidated schools, not necessarily because of fear of corruption of their children through contacts with non-Amish but more because of the teaching of science, gymnasium activities including the wearing of uniforms, and modern facilities. One-room Amish parochial schools staffed by teachers with little formal training persist in many Amish areas of this country. Frequently the Amish get into trouble with the government over matters such as failure to satisfy the minimal require-

¹ Department of Sociology and Anthropology, Pennsylvania State University, Ogontz Campus, Abington, Pennsylvania.

² Department of Sociology, Franklin and Marshall College, Lancaster, Pennsylvania.

ments for schooling, to make Social Security payments, and to electrify their dairy barns.

Some differences in social practices related to dress, use of motorized farm equipment, use of tobacco, type of buggy, etc., exist among Amish groups living in different parts of the country (1, 2). As will be described later, genetic differences are also discernible among different Amish groups.

About 80 per cent of the Amish live in Pennsylvania, Ohio and Indiana (Fig. 1) with scattered groups elsewhere, including Ontario, Florida, and Oklahoma. If spill-over into adjoining counties is included, it is accurate

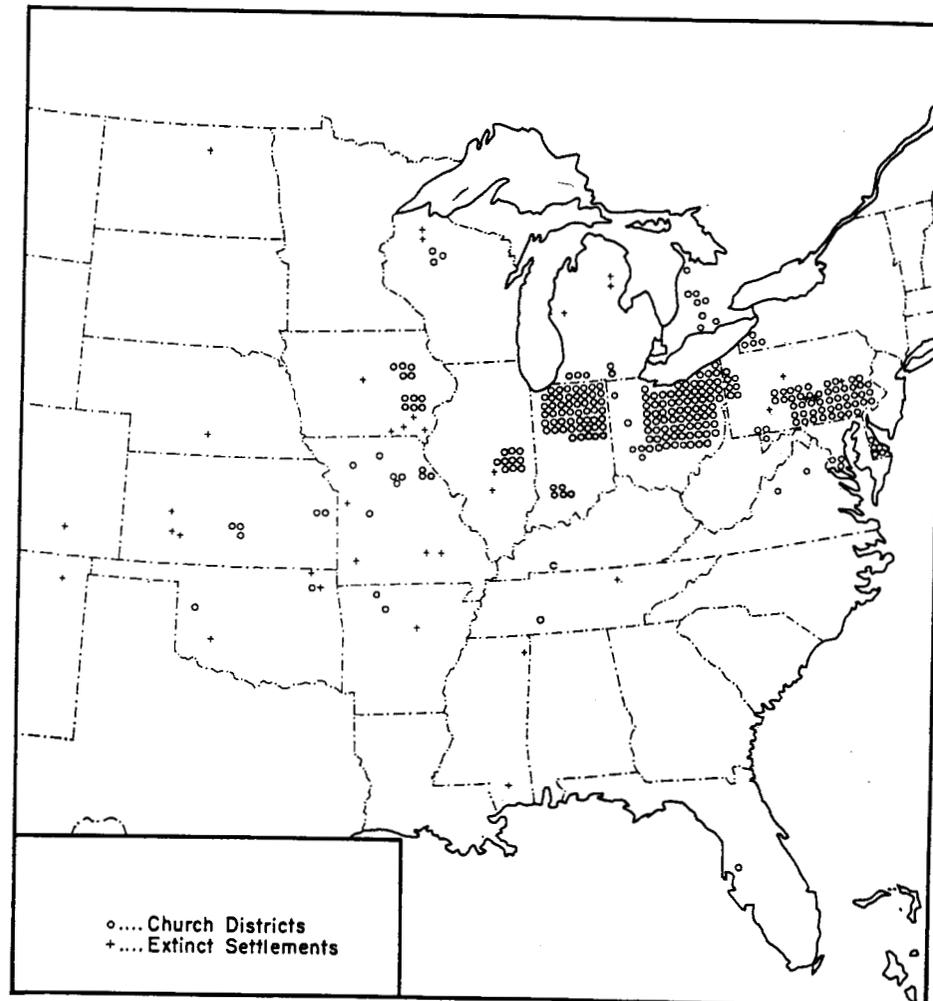


FIG. 1. Geographic distribution of Old Order Amish church districts. From Hostetler (1).

to state that over half the Amish live in three counties (Fig. 2): Lancaster County, Pa.; Holmes County, Ohio; and LaGrange County, Indiana. The basic unit of Amish society is the church district, which is kept small by the limitations of horse-and-buggy transportation, and those imposed by the practice of holding religious services in the home.

Hostetler (1) estimates that in 1960 the Old Order Amish in this country and Canada totaled over 43,000. The estimate is obtained by using the available statistics on church membership and assuming (based on a survey) 113 non-members (children and others not baptized) for each 100 members. As shown in Figure 3, the Amish population has grown steadily since 1905, despite appreciable loss through persons leaving the faith. During a period when the Amish have shown a five-fold increase, the population of the country as a whole has only about doubled.

The age distribution of an Amish population is indicated in Figure 4

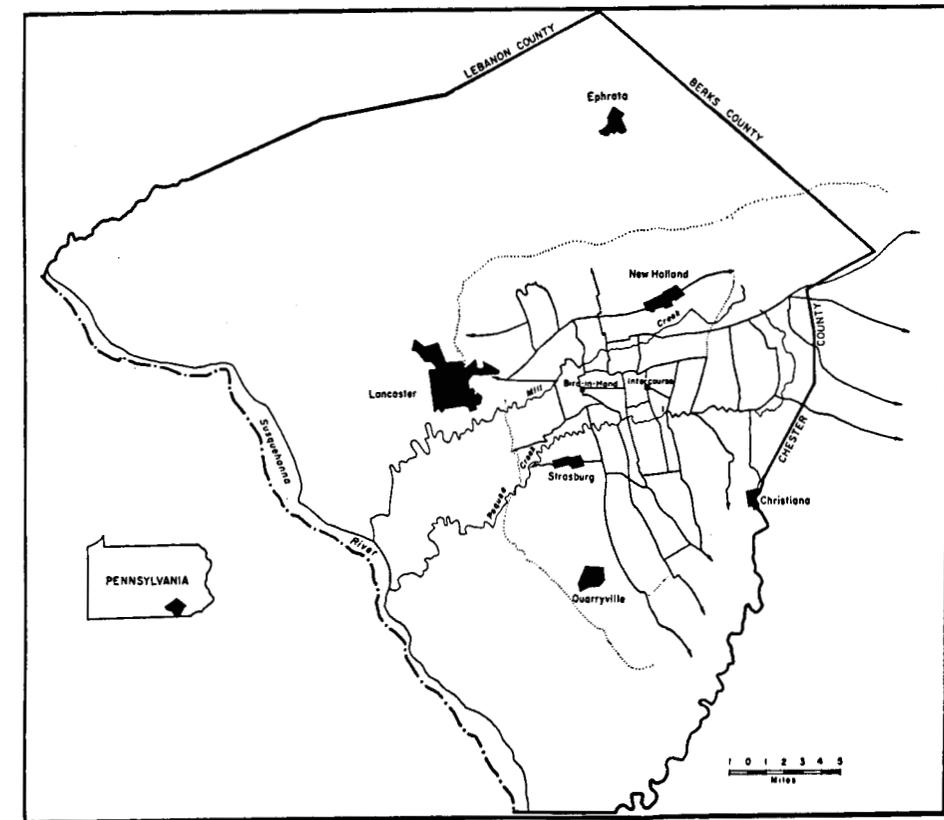


FIG. 2. Church districts in the three areas with largest concentrations of Amish. a. Lancaster County, Pennsylvania. b. Holmes and Wayne Counties, Ohio. c. LaGrange and Elkhart Counties, Indiana. From Hostetler (1).

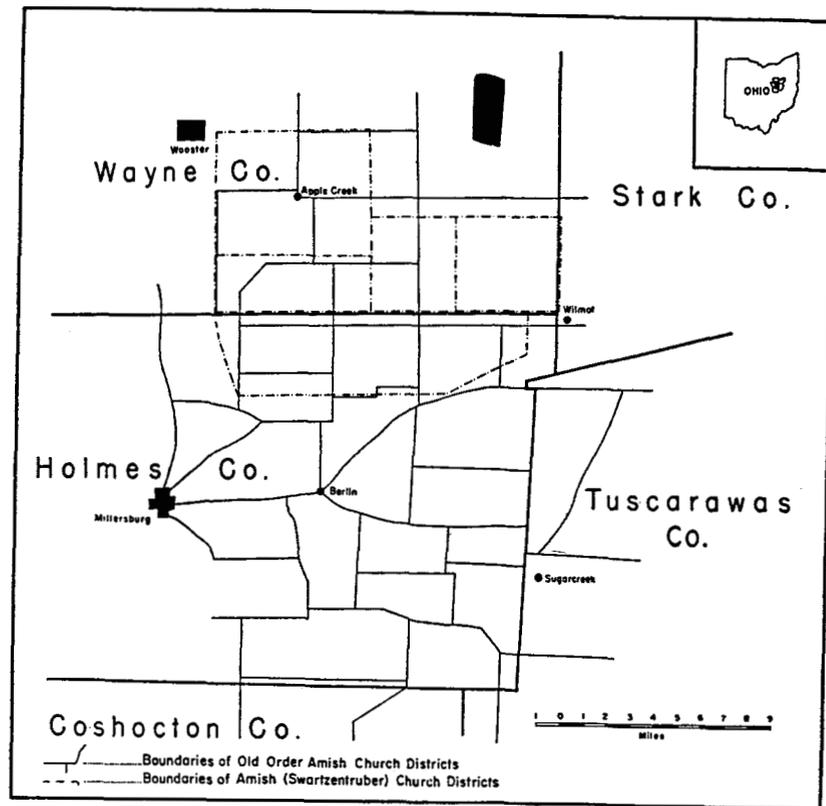


FIG. 2b

and compared with that of a non-Amish rural population. The striking difference is that the Amish lack the constricting waist in the non-Amish population pyramid, attributable to a fall-off in birth rate during the depression and just before the sudden increase in birth rate in the early period of World War II.

Amish origins. Anabaptist movements developed in several areas of Europe in the 1500's. In Switzerland the so-called Swiss Brethren originated about 1525. It was from these that the Amish originated. In the Netherlands their counterpart was the group called "Mennists" or Mennonites after their leader Menno Simons. The name Mennonite was later applied generally to descendants of Swiss, Dutch, and other Anabaptists.

The Amish sect had its origin in the Emmenthal area of the Canton of Berne, Switzerland, in the 1690's, when followers of Jakob Ammann, a Mennonite Bishop, split off from the parent sect.

Appreciable isolation of the Amish and their Mennonite predecessors from the other Swiss had probably already taken place for both geographic

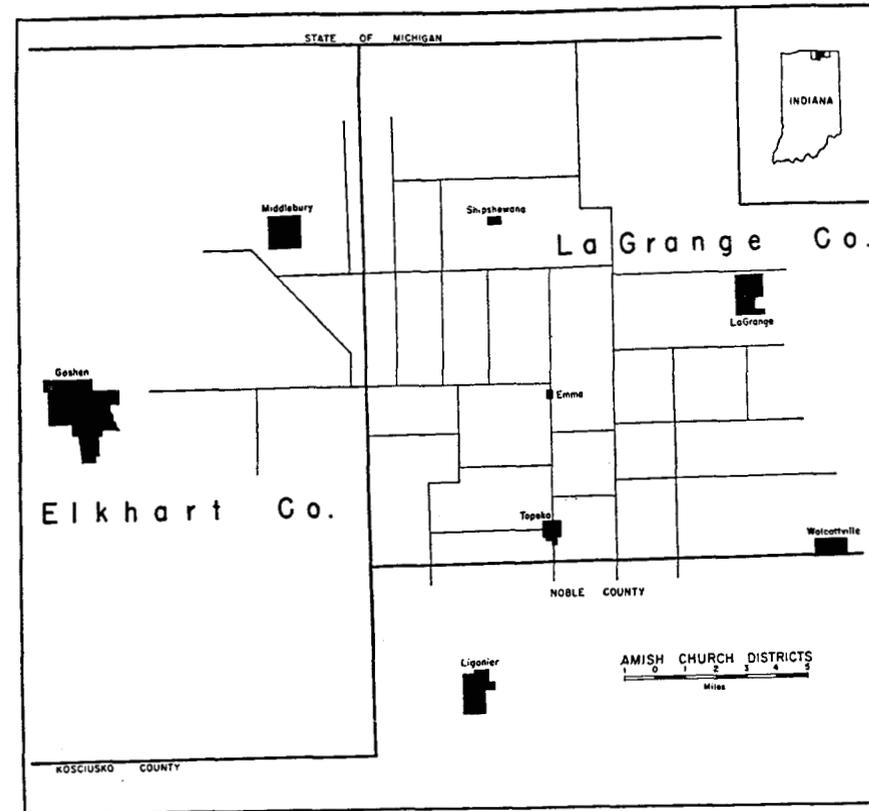


FIG. 2c

and social reasons. The Emmenthal people had fled to that area to avoid religious persecutions.

Some Amish left Berne at the time of the split and went to Alsace-Lorraine, eastern France and the Palatinate. Ammann was, furthermore, a "prophet not without honor save in his own country," for he found a greater following in Alsace than in Berne. It was, however, among the Swiss Brethren who had left Switzerland earlier that he probably made most of his converts. This was a "movement within a movement."

The immigrations of Amish to Eastern Pennsylvania began perhaps as early as 1714 and at least as early as 1727 and continued until about 1770. Most of the present-day Lancaster County Amish are descendants of pre-Revolutionary Swiss immigrants, who may have numbered no more than 200. Later waves of immigration continued until about 1850. These so-called Alsatian immigrants, finding the eastern lands already occupied, moved on to Ohio, Indiana, and Illinois, where they found descendants of early immigrants to Eastern Pennsylvania already living. These differences

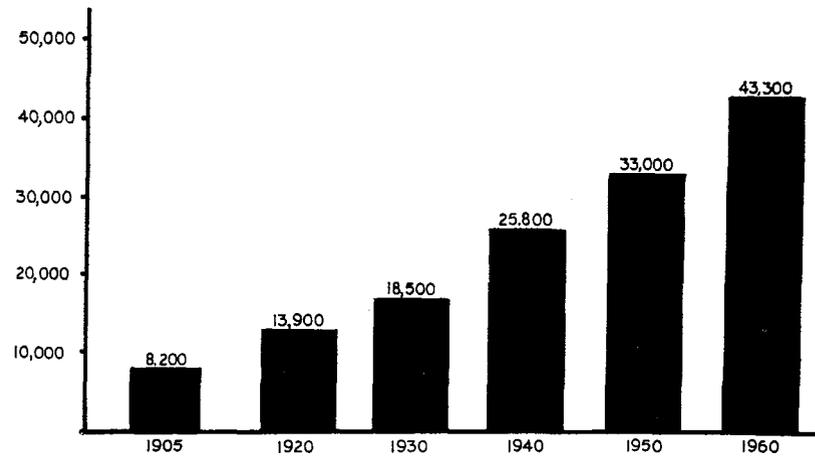


FIG. 3. Growth of total Old Order Amish population in North America from 1905 to 1960, inclusive. Based on estimates by Hostetler (1).

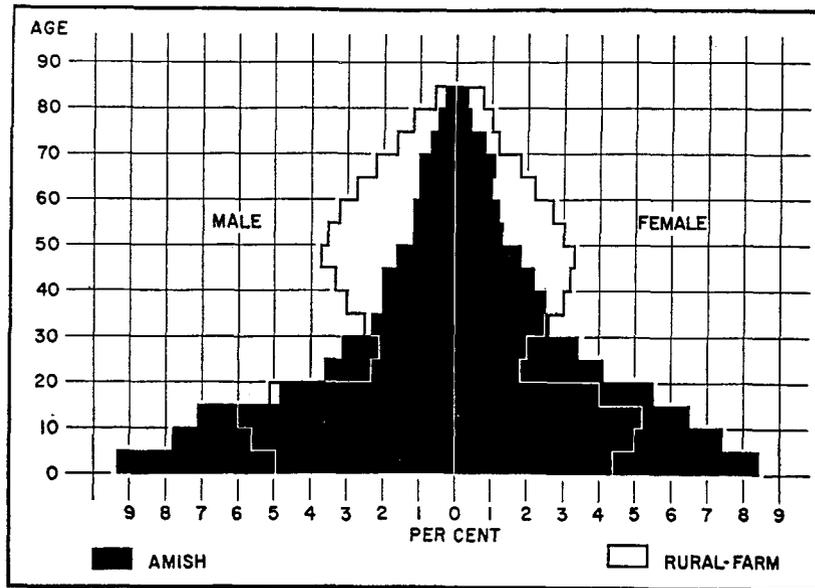


FIG. 4. Age distribution of Amish as compared to rural-farm non-Amish. From Hostetler (1).

in origin are supported by the differences in family names of bishops, ministers and deacons, as indicated in Table I. No overlap was observed between Lancaster and Holmes Counties. Although the material in the table applies only to the clergy, only to the counties named and only to the year 1962, a generalization of partial genetic distinctness seems war-

TABLE I
Names of Old Order Amish Deacons, Ministers, Bishops
From *Mennonite Yearbook* (1962)

Lancaster County, Pennsylvania	LaGrange County, Indiana	Holmes County, Ohio
Beiler		
Blank		
Diener		
Eash (Esh, Esch)	Eash	
Fisher		
Glick		
King		
Lantz		
Lapp		
Riehl		
Stoltzfus		
Smucker		
Zook		
	Beachy	Beachy
		Coblentz
	Frey	Frey
	Gingerich	Gingerich
	Hershberger	Hershberger
		Hostetler
		Keim
		Kline
	Mast	Mast
	Miller	Miller
	Raber	Raber
		Schlabach
	Shrock	Shrock
		Stutzman
	Troyer	Troyer
		Weaver
	Yoder	Yoder
	Anderson	
	Bontrager	
	Farmwalt	
	Graber	
	Lehman	
	Mishler	
	Nissley	

ranted. Fairly extensive overlap between LaGrange and Holmes Counties is shown. The distribution of family names as indicated by the findings of censuses in Lancaster and Holmes Counties (Table II) bears out the distinctness indicated by names of clergy. A set of eight names accounts for about 80 per cent of the families in both counties and the sets are entirely different.

TABLE II
Old Order Amish Family Names

Lancaster Co., Pa.	Holmes Co., O.	Mifflin Co., Pa.
Stoltzfus*..... 23%	Miller..... 26%	Yoder..... 28%
King..... 12%	Yoder..... 17%	Peachey..... 19%
Fisher..... 12%	Troyer..... 11%	Hostetler..... 13%
Beiler..... 12%	Hershberger..... 5%	Byler..... 6%
Lapp..... 7%	Raber..... 5%	Zook..... 6%
Zook..... 6%	Schlabach..... 5%	Speicher..... 5%
Esh**..... 6%	Weaver..... 4%	Kanagy..... 4%
Glick..... 3%	Mast..... 4%	Swarey..... 4%
81%	77%	85%
Totals: 1106 families, 1957	1611 families, 1960	238 families, 1951

* Including Stoltzfoos.

** Including Esch and Eash.

The Lancaster County families are those listed in the *Fisher Family History* (8) which, published in 1957, included all but 4 of the Old Order Amish families in that county. The Holmes County data are from the *Ohio Amish Directory* assembled and privately circulated in 1960 by Ervin Gingerich, Star Route, Millersburg, Ohio. The Mifflin County listing was given by John A. Hostetler, in "The Amish Family in Mifflin County, Pennsylvania" (M.A. thesis, Pennsylvania State College, 1951).

Since they came to this country, there has been relatively little intermarriage between the Eastern Pennsylvania Amish communities and those of Ohio and Indiana. Bender (3) states that "the earlier pre-Revolutionary immigrants of the Berks-Lancaster settlement and the later Alsatian Amish immigrants never really formed a harmonious working relationship" in the sphere of religious fellowship. The existence of subisolates within the larger group is suggested by other peculiarities in distribution of family names: for example, Peachey is limited mainly to Amish of Mifflin County, Pa., whereas Beachy is a frequent name in Ohio and Indiana: both are anglicizations of Bitsche. In Lancaster County Beiler is a frequent Amish name; in Mifflin County the name is written Byler.

Another indication of subisolate formation is the distribution of rare recessive genes. The gene for the Ellis-van Creveld syndrome may have a frequency as high as .07 in Lancaster County Amish (4) but seems to be as exceedingly rare in other Amish as it is in non-Amish. The gene for pyruvate kinase deficiency hemolytic anemia is relatively frequent in the Mifflin County Amish (5) but has not been identified in Amish elsewhere. Limb-girdle muscular dystrophy occurs relatively frequently in the Amish of Indiana (6) but has not been observed in the Eastern Pennsylvania Amish (7).

The effective size of the Amish marriage groups may be quite small.

Even within an area such as Lancaster County, Pa., which has remained demonstrably distinct from others such as Holmes County, Ohio, marriages are probably contracted within rather small radii which do not embrace the entire Amish area of the county. The organization into church districts with limited social exchange between districts probably increases the tendency to formation of subisolates.

All the present-day Amish have their origins from a relatively small number of immigrant ancestors. Whereas they have flourished remarkably on this continent, no Amish can be found today in Europe or elsewhere. Hostetler (1) suggests that the Amish in Europe were "too mobile, too scattered, and too persecuted to constitute a folk culture." He doubts that if all Amish had remained in Europe they would have survived at all as a cultural group. On the other hand, in eighteenth century America land was available in almost unlimited amounts. They could live adjacent to each other on family farms and maintain relatively self-sufficient, homogeneous communities.

Characteristics of the Amish which make the group useful for certain genetic studies include the following:

1) The Old Order Amish constitute a *defined population*, in fact a self-defined population. There can be no question of who is presently Amish, although there may be question of who may have Amish ancestry. Although other "plain people" are often confused with the Old Order Amish, the distinctions are unequivocal.

2) It is a *closed population*. The Amish do not proselytize and marrying outside the faith is forbidden. Although some leave the group, very few "new" persons enter it. The few "outsiders" who have joined the group in the past are easily identified by their name.

3) The origins of the populations are *western European* and are rather well known.

4) *Genealogic records* are extensive. Most Amish can trace their complete ancestry back to the immigrants from Europe. The Fisher genealogy (8), a tome giving the children and other data on more than 3600 families (marital couples and children), relates to almost all living Lancaster County Amish. When published in 1957, only four Amish married couples in Lancaster County did not appear in it (9). *Descendants of Barbara Hochstedler* (10) is a genealogy covering 15,556 parental pairs and their children. *Descendants of Jacob Hochstetler* (11) covers over 9000 married couples. Large genealogies have been published for the Bitsche (Beachy, Peachey), Eash (Esh), Gnagey (Kanagy), Hershberger, Hertzler, Kauffman, Lantz, Lapp, and Mast families and many, more modest, published family records are available. In all, there are at least 60 publications of Amish family records.

The interest of many simple peoples in genealogy is a matter of note. In some primitive people, such as the Navajo Indians, descent, kinship, and clan identification are important in connection with decisions on whom to marry. The Amishman's religion-based concept of his group as a "peculiar people" (see below) may be an important factor in his genealogic interests. He considers the genealogic accounts in the Bible as a significant precedent. The active genealogic research of the Mormons likewise has a religious basis.

5) The *standard of living* is high. The genetic factors in morbidity and mortality are less likely to be swamped by non-genetic ones, such as malnutrition and infection.

6) The *standards of medical care* are relatively high. Although the Amish tend to be attracted to fringe and unorthodox practitioners (12), they do make use of the diagnostic and therapeutic facilities in neighboring medical centers. Because of the quality of diagnostic services, specific hereditary diseases are likely to be identified correctly and ascertainment of cases is facilitated.

7) A great *interest in illness* is evident. For example, *The Budget*, a weekly newspaper which caters particularly to the Amish, frequently carried lengthy and detailed accounts of illness, provided by its Amish correspondents all over the country (12). Recent issues described an infant diagnosed as having osteogenesis imperfecta congenita, a boy with metachromatic leukoencephalopathy, a family in which three sisters have died of atypical Fanconi syndrome, a brother and sister with cranial synostosis, and a case of von Recklinghausen's neurofibromatosis. Through the columns of *The Budget* two distantly related Amish families, each with two sisters with hydrometrocolpos, were discovered (13).

8) Because of the strict endogamy, the relatively small number of immigrant ancestors, and the limited size of the subgroups, a relatively high mean coefficient of *consanguinity* must exist. Although first cousin marriages are uncommon, second cousin marriages are rather frequent in many Amish groups. The average level of consanguinity in many Amish communities may be the equivalent of third or fourth cousins. The only available data are those of Hammond and Jackson (14), who found that among all 627 marriages of descendants of Johannes Schwartz and his wife Anna Ramseyer (Amish living in the vicinity of Berne, Indiana), 21.5 per cent involved second cousins or closer relatives. The situation is probably comparable to that in the Ramah Navaho Indians in whom Spuhler and Kluckhorn (15) found that as much as 57 per cent of the known inbreeding would be missed if consideration were restricted to third cousin relationships and closer and to a single relationship, the closest.

9) The *illegitimacy rate* is probably low. The regulations of the church appear to prevent illegitimacy quite effectively. In some Amish communities premarital conception is probably relatively frequent and the legitimacy of the first-born may, under these circumstances, be uncertain. One study (16) of Amish marriages in Lancaster County (Pa.) from 1890 to 1956 showed that about 4 per cent of first born children were delivered to mothers who had been married eight months or less (average of this group, 4.9 months). Premarital conception *per se* is, of course, no impediment to genetic studies provided the biologic father is accurately identified. Illegitimacy of later children is unlikely.

10) The Amish are *clannish* and usually have information on other Amish, especially as concerns some illness or defect which is present in a close relative.

11) *Socio-economic and occupational circumstances* are notably uniform. All are rural-living, most are farmers, and poverty is non-existent. All, of course, have the same religion. The Amish group is a defined and closed population from the genetic point of view; the uniformity of socio-economic and psycho-religious environmental factors is also an advantage for genetic studies. Reduction in the environmental contribution to variability allows clearer study of the genetic contribution.

12) Because of their dedication to horse-and-buggy transportation and to an agrarian life, the Amish are more *immobile* than most other people in this country. Employment in industry does not attract them to new and distant locations. Although the Amish make use of public transportation or hired cars to visit distant settlements, the contacts which result in marriage are mainly within the range of easy buggy transportation.

13) *Large families*, averaging seven to nine, have long been the rule among the Amish. Whereas non-Amish parents may stop having children after the birth of one or more defective children, Amish parents seem not to be influenced by this factor. Combined with the immobility of the group, the large families present one with rare facility to collect information and specimens for study on a relatively large number of relatives of persons with given disorders. When he died at age 95 years, one Amish man had 410 living descendants: five children, 61 grandchildren, 338 great-grandchildren and six great-great-grandchildren (1).

14) Defective individuals, including the mentally retarded, are usually *not institutionalized* but rather are kept at home. Thus, such cases are more readily identified and studied in relation to the rest of the family.

15) The existence of *several separate Amish isolates*, particularly those of Lancaster County, Pa., and Holmes County, Ohio, makes comparisons

possible. The evidence for partial genetic distinctness of the two Amish groups mentioned has been reviewed earlier in this paper.

Some of the advantages mentioned have been shared by European populations such as those of Switzerland in which useful studies have been done by Hanhart (17) and others and those of Sweden studied by Sjögren (18) and others (19). In an earlier period, when isolates existed in many parts of western Europe it was possible to collect large pedigrees, e.g., Lundborg's pedigree (20) of myoclonic epilepsy, which was historically important as the first illustration of the dynamics of a recessive gene in an inbred group. In the United States the most informative single group for genetic study has been the Utah Mormons, and the reasons include many of the features which have been listed here, particularly good genealogic records, relative immobility, and clannishness (growing out of common religion and socio-economic circumstances) which aids familiarity of relatives with each other.

Difficulties in realizing the full potential of the Amish for genetic studies are related mainly to their suspicion of the motives of "outsiders." Separation from the "world" is probably the most important part of the Amish religious philosophy. Two passages of scripture are frequently quoted as the literal basis for separateness:

Be not conformed to this world, but be ye transformed by the renewing of your mind that ye may prove what is that good and acceptable and perfect will of God. (Romans 12:1)

Be ye not unequally yoked together with unbelievers; for what fellowship hath righteousness with unrighteousness? and what communion hath light with darkness? (II Corinthians 6:14)

The principle of separateness governs all the Amishman's contacts with the outside world, including that with a medical research project. The Amish consider themselves a "chosen people" or "peculiar people" just as do the Jews. Ethnic solidarity, i.e., genetic distinctness, and religious separateness are interdependent.

Combined with the philosophy of separateness, a strong anti-scientific attitude can create problems for a medical research project that does not have obvious and fairly immediate practical usefulness. Amish attitudes toward autopsy vary. Usually considerable resistance is encountered. Partly this is because they wish to have the body returned home as soon as possible, partly because mutilation is feared. Their anti-scientific philosophy may also be involved. Of the 36 deceased Amish persons with the Ellis-van Creveld syndrome reported elsewhere (4), autopsy was performed in only one; 20 of the 36 were less than two weeks old at death.

When approached through local physicians no difficulties have, as a rule,

been encountered, however. In the study of dwarfism in the Amish (4, 21), the assistance of an affected Amish adult in arranging home visits was valuable. Also, several unmarried Amish women collected information both of medical and of genealogic nature and provided introductions to affected families who in many instances were relatives.

Resistance against efforts to alter what is considered to be the will of God is illustrated by the following comment in a letter from a 30 year old Amish dwarf who refused examination:

As for me I think I am exactly the way the Good Lord intended for me to be, even before I was born. So I feel no human hands or brains can do a thing about me or anyone like me, if it is the way the Lord wants it, no matter how highly educated anyone is. I am happy, have work, friends, and can support myself. So what more do such people want?

Types of genetically significant information obtainable from a population such as the Amish include the following:

1) "New" recessively inherited disorders can be discovered. Over 200 rare recessive phenotypes, each perhaps reflecting a separate genetic locus, have been identified in man (22). On the other hand, over 50 recessive phenotypes determined by X-linked genes are known (23). If the X chromosome has 6 per cent as many recessive genes as the 22 autosomes combined—as is suggested by the relative lengths of the mitotic chromosomes—then 50(100/6), or over 800, autosomal recessive phenotypes should be known in man. In inbred species the proportion of autosomal recessive phenotypes expected in relation, for example, to the number of X-linked traits, is realized. Rarity of inbreeding in man accounts for the rarity with which rare autosomal recessive genes meet in homozygous state. On the other hand, an X-linked gene always expresses itself in the hemizygous male even though recessive. Thus, hemophilia A, with a frequency of about one per 10,000 males (and therefore a gene frequency of .0001), would occur in only about 1 per 100,000,000 persons, if it were autosomal recessive (with random breeding) rather than X-linked recessive. If autosomal recessive, hemophilia might be rather unfamiliar.

Discovery of "new" genetic diseases is not mere "stamp-collecting." It is a means for determining the normal genetic constitution of man. The catalogs of simply inherited genetic traits in man (22, 23) are like photographic negatives from which a positive picture of the normal genetic constitution of man can be constructed.

Rare recessive diseases which remain to be discovered are likely to include many inborn errors of metabolism (using the designation in the Garrodian sense). Ample precedence indicates that these "experiments of nature" are valuable tools for elucidating normal biochemical mechanisms

and the pathogenesis of common disorders which are not overwhelmingly genetic in origin.

In the course of the study of dwarfism in the Amish a new recessively inherited disease, cartilage-hair hypoplasia, has indeed been discovered and will be the subject of another report (21).

2) It may be possible to collect evidence of the recessive nature of a disorder so rare that only sporadic cases are observed, or it may be possible to demonstrate the existence of a recessive form of some malformation which is heterogeneous from the etiologic point of view. For example, in the Amish the autosomal recessive nature of one form of hydrometrocolpos may be indicated by the observation of two related sibships in each of which two sisters are affected (13).

Risks attend this approach: almost any condition, e.g., Mongolism, may be claimed to be recessive, merely because of the occurrence in children of consanguineous parents and in members of several sibships traced back to a common ancestor.

3) An endogamous isolate population may have in it many cases of a recessive disease which, although previously known on the basis of a few scattered cases, can be much more adequately studied when a large number of cases of what is quite certainly the same disease are available. In the Mormons, mentioned earlier, Perkoff and his colleagues (24, 25) delineated the syndrome of hereditary nephritis and deafness and brought it to general attention on the basis of a pedigree which for number of affected persons has not been matched by any of the other reported families. Gardner (26) described Gardner's syndrome (intestinal polyposis with soft tissue and osseous tumors) in another extensive Mormon kindred. Neither of these reports was the first to describe the syndromal relationships mentioned, but whereas only scattered cases had been reported previously, the observation of dozens of cases of the syndrome in a single kindred was undeniable evidence for validity of the entity.

Another example: almost as many cases of the Ellis-van Creveld (4) have been identified in the Lancaster County Amish as are reported in all the medical literature. The range of clinical severity and the array of manifestations in this complex syndrome can be well studied on the basis of this unusually large single series of individuals homozygous for what is unquestionably the same gene. Another example of the use of isolate studies to describe the range of expression of a gene is the study of Alström (19) of the hereditary retinal disorder which was called by him heredo-retinopathia congenita and which is responsible for about 10 per cent of blindness in Sweden. Alström (19) stated: "It was not until combined genealogic and genetic-statistical studies had been made, and clinical data collected

over a long period that the congenital development and affinity of these apparently heterogeneous cases could be established with some degree of probability."

There are risks also in this approach. For example, Pfändler (27) collected cases of congenital deafness in Swiss isolates and found a deficiency of cases compared to that expected on the basis of a recessive hypothesis. He interpreted the deficiency as due to sublethality of the gene and loss of homozygotes through death *in utero* or in early infancy. It seems more likely that sporadic ("acquired") cases were included in the series on the unwarranted assumption that all deafmutism in the isolate had the same basis. Amman and Marty (28) described eye abnormalities in a large kindred descendent from an ancestor who lived in Upper Valais, Switzerland, in the seventeenth century. They found seven cases of tapeto-retinal degeneration in two sibships, five cases of macular degeneration in five sibships and three cases of fundus albipunctatus cum hemeralopia in two sibships. They interpreted these varied phenotypes as the result of one and the same gene—a conclusion which may not be justified in an inbred population such as this.

4) If it is possible to trace the ancestry of both parents of several sibships affected by a given recessive disorder back to a single marital couple, then strong evidence is provided that one or the other of that couple was heterozygous for the gene in question. The Ellis-van Creveld syndrome illustrates (4) how this is accomplished. It is estimated (29, 30) that everyone is heterozygous for several genes which in homozygous state would result in serious disease. By investigating all rare recessive diseases in a closed population such as the Amish, it is at least theoretically possible to arrive at a minimal estimate of the part of the genetic load in specific ancestors due to specific recessive genes.

In addition to the above, chromosomal aberrations are of interest in inbred populations. In the study of families with translocations it may be possible to find persons homozygous for a translocation chromosome, a phenomenon of interest in connection with Robertsonian evolution (31, 32)—change in chromosome number with little or no loss of chromosome material. The frequency of Mongolism and other chromosomal aberrations in a defined population such as this is always a matter of interest and particularly so in an inbred group. In plants and in *Drosophila*, genes which in the homozygous state predispose to non-disjunction have been found (33, 34). If such exist in man some inbred populations might have an increased frequency of Mongolism and other non-disjunctional chromosomal accidents, and of combinations of these in the same sibship or same individual.

If complete surveys are possible, *de novo* dominant mutations may be identifiable in a closed population such as the Amish. A probable new mutation for symphalangism (35) and one for spastic paraplegia (36) were identified in the Amish.

Rare dominant traits can be subjected to linkage study, taking advantage of the availability of many relatives for study. The linkage of rare recessives can be studied to some extent: 1) by identifying the heterozygotes by special means and treating the trait as a dominant (37), and 2) by making observations on associations between rare recessive traits in the children of consanguineous marriages. Haldane (38) concluded, however, that the association resulting from linkage is "so slight as to be of doubtful value for the detection of linkage."

Determination of the frequencies of blood groups and other marker traits can give information on the degree of distinctness of the sub-isolates and the operation of genetic drift. In view of the historical data and the findings in Tables I and II, the differences and similarities of the Lancaster County and Holmes County Amish with regard to these markers should be determined.

Demographic information of interest to the geneticist includes mean coefficient of consanguinity, average number of children, mean age at first marriage, percentage of persons living at 20 not married at 40, the frequency of twins, sex ratio, and age specific mortality rates (39). Some data on several of these points have been published (16). Application of MacCluer and Schull's method (40) for estimating frequency of non-paternity in a population is also of interest.

Studies of at least three rare autosomal recessive diseases in the Amish have been published: limb-girdle muscular dystrophy in the Indiana and Ohio Amish (6), hemolytic anemia due to deficiency of erythrocyte pyruvate kinase (5) (41) in the Amish of Mifflin County, Pa., and phenylketonuria (42) in the Indiana Amish. (The second of these may be a "new" disease, for although red cell pyruvate kinase deficiency had been described, first in 1962 (43), the hemolytic anemia in the Amish is much more severe than in previously reported cases, leading to death in the first years of life, and splenectomy is highly beneficial, converting a lethal disease into a condition of mild anemia.) The frequency of mental retardation, often with multiple affected sibs, is high in the Amish and will justify close study—biochemical, chromosomal, genetical, and sociological. "Foot problems" (clubfoot, flat feet, etc.) likewise seem to be unusually frequent in Lancaster County Amish. Preliminary information is available on Amish cases of the following rare autosomal recessive disorders: metachromatic leukoencephalopathy, osteogenesis imperfecta congenita,

congenital deafness, endocardial fibroelastosis, galactosemia, atypical Fanconi's syndrome, albinism, PTA (Factor XI; plasma thromboplastin antecedent) deficiency, and the "Swiss type" of agammaglobulinemia. Hemophilia B (Christmas disease; PTC deficiency), an X-linked recessive disorder, is frequent in the Ohio Amish according to the studies of Doan and colleagues (44) and of Ratnoff (45).

Other anabaptist religious groups of German or Swiss origin are often confused with the Amish, e.g., the Dunkards (in whom Glass (46) did population genetic studies and in whom Jackson (7) is studying porphyria), the Hutterites (on whom Eaton and Weil (52) and Mange (53) have reported and who are currently under genetic investigation by Steinberg (47, 48)) and the team Mennonites (in whom microcephaly (36) has been studied). Amyloidosis has been studied in the Christian Apostolic group of Indiana (49). Some Amish have built church houses and permit automobiles, telephones and electricity. These so-called Church Amish were not included in the estimates of the Old Order Amish population (Fig. 3). Several of these groups are quite inbred and are, as has already been indicated, useful in their own right for genetic study. The Mennonites, from whom the Amish originally split, are a large group and consanguinity is appreciably lower than in the above groups. Noteworthy, however, is a case of Rothmund-Thomson's syndrome (poikiloderma congenita with cataract) among Mennonites in Lancaster County and several in Ontario Mennonites reported by Sexton (50); although a genealogic connection has not been identified, it seems likely the gene was of the same origin because Rothmund's syndrome is very rare. Israels, Suderman and Ritzman (54) described a form of familial jaundice called shunt hyperbilirubinemia, in two Mennonite families in Canada.

In some instances rare recessive diseases identified in the Amish can be traced back to their European ancestors by finding the disease in descendants of relatives who remained in Europe. Jackson and Carey (6) pointed out that the autosomal recessive limb-girdle muscular dystrophy is the most frequent form in the Canton of Berne, and Rossi (51) confirms this. In most other areas, studies of muscular dystrophy have shown the X-linked Duchenne variety to be most frequent. It may be possible to trace red cell pyruvate kinase deficiency (41) and cartilage-hair hypoplasia (21)—both rare conditions except in the Amish—to their European origins by identifying European cases.

SUMMARY AND CONCLUSIONS

After a description of pertinent features, the usefulness of the Old Order Amish groups of the United States and Canada for some types of

genetic studies has been discussed. For historical reasons and because of differences in family names, partial genetic distinctness of the Amish of Lancaster County, Pennsylvania, and those of Holmes County, Ohio, and some other areas is suggested.

REFERENCES

1. HOSTETLER, J. A.: *Amish Society*. The Johns Hopkins Press, Baltimore, Md., 1963.
2. SCHREIBER, W. I.: *Our Amish Neighbors*. University of Chicago Press, Chicago, Ill., 1962.
3. BENDER, H. S.: In: *The Mennonite Encyclopedia*. Mennonite Publishing House, Scottsdale, Pa., 1955, Vol. I, p. 97.
4. MCKUSICK, V. A., EGELAND, J. A., ELDRIDGE, R. AND KRUSEN, D. E.: Dwarfism in the Amish. I. The Ellis-van Creveld Syndrome. *Bull. Hopkins Hosp.*, in press.
5. BOWMAN, H. S. AND MCKUSICK, V. A.: Pyruvate kinase deficiency hemolytic anemia in an Amish isolate. *Amer. J. Hum. Genet.*, in press.
6. JACKSON, C. E. AND CAREY, J. H.: Progressive muscular dystrophy: autosomal recessive type. *Pediatrics*, 1961, **28**: 77.
7. JACKSON, C. E., Bluffton, Ind.: Personal communication.
8. JOHN M. FISHER FAMILY: *Descendants and History of Christian Fisher Family*. Published by Amos L. Fisher, Route 1, Ronks, Pa., 1957.
9. FISHER, AMOS L., Route 1, Ronks, Pa.: Personal communication to J. A. H.
10. HOSTETLER, H.: *Descendants of Barbara Hochstedler and Christian Stutzman*. Mennonite Publishing House, Scottsdale, Pa., 1938.
11. HOSTETLER, H.: *Descendants of Jacob Hochstetler*. Brethren Publishing House, Elgin, Ill., 1912.
12. HOSTETLER, J. A.: Folk and scientific medicine in Amish society. *Hum. Organization*, 1963-64, **22**: 269.
13. MCKUSICK, V. A., BAUER, R. L., KOOP, C. E. AND SCOTT, R. B.: Hydrometrocolpos as a simply inherited malformation. *J.A.M.A.*, in press.
14. HAMMOND, D. T. AND JACKSON, C. E.: Consanguinity in a midwestern United States isolate. *Amer. J. Hum. Genet.*, 1958, **10**: 61.
15. SPUHLER, J. N. AND KLUCKHORN, C.: Inbreeding coefficients of the Ramah Navaho population. *Hum. Biol.*, 1953, **25**: 295.
16. SMITH, E. L.: *Studies in Amish Demography*. Eastern Mennonite College, Harrisonburg, Va., 1960.
17. HANHART, E.: Ergebnisse der demogenetischen Erforschung der Isolate mit besonderer Berücksichtigung der Schweizer Inzuchtgebiete. In: *Principles of Medical Genetics*, Vol. III of *De Genetica Medica* (L. Gedda, ed.), Rome, 1962. Pp. 51-80.
18. ALSTRÖM, C. H. AND STRÖMGREN, E.: Torsten Sjogren. *Acta Psychiat. Scand.*, 1963, **39**: 5.
19. ALSTRÖM, C. H.: *Hereditätin pathia congenita monohybrida recessiva autosomalis*. Berlingska Boktryckeriet, Lund, Sweden, 1957.
20. LUNDBORG, H. B.: *Die progressive Myoklonus-epilepsie (Unverricht's Myoklonus)*. Almqvist & Wiksell, Upsala, 1903.
21. MCKUSICK, V. A., ELDRIDGE, R., HOSTETLER, J. A., EGELAND, J. A. AND RUANGWIT, V.: Dwarfism in the Amish. II. Cartilage-hair hypoplasia. To be published.
22. MCKUSICK, V. A.: Rare recessive phenotypes in man. A catalog for use in studies of inbred populations and the nosology of genetic disease. To be published.
23. MCKUSICK, V. A.: On the X chromosome of man. *Quart. Rev. Biol.*, 1962, **37**: 69. AIBS monograph, 1964.
24. PERKOFF, G. T., STEPHENS, F. E., DOLOWITZ, D. A. AND TYLER, F. H.: A clinical study of hereditary interstitial pyelonephritis. *Arch. Intern. Med.*, 1951, **88**: 191.
25. PERKOFF, G. T., NUGENT, C. A., JR., DOLOWITZ, D. A., STEPHENS, F. E., CARNES, W. H. AND TYLER, F. H.: A follow-up study of hereditary chronic nephritis. *Arch. Intern. Med.*, 1958, **102**: 733.
26. GARDNER, E. J.: Follow-up study of a family group exhibiting dominant inheritance for a syndrome including intestinal polyps, osteomas, fibromas and epidermal cysts. *Amer. J. Hum. Genet.*, 1962, **14**: 376.
27. PFÄNDLER, U.: Une forme semilétale de la surdimutité récessive dans différentes populations de la Suisse orientale. *Bull. Acad. Suisse Sci. Med.*, 1960, **16**: 255.
28. AMMAN, F. AND MARTY, F.: Une famille valaisanne avec plusieurs branches atteintes de formes différentes de dégénérescence tapétorétinienne remontant au même couple ancestral. *J. Génét. Hum.*, 1962, **11**: 221.
29. MORTON, N. E., CROW, J. F. AND MULLER, H. J.: An estimate of the mutational damage in man from data on consanguineous marriages. *Proc. Nat. Acad. Sci.*, 1956, **42**: 855.
30. SLATIS, H. M., REIS, R. H. AND HOENE, R. E.: Consanguineous marriages in the Chicago region. *Amer. J. Hum. Genet.*, 1958, **10**: 446.
31. ROBERTSON, W. R. B.: Chromosome studies. I. Taxonomic relationships... etc. *J. Morph.*, 1916, **27**: 179.
32. FORD, C. E., HAMERTON, J. L. AND SHARMAN, G. B.: Chromosome polymorphism in the common shrew. *Nature*, 1947, **180**: 392.
33. SWANSON, C. P.: *Cytology and Cytogenetics*. Prentice-Hall, Inc., Englewood Cliffs, N. J., 1957.
34. BURNHAM, C. R.: *Discussions in Cytogenetics*. Burgess Publishing Co., Minneapolis, Minn., 1962.
35. ELDRIDGE, R. AND MCKUSICK, V. A.: Symphalangism: new mutation in an Amish family. To be published.
36. MCKUSICK, V. A., HOSTETLER, J. A., EGELAND, J. A. AND ELDRIDGE, R.: The distribution of certain genes in the Old Order Amish. *Cold Spring Harbor Symp. Quant. Biol.*, vol. 29, 1964.
37. DONNELL, G. N., KOLER, R. AND SMITH, S. M.: Studies on linkage between galactosaemia and the blood groups. *Ann. Hum. Genet.*, 1963, **27**: 125.
38. HALDANE, J. B. S.: The association of characters as a result of inbreeding and linkage. *Ann. Eugen.*, 1949, **15**: 15.
39. FREIRE-MAIA, N. AND KRIEGER, H.: A Jewish isolate in southern Brazil. Effective population, intermarriage, fertility, inbreeding, mortality, twinning, sex ratio, genetic load and total mutation rate. *Ann. Hum. Genet.*, 1963, **27**: 31.
40. MACCLUER, J. W. AND SCHULL, W. J.: On the estimation of the frequency of non-paternity. *Amer. J. Hum. Genet.*, 1963, **15**: 191.
41. BOWMAN, H. S. AND PROCOPIO, F.: Hereditary non-spherocytic hemolytic anemia of the pyruvate-kinase deficient type. *Ann. Intern. Med.*, 1963, **58**: 567.
42. MARTIN, P. H., DAVIS, L. AND ASKEW, D.: High incidence of phenylketonuria in an isolated Indiana community. *J. Indiana Med. Ass.*, 1963, **56**: 997.
43. TANAKA, K. R., VALENTINE, W. M. AND MIWA, S.: Pyruvate kinase (PK) deficiency in hereditary non-spherocytic hemolytic anemia. *Blood*, 1962, **19**: 267.

- 44a. WRIGHT, C.-S., DOAN, C. A., DODD, V. A. AND THOMAS, J. D.: Hemophilia; current theories and successful management in traumatic and surgical crises. *J. Lab. Clin. Med.*, 1948, **33**: 708.
 - b. WALL, R. L. AND DOAN, C. A., Columbus, O.: Personal communication.
45. RATNOFF, O. D.: Hereditary defects in clotting mechanisms. *Advances Intern. Med.*, 1958, **9**: 107.
46. GLASS, B.: Genetic changes in human populations, especially those due to gene flow and genetic drift. *Advances Genet.*, 1954, **6**: 95.
47. STEINBERG, A. G., Cleveland, O.: Personal communication.
48. STEINBERG, A. G.: Evidence for a Gm allele negative for both Gm(a) and Gm(b). *Vox Sang.*, 1962, **7**: 89.
49. JACKSON, C. E., FALLS, H. F., BLOCK, W. D., RUKAVINA, J. K. AND CAREY, J. H.: Inheritance of primary systemic amyloidosis. *Amer. J. Hum. Genet.*, 1960, **12**: 434.
50. SEXTON, G. B.: Thomson's syndrome (poikiloderma congenitale). *Canad. Med. Ass. J.*, 1954, **70**: 662.
51. ROSSI, E., Berne, Switzerland: Personal communication, January, 1964.
52. EATON, J. W. AND WEIL, R. J.: *Culture and Mental Disorders. A Comparative Study of the Hutterites and Other Populations*. The Free Press, Glencoe, Ill., 1955.
53. MANGE, ARTHUR P.: The Population Structure of a Human Isolate. Ph.D. thesis, U. of Wisconsin, 1963.
54. ISRAELS, L. G., SUDERMAN, H. J. AND RITZMANN, S. E.: Hyperbilirubinemia due to an alternate path of bilirubin production. *Amer. J. Med.*, 1959, **27**: 693.