PROGRESS REPORT
OF
CONGENITAL MALFORMATIONS
THE INFLUENCE OF GENETIC AND NONGENETIC FACTORS

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DEPARTMENT: Department of Zoology

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Arizona State University
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September 1, 1971

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A research project has been carried out in the Department of Zoology, at Arizona State University, Tempe, Arizona, during the periods 1961-1966 and 1969 - 1971 to evaluate the importance of genetic and nongenetic factors for specific congenital malformations in man. This work has been supported in its entirety by the United States Atomic Energy Commission. It is apparent that before the etiological role of mutation can be evaluated for congenital malformations, it is necessary to obtain this information.

This progress report consists of four reprints of papers published during the past year and a summary of studies in various stages of completion.

Reprints not submitted previously: (Addendum to progress report)

Reid, Robert L., and Charles M. Woolf, 1970 A genetic and karyotype study of complete or incomplete paraxial radial hemimelia in Arizona--Implications for genetic counseling. Arizona Medicine, 27: 6-11. COO-2013-15

Woolf, Charles M., 1971 Congenital cleft lip: A genetic study of 496 propositi. J. Medical Genetics, Vol. 8, No. 1, 65-83. COO-2013-16

Woolf, Charles M., 1971 Missing maxillary lateral incisors: A genetic study. Am. J. Human Genetics, 23: 289-296. COO-2013-17

Woolf, Charles M., 1971 Congenital Hip Disease: Implications for genetic counseling. Social Biology, 18: 10-17. COO-2013-18

During the first eight months (January 1, 1971 - August 31, 1971) of the present contract period, the primary activities were to continue the

studies of syndactyly and spina bifida cystica in Utah, analyze the data to determine whether there are familial aggregations of primary causes of death (as listed on death certificates) of members of Mormon families (parents and offspring) living in Utah, collect data on the incidence of the various types of polydactyly in American White, American Negro and American Indian populations, begin an analysis of the data of the genetics of isolated cleft palate in Utah and Arizona, and initiate studies of congenital hip disease in Apache Indians in Utah and the effect of season of birth on the incidence of this congenital anomaly.

During this period the principal investigator spent in excess of the contracted 100% of two summer months and 10% of the academic year period (9 months) working on the project. During the remainder of the current term (September - December) the principal investigator will devote in excess of 10% of the academic year period to the project.

SYNDACTYLY IN UTAH

As part of a genetic study of certain types of congenital malformations in Utah, family histories were obtained for Caucasian propoiti classified as having polydactyly or syndactyly. These propoiti were obtained from hospital records made available by physicians. The objective of the study was to gain insight into the genetics of the various types of polydactyly and syndactyly. This study was carried out in a population that is predomi-

nantly Mormon (Church of Jesus Christ of Latter-day Saints). The relative stability of the Mormon population in the area, strong family ties and an interest in genealogy, facilitate family history studies of this type among Mormon people in the state of Utah. The propositi were sorted into two groups: (1) polydactyly cases without associated syndactyly, and (2) syndactyly cases with or without associated anomalies. The results of the polydactyly study have been published.¹

Syndactyly is characterized by phenotypic variability and genetic heterogeneity. On the basis of a review of the literature and their own experiences, Temtamy and McKusick² have presented a useful classification of syndactyly types:

Type I Syndactyly: Zygodactyly. Webbing between the third and fourth fingers (complete or partial) with occasional involvement of other fingers. Webbing between the second and third toes (complete or partial). The hands and/or feet may be affected. In members of some families, only the feet are affected.

Type II Syndactyly: Synpolydactyly. Webbing between the third and fourth fingers associated with the presence of all components of part of an extra finger in the web. Webbing of the fourth and fifth toes associated with the presence of all components or part of an extra toe in the web. The hands and/or feet may be affected.

Type III Syndactyly: Fourth and Fifth Finger Syndactyly. Webbing between the fourth and fifth fingers. The fifth finger in the web may be

short with rudimentary or absent middle phalanges. The feet are not affected.

Type IV Syndactyly: Haas Type. Complete webbing of the fingers with six metacarpals and six digits, associated with flexion of the fingers giving the hands a cup-shaped form.

Type V Syndactyly: Syndactyly with Metacarpal and Metatarsal Fusion. Webbing of the third and fourth fingers, second and third toes, associated with metacarpal and metatarsal fusion.

Although genetic heterogeneity is likely present, all of the above types of syndactyly have shown dominant autosomal inheritance in families reported in the literature. Pedigrees have also been presented^{3, 4} demonstrating that a dominant gene may give various expressions of syndactyly in association with preaxial and/or postaxial polydactyly. If, in the presence of the genetic mechanism, syndactyly does not occur in the absence of polydactyly, the condition is classified by Temtamy and McKusick² as a type of polydactyly and referred to as polysyndactyly. Syndactyly is also an integral part of many different syndromes such as anhidrotic ectodermal dysplasia, Laurence-Moon-Bardet-Biedl syndrome, Poland syndactyly, oculodentodigital dysplasia, and Acrocephalosyndactyly (such as Apert's syndrome). Syndactyly may also occur in association with certain types of brachydactyly and other dactyly malformations where there is an absence deformity (such as split hand/split foot).

Upon receiving the names of the propositi from hospital records (surgical, X-ray, nursery), current addresses were obtained from telephone books, city directories or church records. Cases were omitted from the study if current addresses were not available or if family members were distantly located from Salt Lake City, Utah. The homes were visited by experienced field workers who obtained information of epidemiologic interest. Information on the presence or absence of a congenital malformation was obtained for at least the following relatives of the propositi: sibs, children, parents, grandparents, aunts, uncles and first cousins. When more distant relatives had a dactyly anomaly, the pedigrees were extended to include them. When a positive family history was encountered, an attempt was made to obtain a reliable description of the anomalies present in the affected family members. This was done by utilizing medical records (surgical, X-ray) when available, or by obtaining a description of the anomaly from close relatives. For deceased members of older generations, the descriptions were often cursory, and sometimes conflicting. Family histories were obtained for 70 propositi. These propositi were unselected as to type of syndactyly; the only criterion was that the name of each had appeared on a hospital record with the diagnosis of syndactyly. Based upon X-ray and medical records as well as the family history, an attempt was made to classify each propositus as to type of syndactyly. Forty-seven had syndactyly with or without polydactyly. Twenty-three had syndactyly associated with other anomalies.

Syndactyly With or Without Associated Polydactyly:

The 47 propoiti with or without associated polydactyly were classified into four groups: (1) Type I syndactyly, (2) Type II syndactyly, (3) Type III syndactyly, and (4) Syndactyly associated with polydactyly other than synpolydactyly (Type II syndactyly). No propoitus was encountered that could be classified as having Type IV or Type V syndactyly; however, this was not unexpected since both of these types of syndactyly are rare.²

Type I Syndactyly: Twenty-nine (61.7%) of the 47 propoiti were classified as having type I syndactyly. Seventeen (58.6%) of the 29 propoiti had a family history of this disorder. Pedigrees of these 17 families are presented in Figures 1 and 2. Autosomal dominant inheritance is indicated in these pedigrees. Genetic heterogeneity is undoubtedly present for Type I syndactyly. In Pedigrees 1, 2, 5, 13, 14 and 15 (Figure 1), the webbing in affected members is restricted to the second and third toes. Similar types of pedigrees appear in the literature,⁵ including the Schofield pedigree which at one time was used as an example of holandric inheritance.⁶ The number of affected individuals in some of these pedigrees is small, and therefore only a limited sample exists of gene expressions. However, these pedigrees as a group support the conclusion² that in some families a dominant autosomal gene is segregating that causes webbing between the second and third toes with no involvement of the hands. This type of syndactyly will be referred to here as Type Ia syndactyly. A different allele, or more

likely, a mutation at a different autosomal locus, would therefore account for the type of syndactyly which involves the third and fourth fingers and/or second and third toes (referred to here as Type Ib syndactyly). Pedigrees of Type Ib syndactyly are shown in Figure 2 (Pedigrees 3, 4, 6, 7, 8, 9, 10, 11, 12, 16 and 17). In all affected members of these pedigrees the webbing involves either the third and fourth fingers and/or the second and third toes with the exception of the propositus in Pedigree 17. In this individual, webbing involved digits 2 and 3, 3 and 4, and 4 and 5 of each hand. The webbing between digits 2 and 3 and digits 4 and 5 extended only a third of the way to the proximal interphalangeal joint; the webbing between the third and fourth fingers extended to this joint. The webbing was almost identical in each hand.

A disparate sex ratio favoring males among Type I syndactyly cases has been alluded to in the literature.⁵ In the present study, an obvious sex ratio difference is present for Type Ia syndactyly, however, it is not so evident for Type Ib syndactyly. In the six families showing only Type Ia syndactyly, the sex ratio among affected individuals is 9 females to 21 males ($\chi^2 = 4.0$; $0.05 > P > 0.01$). In the eleven families showing more than one case of Type Ib syndactyly, the sex ratio is 21 females to 24 males ($\chi^2 = 0.09$; $0.80 > P > 0.70$).

Type II Syndactyly: Ten (21.3%) of the 47 propiti were classified as having Type II syndactyly. All are characterized by some expression of synpolydactyly involving webbing of the third and fourth fingers and/or fourth and

fifth toes. Five(50%) of the 10 propoiti had a family history of synpolydactyly. Pedigrees of these five families are presented in Figure 3.

Three of the 5 propoiti with a positive family history have a common ancestor. Each was ascertained independently from a different source of records. The immediate family names are dissimilar. The common ancestor was discovered only after the pedigrees of each was expanded by the field workers to include other affected individuals. The kindred to which each belongs was described in the literature in 1947 by Alvord.⁷ The progenitor of this kindred, who had webbing between the third and fourth fingers of the right hand, was a polygamist with 2 wives and 14 children. The pedigrees (Pedigrees 22, 23 and 24) of the families of the three propoiti with a common ancestor are greatly abbreviated, showing only a fraction of the affected individuals (Figure 3).

Accumulated data in the literature⁸ indicate that Type II syndactyly occurs more frequently in males than females. This effect was not shown in the present study. The sex ratio of affected individuals in the five pedigrees is 14 females to 13 males (counting each person only once from Pedigrees 22, 23 and 24). Adding the five propoiti with no family history gives a sex ratio of 17 females to 15 males.

Type III Syndactyly: Four (8.5%) of the 47 propoiti were classified as having Type III syndactyly based on the criterion of webbing between the fourth and fifth fingers. One of these propoiti also had slight webbing between fingers two and three and shortness of the index and little finger.

X-rays were not available for this propositus. Another propositus had a rudimentary middle phalanx of the fifth digit. The other two propoiti had bilateral complete webbing of digits 4 and 5, but there was no apparent abnormality of any of the phalanges. Although Type III Syndactyly shows a dominant mode of inheritance in some families (9), all 4 of the propoiti classified as having this type of syndactyly in this study were sporadic cases. A familial occurrence likely would have been encountered with a larger number of index cases.

Syndactyly Associated with Polydactyly (Other than Synpolydactyly):

Four (8.5%) of the 47 propoiti had expressions of syndactyly and polydactyly other than what is found in cases of synpolydactyly (Type II Syndactyly). Two of these propoiti had a family history of the same condition. Pedigrees of these two families are shown in Figure 4 (Pedigrees 18 and 19). The propositus in Pedigree 18 had partial webbing of the second and third toes of both feet and bilateral preaxial polydactyly of the feet. The X-ray report stated there was virtually complete reduplication of the first digit with the base half of each first metatarsal being bifid in nature. A similar condition was present in one sib; another sib and father lacked polydactyly but had complete bilateral webbing between the second and third toes.

The propositus of the family represented in Pedigree 19 was born with webbing between the fourth and fifth toes of the left foot associated with an extra fifth digit in this foot. Postaxial polydactyly Type B (pedunculated

postminimus) was also present in the right hand. Postaxial polydactyly was present in two sibs; one of these sibs had, in addition, a similar type of syndactyly of the right foot.

Syndactyly Associated with Other Anomalies

Family histories were also obtained for 23 probands with syndactyly associated with brachydactyly, macrodactyly, a deficiency syndrome, or other anomalies. Extreme variation existed among the probands for these malformations. Most of these probands were unilateral for the anomaly. One proband had acrocephalosyndactyly (Apert's syndrome). Three others had the features of Poland syndrome including unilateral aplasia of the pectoralis major muscle. The family histories of all 23 probands were negative for any dactyl malformation.

No data have been published on the incidence at birth of the various types of syndactyly in any population. It seems likely, however, that Type Ia syndactyly, which is rarely treated surgically, is the most frequent type. This is borne out by a study of the Nursery records on file in the Latter-day Saints Hospital in Salt Lake City, Utah. These records have been used to obtain incidence values for various congenital malformations for the years 1951-1961.¹⁰

The types of syndactyly present in the 70 probands used in this study does not represent the frequencies of types present at birth. There is a bias towards types that are treated surgically. The probands with Type Ia syndactyly were obtained from the nursery records; none ever had surgical

treatment of the webbing.

The results of this study demonstrate that a sizeable proportion of the propiiti from Utah with Type I and Type II syndactyly carry an autosomal dominant gene for those anomalies. Seventeen (58.6%) of the 29 propiiti classified as having Type I syndactyly had a family history of this disorder compatible with dominant inheritance. Five (50%) of the 10 propiiti with Type II syndactyly had a family history of synpolydactyly also compatible with this mode of inheritance. The sporadic cases may be mutant individuals where the egg or sperm giving rise to them contained a dominant mutant gene; it is also likely that some may be explained by recessive genes, polygenes, or unknown exogenous factors acting during development. The pedigrees shown in Figures 1-3 testify that the dominant genes giving rise to Type I and Type II syndactyly show reduced penetrance and variable expressivity. An individual with the mutant gene may or may not show syndactyly. If it does manifest itself, webbing may involve toes and/or fingers and may be unilateral or bilateral.

Pedigrees of polysyndactyly have been reported in the literature^{3, 4} with family members showing one or more of the following anomalies: postaxial polydactyly (Type B) of the hands, webbing between the third and fourth or fourth and fifth fingers, broad thumb, preaxial and/or postaxial polydactyly of the feet, webbing of 2 or more digits of the feet. In the affected members of these families polydactyly was present with or without associated syndactyly; syndactyly did not occur by itself. Further sampling

of gene expressions are needed, however, if any deviation occurs in this mode of expression. Two of the four probands with associated polydactyly (other than the synpolydactyly cases) had the features of polysyndactyly.

Expression of this syndrome also appeared in the sibs of one of these probands. The parents of this sibship (see Pedigree 19, Figure 4), and all other relatives are normal, however a possible parentage problem exists.

A suspected biological father of at least three of the children has bilateral webbing of the third and fourth fingers, as well as reported webbing of the third and fourth toes. He has a sister, a niece and a daughter with one or more features of polysyndactyly. The other two probands had preaxial polydactyly of the feet and webbing between the second and third toes.

One case was unilateral and sporadic. Of special interest is the other case because of the family history of this condition (see Pedigree 18, Figure 4), where the proband and sib had bilateral preaxial polydactyly of the feet with webbing between the second and third toes; the father and another sib had bilateral complete webbing between the second and third toes. Preaxial polydactyly without accompanying syndactyly has an obscure etiology; it may have a polygenic mode of inheritance.¹ It is problematical whether the dactyl anomalies present in the father and his three children constitute a new polydactyly-syndactyly syndrome or whether the condition is Type I syndactyly with the occurrence of preaxial polydactyly being fortuitous.

This family needs to be followed in future generations; there should also be a lookout for families with a similar condition. In the study of poly-

dactyly in Utah the families of four propositi (2 with preaxial polydactyly and 2 with postaxial polydactyly) had a family history of syndactyly involving digits 2 and 3 of the feet. It was concluded that this type of syndactyly seems to be genetically independent of polydactyly in these families.

Although this may be the case in most cases, rare genetic mechanisms may predispose to foot anomalies involving preaxial polydactyly and webbing between digits 2 and 3, as exemplified by the affected members of Pedigree 18.

Additional sex ratio data are needed for the various syndactyly types. The results of the present study suggests that Type Ia syndactyly occurs significantly more frequently in males, but that Type Ib and Type II syndactyly occur equally frequent in the two sexes. Evidence in the literature of the excess of males with general syndactyly⁵ and Type II syndactyly,⁸ which is not reflected in certain pedigrees,⁸ may reflect the existence of variation among mutant alleles or loci regarding differential penetrance or some other biological phenomenon, in the two sexes.

The results of the present study coupled with those from the study of polydactyly in Utah,¹ give data that are useful for genetic counseling. Dominant inheritance is well documented for the majority of cases of Type I and II syndactyly. Although familial types of Type III syndactyly were not encountered in this study, the literature testifies that this type of syndactyly may show dominant inheritance. The familial nature of poly-syndactyly was also noted in one family, with suspected dominant inheritance.

Of importance is the observation that syndactyly associated with other anomalies, such as brachydactyly, adactyly, multiple malformations, etc., in general, have a more complex etiology. The family histories for these types of propositi, are usually devoid of dactyl anomalies. The sporadic occurrence of Apert's syndrome and Poland syndactyly has been well documented.² Exceptions are Type B Brachydactyly (symbrachydactyly) which has associated syndactyly, and some varieties of absence deformities (split hand/split foot) which frequently show dominant inheritance. When polydactyly is present without associated syndactyly, the study of cases in the Utah population¹ demonstrated that dominant inheritance is often present for polydactyly involving an extra fifth digit or a triphalangeal digit in place of a thumb, while duplication of the first digit very likely has a polygenic or some more involved mode of inheritance. For all types showing dominant inheritance, genetic counseling is complicated by the phenomenon of reduced penetrance. A normal child of an affected parent may not assume that he is free of the mutant gene.

References Related to the Syndactyly Study

1. Woolf, C. M. and R. M. Woolf, 1970 A genetic study of polydactyly in Utah. Amer. J. Hum. Genet. 22: 75-88.
2. Temtamy, S. and V. A. McKusick, 1969 Synopsis of Hand malformations with particular emphasis on genetic factors. Birth Defects: Original Artical Series (National Foundation), Vol. 5, No. 3, pp 125-184.
3. McClintock, B. S., 1935 Five generations of polydactylism. J. Hered. 56:37.

4. Goodman, R. M., 1965. A family with polysyndactyly and other anomalies. J. Hered. 56:37.
5. Gates, R. R., 1946. Human Genetics. Macmillan Co., New York.
6. Stern, C., 1957. The problem of complete Y-linkage in man. Am. J. Hum. Genet. 9:147-166.
7. Alvord, R. M., 1947. Zygodactyly and associated variations in a Utah family. J. Hered. 38:49-53.
8. Cross, H. E., D. B. Lerberg, and V. A. McKusick, 1968. Type II syndactyly. Amer. J. Hum. Genet. 20:368-380.
9. Johnston, O. and V. V. Kirby, 1955. Syndactyly of the ring and little finger. Amer. J. Hum. Genet. 7:30-82.
10. Woolf, C. M. and J. A. Turner, 1969. Incidence of congenital malformations among live births in Salt Lake City, Utah, 1951-1961. Social Biology 16:270-279.

SPINA BIFIDA CYSTICA IN UTAH

Controversy exists in the medical literature concerning the etiologic importance of genetics for spina bifida cystica (meningocele and myelomeningocele). Family histories have been obtained for 109 probands with spina bifida cystica. The frequencies of this disorder and other congenital malformations (including anencephaly and hydrocephaly) have been obtained in the following relatives of the probands: sibs, parents, grandparents, aunts, uncles, and first cousins. The frequency of spina bifida cystica in the sibs born subsequently to the probands is 1.77% (n = 113). It has been suggested in the literature that a genetic mechanism (polygenes?) giving spina bifida cystica may also express itself as anencephaly. The latter

anomaly is not infrequent in stillborn infants; both anomalies may increase the probability that development will be arrested at an early stage. Hence, a genetic study of spina bifida cystica must consider stillbirths and spontaneous abortions.

This study is still in progress. The pregnancy histories of each mother of a propositus are being brought up to date concerning miscarriages and subsequent fetal deaths and live births. In case of a fetal death, medical records and fetal death certificates are being reviewed for the possible occurrence of a disorder of the central nervous system. The frequency of spontaneous abortions will be compared with a control group. In order to increase the sample size, family histories are being obtained for an additional 50 propoiti. This study will be finished during the next proposed contract period.

FAMILIAL AGGREGATIONS OF CAUSES OF DEATH IN MORMON FAMILIES?

On file in the office of the principal investigator at Arizona State University are records that can be used to test the hypothesis that "causes of death" occur randomly in sibs and the cause of death of a parent has no influence on the cause of death of his offspring.

During the period 1950-1960, the principal investigator was involved in projects to determine whether certain types of common cancer have a genetic component. It was shown that carcinoma of the breast, stomach, large intestine, and prostate have only a weak familial basis (see bibliog-

raphy of principal investigator in research proposal). Although different procedures were used, one productive method employed was taking advantage of the genealogical records on file in the archives of the Genealogical Society of the Church of Jesus Christ of Latter Day Saints (Mormon) in Salt Lake City, Utah. The Mormon Church encourages members to take an active interest in genealogical research. The archives and library of the Genealogical Society are the centers of this activity. One type of record on file in the archives that is useful for genetics research is the family group record. These records are placed in the archives by members of the church and by professional genealogists employed by the Genealogical Society. Each family group record contains space for the entry of the names of a husband and wife and all their offspring, dates and places of birth for all these persons, names of the spouses of the offspring, dates and places of birth for all these persons, dates and places of death for the parents, dates of death for the offspring, plus other information. Propositi who died with a specific type of cancer were selected randomly from death certificates. A survey was then made of the family group records to see if information was available for the families (parents and full sibs) of these individuals. The names of the fathers were used to enter the records. A family group record was available for approximately one-fourth of the propositi. Upon obtaining the genealogical data, the next procedure was to visit the Utah State Division of Vital Statistics. With the aid of the cross index file for death certificates, a careful search was made for the names

of the parents and sibs of the individuals. Death certificates have been filed in this office since 1905. If a relative died in Utah since that time the certificate was usually found. However, the certificate was not found if the relative died previous to 1905, had a change in name, died in some other state, or was still alive. As soon as a certificate was located for a relative, notes were made as to the cause of death and date and age of death.

Control material consisted of individuals of the same sex who died the same year in the same county at approximately the same age as each of the deceased relatives of the propositi. Controls were easily obtained since death certificates in Utah are filed by date of death and county, and bound into books. When a death certificate was found for a relative of a propositi, it became a matter of referring to succeeding certificates until the first qualified control was found. If the next succeeding certificate was for a person of the same sex and approximately the same age as the relative of the propositus, he was used as a control and the cause of death was noted. In order to be of approximately the same age a control had to be within the range set off by the relative's age plus or minus five years. If the next certificate did not qualify, as was usually the case, then it became a matter of turning the pages of the book until the first qualified control was found. Controls were obtained in a completely objective manner.

Although the families were collected for a genetic study of cancer, they can also be used to study other disorders. Ignoring the propositi with some form of cancer, the data could give information as to whether familial

aggregations occur for common causes of death. From the results of other studies, it is believed that the method of ascertainment through cancer propoiti will not seriously bias the results, especially for other common diseases such as hypertensive heart disease, diabetes, cerebral hemorrhage, etc.

About 750 of the families are useable for this study. It is believed that these records are quite unique. Each cause of death has been assigned a number following the International Classification of Diseases (1965 Revision), World Health Organization. The causes of death have been coded for the members of each family as well as each control. One procedure is to scan the families (by computer) for each cause of death and determine how many families had 0, 1, 2, 3, 4, 5, etc., deaths due to that cause. The observed number for the families is then compared with observed numbers in the controls and expected values assuming a poisson distribution. Another procedure is to scan the families and controls for "propoiti" with a specific cause of death, where each person who died of that cause becomes a propoitus. The frequency of that cause of death in the sibs, parents, and offspring of the propoiti is then compared with these values for the controls.

Preliminary studies reveal that familial aggregations of causes of death occur for carcinoma of the stomach, large intestine and prostate, which is not unexpected because of the ascertainment method employed. However, for most causes of death, there is no evidence for a familial aggregation of cases. This is illustrated in Table 1 for reported

causes of death resulting from diseases of the circulatory system. No differences exist between the related and control individuals in the propositus studies. Furthermore, the causes of death occur randomly in families, with a "goodness of fit" expected of the poisson distribution. Contagious distributions would be expected for specific causes of death with a strong genetic component. These are not detected because of the nature of the records used for this study. The results of this study are now being analyzed. A manuscript will be prepared for publication during the present or next proposed contract period.

RACIAL DIFFERENCES FOR POLYDACTYLY

Of interest are the racial differences that exist in the frequency of polydactyly. For example, the incidence among the American Negro population is about nine times higher than that found among Caucasians (Chung and Myrianthopoulos, Am. J. Human Genetics 20:44-60). Polydactyly is the most frequent single malformation appearing in the American Negro. Although the overall malformation rate is relatively similar in the American Negro and Caucasian populations, if polydactyly is removed the overall rate is significantly lower in the American Negro. No data have been published showing the frequency at birth of the different types of polydactyly in any population. Based on comments appearing in the literature, postaxial polydactyly may be the frequent type in the American Negro. A working hypothesis is that postaxial polydactyly has autosomal dominant and polygenic modes of inheritance, and the polygenic component has increased

importance in the American Negro. Negotiations were made to obtain polydactyly birth records for American Negroes and Caucasians from the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland, through the courtesy of Dr. N. C. Myrianthopoulos. The principal investigator visited Bethesda, Maryland, and hand reviewed 382 newborn records (327 Negroes, 47 whites, 8 other ethnic groups) where the diagnosis of polydactyly had been made. Records were also hand reviewed of 102 polydactyly cases occurring in the American Indian population. These records were supplied through the courtesy of Dr. Jerry Niswander, National Institutes of Health, Bethesda.

A paper is now being prepared for publication. The American Indians and Caucasians are relatively similar for the frequencies of the various types of polydactyly. The evidence is clear that the type of polydactyly occurring at a high frequency in the American Negro is postaxial polydactyly Type B (Pedunculated postminimus). The extra digit is in the form of a skin tag which is usually tied off in the delivery room or nursery. Pedunculated postminimus must be classified as a minor congenital malformation. The American Negro is also characterized by a lower frequency of preaxial polydactyly (double thumbs). Polygenes likely account for the differences between these populations. If so, the mechanism maintaining the genes for pedunculated postminimus at a high frequency in the American Negro population needs clarification. This is an intriguing problem in the field of population genetics.

SEASON OF THE YEAR EFFECT FOR CONGENITAL HIP DISEASE

A strong genetic component exists for congenital hip disease (Woolf, et al, Am. J. Human Genetics 20:430-439, 1968). Genetic heterogeneity is likely present, with perhaps dominant and polygenic modes of inheritance being present (Woolf, Social Biology 18:10-17, 1971). Nongenetic factors also play an important etiological role. A significant "season of birth effect" is present. Infants with the disease in Utah tend to be born during the autumn and early winter months. This effect has been noted for other populations. In all cases so far studied, the population is subjected to moderately cold winters. This effect needs further study. Records are being obtained through Crippled Childrens' Services in various parts of the United States to determine if the effect is correlated with cold weather, or whether some other "effect" is interacting. It is also of extreme biological interest that congenital hip disease occurs at a high incidence among the Navajo and Apache Indians of Arizona, but not among the other large Indian tribes in the state such as the Hopi, Pima and Papago Indians. The Navajo and Apache Indians are biologically related, both being of the Athabascan linguistic stock. Records are being obtained for Navajo and Apache Indians with congenital hip disease from the Crippled Childrens' Hospital in Phoenix, Arizona and United States Public Health Service Indian Hospitals at various locations in Arizona. Tests will be run to determine if the factors causing congenital hip disease in these Indian groups interacts with a season of the year effect.

(Note: it was anticipated that this study would be completed during the present project period. However, because of minor cooperative problems with certain public health and hospital officials, and involvement with other research projects, the necessary data have not all been collected. It is anticipated that this project will be completed during the coming year).

CONGENITAL HIP DISEASE AMONG THE APACHE INDIANS IN ARIZONA

Considerable variation exists among published incidence values for congenital hip disease. Representative values are as follows: Birmingham, England, 0.65/1000, Salford, England, 1.55/1000, New York City, 1.6/1000, Malmo, Sweden, 1.7/1000, Jerusalem, Israel, 9.8/1000 (Woolf, et. al., Am. J. Human Genetics 20:430-439, 1968). High incidence populations are not uncommon. Rabin et. al. (Am. J. Public Health 55 (No. 2. Part II): 1-44) observed a prevalence rate of 38/1000 among infants and adults among Navajo Indians living at Many Farms, Arizona. An incidence of 60/1000 was reported for an Indian population living at Island Lake, Manitoba, Canada (Corrigan and Segal, Canad. Med. Ass. J. 62:535-540, 1950). It has not been definitely determined whether genetic or nongenetic factors, or both, account for the increased incidence of hip disease in the Navajo and certain other Indian populations. Rabin et. al. (1965) concluded that the practice of binding infants on a cradle board, which has long been suspected as one cause of the increased incidence in this ethnic group, is not implicated

directly in the etiology of the disease, at least in the population they studied. Some of their cases showed improvement while on the cradle board; other dislocation cases were never on the board.

Preliminary studies have revealed that a high incidence of congenital hip disease also occurs among the Apache Indians in Arizona. Both the Navajo and Apache Indians are members of the Athabascan linguistic stock. There are two separate Apache Indian populations in Arizona, the White River population (n = 6000) and the San Carlos population (n = 4700). It has been suggested that the incidence of congenital hip disease is higher among the White River Apache Indians than among the San Carlos Apache Indians!!!! This suggestion needs to be explored.

An investigation was designed to determine the incidence of congenital hip disease in these two Apache Indian populations. If a difference exists, epidemiologic and inbreeding studies will be carried out. Studies of this kind need the approval of the U. S. Public Health officials and Tribal Council members. Although work on this investigation has been initiated, it was recommended by Indian Health Officers, in Phoenix, Arizona, that the active work involving hospital facilities on the reservation be postponed until the autumn of 1971. It is proposed that a study of congenital hip disease among the Apache Indians will be the major research project of the next contemplated contract period, as measured by funds and time expended.

Figure 1. Pedigrees of Type Ia syndactyly where webbing is restricted to the second and third toes. The propositus in each family is designated by an arrow. In these pedigrees as well as in those to follow, the symbols are interpreted as follows:

2-3	2-3

Bilateral webbing between the second and third toes

3-4	
	2-3

Webbing between the third and fourth fingers of the right hand; webbing between the second and third toes of the left foot

3-4	3-4
	4-5

Bilateral webbing between the third and fourth fingers; webbing between the fourth and fifth toes of the left foot

KINDRED I

TYPE I

KINDRED 2

TYPE I

KINDRED 5

TYPE I

KINDRED 13

TYPE I

K I N D R E D 14

TYPE I

KINDRED 15

TYPE I

Figure 2. Pedigrees of Type Ib syndactyly where the webbing may involve the third and fourth fingers and/or the second and third toes. In some cases other digits may be involved.

KINDRED 3

TYPE I

KINDRED 4

TYPE I

KINDRED 6

TYPE I

KINDRED 7

TYPE I

KINDRED 8

TYPE I

KINDRED 9

TYPE I

KINDRED 10

TYPE I

KINDRED II

TYPE I

KINDRED 12

TYPE I

KINDRED 16

TYPE I

KINDRED 17

TYPE I

Figure 3. Pedigrees of Type II syndactyly. Affected individuals have some expression of synpolydactyly which includes webbing of the third and fourth fingers and/or fourth and fifth toes, with the presence of all components or part of an extra digit in the webb.

KINDRED 20

TYPE II

KINDRED 21

TYPE II

KINDRED 22

TYPE II

KINDRED 23

TYPE II

KINDRED 24

TYPE II

Figure 4. Pedigrees of polydactyly-syndactyly where the anomalies found in the probandus are also present in at least one close relative.

The symbols are interpreted as follows:

2-3 P1	2-3 P1

Bilateral webbing between the second and third toes; bilateral preaxial polydactyly (double big toes).

P5	
	4-5

Webbing between the fourth and fifth toes of the left foot; postaxial polydactyly (extra fifth digit) of the right hand.

KINDRED 18

TYPE I AND
PREAXIAL POLYDACTYLY

KINDRED 19

POLYSYNDACTYLY

Table 1. Deaths (as reported on death certificates) due to diseases of the circulatory system in the sibs of propositi. Controls represent individuals picked at random (from death certificates) of the same sex, who died the same year, in the same county, at about the same age, as each of the family members.

DISEASES	SIBS			CONTROLS		
	Affected	Total	Percent	Affected	Total	Percent
Active rheumatic fever	0	19	0.000	0	14	0.000
Chronic rheumatic heart disease	0	74	0.000	0	60	0.000
Hypertensive disease	10	193	5.181	16	198	8.081
Malignant hypertension						
Essential benign hypertension						
Hypertensive heart disease						
Hypertensive renal disease						
Hypertensive heart and renal disease						
Ischaemic heart disease	50	478	10.460	54	578	9.343
Acute myocardial infarction						
Other acute and sub-acute forms of ischaemic heart disease						
Chronic ischaemic heart disease						
Angina pectoris						
Asymptomatic ischaemic heart disease						
Inflammations of the heart	2	30	6.667	0	63	0.000
Acute pericarditis, non-rheumatic						
Acute and sub-acute endocarditis						
Acute myocarditis						
Chronic diseases of the pericardium and endocardium	6	143	4.196	0	156	0.000
Other forms of heart disease	94	710	13.239	98	764	12.827
Symptomatic heart disease						
Other myocardial insufficiency						
Ill-defined heart disease						

DISEASES	SIBS			CONTROLS		
	Affected	Total	Percent	Affected	Total	Percent
Cerebrovascular disease	88	607	14.498	62	511	12.133
Subarachnoid haemorrhage						
Cerebral haemorrhage						
Occlusion of pre-cerebral arteries						
Cerebral thrombosis						
Cerebral embolism						
Transient cerebral ischaemia						
Acute but ill-defined cerebrovascular disease						
Generalized ischaemic cerebrovascular disease						
Other and ill-defined cerebrovascular disease						
Diseases of arteries, arterioles and capillaries	12	158	7.595	8	202	3.960
Arteriosclerosis						
Aortic aneurysm (non-syphilitic)						
Other aneurysm						
Other peripheral vascular disease						
Other diseases of arteries and arterioles						
Diseases of capillaries						
Diseases of veins and lymphatics	0	11	0.000	0	27	0.000
Pulmonary embolism and infarction						
Phlebitis and thrombophlebitis						
Portal vein thrombosis						
Other venous embolism and thrombosis						
Varicose veins of lower extremities						
Arteriosclerotic diseases	102	677	15.066	102	673	15.156
Chronic ischaemic heart disease						
Generalized ischaemic cerebrovascular disease						
Arteriosclerosis						
Cerebral haemorrhage						
Aortic aneurysm						
Other aneurysm						

DISEASES	SIBS			CONTROLS		
	Affected	Total	Percent	Affected	Total	Percent
Formation of thrombosis and embolism	38	329	11.550	38	405	9.383
Acute myocardial infarction						
Cerebral thrombosis						
Cerebral embolism						
Arterial embolism and thrombosis						
Pulmonary embolism and infarction						
Phlebitis and thrombophlebitis						
Portal vein thrombosis						
Other venous embolism and thrombosis						