The authors review epidemiological investigations of mongolism, indicate the unanswered questions that still exist, and point out what they consider fruitful areas for future epidemiological studies of this problem.

SOME EPIDEMIOLOGICAL ASPECTS OF MONGOLISM: A REVIEW

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SINCE 1866 when Langdon-Down first described Mongolism, or Down's Syndrome, numerous epidemiological observations have been made in attempts to determine etiological factors. Less than three years ago Lejeune and co-workers[1] demonstrated the presence of an extra chromosome in cultured connective tissue cells of mongols, thereby strongly suggesting a chromosomal abnormality as the basic defect in this condition. These results have been confirmed by many other workers.[2-4] It is, therefore, desirable at this time to evaluate the past epidemiological observations in the light of these recent cytogenetic findings and to determine the most profitable directions of further epidemiological studies. We shall first discuss briefly the cytogenetic developments, then review the epidemiological studies and finally indicate possible future areas of research. Limitations of space permit only a selective general review rather than an intensive exhaustive one.

Figure 1 presents a photomicrograph of normal human cells.[5] The portion on the left shows chromosomes at metaphase in the dividing cells of a normal human male. On the right these same chromosomes are shown sorted and matched in homologous pairs. In normal adults and children the modal number of chromosomes is 46 or 23 pairs. Each pair has one representative derived from each parent. Of the 23 pairs, 22 are called autosomes and the 23rd pair are the sex chromosomes consisting of an X and Y in the male and 2 X's in the female. The numerical order specified is in accordance with the international standard system of nomenclature adopted at the Denver Conference, 1960.[6]

Figure 2 presents the chromosomes of a mongoloid child.[7] Note that there are 47 chromosomes with an extra member of one of the small acrocentric pairs of autosomes, probably the pair designated as number 21 or 22. This condition in which there is an extra member of a pair is known as trisomy and has been the most frequent chromosomal abnormality found in mongolism. More recently, however, mongols with 46 chromosomes have been reported. In each of these mongols there is at least one aberrant chromosome with a postulated translocation involving an extra portion of the number 21 or 22 chromosome attached to another chromosome. It has been suggested that this unbalanced state, or extra dose of chromatin, is nearly equivalent to that produced in the trisomic condition.[8]

Trisomy is probably the end result of a process called nondisjunction, which is

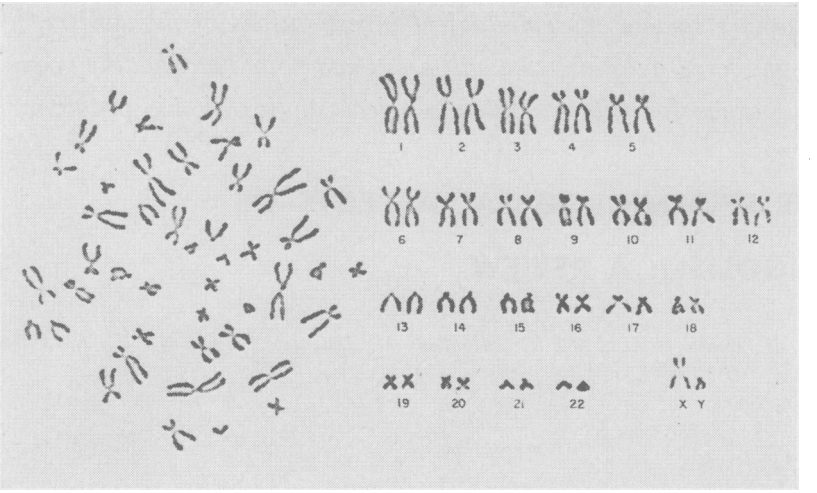

Figure 1—Photomicrograph of Chromosomes at Metaphase in the Dividing Cells of a Normal Human Male. (Courtesy of Barr and Carr, Canadian Medical Association Journal.[5])

the failure of members of a chromosome pair to separate and which most likely occurs at the first or second meiotic division in the formation of either the ovum or sperm. Less likely, although theoretically possible, the nondisjunction might take place at the gonial stage of the gamete or at the first cleavage division of the fertilized ovum or zygote.

Figure 3 illustrates diagrammatically the difference between a normal and a nondisjunctional division.[6] The upper

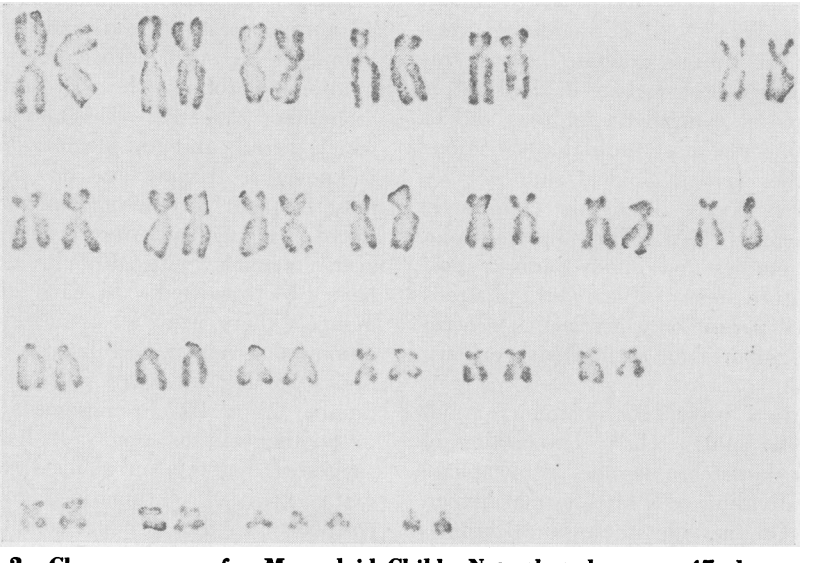

Figure 2—Chromosomes of a Mongoloid Child. Note that there are 47 chromosomes with an extra small acrocentric chromosome. (Courtesy of Hirschhorn and Cooper, American Journal of Medicine.[7])

portion of this diagram shows the orientation of the chromosomes on the equatorial plate followed by separation of members of the chromosome pairs so that each daughter cell has an equal number of chromosomes. In the lower portion, one member of the pair does not separate from its partner; and consequently, one daughter cell has an extra chromosome representative while the other is deficient with respect to that one chromosome. When a gamete (ovum or sperm) carrying the extra chromosome is fertilized by, or fertilizes a normal gamete from the other parent, the resultant embryo, if viable, is trisomic.

Nondisjunction leading to trisomy, and chromosomal breaks resulting in translocations, have been demonstrated in a wide range of organisms, including maize, Drosophila, the house mouse and man[1,9-14] and in both sexes as well.[11,13-15,17-18] Nondisjunction and other chromosomal abnormalities in behavior and structure have been produced by such agents as ionizing radiation, Co_2, and ammonia vapor.[10-14,16-27] There is evidence that specific genes may also affect the frequency of nondisjunction.[11] In addition, interactions between agents have been shown to have an effect. For example, oxygen and cyanide influence the effect of radiation on the frequency of nondisjunction,[10,25,26] and in Drosophila, aging of the females enhances both radiation- and Co_2-induced effects.[24,27]

These cytogenetic findings strongly suggest that, if there are any environmental factors producing the sequence of events leading to the chromosomal defects in mongolism, they must be acting on parental gametes or on the fertilized ovum not later than several days after fertilization. This timing of events has a bearing on the evaluation of various hypotheses and on the selection of areas for further investigation.

The incidence of mongolism has been estimated by numerous investigators. These are summarized in Table 1.[28-42] The periods of study extend as far back as 1923 and are as recent as the late

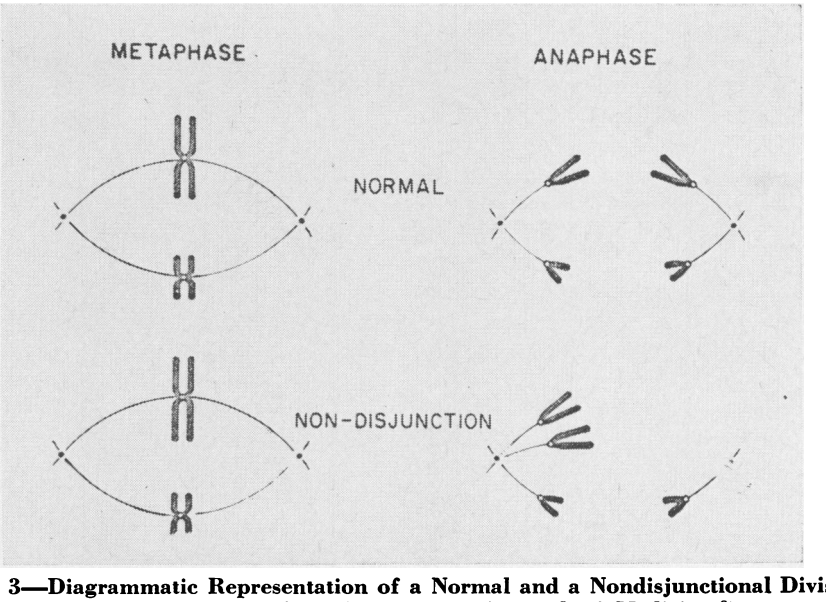

Figure 3—Diagrammatic Representation of a Normal and a Nondisjunctional Division. (Modified by permission of Sohval, American Journal of Medicine.[6])

Table 1—Summary of Estimates of Incidence Rates of Mongolism

Investigator	Ref. No.	No. of Mongols	Population No. Type	Incidence Frequency	Per 1,000	Time Period of Study	Source of Data
Jenkins (1933)	28	6	3,818*	1/636	1.57	1926-31 incl.	United States—Chicago Presbyterian Hospital
Malpas (1937)	29	18	13,964‡	1/776	1.29	1923-32	Great Britain—Liverpool Maternity Hospital
Keller (1938)	30	23	11,000‡	1/478	2.9	About 10 yrs	
Beidleman (1945)	31	48	14,000‡	1/292	3.42	1931-41	United States—Boston Lying-In Hospital
Landtmann (1948)	32	4	3,593‡	1/898	1.11	1945-48	England—University College Hospital, London
Stevenson, Worcester, and Rice (1950)	33	15	29,024† incl. 787 stillbirths	1/1935	0.5	1930-41	United States—Boston Lying-In Hospital
Parker (1950)	34	32	27,931*	1/873	1.15	Jan. 1 '39-	United States—Gallinger Municipal
		3 W	2,905*	1/968	1.03	Dec. 31 '48	Hospital, Washington, D. C.
		29 N	25,026*	1/863	1.16		
Hug (1951)	35	130	67,645‡	1/520	1.92	1930-1949	Switzerland—Zurich
		99	49,218‡	1/497	2.01		St. Gallen
		31	18,427‡	1/594	1.68		
Carter and MacCarthy (1951)	36	100	66,366†	1/666	1.51	1943-1948	England—10 hospitals in London
Øster (1953)	37	52	39,788*	1/765	1.31	1938-1948	Denmark—University Hospital, Copenhagen
Harris and Steinberg (1954)	38	11	8,716*	1/792	1.26	Jan. 1, 1944- Dec. 31, 1950	United States—St. Mary's Hospital, Rochester, Minn.

McIntosh, Merritt, Richards, Samuels, and Bellows (1954)	39	11	5,964**	1/542	1.84	Oct. 1946-March 1952	United States—Sloane Hospital for Women, New York City
Record and Smith (1955)	40	252	231,619†	1/919	1.09	1942-1952	England—City of Birmingham residents
		86	52,729†	1/613	1.63	1944-1955	England—Entire County of
Pleydell (1957)	41	84	52,727*	1/628	1.59	incl.	Northamptonshire
Collman and Stoller (1961)	42			1/688	1.45		Australia—Survey

* Live births
† Total births—(live and stillbirths)
‡ Births and/or maternities (not specified whether live and/or stillborn)

** Pregnancies including abortions and stillbirths
W = white
N = Negro

fifties. They encompass spans of observation as brief as six years and as long as 20 years. Though the range of incidence rates extend from 0.5 per 1,000 births to 3.4 per 1,000, 11 of the 15 studies present estimates of between 1/500 and 1/900 births. This is surprisingly consistent when the geographical and temporal range as well as variability in diagnostic criteria and method of ascertainment are considered. On the other hand, the fact that the two most extreme estimates, those of Beidleman[31] and Stevenson, et al.,[33] were derived from records in the same hospital in an overlapping time period raises many questions.

Of particular interest are Parker's estimates for Negroes and whites at Gallinger Municipal Hospital in Washington.[34] The similarity of the incidence values for whites, 1/968, and for Negroes, 1/863, with one another, as well as that of the Negro estimate with the over-all range of Caucasian values should lead one to question the opinion that mongolism is less common among non-Caucasians. Nevertheless, this represents only a single study sample; and it is possible that the number of cases was not adequate to detect a difference between Negroes and Caucasians, if one truly existed.

It would also be of interest to know whether the incidence of mongolism has changed over time, since if radiation exposure of parents is a major factor in producing chromosomal aberrations, one would expect an increase in incidence rates with increasing exposure of the population to medical radiation.[43-45] It is difficult to evaluate reported incidence rates because of the variability in methods used to estimate them in the different studies and because of the fact that in most studies only crude rates are available. Since there is an association between increasing maternal age and the incidence of mongolism, as will be discussed, the comparison of crude incidence rates leaves much to be desired. Better estimates of incidence rates are needed

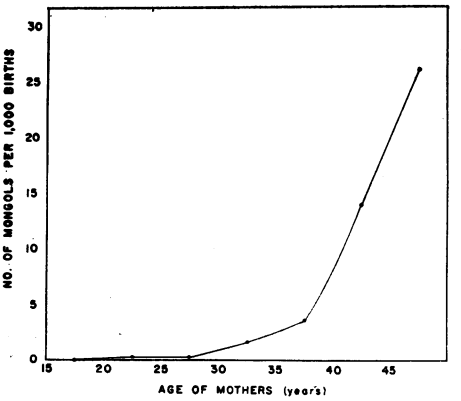

Figure 4—Incidence Rates of Mongolism by Maternal Age. (Rates from Carter and MacCarthy.[36])

for comparative purposes and as a base line for future studies.

Sex Ratio

There has been much conflicting evidence regarding the sex ratio in mongolism. An excess of males was indicated by some investigators and this view had been generally held. More recently, these findings have been criticized because many of the studies were based on institutionalized populations and possibly female mongols are more likely to be kept at home than male mongols. The sex ratio at birth should provide the most satisfactory estimate. On the basis of statistics available at this time, there is certainly no reliable evidence of an aberrant sex ratio in mongolism.[31,34,35,37,40]

Maternal and Paternal Ages and Birth Order

The most striking relationship that has been observed with respect to mongolism is the increasing incidence rate with advancing maternal age. This has been regularly reported in all studies.[8,28,36,37,46] Figure 4 illustrates this relationship with data collected by Carter and MacCarthy from ten hospitals in London and environs. Mothers over 45 years of age have about 100 times the risk of giving birth to a mongol child than do mothers in their twenties. Jenkins,[28] in a further analysis of these maternal age incidence rates, plotted them on logarithmic paper with interesting results. The same data of Carter and MacCarthy shown in Figure 4 are so plotted in Figure 5. We note that up to age 30 the incidence rate does not change with age, but that after 30 years of age the rates are represented by a straight line. This separation of the incidence rates into two components in this manner suggests that there may be two types of mongolism, one that is age dependent and one that is not age dependent. Such a possibility is consistent with other types of data. Recently, Penrose[8] has collected the cases of mongolism associated with chromosomal translocation and found a preponderance of younger mothers. Of additional interest are the reports of ages of mothers of children with trisomy other than that associated with mongolism, indicating in a very limited sample that the maternal ages are on the whole in the older age range.[47] Thus it is postulated that trisomy may be age dependent, and translocation age inde-

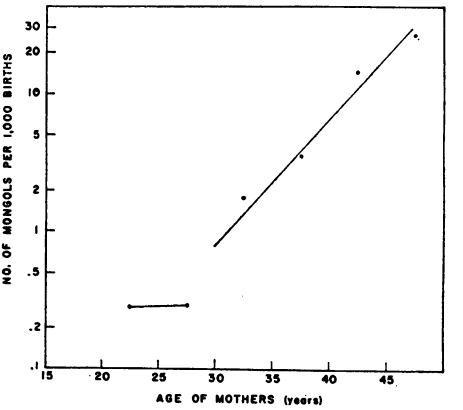

Figure 5—Incidence Rates of Mongolism by Maternal Age. (Rates from Carter and MacCarthy.[36])

pendent. Such a dichotomy in the etiology of mongolism is further suggested by the reported difference in androgyny scores[48] and steroid excretion levels[49] between younger mothers and older mothers of mongols. As yet, these observations can be considered only in the realm of "clinical impressions" and must await further validation.

Mongolism also has been found to be associated with the age of the father at the birth of the affected child, although this relationship is not so marked as that with maternal age. Since maternal and paternal ages are themselves highly correlated, it is of interest to determine whether the association is primarily with one or the other, or both. Penrose[50] has analyzed some data and interpreted them as indicating that the principal relationship is with maternal age and that the paternal age association is a secondary one. A review of these analyses and those of Jenkins[28] suggests that the issue is still unsettled and there is a need for further investigation with adequate control groups. This point is of some relevance with respect to further research orientation. In general, investigators have interpreted the maternal age effect to indicate that, in looking for factors which influence mongolism, one should study maternal factors rather than paternal factors. However, we feel that a possible paternal influence has not been completely eliminated on the basis of available evidence.

Another problem concerns the increase in frequency of mongolism with increasing birth order. This appears to result from the strong association of maternal age with birth order; and apparently, birth order has no independent effect.[51,52]

Maternal Constitutional and Prenatal Factors

Stimulated by the marked association of mongolism with maternal age, there has been much interest in the role of maternal health, reproductive, hormonal and constitutional factors, as well as prenatal events, in the frequency of mongolism. Some studies have reported that mothers of mongols tend to have an earlier age at menarche and later age of menopause as well as an excessively long interval between the birth of the mongol and the previous pregnancy.[28,37,48] There are conflicting reports concerning a higher frequency of miscarriages prior to the birth of the mongol.[31,37,48] It is difficult to evaluate these reports since many have been uncontrolled or inadequately controlled. A study by Lunn[53] indicated that mothers of mongols did not have a larger percentage of abortions prior to the mongol birth than a control group matched by maternal age. However, this was an investigation of 117 mongol children, a number that might be inadequate to detect any but a marked difference.

Several studies have reported a relatively high frequency of maternal complications during the mongol pregnancy, including gestational hemorrhage, threatened abortion, and uterine disorders.[31,54] These findings as well as those of an accumulation of illnesses and intercurrent infections around the time of conception and during the mongol pregnancy must now be interpreted in the light of the recent cytogenetic observations.[37,48,54] Many of these prenatal complications occurred after the time period when they could have produced the type of direct effect necessary for the chromosomal abnormality of mongols. Therefore, these pregnancy difficulties may merely reflect the older maternal ages; or they may be a result of, rather than a cause of, the mongol pregnancy.

In addition to the ovarian hormones, other endocrine factors have been suggested as possible etiological factors. There is conflicting evidence on the frequency of maternal thyroid abnormalities for which some investigators report a high incidence.[37,48,49,55-57] Such a find-

Table 2—Chromosome Analysis of Families of Mongol Index Cases

Classification	Ref. No.	Mongol Index Case	Cytogenetic Category	Maternal Age	Other Relatives with Abnormalities
1. Familial Mongolism with Familial Chromosome Aberration	63	M (46T) F (46T)	Translocation 13–15:21–22	23	Mother, maternal grandmother and normal F sib with (45T)
	64	M (46T)	Translocation 13–15:21–22	23	Mother (45T) Maternal grandmother (45T) 1 male mongol sib 1 male mongol first cousin
	65	M (46T)	"	32	Mother (45T) 2 mongol male sibs dead 1 "normal" female sib dead of leukemia
	66	M (46T)	Translocation 15:21	22	Mother, maternal aunt, maternal grandmother, one male mongol sib dead, one male mongol cousin — all (45T)
	66	F (dead)	?	20	Mother (45T) 21/22:21/22; one male mongol sib dead in infancy
	66	M mosaic	Trisomic 21/tetrasomic 21 mosaic	21	Father normal/tetrasomic 21 mosaic; one female mongol sib dead
	67	F 47 M 47	Trisomy 21/22 Trisomy 21/22	23	Mother translocation 13–15/21
	68	M (46T)	Translocation 13–15/21	27*	2 mongol female sibs 1 mongol maternal aunt
	69	F	Translocation 15:21	?	Mother 15/21 translocation, 1 male mongol sib dead
	69	F 46	Translocation type?		Father 45 chromosomes with translocation 2 mongol sibs dead
2. Familial Chromosome Aberration	70	F (46T)	Translocation	31	Mother (45T)
	71	M (46T)	"	24	Mother (45T)
	72	M (46T)	"	28	Mother (45T)
	73	M (46T) with leukemia	" ?	29	Mother abnormal karyotype with translocation 14?, 1 minute chromosome in "normal" male sib (45)
	74	M (46T)	Translocation 21/22:21/22	39	Father 47 chromosomes trisomic—19?
	8	M (46T)	Translocation 21/22:21/22 (extra metacentric fragment)	33	Parents not available ?
	8	M (46T)	Translocation 21/22:21/22	39	Parents not available ?

* = age at birth of first mongol
s = trisomy
T = Translocation
M = Male
F = Female
? = Unknown condition

Table 2—(Continued)

Classification	Ref. No.	Mongol Index Case	Cytogenetic Category	Maternal Age	Other Relatives with Abnormalities
3. Familial Mongolism	66	F 47s	Trisomic—21	20	Parents normal 1 female mongol sib dead in infancy
	66	M 47s	Trisomic—21	33*	Parents normal 1 male mongol sib dead in infancy
	66	M 47	" —21	38*	Parents normal 1 F mongol sib dead in infancy
	66	M 47s	" —21	45*	Parents normal 1 F mongol sib dead at 6 mos
	66	M 47s	" —21	29	Parents normal 1 F mongol sib dead at 7 yrs
	66	M dead	? ?	20*	Parents normal 1 M mongol sib (Trisomic—21)
	75	M 47	Trisomy	25*	One mongol sib dead

* = age at birth of first mongol
s = trisomy
T = Translocation
M = Male
F = Female
? = Unknown condition

ing, if confirmed, would be of particular interest since there is some cytogenetic evidence that thyroxin may increase "stickiness" of the chromosomes and thus influence nondisjunction.[58] Maternal diabetes mellitus as well as adrenal abnormalities have also been suggested.[48,49,57] In a study of body build as an index of maternal constitution and adrenal function, no differences were found between mothers of mongols and mothers of controls; but there was, as already indicated, a significantly higher mean androgyny score in younger mothers of mongols, i.e., under 27 years, as compared to older ones.

Familial Studies

While the importance of familial studies to determine possible genetic factors in mongolism and to serve as a basis for genetic counseling of parents of mongol children has long been recognized, the cytogenetic observations have added another dimension to such studies.

Results of earlier investigations of familial aggregation were contradictory in that some investigators observed no unusual familial concentration of mongols, whereas others did.[8,37,59,60] This led to the study of the possible familial aggregation of "micro symptoms" of mongolism, such as, fissured tongue, transverse palmar crease, and the position of the palmar triradii.[8,61,62] Even though an excess frequency of such micro symptoms was reported among normal family members of mongols, interpretation of these results is difficult.

Many of the recent family studies of mongolism have included chromosomal analyses of individual families. A collection from the recent literature is summarized in Table 2[8,63-75] which includes: (1) cases of familial mongolism with familial translocation or other aberrations[63-69]; (2) familial translocation or other chromosome aberration, with index mongol as the only diagnosed mongol in the family[8,70-74]; and (3) familial mongolism with no other observed chromosomal abnormalities in family mem-

bers.[66,75] These reports have suggested familial aggregation of certain chromosomal abnormalities, particularly translocation. Of considerable interest are several observations of such translocation in family members who are clinically normal. It has been suggested further that, as in other organisms,[10,17,18] the presence of one type of chromosomal abnormality in a parent may influence the occurrence of another type, such as the one leading to mongolism.[67,74]

Most recently Carter and Evans[76] concluded from their survey of families of 642 mongols that mothers of mongol children have a higher than expected risk of having a second mongol child. Interestingly enough, younger mothers had a greater excess risk than older mothers. Chromosome studies of the families with more than one mongol child in this series of cases revealed chromosomal abnormalities in nonmongol family members of three of the nine families with multiple mongols.[66] At present, these findings on familial aggregation must be considered only suggestive since unknown biases may have been introduced in the selection of cases or even groups examined.

Twin studies, too, have suffered from similar methodological problems.[37,77] Recently Allen and Baroff,[78] cognizant of such difficulties, attempted a systematic investigation of a consecutive series of twins admitted to the New York State schools. They concluded that almost 100 per cent of monozygotic twins are concordant with respect to mongolism as compared to about 4 per cent of dizygotic twins. These results are in agreement with the cytogenetic expectancy. Also strikingly consistent with genetic expectancy is the observation of four mongols among the eight offspring of mongol females reported to have reproduced.[8]

Relationship with Leukemia and Ionizing Radiation

Since Ingalls[79] first demonstrated the simultaneous occurrence of mongolism and leukemia, there have been many case reports, and a few systematic studies indicating that mongols have an increased risk of incurring leukemia.[73,80-84] Wald[85] and co-workers reviewed all the death certificates in Pennsylvania during 1955-1959 and observed that the incidence of leukemia in mongols was significantly higher than that found in the general population. In England, Holland and co-workers[86] found the mortality from leukemia among patients with Down's syndrome to be 20 times greater than expectancy. Moreover, it is of interest that leukocytes of many mongols have an unusual morphological pattern: i.e., polymorphonuclear neutrophils with fewer lobes than found in the general population.[87] These findings are especially interesting as a result of recent observations of chromosomal aberrations in individuals with leukemia. For example, Jacobs[89] reported the presence of a small partially deleted chromosome (called the Philadelphia Chromosome[90-93]) in 14 untreated cases of chronic myeloid leukemia. The abnormal chromosome is thought to be number 21, the same one involved in mongolism. The relevance of this finding is uncertain since the leukemia observed in mongols is usually of the acute variety and none of the subjects with mongolism and acute leukemia who have been studied thus far have the chromosome abnormality observed in chronic leukemia.[94]

In view of the known biological relationship of leukemia to ionizing radiation and the experimental studies of the relationship of ionizing radiation to chromosomal aberrations,[10,16-26,43-45] it is of interest to determine whether parents of mongol children have had excessive exposure to radiation. The results of two studies have been reported. Lunn,[53] in the study mentioned earlier, determined that the per cent of significant histories of x-ray exposure of mothers of mongols was no different from that of mothers of controls. More recently, Uchida[88] reported that 28 per cent of mothers of mongols were exposed to four or more

abdominal x-rays or fluoroscopy as compared to 4 per cent of mothers of cleft lip children and 14 per cent of neighbors. There are several methodological faults with both studies, so that the issue must still be considered an open one and a subject for further investigation.

Nevertheless, this pattern of relationships is provocative and is illustrated in Figure 6 along with others already discussed. The dotted lines indicate associations based on a single report or requiring confirmation for other reasons. The solid lines indicate associations based on several reports and/or on what one would judge as being more reliable evidence. Where arrowheads are placed on lines, direction of association is suggested; otherwise no cause-effect relationship is postulated.

General Comments

Though these associations provide clues as to the etiological factors in mongolism, some, especially those of radiation with mongolism as well as of chromosomal aberrations with leukemia, need further documentation and clarification. As the hypothesized pattern stands now, it falls short of a cause and effect relationship. Theories consistent with the observations can merely postulate the missing steps, but further cytogenetic and epidemiological evidence is needed for their validation.

The observations made during the past two to three years appear to have brought us closer to elucidating the cause of mongolism.[95] Yet, interesting as the results of the cytogenetic investigations may be, it should be emphasized that cytogenetics is a very complex field with numerous technical difficulties. In addition, the sampling of individuals and families for cytogenetic examination has been so irregular that extrapolation of the results to any discernible affected group of population segment is not possible at this time. Hopefully, many of these problems will be resolved in the near future.

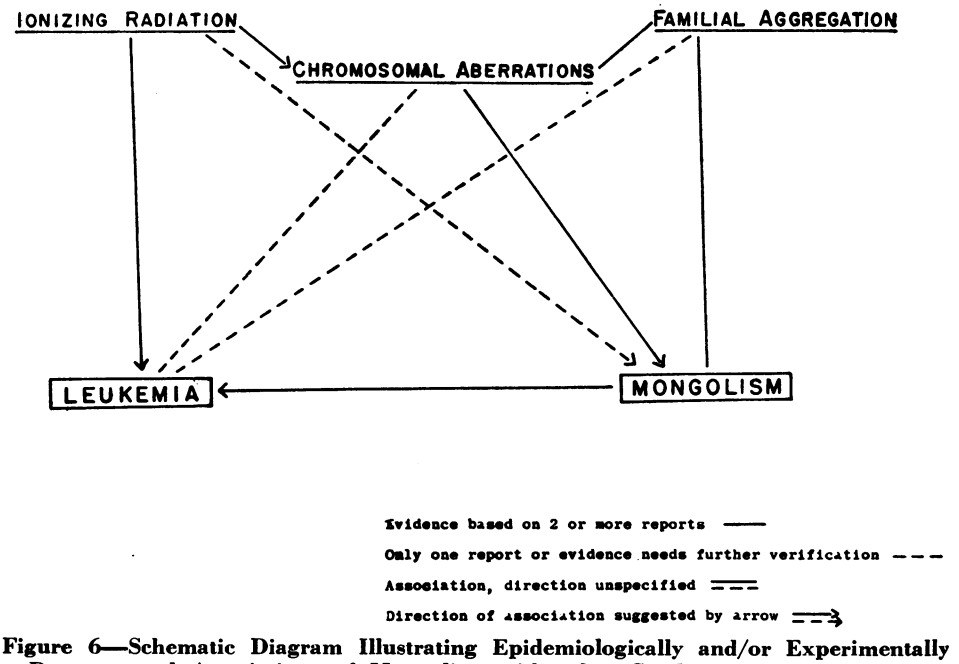

Figure 6—Schematic Diagram Illustrating Epidemiologically and/or Experimentally Demonstrated Associations of Mongolism with other Conditions.

Field epidemiological studies can assist in the evaluation of these findings. A cytogenetic investigation of a sample of the general population would be invaluable in establishing more definitive base lines for chromosomal constitution in phenotypically normal individuals. These also would help in evaluating the significance of findings in those with clinically diagnosed abnormalities and in determining the factors that may be producing these abnormalities.

The following types of studies, one of which we are initiating, are now indicated: (1) a well controlled investigation of parental radiation, reproductive, medical, and drug history; (2) a study of family patterns of mortality and morbidity in all classes of cases and controls; (3) a study of the chromosomal constitution of cases, controls, and their immediate family members; and (4) a study of histologic and histochemical changes of the ovaries and fallopian tubes occurring with age to learn whether these changes might provide an explanation for the increased incidence of mongolism with maternal age. For the epidemiologist, here is an unequaled opportunity to explore the possible contributions that epidemiologic studies might make in determining factors that may have an influence on the genetic constitution of individuals. In view of the increasing recognition of genetically determined human diseases, epidemiologists will doubtless be faced with many similar situations in the future.

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