SYMPOSIUM: *Etiology of Chromosomal Abnormalities*

The Epidemiology of Chromosome Aberrations

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IN THE EPIDEMIOLOGICAL APPROACH to disease, explanations are sought for the observed differences in the rates of occurrence of the trait or condition under study when comparisons are made between defined population groups. Several distinct investigative methods are available. Broad or restrictive definitions of population groups are possible, depending upon the particular epidemiological technique used and the problem investigated.

Epidemiological observations on syndromes associated with chromosomal abnormalities were reported for Down's syndrome before aneuploidy was recognized as a basic pathogenic mechanism in this disorder. Within recent years, other syndromes with autosomal or sex chromosomal abnormalities have been recognized, thus increasing the number of conditions with common pathogenic mechanisms available for epidemiological study. The recognition that nondisjunction is a consistent property in the cause of the various aneuploid disorders has limited the search for etiological mechanisms to certain phases of the reproductive cycle. In general, the recent advances in human chromosomal study have been of assistance in defining the remaining etiological problems which, in turn, can be investigated by several methods, including the epidemiologic.

Reports to date suggest that a null hypothesis, proposing that the distribution of chromosomal abnormalities is random, is incorrect. Rather, observations on the distribution of cases in time and space and by characteristics suggest a nonrandom occurrence of the various aneuploidy syndromes. Clinical observations, case series reports, and family studies offer evidence for aggregation of both similar and dissimilar chromosomal abnormalities within kindreds and within the same individual. For example, Hecht *et al.* (1964), among others, presented data and reviewed evidence for familial aggregations of aneuploids. In the following discussion, only those investigations treating the distribution of aneuploid syndromes in time and space and by certain host characteristics, utilizing retrospective and prospective epidemiological methods, will be covered. Limitation of this review to epidemiological studies as

Presented as part of the Symposium on Etiology of Chromosomal Abnormalities at the annual meeting of the American Society of Human Genetics, August 25–27. 1965, Seattle, Washington.

Supported in part by grants from the California State Department of Health and by U. S. Public Health Service research grant HD 01638 from the National Institutes of Health.

defined by the methods used has been dictated by the nature of the subject. This restriction does not suggest any lesser importance for the findings from clinical and family investigations; rather, results obtained in studies of case series have provided much of the stimulus for epidemiological investigations.

Table 1 presents a summary of eight studies in which the distributions of chromosomal abnormalities were observed for possible differences in incidence, prevalence, or proportion of affected births occurring in defined time periods or spatial subunits of the study population. In most of these reports, case-finding had been restricted to phenotypic recognition of Down's syndrome. Further, a retrospective epidemiological method has been used in seven of the eight studies. Cases were ascertained from a variety of reporting sources and referred in the analysis to the population at risk, which in these studies usually constituted births notified in defined time periods and within specified geographical locations. The eight studies summarized in Table 1, although representing a variety of approaches in the methods used and the study populations selected, present evidence that in general clustering of aneuploids in time and space does occur. Comparability of results between studies is questionable, however, and methodological problems are evident. The various aneuploid syndromes are relatively infrequent, thus requiring large study populations. Diagnostic problems and the relatively high death rates among affected provide further difficulties.

DISTRIBUTIONS IN TIME

Clustering

Several reports have presented data suggesting that the rate of aneuploidy among newborns fluctuates widely over time with clusters of cases of both similar and dissimilar abnormalities observed. In a prospective study, Robinson and Puck (1965) determined sex chromosomal aberrations among 3367 newborns initially by buccal smear and later by amnion sexing techniques. Although variable numbers of newborns were studied in time periods of different lengths, aggregation of sex chromosome aneuploids during the five month period, June to October, 1964, gave a frequency of 0.59% affected when compared with the 0.0% observed in the samples studied during both the preceeding 18 months and the succeeding four months. A similar clustering was also observed for births with Down's syndrome. The authors further reported that the conception times for children born during the five month cluster period fell within the dates of an epidemic of rubella, thus suggesting a possible causal relationship. E. Pergament (personal communication), employing similar techniques, has not observed any association between aneuploidy and rubella, although clustering of aneuploids in time was present in his study population.

Both Pleydell (1957) and Heinrichs, Allen, and Nelson (1963) reported clusters of Down's syndrome births. In the former study, cases were ascertained from various sources in a retrospective manner and were referred to the total population of births in Northamptonshire, England, 1944–1955. The incidence rates showed wide fluctuations due in part to the small numbers

TABLE 1. SUMMARY OF EIGHT EPIDEMIOLOGICAL STUDIES WITH ANALYSIS OF THE DISTRIBUTIONS OF CHROMOSOMAL ABERRATIONS BY TIME AND SPACE

Place	Time Period	Study Method	Result	Reference
Denver	1962–1965	Prospective: series of newborns; nuclear sexing.	Nonrandom distribution in time.	Robinson and Puck (1965)
England	1944–1955	Retrospective method: all cases of Down's syndrome occurring in a defined time period and population.	Clustering in time and space.	Pleydell (1957)
Australia	1942–1957	Retrospective method: all cases of Down's syndrome occurring in a defined time period and population.	Clusters in time and space (urban-rural differences).	Collmann and Stoller (1962a)
South Dakota	1954–1963	Retrospective: phenotypic identification of trisomy 21 and trisomy 18; series of newborns.	Clustering of cases in time.	Heinrichs, Allen, and Nelson (1963)
England	1954–1960	Retrospective: physician reports of observed cases, Down's syndrome, analyzed by quarters.	No seasonal variation.	Slater, Watson, and McDonald (1964)
Milan	1942–1962	Retrospective: phenotypic identification of Down's syndrome among all births in hospital analyzed over time.	Possible higher incidence 1942–1947* compared to 1948–1962.	Beolchini (1964)
Sweden	1911–1958	Retrospective: phenotypic identification of Down's syndrome among all mentally retarded under treatment.	Fewer cases of Down's syndrome born in September as compared to other months.	Lander, Forssman, and Åkesson (1964)
New York State (exclusive of New York City)	1948–1955	Retrospective: Identification of Down's syndrome from vital records. Designed to demonstrate possible associations between congenital malformations and background radiation.	No differences in the spatial distribution of Down's syndrome.	Gentry, Parkhurst, and Bulin (1959)

*Heterogeneity of the maternal age distributions also reported. Older maternal ages over-represented in births 1942–47 in comparison to the 1948–52, 1953–57, 1958–62 quinquennia.

affected, 86 in 52,729 births, thus imposing restrictions on any broad interpretation of clustering. In the latter report (Heinrichs, Allen, and Nelson, 1963), two clusters of Down's syndrome births were observed with 3½–4 year peaks during the period 1954–1960. A third cluster was noted with onset in late 1961 and included two cases of the then recently recognized trisomy 18 syndrome in addition to four cases of Down's syndrome. The group

under observation consisted of a series of births in hospitals serving an area with an estimated 30,000 population.

Seasonal and Annual Fluctuations

Several studies have included data and interpretations on seasonal distributions of births with Down's syndrome identified by retrospective methods. Slater, Watson, and McDonald (1964) gathered case reports from British general practitioners and analyzed the results by internal comparisons as reporting was incomplete and not referable to any defined population of births. Distribution of cases by quarters for all years under study, 1954–1960, showed no differences in the numbers reported. As part of a general investigation into possible associations between season of birth and mental retardation, Lander, Forssman, and Åkesson (1964) reported fewer than the expected numbers of births occurring in September for patients with Down's syndrome among all patients registered to special facilities for the retarded in Sweden, 1911–1958. As noted by the authors, severe limitations on the validity of the data were apparent. The incidence of Down's syndrome, based on the numbers of patients in the sample, was approximately 0.22 per 1000 births, or less than one-fifth the expected rate.

Collmann and Stoller (1962a), in a major retrospective study encompassing the entire state of Victoria, Australia, 1942–1957, did not find any significant monthly or seasonal variation in the incidence of Down's syndrome. However, the authors did observe periodic variations in annual incidence rates, some significant, with maxima and minima occurring at five to six year intervals. When urban and rural fluctuations in incidence rates were compared, the latter were less in amount and lagged behind the former by one year. Apart from the lag and the generally lower rates in rural areas, the epidemic curves for both urban and rural experiences were similar.

Trends Over Time

In several studies, analysis has been directed towards detection of possible secular trends. Collmann and Stoller (1962a) reported no changes in the over-all incidence of Down's syndrome during the years 1942–1957, apart from the individually high and low years on the epidemic curve described above. Beolchini (1964) reported a study of the frequency of Down's syndrome among births in a large urban maternity service, 1942 to 1962. The proportion of affected births during the period 1942–1947 was significantly higher than in the three succeeding quinquennia. However, the maternal ages at parturition were heterogeneous with a greater than expected proportion of older mothers in the sample observed during the 1942–1947 period. Cohen, Lilienfeld, and Sigler (1963) reviewed many of the reported incidence estimates for Down's syndrome, derived mainly from observations on the frequency of affected among births in selected hospitals. Periods of observation ranged from 1923 to 1957. Incidence varied from 0.5 to 3.4 per 1000 births with most of the values lying between 0.5 and 0.9 per 1000. The authors drew attention both to the over-all wide range of reported incidences and also to

the consistency in the majority of the reports. In view of the difficulties in comparing such rates, usually uncorrected for maternal age, no conclusions, other than a lack of evidence for a secular trend in the incidence of Down's syndrome, could be made.

DISTRIBUTIONS IN SPACE

Clusters

Since a suggested temporal cluster of aneuploids implies restriction of the sample not only within some time period but usually to a population occupying a defined geographical area, clustering of cases by spatial characteristics can also be anticipated. Pleydell (1957) reported that two-thirds of the births of patients with Down's syndrome known in Northamptonshire, 1944–1955, occurred within small geographical groupings in the study area. Collmann and Stoller (1962a) employed a definition of cluster which included restriction of affected births to a 12 month period within a geographical subunit of primary census dimensions and where the observed incidence was significantly above the average at the 0.01 level. Based on these criteria 40% of all known births with Down's syndrome in Victoria, 1942–1957, occurred in clusters. Utilizing birth certificate supplemental reports of congenital malformations and death certificate data, Gentry, Parkhurst, and Bulin (1959) attempted to show an association between congenital malformations and background radiation. Geographical divisions of New York State exclusive of New York City were based on geographical characteristics which, in turn, reflected probable average radiation background exposures. Although higher over-all and specific malformation rates were reported for areas with high as compared to areas with lower probable background levels, the incidence of Down's syndrome differed from rates for the other specific malformations tabulated in being equal at 0.3 per 1000 live births in both areas. However, this incidence was calculated from vital reports in about one-fifth of the expected, thus emphasizing the under-reporting of malformations usually encountered in studies utilizing vital data only (Day, 1964).

Urban-Rural

As mentioned above, Collmann and Stoller (1962a) observed a significantly higher incidence of Down's syndrome in urban in comparison with rural divisions of Victoria. However, working with smaller samples, neither Pleydell (1957) nor Øster (1953) observed any urban-rural differences in the occurrence of Down's syndrome.

Racial and National

Although most estimates of the incidence of Down's syndrome have been based on observations in European and North American populations, several are available from other parts of the world. In a recent review, Lejeune (1964) presented a compilation of reports suggesting that no differences in incidence have been demonstrated for Oriental in comparison with Caucasian populations. However, direct comparability of the procedures used by differ-

ent investigators in calculating incidence cannot be assumed. Further, most of the published incidence estimates are crude rates and must be interpreted with caution in view of the pronounced maternal age effect characteristic of Down's syndrome.

A number of nuclear sexing surveys of newborns have been reported. The incidence of sex chromosome abnormalities in males in Europe and North America can be estimated as about 1 per 500 births, while in females the rate is somewhat less, approximately 1 in 600 to 700 births for both XXX and XO complements combined (Maclean *et al.*, 1964). Naik and Shah (1962), on the other hand, failed to observe any discrepancies between phenotypic and nuclear sex in a series of 2058 male and 1832 female newborns in Bombay. Apart from the possibility that the Indian and Western studies varied significantly in technique, the observed differences suggest possible important biological variation. Population exposures to environmental factors of etiological importance in nondisjunction could lead to very discrepant rates of aneuploidy. If clustering of aneuploids in time is a universal phenomenon, the Indian study may have occupied a period of very low incidence of chromosome abnormalities. The various populations may differ in certain genetic characteristics that determine the rates of aneuploidy. Chandra (1965) offered a possible explanation. An association can be shown between certain aneuploids and maternal-fetal blood group incompatibility. The low frequencies of both Rh(D)-negative chromosomes and ABO-incompatible matings in Asian in comparison with Western populations would thus influence the different rates of aneuploidy observed in the various reported studies. However, the case reports cited by Chandra (1965) in support of an incompatibility hypothesis are mostly of the XO type. Evidence thus far suggests that meiotic nondisjunction is not a primary mechanism in the production of the XO abnormality (Lindsten, 1963), while possible maternal age effects and thus meiotic nondisjunctions are important in the origin of the XXY (Ferguson-Smith, 1960) and the XXX (Day, Larson and Wright, 1964) aneuploids. The incompatibility hypothesis, therefore, provides an explanation for variations in rates between populations only for the XO abnormality which, in turn, is the least frequent.

DISTRIBUTION BY HOST CHARACTERISTICS

Much information on social, family, and other characteristics of patients with aneuploidy has been published. In the majority of reports, data have been accumulated from clinical and genetic studies, although confirmed on occasion by epidemiological techniques applied to defined population groups. Collmann and Stoller (1962a) confirmed again the maternal age effect characteristic of Down's syndrome by analysis of data collected within the framework of a major retrospective epidemiological investigation. Over-all, observations of host characteristics among patients with chromosome abnormalities thus far reflect clinical interests more than epidemiological, and, following the general pattern, more information is available for Down's syndrome than for the other autosomal trisomies and the sex chromosome aberrations.

Social Class

Evidence currently available suggests that Down's syndrome is equally frequent among all social classes (Penrose, 1938). However, patterns of marriage and childbearing could influence parturient age distributions markedly, thus confounding any result showing unequal distribution by social status (Øster, 1953). Results of nuclear sexing surveys suggest that chromatin positive males are most frequently found among the higher grades of mental defect (Ferguson-Smith, 1960). There is a similar correlation between social class and mental defect that is attributed to cultural deprivation, among other causes. None of the evidence thus far presented, however, suggests that social class plays a causal role in the origin of male X-polysomy. Rather, the effects of excess X-chromosomal material in the male are to impart a lesser degree of mental defect than is the case with autosomal trisomy.

Medical Factors

The possibility of differential infant and childhood mortality among affected patients could profoundly modify retrospective ascertainment of cases and thus influence rates. As differences in the availability and quality of medical care are associated with living conditions and economic standards, serious methodological problems could arise in comparisons of rates between population groups with differing levels of care.

The influence of preconceptional environmental events and illnesses have been associated with the risk to mothers of having offspring with Down's syndrome. Uchida and Curtis (1961) offered evidence supporting an association between preconceptional radiation of the mother and the birth of a child with Down's syndrome. Schull and Neel (1962) could not confirm this report from their findings among survivors of the atomic bomb explosions in Japan. Numerous other antecedent maternal medical conditions have been suggested as causally associated with Down's syndrome. Benda (1960) has reviewed much of the evidence presented in support of hypotheses delegating primary etiological roles to thyroid disorders, sterility problems, and other maternal abnormalities. In view of the recent and rapid accumulation of cytological knowledge, much of this earlier material is currently neglected, and any hypothesis must now be measured against the facts of aneuploidy and nondisjunction.

Mental Defect

While the autosomal trisomies are associated with severe mental defect, the sex chromosome abnormalities show a lesser association. Nuclear sexing surveys in institutions for the retarded have demonstrated a higher than expected proportion of patients with sex chromosomal abnormalities in comparison with rates reported in newborns. Based on these findings, the risk to all patients with XXY and XXX complements is estimated at three- to fourfold above the risk in euploids (Maclean *et al.*, 1962). Similar association between mental defect and XO Turner's syndrome has not been demonstrated. Comparisons between institutional populations is difficult. Criteria for admission,

availability of beds, and other social, cultural, and geographical factors are involved. In California, surveys of two institutions for the retarded have been performed (Mosier, Scott, and Cotter, 1960; R. W. Day, unpublished observations). The proportion of males with anomalous sex chromatin was 8.0 per 1000 patients in one hospital and 2.6 per 1000 in the other and thus not different from the rate observed in randomly selected newborns. Similar differences were observed in the results from screening the female populations. The frequency in one hospital was again significantly higher, 7.4 per 1000 compared with 0.0 per 1000. Both surveys were performed during overlapping time periods using similar techniques. The hospital with the higher proportion of aneuploids received patients from a more densely populated urban area. The only over-all difference in the characteristics of the two populations was a significantly higher average I.Q. in the hospital with the higher frequency of sex chromosomally abnormal patients. Although a direct comparison of these results is difficult, the possibility remains that the two populations differ in ways that reflect susceptibility or exposure to events governing nondisjunction.

DISCUSSION

Results of epidemiological investigations reported to date suggest that the distributions of births with Down's syndrome and sex chromosome abnormalities are nonrandom in time, space, and by selected host characteristics. The majority of the studies reviewed have used the retrospective method, and frequently data pertaining to an aneuploid condition have been collected as part of a larger study design, often directed towards testing some hypothesis other than those suggested by current information on the nature, origin, and distribution of chromosomally abnormal patients. With the principal interest of recent years focused on the clinical and genetic aspects of aneuploidy, coupled with the extensiveness required in population studies, epidemiological information is as yet fragmentary and scattered.

Large scale prospective studies, with specific and careful diagnostic procedures, covering large numbers of unselected newborns and representing defined populations with varying genetic and environmental characteristics, would clarify some of the epidemiological uncertainties presently apparent. Study designs specifying the method of analysis would remove possible biases introduced when the results may be used to suggest the hypotheses. A prospective study of the magnitude necessary for ascertaining events of relatively low frequency may prove impossible. However, agreement among investigators on a standard protocol could accomplish certain aims as part of ongoing studies.

Etiological implications of the epidemiological findings have been suggested by several investigators. The simultaneous occurrence of rubella and a possible causal association to clusters in time of both Down's syndrome and sex chromosome aneuploids was proposed by Robinson and Puck (1965) but not confirmed by E. Pergament (personal communication). Data bearing on this point may be available retrospectively as a result of the widespread recent

epidemic in North America. Collmann and Stoller's (1962a) report of both a highly irregular distribution in the incidence of Down's syndrome over time and the rural lag in rates compared with urban experience suggested a possible infectious agent originating in urban areas with spread outward to rural, while the population experienced considerable fluctuations in attack rates. While the implication of an infectious agent to explain these observations is plausible, the agent or agents must have wide distribution with similar behavior under many potentially different ecological situations.

The stronger of epidemiological associations are generally unique. However, spatial and temporal nonrandomness has been reported for other congenital malformations. Collmann and Stoller (1962b) found that the distribution of cases of hydrocephaly was similar to that observed for Down's syndrome in the same population during the same time period. Hydrocephaly and the other central nervous system malformations are not associated with any as yet demonstrable chromosome abnormalities. Collmann and Stoller (1962b) further reported periodicity in the occurrence of both anencephaly and spina bifida but with curves distinctly different from the distributions of Down's syndrome and hydrocephaly. Based on Scottish data, Edwards (1958) has reported seasonal fluctuations in the incidence of anencephaly, without evidence of clustering, and similar nonrandom patterns of occurrence for spina bifida and hydrocephaly. However, in New York State exclusive of New York City, the rates for all three neural tube anomalies declined by more than 50% in the period, 1945–1959 (Gittelsohn and Milham, 1962). This finding, not substantiated in the Australian material (Collmann and Stoller, 1962b), suggests several possible hypotheses, among them a change in environmental conditions such as exposure to an infectious agent. In view of the conflicting results from epidemiological observations on the neural tube anomalies, coupled with suggested associations between these malformations and Down's syndrome, future studies, while correlating findings within the entire group of congenital abnormalities, could prove overly susceptible to very broad etiological hypotheses, thereby losing the advantage of unique associations when and if found.

Finally, recent evidence points to the frequency with which chromosomal abnormalities are associated with fetal loss. Carr (1963) reported a distinct chromosome aberration in 12 of 60 aborted fetuses, and Szulman (1965) found 16 of 25 aborted fetuses to have such aberrations, of which only a portion have been recognized as compatible with life. Therefore, accurate estimates of the incidence of chromosome abnormalities should include ascertainment from all available products of conception. The implications for epidemiological studies are obvious.

SUMMARY

Significant differences in the distribution of patients with chromosomal abnormalities in space and time and by selected host characteristics have been observed. While few epidemiological studies of aneuploidy have been reported,

the evidence to date suggests that environmental factors may be important in the origin of nondisjunction. Advances can be anticipated by prospective epidemiological techniques. However, methodological problems include the large numbers needed for investigations, the necessity of specific diagnoses, and the association between high fetal loss and aneuploidy.

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