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Research in the Etiology of Down's Syndrome [1] Intricacies and Pitfalls

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Cytological studies have shown that Down's syndrome (" mongolism ") is the result of a chromosomal anomaly which occurs either in one of the parent's germ cells or at a very early stage in (embryonic) development of the affected individual. The chromosomal anomaly involves the occurrence of a third number 21 chromosome, in addition to the normal complement of two, either separately (i. e., trisomy-21) or attached to one of the other acrocentric chromosomes (i. e., translocation to one of the chromosomes numbered 13-15 or 22 — Denver Report, 1960). Epidemiological studies have indicated that numerous factors are related to, and may affect, incidence of the chromosomal anomalies resulting in Down's syndrome. Studies by Collmann and Stoller (1962a, b) imply fluctuations of annual incidence with a 5-6 year periodicity, a higher incidence in urban compared to rural areas and a clustering of affected births in certain geographic regions. Collmann and Stoller postulated an " infectious agent, probably a virus ", to account for their data. No connection, however, can yet be drawn between such a hypothesis and the established cytogenetic anomaly. Periodic fluctuations in incidence, which are characteristic of recurrent epidemics (Gordon, 1962), have also been reported for congenital anomalies other than Down's syndrome, such as anencephaly, spina bifida, and hydrocephaly (Collmann and Stoller, 1962b; Guthkelch, 1962; Alter, 1962; Slater, Watson and McDonald, 1964).

The well-established correlation between increasing maternal age and increasing incidence of a congenital anomaly is not confined to Down's syndrome, but has also been observed for stillbirths, central placenta praevia, anencephaly, hydrocephaly and spina bifida (Parsons, 1962). In addition, exogenous factors such as somatic and psychic stress have been shown to increase the incidence of Down's syndrome (Benda, 1953).

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Heredity has been shown to be an important factor in the etiology of Down's syndrome in some cases. The occurrence of familial aggregates of the syndrome has been well-established, particularly involving younger mothers of affected children (Penrose, 1961). Numerous studies have investigated characteristics in relatives of affected individuals. Coppen and Cowie (1960) found an increased androgyny score (Tanner, 1951) in mothers who, at the age of 22 or younger, had borne children affected with the trisomy-21 syndrome. Rundle et al. (1961) confirmed these findings and additionally reported a higher urinary dehydroepiandrosterone (D.H.A.) excretion pattern in such mothers, compared to control women. Similar observations of significantly higher D.H.A. excretions were reported earlier by Ek and Jensen (1959), but without control data. All these observations could be interpreted as indicative of a hormonal involvement in the etiology of the chromosomal anomaly. Studies by Davis et al. (1964), however, did not confirm the findings of Rundle et al. (1961) nor those of Ek and Jensen (1959). Moreover, Dutton (1962) observed female androgyny scores in male " mongols " with male patterns of androgen excretion. Dutton therefore concluded that the raised androgyny score in mothers of children affected with Down's syndrome could not be due solely to androgen excretion.

The frequency of insensitive tasters of phenylthiourea-type compounds is lower in Japanese (7%) than in Caucasian (30%) populations. The frequency of Down's syndrome is also lower in Japan (0.084%) than in Caucasian (0.16%) populations, an observation consistent with the hypothesis of a relationship between taste insensitivity and Down's syndrome (Fischer, Griffin and Kaplan, 1963a). Accordingly, it was found that taste sensitivity for quinine and 6-n-propylthiouracil, a phenylthiourea-type compound, is skewed to the insensitive range in a group of 38 parents of children affected with the trisomy-21 syndrome (Fischer et al., 1961; Fischer et al., 1963). The observations appeared " promising but still in need of control data " (Fischer et al., 1961). Data gathered in subsequent investigations have enabled us to control the factors of age, sex, and smoking habits when relating taste sensitivity to incidence of Down's Syndrome (Fischer, Griffin and Mead, 1962; Fischer, Griffin and Kaplan, 1963b; Kaplan et al., 1964; Glanville et al., in press). When we carefully controlled these variables in a more extensive investigation on 142 parents of children affected with the trisomy-21 syndrome, the parents were not less sensitive than the control population. The above and similar studies may, however, involve additional variables, unknown and therefore uncontrolled. Geographic location may be one of the variables relevant to the differing results of the (above) two studies: the first study was based on a Columbus population, the second on residents of the Akron-Cleveland area, the two regions being divided by a " goiter belt " (Hamwi et al., 1955). Possible relations between thyroid function, taste sensitivity and incidence of Down's syndrome have previously been discussed (Fischer, Griffin and Kaplan, 1963a). Socioeconomic and genetic differences in population composition, as well as methodological differences, probably involve unknown variables which influence reproducability of observed taste sensitivity in groups of parents of children affected with Down's syndrome. One possible

variable may relate to the occurrence of differences in volatile compounds remaining in the distilled water (*i. e.*, higher in industrial Cleveland than in Columbus), which is used as solvent and placebo in our testing procedure (Fischer et al., 1961).

Down's syndrome is but one of numerous congenital anomalies with a relatively low incidence in Japan. The incidence of anencephaly is also low (0.07%) compared to Nordic (0.2%) populations (Dekaban, 1936). Phenylketonuria, also, shows a low incidence in Japan and the highest incidence in Nordic populations (Kaplan, 1962). The Above differences reflect ethnic and/or geographic variables, which do not necessarily bear a direct relationship to the etiology of associated genetic or "infectious" states.

In contrast to the difficulties encountered in the use of physiological variables such as urinary D.H.A. excretion and taste sensitivity, examinations of the relatives of affected individuals for characteristic minor morphological signs associated with the syndrome have yielded consistent positive results. Penrose (1954) demonstrated that the position of the carpal triradius on the palm of the hand of the mothers, brothers and sisters, but not fathers, of affected individuals, tended to deviate significantly towards the "mongoloid" type. Turpin and Caratzali (1933) showed that a fissured tongue and transverse palmar crease (*i. e.*, simian fold or four-fingered crease) occur more frequently among the close relatives of affected individuals than would be expected by chance. Our own data confirm the latter observation. In our Cleveland-Akron sample of parents of children affected with Down's syndrome, the simian fold occurred in 7.8% of mothers and 8.6% of fathers compared with 2.2% of the female controls and 2.5% of the male controls (cfr. table). Biochemical or

Table. Simian fold distribution in children affected with Down's syndrome, the parents and siblings of affected children, and unrelated control subjects

	Total subjects	Left only			Right only		Both hands		Either hand				Either hand % full or partial
		none	full	partial	full	partial	full	partial	full	%	partial	%	
Affected children	40	24	5	2	4	1	4	0	13	32.5	3	7.5	40%
Fathers	87	80	1	3	0	1	0	2	1	1.2	6	7.4	8.6%
Mothers	89	82	4	0	1	2	0	0	5	5.6	2	2.2	7.8%
Brothers	59	57	2	0	0	0	0	0	2	3.4	0	0.0	3.4%
Sisters	56	56	0	0	0	0	0	0	0	0.0	0	0.0	0%
Male controls	119	116	1	1	0	1	0	0	1	0.8	2	1.7	2.5%
Female controls	133	130	0	0	1	2	0	0	1	0.7	2	1.5	2.2%

physiological parameters, such as urinary D.H.A. excretion and taste sensitivity, would be preferable to morphological variables for elucidating the etiology of Down's syndrome. At this stage, however, only the morphological measures appear to be reliable.

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