A GENETICAL STUDY OF HIRSCHSPRUNG'S DISEASE*

CONGENITAL INTESTINAL AGANGLIONOSIS

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This investigation was centred round 71 index cases who had been operated on for Hirschsprung's disease at the Red Cross War Memorial Children's Hospital from 1957 till 1966. In each case the diagnosis was confirmed histologically by the absence of autonomic ganglion cells from the wall of the rectum and for a variable but continuous length of gut above the rectum.

Race. Of the 71 index cases, 26 were Whites, 38 Cape Coloured and 7 African. Several extraneous factors influenced the admission of these 71 index cases to this hospital so the data cannot be used for assessing the frequency of the disease in South Africa or for determining whether there is any racial difference in susceptibility to the disease.

Sex. 55 of the index cases were males, giving a sex ratio for the whole series of 3·4:1. This is very close to the sex ratios reported in two other investigations from Bremen and London.

Type of lesion. In 53 cases (75%), the lesion was of the 'short segment' type, i.e. it did not extend above the sigmoid colon. In the remaining 18 (25%) a varying length of gut above the sigmoid colon was affected ('long segment' type); in one of these cases the lesion extended into the distal part of the jejunum. In the 'short segment' group, the male : female ratio was 4·9:1; in the 'long segment' group it was just 1·6:1 There was no disproportionate frequency of either type of lesion among the 3 racial groups.

Of the 71 index cases, it was possible to contact the families of 56 directly; these are referred to as the 'studied cases'. Contact could not be established with 15 families who lived far from Cape Town and whose whereabouts could not be ascertained. The remaining data to be presented refer to the 'studied cases' only.

Maternal age. The mean age of the mothers at the birth of the affected children was 28·7 years. For the White and Coloured mothers only it was 28·3 years. The mean age of all White and Coloured mothers in the general population of South Africa who produced babies in 1958 was 26·2 years (comparable data for African mothers were not available). In each 5-year age period from 15 to 24 years there was a deficiency of mothers of index cases; from 25 to 49 years there was an excess of mothers of index cases in each 5-year period.

Paternal age. The mean age of the fathers at the birth of the affected children was 32·5 years. No data were available for the general population so no comparison between the ages of 'affected' and 'control' fathers could be made.

Birth order. No data from the general population are available with which to compare the findings of this investigation, so no conclusion can be drawn about this factor in relation to Hirschsprung's disease.

Maternal health in pregnancy. The retrospective interrogation of the mothers about illnesses, drugs, X-rays, etc. during their pregnancy did not reveal any obviously relevant factor.

Delivery. No undue difficulties at the time of delivery were recalled by the mothers of the studied cases.

Parental consanguinity. In 3 cases the parents of the studied cases were first cousins once removed (coefficient of relationship, $r = 1/16$). For all 56 studied cases, the mean coefficient of relationship, $F = 0{\cdot}0016$. The presence of this degree of parental consanguinity suggests the possibility of a recessive pattern in the genetics of Hirschsprung's disease.

Affected relatives. In only one of the families studied was there histologically confirmed evidence of more than one affected individual. In this family there were 2 affected sisters and a maternal first cousin (male) with Hirschsprung's disease. In one of the sisters the lesion was of the long-segment type; in the other sister it was of the extra-long-segment type; and in the cousin it was of the short-segment type. In two other families there was well-documented evidence of an older brother of the index case dying from a disease clinically and radiologically indistinguishable from Hirschsprung's disease, but without histological proof. There were no twins in this series.

Associated malformations. Anophthalmos, Down's anomaly, endocardial fibroelastosis, ureteric valves, and mental defect were noted once each among the studied cases. The association with *Down's anomaly* has often been recorded. If our series is added to 3 others which are adequately documented, the incidence of Down's anomaly in Hirschsprung's disease is 8 in 633 cases; in the general population, the incidence of Down's anomaly is about 1 in 600. The association with *anophthalmos* is interesting. This anomaly may be due to a

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disturbance in the outgrowth and migration of cells from the cranial-cervical portion of the embryonic neural tube; and it is from this region of the neural tube that the ganglion cells of the terminal intestine are believed to originate. It is noteworthy that 2 index cases had first cousins with congenital ptosis and another 2 index cases had first cousins who died with spina bifida; these lesions may also be associated with disturbances of development affecting the embryonic neural tube.

CONCLUSIONS

The findings in this South African series support those from Europe and North America in emphasizing the importance of genetic factors in the aetiology of Hirschsprung's disease. Neither our data nor those from elsewhere are suggestive of either a dominant or an X-linked pattern of inheritance. The occurrence of parental consanguinity and the presence of affected relatives in the pedigrees of a few of our studied cases are consistent with a recessive type of inheritance, but no more definite statement about the genetics of Hirschsprung's disease can yet be made. The tendency of the mothers of our studied cases to be older than in the general population points to environmental influences acting at the genetic level. The association with ocular lesions points to the cranial-cervical portion of the neural *tube* (rather than the neural *crest*) as the possible site of the primary embryological defect.

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