# Recessive Genes in Severe Mental Defect*

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HETEROGENEOUS CONDITIONS like mental defect are refractory to genetic analysis. Empirical risks, twin concordances, and elevated consanguinity rates have led to no real understanding of the role of genetic factors, and cytological and biochemical studies have so far clarified only a minority of cases. One methodology which has not so far been tried is that of population genetics. Recent developments in this field, especially segregation and consanguinity analysis, provide a new approach to an old and difficult problem, yielding information about the number of loci and gene frequencies of recessive factors for severe mental defect, their penetrance and mutation rates, and the mechanism which maintains these genes in the population despite the greatly reduced fertility of affected persons. The techniques are applicable to other conditions of heterogeneous etiology, for which severe mental defect may serve as an example of how a recessive component can be isolated from a complex mixture.

## THE WISCONSIN SAMPLE

Mental defectives are mostly nonrecessive, and our problem is to enrich the proportion of recessive cases, yet still permit an estimate of prevalence. Recognized exogenous cases may be dropped at once. Overlap with normal makes the group of mild defectives unsuitable for segregation analysis. Dull and defective persons mate preferentially, are poor informants, and their children rarely segregate into two distinct classes of severely affected and normal. Therefore we considered only severe defectives (i.e., idiots and imbeciles, I.Q. less than 50), both of whose parents were of normal or superior intelligence (I.Q. greater than 85). We excluded mongols, hydrocephalics, and cases due to known trauma, neoplasm, or infection.

To enrich still further the proportion of recessive cases, we decided to restrict the sample to *multiplex* families (i.e., with two or more affected children). These were ascertained, without indicating an interest in familial cases, through a questionnaire to members of local retardation associations and to

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parents of defectives institutionalized in one of the Wisconsin colonies. This questionnaire included queries about the parents and the name, birth date, sex, and grade in school of each child, with the following questions about each:

1. When this child was born, was there a birth injury, jaundice, or need for a blood transfusion?
2. Was there any abnormality or physical defect noticed in the first three years of life?
3. Was there ever any serious disease, such as brain fever (encephalitis)? Any trouble seeing, hearing, or talking?
4. Has this child ever had any disease that left him (or her) crippled or handicapped in any way?
5. Has this child ever had fits, convulsions, or fainting spells?
6. Is this child much slower learning than other children the same age?
7. Has this child ever gone to a special school, like one for slow learners, for the deaf or blind?
8. Has this child ever spent any time at a training school, state hospital, or mental institution?
9. Is this child now living? (If not, give date and cause of death under "Comments").

A covering letter explained that this questionnaire was part of a study on the causes of mental retardation and was signed by the superintendent of the colony or the executive director of the Wisconsin Council for Mentally Retarded Children, who urged co-operation. A reascertainment form was enclosed, with a request that it be returned in place of the questionnaire if the latter had already been filled out from a previous mailing. The stamped return envelope was addressed to a post office box to protect the privacy of the respondents.

At the time the study was begun, the Wisconsin colonies had 3,568 patients, 2,740 of them below I.Q. 50. In all, 1,746 questionnaires were returned. Response was probably better from the selected families with normal or superior parents and two or more unexplained severely affected offspring than from parents themselves retarded and/or with offspring who were mild, exogenous, or isolated cases. We believe, therefore, that most normal parents with familial severe defectives were ascertained, providing they belonged to the Wisconsin Council or had at least one institutionalized child.

The returns were scanned for indications of two or more children retarded in any degree. If there was a suspicion that more than one child was defective, the parents were asked for the names of physicians, schools, and hospitals in contact with the children and for written permission to obtain information from them. Whenever a defective was in one of the colonies, the records in his file were scrutinized. If the records did not clearly permit exclusion on account of parental retardation, strong evidence of exogenous origin, or fewer than two severely defective children, or did not firmly substantiate inclusion, an interview with the parents was arranged. Thirty-six of the 49 families ultimately included were interviewed.

The interview, besides confirming the mentality of the parents and the

TABLE 1. CLINICAL DIAGNOSES IN MULTIPLEX FAMILIES

| Diagnosis | Wisconsin families | Colchester families |
|---|---|---|
| Undifferentiated (four degenerative) | 34 | 7 |
| Diplegia or tetraplegia | 2 | 4 |
| Phenylketonuria | 4 | 2 |
| Microcephaly (one with simian crease, no chromosomal anomaly) | 3 | 2 |
| Deaf-mutism (one blind) | 1 | 1 |
| Coloboma | – | 2 |
| "Endocrine" | – | 3 |
| Cretinism | 1 | – |
| Hurler's syndrome | 1 | – |
| Lipoidosis, Bielschowsky-Jansky | 1 | – |
| Retinitis pigmentosa | 1 | – |
| Leukodystrophy | 1 | – |
| Total | 49 | 21 |

reliability of the questionnaire, was directed to two points: a medical history of each retarded child, to detect postinfectional and post-traumatic cases, and the degree of consanguinity between the parents. The question on consanguinity was asked only at the end of the interview, after family names back to the grandparents, if known, had been ascertained. Information on ancestry was often incomplete but was usually sufficient to detect first or second cousin relationship.

Most of the institutionalized probands were seen by Dr. Harry Waisman. Urine specimens for chemical studies were obtained from most patients, and a few blood samples for chromosome analysis by Dr. Klaus Patau were taken from patients with physical defects. One chromosomal anomaly was demonstrated (Patau, Opitz, and Dewey, 1964), and therefore this family was excluded. Since most families were not karyotyped and small chromosomal anomalies are usually undemonstrable, it seems likely that the etiology of some of the cases included in the study is chromosomal. The chemical studies were unilluminating, and the clinical diagnoses not especially informative (Table 1).

Of the 49 families that met our criteria, 45 had at least one colony member and the remaining four were ascertained only through the Council for Mentally Retarded Children. Colony members were counted as probands. In the families with no colony member, all affected children antedated membership in the Council and so were considered probands if still living. Identical twins were counted as a single individual, and half-sibs were excluded. This gave 81 probands, 26 secondary cases, and 120 normals in the 49 families.

In an additional five families, the medical history was either woefully inadequate or suggestive of an infectious or traumatic cause for one of the defective children. These families were excluded, although the evidence was not decisive. It is possible that some of these would have been included and a few of the selected families omitted if a complete medical history could have been obtained.

Consanguineous marriages in Wisconsin are so rare that it is hardly feasible

TABLE 2. CONSANGUINEOUS MARRIAGES IN THE GENERAL POPULATION

| Relationship | $F$ | Wisconsin, Roman Catholic marriages, 1941–1955 | | | | | | England (Bell, 1940) |
|---|---|---|---|---|---|---|---|---|
| | | Green Bay | LaCrosse | Madison | Superior | Milwaukee | Total | |
| Not related | 0 | 37254 | 24818 | 12548 | 11944 | 83991 | 170555 | 48926 |
| Distant (third cousins?) | 1/256 | — | — | — | — | — | — | 15 |
| Second cousins | 1/64 | 69 | 90 | 10 | 19 | 83 | 271 | 53 |
| 1½ and double second cousins | 1/32 | 15 | 19 | 3 | 3 | 7 | 47 | 2 |
| First cousins | 1/16 | 6 | 7 | 3 | 10 | 15* | 41 | 299 |
| Uncle-niece | 1/8 | — | — | — | — | — | — | 3 |
| Total | | 37344 | 24934 | 12564 | 11976 | 84096 | 170914 | 49298 |

| | Wisconsin | England |
|---|---|---|
| Mean, $\alpha$ | $48 \times 10^{-6}$ | $406 \times 10^{-6}$ |
| Variance, $\sigma^2$ | $16 \times 10^{-7}$ | $248 \times 10^{-7}$ |

*Estimated by the Vice-Chancellor of the Archdiocese of Milwaukee on the basis of dispensations issued to residents of the archdiocese in other states.

to collect a large enough sample from the general population to determine inbreeding rates. Therefore we turned to records of Roman Catholic marriages and consanguinity dispensations (Table 2). It is not known whether consanguineous marriages occur more or less frequently among Roman Catholics than among other groups in Wisconsin or whether there is a different frequency in religious and civil marriages. An additional source of error is that the civil law prohibits marriages of couples who are first cousins once removed or more closely related (unless the wife is over 50 years of age), whether the marriage is performed inside the state or not. Couples who fail to admit consanguinity when applying for a marriage license are guilty of perjury, but no penalty is specified and the marriage is valid. Roman Catholic canonical law, on the other hand, permits dispensation for marriages of couples who are second cousins or closer (Moroni, 1962). Without such a dispensation, a consanguineous marriage is invalid in the eyes of the Church. Dispensations for marriages of first cousins once removed have been granted in all dioceses and for first cousins in all dioceses but Milwaukee, where the Vice-Chancellor has sent couples who applied to him for dispensation of first cousin marriage to another state, and the dispensation was issued there. In his ten years of experience in this position, he estimated that there had been ten such applications. This average of one first-cousin marriage per year was extrapolated over the rest of the period considered.

We have no way of knowing how frequently consanguinity is unknown to the marriage partners or not admitted by them. Since a marriage license cannot legally be issued to a couple who admit relationship as close as first cousins once removed, yet the dispensations show that a number of such marriages have occurred, there must be considerable underreporting of consanguinity when applying for a marriage license.

The data in Table 2 indicate that inbreeding in Wisconsin is lower than most modern populations (Freire-Maia, 1957). The mean inbreeding coefficient is $48 \times 10^{-6}$, compared with $360 \times 10^{-6}$ for a German city, $260 \times 10^{-6}$

TABLE 3. CAUSES OF EXCLUSION FROM COLCHESTER DATA

| | | |
|---|---|---|
| Not low-grade cases | | 627 |
| At least one parent retarded or unknown | | 166 |
| Diagnosis of nonrecessive case | | 107 |
| Mongol | 64 | |
| Postinfectional | 22 | |
| Post-traumatic | 11 | |
| Neoplastic | 7 | |
| Hydrocephalic | 3 | |
| Sibs of probands | | 4 |
| | Subtotal | 904 |
| | Families remaining | 375 |
| | Total | 1279 |

Of the 375 families not excluded, the following 21 were multiplex (i.e., with two or more affected children): 25, 49, 69, 88, 302, 329, 344, 353, 364, 376, 645, 648, 758, 815, 904, 942, 981, 1057, 1064, 1138, 1250.

for Utah Mormons, and 614 $\times$ $10^{-6}$ for rural North Carolina (Woolf *et al.*, 1956).

## THE COLCHESTER SURVEY

We were able to find only one published body of data suitable for segregation and consanguinity analysis, the classic investigation by Penrose (1938) of 1,279 institutionalized mental defectives in Colchester, England, which included a detailed appendix giving the family of each case. For this genetic analysis, affected identical twins in family 94 were counted as a single individual. Making the same exclusions as for the Wisconsin study (high-grade defectives, retarded parents, mongolism, hydrocephaly, and cases due to known trauma, neoplasm, or infection) left 379 institutionalized cases (probands) distributed in 375 families, of which 21 had two or more low-grade defectives (Table 3). There were 25 secondary cases and 1,421 normal siblings.

Bell (1940) reported on the consanguinity rate among provincial general hospital patients in England, for whom $\alpha = 406 \times 10^{-6}$. Her data (Table 2) must serve *faute de mieux* for a general population control for the Colchester study.

## SEGREGATION ANALYSIS

The formal genetics of many rare traits, including severe mental defect, can be described in terms of three parameters:

$p$, the segregation frequency in high-risk families, assumed constant among such families within a phenotypic mating class. For fully penetrant recessive genes from normal $\times$ normal matings, $p = \frac{1}{4}$.

$x$, the proportion of cases in the population that are nonrecessive sporadics (i.e., are due to such mechanisms as mutation, chromosomal nondisjunction, polygenic complexes, phenocopies, and rare instances

TABLE 4. SEGREGATION ANALYSIS

*ra* Table.

| Affected $r$ | Probands $a$ | Wisconsin sample $\pi = .7054$ $n_{ra}$ | Wisconsin sample $\pi = .7054$ $U_\pi$ | Colchester sample $\pi = .2565$ $n_{ra}$ | Colchester sample $\pi = .2565$ $U_\pi$ |
|---|---|---|---|---|---|
| 1 | 1 | — | — | 354 | — |
| 2 | 1 | 16 | −41.948 | 14 | −10.799 |
| 2 | 2 | 25 | 54.753 | 2 | 8.946 |
| 3 | 1 | 3 | −16.914 | 3 | −4.820 |
| 3 | 2 | 3 | −2.478 | — | — |
| 3 | 3 | 1 | 3.986 | — | — |
| 4 | 2 | — | — | 1 | 2.741 |
| 4 | 3 | 1 | 0.756 | — | — |
| 5 | 2 | — | — | 1 | 1.786 |
| Total | | 49 | −1.846 | 375 | −2.147 |
| | | $K_{\pi\pi} = 337.56$ | | $K_{\pi\pi} = 106.05$ | |

*s* Table.

$m = -1.5941, z = -0.3791$

| $s$ | $n_s$ | $E(n_s)$ | $U_m$ | $U_z$ | $\chi^2$ |
|---|---|---|---|---|---|
| 2 | 10 | 8.54 | 6.367 | 7.419 | 0.25 |
| 3 | 6 | 10.47 | 2.369 | 1.929 | 1.91 |
| 4 | 12 | 9.16 | 1.836 | 0.307 | 0.88 |
| 5 | 9 | 6.96 | −0.800 | −1.825 | 0.60 |
| 6 | 3 | 4.90 | −0.992 | −1.166 | 0.74 |
| 7 | 3 | 3.29 | −1.718 | −1.636 | 0.02 |
| 8 | 3 | 2.14 | −2.443 | −2.043 | 0.35 |
| 9 | — | 1.36 | — | — | 1.36 |
| 10 | 2 | 0.85 | −2.596 | −1.814 | 1.56 |
| 11 | — | 0.53 | — | — | 0.53 |
| 12 | — | 0.32 | — | — | 0.32 |
| 13 | 1 | 0.20 | −2.024 | −1.172 | 3.28 |
| >13 | — | 0.28 | — | — | 0.28 |
| Total | 49 | 49 | 0 | 0 | 12.07 |

$K_{mm} = 16.11, K_{mz} = 13.41, K_{zz} = 12.26$

of heterozygous expression of a recessive gene) which have a negligibly low recurrence risk among sibs.

$\pi$, the ascertainment probability, assumed constant among families. This is the probability that a case in the population be a proband, which in these studies of mental defect implies an institutionalized case or one whose parents belonged to the Wisconsin Council for Mentally Retarded Children and responded to our questionnaire.

On these assumptions, the probability of $a$ probands among $r$ affected sibs is

$$p(a|a>0) = \frac{\binom{r}{a}\pi^a(1-\pi)^{r-a}}{1-(1-\pi)^r}$$

When each proband can be independently ascertained only once, this distribution gives most of the information about the ascertainment probability $\pi$, free

TABLE 4. (CONTINUED)

*sr* Table

| Children *s* | Affected *r* | Wisconsin sample $p = .25$ | | Colchester sample $p = .25$, $x = .8808$ | | |
|---|---|---|---|---|---|---|
| | | $n_{sr}$ | $U_p$ | $n_{sr}$ | $U_p$ | $U_x$ |
| 1 | 1 | — | — | 34 | — | — |
| 2 | 1 | — | — | 49 | −5.266 | 11.049 |
| 2 | 2 | 10 | — | 1 | 4.015 | −8.425 |
| 3 | 1 | — | — | 50 | −7.954 | 19.917 |
| 3 | 2 | 4 | −2.261 | 3 | 8.088 | −25.367 |
| 3 | 3 | 2 | 9.536 | — | — | — |
| 4 | 1 | — | — | 54 | −9.367 | 28.498 |
| 4 | 2 | 12 | −14.120 | 1 | 1.376 | −8.486 |
| 4 | 3 | — | — | 1 | 6.709 | −8.486 |
| 5 | 1 | — | — | 35 | −5.756 | 21.777 |
| 5 | 2 | 7 | −11.009 | 4 | 0.218 | −34.058 |
| 5 | 3 | 2 | 6.997 | 1 | 5.388 | −8.515 |
| 5 | 4 | 1 | 8.832 | — | — | — |
| 6 | 1 | — | — | 40 | −5.678 | 27.563 |
| 6 | 2 | 3 | −7.622 | 3 | −3.804 | −25.627 |
| 7 | 1 | — | — | 23 | −2.591 | 16.895 |
| 7 | 2 | 1 | −6.587 | 2 | −5.182 | −17.138 |
| 7 | 3 | 1 | 2.040 | — | — | — |
| 8 | 1 | — | — | 30 | −2.428 | 22.911 |
| 8 | 2 | 2 | −8.187 | 1 | −3.195 | −8.595 |
| 8 | 3 | 1 | 1.240 | 1 | 1.418 | −8.595 |
| 9 | 1 | — | — | 16 | −.793 | 12.486 |
| 9 | 2 | — | — | 1 | −5.240 | −8.620 |
| 9 | 5 | — | — | 1 | 10.760 | −8.620 |
| 10 | 1 | — | — | 11 | −.221 | 8.666 |
| 10 | 2 | 2 | −11.660 | — | — | — |
| 11 | 1 | — | — | 9 | .060 | 7.095 |
| 11 | 4 | — | — | 1 | 2.774 | −8.667 |
| 12 | 1 | — | — | 2 | .061 | 1.568 |
| 13 | 1 | — | — | 1 | .051 | .776 |
| 13 | 3 | 1 | −3.417 | — | — | — |
| Total | | 49 | −36.219 | 375 | −17.289 | .002 |
| | | | $U_\pi = 1.846$ | | | $U_\pi = 2.146$ |
| | $K_{pp} = 445.43$ | | $K_{p\pi} = -22.55$ | $K_{pp} = 306.14$ | | $K_{pr} = -213.02$ |
| | | | $K_{\pi\pi} = 1.30$ | $K_{p\pi} = -37.95$ | | $K_{xx} = 1641.16$ |
| | | | | $K_{x\pi} = 136.09$ | | $K_{\pi\pi} = 13.97$ |

of assumptions about $p$ and $x$. Using the methods of Morton (1959), Table 4 presents the analysis of these data at the maximum likelihood estimates of $\pi = .7054$ for Wisconsin and .2565 for Colchester, which correspond reasonably well with other evidence. Lewis (1929) observed 112 institutionalized imbeciles and idiots among 513 ascertained from all sources in an English population, a proportion of .218. By 1938, the year of the Colchester survey, this rate must have increased, and Penrose (1949) estimated that "in England, probably more than one quarter of all cases of severe defect in the community are to be found in institutions." In the Wisconsin material, 45 of 49 families were ascertained through institutionalized probands, and in 1960

there were 2,740 severe defectives institutionalized in a population of four million, compared with 652 low-grade patients in the Colchester population of two million (Suffolk, Cambridgeshire, and Essex). Thus the ratio of the ascertainment probabilities is estimated as

$$\frac{(2740)(49)}{(652)(45)(2)} = 2.3$$

or more than twice as great in Wisconsin as Colchester.

Information about the segregation frequency $p$ is obtained from the probability of $r$ affected among $s$ sibs, which is

$$P(r=1|a>0) = \frac{sp\pi[x+(1-x)\ (1-p)^{s-1}]}{xsp\pi+(1-x)\ [1-(1-p\pi)^s]}$$

$$P(r, r>1|a>0) = \frac{(1-x)\ \binom{s}{r}p^r\ (1-p)^{s-r}\ [1-(1-\pi)^r]}{xsp\pi+(1-x)\ [1-(1-p\pi)^s]}$$

The Wisconsin sample is based only on multiplex families ($r > 1$), for which the probability is

$$P(r|r>1, a>0) = \frac{\binom{s}{r}p^r\ (1-p)^{s-r}\ [1-(1-\pi)^r]}{1-(1-p\pi)^s-\pi sp(1-p)^{s-1}}$$

Table 4 presents these data for $p = \frac{1}{4}$ and the maximum likelihood estimates of $\pi$ and $x$. The Colchester samples give $x = .881$, showing that most of the cases are nonrecessive sporadics even after mongols and defects of known environmental origin are excluded.

Pooling the information from the *ra* and *sr* tables over both samples, we have the vector of scores

$$U = (U_p,\ U_x,\ U_\pi) = (-53.499, .002, -.001)$$

and the information matrix

$$K = \begin{bmatrix} K_{pp} & K_{px} & K_{p\pi} \\ & K_{xx} & K_{x\pi} \\ & & K_{\pi\pi} \end{bmatrix} = \begin{bmatrix} 751.57 & -213.02 & -60.50 \\ & 1641.16 & 136.09 \\ & & 458.88 \end{bmatrix}$$

The null hypothesis that $p = \frac{1}{4}$ is tested by the square of $U_p$ times the first element of the inverse of the $K$ matrix, or $\chi^2_{[1]} = 3.98$, which is barely significant. The estimate of the segregation frequency from these data is $p = .176 \pm .037$. It would be surprising if differential mortality before the age of diagnosis and perhaps incomplete penetrance did not reduce the segregation frequency below its theoretical value of .25. However, the significance of the discrepancy is so borderline that we shall assume $p = .25$ in what follows. (The exact value of $p$ does not greatly influence our calculations.) Using the Colchester data alone, the standard error of $x$ is

TABLE 5. THE SEX OF AFFECTED

| Source | Males | Females | Total |
|---|---|---|---|
| Simplex, Colchester | 216 | 138 | 354 |
| Multiplex, probands, Colchester | 14 | 11 | 25 |
| Multiplex, secondary cases, Colchester | 10 | 15 | 25 |
| Multiplex, probands, Wisconsin | 55 | 26 | 81 |
| Multiplex, secondary cases, Wisconsin | 16 | 10 | 26 |
| Total probands | 285 | 175 | 460 |
| Total secondary cases | 26 | 25 | 51 |
| Total | 311 | 200 | 511 |

$$\frac{1}{\sqrt{K_{xx}-(K_{x\pi})^2/K_{\pi\pi}}} = 0.26$$

on the hypothesis that $p = \frac{1}{4}$.

One curious feature of the data is the excess of affected males (Table 5). This is highly significant in both the Colchester and Wisconsin samples and for both isolated cases (simplex families), which are largely nonrecessive, and familial cases (multiplex families), which are largely recessive. Therefore male excess cannot be due solely either to sex linkage or to increased susceptibility of males to trauma or infection. Heterogeneity between the sex ratio of probands and secondary cases is not significant, but secondary cases show no disturbance in sex ratio. The simplest hypothesis to fit these facts is that the disturbance in sex ratio is largely due to selective institutionalization of affected males because they are more difficult to manage in the home than affected females, and, indeed, Penrose (1949, p. 49) reported an excess of females among noninstitutionalized cases. If this hypothesis is correct, complete ascertainment of affected persons would reveal only a slight excess of males in multiplex families due to a small proportion of sex-linked cases. However, our data do not rule out an inherently greater susceptibility of males to all types of severe mental defect.

## PREVALENCE

Barrai *et al.* (1965) defined prevalence ($n$) as the number of cases of a trait existing in a given area at a given time. For the Colchester data, obtained under incomplete selection, the prevalence is

$$n = A/\pi = 1478$$

where $A = 379$ is the number of probands. We are especially interested in the high-risk cases, for which

$$n = (1-x)\,A/\pi = 176$$

Since the population is 2,000,000, the frequency of high-risk cases per million of the general population is 88, with standard error

$$\frac{1}{2}\sqrt{\partial K^{-1}\,\partial'}$$

where $\partial$ is the vector of partial derivatives of $n$,

$$\partial = (-A/\pi, -(1-x)A/..^2) = (-1478, -687)$$

and $K^{-1}$ is the inverse of the information matrix for $x$ and $\pi$. We find

$$K^{-1} = \begin{bmatrix} 6.73 & -7.63 \\ & 91.97 \end{bmatrix} \times 10^{-4}$$

and

$$\frac{1}{2}\sqrt{\partial K^{-1}\partial'} = 33$$

The Wisconsin sample presents a slightly more complex problem, since isolated cases were not ascertained. To estimate $\theta$, the ratio of probands in multiplex families to all probands, we assume a negative binomial distribution of family size and estimate its parameters $m$ and $z$ from the probability (Barrai *et al.*, 1965, equation 7)

$$P(s|a>0, r>1) = \frac{\binom{z}{s} m^s (1-m)^{z-s}\{1-(1-p\pi)^s - sp\pi(1-p)^{s-1}\}}{1-(1-mp\pi)^z - mp\pi z(1-mp)^{z-1}}$$

The maximum likelihood estimates are $m = -1.594$, $z = -0.379$, and Table 4 shows that they provide a good fit to the observed distribution of family size, with $\chi^2_{[11]} = 12.26$ by the usual formula and 12.82 by the likelihood ratio test. The prevalence estimate for high-risk cases is

$$n = A/\pi\theta = 310$$

with standard error $\sigma_n = 77$ (Barrai *et al.*, 1965, equation 5). Since the population is four million, this corresponds to a frequency of 78 ± 19 per million of the general population, in close agreement with the Colchester data.

A check on these estimates which does not depend on $p$, $\pi$, or $\theta$ may be made as follows. Lewis (1929) estimated that the prevalence of severe mental defect in the eastern counties of England was 2,020 per million. The Colchester survey had 379 probands among 652 severe defectives, the remainder being excluded as mongols or exogenous. From these data the frequency of high-risk defect per million of the English population is

$$(1-x)\ (379)\ (2020)/652 = 140$$

However, the method of ascertainment was so thorough as probably to include many uncertifiable or precertifiable cases, and indeed, the Royal Commission (1908) found only 1,104 severe defectives per million of a multiply ascertained English population, corresponding to only 76 high-risk cases. Our estimates fall within this range, although closer to the Royal Commission estimate.

For further analysis we need to know the incidence of severe high-risk mental defect among births to normal parents. This depends on two additional parameters:

$j$, the proportion of matings in which both parents are normal (I.Q. >85). Assuming I.Q. to be normally distributed with mean 100, standard

deviation 15, and marital correlation .55 (Penrose, 1949, p. 117), we determine from a table of the bivariate normal distribution (Pearson, 1930) that $j = .75$.

$v$, the probability that the condition is diagnosed and the patient does not die, distributed over the ages of the general population. Tredgold, Tredgold, and Soddy (1956, p. 122) quoted statistics from a mental hospital without an age limit, in which most of the patients were under ten years of age. The annual mortality of aments was 81 per 1,000 inmates, compared with 25 per 1,000 in the general population, from which we estimate $v = .32$. An admissions and mortality table constructed from U. S. statistics (Dunn, 1941) gives $v = .28$. We shall use the average value, $v = .30$.

The incidence of severe high-risk mental defect per million births to normal × normal matings is $I = n/jv$, which is 344 ± 86 for Wisconsin and 391 ± 145 for Colchester.

## CONSANGUINITY ANALYSIS

If high-risk cases are partly recessive and low-risk cases are not, the frequency of sporadic cases may be estimated from consanguinity data independently of segregation analysis. Chung, Robison, and Morton (1959) gave the requisite formulae, $F_I = y\alpha + (1-y)\ F_F$, which by rearrangement gives $y = (F_F - F_I)/(F_F - \alpha)$, and $x = cy$, where $y$ is the proportion of isolated cases that are sporadic, $c$ is the proportion of probands in simplex families, $F_I$ is the mean inbreeding coefficient of isolated probands, $F_F$ the mean inbreeding coefficient of familial probands, and $\alpha$ the mean inbreeding coefficient in the general population. For Colchester (Table 6) we have $c = 354/379$, $F_F = 12500 \times 10^{-6}$, $F_I = 1015 \times 10^{-6}$, $\alpha = 406 \times 10^{-6}$; hence $x = .887 \pm .046$. This is slightly larger than the estimate from segregation analysis. Two similar traits, deaf-mutism and limb-girdle muscular dystrophy (Table 7), gave the same result (Chung, Robison, and Morton, 1959; Morton and Chung, 1959), which is fatal to Neel's (1958) phenodeviant hypothesis, according to which sporadic cases are to a considerable degree due to multiple homozygosity. On this hypothesis, sporadic cases should have an inbreeding coefficient greater than $\alpha$, and so $F_I$ would be greater than $y\alpha + (1-y)F_F$. Then $F_F - F_I$ and therefore $x$ should be underestimated by comparison with segregation analysis, which makes no assumption regarding inbreeding coefficients. Since in none of the three conditions so far studied has the inbreeding coefficient of sporadic cases been elevated, the phenodeviant hypothesis must either be rejected or modified into an untestable form by the *ad hoc* assumption that the recessive genes concerned are all so common that no inbreeding effect is to be expected, an unnecessarily complicated mechanism to entertain in the absence of any clear indication of a genetic component in sporadic cases. It seems likely that multiple homozygosity can be an important cause of morbidity only at high levels of inbreeding rarely attained by human populations.

It is possible to estimate the total gene frequency for a trait due partly to nonrecessive mechanisms and partly to an arbitrary number of nonsynergistic

TABLE 6. INBREEDING COEFFICIENTS OF THE WISCONSIN AND COLCHESTER PROBANDS

$B = .190$

| | Wisconsin | | | | Colchester | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $F$ | $m$ | $(F-\alpha) \times 10^6$ | $(A+BF) \times 10^6$ | $(F-\alpha)/(A+BF)$ | Total $m$ | Simplex | Multiplex | $(F-\alpha) \times 10^6$ | $(A+BF) \times 10^6$ | $(F-\alpha)/(A+BF)$ |
| 0 | 78 | −48 | 335 | −.143284 | 367 | 348 | 19 | −406 | 3207 | −.126598 |
| 1/64 | 3 | 15577 | 3304 | 4.714588 | 3 | 1 | 2 | 15219 | 6176 | 2.464216 |
| 1/32 | — | — | — | — | 2 | 1 | 1 | 30844 | 9145 | 3.372772 |
| 1/16 | — | — | — | — | 5 | 3 | 2 | 62094 | 15082 | 4.117093 |
| 1/8 | — | — | — | — | 2 | 1 | 1 | 124594 | 26957 | 4.621953 |
| Total | 81 | — | — | — | 379 | 354 | 25 | — | | |
| mean $F$ | 579 $\times 10^{-6}$ | | | | 1773 $\times 10^{-6}$ | 1015 $\times 10^{-6}$ | 12500 $\times 10^{-6}$ | | | |

$U = (335/344)(2.967612) = 2.8900$
$K = (.948359)(68.283360) = 64.757$

$U = (3207/3284)(-2.493903) = -2.4354$
$K = (.953656)(174.327346) = 166.248$

$\Sigma U = .4546$
$\Sigma K = 231.005$
$B = .190 + \Sigma U/\Sigma K = .192$
$\sigma_B = 1\sqrt{K} = .066$

TABLE 7. ESTIMATES OF POPULATION PARAMETERS

| Parameter | Definition | Estimates | | |
|---|---|---|---|---|
| | | Severe mental defect | Deaf-mutism | Limb-Girdle muscular dystrophy |
| $x$ | The proportion of sporadic cases, estimated from segregation analysis. | .881 | .258 | .413 |
| $x_F$ | The proportion of sporadic cases, estimated from the inbreeding coefficients. | .887 | .342 | .500 |
| $A$ | The incidence at birth of severe high-risk defect in a randomly mating population. $A = X + \Sigma q^2 t$, where $X$ is the contribution of nonrecessive mechanisms and $\Sigma q^2 t$ is the expressed load due to autosomal recessive genes with frequencies $q$. | $324 \times 10^{-6}$ | $180 \times 10^{-6}$ | $33 \times 10^{-6}$ |
| $B$ | The genetic load expressed as severe defect. $B \doteq \Sigma qt$, the total frequency of contributory autosomal recessive genes per gamete. | .192 | .080 | .008 |
| $B/A$ | The consanguinity ratio. | 593 | 444 | 244 |
| $h$ | The penetrance of usually recessive genes for severe mental defect in heterozygotes $\leq (I - A - \alpha B)/2B$. | .0075 | .0006 | .0017 |
| $Q$ | The mean gene frequency per contributory locus. $Q \leq A/B$. | .0017 | .0022 | .0041 |
| $k$ | The number of contributory loci per gamete. $k \geq B^2/A$. | 114 | 36 | 2 |
| $U$ | The mutation rate to such genes per gamete $= .01sB$, assuming $s \rightarrow 1$. | $192 \times 10^{-5}$ | $80 \times 10^{-5}$ | $8 \times 10^{-5}$ |
| $u$ | The mean mutation rate per contributory locus $\leq .01sQ$. | $1.7 \times 10^{-5}$ | $2.2 \times 10^{-5}$ | $4.1 \times 10^{-5}$ |

recessive genes (Chung, Robison, and Morton, 1959; Morton, 1960). We suppose that the high-risk mental defect whose incidence we have estimated is a mixture of autosomal recessive homozygotes, heteroploid segregations from translocation heterozygotes, sex-linked recessives, and perhaps other genetic and nongenetic mechanisms. Let $X$ denote the contribution of all factors except autosomal recessives. Then the incidence of cases from normal parents is

$$I = 1 - \Sigma c_i e^{-(A+BF_i)} = A+B\alpha$$

where

$$A = X + \Sigma q^2 t$$
$$B = \Sigma qt - \Sigma q^2 t,$$

and $c_i$ is the frequency of the inbreeding coefficient $F_i$ in the general population, $\alpha = \Sigma c_i F_i$, $q$ is a recessive gene frequency, and $t$ is the penetrance in homozygotes. The quantity $\Sigma qt$ is called the total genetic load measured in detrimental equivalents per gamete.

The mean inbreeding coefficient of ascertained abnormals (probands) is

$$\overline{F} = \Sigma c_i F_i (A+BF_i)/\Sigma c_i (A+BF \qquad \{A\alpha + B(\sigma^2 + \alpha^2)\}/I,$$

where $\sigma^2 = \Sigma c_i F_i^2 - \alpha^2$ is the variance of the inbreeding coefficient in the general population. Solving the equations in $I$ and $\overline{F}$, we have

$$A = I - B\alpha$$
$$B = I(\overline{F} - \alpha)/\sigma^2$$

with standard errors

$$\sigma_A = \alpha\sigma_B$$
$$\sigma_B = I\sigma_{\overline{F}}/\sigma^2$$

These estimates provide initial values for the fully efficient maximum likelihood solution (Morton, 1960)

$$U = (A/I)\Sigma m_i (F_i - \alpha)/(A+BF_i)$$
$$K = (A/I)^2 \Sigma m_i \{(F_i - \alpha)/(A+BF_i)\}^2$$
$$B^* = B + U/K$$
$$A^* = I - B^*\alpha$$

where $m_i$ is the number of probands with $F_i$, $U$ is the maximum likelihood score for $B$, $K$ is its variance, and $A^*$, $B^*$ denote improved estimates from $A$, $B$.

Table 6 gives these calculations. For Wisconsin high-risk cases $I = 344 \times 10^{-6}$, $\overline{F} = 579 \times 10^{-6}$, $\alpha = 48 \times 10^{-6}$, $\sigma^2 = 1.6 \times 10^{-6}$; and so $B = .144$ and $A = 339 \times 10^{-6}$.

For Colchester high-risk and low-risk cases, $I = 1478/2jv$ per million, or $3284 \times 10^{-6}$, of which a proportion $1 - x = 2893 \times 10^{-6}$ is sporadic. We take $I = 3284 \times 10^{-6}$, $\overline{F} = 1773 \times 10^{-6}$, $\alpha = 406 \times 10^{-6}$, $\sigma^2 = 24.8 \times 10^{-6}$; and so $B = .181$ and $A = 3211 \times 10^{-6}$. Deducting sporadic cases, $A$ becomes $318 \times 10^{-6}$.

Very similar results are obtained when isolated cases are excluded from the Colchester data. Then $I = 391 \times 10^{-6}$, $\overline{F} = 12500 \times 10^{-6}$; and so $B =$

.191 and $A = 314 \times 10^{-6}$. Since $B$ does not decrease when isolated cases are excluded, it is clear that only high-risk cases contribute to the genetic load measured by inbreeding.

On the null hypothesis that the genetic loads are the same in Wisconsin and Colchester, we use the mean, $B = .162$, to begin the maximum likelihood iteration whose second cycle is shown in Table 6. The final estimate is $B = .192 \pm .066$, with no significant heterogeneity between the Wisconsin and Colchester samples. The maximum likelihood estimate of the frequency at birth of high-risk cases in a randomly mating population is $A = 335 \times 10^{-6}$ for Wisconsin and $A = 313 \times 10^{-6}$ for Colchester. Since these estimates are so similar, we shall use their mean, $A = 324 \times 10^{-6}$, for the remaining calculations.

## DISCUSSION

Böök (1957) studied the effect of first cousin marriage on all grades of mental retardation (I.Q. < 70). For each cousin family, another family living in the nearest house was selected as a control. Using only marriages in which neither parent was retarded, the genetic load is calculated from these data to be .694 ± .341 detrimental equivalents per gamete expressed as mental retardation. While the standard error is large, comparison of this estimate with our value of .192 ± .066 for severe mental defect suggests that some rare recessive genes act to produce mild retardation, although they are difficult to discriminate because of overlap with the polygenes and environmental factors causing the lower part of the continuous, nearly normal distribution of intelligence.

We have shown, after exclusion of mongols and a clearly exogenous group, that cases of severe mental defect are of two types: a *high-risk* type, with a recurrence risk in sibs approximating ¼ and a marked increase in frequency with parental consanguinity, and a *sporadic* type, with a much smaller recurrence risk in sibs and no increase in frequency with consanguinity. Most but not all isolated cases belong to the sporadic group, which comprises 88% of all cases in the general population.

To account for either type, a variety of hypotheses may be entertained, of which the most plausible and popular are the following: (1) unrecognized exogenous factors, (2) chromosomal aberrations, (3) heterozygous expression of usually recessive genes, (4) quasi-continuous variation (Edwards, 1960), (5) phenodeviants (Neel, 1958), (6) rare recessive oligogenes maintained by heterosis, (7) rare recessive oligogenes maintained by mutation.

There is no evidence against the hypothesis that unrecognized exogenous factors (trauma, infection, etc.) account for a large fraction of sporadic cases, and, indeed, the only admissible evidence would be the demonstration of a specific mode of inheritance. However, it is unlikely that exogenous factors account for more than a small proportion of the familial cases on which the estimate of the high-risk frequency is based. In the first place, the recurrence risk in sibs is of the order of ¼, and most exogenous factors must have a lower recurrence risk. Secondly, the pronounced effect of parental consanguinity after exclusion of retarded parents argues for a large genetic com-

ponent in high-risk cases. The magnitude of this consanguinity effect is conveniently measured by the ratio of the inbred genetic load ($B$) to the total load, genetic and unrecognized exogenous, expressed in a randomly mating population ($A$). This ratio is .192/.000324 = 593, which is as high as would be expected if all of the expressed load were due to rare recessive genes (Crow, 1958). Thus the contribution of unrecognized exogenous factors to the high-risk group must be small.

The marked consanguinity effect also argues against chromosomal aberrations as a major cause of the high-risk group. Chromosomal anomalies (especially deletions and duplications) may be a more important cause of sporadic cases, but simple aneuploidy has been ruled out in the great majority of sporadic cases, excluding mongolism (Ferguson-Smith, 1961).

Heterozygous expression of usually recessive genes may account for a proportion of sporadic cases. If all sporadic cases were due to this cause, the penetrance in heterozygotes would be the incidence of sporadic cases divided by the frequency of heterozygotes, which is $(I - A - \alpha B)/2B = .0075$. This is too small a penetrance to be excluded. However, both the high recurrence risk in sibs and the marked consanguinity effect argue against heterozygous expression of usually recessive genes as a major cause of high-risk cases.

Edwards (1960) considered the recurrence risk in sibships for a threshold trait whose frequency is the tail of a normal distribution. He showed that if $I$ is the incidence in the general population, $\sqrt{I}$ is the segregation frequency in sibs of probands. A further interesting property of this model comes from the effect of inbreeding. If the genes act additively on the primary scale, the phenotypic variance is $\sigma^2(1 + h^2F)$, where $h^2$ is the heritability. By a series expansion of the area in the tail of a normal distribution, the probability of nonaffection is approximately $e^{-(A + BF)}$, where $B/A \doteq h^2 \leqq 1$.

For high-risk cases the square root of the incidence is $\sqrt{A} = .02$, which is much less than the observed segregation frequency of .176 ± .037, and the consanguinity ratio ($B/A = 593$) is far greater than the maximum value of unity expected under quasi-continuous variation. For sporadic cases the square root of the incidence is $\sqrt{I - A - \alpha B} = .05$, which is greater than the mean recurrence risk of $(1-x)p = .02$. If the recurrence risk for sporadic cases were as much as .05, the segregation frequency for high-risk cases would be diluted from .25 to $x(.05) + (1-x)(.25) = .07$, which is much less than was observed. There is no evidence of any consanguinity effect on the incidence of sporadic cases. Finally, if the primary scale were the intelligence quotient with mean 100 and standard deviation 15, the incidence of severe mental defect would be the probability of a normal deviate greater than 50/15 = 3.33, which is .004, less than one-eighth the incidence. Thus only a minority of cases of severe mental defect, either high-risk or sporadic, can be due to quasi-continuous variation in the sense of Edwards.

Neel (1958) embraced the phenodeviant hypothesis of Lerner (1954), according to which "a significant fraction of human congenital defect" (Neel, 1958, p. 435) represents the "sporadic occurrence of abnormal morphological

deviants [caused] by the intrinsic properties of multigenic Mendelian inheritance, due to which a certain percentage of individuals of every generation falls below the threshold of the obligate proportion of loci needed in a heterozygous state to ensure normal development. The biology of these characters (some homoeotics in Drosophila, skeletal and other abnormalities in rodents, crooked toes in chickens, and many other traits) is the biology of inbreeding degeneration" (Lerner, 1954, p. 6).

This hypothesis has not been formulated quantitatively by its proponents, and attempts by Morton (1960) to do so were unacceptable to them (Lerner, 1961). The following properties were attributed to phenodeviants by Neel: (1) clustering in a type-specific fashion in sibships, (2) low recurrence risk in sibs and other close relatives, (3) low concordance in monozygotic twins, (4) variation in incidence among populations, (5) reduction in frequency on outcrossing, (6) unequal sex incidence, (7) maternal age, parity, and environmental effects on incidence, (8) occurrence of multiple defects in the same individual, (9) advantageous effects of the responsible polygenes in other combinations.

Lerner (1954) emphasized related but somewhat different properties: (10) marked increase in frequency with artificial selection, (11) greater environmental variance than normals, (12) increase of expressivity with incidence, (13) no precise identification of the loci involved, (14) marked nonlinear increase with inbreeding.

Apart from properties 5, 9, and 14, these attributes do not clearly distinguish a phenodeviant from a conventional polygenic trait with low heritability. Property (5) was tested for various types of mortality and morbidity by Morton (1962) on interracial crosses in Hawaii, with negative results. Property (9) has never been tested in any organism. Therefore property (14), the marked nonlinear increase with inbreeding, is the only operational definition of a phenodeviant in human material and the best operational definition in experimental data. It is critical evidence against the phenodeviant hypothesis for sporadic cases that they show no inbreeding effect, the estimate of the proportion of sporadic cases being no less from the inbreeding coefficient than from segregation analysis. The same result holds for limb-girdle muscular dystrophy (Morton and Chung, 1959) and deaf-mutism (Chung, Robison, and Morton, 1959), the two other complex defects so far tested (Table 7). The high recurrence risk rules out phenodeviants as an explanation of high-risk cases.

We conclude that sporadic cases of severe mental defect may be due to a mixture of unrecognized exogenous factors, chromosomal aberrations (duplications and deficiencies), or heterozygous expression of usually recessive genes, in unspecified proportions, but quasi-continuous variation and phenodeviants are not major causes. For high-risk cases, on the other hand, all of these mechanisms may be ruled out as principal contributors, and we are left with recessive oligogenes maintained by heterosis or mutation.

Regardless of the mechanism maintaining these oligogenes, the genetic loads for high-risk cases are, as we have seen,

$$A = X + \Sigma q^2 t = 324 \times 10^{-6}$$
$$B = \Sigma qt - \Sigma q^2 = .192$$

where $q$ is a recessive gene frequency, $t$ is the penetrance in homozygotes, and the summation is over all contributory loci. The penetrance lies between 1 (if $p = \frac{1}{4}$) and .70 (if the observed reduction in $p$ is due to incomplete penetrance rather than to admixture of nonrecessive cases or death of affected cases before diagnosis). The mean gene frequency per contributory locus is $Q \leq A/B = .0017 \pm .0006$ (Morton and Chung, 1959). The number of contributory loci is $k \geq B^2/A = 114 \pm 78$. The standard error is large, and a confidence interval for $k$ is only approximate. Since the interval is positively skewed, its estimate is improved by taking $\sqrt{k} \pm 1.645\ \sigma_B/\sqrt{A} = 10.67 \pm 6.03$ as the 90% confidence interval for $k$, which gives a lower limit of 22 loci and an upper limit of 279. Imprecise as these estimates are, they suggest that many recessive entities in severe mental defect remain to be characterized.

To make further use of these data, we must know whether these genes are maintained largely by mutation or by heterozygote advantage. If heterozygote advantage were the major mechanism, we would expect a large fraction of the balanced genes to be detrimental in homozygotes, and only a minority would be recessive lethals. We would therefore anticipate a value of $Q$ much greater than its observed value of .0017, and $B/A$ would be much less than its observed value of 593 (Crow, 1958). Morton (1960) showed that at equilibrium the panmictic load due to a heterotic locus is greater than the product of any gene frequency ($q$) by the selection against the homozygote ($s$). Since $s$ approaches 1 for severe mental defect (Penrose, 1949, p. 51), the loci involved would contribute $B = .192$ to the panmictic segregation load $A$, signifying the elimination of nearly one zygote out of five by the relatively small number of genes causing severe mental defect! Even the most enthusiastic proponent of segregation loads does not suppose that the typical recessive lethal is maintained by heterozygote advantage, and we have shown that in the high-risk group, which is responsible for all of the inbreeding effect, we are dealing with recessive lethals.

The consequences are much more consistent with available evidence on a mutational hypothesis, which predicts that a large fraction of the load should be due to lethals (Greenberg and Crow, 1960; Friedman, 1963). Instead of imposing a panmictic load approximating $B = .192$, as the segregation hypothesis would require, the mutational panmictic load per gamete and the mutation rate is $B(\alpha + Q + h)$, where $\alpha$ is the inbreeding coefficient under which the population reached equilibrium, $Q$ is the mean gene frequency at contributory loci, and $h$ is the degree of dominance or penetrance in heterozygotes. The best estimate of $\alpha$ is about .006 (Neel *et al.*, 1949), $Q = .0017$, and $h$ is less than .0075 if due to penetrance in heterozygotes. Estimates of $h$ in man (Table 7) are consistently below the value of .02 generally accepted for Drosophila (Crow, 1958). This is to be expected, since the selection in Drosophila is due in part to larval competition which has no parallel in man. Taking $\alpha + Q + h = .01$, we estimate the total mutation rate to be $U = 192 \times$

$10^{-5}$/gamete/generation and the rate per locus to be $u = 1.7 \times 10^{-5}$/locus/generation, in good agreement with other evidence (Penrose, 1961).

SUMMARY

Two samples of patients with severe mental defect from normal parents, consisting of multiplex families from Wisconsin and both simplex and multiplex families from Colchester, demonstrate that multiplex families are associated with a high inbreeding coefficient and a segregation frequency (recurrence risk) close to one-quarter. The Colchester sample shows further that sporadic cases do not have an elevated inbreeding coefficient. Genetic load theory gives the following estimates for high-risk cases: the load expressed on a randomly mating population, $A = 324 \times 10^{-6}$; the inbred load, $B = .192$; the mean gene frequency per contributory locus, $Q = .0017$; the number of contributory loci, $k = 114$. Neel's phenodeviant theory is excluded by the normal consanguinity of sporadic cases, and Edward's theory of quasi-continuous variation is ruled out for high-risk cases both by the pronounced inbreeding response and the high segregation frequency relative to the population incidence. Not more than a small minority of sporadic cases can be due to quasi-continuous variation if the intelligence quotient is the primary scale. Only genetic load theory predicts the high segregation frequency and inbreeding response in high-risk families, and the evidence is strong that this load is not maintained by heterozygote advantage but is mutational at a rate of about $192 \times 10^{-5}$/gamete/generation, or $1.7 \times 10^{-5}$/locus/generation.

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