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# The Incidence of Genetic Disease in a University Hospital Population

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## INTRODUCTION

With the increase of laboratory and clinical knowledge in genetics, interest in the field of medical genetics and genetically determined disease has grown rapidly in recent years. It has been estimated that not less than 4% of all live births have a genetically determined condition, and at least 1% of all infants have a major chromosomal abnormality [1]. A more specific measure of the impact of genetic disorders is their role in mortality and morbidity. Studies of children's hospitals which are referral in nature show a high percentage of genetic diseases among the causes of death [2, 3]. As for morbidity, Stevenson found in Ireland that 26% of all institutional beds, 6% of all consultations with general practitioners, and 8% of those with specialists were for patients with genetically determined disease [4]. A study in the United States of all admission diagnoses to a pediatrics service in a university hospital showed that 7.1% of all admissions were for diseases of clearly defined genetic origin and 31.5% were possibly gene influenced (B. Childs, personal communication, 1970). A comparable study of admissions to an internal medicine service showed corresponding figures of 1.5% and 12% for adults (A. G. Bearn, personal communication, 1970).

These surveys indicate that genetic disease is a significant cause of death, institutionalization, and admission to the pediatric and medical services of university hospitals. This study was undertaken to better document the incidence of genetically determined disease at a university hospital using a thorough review of 800 hospital records at the Massachusetts General Hospital for primary and secondary diagnoses and family histories. We have classified diseases not only by genetic and nongenetic etiology, but have also defined the mode of inheritance of the genetic disorders. Since this hospital is typical of others in which physicians are trained, these data indicate the types of genetic disorders which physicians should be able to assess and counsel.

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## METHODS

A total of 800 records were chosen, 200 from each of four groups: pediatric inpatients, pediatric medical clinic, adult inpatients, and adult medical clinic. Because hospital admissions vary by season, day of week, and time of day, these records were randomized by choosing 20 days throughout the year 1970, including weekends and holidays. In the pediatric groups the records of all patients admitted on the selected days were reviewed; and in the adult population, every sixth patient was taken from an alphabetical list. Both inpatient groups included medical and surgical patients. The restriction of outpatient records to the general medical clinics avoided the bias that would be introduced if individuals seen in special clinics, such as genetics, cardiology, allergy, and endocrinology, were included. Approximately 95% of all requested records were obtained, and the missing 5%, based on the admitting diagnoses, were not significantly different.

All records obtained were reviewed by one observer and the following information was extracted: (1) diagnosis directly responsible for admission (primary diagnosis); (2) all other coexisting conditions and previous medical history (secondary diagnoses); (3) family history; and (4) socioeconomic data regarding race, religion, method of payment, home town, and source of referral to hospital.

The diagnoses listed in the record were accepted as accurate. An additional source of bias was in the evaluation of secondary diagnoses and family histories, both of which are dependent not only on the memory of the patient but on the interest of the interviewer in obtaining them. These factors probably make the figures for secondary diagnoses and positive family histories minimal estimates.

A classification system was developed to divide diagnoses into categories according to the genetic content of the diseases: single-gene, chromosomal, polygenic, probably genetic, developmental, unknown, and environmental. Although it is realized that such a classification is necessarily subjective, every attempt was made to validate all categorizations through the literature [5–7]. If there was doubt about the category to which a disease belonged, it was placed in the category of the least genetic content, thereby causing a downward bias. In addition, this classification does not consider such aspects as the inheritance of susceptibility to infections and malignancies.

The diseases of adult patients were only classified in the single-gene and chromosomal categories because of the impossibility of defining the etiology and role of genetics in such diseases as hypertension, arthritis, and arteriosclerotic heart disease. Although for many of these diseases a definite genetic influence can be hypothesized [7], there is not sufficient evidence to enable us to classify our affected adults with these common diseases in categories of inheritance patterns.

Patients were divided into socioeconomic groups based on four categories: (1) private or service patients; (2) method of payment; (3) median income of home town; and (4) source of referral to hospital. Hence a private patient who had insurance, was referred by a private physician to the hospital, and came from a town with median income above the state median income would be in the upper socioeconomic group.

Socioeconomic data and information on length of stay and age of patients in the four groups (pediatric inpatient and outpatient and adult inpatient and outpatient) were checked against hospital data for all patients in those groups to determine whether the samples represented the populations from which they were drawn. There were no significant differences.

## RESULTS

### *Single-Gene Disorders*

Single-gene disorders were defined as those which show a Mendelian pattern of segregation with dominant and recessive characteristics. A total of 20 single-gene

conditions were noted in the records screened (tables 1 and 2). Of these, 10 or 50% were in the children's inpatient group and 75% of the total were in children. Furthermore, only among inpatient pediatric patients were single-gene diseases more apt to have been the primary cause for hospitalization. Half of these children had a positive family history for the same disease.

TABLE 1

PRIMARY AND SECONDARY DIAGNOSES

| Group and Disease Etiology | No. Primary Diagnoses | Percentage of Total | No. Secondary Diagnoses | Total Primary and Secondary Diagnoses | Rate per 100 Patients* |
|---|---|---|---|---|---|
| Pediatric inpatient: | | | | | |
| Genetic | 34 | 17.0 | 10 | 44 | 22.0 |
| Single-gene | 8 | 4.0 | 2 | 10 | 5.0 |
| Chromosomal | 0 | ... | 0 | 0 | 0.0 |
| Polygenic | 26 | 13.0 | 7 | 33 | 16.5 |
| Probably genetic | 9 | 4.5 | 13 | 22 | 11.5 |
| Developmental | 55 | 27.5 | 18 | 73 | 36.5 |
| Unknown | 10 | 5.0 | 0 | 10 | 5.0 |
| Environmental | 92 | 46.0 | ... | ... | ... |
| Pediatric outpatient: | | | | | |
| Genetic | 18 | 9.0 | 16 | 34 | 17.0 |
| Single-gene | 1 | 0.5 | 4 | 5 | 2.5 |
| Chromosomal | 0 | ... | 0 | ... | 0.0 |
| Polygenic | 17 | 8.5 | 12 | 29 | 14.5 |
| Probably genetic | 7 | 3.5 | 18 | 25 | 12.5 |
| Developmental | 5 | 2.5 | 21 | 26 | 13.0 |
| Unknown | 4 | 2.0 | 0 | 4 | 2.0 |
| Environmental | 166 | 83.0 | ... | ... | ... |
| Adult inpatient: | | | | | |
| Single-gene | 1 | 0.5 | 2 | 3 | 1.5 |
| Chromosomal | 0 | ... | 0 | ... | 0.0 |
| Adult outpatient: | | | | | |
| Single-gene | 0 | ... | 2 | 2 | 1.0 |
| Chromosomal | 0 | ... | 1 | 1 | 0.5 |

* Total primary and secondary diagnoses per 100 patients.

The records from the children's medical clinic included five single-gene defects from the 200 records screened, although only one of these, Marfan's syndrome, was the actual reason for the visit. Three of the four secondary diagnoses had a positive family history. However, the family history of these genetic diseases was the reason the child was evaluated and found to have this genetic disorder.

In contrast to the pediatric patients, only three single-gene disorders were found in the adult inpatient population. One of these, Alzheimer's disease, was a primary cause for admission and one, familial hyperlipemia, had a positive family history.

Comparable statistics were obtained for the adult medical clinic where two single-gene defects were found, neither of which was the primary reason for the clinic visit. For one, the Pelger-Huet anomaly of granulocyte nucleus morphology, there was a family history of the same abnormality.

TABLE 2

SINGLE-GENE DISORDERS

| Group and Diagnosis | Primary Diagnosis | Secondary Diagnosis |
|---|---|---|
| Pediatric inpatient: | | |
| Cystic fibrosis | + | ... |
| Adrenogenital syndrome | + | ... |
| Thalassemia major | + | ... |
| Thalassemia minor | + | ... |
| Erythroblastosis fetalis | + | ... |
| Isolated growth hormone deficiency | + | ... |
| Phenylketonuria | + | ... |
| Myotonic dystrophy | + | ... |
| Lawrence-Moon syndrome | ... | + |
| Hemophilia | ... | + |
| Pediatric outpatient: | | |
| Marfan's syndrome | + | ... |
| Sickle-cell trait | ... | + |
| High myopic astigmatism | ... | + |
| Colorblindness | ... | + |
| Familial hemolytic anemia | ... | + |
| Adult inpatient: | | |
| Alzheimer's disease | + | ... |
| Lactase deficiency | ... | + |
| Familial hyperlipemia | ... | + |
| Adult outpatient: | | |
| Alzheimer's disease | ... | + |
| Pelger-Huet anomaly | ... | + |

*Chromosomal Abnormalities*

Only one chromosomal abnormality, Klinefelter's syndrome (47,XXY), was found in the total sample, and this was a secondary diagnosis on an adult inpatient.

*Polygenic Diseases*

Polygenic disorders are considered to be due to the additive effect of several minor gene abnormalities [8]. In general, the recurrence risk among siblings and offspring of the affected individuals is about 5%. Common examples are several of the isolated major congenital malformations [7, 8], diabetes mellitus [9], asthma [10], and psoriasis [11]. In both pediatric inpatients and outpatients, polygenic diseases accounted for the largest proportion of specifically genetic disorders (table 1). A total of 26 polygenic disorders which were the primary cause for admission were found in the pediatric inpatient records (table 3). This accounted for 13% of the total admissions for the population. In addition, seven secondary diagnoses were recorded, making the rate of polygenic disorders 16.5 per 100 pediatric inpatients. Approximately 28% of the patients had positive family histories for the same disorders.

In the pediatric outpatient population, 17 or 8.5% of the primary diagnoses were

TABLE 3

POLYGENIC DISORDERS

| DISORDER | GROUP | |
|---|---|---|
| | Pediatric Inpatient | Pediatric Outpatient |
| Central nervous system: | | |
| Myelomeningocele | 1 | 1 |
| Encephalocele | 1 | ... |
| Cardiac: | | |
| Congenital heart disease | 12 (2) | (1) |
| Gastrointestinal: | | |
| Pyloric stenosis | 3 (1) | ... |
| Duodenal ulcer | ... | (1) |
| Musculoskeletal: | | |
| Congenital dislocated hip | 1 (1) | ... |
| Other: | | |
| Asthma | 4 (2) | 4 (1) |
| Psoriasis | 1 | 1 |
| Eczema | (1) | 2 (7) |
| Cleft palate | 1 | (1) |
| Diabetes mellitus | 2 | 4 |
| Allergies | ... | 4 (1) |
| Rheumatoid arthritis | ... | 1 |

NOTE.—Parentheses indicate number of secondary diagnoses in each category.

found to be polygenic in etiology. An additional 12 patients had secondary diagnoses, for a total of 29 polygenic disorders in the sample population. This was a rate of 14.5 per 100 patients. Nearly 58% of this group had a family history of the same disorder. The large number of positive family histories in the outpatient group is mainly a result of the greater proportion of patients with asthma, eczema, and allergies in the group.

*Probably Genetic*

We classified as probably genetic those disorders that occur more often than randomly expected in families of affected patients and for which a genetic etiology has been postulated (table 4). These include, for example, Hirschsprung's disease [12], migraine headache [13], and benign familial macrocephaly [14]. In the pediatric group, 11.5% of inpatients and 12.5% of outpatients had either primary or secondary diagnoses that were probably genetic. Family histories were positive in one-third of the inpatients and 22% of the outpatient pediatric populations.

*Developmental Anomalies*

Disorders arising from abnormal development in utero were classified as developmental (table 4). Except for environmental causes, they were the most common

TABLE 4

MISCELLANEOUS DISORDERS

| DISORDER | GROUP: Pediatric Inpatient | GROUP: Pediatric Outpatient |
|---|---|---|
| Probably genetic disorders: | | |
| Seizure disorder | 5 (2) | 2 (10) |
| Migraine headache | 3 (1) | 1 |
| Parry-Romberg syndrome | 1 | ... |
| Febrile seizures | (6) | (3) |
| Benign familial macrocephaly | (2) | ... |
| Hirschsprung's disease | (1) | 1 |
| Dyslexia | ... | 3 (2) |
| Osgood-Schlatter's disease | ... | (3) |
| Developmental anomalies: | | |
| Urinary tract anomalies | 36 (7) | 3 (5) |
| Hernia | 9 (7) | (9) |
| Undescended testes | 3 | (2) |
| Thyroglossal duct cyst | 1 | ... |
| Hemangiomas | 1 | ... |
| Cystic hygroma | 2 | ... |
| Aneurysmal bone cyst | 1 | ... |
| Agenesis left lung | 1 | ... |
| Ectopic anus | 1 | ... |
| Horseshoe kidney | (1) | ... |
| Extrahepatic biliary atresia | (1) | ... |
| Imperforate anus | (1) | ... |
| Ptosis | (1) | (2) |
| Esotropia | ... | 2 (3) |
| Unknown etiology: | | |
| Cerebral palsy | 3 | ... |
| Wilm's tumor | 3 | ... |
| Congenital encephalopathy | 1 | ... |
| Peripheral vasomotor instability | 1 | ... |
| Chrondromalacia | 1 | ... |
| Chronic renal disease | 1 | ... |
| Mental retardation | ... | 2 |
| Detached retina | ... | 1 |
| Urethral stones | ... | 1 |

NOTE.—Parentheses indicate number of secondary diagnoses in each category.

reason for pediatric inpatient admissions, accounting for 27.5% of the primary diagnoses in this group. An additional 9% had developmental anomalies as secondary diagnoses. By contrast, among outpatients only 2.5% and 10.5% of the primary and secondary diagnoses, respectively, were developmental.

The fact that 8% of the patients had a positive family history for the same developmental abnormality suggests that some may have a genetic etiology. However, for some anomalies, such as inguinal hernia, both genetic [15] and viral [16] etiologies have been established with neither having distinguishing characteristics. Other anomalies, such as ureteral reflux [17], may be shown to be polygenic in origin when more data are available; four of the pediatric inpatients had ureteral reflux as a primary diagnosis. This is particularly relevant in our study, in which

67% of the developmental anomalies involved the urinary tract. This reflects the interest of some of the surgical staff members and represents a considerable bias. However, even if all of the patients with genitourinary anomalies were removed, the rate of developmental abnormalities would still be comparable to that of the polygenic disorders.

*Unknown*

Conditions were diagnosed as unknown when it was not possible to assign either a genetic or an environmental etiology to them, or whenever the information given in the record was insufficient. These disorders probably represent a mixed etiology, with some genetic and environmental factors which have not yet been defined. For instance, Wilm's tumor was classified as unknown rather than environmental (as other malignancies were classified) because of positive family histories for Wilm's tumor in two of the cases and previous reports of familial incidence [18].

*Environmental*

The environmental group was comprised of those patients who had infections, accidents, malignancies, or other diagnoses in which an environmental influence was the primary cause for the disease. This group was the largest in both the pediatric inpatient and outpatient populations.

*Socioeconomic Factors*

A large metropolitan university hospital such as the Massachusetts General Hospital draws a heterogeneous group of patients who make different demands on the facilities. We found that inpatients are quite different from outpatients at this hospital. The inpatients, both pediatric and adult, came more often from higher economic backgrounds than the clinic patients and were more often referred to the hospital for care of specialized problems. The majority of the clinic patients were from Boston and used the hospital for their primary medical care.

When the inpatients were separated into three economic levels, these different utilization patterns again became evident. Children from the upper economic group were more frequently referrals from the suburbs and represented 75% of the admissions for single-gene defects. In addition, they had twice as many polygenic diseases in comparison with the lowest economic group. Nearly 43% of the admissions in the upper economic group were for developmental anomalies compared with 22.2% for the middle economic level and 3.8% for the lowest. Admissions for nongenetic reasons accounted for 79.2% of the total for the lower economic group, 46.7% for the middle, and only 28% for the upper. When the number of secondary diagnoses were evaluated, however, no significant difference between the economic classes was found.

*Sex Differences*

A sex difference was evident in that male pediatric inpatients were more often from the surrounding neighborhood than were females. In addition, there were male

excesses in the congenital heart disease, hernia, accident, and infection groups, and a female predominance in the urinary tract anomalies.

## DISCUSSION

Data such as these can only be meaningful when seen in the perspective of the community from which the population is drawn and the hospital which is giving the service. The sample population reflects the different sources from which the patients come, with many outpatients from the predominantly Italian neighborhood in which the hospital is situated and referral inpatients from the wealthier suburbs. In addition, these patients, especially the referral patients, reflect the interests and specialities of various individuals on the staff, particularly with regard to urinary tract anomalies and congenital heart disease. The absence of obstetrical services in the hospital also removes a population in which genetically determined disorders would be highest and probably explains the absence of chromosomal disorders in the sample studied.

The advantages and disadvantages of a retrospective study of hospital records should be noted. Any advantages are relative; it can be stated that a thorough record review does provide more complete data than a listing of either admission or discharge diagnoses. One disadvantage is that the amount of family history recorded in the record varies with the interest of the physician and the knowledge of the historian. In haste, seemingly unrelated aspects of the family history may not be recorded. Another disadvantage is that every patient is not evaluated with equal care. For example, seven of the 20 single-gene disorders (thalassemia minor, sickle-cell trait, high myopic astigmatism, colorblindness, lactase deficiency, familial hyperlipemia, and the Pelger-Huet anomaly) would probably have been found in more individuals if each disorder had been carefully sought in all 800 patients. The prevalence figures found in medical charts reflect a clear bias of both the patients' concerns and the physicians' interests and thoroughness.

This study also indicated two other limitations of reviewing the prevalence of genetic disease in a population. First, there is uncertainty as to whether or how often several common adult diseases (arthritis, emphysema, hypertension, and ischemic heart disease) have a genetic etiology. Second, it is apparent that the definition of disease is very arbitrary. For example, should adult lactase deficiency be considered a disease in view of the associated symptoms of lactose intolerance or should it be considered a human polymorphism [19]? Should thalassemia minor, sickle-cell trait, and the Pelger-Huet anomaly [20] be considered genetic traits, rather than diseases, since it is only when individuals are homozygous for these mutant genes that they have any symptoms or disability?

These data clearly indicate the prominence of genetic diseases in a university hospital population. They also indicate the types of genetic evaluation which the physician should be prepared to carry out. The major impact of genetic disease in both the referral (inpatient) and neighborhood (outpatient) pediatric patients is in polygenic disorders. The primary diagnoses in 11% of 400 children had a polygenic mode of inheritance. The least likely, but probably best known, genetic

disorders are those due to single mutant genes. The highest incidence of these disorders was 4% of the primary diagnoses among pediatric inpatients. This figure is comparable to the incidence of 6.4% reported by Childs at the Johns Hopkins Hospital (B. Childs, personal communication, 1970). We consider the lower 0.5% incidence of single mutant gene disorders in the outpatient pediatric population of the Massachusetts General Hospital a reflection of the nonreferral nature of this group and therefore perhaps a better indicator of actual incidence. The incidence of single-gene disorders as primary and secondary diagnoses among adult inpatients was 1.5%, which is the same percentage reported by Bearn (personal communication, 1970) for adult medical admission at the Cornell Medical Center.

The recognition of the frequency of different types of genetic diseases among their patients is an important initial step for both interns and residents and those responsible for their training. We readily admit that teaching primary physicians to provide genetic counseling is a difficult task. Recent studies on counseling for single mutant gene diseases [21, 22] and polygenic disorders [23] indicate some of the problems. However, in view of the frequency of genetic disorders, it seems more appropriate to improve methods for counseling by all physicians and surgeons, not just those engaged in fulltime work in medical genetics.

SUMMARY

A total of 800 medical records were chosen randomly from each of four groups: pediatric and adult inpatient admissions and pediatric and adult outpatient visits. Each record was evaluated for admitting and discharge diagnosis, all other coexisting conditions, family history, and socioeconomic status. All genetic diagnoses were classified by mode of inheritance. The data indicate that 17% of the pediatric inpatients and 9.0% of the pediatric outpatients had primary diagnoses of genetic origin, the majority being polygenic disorders with a few single-gene or chromosomal anomalies. There was only one single-gene disorder and no chromosomal abnormalities among the 400 primary diagnoses for adults. While many of the common diseases of adults are probably polygenic in origin, classification is not possible at this time. The data obtained indicate the magnitude of the need for physicians to be able to evaluate and counsel genetic diseases, particularly polygenic disorders.

## REFERENCES

1. World Health Organization: Genetic counseling. *WHO Tech Rep Ser* no. 416, 1969
2. Carter CO: Changing patterns in the cause of death at the Hospital for Sick Children. *Great Ormond Street J* 11:65–68, 1956
3. Roberts DF, Chavez J, Court SDM: The genetic component in child mortality. *Arch Dis Child* 45:33–38, 1970
4. Stevenson AC: The load of hereditary defects in human populations. *Radiat Res* 1, suppl.:306–325, 1959
5. McKusick VA: *Mendelian Inheritance in Man,* 3d ed. Baltimore, Johns Hopkins Press, 1971
6. Smith DW: *Recognizable Patterns of Human Malformation.* Philadelphia, Saunders, 1970

7. CARTER CO: Genetics of common disorders. *Brit Med Bull* 25:52–57, 1969
8. SMITH DW, AASE JM: Polygenic inheritance of certain common malformations: evidence and empiric risk data. *J Pediat* 76:653–659, 1970
9. RIMOIN DM: Inheritance in diabetes mellitus. *Med Clin N Amer* 55:807–819, 1971
10. LUBS M-LE: Empiric risks for genetic counseling in families with allergy. *J Pediat* 80:26–31, 1972
11. WATSON W, CANN HM, FARBER EM, NALL NL: The genetics of psoriasis. *Arch Derm* 105:197–207, 1972
12. PASSARGE E: The genetics of Hirschsprung's disease. *New Eng J Med* 276:138–143, 1967
13. REFSUM S: Genetic aspects of migraine, in *Handbook of Clinical Neurology,* vol 5, edited by VINKEN PJ, BRYN GW, Amsterdam, North–Holland, 1968, pp 258–269
14. DE MYER W: Megalencephaly in children. *Neurology* 22:634–643, 1972
15. WEINER B: Congenital inheritance of inguinal hernia. *J Hered* 40:219–220, 1949
16. LANG D: The association of indirect inguinal hernia with congenital cytomegalic inclusion disease. *Pediatrics* 38:913–916, 1966
17. BURGER RH: A theory on the nature of transmission of congenital vesioureteral reflux. *J Urol* 108:249–254, 1972
18. BROWN WT, PURANIK SR, ALTMAN DH, HARDIN HC JR: Wilm's tumor in three successive generations. *Surgery* 72:756–762, 1972
19. WELSH JD, ROHRER V, KNUDSEN KB, PAUSTIAN FF: Isolated lactase deficiency: correlation of laboratory studies and clinical data. *Arch Intern Med* 120:261–269, 1967
20. LANZKOWSKY P, COLUSSI P, MCKENZIE D: Pelger-Huet anomaly of the granulocytes in a Cape Colored family. *J Pediat* 67:826–832, 1965
21. SIBINGA MS, FRIEDMAN CJ: Complexities of parental understanding of phenylketonuria. *Pediatrics* 48:216–224, 1971
22. LEONARD CO, CHASE GA, CHILDS B: Genetic counseling: a consumer's view. *New Eng J Med* 287:433–439, 1972
23. REISS JA, MENASHE VD: Genetic counseling and congenital heart disease. *J Pediat* 80:655–656, 1972