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Genetic Disorders in Children and Young Adults: A Population Study

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Summary

The data base of an ongoing population-based registry with multiple sources of ascertainment was used to estimate the present population load from genetic disease in more than 1 million consecutive live births. It was found that, before approximately age 25 years, ≥53/1,000 live-born individuals can be expected to have diseases with an important genetic component. This total was composed of single-gene disorders (3.6/1,000), consisting of autosomal dominant (1.4/1,000), autosomal recessive (1.7/1,000), and X-linked recessive disorders (0.5/1,000). Chromosomal anomalies accounted for 1.8/1,000, multifactorial disorders (including those present at birth and those of onset before age 25 years) accounted for 46.4/1,000, and cases of genetic etiology in which the precise mechanism was not identified accounted for 1.2/1,000. Previous studies have usually considered *all* congenital anomalies (ICD 740–759) as part of the genetic load, but only those judged to fit into one of the above categories were included in the present study. Data for congenital anomalies are therefore also presented separately, to facilitate comparison with earlier studies. If all congenital anomalies are considered as part of the genetic load, then ≥79/1,000 live-born individuals have been identified as having one or other genetic disorder before approximately age 25 years. These new data represent a better estimate of the genetic load in the population than do previous studies.

Introduction

Better information on the frequency of genetic diseases existing in our population is essential for planning rational health care strategies and for estimating any possible future increase in genetic load from mutagens. In the past, data of this sort have come partly from special surveys and partly from population-based registries. These two kinds of source tend to complement one another. In the past, valuable information has been obtained from the British Columbia Health Surveillance Registry (HSR) for the purposes of genetic risk assessment (Trimble and Doughty 1974; Trimble and Smith 1977), and these data have been quoted in most of the subsequent reports from official committees concerned with the genetic aspects of radiological protection (see, e.g., UNSCEAR 1977; 1982, pp. 543, 546). The HSR has grown substantially since the earlier study, and, in addition, further categorization of the data by etiology is possible. Analysis of the updated data was therefore undertaken to obtain a more accurate estimate of the population load for genetic disease.

The HSR records and classifies cases of handicapping conditions, congenital anomalies, and familial disorders in the population of that province (see Health Surveillance Registry: annual report 1981). The information is provided by a number of government agencies concerned with health, rehabilitation, and human resources and by hospitals, treatment and rehabilitation centers, voluntary agencies, physicians, and the vital registration system.

The HSR has been widely used for studies of particular hereditary diseases and congenital malforma-

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Table 1

Total Live Births, Registered Cases, and Rates in British Columbia, by Three Birth Periods

	1952–63		1964–73		1974–83		TOTAL 1952–83	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
Live births	437,503		344,665		387,705		1,169,873	
All registered cases	19,476	44,516.3	25,909	75,171.5	29,919	77,169.5	75,304	64,369.4
Cases with single ICD code	13,123 (67%)	29,995.2	19,746 (76%)	57,290.4	21,639 (72%)	55,813.1	54,508 (72%)	46,593.1
Cases with two or more ICD codes	6,353 (33%)	14,521.0	6,163 (24%)	17,881.1	8,280 (28%)	21,356.4	20,796 (28%)	17,776.3

[a] Per 1 million live births.

tions (Baird and Miller 1968; Renwick 1968; Lowry et al. 1972, 1976, 1986; Lowry and Trimble 1977; Baird and MacDonald 1981; Baird 1983; Baird and Sadovnick 1985, 1987; Wilson and Baird 1985). Because the HSR is maintained within the vital registration system, it has been possible to arrange for the HSR records to be routinely linked with the identifying particulars and relevant information contained in birth registrations of individuals. The existence of this ongoing data base makes it possible to estimate the number of individuals born within the population since 1952 who have been identified as having a disorder with a wholly or partially genetic cause. Confidentiality of the personal information contained in the records is maintained under the same legal safeguards that are applied to the vital records.

Methods

The HSR was established in 1952, in the Division of Vital Statistics of the Provincial Ministry of Health, and is located in Vancouver (Lowry et al. 1975; Baird 1983, 1987).

By the end of 1984 the HSR master file contained information on 154,071 individuals. Of these, 75,304 had been born in British Columbia between 1952 and 1983 inclusive, and it is from this group of records that the present analysis was performed. An overall summary of the data available in the HSR is presented in table 1. In all, there are more than 60 sources of registration, and currently approximately 9,000 new cases are reported each year to the HSR from a population of 2,890,000, in which there are now some 40,000 live births annually. Of the more than 100,000 registrants who are still living, ~44% are less than age 20 years.

To avoid duplicate entry of cases, each new record is compared with an alphabetic index before inclusion in the HSR data base. HSR records are linked manually with provincial birth registration numbers, further reducing the likelihood of duplication. As well as an ICD9 code, each diagnosis is given an "etiology" code. These etiology codes are assigned on intake, case by case, and include the categories autosomal dominant, autosomal recessive, X linked, autosomal chromosomal disorders, sex-chromosomal disorders, genetic but precise mechanism unknown, and multifactorial. As well, other etiology codes, such as trauma, unknown, infection, and teratogen, can be applied.

Since data from a greater number of years were available to us than to earlier investigators (Trimble and Doughty 1974), we have been able to divide the records into three time periods that are each $\geq$10 years in length (1952–63, 1964–73, and 1974–83). This has meant that for each category of disorder we have been able to choose the "decade" that seemed likely to reflect most closely the genetic load for that disorder in the population. Thus each of our rates is based on $\geq$10 years of data. The choice of "best" decade has been made for each individual diagnosis within each etiological group, as has the grouping into dominant, recessive, etc.

It is necessary to follow a hierarchical approach to ensure that individuals are not counted more than once. Although in general we have followed the same hierarchical approach as Trimble and Doughty (1974), we have chosen not to proceed from single-gene disorders to chromosome disorders to "congenital anomalies" and *then* to "other multifactorial." Rather, multifactorial disorders have been identified separately and have been examined after chromo-

some disorders in the hierarchy. Rather than count all the many diagnoses that might possibly have some multifactorial component, we have restricted ourselves to those relatively common conditions that are generally accepted as having a major multifactorial component. Detailed data are provided, so that the reader may compare our results with those of other studies. Data on all congenital anomalies are also presented separately, so that the data can be compared with those of other studies.

We have not made any adjustments to the rates to compensate for underascertainment, outmigration, etc. The reason for this is that there is little or no hard evidence on which to base these adjustments. If the rates are to be used as a baseline against which to determine whether changes are occurring in the frequency of certain disorders, then any observed increase (or decrease) is likely to be affected by similar distortions, such that the *relative* change should therefore be unaffected.

For the purpose of assessing the genetic load in the population, it is desirable that all cases of hereditary and partially hereditary disease known to the HSR be counted as such, regardless of the presence of nongenetic disorders in the same individual. Similarly, among the cases of genetic disease as a broad category, there is likely to be a small proportion of individuals who, purely by chance, are affected by two, quite independent, hereditary conditions. So that this information would not be lost, cross-tabulations were done, indicating specifically which genetic diseases and which genetic etiologies occurred in the same individuals; and these disorders were evaluated and included.

A multifactorial disorder is one in which alleles at several gene loci determine vulnerability to express a disorder. The term "multifactorial" will be used in this sense throughout this report. Rates for the multifactorial disorders as defined below were derived for the three time periods.

The etiology category "genetic unknown" is used by the HSR when it is evident that the condition has a genetic basis (e.g., Charcot-Marie-Tooth disease) but when it is not known whether the particular case is autosomal dominant, X linked, multifactorial, or autosomal recessive. These cases have been added separately to the estimate of genetic load. Since in total there were more than 1,300 of these cases, it was impossible to review them manually, so simple totals have been produced for each decade for this group.

Results

1. *Autosomal Dominant*

The first culling of the data set extracted all those cases in which any attached diagnosis had a dominant etiology indicated. Cases with only a single dominant diagnosis (with or without additional diagnoses of lower rank) accounted for almost 75% of the 1,041 dominant cases identified. However, there were 280 cases in which there was more than one ICD diagnostic code with a dominant etiology code. A single most appropriate ICD number was arrived at by consensus of the two medical geneticists among us (P.A.B. and R.B.L.) after review on a case-by-case basis; and only a very small number of such cases had more than one dominant disease.

In this way a final summary tabulation, with dominant cases classified by a single ICD diagnosis and by three periods of birth years, was prepared (table 2). The low rate for the third period almost certainly reflects the typically late onset of disability in dominant disorders. The fact that the rate for the oldest cohort (1952–63 births) is substantially lower than that for the middle cohort (1964–73 births) probably reflects the increased completeness of ascertainment in more recent years as important sources of ascertainment were added during the early 1960s (Baird 1983, 1987). It is recognized that these are minimal estimates of rates, since cases with relatively mild manifestations may not be diagnosed or may not come to the attention of the ascertainment sources. Some cases from the "genetic unknown" category also likely belong here, a circumstance also leading to a minimal estimate of dominant disorders.

Rates per million live births were calculated for each diagnosis within each of the three periods (table 2), and then, for each diagnosis, the most appropriate of the three rates was chosen, to arrive at a sum for the highest individual rates. The highest rate was usually chosen on the assumption that under- rather than overascertainment is the more likely source of error, particularly for conditions that are late in appearing. This process resulted in an overall rate for dominant disorders of 1,395/1 million live births.

2. *Autosomal Recessive*

After the dominants had been removed, all cases with an HSR etiology of autosomal recessive were listed. These totaled 1,181. Compared with the dominant disorders, there were relatively few ambiguous cases, and these were dealt with by the same proce-

Table 2

Frequencies of the Most Common Dominant Disorders

ICD9, Dominant Condition	1952–63		1964–73		1974–83		Total	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
190.5, Retina, malignant neoplasm	6	13.7	14	40.6	16	41.3	36	30.8
237.7, Neurofibromatosis	34	77.7	33	95.7	32	82.5	99	84.6
277.8, Other disorders of metabolism	1	2.3	7	20.3	11	28.4	19	16.2
282.0, Hereditary spherocytosis	12	27.4	18	52.2	20	51.6	50	42.7
286.4, Von Willebrand disease	5	11.4	7	20.3	8	20.6	20	17.1
359.2, Myotonic disorders	14	32.0	8	23.2	6	15.5	28	23.9
362.7, Hereditary retinal dystrophies	13	29.7	0	0.0	0	0.0	13	11.1
379.5, Nystagmus and other irregular eye movements	14	32.0	2	5.8	3	7.7	19	16.2
389.1, Sensorineural deafness	3	6.9	15	43.5	4	10.3	22	18.8
743.3, Congenital cataract and lens anomalies	21	48.0	10	29.0	5	12.9	36	30.8
755.0, Polydactyly	6	13.7	16	46.4	14	36.1	36	30.8
755.5,[b] Other anomalies of upper limbs, including shoulder girdle	3	6.9	2	5.8	9	23.2	14	12.0
756.0,[b] Anomalies of skull and face bones	9	20.6	11	31.9	14	36.1	34	29.1
756.4, Chondrodystrophy	48	109.7	21	60.9	20	51.6	89	76.1
756.5, Osteodystrophies	24	54.9	31	89.9	29	74.8	84	71.8
756.8, Other specified anomalies of muscle, tendon, fascia, etc.	13	29.7	14	40.6	7	18.1	34	29.1
756.9, Unspecified anomalies of musculoskeletal system	2	4.6	8	23.2	0	0.0	10	8.5
757.3,[b] Other specified congenital anomalies of skin	11	25.1	5	14.5	6	15.5	22	18.8
759.5, Tuberous sclerosis	13	29.7	23	66.7	22	56.7	58	49.6
759.8, Other specified congenital anomalies	17	38.9	16	46.4	9	23.2	42	35.9
All other dominant conditions[c]	110	251.4	85	246.6	81	208.9	276	235.9
Total	379	866.3	346	1,003.9	316	815.1	1,041	889.8
Sum of highest individual rates								1,395.4

[a] Per 1 million live births.
[b] Special HSR code.
[c] Each individual rate was used to determine the sum of the highest individual rates for these conditions.

dure as previously outlined for dominants. A summary of the final tabulation is shown in table 3. The overall rate was 1,008/1 million, with the middle cohort again showing the highest rate, at 1,178/1 million. When the highest rates for each individual diagnosis were summed, the rate for autosomal recessive disorders was 1,655/1 million live births.

3. *X-linked Disorders*

Owing in part to the relatively small number of cases in this category, there were few ambiguities; and these were quickly resolved. The 394 cases gave an overall rate of 337/1 million, with an overall "maximum" rate of 532/1 million live births (table 4).

4. *Autosomal Chromosome Disorders*

These disorders were identified by listing all those cases with ICD codes 758.0–758.5 and 758.9 and/or an etiology code indicating an autosomal chromosome disorder. Review of a few cases with ambiguous or multiple etiologies resulted in the classification shown in table 5. There were 1,643 cases registered, for an overall rate of 1,404.4/1 million live births. The maximum detailed rate for autosomal chromosomal disorders was 1,693.2/1 million live births.

5. *Sex-Chromosome Disorders*

Sex-chromosome disorders comprised the smallest group of cases in the hierarchy, with a total of 136 cases registered during the 32-year period. The correspondingly few ambiguities were quickly resolved, resulting in the numbers and rates shown in table 6. The detailed summation of individual rates resulted in a maximum estimate of 152.3/1 million live births.

6. *Multifactorial Disorders*

As pointed out in Methods, a difference in this analysis compared with that used in others is that, after ranking single-gene and chromosome disorders,

Table 3

Frequencies of the Most Common Recessive Disorders

ICD9, Recessive Condition	1952–53		1964–73		1974–83		Total	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
255.1, Hyperaldosteronism	13	29.7	7	20.3	1	2.6	21	18.0
255.2, Adrenogenital disorders	5	11.4	8	23.2	12	31.0	25	21.4
270.1, Phenylketonuria	26	59.4	18	52.2	31	80.0	75	64.1
270.2,[b] Other disturbances of aromatic amino acid metabolism	22	50.3	19	55.1	16	41.3	57	48.7
271.0, Glycogenosis	3	6.9	12	34.8	8	20.6	23	19.7
272.7, Lipidoses	4	9.1	10	29.0	4	10.3	18	15.4
277.0, Cystic fibrosis	80	182.9	105	304.6	87	224.4	272	232.5
277.5, Mucopolysaccharidosis	8	18.3	11	31.9	2	5.2	21	18.0
279.0, Deficiency of humoral immunity	4	9.1	12	34.8	4	10.3	20	17.1
282.4, Thalassemias	15	34.3	7	20.3	16	41.3	38	32.5
330.1, Cerebral lipidoses	5	11.4	10	29.0	3	7.7	18	15.4
335.0, Werdnig-Hoffmann disease	6	13.7	19	55.1	15	38.7	40	34.2
358.8,[b] Other myoneural disorders	18	41.1	4	11.6	0	0.0	22	18.8
359.1, Hereditary progressive muscular dystrophy	19	43.4	3	8.7	0	0.0	22	18.8
362.7, Hereditary retinal dystrophies	21	48.0	10	29.0	0	0.0	31	26.5
389.1, Sensorineural deafness	9	20.6	12	34.8	8	20.6	29	24.8
389.9,[b] Unspecified deafness	20	45.7	12	34.8	4	10.3	36	30.8
753.1, Cystic kidney disease	11	25.1	10	29.0	7	18.1	28	23.9
756.5, Osteodystrophies	1	2.3	8	23.2	7	18.1	16	13.7
759.8, Other specified congenital anomalies	7	16.0	18	52.2	21	54.2	46	39.3
All other recessive conditions[c]	104	237.7	91	264.0	126	325.0	321	274.4
Total	401	916.6	406	1,178.0	372	959.5	1,179	1,007.8
Sum of highest individual rates								1,655.3

[a] Per 1 million live births.
[b] Special HSR code.
[c] Each individual rate was used to get the sum of highest individual rates for these conditions.

we did not then examine "congenital anomalies" and *then* "other multifactorial." Rather, we avoided using the category of congenital anomalies in the ranking process at all, since it is—unlike the other categories—not an etiological classification. Thus we moved directly from sex-linked disorders to examine the frequency of selected multifactorial disorders.

The procedure adopted was to have the medical geneticists among us (P.A.B. and R.B.L.) identify 22 diagnoses that are generally thought to have a major multifactorial genetic component. Cases with at least one of these diagnoses were then identified in the group remaining after the removal of the previously described hierarchy of single-gene disorders through chromosomal disorders. Selection of cases with an ICD code in this list of 22 diagnoses was based primarily on ICD code number—excluding however, those cases in which the HSR etiological code indicated a known cause, e.g., prenatal infection, known teratogen, or birth trauma.

Various methods were explored to deal with the problem of cases having multiple diagnoses. It was found that the most effective way of handling this problem was to first count for each diagnosis of interest the cases having only one diagnosis and then choose the most appropriate birth period, to give the "minimum estimate." This statistic is shown in table 7. Cases with more than one diagnosis were then grouped according to second (or more) diagnosis, for the medical geneticists to evaluate which cases, if any, should be accepted as having a multifactorial disorder. Adding these cases yielded "expanded-minimum" estimates (table 8). The cases added were those for which the other code(s) indicated a disorder(s) likely to be a consequence of the initial multifactorial condition.

Thus the individuals counted in table 8 have either one disorder only or disorders that, although coded to different ICD9 codes, are indeed basically the consequence of one condition. An example would be an

Table 4

Frequencies of the Most Common X-linked Disorders

ICD9, X-LINKED CONDITION	1952–63		1964–73		1974–83		TOTAL	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
257.8, Other testicular dysfunction	8	18.3	0	0.0	7	18.1	15	12.8
270.6, Disorders of urea-cycle metabolism	1	2.3	0	0.0	3	7.7	4	3.4
275.4, Disorders of calcium metabolism	0	0.0	2	5.8	0	0.0	2	1.7
277.5, Mucopolysaccharidosis	3	6.9	3	8.7	0	0.0	6	5.1
279.0, Deficiency of humoral immunity	6	13.7	2	5.8	0	0.0	8	6.8
282.2, Anemia due to disorder of glutathione metabolism	3	6.9	2	5.8	14	36.1	19	16.2
286.0, Congenital factor VIII disorder	28	64.0	24	69.6	14	36.1	66	56.4
286.1, Congenital factor IX disorder	7	16.0	10	29.0	1	2.6	18	15.4
288.1, Functional disorder of neutrophil polymorphs	0	0.0	0	0.0	3	7.7	3	2.6
317–319, Mental retardation	13	29.7	5	14.5	5	12.9	23	19.7
359.1, Hereditary progressive muscular dystrophy	43	98.3	34	98.6	13	33.5	90	76.9
368.5, Color-vision deficiencies	29	66.3	32	92.8	14	36.1	75	64.1
588.1, Nephrogenic diabetes insipidus	3	6.9	2	5.8	4	10.3	9	7.7
743.5, Congenital anomalies of posterior segment	2	4.6	2	5.8	3	7.7	7	6.0
756.0,[b] Anomalies of skull and face bones	2	4.6	1	2.9	3	7.7	6	5.1
757.3,[b] Other specified congenital anomalies of skin	3	6.9	3	8.7	7	18.1	13	11.1
759.8, Other specified congenital anomalies	1	2.3	0	0.0	3	7.7	4	3.4
All other X-linked conditions[c]	5	11.4	10	29.0	11	28.4	26	22.2
Total	157	358.9	132	383.0	105	270.8	394	336.8
Sum of highest individual rates								532.4

[a] Per 1 million live births.
[b] Special HSR code.
[c] Each individual rate was used to get the sum of highest individual rates for these conditions.

individual with cleft lip and palate who also had malocclusion. Included in this table are some conditions—such as schizophrenia, idiopathic scoliosis, and dislocatable hip—whose multifactorial etiology is controversial. Such disorders are included because there is evidence that they may be multifactorial, and they have been listed separately so that, if the reader wishes, they may be omitted. There are several other common disorders—such as alcoholism, hypertension, or the neuroses—that have not been included in the multifactorial category but that undoubtedly have an important genetic component; but whether in fact the actual basis is multifactorial is not clear.

The number of individuals counted in this way is a

Table 5

Frequencies of Autosomal Chromosome Conditions

ICD9, AUTOSOMAL CHROMOSOME	1952–63		1964–73		1974–83		TOTAL	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
758.0, Down syndrome	571	1,305.1	460	1,334.6	394	1,016.2	1,425	1,218.1
758.1, Patau syndrome (trisomy 13)	3	6.9	15	43.5	22	56.7	40	34.2
758.2, Edward syndrome (trisomy 18)	1	2.3	31	89.9	57	147.0	89	76.1
758.3, Autosomal deletion syndromes	4	9.1	4	11.6	26	67.1	34	29.1
758.5, Other conditions due to autosomal anomalies	6	13.7	14	40.6	31	80.0	51	43.6
758.9, Anomaly of unspecified chromosome	1	2.3	0	0.0	3	7.7	4	3.4
Total	586	1,339.5	524	1,520.3	533	1,374.8	1,643	1,404.4
Sum of highest individual rates								1,693.2

[a] Per 1 million live births.

Table 6

Frequencies of Sex-chromosomal Conditions

ICD9, Sex-chromosomal Condition	1952–63		1964–73		1974–83		Total	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
758.6, Gonadal dysgenesis	33	75.4	26	75.4	23	59.3	82	70.1
758.7, Klinefelter syndrome	28	64.0	11	31.9	5	12.9	44	37.6
758.8, Other sex-chromosome anomalies	3	6.9	2	5.8	5	12.9	10	8.5
Total	64	146.3	39	113.2	33	85.1	136	116.3
Sum of highest individual rates								152.3

[a] Per 1 million live births.

minimal and conservative estimate of the proportion of the population with multifactorially determined disease. This is because individuals who have additional disabilities of any kind have not been included. It would not have been practical to evaluate on an individual basis the large number of cases that had a possibly multifactorially caused condition, occurring with other disabilities, to see whether it was appropriate to allocate any one of these cases to the multifactorial category. Included were only those groupings for which it is very clear that the additional diagnostic code is a known consequence of the mul-

Table 7

Multifactorial Cases with Only One Diagnosis on Their Record

ICD9, Multifactorial Condition	1952–63		1964–73		1974–83		Total	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
250, Diabetes mellitus	526	1,202.3	382	1,108.3	103	265.7	1,011	864.2
295, Schizophrenic psychoses	181	413.7	1	2.9	0	0.0	182	155.6
296, Affective psychoses	10	22.9	0	0.0	0	0.0	10	8.5
317.1,[b] Borderline mental retardation	314	717.7	63	182.8	1	2.6	378	323.1
317.2,[b] Mild mental retardation	181	413.7	37	107.4	5	12.9	223	190.6
345, Epilepsy	807	1,844.6	502	1,456.5	228	588.1	1,537	1,313.8
378,[b] Strabismus	924	2,112.0	3,566	10,346.3	1,450	3,740.0	5,940	5,077.5
493, Asthma	124	283.4	53	153.8	71	183.1	248	212.0
550, Inguinal hernia	0	0.0	196	568.7	1,997	5,150.8	2,193	1,874.6
691.8, Eczema	37	84.6	4	11.6	3	7.7	44	37.6
740, Anencephaly	58	132.6	45	130.6	50	129.0	153	130.8
741, Spina bifida	214	489.1	117	339.5	67	172.8	398	340.2
742.0, Encephalocele	5	11.4	7	20.3	8	20.6	20	17.1
742.3, Congenital hydrocephalus	48	109.7	99	287.2	76	196.0	223	190.6
745–7, Congenital anomalies of heart and circulatory system	1,177	2,690.3	1,699	4,929.4	1,734	4,472.5	4,610	3,940.6
749, Cleft palate and cleft lip	468	1,069.7	445	1,291.1	431	1,111.7	1,344	1,148.8
750.5, Congenital hypertrophic pyloric stenosis	23	52.6	805	2,335.6	909	2,344.6	1,737	1,484.8
751.3, Hirschsprung disease, etc.	9	20.6	60	174.1	43	110.9	112	95.7
752.6, Hypospadias and epispadias	102	233.1	558	1,619.0	620	1,599.2	1,280	1,094.1
754.7,[b] Clubfoot	679	1,552.0	1,433	4,157.7	1,967	5,073.4	4,079	3,486.7
754.3, Congenital dislocation of hip	197	450.3	878	2,547.4	1,322	3,409.8	2,397	2,048.9
754.9,[b] Congenital dislocatable hip	0	0.0	12	34.8	622	1,604.3	634	541.9
Total	6,084	13,906.2	10,962	31,804.8	11,707	30,195.6	28,753	24,577.9

[a] Per 1 million live births.
[b] Special HSR code.

Table 8

Frequencies of Multifactorial Cases by Period of Choice

ICD9, Multifactorial Conditions	Period of Choice	Minimum (Single Diagnosis)		Additional (Multiple Diagnoses)		Expanded Minimum	
		N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
250, Diabetes mellitus	1952–63	526	1,202.3	37	84.6	563	1,286.8
295, Schizophrenic psychoses	1952–63	181	413.7	13	29.7	194	443.4
296, Affective psychoses	1952–63	10	22.9	3	6.9	13	29.7
317.1,[b] Borderline mental retardation	1952–63	314	717.7	98	224.0	412	941.7
317.2,[b] Mild mental retardation	1952–63	181	413.7	78	178.3	259	592.0
345, Epilepsy (excluding 345.6)	1952–63	807	1,844.6	39	89.1	846	1,933.7
378,[b] Strabismus	1964–73	3,566	10,346.3	27	78.3	3,593	10,424.6
493, Asthma	1952–63	124	283.4	27	61.7	151	345.1
550, Inguinal hernia	1974–83	1,997	5,150.8	394	1,016.2	2,391	6,167.1
691.8, Eczema	1952–63	37	84.6	0	0.0	37	84.6
740, Anencephaly	1974–83	50	129.0	9	23.2	59	152.2
741, Spina bifida	1974–83	67	172.8	11	28.4	78	201.2
742.0, Encephalocele	1974–83	8	20.6	2	5.2	10	25.8
742.3, Congenital hydrocephalus	1964–73	99	287.2	25	72.5	124	359.8
745–7, Congenital anomalies of heart and circulatory system	1964–73	1,699	4,929.4	30	87.0	1,729	5,016.5
749, Cleft palate and cleft lip	1964–73	445	1,291.1	45	130.6	490	1,421.7
750.5, Congenital hypertrophic pyloric stenosis	1974–83	909	2,344.6	8	20.6	917	2,365.2
751.3, Hirschsprung disease, etc.	1964–73	60	174.1	4	11.6	64	185.7
752.6, Hypospadias and epispadias	1964–73	558	1,619.0	70	203.1	628	1,822.1
754.7,[b] Clubfoot	1974–83	1,967	5,073.4	16	41.3	1,983	5,114.7
754.3, Congenital dislocation of hip	1974–83	1,322	3,409.8	11	28.4	1,333	3,438.2
754.9,[b] Congenital dislocatable hip	1974–83	622	1,604.3	12	31.0	634	1,635.3
Total		15,549	41,535.3	959	2,451.7	16,508	43,986.9
Final rate[a] after adjustment for multiply affected individuals							46,582.6

Note.—See explanatory comment for this table in Appendix A.

[a] Per 1 million live births.

[b] Special HSR code.

tifactorial condition under consideration. Thus those individuals with additional disabilities are arbitrarily not assigned to the multifactorial group, a decision resulting in a conservative estimate of the number of cases.

All HSR cases in which a specific etiology code had been assigned to a condition that otherwise might have been interpreted as multifactorial have been omitted from the table. For example, if there was a known genetic etiology or a known environmental cause, conditions such as congenital heart disease, or cleft lip and palate, have not been included. It is necessary to make a few explanatory comments about some of the conditions, and this is done in Appendix A.

There are two ways in which the count of multifactorial cases will be falsely low because of a simple inherent bias in the counting process that could be present whenever a case has more than one diagnosis. Only those cases with a single diagnosis (or with essentially the same second [or more] diagnosis) were counted. This means that the *chance* occurrence of a second *non*multifactorial diagnosis occurring in the same individual would lead to omission of that case. Similarly, the chance occurrence of a second, unrelated *multifactorial* diagnosis occurring in the same individual would mean that that person was not counted.

Each of these possibilities has been examined, and an adjusted rate has been determined. The estimate of the multifactorial rate should be increased by ~809.5/1 million live births, to allow for the chance occurrence of an additional nonmultifactorial diagnosis. In terms of the original "expanded minimum" estimate of 43,986.9 multifactorial conditions/1 million live births (table 8), the double multifactorial

Table 9

Frequencies of Genetic Unknown Cases

Genetic Unknown	1952–63		1964–73		1974–83		Total	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
Single diagnosis	469	1,072.0	294	853.0	155	399.8	918	784.7
Multiple diagnoses	234	534.9	122	354.0	88	277.0	444	379.5
Total	703	1,606.9	416	1,207.0	243	626.8	1,362	1,164.2

[a] Per 1 million live births.

diagnoses contribute another 1,696.4 and the triple another 89.8, rates that, when added to the *non*multifactorial rate of 809.5, give a *final estimate, for multifactorial disorders, of 46,582.6/1 million live births.*

7. *Genetics Unknown*

The cases receiving this etiology code are those for which it is evident that there is a genetic basis but in which the precise mechanism is not clear. Some examples would be (1) an infant with a known genetic disorder that may be inherited as a recessive or a dominant but for which it is not known which mechanism is responsible in that particular case; (2) same-sex twins, both with the same constellation of unusual congenital anomalies; (3) several familial cases of a disorder that may be autosomal dominant or X linked but in which it is not clear from the pedigree which is responsible; or (4) sibs with a similar pattern of retardation and physical anomalies. Ideally these cases would be individually studied and, if at all possible, assigned to categories in the hierarchy of categories discussed above. This is not possible, as more than 1,300 cases are involved. Rather than being omitted from a consideration of genetic load in the population, they are included in table 9.

8. *Congenital Anomalies*

As explained earlier, in this analysis congenital anomalies were not considered as part of the hierarchical system, since they are, by definition, related less to etiology than to time of appearance. However, since many other studies have included all congenital anomalies in determining genetic load, data on congenital anomalies are presented here. Table 10 summarizes the information for conditions having ICD numbers within the congenital anomaly range—i.e., 740.0–759.9—and that have been included in the categories considered in our study. The overall rate for congenital anomaly cases having a genetic etiology of some kind was 26,584.2/1 million live births,

Table 10

Congenital Anomalies (740–759) with Specific Genetic Etiology

Congenital Anomalies	1952–63		1964–73		1974–83		Total		Sum (%) of Highest Individual Rates	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]	*N*	Rate[a]		
Dominant conditions	202	461.7	198	574.5	181	466.8	581	496.6	741.5	2.8
Recessive conditions	52	118.9	71	206.0	74	190.9	197	168.4	290.3	1.1
X-linked conditions	10	22.9	13	37.7	20	51.6	43	36.8	66.4	0.2
Autosomal chromosome conditions	586	1,339.4	524	1,520.3	533	1,374.8	1,643	1,404.4	1,693.1	6.4
Sex-chromosome conditions	64	146.3	39	113.2	33	85.1	136	116.3	152.3	0.6
Multifactorial conditions	...	...	...	...	...	...	...	...	23,076.0[b]	86.8
Genetic unknown	247	564.6	176	510.6	116	299.2	539	460.7	564.6[c]	2.1
Total	...	...	...	...	...	...	...	...	26,584.2	100.0

[a] Per 1 million live births.

[b] Different from that in table 8 because the number includes, in addition, conditions outside the 740–759 range.

[c] Sum for the decade (1952–63) showing the highest rate.

Table 11

Congenital Anomalies: Total Diagnoses by ICD Category 740–759

ICD9, Congenital Anomaly	1952–63		1964–73		1974–83		Total	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
740, Anencephaly	74	169.1	60	174.1	89	229.6	223	190.6
741, Spina bifida	377	861.7	267	774.7	261	673.2	905	773.6
742.0, Encephalocele	12	27.4	26	75.4	46	118.6	84	71.8
742.3, Congenital hydrocephalus	182	416.0	273	792.1	347	895.0	802	685.5
740–2,[b] Other nervous system disorder	158	361.1	268	777.6	372	959.5	798	682.1
743, Eye	382	873.1	507	1,471.0	603	1,555.3	1,492	1,275.4
744, Ear, face, neck	158	361.1	626	1,816.3	858	2,213.0	1,642	1,403.6
745–7, Heart and circulation	1,981	4,528.0	3,628	10,526.2	5,073	13,084.7	10,682	9,130.9
748, Respiratory	38	86.9	748	2,170.2	748	1,929.3	1,534	1,311.3
749, Cleft palate and cleft lip	812	1,856.0	757	2,196.3	809	2,086.6	2,378	2,032.7
750.5, Pyloric stenosis	38	86.9	900	2,611.2	1,063	2,741.8	2,001	1,710.4
751.3, Hirschsprung disease, etc.	16	36.6	81	235.0	89	229.6	186	159.0
750–1, Other digestive system disorder	212	484.6	667	1,935.2	1,277	3,293.7	2,156	1,842.9
752.6, Hypospadias and epispadias	174	397.7	788	2,286.3	990	2,553.5	1,952	1,668.6
752–3, Other genito-urinary disorder	421	962.3	2,866	8,315.3	3,369	8,689.6	6,656	5,689.5
754.7,[c] Clubfoot	1,065	2,434.3	1,896	5,501.0	2,694	6,948.6	5,655	4,833.9
754.3,[c] Congenital dislocation of hip	313	715.4	1,109	3,217.6	1,713	4,418.3	3,135	2,679.8
754.9,[c] Congenital dislocatable hip	4	9.1	23	66.7	779	2,009.3	806	689.0
754–6, Other musculo-skeletal disorder	1,255	2,868.6	2,256	6,545.5	3,261	8,411.0	6,772	5,788.7
757, Integument disorders	227	518.9	678	1,967.1	1,165	3,004.9	2,070	1,769.4
758, Chromosomal anomalies	665	1,520.0	574	1,665.4	630	1,624.9	1,869	1,597.6
759, Other	137	313.1	248	719.5	424	1,093.6	809	691.5
Total diagnoses	8,701	19,887.8	18,671	54,171.4	26,660	68,763.6	54,032	46,186.2
Total cases	7,065	16,148.4	14,707	42,670.4	20,474	52,808.2	42,246	36,111.6

[a] Per 1 million live births.
[b] All conditions in 740–2 not listed separately in the table.
[c] Special HSR code.

or 2.7% of live births. If all cases of congenital anomaly are considered, *including* those to which no genetic etiology has been attributed in this study, the combined rate of congenital anomalies in the decade having the best ascertainment was approximately twice as great, i.e., 52,808.2/1 million live births, or 5.3% of live births. This result is shown in table 11, which summarizes *all* congenital anomalies in ICD category 740–759. If inguinal hernia is added, ~6.1% of live borns in our population in the most recent decade had a congenital anomaly, compared with a figure of 7.2% for recent Hungarian data. These data are shown in table 12.

The average number of diagnoses per case has risen during the years—but not substantially given the great increase in the number of diagnoses that can now be listed. Thus there were 1.23 diagnoses/case in the 1952–63 period, 1.27 in the middle period, and 1.30 in the last. For the three decades the number of cases as a percentage of total diagnoses was 81%, 79%, and 77%, respectively. As a very crude first step, the percentage of total diagnoses might therefore be adjusted downward to ~80%, to give a rate reflecting a case rate.

9. *Effect of Pregnancy Termination*

In utero diagnosis of genetic abnormality has become increasingly common in recent years, and this could bias the estimates of genetic defect in live-born children, since a positive test may lead to termination of the pregnancy. The potential impact has been calculated from the records of the Provincial Prenatal Diagnosis Program. Only the birth period 1974–83 would be affected; and the estimates of incidence arrived at earlier in this report are based mainly on the first and second birth periods. Also, not all the affected fetuses detected in the program would have survived to be born alive.

The calculated impact of pregnancy terminations on the rates in this study has been extremely small;

Table 12

Comparison of Incidence of Various Congenital Anomalies in Three Studies, without Exclusion of Nongenetic Cases

ICD9, Type of Anomaly	Incidence per 1,000 Live Births				
	Hungary (All Cases)	British Columbia 1967–69 (All Cases)	Present Study (All Cases[a])		
			1952–63	1964–73	1974–83
740–742, Central nervous system	2.2	1.7	1.5	2.1	2.3
743, Eye	0.3	0.8	0.7	1.2	1.2
744, Ear, face, neck	0.5	0.8	0.3	1.5	1.8
745–747, Heart and circulatory system	7.9	4.3	3.6	8.4	10.5
748, Respiratory system	0.3	0.2	0.1	1.7	1.5
749, Cleft palate and cleft lip	1.5	1.8	1.5	1.8	1.7
750–751, Disorders of other parts of digestive system	2.8	1.8	0.5	3.8	6.3
752–753, Urogenital system disorder	9.1	2.8	1.1	8.5	9.0
754–756, Musculoskeletal system disorders	31.3[b]	6.6	4.8	12.3	17.4
757, Integument disorders	0.7	0.2	0.4	1.6	2.4
758, Chromosomal anomalies	1.3	1.4	1.2	1.3	1.3
759, Other	2.0	0.2	0.3	0.6	0.9
740–759, Total	59.7	22.2[c](44.8[d])	16.2[c]	42.7[c]	52.8[c]
550, Inguinal hernia	11.0	0.1	0.02[c]	2.1[c]	7.9[c]
553, Umbilical hernia	0.9	0.3	...	...	...
227–228 (ICD8), Congenital tumors	0.1	1.0	...	...	...
Grand total	71.7	23.6[c](46.2[d])	16.2[c]	44.8[c]	60.7[c]

[a] Most of these rates are based on total diagnoses—and therefore have been adjusted downward by a factor of 0.8 (see text).
[b] Incidence would be 5.5 if congenital dislocation of the hip were excluded.
[c] Based on actual cases, and not adjusted.
[d] Adjusted for underestimation.

for cases, the maximum incidence of terminations would be 0.027% (details available on request).

Discussion

Congenital Anomalies

Many studies have treated congenital anomalies defined by ICD codes 740–759 as being *all* of "potentially genetic or partially genetic" origin. However, this is not an etiological category but a convenient and important grouping of conditions that are quite heterogeneous in their causations. The present records of the HSR make it possible to identify those cases within the congenital anomaly group that were thought to have a genetic etiology. This is a considerable advance because many earlier studies did not attempt to quantify the relative importance of the genetic *versus* the nongenetic categories within the broader "congenital anomalies" grouping.

On the basis of data in the congenital anomaly section, it is possible to analyze how many of the registered individuals suffer from conditions that are included in the genetic categories defined above. In the present study considerable effort was devoted to counting only those cases for which there was believed to be a significant genetic component in the causation. All other cases have been excluded from the data so that, in a given birth cohort, frequencies of congenital anomalies as part of the genetic load have been reduced accordingly. This reduction should not be confused with failures to ascertain cases.

It is misleading to compare our figures on congenital anomalies of genetic etiology with those obtained by Trimble and Doughty (1974). This is because Trimble and Doughty categorized all congenital anomalies as being partly genetic. They therefore did not attempt to separate the genetic category of congenital anomalies, as we have done. In the present analysis we have *first* counted 22 selected multifactorials (46,582.6/1 million live births). In this selected group, congenital anomalies occurred at a rate of 21,790.4/1 million live births. Some congenital anomalies are included in the other categories in

Table 13

Incidence of Genetic or Partially Genetic Diseases per 1,000 Live Births According to Various Reports

Disease Category	British Columbia 1967–69 Study		Present Study (1952–83): Sum of Highest Rates	UNSCEAR Reports			
	Minimal	Adjusted		1966	1977[a]	1982	1986
Dominant[b]	0.6	0.8	1.4	10.0	10.0	10.0	10.0
X linked	0.3	0.4	0.5	...	...	...	...
Recessive	0.9	1.1	1.7	2.0	1.1[c]	2.5	2.5
Chromosomal:							
Numerical	1.6	2.0	1.9	4.0	4.0	4.0	3.4
Structural	...	...	...	...	...	...	0.4
Multifactorial:							
Congenital	36.0	43.0	23.1	25.0	90.0	90.0	90.0[d]
Other	16.0	47.0	23.9	15.0	...	...	...
Genetic unknown	...	...	1.2	...	...	...	...
Total[e]	55.0	94.0	53.2	56.0	105.0	107.0	106.0

[a] The values used in the report of the BEIR committee in 1980 (8) were essentially identical to those in the 1977 UNSCEAR report.

[b] The figures from the UNSCEAR reports include autosomal and X-linked dominants.

[c] The change from 1.1 to 2.5 was made by UNSCEAR to include those disorders whose mutant genes are maintained by heterozygous advantage.

[d] Includes congenital anomalies and other multifactorial disorders.

[e] The sums are not exact owing to rounding.

our hierarchy. However, in our estimate of genetic load, in total we have excluded from consideration approximately half of all congenital anomalies, as being of unknown cause; they have not been counted as genetic. As well, some congenital anomalies were not counted as genetic by us because they had an identifiable environmental cause.

Table 12 shows a comparison of our data on *all* congenital anomalies (without the division into genetic and other etiology) with those from the previous analysis of British Columbia data and with those from a recent analysis of Hungarian data (Czeizel and Sankaranarayanan 1984). For ease of comparison, in this section the data are expressed per thousand rather than in the per-million-live-births form used in previous sections. Data from a U.S. study (Myrianthopoulos and Chung 1974) and from UNSCEAR (1982, pp. 543, 546; 1986) are also available, but they are expressed in somewhat different terms. In table 12 the Hungarian and earlier British Columbia data are expressed as frequencies of all live births with one or more congenital anomalies, listed by ICD category. The rates in the "present study" column include all cases of congenital anomalies. Note that a crude adjustment factor of 0.8 has been applied to the present-study data in the table to make the rates more comparable with *case* rates, since the number of cases in each birth period was ~80% of the total number of diagnoses.

Thus it can be seen that much of the difference between the earlier and the present analyses of the British Columbia data (table 13, "congenital" category) is due to our decision to exclude (as not genetic or partly genetic) a proportion of the cases of congenital anomalies.

Influence of Age at Onset of Severity of Symptoms

Most of the registrants in the earliest (1952–63) period of the present study would have reached an age of ~25 years by the end of the HSR updates in 1983, but the later cohorts are younger. This fact creates a serious underestimation of those genetic diseases whose onset and potential diagnosis occur later in life. At the moment, this underestimation is believed to be most serious in the case of dominant genetic conditions (table 2), many of which have their onset in adult life. Two examples of these are cited in Appendix B. Overall, the total incidence of dominant

diseases, including those of late onset, is believed to be ~7/1,000 live births (Trimble and Smith 1977; Vogel and Motulsky 1986).

The present study of the incidence of dominant conditions in the HSR is providing higher numbers as the initial cohort grows older (table 2); however, it is important to note that the present study does not provide good incidence data on genetic disorders having an older age at onset, a category that includes many dominant conditions.

Although a complete listing of all dominant disorders is required for assessment of the impact on the health of the general population, the dominant disorders of major importance for assessment of the effect of increased mutation rates are those of early onset, which are included in tables 2 and 13. The most common dominant disorders having late onset are not maintained by high mutation rates; investigators were, for example, unable to find a single clear case of a new mutation among several thousand Huntington chorea patients (Vogel and Motulsky 1986). New mutations are believed to be responsible for most of the cases of dominant disorders (e.g., achondroplasia) having severe effects on the health of children.

The United Nations scientific committees used the adjusted values for incidence of recessive disorders in the earlier British Columbia study as the best estimate available in 1977 (table 13). This estimate was later increased from 1.1/1,000 live births to 2.5/1,000 live births when disorders whose mutant genes are maintained by heterozygous advantage were included. This increase is supported by the present study's unadjusted value of 1.7/1,000 live births.

Similar problems of incomplete ascertainment apply to the present data on disorders attributed to changes in chromosome number (tables 5, 6). The rates for chromosome anomalies observed by surveys in the literature (Hamerton et al. 1975; Jacobs 1978) are higher than those observed by the HSR. The rates published refer to consecutive series of individuals tested and can be expected to be higher than those recorded in the HSR. This is to be expected, since underascertainment by the HSR is likely for many cases of less obvious chromosome anomalies (e.g., deletions) and for individuals who die prior to testing. The recorded values for Klinefelter syndrome are undoubtedly much too low; the true incidence should be at least as high as that for Down syndrome (UNSCEAR 1977, pp. 514–523; Vogel and Motulsky 1986). The low incidence recorded for Klinefelter syndrome in both studies of British Columbia data probably reflects the less severe nature of the health problems associated with Klinefelter syndrome as compared with Down syndrome. The fraction of all cases brought to the attention of diagnosing physicians will be much smaller in the case of Klinefelter syndrome than in that of Down syndrome. As will be noted below, this underestimation of chromosomal diseases probably has little significance for assessment of the genetic effects of exposure to low doses of radiation or other mutagenic agents, since these exposures are thought to produce little or no increase in the rate for genetic disease attributable to changes in chromosome number (UNSCEAR 1982, pp. 543, 546; 1986).

The incidence of diseases in the multifactorial category given in reports of international and national scientific committees since 1974 (table 13), is the adjusted incidence obtained in the first analysis of the HSR British Columbia data. In the comparison shown in table 13, it should be remembered that, by definition, approximately half of the cases of congenital anomalies in the present study have been excluded from the figures shown for the multifactorial category, as not being of genetic or partly genetic etiology.

The results of the present analysis provide the basis for an improved estimate of the incidence of the genetic or partially genetic diseases having serious health consequences in children and young adults before age 25 years. The definition of "genetic or partly genetic" used in the present study leads to a lower number of congenital anomalies being included in the data. The incidence of genetic diseases having minor health consequences and the incidence of genetic diseases having late onset in life cannot be estimated from the present data. However, the results of the present study provide valuable information on the incidence of genetic disorders in children and young adults.

Relevance to Assessment of Health Hazards of Mutagenic Agents

Dominant mutations (table 2), together with X-linked mutations (table 4), are usually considered to provide the most important contribution to any increase in genetic diseases that results from exposure to environmental mutagens. Contributions from autosomal recessive mutations (table 3) are smaller and would not be evident for many generations (Searle and Edwards 1986). Current thinking suggests that genetic diseases attributable to alterations

in chromosome number (tables 5, 6) would not be increased appreciably by exposure to low levels of radiation or other environmental mutagens. Small increases in incidence of genetic disorders would result from induced changes in chromosomal structure, notably unbalanced translocations. Diseases attributable to these structural chromosomal anomalies may be of diverse nature and do not appear to be restricted to particular ICD categories.

Evaluation of the contribution from partially genetic disorders (tables 7–9) represents a continuing problem, which will presumably not be solved in the near future. In the first place, it is uncertain how the incidence of these multifactorial disorders would be affected, if at all, by an increase in normal rates of mutation. The UNSCEAR reports (UNSCEAR 1977, pp. 514–523; 1982, pp. 543, 546) have assumed that ~5% of these multifactorial diseases will respond to increased mutation rates in a manner similar to that of monogenic dominant diseases. On the other hand, the 1980 BEIR report assumed a mutational component of 5%–50%. The differences in these assumptions can result in considerable variations in the relative importance of multifactorial diseases when any assessment is made of the potential health hazards of environmental mutagens.

A second problem is the incidence of multifactorial disorders over the whole life span of the population. Although the value of 90/1,000 live births for all multifactorial disorders (including congenital anomalies) in children has been widely accepted (table 13), this value would be increased to ~600/1,000 if multifactorial disorders of late onset (e.g., thyrotoxicosis, adult diabetes, psychoses, hypertension, myocardial infarction, and ulcers) were included (UNSCEAR 1986). Inclusion of certain cancers would further increase the total incidence of multifactorial diseases. Despite these uncertainties, multifactorial diseases that become evident in children or young adults (tables 7–9) would continue to have the largest personal health impact in terms of years of life lost or years of impaired life.

Some well-organized population-based registries are quite effective at registering young people who are actually sick or handicapped. For the purpose of assessing genetic harm to health, these individuals are particularly relevant. What is not generally recognized is that the omission of "cases" who are not noticeably affected helps, rather than hinders, assessment of the actual harm that is due to genetic disease. In the present data, the further exclusion of individuals with congenital anomalies when there is little evidence of a genetic or polygenic component in the causation represents an additional refinement.

Table 14

Frequencies of Genetic Disorders in 1,169,873 Births, 1952–83

Category	Rate per 1 Million Live Births	% of Total Births
A.		
Dominant	1,395.4	0.14
Recessive	1,655.3	0.17
X linked	532.4	0.05
Chromosomal	1,845.4	0.18
Multifactorial	46,582.6	4.64
Genetic unknown	1,164.2	0.12
Total	53,175.3	5.32[a]
B.		
All congenital anomalies 740–759	52,808.2	5.28
Congenital anomalies with genetic etiology (included in section A above)	26,584.2	2.66
C.		
Disorders in section A (above) plus those congenital anomalies not already included	79,399.3	7.94

[a] Sum is not exact owing to rounding.

In summary (see table 14), it is conservatively estimated that ~53.0/1,000 live-born individuals can be expected to have genetic or partially genetic diseases before age 25 years. Single-gene disorders are responsible for ≥3.6/1,000, chromosomal disorders for ≥1.8/1,000, and multifactorial for by far the greatest number, i.e., ≥46.6/1,000. In the present study congenital anomalies as an entire group have not been included in this total estimate of genetic load. Only those congenital anomalies for which there is evidence of single-gene, chromosomal, or multifactorial causation have been included.

Data are also presented separately on all congenital anomalies in the present study. In the most recent birth period (1974–83), 52.8 congenital anomalies/1,000 live births have been observed. Approximately half of this figure has not been included in our genetic load figure, in contrast with the practice in most other studies. If *all* congenital anomalies (~52.8/1,000) were to be included in the estimate of genetic

load, then, in total, the frequency of genetic disorders in the population less than age 25 years would be ~79.4/1,000.

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Appendix A

Multifactorial Conditions

The HSR has coded congenital dislocated hip and congenital dislocatable hip to 754.3 and 754.9 respectively. The latter is not a standard ICD9 code but a special code used by the HSR. Since it is likely that the "dislocatable" category may also have a multifactorial etiology, these cases have been included in tables 7, 8, and 11. The HSR also has a special interpretation of the clubfoot category. Cases normally coded in ICD9 to 754.5, 754.6, and 754.7 are all coded to 754.7. This, then, is felt to reflect the number of individuals with clubfoot of different kinds.

Since malocclusion is such a common concomitant of cleft lip and palate, it was felt justifiable to treat individuals with both these disorders as still having a multifactorially determined condition, and they have been included in the "expanded minimum" estimate in table 8. Similarly, in the category of congenital heart disease, even if more than one heart malformation was present, it was still felt appropriate to assign the case to the category of multifactorial, provided that the case had no additional malformations coded outside the heart-malformation section. Individuals with asthma or atopic eczema are likely to have the same general allergic diathesis, and thus individuals having both or either condition are included in tables 7, 8, and 11.

Approximately 25% of the patients with Hirschsprung disease had nonregional anomalies and thus have been omitted from the total for cases of Hirschsprung having multifactorial etiology. Although a further 7% of cases of Hirschspring disease had local regional anomalies, it was felt that these had occurred secondarily to the local bowel dilatation. Thus, those cases with associated regional anomalies have been included in the count of those individuals having multifactorial conditions (Spouge and Baird 1985).

In a recent HSR study, the incidence of isolated hypospadias in the province during 1966–81 was found to be 3.55/1,000 live-born male infants (Leung et al. 1985). Cases with additional anomalies were included in that study, but the main reason for the much lower rate (1.8/1,000) found in the present study is, of course, that in the present analysis we are using total live births—rather than male live births only—as the denominator.

From an earlier study (Trimble and Baird 1978) for the period 1952–72 we know that the overall incidence of anencephaly was 0.6/1,000 births and that that of spina bifida was 0.8/1,000 births. Therefore, the rates given here for anencephaly and spina bifida are very low estimates because of the conservative case-acceptance method used for including cases in the multifactorial category. Any case with any kind of additional anomaly, apart from adrenal hyperplasia, was, by definition, excluded from the multifactorial category.

Since some degree of mental retardation is a frequent complication of hydrocephalus, cases of hydrocephalus have been accepted as multifactorial if retardation is present as well. Since premature birth may be a causative factor of intracranial bleeding and consequent hydrocephalus, those cases in which prematurity was present have been omitted from table 8, as being better not considered as multifactorial in etiology.

It was decided that it was appropriate to treat those cases of borderline or mild mental retardation that had no other malformations or disorders as multifactorial in etiology. It is probable that a proportion of cases assigned to the so-called moderate or unspecified categories should also appropriately be added to the multifactorial table, but what this proportion is is difficult to estimate. It is felt that the conservative approach of not including these in the multifactorial category is the more appropriate approach.

Diabetes mellitus is also a very difficult category to assign rigorously. Any cases associated with known specific cause, e.g., diabetes mellitus occurring in Klinefelter syndrome, have been omitted from tables

7 and 8. It is recognized that diabetes mellitus is a heterogeneous group, in that the juvenile-onset and adult-onset types are likely to have different genetic components to their etiology. In our present state of knowledge it is felt that the majority of diabetes mellitus cases of unknown cause are likely to have a genetic component; and they were included in this table of multifactorial conditions. Further, none of the cases in this study would be more than age 32 years by the end of 1983.

Epilepsy is also a difficult category to interpret; and it is likely that heterogeneity exists in this disorder. However, since there is undoubtedly a genetic component to this disorder, it was felt appropriate to include this group in the "multifactorial" load if no specific cause for the epilepsy had been identified

Appendix B

Underascertainment of Dominant Conditions

In the present analysis Huntington chorea (ICD 333.4) was found to have an incidence rate of 16/1 million live births for persons in British Columbia born between 1952 and 1963, with zero incidence being reported for live births in more recent decades. The average age at onset of Huntington chorea is 41–45 years; only ~3% of all cases are diagnosed before age 25 years (Vogel and Motulsky 1986). Thus the actual incidence of Huntington chorea over the whole population of all ages is closer to 400/1 million live births than to 16/1 million live births (Trimble and Smith 1977; Vogel and Motulsky 1986). Another example is monogenic familial hypercholesteremia (included in ICD 272). The incidence of all cases reported under ICD 272 in the present study was <40/1 million live births; the true incidence of dominant hypercholesteremia is believed to be closer to 2,000/1 million live births when cases diagnosed after age 25 years are included (Trimble and Smith 1977; Vogel and Motulsky 1986).

References

Baird, P. A. 1983. Neural tube defects in the Sikhs. Am. J. Med. Genet. 16:49–56.

———. 1987. Measuring birth defects and handicapping disorders in the population: the British Columbia Health Surveillance Registry. Can. Med. Assoc. J. 36:109–111.

Baird, P. A., and E. C. MacDonald. 1981. An epidemiological study of congenital malformations of the anterior abdominal wall in more than half a million consecutive livebirths. Am. J. Hum. Genet. 33:470–478.

Baird, P. A., and J. R. Miller. 1968. Some epidemiological aspects of Down syndrome in British Columbia. Br. J. Prev. Soc. Med. 22:81–85.

Baird, P. A., and A. D. Sadovnick. 1985. Mental retardation in over half a million consecutive livebirths: an epidemiological study. Am. J. Ment. Defic. 89:323–330.

———. 1987. Life expectancy in Down syndrome. J. Pediatr. 110:849–854.

Czeizel, A., and K. Sankaranarayanan. 1984. The load of genetic and partially genetic disorders in man. I. Congenital anomalies: estimates of detriment in terms of years of life lost and years of impaired life. Mutat. Res. 128:73–103.

Hamerton, J. L., N. Canning, M. Ray, and S. Smith. 1975. A cytogenic survey of 14,069 newborn infants. I. Incidence of chromosome abnormalities. Clin. Genet. 8:223–243.

Health Surveillance Registry: annual report 1981. 1981. Division of Vital Statistics, Ministry of Health, Province of British Columbia, Victoria.

Jacobs, P. A. 1978. Epidemiology of chromosome abnormalities in man. Am. J. Epidemiol. 105:180–191.

Leung, T. J., P. A. Baird, and B. McGillivray. 1985. Hypospadias in British Columbia. Am. J. Med. Genet. 21:43–52.

Lowry, R. B., D. C. Jones, D. H. G. Renwick, and B. K. Trimble. 1976. Down syndrome in British Columbia, 1952–73: incidence and mean maternal age. Teratology 14:29–34.

Lowry, R. B., J. R. Miller, A. E. Scott, and D. H. G. Renwick. 1975. The British Columbia registry for handicapped children and adults: evolutionary changes over twenty years. Can. J. Public Health 66:322–326.

Lowry, R. B., N. Y. Thunem, and M. Silver. 1986. Congenital anomalies in American Indians of British Columbia. Genet. Epidemiol. 3:455–467.

Lowry, R. B., B. Tischler, W. H. Cockcroft, and D. H. G. Renwick. 1972. Incidence of phenylketonuria in British Columbia, 1950–71. Can. Med. Assoc. J. 106:1299–1302.

Lowry, R. B, and B. K. Trimble. 1977. Incidence rates for cleft lip and palate in British Columbia, 1952–71, for North American Indians, Japanese, Chinese and total populations: secular trends over twenty years. Teratology 16:277–283.

Myrianthopoulos, N. C., and C. S. Chung. 1974. Congenital malformation in singletons: epidemiological survey. Birth Defects 10:1–58.

Renwick, D. H. G. 1968. The combined use of a central registry and vital records for incidence studies of congenital defects. Br. J. Prev. Soc. Med. 22:61–67.

Searle, A. G., and J. H. Edwards. 1986. The estimation of risks from the induction of recessive mutations after ex-

posure to ionising radiation. J. Med. Genet. **23**:220–226.

Spouge, D., and P. A. Baird. 1985. Hirschsprung's disease in a large birth cohort. Teratology **32**:171–177.

Trimble, B. K., and P. A. Baird. 1978. Congenital anomalies of the central nervous system: incidence in British Columbia. Am. J. Med. Genet. **2**:1–5.

Trimble, B. K., and J. H. Doughty. 1974. The amount of hereditary disease in human populations. Ann. Hum. Genet. **38**:199–223.

Trimble, B. K., and M. E. Smith. 1977. The incidence of genetic disease and the impact on man of an altered mutation rate. Can. J. Genet. Cytol. **19**:375–385.

UNSCEAR report: genetic and somatic effects of ionizing radiation. 1986. United Nations, New York.

UNSCEAR: Ionizing radiation: sources and biological effects. United Nations Scientific Committee on the Effects of Atomic Radiation. 1982. Report to the General Assembly with annexes, United Nations, New York.

UNSCEAR: report of the United Nations Scientific Committee on the Effects of Atomic Radiation. 1966. General Assembly Official Records, 17th Sess., Suppl. 16 (A/5216), United Nations, New York.

UNSCEAR: sources and effects of ionizing radiation. United Nations Scientific Committee on the Effects of Atomic Radiation. 1977. Report to the General Assembly, United Nations, New York.

Vogel, F., and A. G. Motulsky. 1986. Human genetics: problems and approaches. 2d ed. Springer, New York.

Wilson, R. D., and P. A. Baird. 1985. Renal agenesis in British Columbia. Am. J. Med. Genet. **21**:153–165.