Effects of Father's Age on the Risk of Child Handicap or Death

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INTEREST in the relationship between age of father at the time of birth and the likelihood that a child will be affected by some genetic or partially genetic condition stems largely from the hope that such studies may serve to throw light on the extent and importance of possible differences in mutation frequency in male gametes at different stages in the reproductive cycle (see Penrose, 1955; Sonneborn, 1956). However, before the approach is likely to yield substantial information of the kind sought, there are problems of interpretation that must be considered and difficulties of acquiring appropriate empirical data in adequate quantities that must be surmounted.

Paternal age effects that are not mutational in origin may occur wherever a subgroup of the population exhibits an elevated risk of one kind or another in combination with a distribution of father's ages at the times of birth which differs from that for the population as a whole. Such contributions from population heterogeneity may be positively identified only where the empirical data for whole populations can be broken down by various relevant social, racial, and economic characteristics of the individuals involved.

Appropriate information exists in substantial quantity in the form of records of stillbirths, child deaths, child hospital admissions, physicians' notices of congenital anomalies detected at birth, and special registrations of handicapping conditions of children. However, only a minute fraction of the potentially available data has so far been extracted from such sources. In part, this failure has been conditioned by the organizational difficulties of bringing together diagnostic information which may be available on one type of record (e.g. of hospital admission or of death) and parental age information which may be contained in another, independently derived record (e.g. of birth) relating to the same individual. While such a "record linkage" operation may be performed quite simply by hand where only a few individuals are involved, it becomes excessively laborious where similar procedures are employed to process thousands or tens of thousands of such documents.

For the present study, use was made of rapid computer methods to link routinely records of child handicaps and deaths to the birth registrations of the same children (see Kennedy, 1961; Newcombe *et al.*, 1959; Newcombe and Kennedy, 1962). The data made available in this manner are regarded as serving primarily to illustrate the potentialities of the record linkage procedures.

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MATERIALS

Records from the British Columbia Register of Handicapped Children and Adults relating to 3,688 children born within that province in the six year period 1953–58 and registered during 1953–61 served as the basic file. Because these documents lacked parental age information, they were matched by computer against the birth files for those years, each being linked automatically with the birth registration of the particular handicapped child to produce a composite record containing both the diagnostic and the parental age information. Only those handicapped children for whom the ages of both parents were available are represented in the present data.

Registrations of 5,240 deaths to the end of 1959 of children born in British Columbia over the same six year period, similarly linked by computer to the appropriate birth registrations to obtain the necessary parental age information, were included with the handicap records to increase the total numbers of cases of the various diseases and disease categories. The linkage operations were carried out in such a way as to ensure that no child would be counted more than once in the tabulations, even where registered both as handicapped and as having died.

Further cases of the central nervous system malformations spina bifida, meningocele, hydrocephalus, and anencephaly, numbering 178 in all, were obtained from the files of stillbirth registrations over the same years.

Because fathers' ages are commonly omitted from the birth registration forms for illegitimate children, only records relating to legitimate children were used. Failures to link the handicap and death records back to the birth registrations were rare, leaving little room for bias from this source (for details see Newcombe, 1964; Newcombe and Tavendale, 1964).

No attempt was made to include for analysis information on occupation of father or racial origin (available from the birth registration forms but not from the punchcard files used in the above procedures) or on the religions of the parents (available from the marriage registrations of the parents, where the birth and marriage records are linked into family groupings). Such information will be important in the future when the accumulated records of handicaps and deaths are sufficiently numerous to permit breakdown of the data by a multiplicity of factors without a large proportion of the resulting cells being empty. With the present sizes of the files, the additional information would be of only limited use.

Controls were drawn from published statistics for all legitimate births in British Columbia over the basic six year period (see Vital Statistics Reports, 1953 to 1958). Strictly, these should have excluded the experimental groups, but, since the latter were small, little gain in precision would have been achieved by carrying out the required subtractions throughout.

The nature of the files and of the record linkage operation have been described in greater detail in previous accounts dealing with the effects of maternal age and birth order (Newcombe, 1964; Newcombe and Tavendale, 1964). These accounts also describe the computer methods used to obtain the tabulations from the punchcard and magnetic tape files.

Since these previous studies were carried out, however, much faster computer methods have been developed for "linking" independently derived records relating to the same persons or families. These methods have been based on use of a more modern computer (Control Data G20), which has calculation speeds of about 100 times and tape reading speeds of about 35 times those of the machine used earlier (Burroughs Datatron). As tested with files of birth and marriage records, the new procedures have been found capable of merging and linking at the rate of 2,300 incoming records per minute and at costs that are considerably less than those of preparing the punchcard files in the first place. Thus, there is no reason to suppose that the kind of integration of record files necessary for extraction of the present limited data might not readily be carried out as a routine operation in the future.

STATISTICAL METHODS

Because of the existence of substantial maternal age effects and the close correlation between maternal and paternal ages, a statistical procedure is needed which will permit identification of effects of paternal age which are independent of contributions from a maternal age effect.

Linear regression methods have been avoided in the present study because they tend to be insensitive or even misleading where the trend is other than linear with advancing age. While regression methods may be adapted to studies of nonlinear relationships, the choice of a suitable adaptation necessarily implies some preconception concerning the likely nature of the relationship one seeks to detect. In the case of possible paternal age effects, it is not clear at the outset whether to look for elevated risks to offspring of very young fathers, fathers of advanced age, or to those of fathers in some intermediate age group. Even if the age-risk curve were assumed to be J-shaped, like that for certain effects of the mother's age, or U-shaped, a regression test for such a relationship would fail to detect other transitions, of unpredicted kinds, from one age group to another.

One solution lies in carrying out the calculations of the risk for each paternal age group, relative to that for all other age groups combined, separately for each maternal age group. Significant deviations from unit relative risk, where mother's age is held constant, will reflect a paternal age effect from which contributions from maternal age effects have been removed. Furthermore, a statistical method exists which may be used to combine the relative risk figures for a given paternal age group, as derived separately from data for a number of different maternal age groups, into a single weighted mean relative risk (see Woolf, 1955). The same method provides confidence limits for the weighted means and chi-square tests of significance for deviations of these values from unity and for any heterogeneity in the data which have been so combined.

This approach has a number of advantages. It makes no assumptions concerning possible trends and may therefore be used to detect differences in relative risk from one paternal age group to another of kinds that may not

TABLE 1. HANDICAPPED AND DEAD CHILDREN BORN IN BRITISH COLUMBIA 1953–58, BY FATHER'S AGE GROUP AND MOTHER'S AGE GROUP

From child handicap and death records, combining all causes.

Father's age group	Number of children by mother's age group							Total
	0–19	20–24	25–29	30–34	35–39	40–44	45–99	
0–19	112	15	—	—	—	—	—	127
20–24	504	881	108	9	2	1	—	1505
25–29	137	1183	1060	174	24	2	—	2580
30–34	25	315	858	702	114	8	—	2022
35–39	7	65	272	566	378	53	1	1342
40–44	—	20	81	235	296	123	5	760
45–49	1	5	29	97	141	112	12	397
50–99	—	5	16	31	69	60	14	195
Total	786	2489	2424	1814	1024	359	32	8928

have been anticipated. Its use can be extended to permit, in similar fashion, simultaneous exclusion of the possible contributions from a number of variables where the data are sufficient to occupy most of the additional "cells" created by the necessary further breakdown into finer subgroups. Where the data are limited, as in the present application to restricted categories of disease, it is permissible to broaden the paternal age groups of older or of younger fathers and to test for differences between those broad groupings. The method is also flexible enough to permit study in a variety of ways of any heterogeneity which is detected, so as to provide insight into the nature of the interactions between variables which have given rise to it. Such a use will be described later.

For the sake of uniformity, the same chi-square method has been employed throughout, even where the numbers in the individual cells may have been too small for exact application of the test. More precise P values would in any case be of limited use because, among the large numbers of statistical tests carried out (i.e. more than 120), a few such values would be expected to fall beyond the conventional 5% or 1% levels of significance by chance alone. Fortunately, neither consideration affects to the same extent interpretations of comparisons for which the calculated significance substantially exceeds the one-in-a-thousand level.

RESULTS

Combined Data for All Causes

From the pooled data for all causes of handicap and death, distributed simultaneously by paternal and by maternal age groups (Table 1), and the corresponding control distribution (Table 2) have been derived relative risk curves for paternal age classes (Fig. 1), maternal age classes (Fig. 2), and for paternal age classes when the contributions from the large maternal age effects have been removed (Fig. 3). The 95% confidence limits have in each case been calculated by Woolf's method, in the first two figures as relating to simple relative risks and in the third as relating to weighted mean

TABLE 2. LIVE BIRTHS IN BRITISH COLUMBIA 1953–58, BY FATHER'S AGE GROUP AND MOTHER'S AGE GROUP

From the published statistics for legitimate births.

Father's age group	Number of children by mother's age group							
	0–19	20–24	25–29	30–34	35–39	40–44	45–99	Total
0–19	1838	347	12	—	—	—	—	2197
20–24	9602	21354	2934	257	38	5	—	34190
25–29	3019	26997	26507	4220	487	35	—	61265
30–34	504	6516	21150	17719	2868	213	3	48973
35–39	86	1397	6014	12791	8105	777	10	29180
40–44	23	361	1672	4555	6200	2171	49	15031
45–49	10	118	508	1377	2399	1602	154	6168
50–99	5	67	256	649	1060	925	144	3106
Total	15087	57157	59053	41568	21157	5728	360	200110

relative risks obtained by combining, in accordance with this method, the values for each particular age group of father as derived from data for the separate maternal age groups.

A statistically significant paternal age effect which is essentially independent of contributions from the large maternal age effect can be detected by this method for fathers' age groups 45–49 and 50–99 (Fig. 3; see also Table 12). The shape of the curve as a whole appears similar to that for relative risks when plotted against maternal age, although the differences are less striking.

An identical test could, in principle, be applied to data broken down by cause of disease. However, in view of the small number of cases represented in the individual cells of such a finer breakdown, it has seemed desirable to compare rather broader paternal age classes. This has been done in two ways.

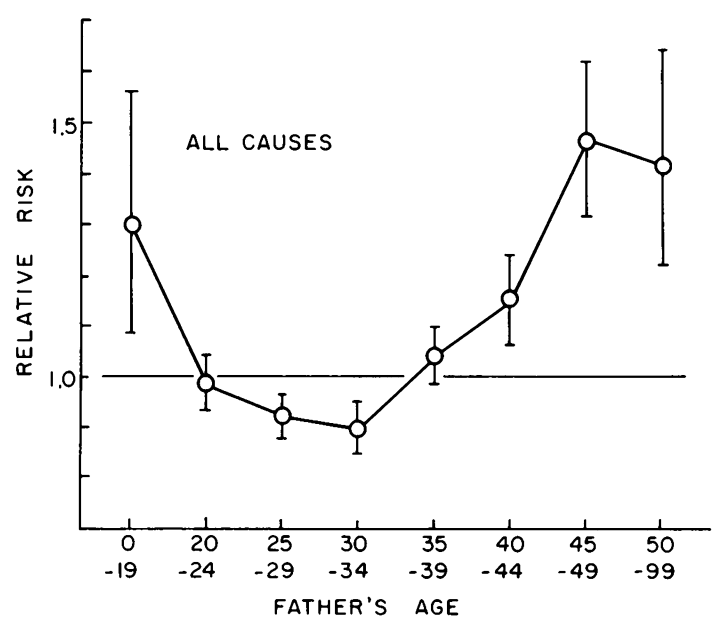

FIG. 1. Relative risk by father's age group (ignoring mother's age).

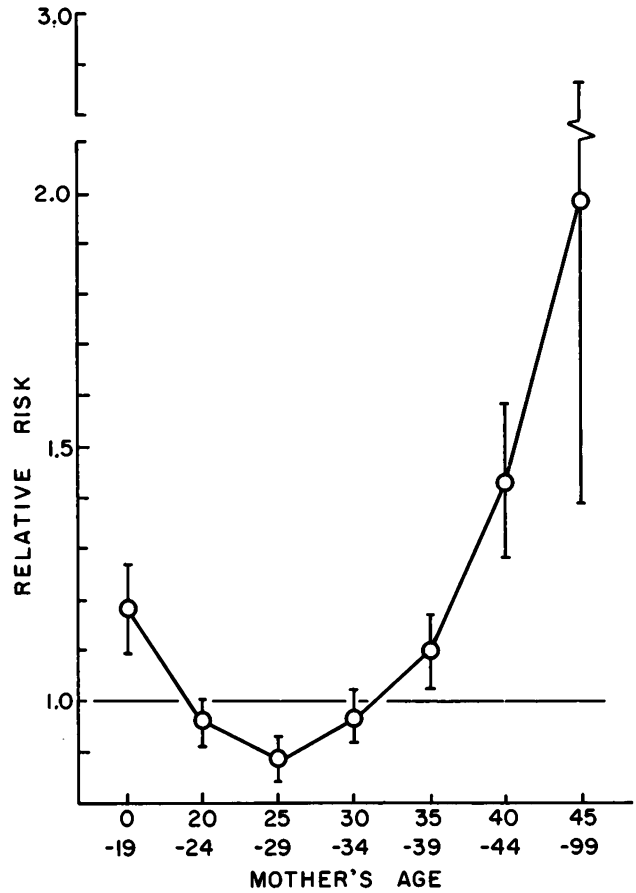

FIG. 2. Relative risk by mother's age group (ignoring father's age).

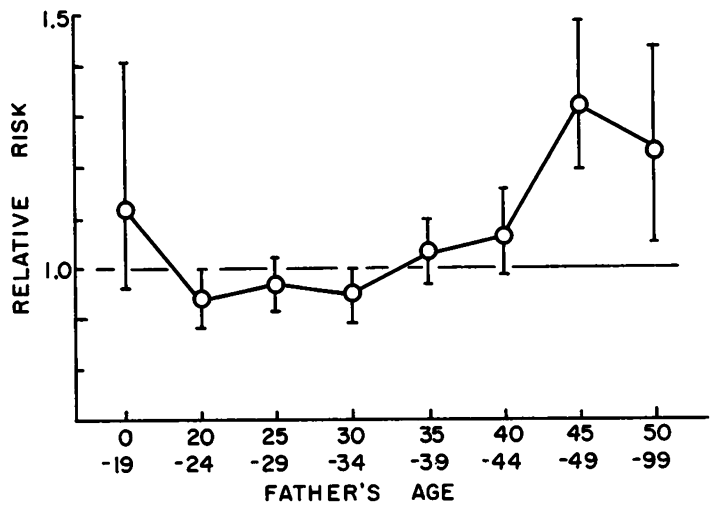

FIG. 3. Relative risk by father's age group, excluding contributions from effects of mother's age.

TABLE 3. EXCLUSION OF MATERNAL AGE EFFECT: RISKS TO CHILDREN OF YOUNGER FATHERS

All causes of handicap and death.

Maternal age group	Risk to fathers 0–24 years old cases	Risk to fathers 25–39 years old cases	Relative risk to younger age group	χ^2
0–19	616	169	1.15	
20–24	896	1563	.92	
25–29	108	2190	.90	
30–34	9	1442		
35–39	2	516		
40–44	1	63	.86	
45–99	0	1		
Weighted mean relative risk (df = 1)			0.95	1.8
Heterogeneity (df = 5)			—	6.8*

*$P < .25$

TABLE 4. EXCLUSION OF MATERNAL AGE EFFECT: RISKS TO CHILDREN OF OLDER FATHERS

All causes of handicap and death.

Maternal age group	Risk to fathers 40–99 years old cases	Risk to fathers 0–39 years old cases	Relative risks to older age group	χ^2
0–19	1	785		
20–24	30	2460	1.17	
25–29	126	2298	1.27	
30–34	363	1451	1.33	
35–39	506	518	1.16	
40–44	295	64		
45–99	31	1	1.02	
Weighted mean relative risk (df = 1)			1.23	31.1†
Heterogeneity (df = 6)			—	5.6*

*$P < .5$
†$P < .001$

To screen for special risks to offspring from younger fathers, comparisons have been made between paternal age classes 0–24 versus 25–39. Similarly, to screen for special risks associated with older fathers, paternal age class 40–99 has been compared with all other ages of fathers combined.

These two tests, when applied to the pooled data for all causes of handicap and death indicate no effect for young fathers (Table 3) but a highly significant effect for older fathers (Table 4).

Broad Categories of Disease

The tests have been applied separately to broad categories of disease, and to particular diseases, as recognized in the International Classification of Diseases (1955). Most of the broad categories of disease show an increased incidence in offspring from older fathers and some slight indication of an elevated risk among offspring of very young fathers (Table 5). However,

TABLE 5. DISTRIBUTION OF CASES BY PATERNAL AGE: BROAD CATEGORIES OF DISEASE*

Paternal age group	Numbers of handicapped and dead children by broad categories of disease										
	I	II	III	V	VI	VIII	IX	XIII	XIV	XV	Other
0–19	3	4	2	6	11	17	6	4	20	44	10
20–24	38	26	13	74	146	187	41	86	284	464	146
25–29	66	49	26	164	253	295	69	154	494	804	206
30–34	74	41	23	136	203	198	49	110	398	624	166
35–39	53	26	13	96	136	125	34	67	248	439	103
40–44	22	20	10	70	71	63	18	32	176	228	52
45–49	15	10	4	42	31	49	12	17	69	113	35
50–99	5	1	1	20	19	21	5	7	37	65	14
Totals	276	177	92	608	870	955	234	477	1726	2781	732
Handicap	127	177	92	608	720	—	—	477	1263	66	158
Death	149	—	—	—	150	955	234	—	463	2715	574

*International Classification of Diseases (1955), Roman numerals and equivalent code number ranges relating to broad categories of disease referred to in the Table:

I (001–138) infective and parasitic diseases;
II (140–239) neoplasms;
III (240–289) allergic, endocrine, metabolic, and nutritional diseases;
V (300–326) mental, psychoneurotic, and personality disorders;
VI (330–398) diseases of the nervous system and sense organs;
VIII (470–527) diseases of the respiratory system;
IX (530–587) diseases of the digestive system;
XIII (720–749) diseases of the bones and organs of movement;
XIV (750–759) congenital malformations;
XV (760–776) certain diseases of early infancy.

The category called "other" includes about 21% handicaps and 79% deaths; accidents account for 60% of all causes.

TABLE 6. RELATIVE RISKS OF BROAD CATEGORIES OF DISEASE AMONG CHILDREN OF YOUNGER AND OF OLDER FATHERS

With and without exclusion of contributions from maternal age effects.

Broad category code	cases	Younger fathers (0–24 *vs* 25–39)				Older fathers (40–99 *vs* 0–39)			
		risk	χ^2	Excluding age effect of mother: risk	Excluding age effect of mother: χ^2	risk	χ^2	Excluding age effect of mother: risk	Excluding age effect of mother: χ^2
I	276	0.81	1.4	0.75	1.9	1.30	2.4	1.41	2.8
II	177	0.99	0.0	0.97	0.0	1.54	4.7	1.46	2.4
III	92	0.93	0.1	1.12	0.1	1.41	1.5	2.25	5.3
V	608	0.77	4.4	0.79	2.4	2.01	49.8†	1.15	1.1
VI	870	1.02	0.0	1.02	0.0	1.17	2.5	1.19	2.2
VIII	955	1.26	8.4*	0.94	0.4	1.17	2.8	1.61	17.8†
IX	234	1.18	1.0	0.84	0.7	1.27	1.7	1.56	3.5
XIII	477	1.04	0.1	0.87	0.8	0.96	0.1	1.19	1.0
XIV	1727	1.03	0.1	1.07	0.6	1.41	27.7†	1.28	9.1*
XV	2781	1.04	0.7	0.95	0.7	1.16	1.9	1.32	4.3
Other	732	1.26	6.2	1.16	1.6	1.24	15.4†	1.13	3.4

*$P < .01$
†$P < .001$

only two statistically significant paternal age effects remain when contributions from maternal age effects are removed (Table 6). Respiratory diseases, a category represented wholly by deaths, most of them from pneumonia (703 cases out of the total of 955) but including lesser numbers from bronchitis (91), acute laryngitis and tracheitis(68), and influenza(49), are 60% more common among offspring from older fathers (Table 7); and congenital malformations are about 30% more common (Table 8). It will be noted that pa-

TABLE 7. EXCLUSION OF MATERNAL AGE EFFECT: RISKS TO CHILDREN OF OLDER FATHERS

Respiratory diseases (Code VIII).

Maternal age group	Risk to fathers 40–99 years old cases	Risk to fathers 0–39 years old cases	Relative risks to older age group	χ^2
0–19	1	108	3.67	
20–24	4	306	1.36	
25–29	22	239	2.14	
30–34	37	124	1.59	
35–39	45	42	1.28	
40–44	21	3	1.65	
45–99	3	0		
Weighted mean relative risk (df = 1)			1.61	17.8*
Heterogeneity (df = 5)			—	3.6

*$P < 0.001$

TABLE 8. EXCLUSION OF MATERNAL AGE EFFECT: RISK TO CHILDREN OF OLDER FATHERS

Congenital malformations (Code XIV).

Maternal age group	Risk to fathers 40–99 years old cases	Risk to fathers 0–39 years old cases	Relative risks to older age group	χ^2
0–19	0	124	1.68	
20–24	8	461		
25–29	18	457	.92	
30–34	82	286	1.52	
35–39	101	102	1.18	
40–44	68	13	1.08	
45–99	5	1		
Weighted mean relative risk (df = 1)			1.28	9.1†
Heterogeneity (df = 5)			—	8.3*

*$P < 0.15$
†$P < 0.003$

ternal age is not significantly correlated with the risks of death or handicap due to causes referred to collectively as "other," of which 60% are accidents.

Particular Causes of Disease

Data broken down by particular causes of disease have been analyzed in a similar manner (Tables 9 and 10). Only one significant effect of fathers' age, exclusive of contributions from the maternal age effects, was found. Congenital malformations of the nervous system and sense organs, other than the central nervous system anomalies spina bifida, meningocele, hydrocephalus, and anencephaly, are about twice as common among offspring of older fathers (Table 11). The risk is especially high for those older fathers who happen to be married to young mothers, i.e. about 6.8 per thousand as compared with 0.57 per thousand for young fathers married to young mothers. This apparent heterogeneity in the paternal age effect as seen in data broken down by successive maternal age groups will be discussed later.

TABLE 9. DISTRIBUTION OF CASES BY PATERNAL AGE

Particular diseases.

Paternal age group	Numbers of handicapped and dead children by particular diseases*									
	325	325.4	351	353	384	748	Y38.0	751 Y38.2	752 Y38.1	753
0–19	4	2	3	1	4	3	—	—	—	3
20–24	48	7	32	16	39	65	15	12	24	20
25–29	125	14	49	18	72	112	32	21	33	29
30–34	101	26	38	16	69	86	28	11	37	37
35–39	72	35	37	9	44	47	20	11	13	24
40–44	61	35	18	4	19	20	6	8	7	18
45–49	31	20	7	2	12	10	4	2	1	3
50–99	20	13	6	1	7	4	2	1	0	1
Totals	462	152	190	67	266	347	107	66	115	135
Stillbirths	—	—	—	—	—	—	107	8	69	—
Handicaps	462	152	190	67	266	347	—	45	30	116
Deaths	—	—	—	—	—	—	—	13	16	19

Paternal age group	Numbers of handicapped and dead children by particular diseases*								
	754	755	756	757	758	759	760	762	774 776
0–19	8	4	3	—	—	2	3	9	16
20–24	117	38	25	7	19	20	23	126	189
25–29	160	93	37	33	50	37	51	207	302
30–34	150	57	26	24	25	30	41	154	235
35–39	90	48	17	11	18	17	24	102	170
40–44	70	24	14	5	13	11	19	49	93
45–49	34	13	4	5	2	2	10	31	29
50–99	17	7	2	2	4	3	7	19	16
Totals	646	284	128	87	131	122	178	697	1050
Stillbirths	—	—	—	—	—	—	—	—	—
Handicaps	405	284	42	87	131	122	—	—	—
Deaths	241	—	86	—	—	—	178	697	1050

*International Classification of Diseases (1955), code numbers relating to particular diseases referred to in the Table.

325 — mental deficiency;
325.4 — mongolism;
351 — cerebral spastic infantile paralysis;
353 — epilepsy;
384 — strabismus;
748 — clubfoot;
751, Y38.2 — spina bifida and meningocele;
752, Y38.1 — congenital hydrocephalus;
Y38.0 — anencephalus;
753 — other congenital malformations of the nervous system and sense organs;
754 — congenital malformations of the circulatory system;
755 — cleft palate and harelip;
756 — congenital malformations of the digestive system;
757 — congenital malformations of the genitourinary system;
758 — congenital malformations of bone and joint;
759 — other and unspecified congenital malformations;
760 — intracranial and spinal injury at birth;
762 — postnatal asphyxia and atelectasis;
774 — immaturity with mention of other subsidiary conditions;
776 — immaturity, unqualified.

Interpretations

Understanding of the observed effects of paternal age differences would be greatly facilitated if the files could be further broken down by social variables, such as occupation of the father and the races and religions of the parents, that might be simultaneously correlated with both the risk of death

TABLE 10. RELATIVE RISK OF PARTICULAR DISEASES AMONG CHILDREN OF YOUNGER AND OF OLDER FATHERS

With and without exclusion of contributions from maternal age effects.

Particular diseases code	cases	Younger fathers (0–24 *vs* 25–39) risk	χ^2	Excluding age effect of mother risk	χ^2	Older fathers (40–99 *vs* 0–39) risk	χ^2	Excluding age effect of mother risk	χ^2
325	462	0.67	7.2*	0.70	4.0	2.31	59.5†	1.19	1.4
351	190	1.08	0.2	1.25	0.8	1.41	3.1	0.96	0.2
353	67	1.51	2.1	2.27	4.4	0.84	0.2	0.72	0.5
384	266	0.89	0.5	0.92	0.1	1.21	1.1	1.35	2.2
748	347	1.06	0.2	0.81	1.5	0.79	1.8	0.93	0.1
— Y38.0	107	0.72	1.4	0.88	0.1	0.91	0.1	0.80	0.4
751 Y38.2	66	1.07	0.0	1.40	0.6	1.45	1.2	1.38	0.6
752 Y38.1	115	1.11	0.2	1.52	1.8	0.54	2.8	0.83	0.2
753	135	0.98	0.0	1.07	0.0	1.41	2.2	2.07	7.8*
754	647	1.21	3.4	1.30	4.3	1.66	25.4†	1.32	4.8
755	284	0.81	1.5	0.87	0.5	1.33	3.0	1.16	0.5
756	128	1.34	1.8	1.30	1.0	1.34	1.4	1.37	0.9
757	87	0.39	5.5	0.39	5.0	1.16	0.2	1.04	0.0
758	131	0.78	0.9	0.84	0.3	1.23	0.7	1.42	1.2
759	122	1.00	0.0	1.08	0.1	1.09	0.1	1.10	0.1
760	178	0.86	0.5	0.89	0.1	1.83	10.5*	1.10	1.8
762	697	1.12	1.3	0.98	0.0	1.20	2.7	1.07	0.2
774 & 776	1050	1.10	1.7	0.95	0.3	1.09	1.0	1.09	0.7
325.4	152	0.46	4.9	0.66	0.8	5.86	117.2†	1.21	0.7

*$P < .01$
†$P < .001$

TABLE 11. EXCLUSION OF MATERNAL AGE EFFECTS: RISKS TO CHILDREN OF OLDER FATHERS

Congenital malformations of the nervous system and sense organs, excluding spina bifida, meningocele, hydrocephalus, and anencephaly; code 753.

Maternal age group	Risk to fathers 40–99 years old cases	Risk to fathers 0–39 years old cases	Relative risk to older age group	χ^2
0–19	–	12	11.97	
20–24	4	29		
25–29	2	38	1.22	
30–34	6	24	1.33	
35–39	7	8	1.04	
40–44	3	1	.62	
45–49	–	–		
Weighted mean relative risk (df = 1)			2.07	7.8*
Heterogeneity (df = 4)			–	17.5†

*$P < .01$
†$P < .002$

or handicap and also with differences in the paternal age distributions. Before a finer breakdown would be profitable, however, larger quantities of data would be needed to occupy the increased number of cells so created. Nevertheless, even the present files do yield some indications that population heterogeneities may contribute substantially to the observed effects.

From the combined data for all causes of handicap and death there is evidence that the relative risk associated with a particular age group of

TABLE 12. TESTS FOR HETEROGENEITY IN THE RELATIVE RISKS ASSOCIATED WITH PARTICULAR FATHER'S AGE GROUPS, WHEN CALCULATED SEPARATELY FOR DIFFERENT MATERNAL AGE GROUPS (All causes)

From data in Tables 1 and 2.

Mother's age group	Relative risk for particular father's age groups							
	0–19	20–24	25–29	30–34	35–39	40–44	45–49	50–99
0–19	1.20	1.02	.84	.95	(1.57)	—	(1.92)	—
20–24	1.00	.92	1.01	1.13	1.07	1.27	(.97)	(1.72)
25–29	—	.89	.95	.98	1.11	1.19	1.40	1.53
30–34	—	(.80)	.94	.85	1.02	1.21	1.65	1.10
35–39	—	(1.09)	1.02	.80	.94	.98	1.25	1.37
40–44	—	(6.39)	(.91)	(.59)	1.10	.85	1.16	1.04
45–99	—	—	—	—	(1.13)	(1.18)	.80	1.17
Weighted mean	1.17	.94	.97	.95	1.03	1.07	1.32	1.23
χ^2 (df = 1)	2.5	3.4	1.6	4.0	1.0	2.6	24.4†	6.8*
χ^2 heterogeneity	.4	7.2	3.6	18.0	4.7	9.9	8.2	3.7
df	1	5	5	5	5	5	6	5
P	—	—	—	.003	—	.08	—	—

Parentheses indicate that one or more of the four numbers from which the relative risk is calculated is less than 10.

*$P < .01$

†$P < .001$

father (as compared with all other ages of father combined) is not uniform from one maternal age group to another, when calculated for data that have been parcelled out in this fashion. Significant heterogeneity of such a kind is observed, for example, for father's age group 30–34 (Table 12). There is in fact some indication that the relative risk associated with a particular paternal age group diminishes with increasing age of the spouse.

This suggests that husband-wife age differences *per se* may be an important factor. When the relative risk values in Table 12 are redistributed by the differences in age group of husbands and wives, the higher values appear to be associated especially with those married couples in which the wife's age is much less than the husband's (Table 13). The weighted means, in fact, regress smoothly from a value of approximately 0.9 (which is significantly less than unity) for parents of the same age group to values in the vicinity of 1.3 (which are significantly higher than unity) where the wife is younger than the husband by three or more five-year age groups.

Such an interaction might perhaps arise where the practice of marrying a wife much younger than oneself is associated with low socioeconomic status and with the special high risks that are tied to social factors.

Another example of nonuniformity in the paternal age effect through a succession of maternal age classes is observed for congenital malformations of the nervous system and sense organs, other than spina bifida, meningocele, hydrocephalus, and anencephaly (Table 11), older fathers being associated with higher relative risks (as compared with other paternal age groups) when married to young wives. The difference is large and is highly significant. Again, such an interaction between the maternal and paternal age groupings might conceivably result where marriages between older men and very young women are especially common within a high-risk subgroup of the population.

TABLE 13. TEST FOR AN EFFECT OF PARENTAL AGE DIFFERENCE *per se*

Rearrangement of relative risk values from Table 12.

	Relative risk for particular father's age groups, by difference in age group of father and mother										
	Wife younger than father						Same age group	Wife older than father			
Father's age group	−6	−5	−4	−3	−2	−1	0	+1	+2	+3	+4
0–19	—	—	—	—	—	—	1.20	1.00	—	—	—
20–24	—	—	—	—	—	1.02	.92	.89	(.80)	(1.09)	(6.39)
25–29	—	—	—	—	.84	1.01	.95	.94	1.02	(.91)	—
30–34	—	—	—	.95	1.13	.98	.85	.80	(.59)	—	—
35–39	—	—	(1.57)	1.07	1.11	1.02	.94	1.10	(1.13)	—	—
40–44	—	—	1.27	1.19	1.21	.98	.85	(1.18)	—	—	—
45–49	(1.92)	(.97)	1.40	1.65	1.25	1.16	.80	—	—	—	—
50–99	(1.72)	(1.53)	1.10	1.37	1.04	1.17	—	—	—	—	—
Weighted mean		1.31		1.29	1.11	1.11	.93	.91	.87	1.65	
χ^2 (df = 1)		7.6*		19.8†	10.9†	.2	11.6†	3.6	.8	1.3	

*$P = .006$
†$P < .001$

TABLE 14. BREAKDOWN BY RACIAL ORIGIN. RISKS TO CHILDREN OF OLDER FATHERS. RESPIRATORY DISEASES

Data of Table 7 broken down by Indian *vs.* non-Indian.

	Indians				Non-Indians			
Maternal age group	Risk to fathers 40–99 years old cases/controls	Risk to fathers 0–39 years old cases/controls	Relative risk to older group	χ^2 (df = 1)	Risk to fathers 40–99 years old cases/controls	Risk to fathers 0–39 years old cases/controls	Relative risk to older group	χ^2 (df = 1)
0–19	1/0	33/135			0/8	75/2103		
20–24	4/10	75/288	1.96		0/84	231/8634	0.34	
25–29	12/28	79/235	1.27		10/399	160/8753		
30–34	22/52	37/146	1.67		15/1151	87/5561	0.83	
35–39	23/88	15/41			22/1550	27/1733	0.91	
40–44	13/41	1/7	0.85		8/778	2/169		
45–99	2/5	0/0			1/65	0/1	0.91	
Weighted mean relative risk			1.26	1.5			0.98	0.0

More direct evidence exists of a contribution from the heterogeneity between population subgroups to an observed paternal age effect. The large and statistically significant increase in risk of respiratory disease among offspring of older fathers (Table 7) is associated with the unduly high proportion of North American Indian children among those reported as dying from such ailments. Identification of Indian parentage is relatively simple for births up to and including those in 1956, because of the use of a special series of birth registration numbers which, unfortunately for present purposes, was discontinued in 1957. Thus it is possible from the registration numbers alone to identify the 7,031 Indian children born in 1953–56 out of the 11,132 known to have been born in the whole six year period 1953–58, i.e. 63% of the total. Although Indian children account for only 5.2% of the birth population as a

whole, more than half of those children dying of respiratory diseases, where the fathers were in the age group 40–99 years, are known from their birth registration numbers to be Indian.

Fortunately, a more precise study of the contribution from such racial heterogeneity to this particular paternal age effect was possible. By reference to the death statistics cards, cases of Indian origin were identified for all of the birth years 1953–58, and control data were obtained by carrying out special tabulations on birth name cards for the year 1955 (Table 14). The parental age distributions among the controls were found to differ markedly for Indians and non-Indians, in that a greater proportion of older fathers occurred among the Indians. Thus, it is not surprising that much of the paternal age effect disappeared when the data for respiratory diseases were analyzed separately for Indians and for non-Indians.

Some further insight into the causes of this particular paternal age effect is gained by searching for pairs of sibs among the children dying of respiratory diseases. Among affected Indian children, a much higher proportion who had similarly affected siblings was observed than among non-Indians, i.e., 16% (51/317) as compared with 2.5% (16/638). Thus, not only was the risk of child death from such diseases greater for Indian families, i.e., 31.3 per thousand liveborn children as compared with 3.1 for non-Indians, but the likelihood of repeat occurrences in the same families was also higher. Contagion from a moribund child to his siblings does not appear to be a major factor, because rarely did the deaths within a family occur close together, i.e., within a month or two of one another. This was true of both groups, the proportions of such closely spaced pairs of deaths being 2/25 for Indians and 1/8 for non-Indians. A continuing adverse environment in certain families, to which each child in turn is subjected, may be inferred.

The kind of interpretation that has been discussed up to this point might or might not apply to the increased risk of congenital malformation, as a disease category, among children from older fathers (Table 8). There is no obvious heterogeneity with respect to this effect as seen in data broken down by maternal age groups, and the effect does not appear to be associated in any striking way with particular kinds of malformation (Table 10). An elevated mutation rate in aging fathers could perhaps be a contributory factor, but, if so, this cannot be established at the present time.

DISCUSSION

To enable the various possible causes of the observed paternal age effects to be further disentangled, a larger supply of empirical data is needed, of a kind which can be broken down not only by diagnostic category, birth order, and parental ages but also by such social factors as race, religion, and father's occupation. Such data exist in many regional vital statistics systems, both as relating to cases and to the birth populations from which they were drawn. Unfortunately, however, the files are not usually so organized as to permit the information to be extracted economically in the required form.

It is by no means certain that the needed information will be as readily ob-

tainable in the future as it is now. For example, the merit of retaining on the birth registration forms a question dealing with racial origin is sometimes challenged on the grounds that more accurate statistical information could be obtained by survey methods. Unfortunately, however, the products of such surveys would be virtually useless in analyses of the present kind unless they dealt with the whole population so as to include the families of all of the "affected" children. Even under these conditions there would remain the major problem of linking by name specific for each individual the survey information for each of the cases and for a very large control group representing the birth population from which they were drawn. On the other hand, if the information as currently collected does not become more widely used in the future, the case for retaining such a question on the birth registration form will be weakened thereby.

Current interest in congenital anomalies, stimulated in part by the thalidomide incident, has served to focus attention on the need for more accurate counting of the children affected by this category of conditions. The usual stated purposes of such counts are those of assessing the magnitude of the associated health problem and of detecting possible future increases in particular anomalies. And yet, the value of such ascertainments of cases will be largely lost if provision is not made also for future statistical investigations into possible causal relationships, preferably representing a degree of sophistication greater than that which was possible in the present study.

SUMMARY

Special risks to children, associated with differences in the ages of the fathers, have been studied using a special file of 8,928 registrations of child handicaps and deaths among individuals born in the Canadian province of British Columbia in the six year period 1953–58. To secure the necessary paternal and maternal ages at the times of birth, the handicap and death records were "linked" by computer to the birth registrations of the affected individuals by searching and matching within the accumulated files of births for the six year period.

The combined data for all causes show a significantly increased risk among children of fathers aged 45 and over. This effect persists after possible contributions from a maternal age effect and the close correlation of fathers' with mothers' ages have been removed.

A similar and statistically significant paternal age effect is observed also in those parts of the data relating to two broad categories of condition, the respiratory diseases and the congenital malformations, and to a particular small group of congenital malformations of the nervous system and sense organs which excludes the more common central nervous system anomalies spina bifida, meningocele, hydrocephalus, and anencephaly.

Possible origins of the paternal age effects are discussed. The effect shown by the pooled data for all causes of disease appears to be associated especially with older fathers who have married wives much younger than themselves, a circumstance suggestive of a contribution from population heterogeneity.

Supporting this interpretation, the elevated risk of respiratory disease among offspring of older fathers largely disappears when data for North American Indians and for non-Indians are treated separately.

Elevated frequencies of mutant genes or chromosomes in the reproductive cells of aging fathers might perhaps contribute to the effect as seen in the data for congenital malformations. Such a contribution would be difficult to establish, however, without greater amounts of data, broken down by such potentially important social variables as race, religion, and father's occupation. The needed information exists in substantial quantity in a number of regional vital statistics systems but is not for the most part in a readily accessible form.

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