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Measuring the Public Health Impact of the Aneuploidies

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If the protection of man against mutagenic agents in general, and against those that cause aneuploidies in particular, is to have an increasingly rational basis with the passage of time, quantitative or at least semiquantitative assessments of risks are needed. These should take into account both the likely numbers of induced cases and the likely severities of the different conditions. In the past, quantitative data relating to severity have been limited or nonexistent, but the data sources exist by which follow-up studies may be carried out to determine age-specific and cumulative risks of hospitalization and death, the durations of hospital stays, and the economic burden to society which these represent. To illustrate the use of such sources, the cumulative risks of death in children with anomalies of the autosomes and of the sex chromosomes, over the first 19 years of life, are compared with those for other kinds of hereditary and environmentally caused handicaps that are reported in that age group.

Introduction

Although most of the discussion in this workshop will have to do with the occurrence of aneuploidies in lower organisms; the ultimate objective of our deliberations would appear to be the protection of man against possible increases in the frequency of chromosomal diseases arising from the presence of mutagens in the environment. I note in this connection that the first session and the last formal presentation deal respectively with the "human aspects" and the "moral implications" of aneuploidy, and that the sponsoring organization has as its prime mission the protection of man against environmental cause of ill health.

It would appear appropriate, therefore, to consider for a moment the kinds of information that are most needed if the protection of man against harmful environmental agents, and more specifically against the various kinds of environmental mutagens, is to have an increasingly rational and quantitative basis with the passage of time.

If it were possible simply to ban the use of all agents known to have mutagenic effects, the task of the scientist could be largely limited to that of designing screening procedures that would identify any substances that had, or were likely to have, mutagenic activity in man. Experience with radiation protection, however, has taught us that the problem is essentially quantitative in nature, and that the goal of absolute safety, if pursued without regard to competing risks, can bring hardships of other kinds, for example, debate over the merits of mammography centers, not on a question of banning the procedure, but rather on ascertaining what ages and other circumstances render the benefits likely to outweigh the risks. The same would be true for use of a mutagenic and presumably carcinogenic drug such as metronidazole (Flagyl) for amebic dysentry and vaginal trichomoniasis when alternative forms of therapy are less effective or more toxic or both.

It is therefore not sufficient that environmental mutagens be identified, unless something is known about their potencies, to provide at least a clue concerning the amount of human trouble that might result from exposure to them.

In the case of radiation, the chairmen of various committees and subcommittees concerned with protection have, with considerable difficulty, persuaded geneticists to come up with what they think are the most likely numbers of affected individuals resulting from the exposure of a given number of people to particular levels of radiation. But even such numbers are poor indicators of harm if one lacks a satisfactory measure of the spectrum of

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severities among the various individuals affected by the hereditary conditions. For both the chromosomal and the nonchromosomal genetic disease of man there is a curious lack of quantitative data pertaining to severity. Thus, reports which attempt to compare, for example, the magnitude of the somatic harm with that of the genetic harm, and to derive an indicator of the total detriment of the two kinds taken together are pretty much forced to give equal weight to a cancer death and to a genetic disease, in the belief that the geneticists have included only the cases with serious manifestations.

For cancer deaths, of course, the magnitudes of the harm to individuals will vary in measurable ways with respect, for example, to the extent of the loss of life expectancy, the amount of use made of health care facilities, and the economic burden to society. The spectrum for each such variable is quantifiable, and there is considerable interest in the acquisition and use of relevant raw data pertaining to cancer. In principle, the same sorts of indicators of severity could be applied also to the hereditary diseases, in particular to the chromosomal anomalies, but human geneticists tend to be much less preoccupied with the quantitative public health aspects of their speciality than are the cancer epidemiologists.

This brings me to the main thrust of the present paper. When estimating radiation risks we have tended to equate induced cancer deaths with induced genetic defects, and to add the two together as a measure of the total harm. What is lacking is some knowledge of the numbers of individuals who are only mildly affected by the hereditary conditions, and the numbers for whom the disease is equal to or worse than dying of cancer and losing on the average some 10-12 years of life expectancy.

At least a few statistical measures of severity are now possible, however, for the hereditary traits including the aneuploidies, and I propose to discuss briefly the methods by which these measures may be applied and to give examples.

Data Sources

The data sources to which I will refer relate to the population of the Canadian province of British Columbia which now numbers somewhat over 2,000,000 people. The province has an exceptionally well organized registry of handicapping conditions, plus a surveillance scheme for congenital anomalies, so that exceedingly few cases of serious hereditary conditions appearing in the first decade or two of life escape inclusion in the recording system.

The unique feature of the data base, however, does not lie just in the contents of these files, but has to do rather with the special manner in which they are organized for follow up. Each ill-health record is linked by computer search with the appropriate birth registration (if that event occurred in British Columbia during 1946 or later) and with the appropriate death registration (if the individual died in the province). Added into these follow-up histories are the records of hospitalizations of children over a 10-year period, based on the files of a universal system of hospital insurance. The death registrations and hospital records serve also as a check on the completeness of registration of some of the handicapping conditions of interest (*1-5*). Needed for such follow-up are the full birth names and birth dates, plus provinces, states or countries of birth, and where possible the mother's maiden surname as identifying sibling group and aiding further the resolution of ambiguous matches.

This work, which was carried out at Chalk River, mainly by Miss Martha Smith, has now been entirely transferred to the Department of Medical Genetics at the University of British Columbia, under Dr. James R. Miller who is assisted by Mr. Soo Hong Uh. The late Dr. Benjamin K. Trimble was in direct charge of the work there until the time of his death last year. The total machine-readable files, including the vital registrations back to 1946, numbered well over a million records of health related events, all containing personal identifying information to permit the compilation of individual lifetime histories.

The computer linkages are exceedingly rapid, and it has been possible to carry out searches of the large birth files and to obtain linkages with incoming handicap, surveillance, hospital, and death records at a rate of some 40,000 per minute (*6*). In this manner lifetime health histories have been constructed for handicapped children, and for control groups consisting of all children born in the same years. From these histories it is possible to derive such measures of severity as the age-specific death rates, hospitalization rates, and durations of stay in hospital. Permission to use the vital records in this study was obtained through Statistics Canada, from the Health Branch, Department of Health and Welfare, Province of British Columbia. The permission was conditional upon strict observance of the oath of secrecy respecting the nonstatistical information contained in the records.

To such measures of severity may be added registration itself, as representing some sort of threshold. It is appropriate to consider this first.

Registration as a Measure of Severity

Even good registries of handicapping conditions are commonly regarded as failing to ascertain many

Table 1. Frequencies of chromosome anomalies.

	Chromosome anomalies/ 100 liveborn	
	Special surveys[a]	Handicap registrations[b]
Down's syndrome	0.12	0.16-0.19
Other autosomal trisomies	0.02	0.01
Sex chromosome anomalies	0.22	—
Autosomal structural anomalies	0.24	—
Total	0.60	0.16-0.20

[a]UN data (9).
[b]Data of Trimble and Doughty (7).

cases of the important hereditary diseases, but such under-registration tends to be highly selective, and the extent of it is relevant and informative. For example, whereas Down's syndrome and the other autosomal trisomies clearly represent major handicaps for the affected individuals and severe burdens on the families and society, the same cannot be said of the majority of the sex chromosome anomalies, or of most translocations and other rearrangements. The British Columbia registry does in fact, fail to include about two-thirds of the total cases of chromosome anomalies as estimated in a recent United Nations report (7-9). The exclusions, however, are of the less severe traits; included in the registry are, if anything, more cases of automosal trisomies than would be expected from the data in the UN report (Table 1).

Clearly, if one were attempting to assess the public health impact of the chromosome anomalies, it would be quite misleading to use the survey totals quoted in the UN document, without weighting for severity. The registration process in British Columbia has already created a distinction on the basis of severity. The extent of the affliction in the case of Down's syndrome, which is well registered, is probably much greater than that associated with a 10-year loss of life expectancy due to a cancer death, but one would hesitate to say the same concerning the extent of the afflication with Turner's or Kleinfelter's syndrome which are incompletely registered.

The total number of cases of all types of chromosome anomaly has therefore limited meaning as a measure of public health impact, but it does get used in the process of assessing radiation risks, along with the numbers of other genetic disorders, and often in proximity with the numbers of cancer deaths.

Death Rates as Indicating Severity

There is, of course, no single quantifiable indicator of severity that can be applied with equal appropriateness to all diseases including those caused by the aneuploidies. One is forced to consider first those indicators that are most readily available. In the case of the British Columbia files, each of the personal health related records has been linked into an individual chronological history in a fashion that would permit one to extract the sequence of successive hospitalizations of an individual, so that from these one could derive both the age specific and the cumulative frequencies of admissions and discharges, and the durations of stay. However it seemed simpler and more appropriate to start first with age-specific and cumulative frequencies of death, not that this provided as good a measure of severity, but simply because the other kinds of data would be more difficult to interpret if one had not already analyzed the information pertaining to death. Furthermore, the methods for analysis of the data on hospitalization would be easier to develop if similar methods had been worked out first for the mortality data.

There is another reason for emphasizing death frequencies in study populations as a useful even if imperfect measure of severity. This is that the mortality data will become much more readily accessible in the future, both in Canada and in the U.S.A. Canada now has a computerized "mortality data base" with which it is possible to search rapidly for death records on a very large scale indeed, and the United States is in the early stages of developing the plans for a national death index, intended to serve a similar purpose. Undoubtedly both facilities will be used increasingly by epidemiologists, for the purpose of assessing the public health impacts of harmful agents in the workplace, and perhaps also in the environment away from work. So there is no reason why human geneticists could not, in the same fashion, follow up any large group of individuals known to have hereditary—more specifically, chromosomally caused—disabilities.

Human geneticists do provide, from time to time, anecdotal evidence that this or that disease is really quite severe, but almost never are the statistics adequate to describe the range of severity for any particular condition, let alone for the whole of any broad category of genetic disease such as that due to aneuploidies. As a result, one begins to wonder whether subjective impressions in these matters are to be trusted, and why there is so little interest in collecting appropriate quantitative data on an adequate scale.

With this in mind I will first show a graph illustrating the kind of results obtained from the British Columbia files by Tony Chu, a computer science student who worked with us during the summer of 1977,

and will then go on to describe some of the difficulties in defining precisely what it is one wants to measure.

Some Results

Perhaps the simplest comparison made possible by the linked personal histories has to do with the cumulative numbers of deaths in cohorts of children. In Figure 1 the deaths in handicapped children are expressed as a factor by which these exceed the expected numbers of deaths as based on all births in the same years. The figure compares registered cases of sex chromosomes (S.C.) and autosomal chromosome (A.C.) diseases with the rest of the broad etiological categories represented in the handicap registry, i.e., with the recessive (REC), dominant (DOM), congenital malformation (C.M.), sex-linked (S.L.), multifactorial excluding the congenital malformations (MULT), environmentally caused (ENV), and unknown (UNKN) categories. The graphs are based on some 26,189 affected children in all, of whom 928 have chromosomal diseases. Cumulative mortality is shown in this manner up to the end of each year of life over the first 19 years.

To judge from these comparisons, the chromosomal diseases would appear to be (a) less severe than the recessive diseases, (b) about equal in severity to the dominant diseases and congenital malformations, and (c) much more severe than the remaining four categories.

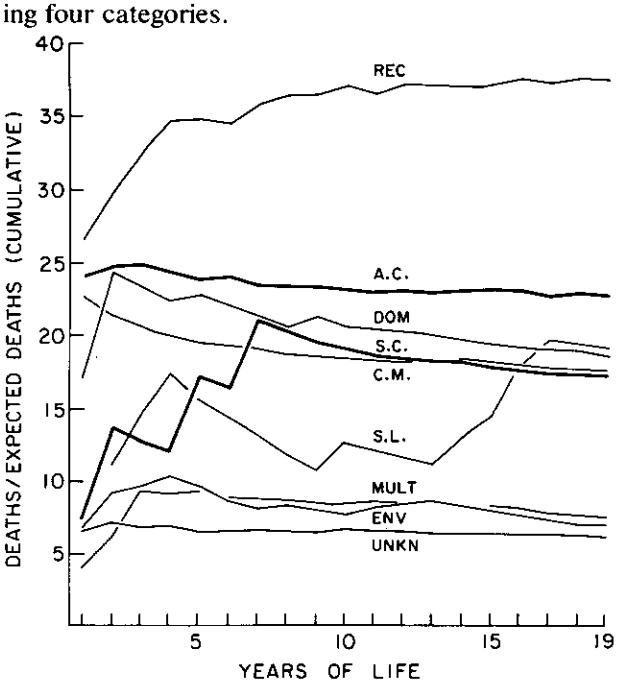

FIGURE 1. Age-specific cumulative mortality among cases of chromosomal and nonchromosomal genetic diseases and other handicapping conditions.

These different degrees of severity apply, however, only to the cases that actually got into the registry, and are clearly not applicable to those manifestations that were too mild to be registered. For example, the curve for the sex chromosome diseases is based on only 43 cases, as against 885 for the autosomal chromosomal anomalies which are mainly Down's syndrome. Whereas virtually all of the latter category would be severe enough as to be registered as handicapping, only a fraction of the sex chromosome anomalies are registered, and these were presumably not a random sample but were probably selected for a much higher degree of severity than is usual in that category.

In assessing the public health impact of the chromosomal diseases one should clearly not take data on degrees of severity as derived from the cases that have attracted special attention, and then infer that these severities are typical of the total number of cases as derived from surveys that have aimed at complete ascertainment.

Some Complications

Ideally, severity ought to be measured on the basis of such follow-up histories, but with the follow-up extended over the whole of the life span. If one thinks, for example, in terms of comparisons with cancer, it is the severities of all of the cases occurring over the whole of the life span that are of major interest. Of all cancer cases it can be said that roughly one-half are curable and that the remaining affected individuals lose on the average some 10-12 years of life expectancy. It is in such terms that one would like to express the severities of hereditary diseases when using mortality as the indicator. Unless the two sorts of conditions are treated in a similar fashion, it will always be difficult to compare in any rational way the relative importance of the genetic risk with the somatic risk from exposure to agents which cause both kinds of effect.

Among the hereditary diseases, those with recessive etiology tend to have their full impact early in life, whereas a majority of severe dominant traits (like multiple polyposis of the colon and Huntington's chorea) have late onsets. Of the chromosomal diseases, Down's syndrome tends to be severe and to have its full impact early in life, whereas the sex chromosomal anomalies tend to be mild and to escape notice until after puberty. Thus, again, from the standpoint of public health importance, whatever the measure of severity chosen, it requires to be applied over the whole of the lifespan.

For the chromosomal diseases, mortality may be one of the least useful of the indicators of severity, and this would be particularly true of Down's syn-

drome which results in prolonged stays in institutions from an early age. In such circumstances, the burden on society is perhaps inversely related to mortality. Nevertheless, data on mortality are more readily obtainable by follow up, using the death registrations, than are data on institutionalization using hospital records that are not centralized in any readily accessible form. For this reason, mortality data should be used where possible, and this use ought to serve as a model for subsequent efforts to measure severity statistically in terms of the social burden arising out of the use of institutional facilities.

Practical Problems

For those who might think that the existence of a computerized data base of personal records, linked into individual histories, makes it possible to extract relevant data at the press of a button, I should mention a few of the practical problems. These are associated chiefly with incompleteness of the files.

In the case of the British Columbia files, birth and death records were available back to 1946 in machine-readable form. However, the handicap registrations were not equally complete for all birth years, and also the ages at which affected individuals were registered varied widely. In general, (a) the most recent birth cohorts had not had sufficient time to permit a high proportion of registerable conditions to be detected and reported, (b) the earliest birth cohorts were born at a time when handicap registration was much less complete than it is now, and (c) the intermediate birth cohorts fall far short of having life time histories as long as one would wish for the purpose of quantifying severity (6). Despite all of this, an attempt had to be made to derive as much guidance as possible from the files, and so even the shorter periods of follow up were used to the full.

Delayed ascertainment of the condition created special problems. Ought one, for example, to assume that the expression of a disease had not been severe prior to registration of a case, and that the risk of death was normal in that earlier period? Or, should one assume that the degree of severity observed after registration was typical of that over the prior period? For a cancer, the former assumption might be closer to the truth, but for a chromosomal disease this is less certain. In carrying out the arithmetic, one or other of the two arguments must be made, or, better still, both may be made so as to arrive at a maximum and minimum estimate of lifetime severity.

Is the Public Health Approach Necessary?

For those who are primarily involved in the use of lower organisms to screen for various kinds of mutagenic activity the present concern with measuring the public health impact will seem remote and premature. But, as soon as an attempt is made to protect man against a particular mutagen, the unanswered, and often unanswerable, question concerning the importance or lack of importance of the public health impact gets raised almost immediately. Rarely can one avoid it by simply advising that a mutagen be banned or that exposure to it be kept as low as possible. What tends to be forgotten in this approach is that some mutagenic agents are exceedingly useful to society and difficult to replace, while others are not readily avoidable without substantial expenditures of society's limited resources.

Public health officials are continually bombarded with proposals for improving the environment in which we live and they must necessarily strive to rank these in some sort of priority. At the very least even an exceedingly crude and tentative indication of the magnitude of the public health impact of a harmful substance is needed, if we are to achieve a reduction in the exposure to it with the assurance that the harm or cost associated with this reduction has not resulted in greater human hardship than that which one sought to avoid. Only for a virtually useless substance, that costs little to get rid of and that nobody wants very much, is the idea of a simple ban likely to be immediately acceptable in the absence of some sort of assessment of the harm it may be causing to the health of the public.

For the last 20 years or more geneticists have been trying to assess the public health impact of radiation, in terms of the numbers of cases of induced hereditary disease, but with little or no emphasis on statistical indicators of collective severity. The latest UN report lists surveys that include some 55,679 newborn infants of whom 336 were found to have chromosomal abnormalities; no mention was made in the report, of plans to follow any of these 336 infants to determine how severely affected the individuals will be throughout their subsequent lives. Perhaps a quarter of the number will be institutionalized until they die. But, for the rest, the public health impact is essentially unquantified. Fortunately, the methods for individual follow-up now exist by which one can begin to rectify this kind of omission and the resulting epidemiological gap in our understanding of man's genetic well-being.

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