AN EPIDEMIOLOGIST TAKES A LOOK AT RADIATION RISKS

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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DIVISION OF BIOLOGICAL EFFECTS

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January, 1973

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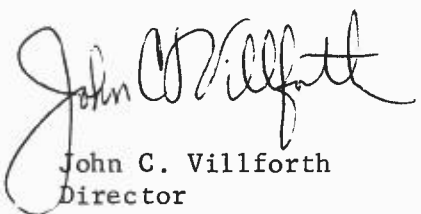
FOREWORD

The Bureau of Radiological Health conducts a national program to limit man's exposure to ionizing and nonionizing radiations. To this end, the bureau (1) develops criteria and recommends standards for safe limits of radiation exposure, (2) develops methods and techniques for controlling radiation exposure, (3) plans and conducts research to determine health effects of radiation exposure, (4) provides technical assistance to agencies having radiological health programs, and (5) conducts an electronic product radiation control program to protect the public health and safety.

The bureau publishes its findings in appropriate scientific journals and technical report and technical note series for the bureau's divisions, offices, and laboratories.

The technical reports published by the intramural and extramural programs of the Division of Biological Effects contain information which is timely and useful to the radiological health program. Subjects covered by these reports are varied, for the division is charged with developing--through animal investigations and population studies--knowledge of the biological effects of radiation delivered to man from his environment and from his use of substances and devices that emit radiation. The reports are distributed to persons and repositories that have expressed an interest in the biological effects of radiation; in addition, the reports are available from the National Technical Information Service.

Readers are encouraged to report omissions or errors to the bureau. Additional comments or requests for further information are also solicited.



John C. Villforth
Director
Bureau of Radiological Health

PREFACE

The Division of Biological Effects provides the biological research competence for the Bureau of Radiological Health. The division supports experimental radiobiologic and epidemiologic investigations conducted intramurally and by contract to examine ionizing and nonionizing radiation bioeffects in animals and man. Dosimetric studies to support the investigations are also conducted within the division. This research, together with evaluations of existing literature, provides scientific information for the development of radiation exposure and electronic product radiation emission standards designed to protect public health and safety.

In the ionizing radiation bioeffects area, studies are conducted with animals, tissues, and cells at the Rockville, Maryland, laboratory. The division also supports a major experimental study, through contract at the Collaborative Radiological Health Laboratory, Colorado State University. This lifetime study investigates the biological effects of radiation exposures of beagles at various pre- and postnatal ages. Human epidemiologic studies are carried out to determine the incidence and course of radiation-related conditions and diseases.

In the area of nonionizing radiation, the division has developed a program in microwave health effects research, and is developing experimental and epidemiologic activities in sonics and light. Within its available resources, the division supports experimental investigations of microwave bioeffects in cells, organs, and animals, and epidemiologic studies of microwave-exposed humans.

The division is involved in cooperative efforts with other agencies that have interests and responsibilities in health-related nonionizing and ionizing radiation bioeffects. These include the National Academy of Sciences, the National Science Foundation, the Atomic Energy Commission, the National Institutes of Health, the National Institute of Occupational Safety and Health, the Department of Defense, the Department of Labor, the Environmental Protection Agency, and the Department of Transportation.

Moris L. Shore, Ph.D.
Director
Division of Biological Effects

Dr. Alice M. Stewart is a world authority in the field of human epidemiologic research. Her work is widely quoted, and has critically examined the relationship between radiation exposure and the risk of developing cancer in humans, giving us new insights into the scope of epidemiologic research.

Dr. Stewart was a Visiting Scientist in the Division of Biological Effects, Bureau of Radiological Health, on sabbatical leave from the Department of Social Medicine, Oxford University. She received her education at Cambridge University and the Royal Free Hospital in London. She holds an M.D. (Cantab.) and F.R.C.P. (Lond.). After 15 years as a practicing physician, she joined the newly-formed Department of Social Medicine "to investigate the influence of social and genetic factors on the incidence of human disease and disability by measures other than those employed in the practice of remedial medicine." She has made numerous contributions with her work on childhood malignancies, thus advancing an understanding of the delayed effects of small doses of radiation.

INTRODUCTION

The appointment of Dr. Alice Stewart of Oxford University as a Visiting Scientist in the Division of Biological Effects, Bureau of Radiological Health, made it possible for her to present a set of five monthly lectures to a large audience of bureau and other scientific personnel. The purpose of the series of presentations was to explore in some detail the use of epidemiologic surveys generally, and specifically, the Oxford Survey of Childhood Cancers, in evaluating the hazards of ionizing radiation. Since the audience was composed primarily of non-epidemiologists, the lectures represented part of a continuing effort to have an interdisciplinary approach to the bureau's mission of reducing unnecessary exposure to x rays.

Dr. Stewart has presented both the limitations and the advantages of the epidemiologic approach and has discussed indications for its use; this publication will provide wider dissemination of this timely information. These lectures reflect Dr. Stewart's interpretations of her own investigations as well as the studies of other investigators. We hope that the reader will gain an appreciation of the unique contribution epidemiologic studies must make in the assessment of radiation effects.

CONTENTS

CHAPTER 1

SCOPE AND LIMITATIONS OF EPIDEMIOLOGIC SURVEYS

If I have understood Dr. Shore correctly the purpose of these lectures is to give radiation physicists and biologists an opportunity to see the problem of low level radiation through the eyes of an epidemiologist. So it is only fair to warn you that I do not necessarily see eye to eye with current fashions in epidemiology. For instance, these fashions would have us believe that, given the choice, an epidemiologist would always prefer to follow an exposed population (prospective survey) rather than attempt a piecemeal reconstruction of the events leading up to a particular crisis or end point (retrospective survey). Nevertheless, even when there was good reason to believe that a child might develop a malignant disease as a result of being involved in an obstetric x-ray examination, I and my colleagues decided that an extension of the Oxford Survey of Childhood Cancers (OSCC) would be a more profitable undertaking than a followup of children x-rayed in utero *(1,2)*.

The choice was deliberate, and was made as a result of discovering that this totally unexpected finding did not explain the observation which had prompted the survey in the first instance. What had originally attracted our attention had emerged from a study of official statistics of mortality by my colleague, David Hewitt, who demonstrated a threefold increase in leukaemia mortality for children between 2 and 4 years of age during the period 1930 to 1950, and virtually no change in the rate for younger children *(3)*.

The "extra" x-rayed cases which had turned up in the Oxford Survey showed no signs of being concentrated among children who developed cancers within 4 years of birth, and there were not nearly enough of these cases to have a noticeable effect on the leukaemia death rate. There were also other findings which could not be explained in terms of radiation-induced cancers; such as, a twentyfold increase in the risk of dying from leukaemia for children who were mongols; a twofold excess of first born children among the lymphatic leukaemias and acute unspecified leukaemias which proved fatal between 2 and 4 years of age (fig. 1), and twice the expected number of children who had an attack of pneumonia within 2 years of developing leukaemia *(1)*.

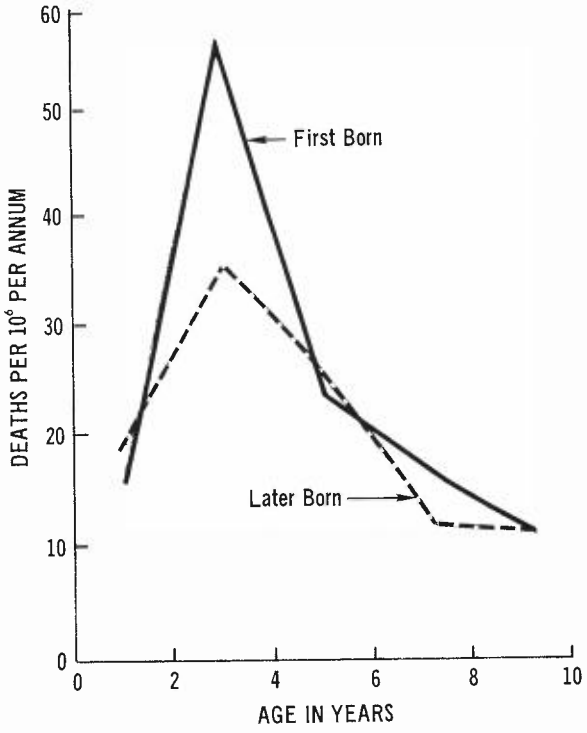


Figure 1. Leukaemia mortality for first born children and later born children (1953-55 deaths ascribed to lymphatic and acute unspecified leukaemias and included in the first phase of the Oxford Survey).

For these and other reasons relating to an earlier investigation which I propose to describe to you *(4)*, we finally decided that it would be better to retain our "open" approach to the problem of cancer etiology, rather than embark on a totally new survey which would necessitate meticulous counting of cancer deaths in a population of x-rayed children that was large enough to distinguish between a 1 in 1,200 risk of dying from a malignant disease within 10 years of the exposure date (that is, the normal risk for children under 10 years of age) and, say, twice this very small risk. This decision may be easier for you to understand when I tell you that David Hewitt estimated that to do the job properly we might have to keep a quarter of million children under observation for 10 years and be certain of recognizing every cancer death *(5)*.

From then onwards the declared purpose of the Oxford Survey was to discover how 10 percent x-rayed cases differed from 90 percent of non-x-rayed cases, and whether the timing of the radiation exposures and the number of films had influenced the frequency and age distribution of the "extra" x-rayed cases. So there was a need to collect information not only from parents of live and dead children but also from obstetricians, radiologists, and pathologists. Since it was impossible to synchronize the interviewing of parents and the collection of data from hospitals and clinics, and also necessary to make things easy for hundreds of data collectors (and to be sure that all our data collecting procedures were operating efficiently), we soon discovered that the method of data handling which had been used during the first phase of the survey was totally inadequate for the second phase.

The first phase of the Oxford Survey covered 1953-1955 cancer deaths in the age range 0-9 years and necessitated the active cooperation of more than 200 public health departments, but we were only tapping one source of information (parents) and checking one item of information (obstetric radiography). We were therefore able to rely upon ad hoc procedures for keeping track of the traced, pending, and "lost" cases, and upon IBM coding transfers and 80-column punch cards for the conveying of data from interview schedules to card sorting machines. During the second phase it was necessary to have a system of recordkeeping which kept the policy makers and the coding clerks abreast of what was happening in relation to a much more complicated system of data collection and data checking. In fact we needed a system which distinguished between completed data sets on the one hand and either temporarily or permanently incomplete sets on the other hand. We also needed a system which recognized partially and fully coded records; maintained a full display of the available records; allowed us to recognize when the fully coded records had been transferred to magnetic tape; and allowed us to hold in semi-coded formation a number of facts whose value would not be known until the first data tape had been intensively studied. It was also necessary to do this during a period of rapid advancement in computer technology (with constant changes in machine facilities) and in the context of a survey which was relying upon public health departments for interview data and upon other branches of the National Health Service for the other facts, and could only count upon the voluntary cooperation of the doctors who completed the survey schedules.

Every textbook on the subject has something to say about the role of retrospective and prospective surveys in epidemiological research, and most of them would have us believe that the former are a poor substitute for the latter *(6)*. What one is never told is that although the IBM method of data conveying may be perfectly adequate for prospective surveys with single, predetermined end points, this and

equivalent methods are a snare and delusion in relation to broadly based retrospective enquiries. Textbooks also contain no hint that, given better methods of data handling than the ones in current use, epidemiologists might revise their ideas about the best method of dealing with a number of problems. A step in the right direction would be recognition of the fact that the more ambitious medical surveys are being ill-served by all the commercial enterprises which claim to know how data should be handled prior to being stored on magnetic tape.

In my next lecture I will be describing a method of data processing which we developed in relation to the Oxford Survey, and without which the second phase of the survey would not have achieved more than the first phase. As, however, today's talk is about the scope and limitation of epidemiology I cannot refrain from saying that, in my opinion, the gap between performance and promise in this subject is wider than it need be because doctors have not taken an interest in the design of coding transfers, and have meekly accepted a method of data conveying which rates the convenience of punch-card operators higher than the basic needs of research workers.

Another stumbling block in epidemiological research is the idea that surveys should be as neat as experiments, and that investigators who allow them to develop new shoots or "ramifications" based on interim findings are courting disaster. To explain what I mean by a "ramifying survey" (or the opposite of a tidy survey following a predetermined route), I propose to tell you about an investigation whose only connection with low level radiation is a personal one. It is, however, a means of showing you why I am so strongly opposed to the idea that epidemiological investigations should be modeled upon animal experiments, and how I came to believe that they should be modeled on a physician's "case-history" approach to a diagnostic problem.

The survey I am about to describe concerned shoemakers and their risk of developing tuberculosis *(4)*, and it was referred to the Oxford Department of Social Medicine in 1947, within a few months of my deciding to leave clincal medicine and join a research department which had been briefed "to investigate the influence of social and genetic factors on the incidence of human disease and disability by measures other than those employed in the practice of remedial medicine" *(7)*. Twenty-five years ago no one had thought of classifying epidemiological surveys as retrospective and prospective, and my experience of bedside medicine was far greater than my experience of surveys. So when I was told that a mass radiology unit had discovered "too many" cases of pulmonary tuberculosis among boot and shoe factory operatives, I did not immediately assume that a prospective survey was the best method of discovering whether the suspected cause, namely leather dust, was the true cause. I had, in fact, no clear idea what to do except to

ask the sort of questions which I would have asked if, instead of having a "boot and shoe factory" as a patient, I was dealing with a problem case referred to me by another doctor.

I had just returned to Oxford from a spell of work with the MRC Pneumoconiosis Research Unit in South Wales, so I was naturally inclined to agree with the idea that the shoemakers' trouble was due to leather dust. As, however, it never occurred to me to do anything except take a close look at everything which might have a bearing on the problem, we soon discovered that we were dealing, not with a specific occupational hazard, but with one of the many problems posed by airborne infections in relation to one of the many occupations which offer jobs to men who are only fit for light work and provide working conditions which favor the spread of airborne infections and allow individuals who may be carriers of tuberculosis to mix freely with school leavers and other susceptible individuals *(8)*.

For instance a closer look at the records of the mass radiography unit which had toured the area in 1946, not only confirmed the high incidence of tuberculosis in the shoemaking factories but also revealed a positive correlation between factory size and the incidence of newly discovered cases, and showed that this correlation did not apply to the known (or previously notified) cases, which were found to be evenly distributed between our groupings of large, medium, and small sized factories *(9)*. In other words, here was a hint that the most infectious form of tuberculosis was being transmitted to fellow workers by carriers, and that the risk of contracting the disease from a fellow worker was related to the size of the working units.

We also obtained permission to examine the "factory hygiene" assessments of a working party appointed by the Board of Trade for this purpose, and the wartime records of civilian medical boards which had been appointed by the Government for the express purpose of grading civilians in the age range 14 to 45 years according to their fitness for military service. From the first source we discovered that the larger the shoemaking factories the "better" were the working conditions, (that is, neither good ventilation nor absence of dust was proof against the spread of tuberculosis in a working community). From the second source we discovered that the proportion of men who were unfit for military service was above average for shoemakers, and that among these men there was a high proportion of semi-cured cases of tuberculosis *(10)*.

Meanwhile a study of occupational statistics had shown that, in contrast to occupations with a silica dust hazard, the "extra" risk of dying from tuberculosis for boot and shoe factory operatives decreased with age (fig. 2).

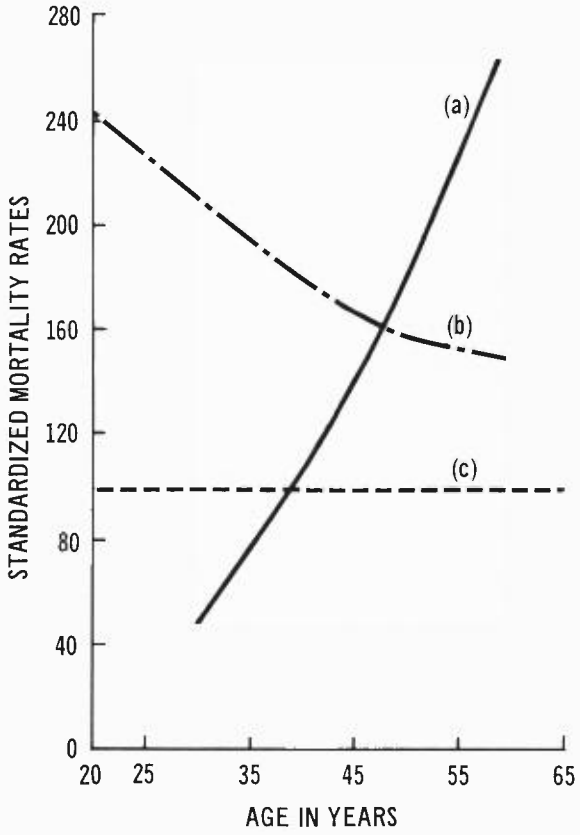


Figure 2. Pulmonary tuberculosis: standardized mortality rates for males aged 20-65 years in England and Wales 1930-32. (a) Masons and stone quarriers. (b) Boot and shoe factory operatives. (c) All occupations.

From this source we also discovered that the shoemaking industry belongs, with the printing trade, to the category of "safe" trades (which become breeding grounds for tuberculosis whenever they cease to be home industries and move into factories), also to the category of "family" trades (which no sooner move into factories than they begin to have an increased resistance to tuberculosis) *(11)*. The increased resistance to tuberculosis of shoemakers and printers was evidently the result of an increased probability of encountering tuberculosis as a child (we discovered this by interviewing workers in different trades and asking questions about the occupations of fathers and mothers and about tuberculosis contacts within the family), and a

consequent increase in the proportion of new entrants to the industry with some immunity to this disease. The slow acquisition of this resistance factor proved to be an important component in two "slow-motion epidemics" which we detected, one of which had begun in the middle of the 19th century and had affected shoemakers for the next 100 years, and the other which began at the beginning of the 19th century and affected printers for the next 100 years *(11)*.

Most of the data sources which we tapped during the course of the tuberculosis survey provided us with information about past events, but we also used pay registers to estimate the age and sex distribution of contemporary working populations; workshop plans (showing the positions of different machines) to estimate distances between workers in different occupations; tuberculosis notifications to observe the effect of the Mass Radiography Survey on subsequent notifications *(12)*; bacterial air counts (made at the weekends) to measure the effectiveness of partitions in preventing the spread of airborne bacteria *(13)* and sickness absence records during an influenza epidemic to observe the effect of a sudden increase in the carrier rate on the spread of an airborne infection *(14)*.

The final conclusions based on these heterogeneous data included the suggestion that, for airborne infections, the relative risk of contracting the disease from a fellow worker is negligible for diseases with high carrier rates (exemplified by influenza during an epidemic), but is considerable for diseases with low carrier rates (exemplified by influenza between epidemics, also by tuberculosis in countries with low rates of tuberculosis mortality). In other words, contrary to what one might have supposed, the need for sheltered workshops for potential carriers of tuberculosis is greater in countries where the disease is uncommon, and where there are large numbers of sedentary trades employing large aggregations of workers (for instance, the United States) than it is in countries where the disease is common and most of the sedentary workers are employed in home industries (for instance, rural India or Pakistan).

My excuse for this lengthy description of a survey which is no immediate concern to radiation biologists is that it taught me so much about the complex nature of seemingly "safe" situations. I also regard the boot and shoe survey as a "curtain raiser" for the Oxford Survey (and therefore as suitable introduction to my talks on low level radiation) because, in addition to opening my eyes to the possibilities of loosely knit or ramifying surveys, it also stopped us from taking a wrong turn after we discovered the association between childhood cancers and obstetric radiography. I say this because the earlier survey showed us that it is not at all important for epidemiologists to take events in their correct sequence, but is extremely important for them to be on the lookout for unexpected

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associations and unexpected consequences of known associations. Thanks to the earlier survey I also learned these lessons sufficiently early in my social medicine career to be highly critical of the idea that a "good" survey is one which resembles an animal experiment, and a "bad" survey is one which runs the risk of obtaining data from biased sources *(15)* (as though we could know all the relevant factors in advance of the observations and had no means of dealing with the bias once it had been detected!).

Since it is clearly impossible to do with human populations what it is easy to do with experimental animals (namely to keep them under continuous surveillance), and equally impossible to do with animals what it is easy to do with human beings (namely, to ask them to give an account of themselves), I am constantly surprised by the present attitude towards prospective and retrospective surveys on the one hand, and statistical methodology and "census technology" on the other. If I had my way, epidemiologists would be medically qualified persons who were prepared to ignore the first distinction when it suited their purposes to do so. They would also be prepared to place the responsibility for data analysis firmly in the hands of statisticians (that is, they would not try to be experts in this difficult subject or expect other doctors to be experts) but would retain responsibility for the direction taken by the survey at the outset and throughout its course. In short, they would play the role of explorers and archeologists, who take an interest in everything; who are constantly on the lookout for ways of cross-checking their data sources, and who realize that the end products of data collection are as valuable and esoteric as the logbook of an uncharted journey, or the broken shards of an archeological "dig."

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CHAPTER 2

THE OXFORD METHOD OF PROCESSING MEDICAL RECORDS FOR COMPUTER ANALYSES AND ITS USEFULNESS IN DETECTING DELAYED EFFECTS OF RADIATION

Traditional methods of data processing make no provision for assembling records unless they are in a form suitable for computer consumption, when they are assembled on transfers resembling punch-cards or computer inputs which necessitate double punching to ensure that there have been no last minute mistakes.

A new method is described which makes it possible to assemble in inventory formation any number of processed or semi-processed records and thus to dispense with double punching as a means of data verification. With records in this formation they can be fed into a computer as tape corrections and be reassembled by the computer in their original form. Thus it is possible to use paper tapes instead of punchcards and to dispense with punchcard transfers as well as verification.

It is anticipated that the surveys which will benefit most by the new method will be the ones which are free to move in different directions during the period of data collection. Hitherto inefficient methods of data assemblage have prevented us from seeing that enquiries which fall into this category (case history or retrospective studies) are capable of exploring in depth the problems they reveal and thus that they have far greater potentialities than the enquiries which can only explore known problems and move along predetermined lines (cohort or prospective studies).

There are certain terms used by statisticians to describe different arrangements of numbers which are helpful in understanding the principles upon which data processing in general, and coding frames in particular, should be based. One is a vector, or a series of numbers describing different aspects of an object. Another is a matrix, or an assemblage of numbers describing two sets of related vectors running in opposite directions across the page. Finally there is an inventory, which is a matrix consisting of one similar and one dissimilar set of vectors arranged in rows and columns respectively. Thus in statistical parlance the computer printouts which are used by epidemiologists to inspect their data before analysing them are inventories, because removing a row vector, or propositus, merely reduces the size of the sample, whereas removing a column vector, or topic, alters the nature of the sample.

For obvious reasons, computer printouts cannot be obtained until all the data they describe have been coded, punched and sorted; proceedings which often involve the use of costly machines that are impossible to consult without the aid of experts who are not directly concerned with the survey. But, as every epidemiologist knows, there is often an urgent need to discover at a much earlier date — or from time to time throughout a prolonged period of data collection — how successful one is being in tracing individuals and recording their attributes and experiences. These subsidiary needs are usually met with ad hoc filing systems and lists which are never very satisfactory and are often a reason for curtailing the scope of a survey which might otherwise have branched out in various directions, depending on interim findings.

Because none of the conventional methods of data processing make any provision for recording the progress of a survey as distinct from the findings, it follows that they are also unsatisfactory from the point of view of recording topics which would benefit by being seen in inventory formation but in semi-coded form. There is no shortage of topics of medical interest which fall into this category — for instance, the shadows seen in standardised x rays, the component parts of biopsies, and all the interrelationships between parents and their children which go under the heading of sibship data. But in spite of a plethora of material crying out for inventory style data processing, textbook descriptions of conventional methods rarely, if ever, mention the benefits which would have accrued to epidemiology if, instead of allowing the traditional units of computer inputs or punchcards to dominate data processing procedures, we had developed a system based on computer printouts or inventories.

For instance, if all handwritten versions of survey data were kept in row and column formation until they were fed into a computer, we might recognise faults which at present are missed until they appear alongside the correct entries in the computer printouts, by which time they are a great nuisance to alter. Mistakes of this kind are made, not by punchers — who are equipped with machines for data verification — but by coders who have to improvise their own checking systems. They are due to such things as accidentally transposing two digits of a number, placing a number in the wrong position, or forgetting to attach a number to an entry in the original record. Thus they are apt to produce either numbers of totally the wrong order of magnitude or odd gaps in the record. For example 62 instead of 26 for age of mother; or 21 for sibship size instead of age at marriage; or "not known" for the sex of a father. Oddities of this kind are much easier to recognise in inventory formation which automatically concentrates numbers of similar size in vertical sequences (which are easy to read) and numbers of dissimilar size in horizontal sequences (which are difficult to read).

But it is common practice for transfers to contain only rows of wide-range numbers (fig. 1).

The format shown in this figure could be described as a triple row vector transfer, and is typical of a whole series of coding frames which are geared to punchcards (that is, to the row vectors of inventory printouts) but in which any column formation of topics is made impossible by the inclusion of more of them than can be comfortably held in a single row of numbers. An alternative format described by the makers as a general purpose card punching form is shown in figure 2. Inasmuch as these forms present numerical data in inventory formation they are a great improvement on row vector transfers. As, however, this formation has been achieved without reducing the number of topics described on the form below the number that can be held on an 80-column punchcard, the completed forms are so disagreeable to read that they often escape proper checking before being punched.

The congested and illegible appearance of completed transfers of the type shown in figure 2 can be traced to the fact that the makers not only sell computers and computer accessories but also undertake to punch handwritten data, provided they are entered on their forms. Thus they are interested in the design of coding frames from the point of view of supplying work in whole-card packages rather than card-section packages but not from any point of view, and have a strong incentive for not encouraging any method of data inspection which does not involve a machine. Consequently, all the inventory formations of handwritten data which have been produced over the years by epidemiologists are travesties of what they might have been if any of us had thought fit to press for a better design of transfer.

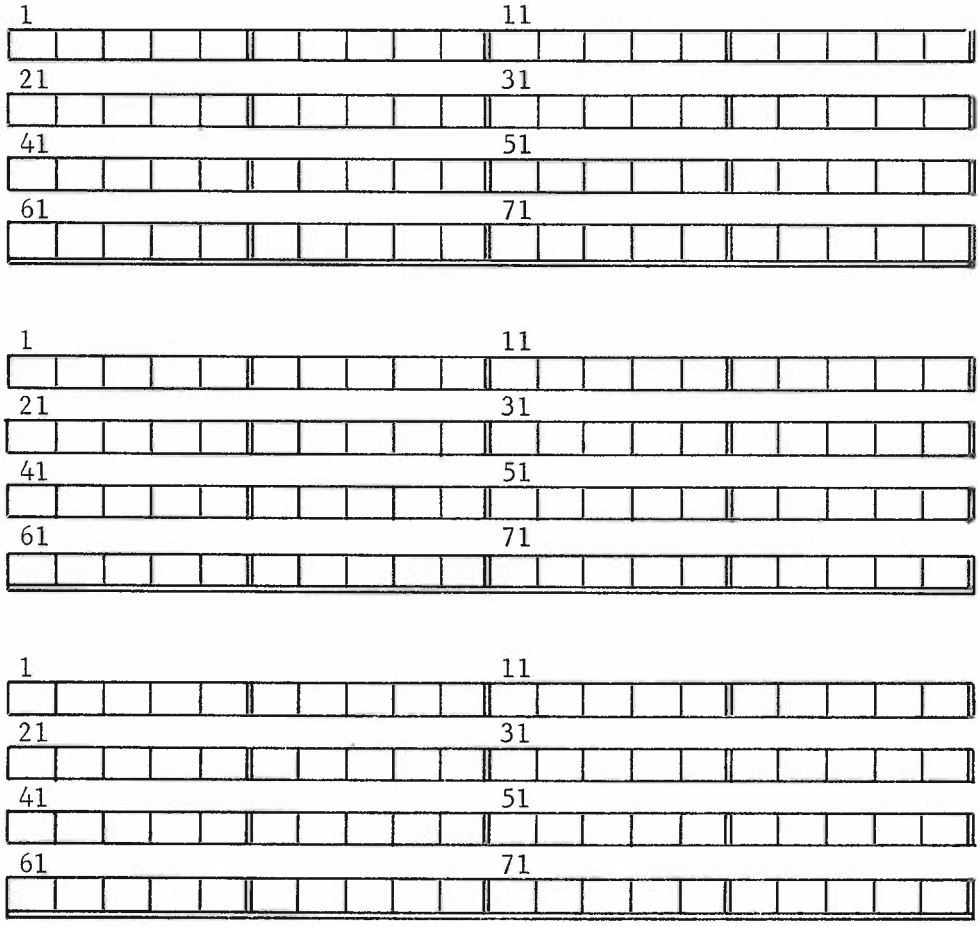
As a subject worthy of the consideration of epidemiologists the design of transfers does not exist. Even in textbooks, which devote whole chapters to data processing, the sections on coding frames deal only with the twin problems of how to collect data and how to convert them into vectors and never with the related problem of how to see the effects of one's decisions before it is too late to alter them (that is, they deal with frames of reference as opposed to actual frames). Thus beginners are left with the idea that no problem exists, while old hands continue to work under unnecessary difficulties by taking for granted that it is impossible to handle findings or scientific data and progress records or track data in the same way, and imperative to work with transfers which mimic punchcards if one wishes to invoke the aid of a computer.

This is a rather surprising fact when one considers that the only difference between the general purpose coding card in figure 2 and one which would suit the needs of the human eye and hand is that it should

CODE SHEET

Content _____ Health Survey Research Study _____

Deck Nos. _____ Study No. _____



Punched by _____ Date _____

Verified by _____ Date _____ Coder _____ Date _____

Date checked _____

Figure 1.

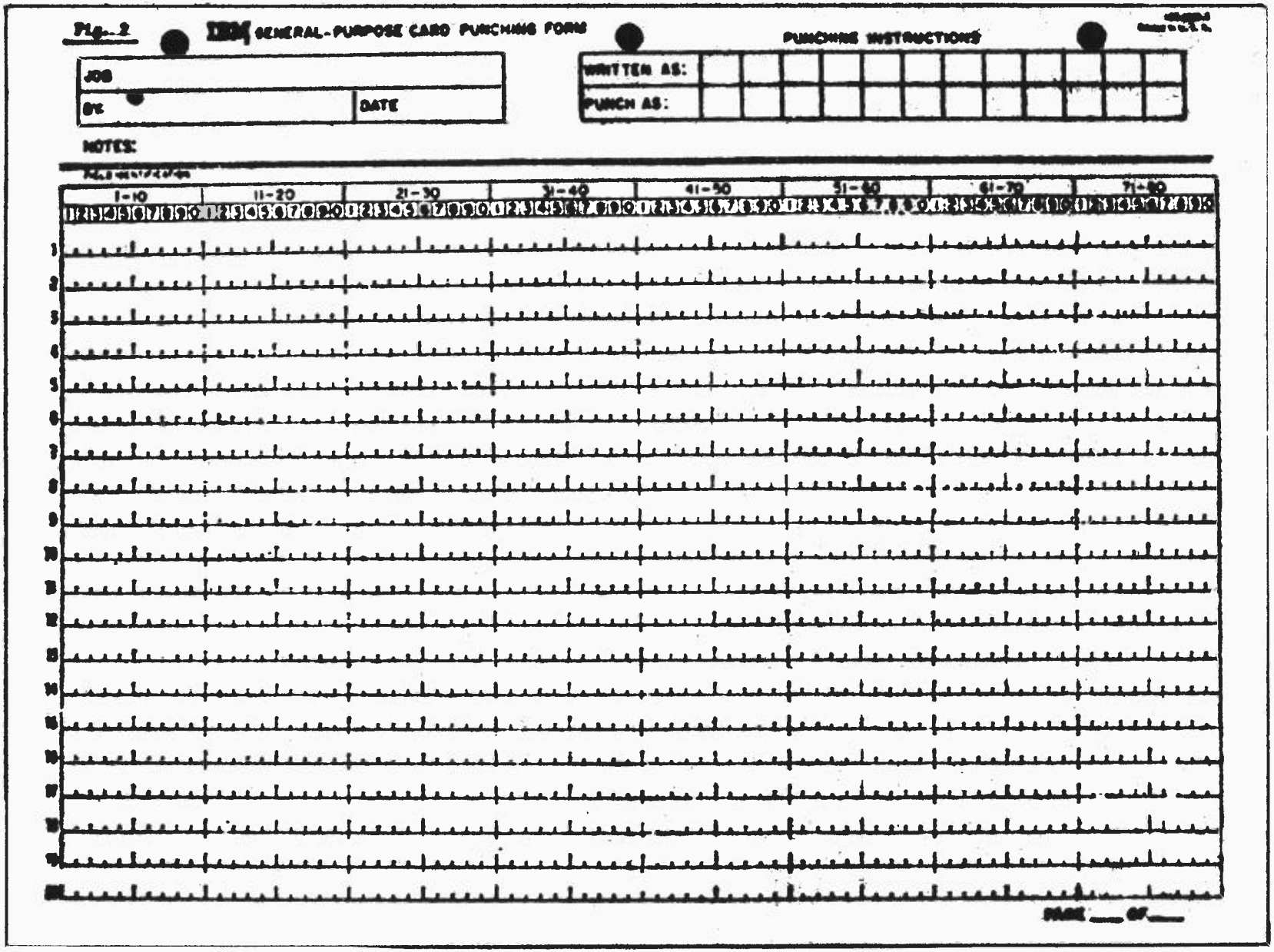


Fig. 2
IBM GENERAL-PURPOSE CARD PUNCHING FORM
PUNCHING INSTRUCTIONS
WRITTEN AS:
PUNCH AS:
JOB
BY
DATE
NOTES:
1-10
11-20
21-30
31-40
41-50
51-60
61-70
71-80
PAGE ___ OF ___

Figure 2.

be easy to read whatever the form of the data, and easy to handle whatever the amount of the data. It might in practice be convenient to distinguish between records which were destined for statistical analysis and records of ephemeral interest, or between fully processed and semi-processed scientific data, but this could be done by having different coloured paper for different usages and would not preclude having frames designed to hold words as well as numbers. It is true that such frames could no longer mimic punchcards, but they could still serve as transfers if the data were deemed worthy of computer analysis, for there is surely no reason why all the contents of an 80-column punchcard should be held on one page.

There are in fact two basic requirements for an all purpose data-processing frame, the first of which is partially satisfied by some transfers which are currently available; namely a format which holds like-vectors in row formation and unlike-vectors in column formation. If, however, there is to be no limit to the number of vectors in both directions, the frame must consist not of sheets of paper which are divided into rows and columns on one side only and held together by treasury tags inserted into holes at the top of the page (fig. 2), but of several pages printed on both sides and capable of being assembled first into looseleaf books (fig. 4) and eventually into sealed inventories with proper titles.

The second requirement concerns the space allocation for the inventory denominations or actual entries in the frame and states that these spaces may vary in one direction — to allow the component parts of the row vectors to be large or small (that is, space for words as well as numbers) — but not in the other direction. Which is the same thing as saying that the width of like vectors need not vary, but the width of unlike vectors should be infinitely variable. As, however, all inventory denominations are shared by row and column vectors, the width of a column vector must always be settled in advance of the entries. It only requires three quite simple devices to satisfy these requirements, viz: —

1. numbering the rows and columns in an inventory in page sequences;
2. equating row vectors with actual rows;
3. having a separate sheet of paper, or title page, for relating column vectors to actual columns.

Since a separate title page provides ample space for describing the column contents of two working pages of an inventory (fig. 3) there is no need for different column numbers on different pages. But an arrangement which allows a hundred row numbers to spread over four working pages is far better than one which insists on having the same row numbers on every page. With four choices of row number it

Serial Nos.	2000-2990
Subject	Sibship Data

TITLE: OSCC (Series 9) Sibships of Index Children and Their Parents

Left	Tape	Code	Right	Tape	Code
			19/23, etc. = Age of Mother/Father at Marriage		
1.			♂ = Male Live Birth		
Congenital Defects and			♀ = Female Live Birth		
2. Causes of Death of			2. Case Sibship ○ = Index Child		
Case and Control Sibs			S = Stillbirth		
3. (Cross-referenced from			3. M = Miscarriage		
opposite page, i.e.,			[ ] = Twins		
4. underlining = a child with			4.		
a congenital defect, and ✗ =			♀ ♂ = Congenital Defect		
5. a dead sibling)			5. ✗♀ ✗♂ = Death		
			Final No. = Year of Ascertainment (e.g. 70 = 1970 etc.)		
6.			6. (Control Sibship)		
Mother cases	Sibship Position of Parent/Sibship Size (i.e. $\frac{1}{3}$ = 1st of three children)		Raised Nos. = Gaps (in calendar years) Between Births		
7. Father			7.		
Mother controls					
8. Father			8.		

Figure 3.

1.

	1	2	3	4	5	6	7		8	
00							(M)	(F)	(M)	(F)
01	Case ×	♀ Ac. Lymphoblastic Leuk. (Sib pair (103))					1/2	1/1	3/3	8/10
02										
03	Case ♂	Cong. dislocation / hip					4/6	1/6	2/2	2/4
04							1/2	1/2	4/11	1/4
05										
06							1/1	11/11	1/2	2/2
07										
08										
09			Control ♂ Cong. heart (54)				3/5	7/7	1/1	4/5
10							3/3	1/2	2/4	1/4
11							1/1	3/3	1/3	1/3
12							3/3	2/2	1/3	1/2
13										
14										
15										
16										
17										
18	Case ♀	Brain Tumor 2½ yrs. Sib pair (97)					5/6	5/5	1/1	4/5
19			Control: ♀ Prematurity 4 days				1/3	6/6	2/4	1/4
20										
21							4/6	2/6	5/7	6/6
22							5/5	3/6	2/10	2/4
23										
24							1/2	3/4	1/3	1/5

Figure 4

2.

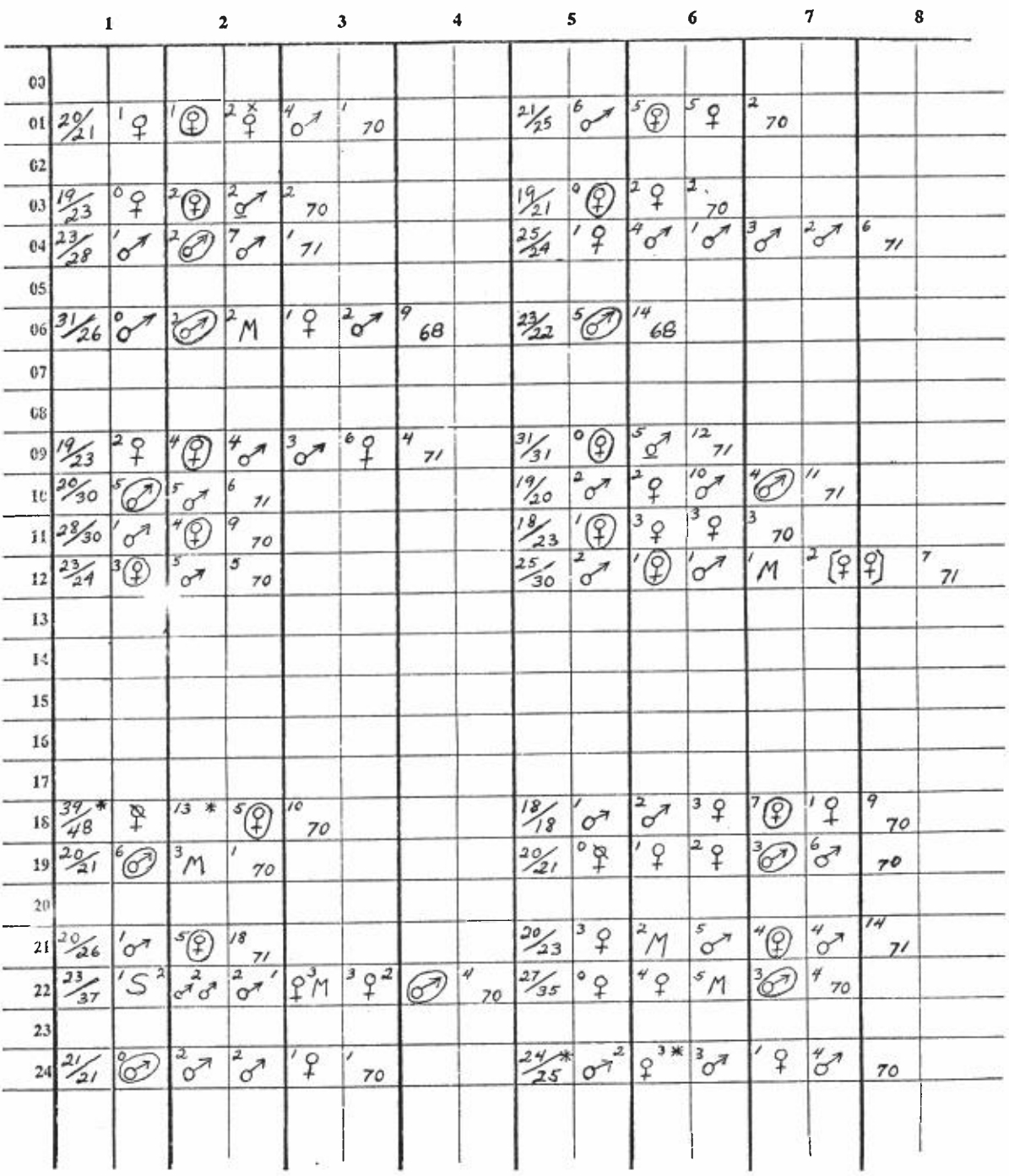


Figure 4 (cont'd).

is essential to number pages in accordance with the rows they contain, but there is no reason why there should be more than four page numbers (1-4) or why the rows on page 1 should not be numbered 00-24 and the rows on page 2 should not be numbered 25-49, and so on (fig. 5). This arrangement allows either the same or different samples to be described on pages carrying the same printed numbers, but if two such pages describe two samples each sample is denoted by row numbers which begin with different (handwritten) digits and end with the same (printed) digits. Thus descriptions of row vectors, 9, 115 and 1224 would always appear on page 1 of an inventory, but descriptions of row vectors, 19, 126 and 1075 would be found on pages 1, 2 and 4 respectively. In practice row numbers and serial numbers (or the numbering system imposed at the outset of the survey to denote the individuals concerned) would usually be the same. But should a new sequence of cases or controls be required this could be done by treating serial numbers as a column vector denomination and giving to each individual an "extra" or inventory row number.

If handwritten versions of survey data are to satisfy the requirement of being easy to handle, they should be in conventional book formation rather than the "reporter notebook" formation implied in figure 2. Either way would prevent one mislaying parts of an inventory, but only the former is compatible with the column vector display which occurs naturally when the facing pages of a book inventory are allowed to carry the same printed numbers. Since all pages cannot have facing pages this arrangement requires five working sheets and one title sheet for 100 row vectors but only nine working sheets and one title page for 200 row vectors, and so on. It also necessitates having different numbers printed on the back and front of the four working sheets in order to carry forward the sequence of row vector numbers. The obvious choice of page numbers for a set of four working sheets (reading from back to front of each sheet) is 4 and 1, followed by 1 and 2, followed by 2 and 3, followed by 3 and 4. For this would carry the sequence of row numbers forward indefinitely (fig. 5) and only leave one unpaired or "free" page at the front and back of each inventory, or about the right amount for "extra topics" such as instructions to punchers, meaning of code numbers, and so forth.

It should by now be obvious that one of the basic requirements of an all-purpose coding frame has been met; namely, a capacity to hold any number of row vectors in a form which is easy to read and to handle. But there still remains the other requirement; namely a capacity to hold in the same formation any number of column vectors, however wide the denominations. To meet this it is necessary to have a second set of working sheets identical in every other respect with the first set, but carrying the same page and row numbers back and front and printed on coloured paper instead of white paper. Then by

1.

	1		2		3	
00						
01						
02						
03						
04						
05						
06						

2.

	1		2		3	
25						
26						
27						
28						
29						
30						
31						

3.

	1		2		3	
50						
51						
52						
53						
54						
55						
56						

4.

	1		2		3	
75						
76						
77						
78						
79						
80						
81						

Figure 5.
Snippets for four working pages. Note correspondence between row numbers and page numbers (see text).

Design of an inventory capable of holding 6,400 numbers in book formation on 9 quarto-sized sheets of paper

Working sheets		Printed Nos.		No. of items (numerical data)	Visible items (facing pages)
Set	Type	Pages	Rows		
1st	White	4	75-99	nil	
		1	00-24	800	1600
1st	Coloured	1	00-24		
		1	00-24	800	
2nd	White	1	00-24		
		2	25-49	800	1600
2nd	Coloured	2	25-49		
		2	25-49	800	
3rd	White	2	25-49		
		3	50-74	800	1600
3rd	Coloured	3	50-74		
		3	50-74	800	
4th	White	3	50-74		
		4	75-99	800	1600
4th	Coloured	4	75-99		
		4	75-99	800	
1st	White	4	75-99		
		1	75-99	nil	

Figure 6.

combining the two sets as in figure 6 and adding as many title pages as there are "second sets" of working pages, the original book formation would be retained however many row and column vectors were described in the inventory. Figure 5 shows the effect of doubling the column vector allocations and indicates the way in which further allocations might be made, but the point is that frames of this type have the unlimited storage capacity of magnetic tapes, and the same presentation features as a computer-made inventory of the tape contents.

Though not essential, a colour difference between the two types of working pages and several choices of colour for title pages are a help. A choice of two colours for working pages is sufficient to show investigators and readers when they have moved to a new set of row vectors, but a choice of several colours for title pages would make it easy to recognise inventories of, say, data which are in the form required for computer analysis; semi-coded scientific data; track data destined for computer consumption (for example, tape corrections); and other track data which are unlikely to be fed into a computer though this would remain a possibility.

Likewise, alternate light and dark ruling of the columns as shown in figure 4 is convenient but not imperative. This type of ruling produces a more readable display of numbers than the ones which emerge from conventional squared paper and thus it encourages coders to take an interest in emerging patterns and helps them and their proofreaders to recognise false entries or gaps. Double columns are also a convenient device for listing the findings for cases and controls side by side, and for recording lengthy numbers which begin with a rapidly moving set of digits, but end in a stationary or more slowly moving set (for example, months within calendar years). Finally, if one knows in advance that there are only going to be two inventory denominations, then one double column can be made to hold as many row vectors as are normally held on two facing pages (16 double columns) by using a combination of column and row numbers to denote each row vector. This is known as a compressed inventory to distinguish it from the usual or dual-page inventory and is the reason why the columns in figure 4 are numbered in pairs and why there is a spare row for numbering single columns should this be needed.

A compressed inventory can obviously be used for describing any situation which ensures that the column vectors will not occupy more than one page or 16 columns, but it is particularly useful for handling very sparse entries. For example, the rows in a computer printout which are free from faults are likely to be far more numerous than the rows with faults. Also the commonest mistake will be one which affects only one number in a row and thus only requires two entries in a tape correction inventory, namely, the position on the data tape requiring correction, and the proper entry. On the usual basis of two facing

pages to 25 row vectors such an inventory would yield what a statistician would describe as a "rare matrix," but one could be made 16 times as compact by equating double columns with facing pages in the way described.

With conventional methods of data processing, tape corrections present a notoriously tedious problem because they involve identifying and repunching all the contents of the affected 80-column punchcards and then sorting the new cards into a card number sequence in order, first, to detect duplicates, and, secondly, to provide the correct sequence of cards before instructing the computer to incorporate the corrections in the data tape; otherwise the whole proceeding would be prohibitively costly. But a compressed inventory formation makes it possible to hold any number of tape corrections in the right sequence and to discover if the fault has already been recognised by someone else. There is even no need to use a less compressed inventory than one described just because there happen to be a few mistakes involving several numbers in a row of the printout. To cater for these it is only necessary to keep a few row vector transfers in looseleaf formation at the back of the working pages, and to invent a symbol which will tell the person who is given the task of transferring all the corrections to paper tape when to turn to the replicas for these.

Because inventories of scientific and track data usually describe cases or controls it does not mean that the row numbers of working sheets can never denote anything else. For instance it is very important to keep a record of the true meaning of all code numbers or inventory denominations, and convenient to recognise either accidental or deliberate gaps in code number sequences. But, unlike serial numbers, code numbers have nothing in common except the symbols. Consequently the patterns which emerge when row numbers of working pages denote code numbers, and selected columns give their meanings might at a stretch be described as a matrix, but it could hardly be called an inventory. However, just as there is no reason why inventory formation of survey data should be restricted to numbers (as in a statistical inventory) so there is no reason why code numbers and their meanings should not benefit from inventory formation.

With column vectors describing the different uses to which the same numbers have been put during a survey, it is easy to distinguish between official codes which allow no latitude (because there are no gaps in a fixed number sequence) and ones which permit considerable latitude (by having several unused numbers in the code sequence). For instance the International Classification of Diseases and Causes of Death which recognises 17 main categories begins with 001 as the number to denote "respiratory tuberculosis with mention of occupational disease of the lung" and ends with 999 as the number to denote "adverse reaction to other therapeutic procedures." But it also leaves unused 199 numbers

beginning with 18 in the sequence describing infective and parasitic disease (Category I) and ending with 6 in the sequence describing injuries and accidents (Category XVII). So here is a code which not only has widely accepted meanings attached to most of the numbers, but also more "free" numbers than any investigator is likely to need. Yet time and again clinicians and pathologists with something important to say to epidemiologists have insisted on using an improvised classification on the grounds that the International Classification of Diseases numbers have not covered all their needs. If the writers of these papers had ever been shown a series of codes suitable for data of epidemiological interest in matrix formation, they would at least have realised that there might be a possibility of confusion between a rigid or sealed code and an official code which may be open or sealed. But once again epidemiologists seem to be unaware of their textbook and research needs at a technical level.

The techniques of inventory style data assemblage are easily acquired and need not include the usual verification procedure for computer inputs. This operation can be omitted because there is no difficulty in asking a computer to produce a printout which is an exact replica — not of the actual computer input or punched document — but of the transfer or source of the input which is clearly better for checking purposes than the punched document, be it a card or a tape. Verification of computer inputs is considered to be a weighty reason for preferring punchcards to paper tape as a data processing medium in epidemiological surveys. The other reason being the assumed impracticability of updating (that is, correcting) a lengthy data tape without punchcards to bridge the gap between the "fluidity needs" of data collection and the "rigidity needs" of magnetic tape. An easy solution to the second problem has already been suggested and it only remains to explain how the data are actually transferred from inventories to magnetic tape to realise that even in epidemiological surveys paper tapes may be preferable to punchcards.

The final stage of data processing begins with an instruction to the computer about how much space to reserve on magnetic tape and how to recognise a vector. What is actually required is sufficient space to accomodate all the available topics and any which might arise because of last minute additions to the survey population or computer calculated additions to the column vectors. After receiving the requisite number of rows and columns the computer is told to enter the first row number followed by as many symbols for "no record" as there are column vectors and to repeat this instruction until all the row vectors are accommodated. Firstly it is told to expect a series of amendments which will always take the form of numbers to replace "no record" symbols and will always be presented in row vector and row denomination sequences (that is, in the order we usually associate with tape corrections). Meanwhile the amendments are being assembled from the inventories containing the fully processed scientific data by

technicians who have been given the data tape positions of the column vectors in each inventory and told to punch the contents in the form expected by the computer — that is to say either onto card or tapes (depending on local requirements) but always row by row and never column by column.

Should delay in the collection of a few records affect an inventory which is otherwise ready to be punched, the technician will be told by the proofreader to omit all but the row numbers of the affected row vectors, which he will recognise by the fact that they have been ringed in pencil. The ringed numbers are entered on the spare page in front of the working pages where they remain until future deletions show that they are ready to be included in a later punching session when the relevant rings will be rubbed out to show how many still remain unpunched. Thus, by treating all entries on the storage tape as corrections, the contrasting needs of data collection and magnetic tape are met without the intervention of punchcards unless for any reason the computer will only accept cards, in which case the transferring of the records from the inventories will not be difficult but it will be a shade more tedious than with paper tapes.

CHAPTER 3

DIFFERENT APPROACHES TO THE PROBLEM OF LOW-DOSE RADIATION CANCERS IN MAN

Radiobiologists have long been puzzled by the contradictory findings of epidemiologists in relation to the problem of whether obstetric radiography is affecting the prevalence of childhood cancers. For instance, the Oxford survey and other retrospective studies have always shown that children exposed to obstetric radiography are more at risk of dying from a malignant disease before 10 years of age than children who have no reason to be x-rayed before birth (*1-5*). Nevertheless on the numerous occasions when x-rayed children have been the subjects of followup studies, they have usually emerged as groups with exceptionally low rates of cancer mortality (*6-10*). There was, however, one occasion when a group of children who had been x-rayed for obstetric reasons began by developing "too few" cancers and ended by developing "too many" (*11*).

The latest ramifications of the Oxford survey, which deal with the secular trend of leukaemia mortality and with the deaths from other cancers (*12-14*), have gone some way towards resolving this paradox by showing that complications of leukaemia often predate diagnosis, and that when (as often happens) the complication proves fatal, the death is ascribed to a terminal infection (for example, pneumonia) and not to the underlying cause. Other findings of the Oxford survey (*15, 16*) have also shown that these mistakes could be having a disproportionately large effect on leukaemia deaths before 5 years of age, because these cases are initiated in utero, and are therefore in a position to add to the normally high risk of dying at or shortly after birth. The mistaken diagnoses could also be affecting the spontaneous or nonradiogenic leukaemias of children more than the radiogenic cases, because the former have usually been present since the first half of fetal life, and could, therefore, be in a more critical state of the disease by birth than the radiogenic cases, which are usually initiated shortly before birth. The relatively late "initiation ages" of the radiogenic cases also mean that the leukaemias which are diagnosed between 5 and 10 years of age include a higher proportion of radiogenic cases than the ones which are diagnosed earlier.

I expect you would like to know precisely how these discoveries were made, but this must wait until I have time to describe the Oxford survey in detail. They had to be mentioned today because they disturb so many of the assumptions which have been made in relation to the

prospective surveys with negative findings. If, for instance, there is a tendency to confuse leukaemia with other causes of death, we should not expect a child population which has been depleted by a large number of stillbirths, infant deaths, and fatal infections to have as many deaths ascribed to leukaemia as a normal population. Yet this assumption was made in a recent followup of A-bomb survivors who were exposed in utero (9). It would also be dangerous to assume that the number of spontaneous leukaemias in a group of children exposed to obstetric radiography had not been influenced both by the mother's decision to attend, or not to attend, an antenatal clinic (which could affect the number of low-income families at risk of being x-rayed before birth more than the number of high-income families) and the doctor's decision to order, or not to order, an x-ray examination (which undoubtedly reduces the proportion of difficult births among the non-x-rayed children).

If confusion between leukaemia and other causes of death affects young children more than older children (and, therefore, spontaneous leukaemias more than radiogenic leukaemias) it would clearly be important in any prospective survey to relate the cancer deaths to the duration of the followup period (cohort analysis) and to compensate for any shortage of children in the longer followup periods. Moreover, if there were any reason to think that financial or other considerations were influencing the situation, it would be important to keep track of all causes of death and to enlarge the initial specifications. For instance, in the United States, a propsective survey which was not confined to white children should include some information about the background of every child, in case the attitude towards antenatal care was influenced by ethnic considerations as well as financial ones.

Since the purpose of an obstetric x-ray examination is to anticipate a difficult birth, the children concerned are not only members of a population which will experience more deaths during the first year of life than a normal population, they are also members of a population which has already experienced a high stillbirth rate. This fact (or the possibility that a leukaemia might be mistaken for a stillbirth) has been forgotten by the many epidemiologists who have based their prospective studies, not on an exposed population, but on "children discharged alive from the hospitals where they were born" (8, 11). One research worker did discover that neonatal and later deaths were affecting the situation (17), but he overlooked the possibility that, in an American city, the proportion of coloured mothers who think twice before attending an antenatal clinic (or agreeing to an x-ray examination) could be much higher than the corresponding proportion of white mothers. Lilienfeld, in fact, discovered that the all causes death rate was higher for the white children who were x-rayed in utero than the white controls. But because his original specifications

did not include any social data he was not in a position to discover why the position was reversed for the black cases and controls (table 1).

TABLE 1. *Neonatal and later deaths in x-rayed and non-x-rayed children, Baltimore survey*

(Lilienfeld 1971)

Category[a]	Colour	Neonatal deaths	Later deaths[b]	Numbers at risk
Cases	White	194	148 (6)	10,169
	Coloured	210	157 (-)	9,720
	Both	404	305 (6)	19,889
Controls	White	235	166 (4)	19,432
	Coloured	385	287 (3)	16,321
	Both	620	453 (7)	35,753
		Mortality rates per 10,000		(Totals)
Cases	White	19.1	14.5	33.6
	Coloured	21.6	16.2	37.8
	Both	20.3	15.3	35.6
Controls	White	12.0	8.6	20.6
	Coloured	23.5	17.7	41.2
	Both	17.3	12.7	30.0

[a]Cases = Children x-rayed before birth.)
[b]Controls = Non-x-rayed children.) Figures in brackets = leukaemia deaths.

The original purpose of this survey was to discover whether obstetric radiography had increased the risk of developing leukaemia, and most of the 55,642 children were followed for more that 5 years. A record was kept of all causes of death, but in the final analysis the causes were not related either to the age at death or to the duration of the followup period. In any case, only 13 of the 1,782 deaths were ascribed to leukaemia, so even if the analysis had allowed for social factors, and had only allowed the children who were followed for the full 10 years to affect the final conclusions, we should not have learned very much about the delayed effects of low-level radiation from this survey.

Since the alternative name for a prospective survey is a "cohort study" *(18)* one might have expected followup studies of x-rayed children to include a cohort analysis, or one in which children born at different

times, and followed for different periods, made separate contributions to the final conclusions. In fact all of the prospective surveys with negative findings have allowed a merging of the birth cohorts, and therefore allowed the children who were followed for relatively short periods to influence the results much more than the finding for children who were followed for more than 5 years; and they have sometimes stopped short at 6 years.

For instance, a survey of 16,984 children who were born in Queen Charlotte's Hospital in London between 1953 and 1958 reported eight leukaemia deaths during these same years (6). For the children who were not x-rayed in utero, the observed number of leukaemia deaths represented a risk of 1 in 1,800 (which approximates to the normal risk for children in this age range) and for the children who were x-rayed they represented a risk of 1 in 4,300. Since there was no question of the radiation making the exposed children only half as likely to die from leukaemia as normal children, and since most of the children were followed for less than 3 years, this observation should have alerted research workers to the possibility that (for some reason to do with the need for an unusual type of obstetric examination) children who are x-rayed before birth have a lower than average risk of dying from leukaemia during the next 3 years.

When, however, Court Brown and his associates (8) assembled from eight hospitals in London and Edinburgh a population of 39,166 children who had been x-rayed before birth, and followed the group for periods which varied from less than 3 to over 10 years, they ignored all causes of death except leukaemia and made no attempt to relate these deaths to the duration of the followup period. For the group as a whole, and for various subgroups, the observed numbers of leukaemia deaths were smaller than the expected numbers (table 2). Since these expectations were based on official statistics they could have been used to set the standard for each year of birth (or birth cohort) and each followup period. The results of such an analysis are shown in table 3 where one can see that if the study had been confined to the 11,448 children who were followed for at least 8 years (and thus come nearer to resembling a retrospective study of cancer deaths before 10 years of age) the observed number of leukaemia deaths (7) would have exceeded the expected number (4.1). What is more, if the findings of the children followed for shorter periods had been shown separately from the findings for longer periods, we would have been given a second chance to see that the children who were involved in obstetric x-ray examinations have a lower than average risk of dying from leukaemia during the next 3 years.

The importance of waiting until one can see beyond the period affected by a high rate of stillbirths and neonatal deaths can be seen in relation to a followup of 734,243 children who were born in 37 maternity hospitals in the northeast United States and were 90

TABLE 2. *Prospective survey of children born and x-rayed in London and Edinburgh hospitals (1945-1956 births)*

Published Data[a]

Specifications		Leukaemia deaths	
		Observed	Expected[b]
Sex	Male	7	6.2
	Female	2	4.4
Age at death	Under 5 years	6	7.5
	5-13 years	3	3.0
Radiographs	One	4	5.4
	More than one	5	4.3
Hospitals	London	5	5.7
	Edinburgh	4	4.8
Leukaemia deaths		9	10.5
Numbers of	Boys	20,982	
	Girls	18,184	

[a]Court Brown et al. (1962) (6).

[b]Based on official statistics for 1945-1958.

TABLE 3. *Cohort analysis of the data shown in table 2*

Cohorts			Leukaemia deaths		
Numbers	Birth years	Followup period	Observed	Expected	Ratio
8,797	1955-57	Less than 4 years	-	1.0)	0.31
18,921	1950-54	4 to 8 years	2	5.4)	
11,448	1945-49	Over 8 years	7	4.1	1.71
39,166	1945-57	1 to 14 years	9	10.5	0.90

percent white children (11). For several years the findings of this survey was falling into line with the observations of Court Brown and his associates; and before the earlier survey was published MacMahon had told the American Public Health Association that he had a marginally higher frequency of non-x-rayed children (7.3 percent) among his cancer deaths than x-rayed children (7.0 percent) (19). However, by the time there were no children under 5 years of age, and two-thirds of them had been followed for at least 8 years, there were 15.3 percent of x-rayed children with cancers and 10.6 percent of non-x-rayed children. By this time there was a sufficiently large number of leukaemia deaths among the x-rayed children (47) to notice that the "extra" cases were older than average, and concentrated in a narrower age range than the corresponding set of solid tumors (table 4). This observation has rarely been mentioned but it anticipates an important discovery of the Oxford survey (15, 16); namely, that for each type of cancer caused by obstetric radiography there is a constant interval between the exposure date and the diagnosis. Since there is no limit to the number of childhood cancers which can be caused by obstetric radiography, the constancy of the individual latent periods is much easier to demonstrate in a group which consists mainly of lymphatic leukaemias than one which includes all solid tumors.

TABLE 4. *Observed and expected numbers of cancers in x-rayed children*

(MacMahon 1962)

Cause of death	Age at death	Observed	Expected	Ratio
	0-	19	8.1	1.1
	3-	17	11.1	1.5
Leukaemia	5-	21	10.4	2.0
	8 and over	-	2.9	-
TOTAL		47	32.5	1.4
	0-	15	10.0	1.5
	3-	9	7.3	1.2
Other cancers	5-	12	6.3	1.9
	8 and over	2	2.9	0.7
TOTAL		38	26.5	1.4
	0-	24	18.1	1.3
	3-	26	18.4	1.4
All cancers	5-	33	16.7	2.0
	8 and over	2	5.8	0.3
TOTAL		85	59.0	1.4

But before I finally bring the Oxford survey into the center of the stage, which has so kindly been prepared for me by Dr. Shore, I would like to say a few words about the A-bomb survivors who were under 10 years of age in 1945, and to mention very briefly a survey which has left the impression that preconception exposures influence the frequency of childhood leukaemia as much as prenatal exposures (4); and a survey which has left the impression that x-ray examinations of the chest and abdomen are influencing the frequency of adult forms of myeloid leukaemias (20).

A-BOMB SURVIVORS

A 10-year followup of 1,291 A-bomb survivors who were exposed in utero discovered one cancer death in a girl who was 6 years old when she developed a hepatoblastoma, and gave as the expected number of cancers either 0.75 or 36.9 (9). The small figure represented the number of nonradiogenic or spontaneous cancers which were expected on the assumption that the study population was comparable to all children born in Japan between 1945 and 1946, and the large figure represented the number of radiogenic cancers which was expected on the assumption that the study population was comparable to children in the Oxford survey who were irradiated in utero (21, 22) (table 5).

TABLE 5. *Observed and expected number of cancer deaths in 1,292 A-bomb survivors exposed in utero (Jablon and Kato (9))*

Prenatal exposures		Cancers under 10 years		
Mean radiation dose in rads[a]	Numbers at risk	Observed	Expected[b]	
			Nonradiogenic	Radiogenic
<1	551	-	0.32	-
12	467	-	0.37	3.1
106	215	1	0.12	13.0
396	17	-	0.01	3.9
1,847	16	-	0.01	16.9
No record	26	-	0.02	-
50	1,292	1	0.75	36.9

[a] Estimates based on maternal exposures.

[b] Nonradiogenic = at Japanese national rates.
Radiogenic = Kneale 1970 (21).

If, however, an increased risk of dying from other causes is accompanied by a decreased risk of dying from leukaemia, both assumptions could be wrong. Indeed, it is possible that the one cancer death which was recorded by Jablon and Kato would have exceeded the expected number of nonradiogenic cancers in a group 10 times the size of the study population, provided all members of the group had been fully exposed to the aftermath of the atomic explosions. In this connection it is of interest to note that if one is allowed only one cancer death before 10 years of age one would expect it to occur before 5 years of age; to be a leukaemia rather than a solid tumor; and to affect a boy rather than a girl. In other words the one cancer death which was observed was sufficiently unusual to suspect that it had an unusual origin.

There has also been a followup of more than 10,000 A-bomb survivors who were children in 1945 (*10*) which can be used to show that when the exposed individuals are children, not fetuses, and when the radiogenic cancer is a solid tumor, not a leukaemia, the latent period could easily exceed 15 years. This conclusion is based on 810 children who received more than 100 rads and developed 10 times as many neoplasms (other than leukaemia and thyroid cancers) between 1955 and 1969 as was expected on the basis of Japanese mortality rates for 1963. The exposure ages for these cases ranged from 2 to 9 years (average 6 years) and the intervals to diagnosis or death ranged from 13 to 24 years (average 19 years). So it is reasonable to assume that the cancers which are initiated during childhood are more chronic diseases than the ones which are initiated before birth, and that a survey which was restricted to children would not be in a position to detect the carcinogenic effects of any form of diagnostic radiography other than obstetric radiography.

Although the A-bomb survivors who received more than 100 rads during childhood developed "too many" solid tumors during the next 25 years, the children who received lesser amounts of radiation developed "too few" (18 observed and 32 expected). Jablon and his associates who reported this finding hinted at an association between a cancer-resistance factor and low-level radiation. As, however, the risk of dying from infections was much higher for children who were living in the bombed cities than for children in other parts of Japan, once again it may have been a mistake to base expectations on national statistics. An obvious alternative to using the population at large as a control group was to use the A-bomb survivors who received no radiation. We know that such a group exists because no less than 10 of the 15 solid tumors which were found among the 10,729 children in the 0-9 rad group appear in the lists of cancer deaths and notifications opposite the label "0 rads".

Pending identification of a group of children who were exposed to the aftermath of the explosions but not to the radiation, we can see in

table 6 the results of comparing the A-bomb survivors who received 0-9 rads with the children who either received larger amounts or were living elsewhere in 1945 (local controls or NIC group). According to this analysis there was a twofold excess of leukaemias and solid tumors among the children who received more than 10 but less than 100 rads (15 observed and 78.6 expected) and a 16-fold excess for the children who received more than 100 rads (28 observed and 1.7 expected). In addition, the observed numbers of cancers was higher for the local controls (19) than the expected number (10.8) which is what we would expect if the risk of dying from other causes was lower for these children than for the A-bomb survivor.

TABLE 6. *1950-1969 cancer deaths and notifications affecting A-bomb survivors and local controls who were under 10 years of age in 1945 (Jablon et al. (10)).*

	All deaths and notifications (1950-69) including thyroid cancers				
Radiation category	Numbers of children	Diseases	Observed	Expected[a]	O : E ratio
10-99 rads	3,669	Leukaemias[d]	6	2.74	2,19
100+ rads	810		12	0.60	20.00
Local Controls[b]	5,010		--	3.74	--
Total[c]	9,489		21	7.08	2.54
10-99 rads	3,669	Solid Tumors	9	5.12	1.76
100+ rads	810		16	1.13	14.16
Local Controls	5,010		19	6.99	2.72
Total	9,489		44	13.24	3.32
10-99 rads	3,669	All Cancers	15	7.86	1.91
100+ rads	810		28	1.73	16.18
Local Controls	5,010		19	10.73	1.77
Total	9,489		62	20.32	3.05

[a] Expected on the basis of 10,729 A-bomb survivors who received less than 10 rads and accounted for 23 of the cancers, including thyroid cancers.

[b] Children who entered the bombed cities after the explosions and before October 1950 (so-called N.I.C. group).

[c] Excluding 299 A-bomb survivors who received unknown amounts of radiation and accounted for three of the cancers.

[d] Including nine deaths between 1950-54 which have been distributed between the radiation categories in the same proportions as the 17 deaths between 1955 and 1959 (i.e. three cases to the children who received less than 10 rads, two to the recipients of 10-99 rads, and four to the recipients of larger amounts).

PRECONCEPTION EXPOSURES

One of the reasons which has been given for doubting the Oxford survey, and other studies with positive findings *(23, 24)*, is the discovery of an association between preconception exposures and childhood leukaemias which is as strong as the association with prenatal exposures (table 7). Graham and his associates reported the association *(4)*, and Miller, who compiled the table, pointed out that it was ridiculous to suggest that the two types of exposure could have the same effect. This claim was never made by Graham et al. On the other hand, the fact that they included in their analysis a number of tables relating numbers of films and numbers of leukaemia cases shows that they were prepared to consider a direct association. Their failure to consider the thousand and one reasons why the parents of leukaemic children might be more often x-rayed than the parents of healthy children also shows that they were not prepared to consider an explanation supported by their own data. They observed an excess of stillbirths in the sibships of their leukaemic children but never considered the possibility that this might be a sign that, included among the nonradiogenic cases, there might be some which would have been recognized as "familial leukaemias" if the second child had not been stillborn or aborted.

TABLE 7. *Relative risk of various childhood cancers following intrauterine or preconception exposures to diagnostic radiation (Miller 1969 and 1970)*

Oxford Survey		Leukaemia	1.5
		Lymphosarcoma	1.5
		Cerebral tumors	1.5
Stewart and Kneale (1969)	Prenatal	Neuroblastoma	1.5
		Wilms tumors	1.6
		Other cancers	1.5
New Oxford Survey	Prenatal	Leukaemia	1.5
		Neutral tumors	1.6
MacMahon (1962)		Other cancers	1.4
Tri-State Survey	Prenatal	Leukaemia	1.4
Graham et al. (1966)	Preconception[a]	Leukaemia	1.6
	[b]	Leukaemia	1.3

[a]Mothers of the leukaemia children.
[b]Fathers of the leukaemia children.

When one considers that about 95 percent of childhood cancers are not explained by obstetric radiography, it is not difficult to believe that there could be a small number of inherited cases who (instead of having an obviously affected sibling) have a "sibship gap" corresponding to a precancer which caused either a stillbirth or an abortion or a nonconception. This hypothesis, which is supported by the findings of the Oxford survey, would allow the parents of cancer-prone children to be less healthy than the parents of healthy children, and, therefore, more at risk of being examined by a radiologist for reasons which were distantly but not directly related to the cancer death in the next generation. This line of reasoning would also allow us to forget that the findings of the Oxford survey have been regarded as unreliable merely because they suggest that the radiosensitivity of fetal tissues is a measure of their natural cancer sensitivity *(25)*. Once again I am anticipating my next lecture, but I felt I had to offer an alternative explanation of the figures in table 7 to the one suggested by Miller.

ADULT LEUKAEMIA AND DIAGNOSTIC RADIOGRAPHY

Ten years ago I was the joint author of a paper which was based on a survey of adult leukaemias, and finally came to the conclusion that 8 percent of the myeloid cases had been caused by x-ray examinations of the chest and abdomen *(20)*. As, however, all the "extra" examinations happened within 5 years of the leukaemia being diagnosed, I would like to retract what I said in 1962 and to give as the probable reason for the extra examinations the heightened sensitivity to infections which not only accompanies leukaemia but predates the development of recognizable signs and symptoms by several years. How we finally came to discover that "preleukaemic" individuals are not nearly as healthy as they seem to be, will, I hope, be explained in my final lecture, but I must give you a more consecutive account of the Oxford survey.

In summary, authors of prospective studies have assumed that children who are irradiated in utero have the same chance of developing nonradiogenic leukaemia within 5 years of birth as nonexposed children. There are, however, associations between obstetric radiography and difficult births, between difficult births and stillbirths, between stillbirths and leukaemia, and between leukaemia and infections which make this a false assumption. For 5 or 6 years after birth, children who are x-rayed for obstetric reasons have a lower than average risk of dying from a nonradiogenic leukaemia, and A-bomb survivors who were exposed in utero or during childhood had a period of reduced risk which lasted 10 or 15 years. The reduced risks are due not to an abnormally

low incidence of nonradiogenic leukaemias, but to the difficulty of recognizing the underlying causes of stillbirths and infection deaths. They are also a reminder that childhood cancers have fetal origins and that adolescent cancers have usually been present since early childhood, and, in the case of bone sarcomas, since before birth.

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CHAPTER 4

THE OXFORD SURVEY

There are several papers in medical journals describing the methods and findings of the Oxford Survey, but the only ones regularly mentioned in the radiation literature are the 1958 report, which includes an estimate of the number of cancer deaths caused by prenatal irradiation during the period 1953-55 (*1*), and the 1970 report, which deals with radiation dose effects and includes an independent assessment of the dose to the fetus from a pelvic radiograph of known vintage (*2*). We would naturally expect radiobiologists to be more interested in data relating to diagnostic doses of radiation than in other aspects of an open-ended survey which already embraces two studies of leukaemia mortality (*3-6*) and two data-collecting projects; namely, the pilot study of 1953-55 deaths (*1*) and the cohort study of 1945-1960 births (*7*). As, however, the studies of leukemia mortality have shown that the first effect of a haemopoietic neoplasm is to lower resistance to other diseases, and that this effect is felt a year or more before the malignant cells declare themselves, we are now faced with the possibility that the relationship between ionizing radiation and human cancers will never be fully understood until we have learnt to pay as much attention to "exposure concomitants" and "latency situations" as we have already learnt to pay to dose-response curves.

In fact, anyone who is interested in the population effects of low-level radiation should be conversant with what has been learnt by approaching the problem of cancer etiology retrospectively and concentrating on cases with latent periods of less than 10 years (that is, childhood cancers), and even if he has no intention of working with epidemiologists he should understand why the surveys which were modeled on the history-taking methods of clinical medicine found it so much easier to recognize the carcinogenic effects of diagnostic radiography than the ones which were modeled on the followup methods of animal experiments. Finally, even if a radiation physicist or biologist is more interested in what can be discovered in the future than what has already been observed, he might be curious to know how a department of social medicine (with no experience of radiobiology) came to be interested in the problem of low-level radiation, and why the department which made a more or less accidental discovery continued to take an interest in the delayed effects of

obstetric radiography even when it was known that the number of deaths caused by prenatal irradiation was small in relation to the number of children at risk of dying from birth injuries.

BACKGROUND TO THE PILOT PHASE OF THE OXFORD SURVEY

For several years before the Oxford Survey was launched, the leukaemia experiences of A-bomb survivors and the unfavourable trend of leukaemia mortality were attracting the attention of research workers, and there was widespread anxiety lest manmade radiations were responsible for the fact that the rise in the leukaemia death rate was most noticeable in technologically advanced countries. However, no one seemed to have noticed that children were behaving in a very odd way until David Hewitt drew attention to the persistently low rates of leukaemia mortality in infants (3), and also showed that the increased risk of dying from this disease in the 1950's compared with the 1930's was positively correlated with age towards the beginning of the life-span and negatively correlated with age towards the end of the life-span.

In the normal course of events, resistance to any form of tissue damage, whether it is a consequence of disease or the result of violence, increases with age so long as we are children, and decreases with age once we have passed maturity. Therefore the risk of dying - as distinct from the risk of incurring tissue damage - decreases with age during childhood and adolescence, and increases with age thereafter. Indeed, the effects of immaturity and senescence on the body's defences against diseases and injuries are so strong that although we nowadays go to great lengths to protect infants and old people there is still a twentyfold reduction in the risk of dying between 6 months of age and 30 years; a twentyfold increase during the next 30 years; and a fiftyfold increase between 30 and 70 years (8).

It follows that any disease which causes as many deaths between 4 and 5 years of age as it does between birth and 1 year of age is regarded with suspicion by anyone who is trained to observe the social or population consequences of disease. So we no sooner discovered that a disease which was causing anxiety in several quarters once had a flat rate of mortality between 0 and 5 years and now had a sharply peaked one (fig. 1) than we began to search among the antecedents of these early deaths for something of interest. In other words, the data collecting phase of the Oxford Survey followed recognition of one consequence of a still unresolved social problem (namely the recent rise in leukaemia mortality) and was undertaken with the following ideas in mind.

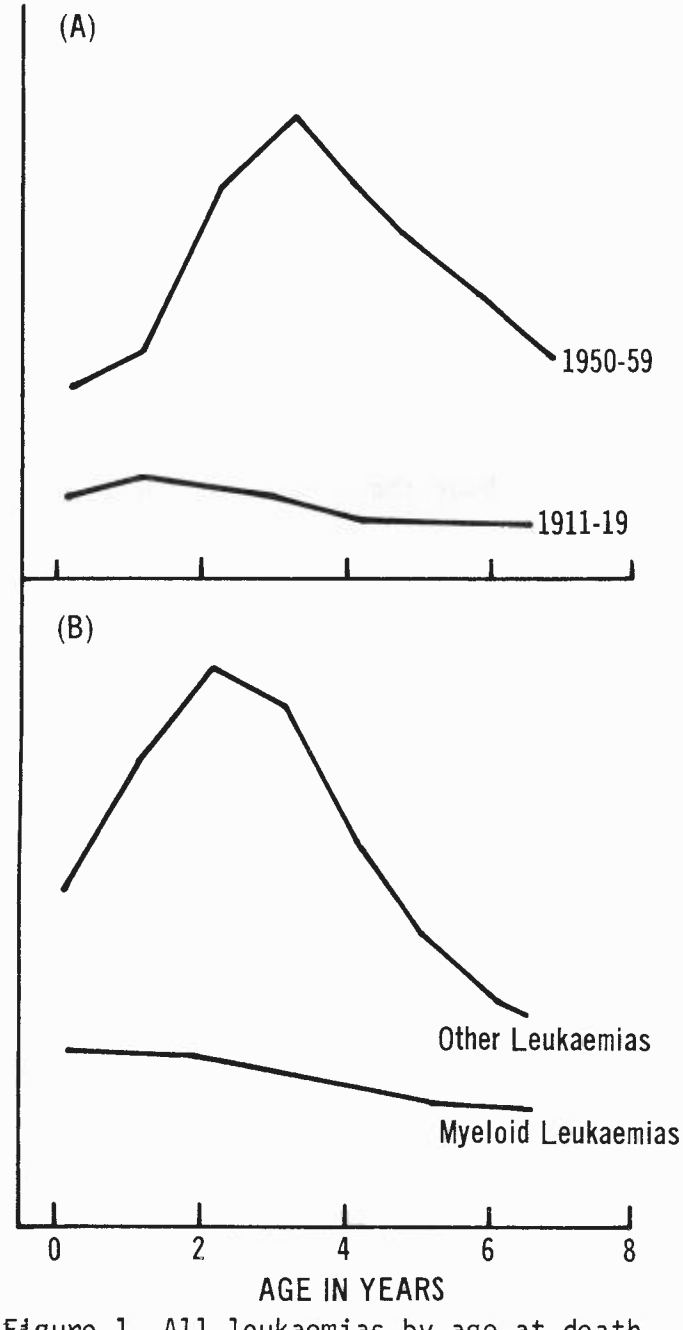


Figure 1. All leukaemias by age at death in two decades. (E. & W. Official Statistics).
Myeloid and other leukaemias by onset ages (1953-65 deaths, Oxford Survey).

We thought that what was happening to children between the ages of 2 and 4 years might be distantly related to what was happening to the A-bomb survivors who had escaped obvious radiation injury but were nevertheless developing myeloid leukaemia. We also decided that whatever was causing the unfavourable trend of leukaemia mortality must be out of range of infants, since we could see that slightly older children were reacting more violently to the "new" influence than either young or middle-aged adults. However, instead of offering a solution to one or other of these problems, the Oxford Survey merely added to the sense of confusion by showing that, although children who were exposed to obstetric radiography seemed to be more cancer-prone than other children, they also seemed to be less likely to develop myeloid leukaemia than other forms of cancer (table 1). The survey of 1953-55 deaths also discovered that the only noteworthy differences between the leukaemias and the solid tumours made no sense in terms of current theories about the origins of cancers (1). For

TABLE 1. *Comparative incidence of direct fetal irradiation in eight diagnostic groups*

Diagnosis	No. of Cases	Irradiated in utero		
		Percent	Actual No.	Expected No.
Lymphatic leukaemia	292	14.4	42	40.31
Myeloblastic "	124	7.3	9	16.24
Blast-cell and other leukaemias . .	203	13.8	28	27.93
Lymphosarcoma, other reticuloses. .	109	7.3	8	14.24
Malignant tumors of C.N.S.	212	12.7	27	28.75
Malignant tumors of kidney	120	15.8	19	16.68
Malignant tumors of suprarenals . . (incl. all neuroblastomas)	87	18.4	16	12.68
Malignant tumors of other sites . .	152	19.1	29	21.16
Total . .	1,299	13.7	178	177.99

In an 8 x 2 table, the comparison of actual and expected numbers irradiated and not irradiated yields $\chi^2(7) = 11.832$, compared with 12.017 at the level P = 0.10.

example, first-born children seemed to be more leukaemia-prone than other children before 5 years of age but not afterwards. There was also an unmistakable association between leukaemia and mongolism which had never been seen by Lionel Penrose in all the time that he had been observing mongol children in what used to be called "mentally defective colonies" (9). Finally, the case children had experienced "too many" attacks of pneumonia within 2 years of developing their malignant diseases (especially leukaemias), although the incidence of measles and other infectious diseases was no higher for cases than controls.

OBSTETRIC RADIOGRAPHY

Before the cancer hazard was discovered obstetric radiography was developing along lines which were making the examinations more of a luxury than a necessity. For instance, there were several obstetricians in England who were advocating routine x-ray pelvimetry of pregnancies on the grounds that first births were more hazardous events than later ones, and in the United States there were even obstetricians who were advocating routine pelvimetry for all pregnancies on the grounds that all births are dangerous (10). So it only needed the slightest hint of a cancer hazard for the unborn child to reduce both the number of pregnant women who were referred for these examinations (obstetricians' reaction to the preliminary report of the Oxford Survey, which was published in October 1956 (11)) and the number of examinations requiring more than one exposure (radiologists' reaction see fig. 2 and table 3).

Given that there was a cancer hazard associated with obstetric radiography these reactions would make children who were born before 1957 more at risk of developing radiogenic cancers than children who were born later (that is, they would be members of "high risk" birth cohorts). On the other hand, even complete cessation of obstetric radiography would be powerless to affect any cancers (radiogenic or nonradiogenic) which were already in the pipeline, and it was possible that these cases might continue to appear for several years to come. There was also a hope that a method of data collection which had succeeded in obtaining medical histories from 82 percent of the children who died between 1953 and 1955 would be equally successful if applied to the children who were born between 1953 and 1957 and developed cancers before 10 years of age (cohort or year of birth sample of cancer deaths which would take 15 years to assemble, or 12 more years). So instead of replacing our case-history or retrospective study of childhood cancers with a followup of children x-rayed in utero, we decided to prolong the original survey and to bear in mind the following possibilities.

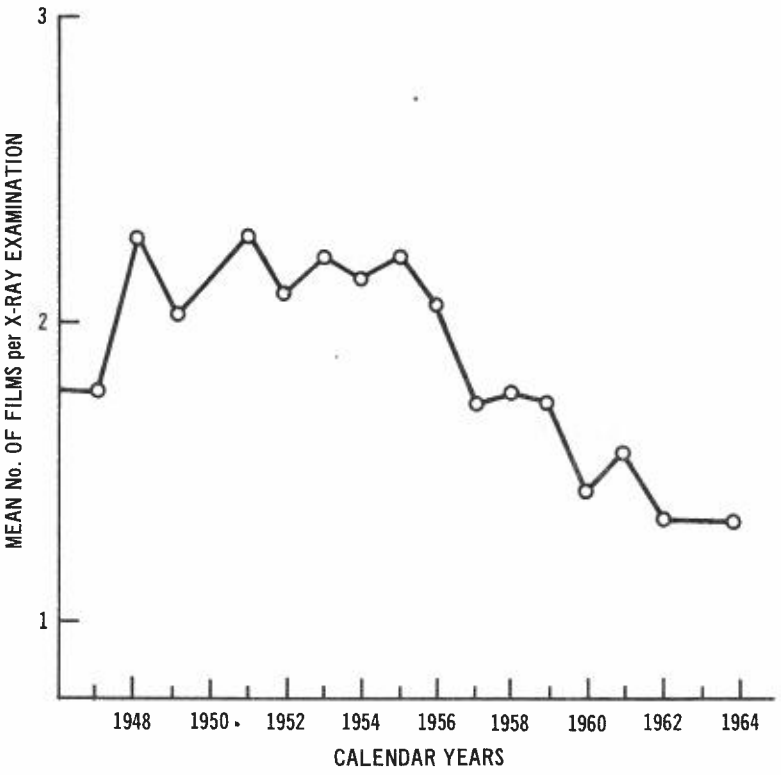


Figure 2. Time trend of film numbers.

BACKGROUND TO THE COHORT PHASE OF THE OXFORD SURVEY

The pilot study had shown us that, although we might be able to trace two-thirds of the x-ray records of children who died from malignant diseases, we would still be dependent upon numbers of radiographs for our estimates of fetal doses, because only one hospital had given us the dose in rads. As, however, three-quarters of the children were over 7 months of fetal age before they were exposed (and all were under 10 years at death) we ought to be able to use the onset ages of the x-rayed and non-x-rayed cases to decide whether the "extra" (x-rayed) cases were (1) an artefact due to biassed reporting by mothers of cases and controls; (2) a selection effect due to the obstetricians' choice of x-rayed subjects; (3) a promotion effect due to the radiation converting precancers into overt cancers; or (4) an initiation effect due to radiation-induced mutations transforming normal cells into cancer cells.

An artefact would allow the cases to be classified by their radiation histories without affecting their onset-age distributions; and either selection bias or a promotion effect would make the extra cases younger than average. If the extra cases were the result of radiation-induced mutations, they might be older or younger than average, depending upon whether the nonradiogenic cases were initiated before or after birth. But if we were to discover that the extra cases were older than average and had a narrow choice of onset ages, we could be as certain that they were radiogenic as we would be if the number of extra cases was proportional to the radiation dose.

As things have turned out, we have been able to show that the effect of obstetric radiography on the incidence of childhood cancers is directly proportional to the radiation dose, and we have been able to convert an estimate of relative risk into an estimate of absolute risk (2). Nevertheless, the data relating to cancer latent periods are probably more important than the data relating to radiation dose effects, since a great deal hangs on whether there is a constant or variable interval between initiation and onset. In other words, whether we are dealing with a straightforward (malignant growth) process or one which proceeds in stages.

LATENCY STUDIES

The first of the latency studies (all of which are based on children who died within 10 years of birth) belongs to the pilot phase of the Oxford Survey. As, however, the data were not examined from this point of view until after the 1958 report had been published, it is not widely known that Mervyn Wise was the first person to discover that children who die from leukaemia within 5 years of birth must have been in a preclinical phase of the disease since the first half of fetal life (12). For reasons which are related to the high frequency of first births among the peak incidence of leukaemia deaths (see fig. 2, chap. 1) the Wise analysis was restricted to 306 children who had no older sibling and died from leukaemia during the period 1953-55. There was, however, no mistaking the fact that the children who were not x-rayed before birth were younger when they died than their x-rayed contemporaries (table 2).

By the time this table was published (1961) a series of prospective surveys had left impressions which were easier to reconcile with the idea that low-level radiation reduces the risk of developing leukaemia than with the idea that even the smallest quantum of radiation carries

TABLE 2. *Mean ages at death of first-born children who died of leukaemia before the age of 10 years during the years 1953-55 (Oxford data)*

Year of birth	Age at death in years (range[a])	First-born children				Differences between (1) and (2) in months
		(1) Irradiated in utero		(2) Others		
		No.	Mean age at death in months	No.	Mean age at death in months	
1945	7-10	1	112.00	14	100.02	+ 11.98
1946	6-9	3	97.67	14	92.29	+ 5.38
1947	5-8	3	73.00	29	85.97	- 12.97
1948	4-7	6	76.67	22	69.91	+ 6.76
1949	3-6	8	65.75	30	58.90	+ 6.85
1950	2-5	7	48.29	39	46.94	+ 1.35
1951	1-4	8	36.88	49	36.24	+ 0.64
1952	0-3	6	32.83	31	25.42	+ 6.41
1953	0-2	4	27.75	20	19.70	+ 8.05
1954	0-1	3	11.67	9	8.17	+ 3.50
					Mean difference	+ 3.68

[a]Maximum age-range for each year of birth = 4 years.

a cancer hazard (see chap. 3). So there was very little appreciation of the fact that the extra (x-rayed) cases in the Oxford Survey were not an artefact and were not the result of a selection effect or a promotion effect. In fact, Wise had shown that the third trimester of fetal life was a relatively late date for initiating a leukaemia which caused death before 10 years of age, but it is doubtful whether anyone outside the Oxford Department of Social Medicine was aware of this important discovery.

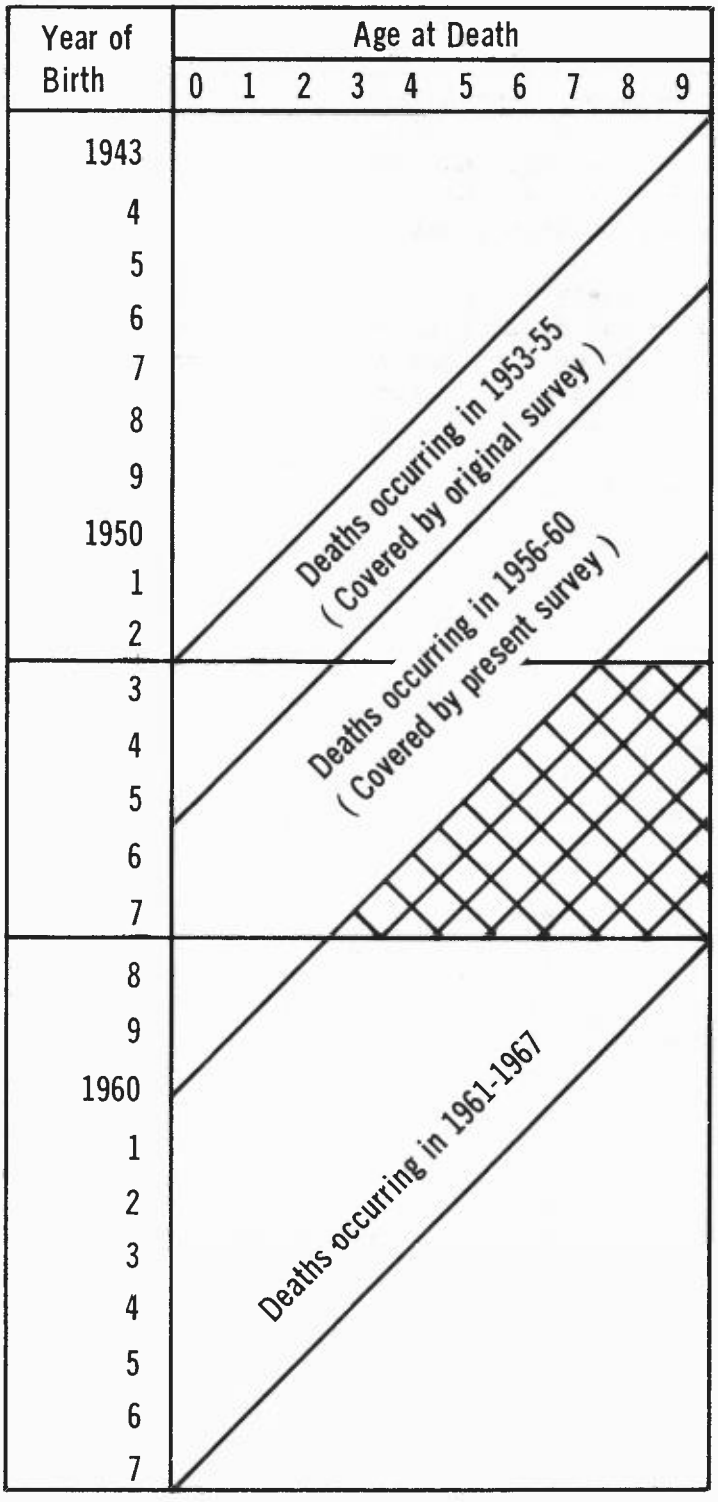
Our next attempt to show that the interval between birth and death was different for the x-rayed and non-x-rayed cases was based on 2,134 children who had their deaths ascribed to leukaemia or lymphosarcoma (13). This group was sufficiently large and sufficiently homogeneous to prove that the triple association between leukaemia, first births and obstetric radiography was a consequence of three

separate associations. In fact, the association between the x rays and leukaemia applied with equal force to first births and later births; the "extra" first births were concentrated among the children who died from leukaemia between 2 and 4 years of age, and the "extra" x-rayed cases among the children who died between 4 and 6 years. There was also a concentration of mongols and sib-concordant cases among the children who died before 2 years of age, and a deficit of myeloid leukaemias among the deaths between 2 and 6 years of age.

The occasion for this analysis was a book on "Current Topics in Radiation Research," so we had to explain why we had said nothing about radiation doses and why we attached so much importance to age at death. One reason why we were not anxious to discuss relationships between numbers of radiographs and fetal radiation doses was that we were still dependent upon hand-sorting of our ledgered data, or records which could not be "frozen" for any length of time without causing disturbance to our data processers (see chap. 2). But we also had other reasons for our preoccupation with age at death which are just as valid today as they were in 1965, when we had occasion to say: "There are two reasons why it has seemed more profitable to concentrate on these aspects of timing rather than, for example, on x-ray dosage. In the first place, the date of an exposure is often ascertainable even when the dose received can hardly be guessed within an order of magnitude. In the second place, a dose-response curve carries no implications beyond the field of radiobiology, but the demonstration of characteristic time intervals may provide pointers to the origin of leukaemia cases which occur independently of radiation" (*13*).

Two years earlier (*14*) we had also had occasion to say: "Before asking our Public Health colleagues if they are willing to survey cancer deaths during the period 1961-67 we will try and explain why it is considered desirable to continue the collection of data until at least five cohorts have reached the age of 10 years (fig. 3). The first and most important reason rests on the assumption that each type of cancer has a characteristic latent period - or distribution of latent periods - so that continuous observation over 10 or more years may be needed in order to recognize the full consequences of certain events. This important assumption seems justified both by experimental carcinogenesis and by observations in man (for example, dyestuff tumors and radiogenic leukaemia in adults) and is tantamount to saying that it may take 15 years or more for all prenatally induced cancers in five consecutive cohorts to become manifest.

"Another reason why it is desirable to extend the "age-span followup" of the youngest cohorts in the original survey (1953-55 births) is the continued scepticism which has recently been expressed about the carcinogenic possibilities of diagnostic x rays (Lancet,



Cross hatched area represents observations needed to complete 10-year follow-up of five successive cohorts (1953-57)

Figure 3. Achievement of a cohort followup.

1963 [15]). It is now certain that there is a statistical association between prenatal x rays and childhood cancers (MacMahon, 1962 [16]), but there are still doubts as to whether this reflects a causal relationship, doubts which we cannot hope to dispel until the results of comparing cases with controls have been reinforced by comparisons between x-rayed cases and non-x-rayed cases. Since the extent to which obstetricians have employed x-ray examinations has varied over the years, the second type of comparison will be difficult to make until sufficient time has elapsed for the prenatal experiences of different cohorts to reveal their full consequences. Nevertheless, some progress along these lines has already been made.

"Wise (1961 [12]) began by studying first-born children who had died of leukaemia during 1953-55. In his group of 306 such cases, 10 birth cohorts were represented (1945 to 1954), and in nine of these the mean age at death of cases with a history of prenatal irradiation was older than the mean age of the non-x-rayed cases.

"At the time when Wise made this observation only two cohorts had been followed from birth to 1 year of age (1953-1954) and only one had been followed from birth to 2 years of age (1953). Now we have reached the stage when there are seven cohorts which have been followed for 12 months (1953-1959), and four cohorts which have been followed for 4 years (1953-1956). We are, therefore, in a better position to discover whether there are (in addition to the difference in the mean age at death) other significant differences between the age-distributions of x-rayed and non-x-rayed cases - differences which should not exist if prenatal radiography carries no risk of cancer. In the absence of such a risk, the proportion of x-rayed cases in a given cohort should be the same, whatever the age at death.

"Should there be any significant variation with age in this proportion it will be necessary to infer either (a) that the x-ray exposures have affected the risk of death or (b) that the malignant changes preceded the exposures and influenced the decision to x ray the mother. Depending on the pattern of variation observed, some guidance may also be obtained on the choice between (a) and (b) as a working hypothesis. If, for instance, a preexisting condition occasioned the x rays, then any "extra" deaths of exposed children should be concentrated in the youngest age groups - as shown by Magnin (1962) [17] for other causes of childhood deaths .....

"To sum up: the presumed existence of long and variable latent intervals for childhood cancers is the chief reason for asking Public Health Departments to continue the survey until all deaths before 1968 have been recorded. If they agree, it should not only be possible to settle the dispute about prenatal radiography, but also to estimate

the "incubation periods" for the radiogenic leukaemias and cancers of childhood, and to discover whether there has been a trend towards safer obstetric radiography in recent years" (14).

The first attempt to demonstrate the latent periods of solid tumors, and to show that different types of leukaemia are not homogeneous in this respect, was made in 1970, by which time five of the high risk cohorts had been followed for 10 years (table 3) and a new method of analysing truncated contingency tables had been developed (18). Table 3 was compiled in 1969 when three-quarters of the children who died between 1953 and 1965 had been traced and matched with live controls (table 4) and there were six diagnostic groups which included more than 90 x-rayed cases (table 5). These particular cases were used to show that there had been a period of at least 17 years during which there had been erratic changes in the cancer hazard associated with obstetric radiography (table 6) (19) or changes which were clearly reflecting the uncertain attitudes of the obstetricians who ordered the examinations and the radiologists who performed them since we now know that technical improvements alone would have produced a steady decrease in the hazard between 1930 and the present date (2).

The same case group was included in an analysis of cancer latent periods which was originally based on 403 extra x-rayed cases affecting 6,847 of the children who died between 1953 and 1965 (20) but was repeated a year later using a different disease classification and omitting 19 children whose hydrocephalic state at birth probably influenced their radiation histories (21) (tables 7 and 8, also figs. 4-12). By this time there were 1,741 children with lymphatic leukaemias, including 263 who were x-rayed before birth, or 99 more than the expected number. But instead of the extra cases being evenly distributed between the different age groups, there were seven of them among the 368 children who were under 2 years when symptoms developed (2 percent); 76 among the 996 children between 2 and 6 years of age (8 percent); and 16 among the 377 older children (4 percent). There were also 551 children with myeloid leukaemia including 81 who had been x-rayed before birth, and in this group no less than 17 of the 28 extra cases were found among the 89 children who were over 8 years of age (20 percent).

Division of the haemopoietic neoplasms into five diseases caused very little disturbance of the mean onset ages of the obviously non-radiogenic cases (table 7), but division of the solid tumors into six groups revealed one disease with a mean onset age of 52 months, and two with means of 32 months (table 8). Among the solid tumors there were 1,261 children with neuroblastomas or nephroblastoma with 87 extra cases concentrated towards the beginning and end of the age range; also 254 children with tumors of bone and cartilage with 12 extra cases, only one of which was under 6 years of age.

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TABLE 3. *Oxford survey-140 sets of case/control pairs, classified by year of birth and age at death of the cases*

	Traced cases Birth dates classified by age at death in years											X-rayed in utero	
	0	1	2	3	4	5	6	7	8	9	Total	Cases	Controls
1943	–	–	–	–	–	–	–	–	–	17	17	2	1
1944	–	–	–	–	–	–	–	–	14	28	42	4	3
1945	–	–	–	–	–	–	–	13	32	21	66	7	4
1946	–	–	–	–	–	–	21	38	35	35	129	17	3
1947	–	–	–	–	–	25	53	49	43	30	200	24	6
1948	–	–	–	–	32	61	53	46	35	31	258	35	21
1949	–	–	–	39	61	55	52	44	29	40	320	49	25
1950	–	–	26	71	56	53	42	44	48	31	371	60	34
1951	–	27	71	75	70	44	40	43	43	43	456	80	40
1952	24	43	91	63	55	47	46	42	31	37	479	85	57
1953	49	64	69	64	75	49	53	32	35	39	529	75	67
1954	46	60	55	77	61	43	48	27	40	29	486	84	70
1955	31	52	58	78	56	57	46	32	33	28	471	102	53
1956	50	43	69	71	63	45	42	46	28	14	471	101	69
1957	41	52	62	58	46	64	34	31	15	–	393	68	41
1958	47	62	88	59	63	52	34	18	–	–	423	59	47
1959	45	61	68	74	57	53	24	–	–	–	382	31	29
1960	39	53	73	62	45	17	–	–	–	–	289	36	27
1961	41	55	51	45	28	–	–	–	–	–	220	24	19
1962	42	51	53	12	–	–	–	–	–	–	158	19	11
1963	54	46	20	–	–	–	–	–	–	–	120	14	10
1964	32	22	–	–	–	–	–	–	–	–	54	7	6
1965	13	–	–	–	–	–	–	–	–	–	13	2	2
Totals	554	691	854	848	768	655	588	505	461	423	6,347	985	645

TABLE 4. *Derivation of the 6,347 cases shown in table 3.*

Year of death	Cancer deaths (0-9 years) in England, Scotland, and Wales			
	Notified	Traced	Pending[a]	Lost[b]
1953	634	525	-	109
1954	602	501	-	101
1955	654	565	-	89
1956	665	515	-	150
1957	600	469	-	131
1958	674	524	-	150
1959	636	530	-	106
1960	660	546	-	114
1961	659	528	-	131
1962	632	489	26	117
1963	703	498	73	132
1964	655	397	136	122
1965	683	260	266	157
Total	8,457	6,347	501	1,741

[a]Cases traced after table 3 was compiled (see tables 7 and 8).

[b]That is, lacking interview data and a matched control but usually with a full complement of hospital records.

TABLE 5. *Diagnostic classification of 6,347 traced cases and 985 x-rayed cases*

Diagnostic group	Traced cases	X-rayed in utero	
		Number	Percent
Leukaemias	2,947	458	15.5
Lymphosarcomas	500	78	15.6
Cerebral tumors	1,030	154	15.0
Neuroblastomas	636	99	15.6
Wilms' tumors	572	93	16.3
Other cancers[a]	662	103	15.6
All cancers	6,347	985	15.5
Controls	6,347	645	10.2

[a]Including neoplasms of bone (122), reproductive organs (94), connective tissue (91), liver (78), retina (47), bladder (34), mouth and nasopharynx (33), and endocrine glands (11).

TABLE 6. *Estimates of the radiogenic component of the juvenile cancer load sustained by 17 cohorts, cancer risk associated with obstetric radiography, and the risk of being x-rayed during the years 1946-62.*

Birth cohorts	Radiogenic component of the juvenile cancer load[a]		Extra cancer risk if x-rayed in utero[b]		Risk of being[c] x-rayed in utero
	Number[d]	Standard error	Percent	Standard error	Percent
1946	34	10.5	322	241	2.3
1947	45	10.9	329	183	3.0
1948	21	12.4	55	42	8.1
1949	39	11.9	114	49	7.8
1950	39	11.8	94	38	9.2
1951	49	11.5	125	41	8.8
1952	33	11.6	62	27	11.8
1953	9	11.7	15	22	12.7
1954	16	12.4	24	21	14.4
1955	55	12.5	109	34	11.3
1956	41	13.2	62	24	14.6
1957	35	11.5	76	32	10.4
1958	17	12.5	34	27	11.1
1959	1	11.4	4	35	7.6
1960	24	13.9	58	39	9.3
1961	13	12.7	32	37	8.6
1962	19	13.7	62	57	7.0
Total	490	-	-	-	-

[a] See text.

[b] As percent of normal risk of dying from cancer before age 10 (about 1 in 1,200).

[c] Control data.

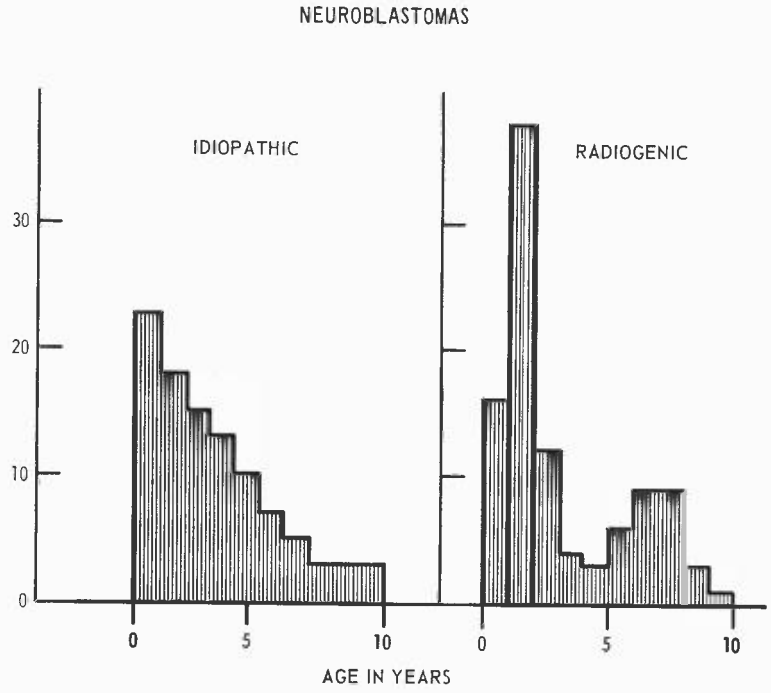
[d] The corresponding numbers of nonradiogenic cases would have been in the region of 470 per cohort (total 8,000). Had all cases been traced, the totals for radiogenic and nonradiogenic cancers would have been about 645 and 10,500 (that is, 6 percent and 94 percent) of the cancer deaths, respectively.

TABLE 7. *Onset age distributions of the haemopoietic neoplasms caused by obstetric radiography (radiogenic cases) and caused in other ways (nonradiogenic cases).*

Haemopoietic neoplasms		Lymphatic leukaemia	Myeloid leukaemia	Other and unspecified leukaemia	Lymphomas	All haemopoietic neoplasms
	Onset age in years	Percent	Percent	Percent	Percent	Percent
"Extra" x-rayed cases (Series A) (or radiogenic cases)	0-	7	-	8	7	5
	2-	39	-	35	38	38
	4-	38	14	32	12	29
	6-	13	26	21	10	19
	8-9	3	60	4	33	9
Nonradiogenic cases (Series B)	0-	22	26	25	29	25
	2-	34	24	33	22	29
	4-	22	20	22	19	21
	6-	14	17	13	17	14
	8-9	8	13	7	13	11
All cases (numbers).....		1,742	551	923	488	3,704
X-rayed cases (Series A).....		99	28	63	25	215
X-rayed cases (Series B).....		164	53	86	46	349
Non-x-rayed cases		1,479	470	774	417	3,139
Mean onset age in months						
Series A		43	79	46	55	49
Series B		41	43	39	43	41
Difference A : B		+2	+36	+7	+12	+8

TABLE 8. *Onset age distributions of the solid tumors caused by obstetric radiography (radiogenic cases) and caused in other ways (nonradiogenic cases).*

Solid tumors		Cerebral tumors	Neuroblastomas	Nephroblastomas	Bone and cartilage	Residue	All solid tumors
	Onset age in years	Percent	Percent	Percent	Percent	Percent	Percent
"Extra" x-rayed cases (Series A) (or radiogenic cases)	0-	12	54	29	-	40	34
	2-	5	16	40	-	15	13
	4-	15	9	9	3	18	14
	6-	45	17	11	89	22	28
	8-9	23	4	11	8	5	11
Nonradiogenic cases (Series B)	0-	29	41	35	19	48	35
	2-	23	28	35	19	24	26
	4-	19	17	20	17	12	17
	6-	18	9	7	24	9	13
	8-9	11	5	3	21	7	9
All cases (numbers)...		1,022	668	593	254	587	3,124
X-rayed cases (Series A)..		65	42	41	12	40	209
X-rayed cases (Series B)..		82	63	55	21	60	281
Non-x-rayed cases.....		875	563	497	221	487	2,643
Mean onset age in months							
Series A		62	30	37	71	37	44
Series B		43	32	32	52	31	37
Difference A : B		+21	+2	+5	+19	+6	+7



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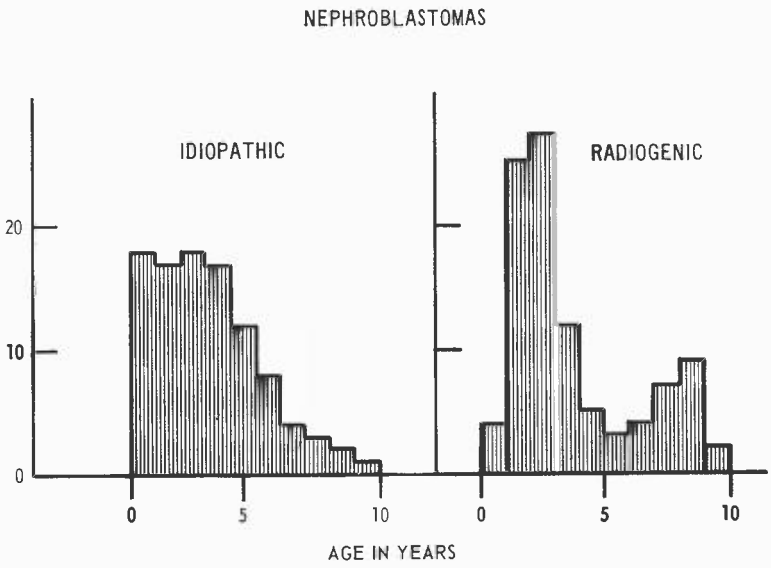

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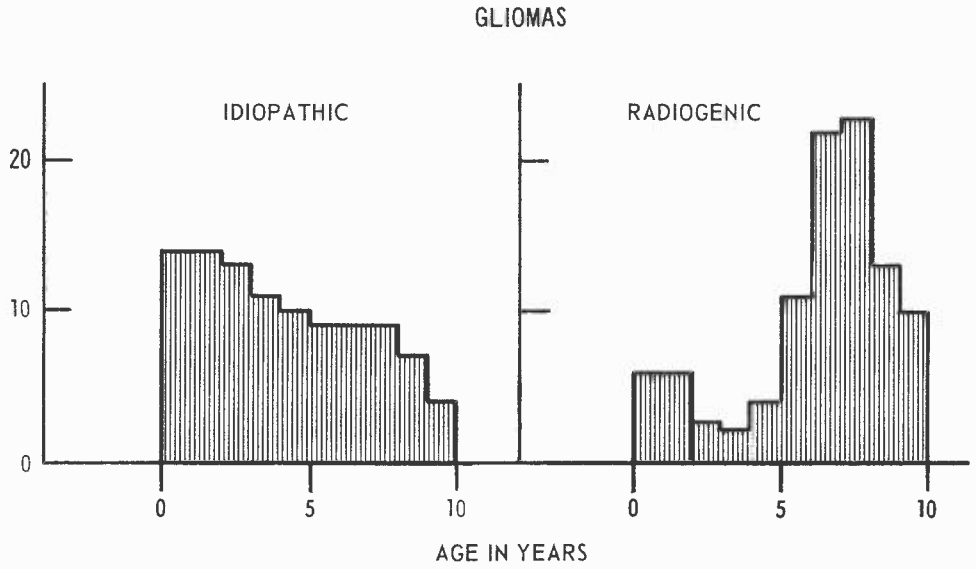

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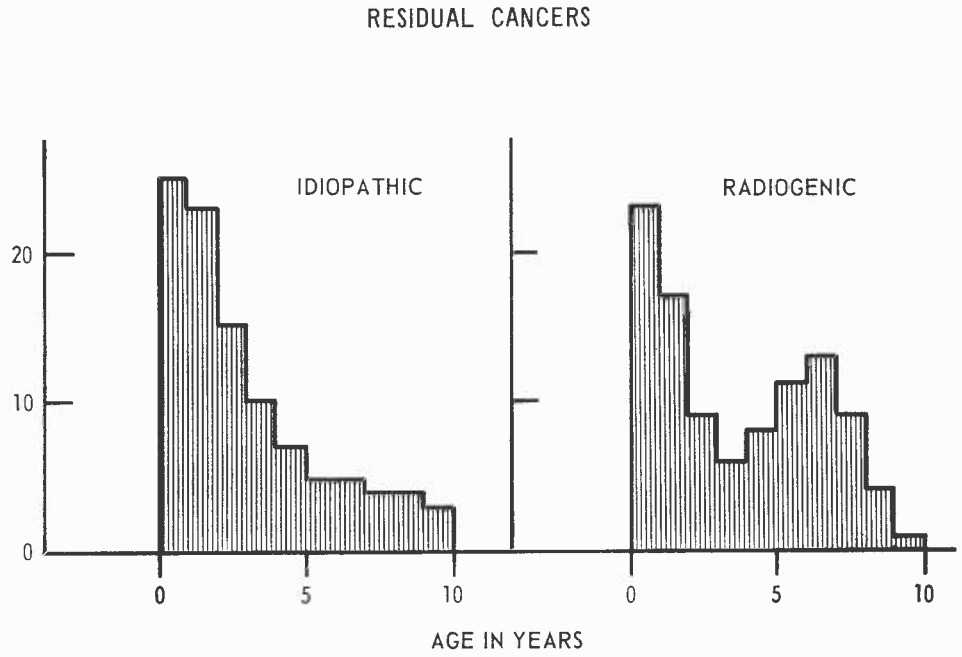

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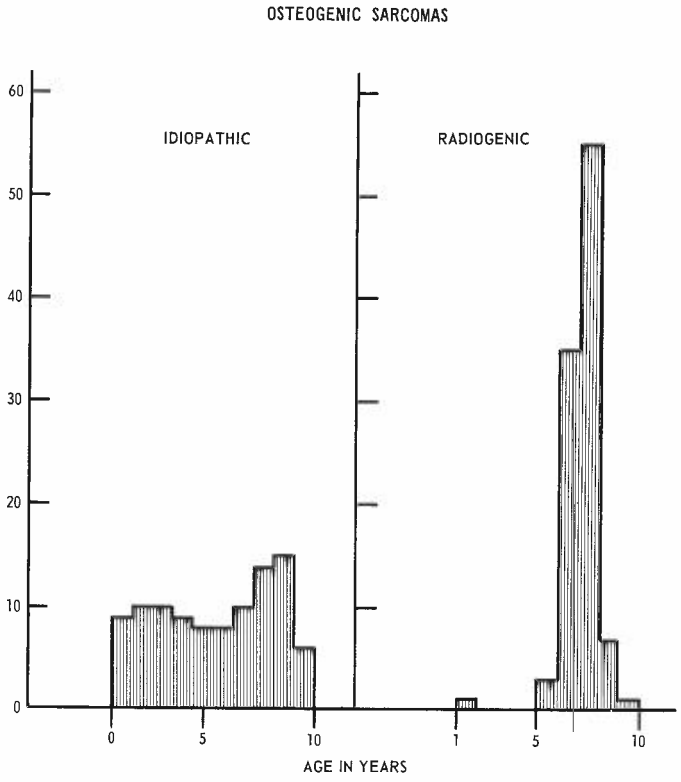

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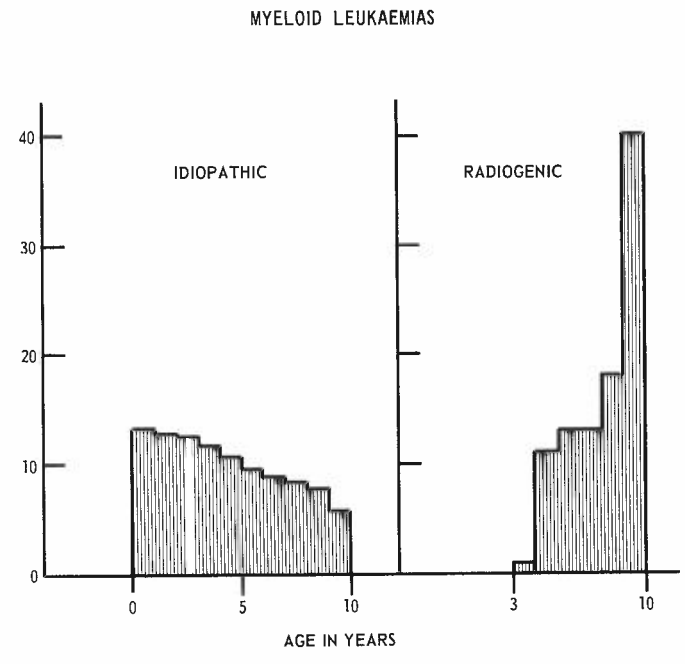

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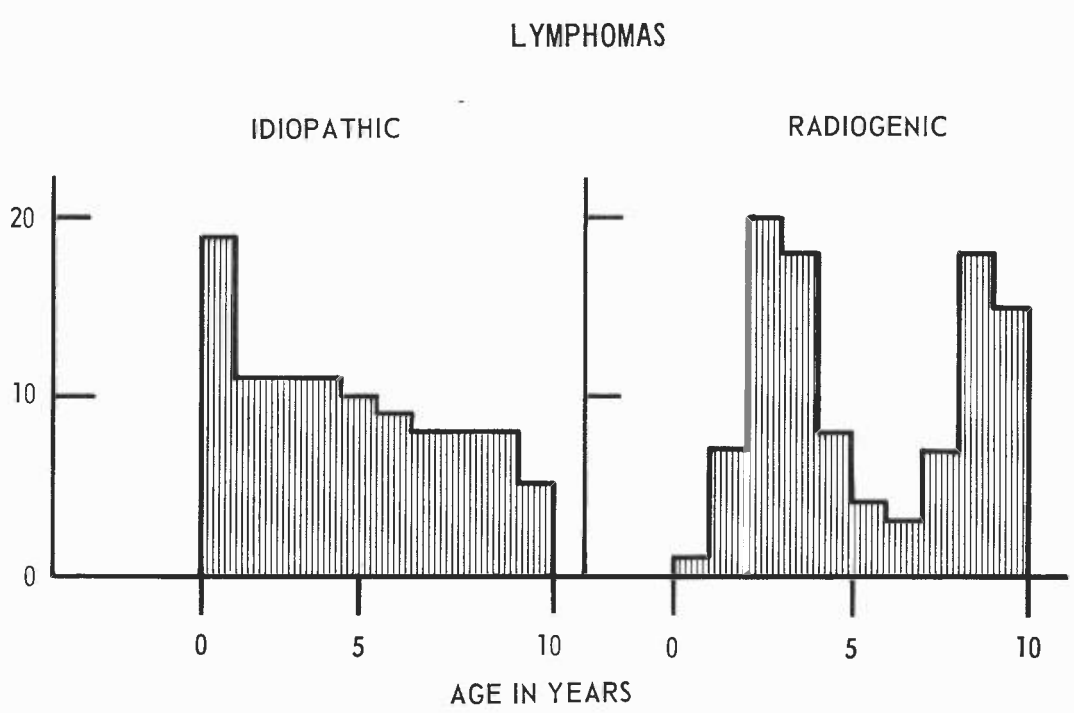

Figure 10.

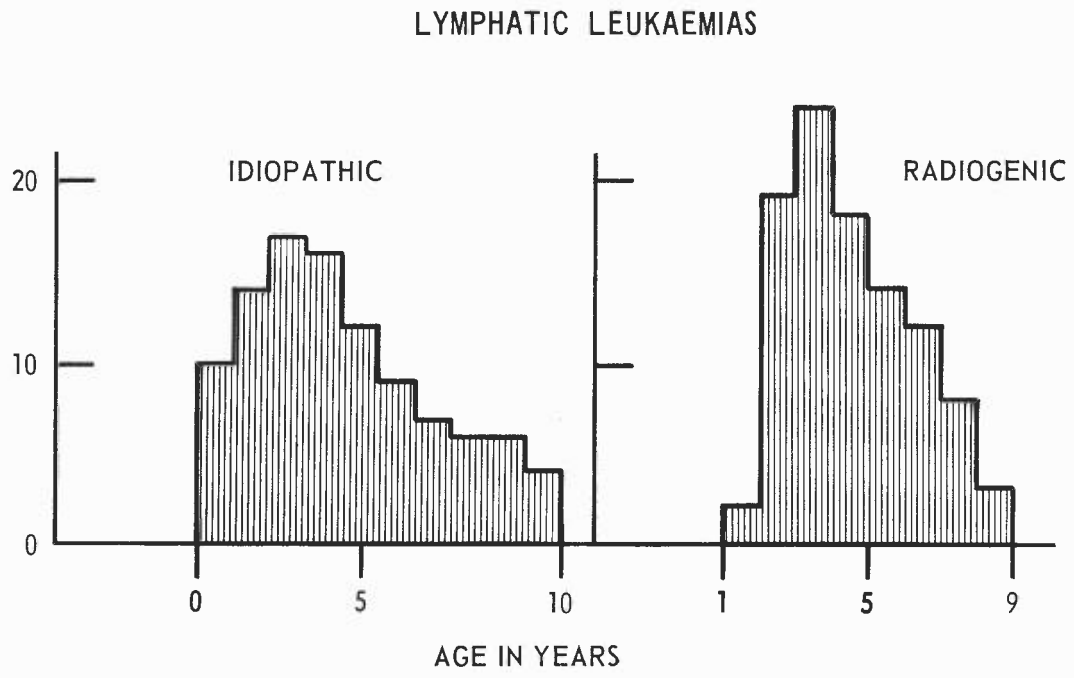

Figure 11.

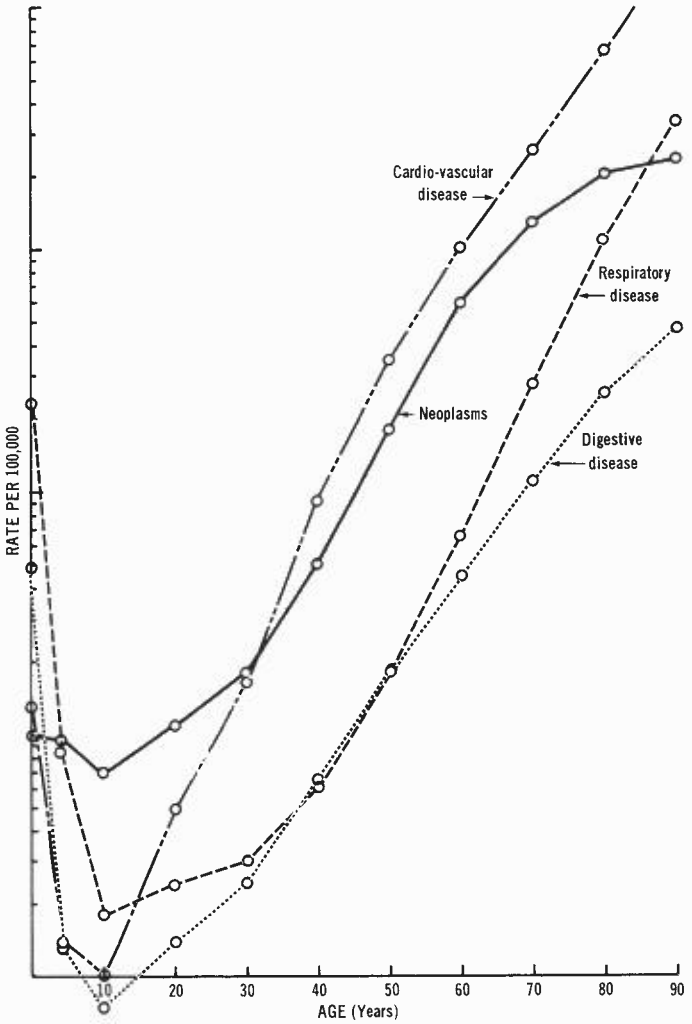

Figure 12. Age specific mortality from various cancers.

Since we know that three-quarters of the extra cases were initiated shortly before birth, both the big difference in age of the normal and extra myeloid leukaemias and the biphasic appearance of the histograms depicting extra neuroblastomas and nephroblastomas (see figs. 4 and 5) suggest that cancers with short latent periods have a much shorter time in which to produce immature forms of "embryomas" than cancers with long latent periods. In other words, there could be an association between the rate of change from embryonic to mature forms of different tissues, and the rate of change from embryonic to mature forms of cancers which has never been recognized because it is only in rare instances that the embryomas resemble their mature

equivalents. If this is a correct interpretation of the Oxford data we would have a relatively simple explanation for the persistent shortage of myeloid leukaemias in young children.

It is appropriate to speak of a "persistent" shortage of myeloid leukaemias in young children because the proportion of myeloid cases is much higher in countries where there was a flat rate of mortality between 0 and 5 years of age and very few recognized cases (for example, Nigeria) than in countries where there is a sharply peaked rate and many recognized cases (for example Britain, see fig. 1). In Britain and other technologically advanced countries the stillbirth rate has not decreased anything as much as the infant mortality rate, and deaths within a month of birth have not decreased as much as later deaths. So provided embryonic forms of myeloid leukaemia exist and develop faster than lymphatic embryomas, we could assume that many fetuses with myeloid leukaemia die during labour, leaving a high proportion of lymphatic embryomas to die during the next 5 years, either from infections or leukaemia. If, moreover, the transition from embryonic to adult forms of leukaemia is settled before birth for myeloid cases and after birth for lymphatic cases, we could expect the myeloid leukaemias caused by obstetric radiography to have longer latent periods than the lymphatic leukaemias.

If the latent periods of childhood cancers depend to some extent on the developmental status of the tissues when the process starts, this would explain why a division into onsets before and after 5 years of age disturbed the uniform arrangement of the x-rayed cases shown in table 5 (see table 9). I have mentioned this because the "unlikely"

TABLE 9. *Proportions of x-rayed cases by cell types and onset ages.*

Diseases	Age at the onset of symptoms in years			
	Under 5	Percent x-rayed	Over 5	Percent x-rayed
Lymphatic leukaemia	1,198	14.9	544	15.6
Myeloid leukaemia	381	12.6	247	17.8
Other leukaemia	596	15.3	250	18.8
Lymphomas	290	14.1	198	15.2
Cerebral tumors	663	13.9	380	17.1
Neuroblastomas	527	15.0	141	18.4
Nephroblastomas	491	15.7	102	18.1
Osteogenic sarcomas	47	10.6	91	16.5
Other solid	561	15.0	140	19.3
Total	4,754	14.6	2,093	17.1

symmetry of table 5 has been quoted by Dr. Miller as a reason for not regarding the Oxford Survey as a reliable source of information about the carcinogenic effects of low-level radiation. If, however, childhood cancers are really fetal cancers, we should not expect the cases caused by obstetric radiography to bear the same relationship to other (fetal) cancers as the cases caused by the A-bomb to other (adult) cancers.

RADIOSENSITIVITY AND CANCER SENSITIVITY

We need only consult official statistics of mortality to discover that the risk of a child dying from leukaemia is three times as great as the risk of dying from a cerebral tumor and five times as great as the risk of dying from a kidney tumor; and need only consult the Oxford Survey to discover that the obstetric radiography hazard is greater for leukaemia than for cerebral tumors or kidney tumors. There is, in fact, such close correspondence between the radiosensitivity of fetal tissues (as judged by the Oxford Survey) and their natural cancer sensitivity, and such lack of correspondence between the radiosensitivity of adult tissues (as judged by the ICRP) and their natural cancer sensitivity (table 10) that we are forced to the conclusion that there are very few causes of childhood cancers (and very many causes of adult cancers) which do not fall into the category of random

TABLE 10. *Cancer and radiosensitivity ratings for adults and children.*

Cancer sites	Cancer ratings[a]		Radiosensitivity ratings	
	Adults	Children	Adults (ICRP)	Children (Oxford Survey)
Digestive	1	6	5	6
Respiratory	2	8	4	8
Genito-urinary	3	3	7	3
Breast	4	9	6	9
Skin	5	7	9	7
Lymphoma	6	4	3	4
Leukaemia	7	1	1	1
Neurological	8	2	10	2
Skeletal	9	5	8	5
Thyroid	10	10	2	10

[a]Cancer Notifications England and Wales (1962-65). Registrar General's Statistical Review; Supplement on Cancers.

mutations, or the nuclear accidents which are an inevitable consequence of whole-body exposure to radiation and a possible cause of a mutant cell species.

For mutant cells to produce a tumor they must have a high growth potential and be in a position to express this characteristic, which implies survival of the cell species as well as survival of the host. So when theorizing about the causes of cancers, two possibilities must be considered; either tumor formation demands an initiator followed by a promotor, in which case the longer the interval between the two events the greater the chance of grafting malignant properties on to a "premalignant" tissue (Multi-hit theory), or the process demands an initiator followed by an inhibitor, in which case there might be only a brief period before it became difficult for even a powerful inhibitor to destroy all the mutant cells (Single-hit theory).

The first theory is clearly impossible to reconcile with constant intervals between the initiating event and the tumor detection (see tables 7 and 8) and we have been told that no single-hit theory can account for the steep age-dependence of cancer mortality (22) (fig. 12). If, however, tumor formation is a pathological process which is easily nipped in the bud by a healthy tissue, and is only a recognizable process after it has become irreversible, there would be no substance in the second objection.

The fact that malignant cells can be present in increasing numbers without causing symptoms is only mildly surprising when one considers the natural history of tuberculosis and syphilis: how often the primary and secondary stages of these diseases are missed; how long are the intervals between the primary and tertiary stages; and how ubiquitous are the pathogens by the time they declare themselves. And the age dependence of cancer mortality should occasion no surprise, since it is only an expression of a natural law illustrated in fig. 12 and made memorable by Shakespeare:

"Nativity, once in the main of light,
Crawls to maturity, wherewith being crowned,
Crooked eclipses 'gainst his glory fight,
And Time that gave doth now his gift confound.
Time doth transfix the flourish set on youth,
And delves the parallels in beauty's brow;
Feeds on the rarities of nature's truth,
And nothing stands but for his scythe to mow."

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CHAPTER 5

THE OXFORD SURVEY (CONTINUED)

I have left discussion of risk estimates and dose-response curves to the last of my five lectures, not because I consider them to be unimportant, but because I wanted you to realise that what is often regarded by physicists and biologists as the only epidemiological proof that low-level radiation causes human cancers - namely, a dose-related number of "extra" cases - is regarded by me and my statistical colleagues as no more than an important link in a relatively long chain of evidence. I also wanted to make you aware of the facts which suggest that the latent periods of cancers are just as distinctive (and as variable) as the incubation periods of infective diseases, and thus to alert you to the following possibilities.

If a disease is the result of a continuous process which takes much longer from inception to diagnosis than from diagnosis to death, the so-called presenting signs and symptoms should be regarded as an accumulation of latent period effects which may or may not have been disturbing the general health of the patient before the diagnosis is established. In such circumstances a patient may live long enough for his doctor to recognize, in retrospect, that the first symptom was not the one originally recorded but an unexpected complication of a minor injury or illness several months before the diagnosis was made. But the chance of spotting such an event would depend partly upon the final diagnosis; partly upon the patient's age and usual state of health; and partly upon the risks to which he was exposed during all or part of the latent period.

For instance, a cancer presented as a superficial lump (for example, a breast tumor) would not only be recognized more easily than one which had no tendency towards tumor formation (for example, leukaemia), it would also be recognized more often, because the risk of dying during the latent period is smaller for a localized growth than a diffuse one. Likewise leukaemia in a young man would be recognized more easily and more often than leukaemia in a child or an old age pensioner because the latter are more infection-sensitive than the former. And since the scar tissue caused by a chronic infection, such as malaria, could easily affect the course of a neoplastic process which normally "rides free" in the haemopoietic tissues, leukaemia in African children who have become resistant to malaria before they have learned to walk could easily take a different form

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from the disease as it is found in European children (1). What is more, if cancers are the result of continuous processes which are not easy to recognize until they have become irreversible (that is, the cells concerned have achieved "tumor dominance" before producing symptoms), they will be recorded more often in populations with high standards of hygiene, nutrition, and medical care than in communities where the risk of dying as a young adult is high, and where sudden death of a child or an old person is such a common event that no one expects to identify a specific cause in more than a small proportion of cases (2).

Finally, I must confess that before discussing an aspect of radiation research which has been studied more intensively by biologists than by epidemiologists--namely, the shape of dose-response curves in marginally different situations--I not only wanted you to appreciate the true worth of our interview data, I also wanted you to be queuing up for membership of my "Autolycus Society." You will recollect that Autolycus made it his business to distribute broadsheets at fairs and country markets, and was described by Shakespeare as a "snapper-up of unconsidered trifles," so he should be the patron saint of the brand of epidemiology practised in Oxford in relation to low-level radiation.

To be serious, I wanted you to see for yourselves that there is nothing to be gained by labeling epidemiological surveys as "good" when they take events in the order of happening, and as "bad" when they reverse the order (or vice versa) and to recognize that every population problem which lends itself to a survey should be treated like a patient (that is, given the individual care and attention which may necessitate breaking rules from time to time). I also wanted you to agree with me that radiation epidemiology is best served by making orderly collections of facts even when there is only a small chance of their being relevant to a specific problem such as the carcinogenic effects of small doses.

RISK ESTIMATES

The 1958 report of the Oxford Survey (3) included the following estimates of risk based on cancer deaths (0-9 years) during the period 1953-55 - prefaced by the statement that they "necessarily represent a rough appraisal of the situation." In a group of 619 leukaemias and 680 other cancers, 13.7 percent of the children were x-rayed before birth and 86.3 percent were not; and in a control group there were 7.2 percent of children who were x-rayed in utero and 92.8 percent who were not. On this showing, the x-rayed children were 2.04 times or twice as likely to die from a malignant disease within

10 years of birth as their controls. As, however, the survey covered England and Wales and only 1 in 1,200 children in Britain died in this way during the period 1953-55, less than one in a thousand of the obstetric x-ray examinations performed between 1943 and 1955 had had fatal consequences. Alternatively, (13.7 - 7.2) x 1299, or between 80 and 90 of the survey cases might be ascribable to the x-ray examinations.

These provisional estimates were based on the assumption that the mothers who laid false claim to an x-ray examination were equally common in the case and control groups (in fact the exclusion of obviously faulty records had increased the case/control ratio for x-rayed children from 1.86 to 1.91), but they made no allowance for the possibility that the mothers of live children had been more forgetful than the mothers of dead children (because there had been no checking of "disclaimers"), or for the possibility that the age-biassed representation of the exposure years (1943 to 1955) was affecting the results. Note that the children who were born in 1943 were all 9 years old, and that the children who were born in 1955 were all under 1 year of age, and that we as yet knew very little about intervals between exposure and onset. We had, however, discovered that exceptionally early and exceptionally heavy exposures were especially common among the children with cancers, and we could be certain that this finding was not due to biassed reporting of the examinations, because the relevant facts had been obtained not from the mothers but from the hospitals where the x rays were taken.

The cohort phase of the Oxford Survey took up the story in 1958, and by 1965 we were in a position to make the following assessments of the interview data (*4*):-

"The limited amount of checking which was done during the first part of the survey had not ruled out the possibility of there being a relatively large number of unclaimed exposures in the control group, and some allowance for this (based on the claims for chest x rays during the relevant pregnancy) was made when assessing the apparent risk of fetal irradiation. Critics of retrospective surveys in general, and the Oxford Survey in particular, were quick to notice this flaw in the evidence and promptly made a counter-suggestion, namely, that the observed difference between cases and controls was due to memory bias on the part of the mothers. They insisted that when women are questioned about a pregnancy which took place several years ago they are more likely to forget events during this period if the child is still alive and well than if he or she has since died. If this had been true, one might have expected, for example, similar differences in the claims for chest x rays, toxaemia, and anaemia. Since this was not the case, opponents of the view that fetal irradiation was potentially dangerous had to argue either that the alleged memory

bias applied selectively to abdominal x rays or that the other three events had actually protected children against cancers!

"There now exists independent evidence for the view that obstetric radiology as practised some years ago perceptibly increased the prevalence of childhood cancers. It is, however, still of interest to know whether memory bias has affected the records compiled during the second part of the survey. During this phase two sources of contemporary records of fetal irradiation were explored, namely, antenatal clinics and x-ray departments, and neither was found to be perfect. Besides 57 claims which could not be checked because no records had survived, there were 57 which were not confirmed by antenatal records but confirmed by radiologists' records, and a further 18 in which this position was reversed. Nevertheless, when studying the reporting performance of mothers and interviewers, it was convenient to proceed as if the antenatal records which were still available at the time of followup provided complete and infallible records of the four events which had been systematically screened; namely abdominal x rays, chest x rays, toxaemia, and anaemia. We have, therfore, regarded entries in the survey questionnaires as "correct" if they conformed with these contemporary records and as "incorrect" if they differed; and we have temporarily discarded all questionnaires which could not be paired with antenatal records (table 1).

"By adopting these conventions it was possible to make two assessments of the mothers' statements. Since these were designed to detect lack of sensitivity (that is, an event was "forgotten") and lack of specificity (that is, a "false" positive statement had been made), we have, following Fletcher and Oldham (1964) [5], called them sensitivity and specificity assessments. The measure of sensitivity was the proportion of pregnancies with positive records "correctly" reported by mothers, and the measure of specificity the proportion of pregnancies with negative records "correctly" reported by mothers. As a summary measure of these two aspects of reporting performance we have taken the arithmetic mean of the sensitivity and specificity indices and called it the discrimination index. If pregnancies with positive and negative records had been equally common, the discrimination index would have corresponded to the proportion of histories "correctly" reported by the mothers. The actual proportion of histories correctly classified was generally much higher than this.

"Finally, we have also considered whether the survey data showed more complete reporting by case than control mothers, or vice versa, since this is the aspect of reporting performance which is most relevant to the danger of drawing mistaken inferences from retrospective surveys. This danger is especially obvious when, as in the present survey, data are supplied by lay informants representing two contrasting

TABLE 1. *Mothers' retrospective claims to four antenatal events classified according to contemporary records*

(1956-60 cases and controls)

Survey interviews (mothers' statements)	Contemporary records (antenatal clinics)	Cases				Controls			
		Events during pregnancy of survey child[a]							
		(1)	(2)	(3)	(4)	(1)	(2)	(3)	(4)
Claimed	Confirmed	205	191	128	42	138	155	93	26
	Denied	76	95	35	75	45	101	48	86
	No record	136	121	64	66	69	96	54	65
	Total	417	407	227	183	252	352	195	177
Disclaimed	Confirmed	1,092	1,028	1,156	1,190	1,179	1,051	1,159	1,183
	Denied	7	66	64	49	12	67	77	60
	No record	889	904	958	983	962	935	974	985
	Total	1,988	1,998	2,178	2,222	2,153	2,053	2,210	2,228
Totals	-		2,405				2,405		

[a]Events: 1. Abdominal x rays.
2. Chest x rays.
3. Toxaemia (either stated toxaemia or highest recorded diastolic blood pressure over 90).
4. Anaemia (either stated anaemia on surviving record or haemoglobin below 65 percent).

groups. Hence the prevailing prejudice against this type of survey and the general reluctance to accept the idea that prenatal irradiation is potentially dangerous. To assist judgement in this matter we have taken as a measure of reporting bias the ratio of positive survey reports (whether or not "correct") to positive records (whether or not reported by mothers). Four such ratios for cases and four for controls have been calculated, also four quotients of paired ratios, since these should give some indication of the effect of differing bias in case and control reports on relative risk estimates (table 2).

"According to the discrimination indices, the event most accurately reported both by cases and controls was abdominal irradiation; and the least accurately reported was anaemia. Chest x rays were better reported than toxaemia, and for all four items a slightly better level of discrimination was obtained for case than control reports. It should not be surprising that reports which depend solely on recollection of a specific event (for example, an x-ray examination) whould be more reliable than those involving medical judgements which may never have been communicated to the patient (for example, toxaemia or anaemia). By the same reasoning, reporting of toxaemia should be more reliable than reporting of anaemia; for if a mother shows unmistakable signs of toxaemia she is told that it is important for her to rest and she is often admitted to a hospital for this purpose. If, on the other hand, she is given iron pills she may not know whether this is because she is suffering from anaemia or because her doctor favours iron medication for all pregnant women."

Comparisons with other standards of reporting performance were difficult because so few relevant facts had been published. We were, however, able to show that the level of agreement between the interview data and the hospital data was comparable to the level of agreement achieved by two clinicians during a survey of byssinosis in cotton operatives (6). On this occasion, observers A and B independently examined 275 men for six of the most characteristic signs of byssinosis and then made a diagnosis. By taking first A and then B as the "infallible standard," the following levels of discrimination were derived from the published data:

Signs	Discrimination factor
Absent apical impulse	.711
Kyphosis	.706
Clubbing of fingers	.676
Abnormal chest sounds	.628
Movement en bloc of the chest	.606
Hoover's sign	.578
Final diagnosis	.928

Since Schilling and his colleagues (6) considered that these standards compared favourably with the performance of chest physicians doing a comparable test, we can regard it as a matter for congratulation that our survey doctors obtained such reliable answers from the mothers they interviewed.

SHAPE OF THE DOSE-RESPONSE CURVE

By 1970 the number of survey children with records of antenatal events exceeded 15,000, and included 7,649 children who died from malignant diseases during the period 1953-1965 and an equal number of healthy controls (7).[1] In this group there were 1,141 x-rayed cases, including 703 with records of how many films were actually or probably taken, and 774 x-rayed controls, including 484 with records of film numbers (table 3). In the table the children are arranged in birth cohorts and the x-ray examinations are classified by film numbers; and in the corresponding figure the film numbers have been plotted against the extra cancer risk for the x-rayed children relative to the normal risk for non-x-rayed children (fig. 1). The plot was described as a crude dose-response curve because we had reason to believe that the birth dates had affected both the quantity of radiation received by a fetus when exposed to a single film and the number of films needed to complete a single x-ray examination (see fig. 1, Chap. 4).

The crude dose-response curve suggested a linear relationship between the cancer risk and the radiation dose which was confirmed when the following model was fitted by "iterative modified minimum chi-square estimation":

$$e_{fi} = e_{1i} f^{P}$$

e_{fi} = E.C.R. for f films in year i

e_{fi} = E.C.R. for one film in year i

P = index of variation with f

According to this model, if there were no dose-response effect, P would equal 0, and we could draw the conclusion that the observed

[1] 6,484 of the children with cancers were included in the latency studies (see Chap. 4) and 801 were between 10 and 15 years of age when they died.

TABLE 2. *Analysis of the checked statements in table 1.*

Pregnancy events	Sensitivity[a]	Specificity[a]	Discrimination[a]	Claims[a] / Records	Quotient[a]
1. Abdominal x rays..Cases	.967	.935	.951	$\frac{281}{212} = 1.325$	1.086
..Controls	.920	.963	.942	$\frac{183}{150} = 1.220$	
2. Chest x rays.....Cases	.743	.915	.829	$\frac{286}{257} = 1.113$	0.965
.....Controls	.698	.912	.805	$\frac{256}{222} = 1.153$	
3. Toxaemia.....Cases	.667	.971	.819	$\frac{163}{192} = 0.849$	1.024
.....Controls	.547	.960	.754	$\frac{141}{170} = 0.829$	
4. Anaemia.....Cases	.456	.941	.699	$\frac{117}{91} = 1.286$	0.987
.....Controls	.302	.940	.621	$\frac{112}{86} = 1.302$	

[a]See text.

TABLE 3. *Obstetric x-ray records by date of birth and numbers of films*

Group	Year of birth	X-rayed in utero		Number of films						Totals
		Yes	No	1	2	3	4	>5	No record	
Cases	1943-49	212	1,610	29	34	19	8	14	108	1,822
	1950-54	437	2,298	92	80	45	30	33	157	2,735
	1955-59	381	1,772	109	71	35	19	15	132	2,153
	1960-65	111	828	44	16	4	3	3	41	939
	Total	1,141	6,508	274	201	103	60	65	438	7,649
Controls	1943-49	110	1,712	19	11	5	3	1	71	1,822
	1950-54	316	2,419	73	74	30	15	17	107	2,735
	1955-59	248	1,905	79	52	18	9	10	80	2,153
	1960-65	100	839	47	14	5	1	1	32	939
	Total	744	6,875	218	151	58	28	29	290	7,649
Cases/control ratios		*1.48*	*0.95*	*1.26*	*1.33*	*1.78*	*2.14*	*2.24*	*1.51*	*1.00*

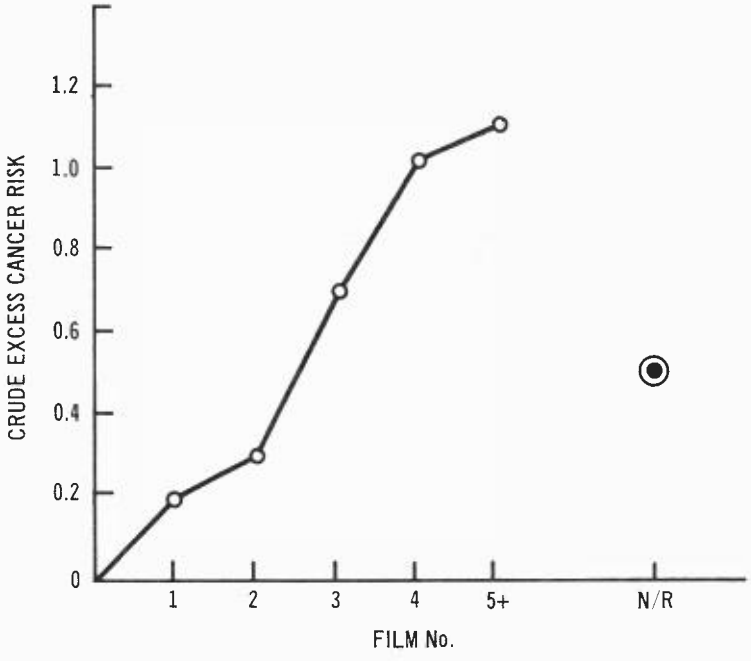

Figure 1. Crude dose-response curve. Crude excess cancer risk as proportion of the normal risk (N.C.R.) N/R = no record.

association was merely the result of the in utero state of the cancer-prone children "attracting" extra x-ray examinations (hidden association theory). If there were a linear dose-response effect, P would equal 1 and we could assume that the number of extra cancers was directly proportional to the radiation dose (one-hit theory), and if there were a quadratic response (that is, P was equal to 2), we could assume that it was only above a given dose level that the radiation was having any carcinogenic effects (threshold dose theory).

Since the fitted value of P was 0.915 with a standard error of 0.329 (and the overall fit of the model was given by a chi-square value of 13.86 at 23 degrees of freedom), we not only decided that a linear dose-response relationship provided an adequate description of the actual observations, but also concluded that the extra cancers were a direct consequence of radiation-induced mutations.

In table 4 and fig. 2 other parameters, such as the extra cancer risk value for the single film, were combined with the normal cancer risk estimates, and with independent estimates of mean fetal doses for

TABLE 4. *Calculation of cancer risk incurred by children who are exposed to 1 rad of ionising radiations shortly before birth*

Period	Live births (Great Britain)	N.C.R. estimates		E.C.R. estimates			Mean fetal dose per single film[a] millirads
		No. of cancer deaths (0-9 yr)	Rate per million live births	Risk per single film (e_{11})	S.E.	Extra cancer deaths (0-9 yr.) per million children exposed to 1 film	
1943-49	6,014,408	3,688	613.2	0.581	0.208	365.3	460
1950-54	3,863,300	3,024	782.8	0.226	0.095	176.9	400
1955-59	4,065,304	3,163	778.0	0.357	0.129	277.7	250
1960-65	5,642,275	3,532	626.0	0.098	0.110	61.3	200

Absolute radiation risk expressed as numbers of extra cancer deaths (0-9 yr.) per rad per million children at risk* = 572 (S.E. 133).

N.C.R. = Normal cancer risk. 1943-59 estimates based on actual deaths during the period 1943-68; 1960-65 estimates based on expected deaths during the period 1960-74.

E.C.R. = Extra cancer risk for children x-rayed before birth (see text).

[a]From the regression of E.C.R. rates on mean fetal doses.

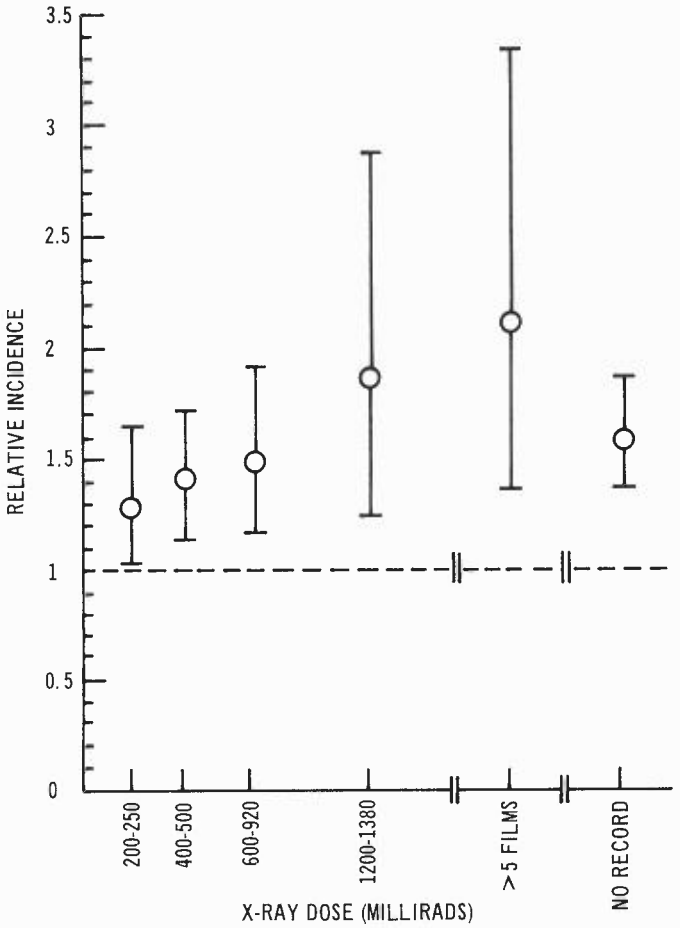

Figure 2. Frequency of childhood cancers following prenatal exposure to stated doses of radiation relating to the frequency among nonexposed children (Oxford Survey) (see ref. 7).

single films taken during stated periods, to produce a measure of the risk incurred by mature fetuses when wholly exposed to 1 rad of radiation (*8*). According to this measure of the delayed effects of whole-body exposure, if 1 million children were exposed to 1 rad shortly before birth (in the conditions which prevailed in Britain between 1945 and 1965) we could expect the next 10 years to reveal between 300 and 800 extra radiation cancers.

FETAL AGE EFFECTS

In the case and control groups examined in 1970 over two-thirds of the x-ray examinations were precisely dated (table 5). So we were able to see that the case/control ratio for a small number of first trimester exposures (8.25) was much higher than the corresponding ratios for the much larger number of exposures during the second and third trimesters (1.49 and 1.43, respectively). The exceptionally high ratio for the exceptionally early exposures can be regarded as a sign that immature fetuses are more sensitive to the carcinogenic effects of radiation than mature fetuses, but it does not provide an accurate measure of the effect of fetal age on cancer sensitivity for two reasons. In the first place, the exceptionally early exposures included a relatively high proportion of multiple exposures. Secondly, the probability of surviving until the end of a cancer latent period is much smaller for an immature fetus than a mature one.

TABLE 5. *Case/control ratios for children x-rayed during stated periods between conception and birth*

Date of x-ray examinations	Cases	Controls	Case/control ratios
1st trimester	33	4	8.25
2d trimester	67	45	1.49
3d trimester	698	489	1.43
No record	343	236	1.45
All examinations	1,141	744	1.48

THE EFFECT OF AGE AND OTHER FACTORS ON THE INCIDENCE OF UNRECOGNIZED CANCERS

As early as 1958 the Oxford Survey was leaving the impression that there might be a period of 2 years before the onset of leukaemia when the children concerned were more likely to develop complications of minor infections than normal children or children who were incubating solid tumors (3,9). The evidence took the form of an exceptionally high incidence of pneumonia following measles and whooping cough in children who developed leukaemia within 20 months of recovering from the pneumonia (and being treated with antibiotics). There were also

signs that until first-born children went to school (but not afterwards) they were more likely to have their deaths ascribed to leukaemia than children who were more at risk of developing infectious diseases because they had older brothers and sisters of school age. It was not, however, until the latency studies had confirmed the in utero origins of childhood cancers that we began to make an intensive study of the secular trends of mortality for leukaemia and other diseases (10-12). These studies were based on official statistics and showed that the poor resistance to infections (which is such a striking feature of overt leukaemias) is also a feature of latent leukaemias. In fact, children who are incubating leukaemia are far more likely to have their deaths ascribed to pneumonia than normal children (300 to 400 times the normal risk!). Also children who had their deaths ascribed to pneumonia when they were really suffering from leukaemia were over 6 times as common 50 years ago as they are today, and the extra deaths which have been recorded since 1920 are probably lymphatic leukaemias not myeloid leukaemias (see fig. 1, Chap. 4).

If one is studying a group of children whose deaths were ascribed to malignant diseases, one is bound to miss all the children who were suffering from these diseases but had their deaths ascribed to other causes. If, however, the group includes all the cancers incurred by a given fraction of a population with a complete set of vital statistics, one can use the expected frequency of, say, twins to discover whether an exceptionally high risk of dying at or shortly after birth has affected the cancer death rate, and the expected proportions of boys and girls (sex ratio) to discover whether events associated with an exceptionally high risk of dying in utero had affected cancer mortality.

In practice, twins are 6 or 7 times as likely to be exposed to obstetric radiography as other children, (13) and both sib-concordant and twin-concordant cancers (or the same disease in two or more members of a sibship or both members of a twin set) are much commoner than they would be if there were no such thing as a "familial" or inherited cancer (14-16). We should, therefore, expect cancers to be appreciably commoner in twins than in singletons (because of the x-ray hazard) and commoner in monozygotic twins than in dizygotic twins (because of the familial hazard). When, however, the twins in the Oxford Survey were classified by their radiation histories and zygosity status, we discovered a marked deficit of non-x-rayed monozygotic twins (17, 18). We also discovered: (1) that among the children who developed cancers within 15 months of conception there were a few who had nearly died in utero (that is, the mother reported a threatened abortion) and that nine-tenths of these rare cases were girls; (2) that in families with two or more sib-concordant cancers there were twice as many healthy girls as healthy boys; and (3) that among the published cases of twin concordant cancers there were 3 times as many FF pairs as MM pairs.

On the strength of these observations we have not only decided that there is a shortage of myeloid embryomas (which is best explained by postulating exceptionally high stillbirth and neonatal mortality risks for these cases), we also feel that there is a shortage of all forms of cancer in the youngest age group (under 1 year) which is best explained by postulating (1) a high incidence of nonconceptions in the matings of adults carrying "cancer" genes and (2) a high incidence of in utero deaths following paraconception cancer initiations.

THEORETICAL CONSIDERATIONS

Having brought you up to date with several aspects of the Oxford Survey, you are now in a position to take sides in the controversy which has raged for years over the question of whether or not low-level radiation carries a cancer hazard. Two surveyors of the scene have come down strongly on the side of there being no direct association between childhood cancers and prenatal irradiation, not because they are impressed by the surveys with negative findings (see Chap. 3) but because they are quite certain that obstetric radiography is not performed at random. With this conclusion I agree (*19, 20*). I am not, however, impressed by the theories of Sterling and Burch which postulate a hidden association between the need for an obstetric x-ray examination and a high incidence of childhood cancers, although I am prepared to admit that a cerebral tumor which has caused a fetal hydrocephalus would increase the probability of an obstetric x-ray examination.

Since we know that attendance at an antenatal clinic does not carry the same implications as other hospital attendances (that is, it means that the patients are health-minded, not ill), it was a mistake on the part of Sterling to equate children who were given radiotherapy for an enlarged thymus with children who were involved in obstetric x-ray examinations. We also know that obstetric radiography is associated with a high incidence of stillbirths and neonatal deaths, and that it is not possible to die from a cancer if one is stillborn or had one's death ascribed to "prematurity," and so forth. So I think that even if Burch is right when he assumes (without a shred of evidence) that the mothers of cancer children are more in need of obstetric radiography than mothers of healthy children, we should still expect "too few" cancer deaths in the exposed children before 5 years of age. It is also difficult to follow Burch when he begins by saying "if obstetric radiation induces a childhood malignancy, then it must do so by converting a previously nonpredisposed fetus into one that is genetically predisposed" and ends by saying "we shall need a fuller understanding of the etiology and pathogenesis of 'natural' and radiation-induced malignancies before we can confidently reject the notion that obstetric x rays induce at least some childhood malignancies" (*21*).

There is no reason why diagnostic radiography should not be associated both with a high incidence of nonradiogenic cancers (when the subjects are attending hospital with specific complaints) and with a low risk of dying from any cause during the next 5 years (when the subjects have passed a preemployment health test). The point is that they are always performed in circumstances which make it difficult to recognize the carcinogenic effects of low-level radiation either because they are associated with a high risk of dying before the extra cancers have time to develop or because they inflate the expected numbers of nonradiogenic cancers. In fact, there are so many causes of confusion that if it had not been for the Oxford Survey doing the right thing for the wrong reason we might still be labouring under the delusion that low-level radiation has an (advantageous) effect on cancer incidence which increases as the dose decreases!

This "homeopathic" theory has its roots in ABCC data and managed to wear an air of respectability for many years because the epidemiologists who were using prospective surveys to study obstetric radiography were making essentially the same mistake as the Atomic Bomb Casualty Commission. The Commission was making no allowance for the effect of appalling living conditions on the recognition of cancers in general and childhood cancers in particular, and the epidemiologists were forgeting that difficult births are associated not only with a high incidence of x-raying but also with a high incidence of still-births and infant deaths. But it is only necessary to remember that a high all-causes death rate goes hand in hand with a low cancer death rate, and to remember that childhood cancers have fetal origins, to realize that there is only one sense in which radiation can be said to have a beneficial effect. When radiation causes a nonlethal mutation which not only increases the growth potential of a somatic cell but also initiates a process which allows the affected cells to achieve "tumor dominance" it can be said to have conferred a temporary benefit on the mutant cells. If the said mutation had affected a germ cell it could conceivably have conferred a lasting benefit on the affected species, but a somatic mutation could only be harmful to the individuals concerned. I suspect that the spurious nature of the impressions left by ABCC data and other surveys which found "too few" cancers following exposure to low-level radiation would have been recognized much earlier if the somatic mutation theory of cancer causation had not fallen into disrepute, and if epidemiologists had not been so prejudiced against retrospective and loosely knit surveys. The somatic mutation theory is deemed to be unacceptable because the steep age-dependence of cancer mortality is supposed to be accompanied by an age-dependent rate of cancer initiations (19). If, however, a particular type of mutation merely sets in motion a pathological process which begins by having an extremely high probability of being interrupted and ends by being all but irreversible, we could be dealing with a situation in which age does not affect the event

but does affect the later probabilities. If this is so, we would have to allow age to have a powerful say in what happens within a short time of a cancer mutation and virtually no say in what happens after the mutant cells have achieved tumor dominance. I say this because, by and large, young adults (whom we imagine to be able to suppress early cancers much better than older or younger individuals) do not respond as well to cancer therapy as older patients. There is, however, no reason why youth should not be on the side of all dominant cell-species whether they be composed of mutant or normal cells.

According to this theory, we should expect latent or clone-sized cancers to be far commoner than overt or tumor-sized cancers. We should also expect the cancer risk associated with mutations (whether induced or spontaneous) to be influenced both by the age of the host and by the normal rate of division of the mutated cells. In other words, what is difficult to understand about cancers is not the age-related risk of dying (this applies to all diseases - see fig. 12, Chap. 4) but the following facts: (1) myriads of malignant cells can be present in the body without causing symptoms; (2) this silent period can persist for years in children and possibly decades in adults; (3) the interval between the start of the process and onset of symptoms is always shorter for myeloid leukaemia than for other cancers, including lymphatic leukaemia, or the disease with the slower rate of cell division, and (4) an infection death while incubating a cancer is a greater risk for haemopoietic neoplasms than solid tumors.

These features of the natural history of human cancers suggest that remote influences, possibly in the form of hormones, operate as age-dependent cancer "inhibitors" or "adjuvants" (that is, as constraining or promoting influences), and thus make it possible for a set of randomly distributed mutations to produce more cancers in, say, the bone marrow than in other sites. We know that cancer cells have a high growth potential, and we have reason to believe that they are not subject to normal biological controls. We also know that there is a recurrent need for cells with a high growth potential, and that no multicellular organism could survive if individual cells were to take the initiative in deciding whether extra ones were needed. A normal cell can be counted upon to react characteristically to a number of signals, but it is clearly "forbidden" to take the initiative however compelling the situation. I have no idea how this system works, but like to imagine that at every locus on the genes of somatic cells there is a switch which is usually kept in the "off" position but can be made to stick in the "on" position by accident (that is, as a result of a nonlethal mutation), and like to imagine that a complete set of functioning switches is needed not only to prevent cancers but to maintain the life of all multicellular organisms (22).

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ERRATA TO

AN EPIDEMIOLOGIST TAKES A LOOK AT RADIATION RISKS

DHEW Publication No. (FDA) 73-8024

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The following changes should be made in all copies of this publication:

Page 29, Table 1 - Corrected values are indicated by asterisks.

		Mortality rates per 1,000*		(Totals)
Cases	White	19.1	14.6*	33.7*
	Coloured	21.6	16.2	37.8
	Both	20.3	15.3	35.6
Controls	White	12.1*	8.5*	20.6
	Coloured	23.6*	17.6*	41.2
	Both	17.3	12.7	30.0

Page 31, Table 3 - Ratio of observed to expected should be 0.86 instead of 0.90.

Page 32, Table 4 - Number of observed leukaemias under age 3 should be 9 instead of 19.

Page 33, Line 11 - Number of A-bomb survivors should be 1,292 instead of 1,291.

Page 33, Table 5 - 1. Right-hand heading should be "Cancer deaths under 10 years."

2. Expected nonradiogenic deaths for mean radiation dose 12 should be 0.27 instead of 0.37.

3. Footnote "a" should read "Author's estimates of mean values based on maternal exposures presented by Jablon and Kato.

Page 35, Line 6 - 78.6 should be 7.86.
Line 9 - (10.8) should be (10.73)

OVER

Page 35, Table 6 - Total observed leukaemias should be 18 instead of 21.

Page 50, Table 2 - Figure for 1952 should be +7.41 instead of +6.41, making the mean difference 3.80 instead of 3.68.

Page 56, Table 4 - Total lost should be 1,609 instead of 1,741.

Page 78, Table 2 - Last quotient should be 0.988 instead of 0.987.

Page 79, Table 3 - Total x-rayed in utero should be 774 instead of 744.

Page 83, Table 5 - All controls should be 774 instead of 744.

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April, 1973

Division of Biological Effects
Bureau of Radiological Health