THE NON-THRESHOLD DOSE/EFFECT RELATIONSHIP*

by

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For this brief discussion I am oversimplifying the dose/effect relationship of ionizing radiation and making use of the simple logrithmic expression,

$$E(\text{effect}) = \text{Constant} \times [\text{Dose(rem)}]^n = CD^n$$

for human exposure below a few hundred rem as indicated in Fig. 1. It follows that when $n > 1$ and approaches 2 or 3 this approximates the threshold bypothesis; when $n = 1$ we have the linear hypothesis and when $n < 1$, e.g. when $n = 1/2$, we have the non-threshold hypothesis where as indicated in Fig. 1 the slope of the curve or the effect per rem is greater at low doses than at high doses.

In the few minutes I have I will discuss only somatic effects and in particular radiation induced malignancy, but as indicated by Fig. 2 some of the same arguments can be applied to genetic damage. Here it is noted that the early work of Russell suggested the genetic damage to mice (and presumably to man) per roentgen at low dose rates and low doses is only about 10% of that at high dose rates and high doses, but more recent publications[2] suggest that maybe the mutation frequency curve turns back up at very low dose rates near natural background and perhaps we are not warranted in making use of this 10% factor for genetic mutations.

Prior to about 1960 most health physicists and radiobiologists subscribed to the threshold hypothesis but since that time an overwhelming

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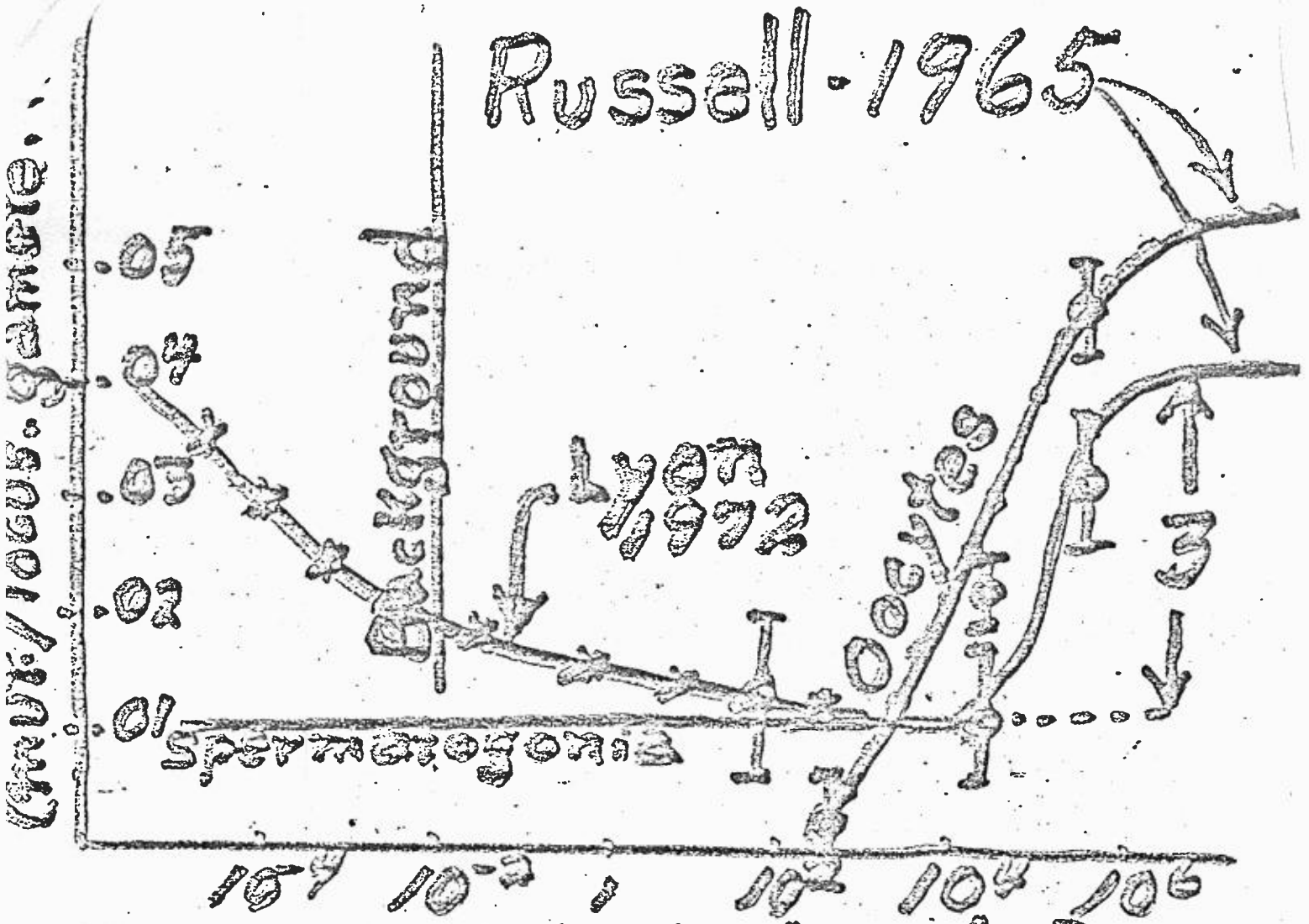


Corrections:

for dose rate: $\frac{1}{2} \times \frac{1}{3} = \frac{1}{6}$

for dose: $\frac{1}{2}$

Total: $\frac{1}{6} \times \frac{1}{2} \sim \frac{1}{10}$

% Increase in Cancer
0.0
0.1 Sv
0.2 Sv
0.3 Sv
0.4 Sv
0.5 Sv
Case C Effective Dose
Case A Effective Dose
Case B Effective Dose
Effective Dose
Fig 2

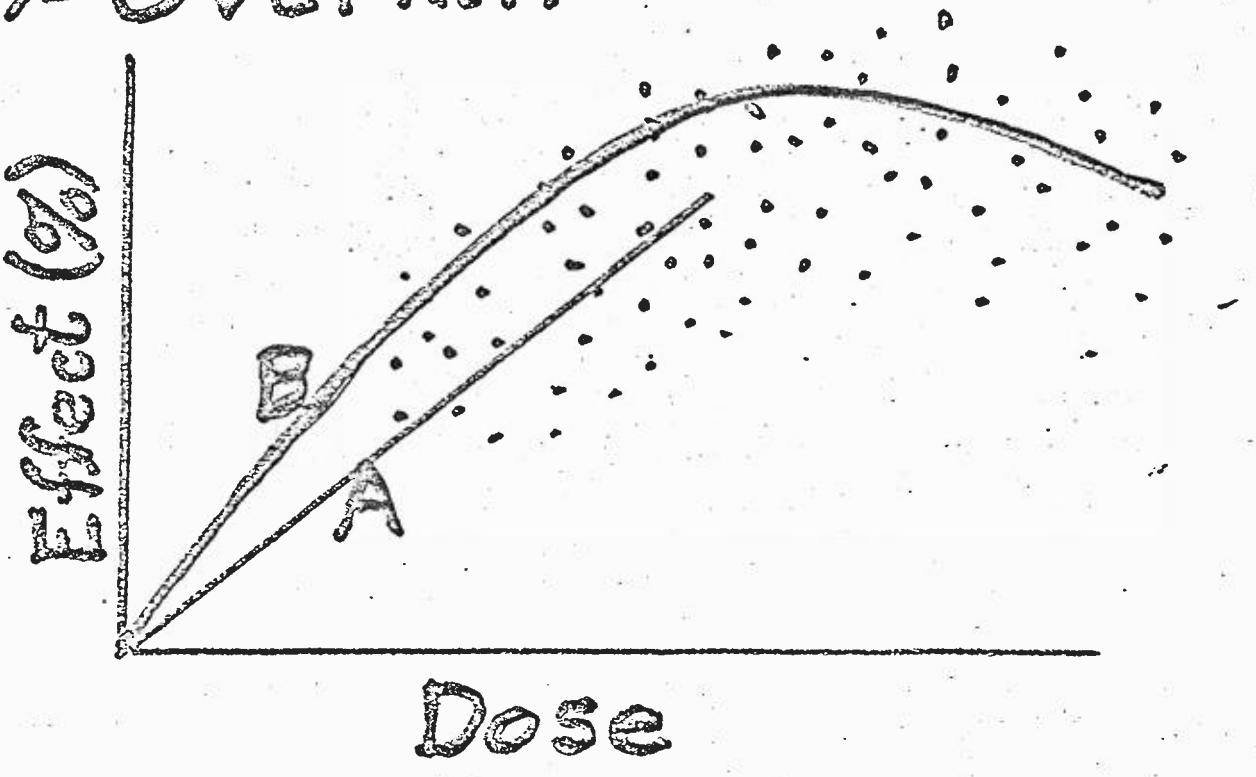
number of studies--many of them at low doses--have failed to give evidence of a safe threshold dose but rather have supported a non-threshold dose/effect relationship. Also, during this period a number of studies (and especially studies of human populations) have suggested the risk of cancer from low exposure is much greater than it had been considered to be some years earlier. As a result of these developments ICRP[3] in 1971 concluded "the ratio of somatic to genetic effects after a given exposure is 60 times greater than was thought 15 years ago." During this period national and international standards setting bodies (such as NCRP, AEC, FRC and ICRP) discarded the threshold hypothesis in favor of the linear hypothesis; however, many of those responsible for this change maintained this provided a generous factor of safety at low doses and dose rates and some even went so far as to make the false statement that there were no data on low level human exposure. These persons for unexplained reasons fail to recognize low exposure studies involving many thousands of subjects such as , for example: 1) Studies of Stewart and Kneale[4] of cancers in children who had received in utero exposure (doses from 0.2 to 0.8 rem to fetus), 2) Studies of Mancuso, Stewart and Kneale[5] of radiation workers at Hanford, Washington (average dose about 1 rem), 3) The Tri-State Studies of Bross[6] (doses < 1 rem) and 4) Studies of Modan et al.[7] of thyroid carcinoma in persons irradiated for tinea capitis (average thyroid dose 6.5 rad).

There are many reasons why some people still cling to the threshold hypothesis, why the risks of low level exposure are often underestimated and why many scientists fail to recognize that in many cases not only does the linear hypothesis fail to provide a generous safety factor but it actually is nonconservative, i.e. $n < 1$. A few of the reasons for this divergence of opinion and why the linear hypothesis often underestimates the cancer risk are:

1. Overkill. At high doses the cancer incidence curve drops over parabola shaped (as shown by Curve B in Fig. 3) because many of the animals do not live long enough to die of cancer. However, this overkill effect begins at intermediate doses such that if one extrapolates this curve from intermediate exposure levels as shown in Fig. 3 to zero without appropriate correction for overkill the cancer risk (as shown by Curve A) is underestimated.

Why the Linear Hypothesis Underestimates the Cancer Risk:

1- Overkill



2- Short Followup

3- Animal vs. Human Studies

4- Animals of Short life Span

5- Cell Sterilization

6- Heterogeneity of Population

7- Damage to Immune Surveillance System

2. Short follow-up of both animal and human studies can only underestimate the cancer risk, especially for those cancers that have a very long period of incubation.

3. Animal vs human studies. Man's oncogenic response in many respects is significantly different from that of test animals. For example his ovarian tumor response has long been known to be less than that of some strains of mice and one would expect his response to bone marrow tumors and myelogenous leukemia to differ considerably from that of animals in which all the bone marrow remains active (red instead of partly yellow) during the entire life. Warren and Gates[8] found very large differences in carcinogenic response even among strains of the same animal, e.g. a large life shortening and leukemia incidence in one strain of mice and essentially no such obserable effects on another strain of mice for the same dose.

4. Short life-span animals with life spans ranging from 5 to 20 years are of necessity used to simulate the effects of radiation on man with a 70 year life span--this in spite of the fact that the latent period of some cancers in man is 30 to 50 years. It is generally accepted that oncogenesis and the cancer incubation (latent) period relates to the time since an exposure was received, yet sometimes the simplifying assumption is made that the malignancies developing in a fraction of the animal's life span following radiation exposure relates to the malignancies that would develop in man in the same fraction of his life span following the same dose.

5. Cell sterilization. Many studies (Fig. 4) are made on human and animal populations where the organ doses are so large that cell sterilization destroys preferentially those weak cells which are most likely to develop into cancer cells (they present a large cross section for cancer initiation) and extrapolation of these data to zero dose seriously underestimates the cancer risk at low doses. A classic example of this type of bias is the use by standards setting bodies (NCRP, ICRP, UNSCEAR) of very high thyroid doses of ^{131}I to human subjects in estimating the risk of low doses of ^{131}I. Perhaps someone should have reminded these organizations that a thyroid carcinoma

cannot orginate from a cell that was killed by ^{131}I!

6. Heterogeneity of population. The widely publicized paper[5] showing an increase of statistical significance in the incidence of cancers of bone marrow, pancreas and lung in relation to the recorded radiation exposures of Hanford radiation workers was published while I was editor-in-chief of the journal HEALTH PHYSICS and one of the criticisms I received most often for publishing this paper (in spite of the fact that it was reviewed by four very capable reviewers) was these data are useless because there are too many uncontrolled variables--sick, persons on drugs, fat, slim, black, white, young, old, chemical hazards, genetic differences, smokers, non-smokers, etc. I can hardly imagine a more ridiculous criticism. The authors of this work did correct for sex and internal dose and the other variables are being taken into account as fast as possible on a greatly reduced operating budget, but I interpret these critics were saying essentially one should ignore these human data and instead base our standards for low level exposure on animal studies where all these variables can be controlled. The cancer coefficient for this Hanford population was higher (7 to 8 $\times 10^{-3}$ radiation induced cancers per person rem) than that of other studies, so what should we do? Should we continue to base our standards on the data from the survivors of the atomic bombings of Hiroshima and Nagasaki or on the cancer incidence of ankylosing spondylitis patients treated with x-rays when as shown in the following they seriously underestimate the cancer risk? Man is not an inbred, caged animal; he is a dukes mixture of almost everything one can imagine. This is the kind of human study we so badly need and what the Hanford study was except for one exception--the "healthy worker snydrome." This is a healthy group (several cuts above the average) and one that is under the best of medical care. Maybe when we understand better the healthy worker syndrome we can explain why workers with 5 rem or more of recorded dose had an increase in longevity of 10 years. Maybe this is why the workers had a high incidence of myelomas and a low incidence of leukemias?

I believe it is the heterogeneity of a human population that causes a higher incidence of malignancies per rem at low doses than at high doses in so many studies (i.e. $E = cD^n$ in which $n < 1$ and often $n = 1/2$). Studies of Bross[6] seem to confirm the existence of subgroups in the population that are more susceptible to radiation induced malignances and the influence of cocarcinogenistic and synergistic factors. For example he found a very large increase in cancer risk (i.e. by 5000%) for children who received in utero-x-ray exposure and later developed certain respiratory diseases.

7. Damage to the immune surveillance system or man's reticuloendothelial system by ionizing radiation probably is an important reason why his dose response in so many cases follows the relation $E = cD^{\frac{1}{2}}$. Normally this immune system holds in check all sources of foreign protein including small colonies or clones of cancers in situ (cancers before they can be clinically ~~chemically~~ recognized). However, radiation damages the ability of these scavanger cells to recognize virus and bacteria as well as as cancers in situ so as shown by Fig. 5 there is a large increase in non-cancer deaths per rem and a low increase in cancers per rem for those exposed to high radiation doses and a low increase in non-cancer deaths per rem and a high increase in cancers per rem for those exposed to low radiation doses. This, of course, is because of the short incubation period of many of the common diseases such as pneumonia which develop fast when a large fraction of the immune surveillence cells have been damaged or destroyed by high radiation doses. The weak persons who are most likely targets for death by cancer are taken early by a disease like pneumonia before they have time to die of cancer. This undoubtably is one reason why the data on the survivors of the bombings of Hiroshima and Nagasaki tend to support the relation $E = cD^{\frac{1}{2}}$ and why at the same time they underestimate the risk of cancer viz. most of the cases under study received intermediate to high doses.

I have long been and continue to be a strong supporter of the studies of the survivors of the bonbings of Hiroshima and Nagasaki (i.e. while I was director of the Health Physics Division of ORNL we were in charge of the dosimetry for this study). I consider it

Increased Death Rate Following Exposure

(5)

unfortunate, however, that this data is being misused by ICRP, NCRP, UNSCEAR, BEIR-I & II and other standard setting bodies. They ignore completely the factors 1-7 discussed above. The ABCC data identified the radiation induced cancers as A in Fig. 6 (i.e. the difference in cancers per rem among the blast and fire victims and the low exposure group as controls). Ideally they should have identified C (i.e. the difference in cancers per rem among the blast and fire victims and blast and fire victims that received no exposure as controls). Practically, at best an effort should be made to correct for fire, blast and other traumatic influences of death, sickness, disease, hunger, etc. Kneale and Stewart[9] have shown that a year or more before cancers developed to the point of clinical recognition among the children in the ABCC study they were showing signs of being abnormally sensitive to infection and Kneale[10] has shown that the terminal phase of preleukemia is associated with a high risk of dying of pneumonia. However, long before this and in the early period after the events associated with the bomb explosion it would be the weaker and those more prone to develop cancer later on that succumbed to death from the radiation syndrome. Thus the stronger and less cancer prone survivors became the population upon whom cancer risk to a normal population is being judged by the standards setting agencies. Rotblat[11] based the cancer risk on B in Fig. 6 (i.e. the difference in cancer incidence per rem among early entrants into Hiroshima who were exposed to fallout and neutron induced activity and late entrants who received essentially no radiation exposure. Neither of these groups was subjected to fire, blast and trauma that existed shortly after the blast. He found a leukemia risk of 1.6×10^{-4} leukemias per person rem which is 8 times that commonly assigned to the Hiroshima survivors of the atomic bombing and is more in line with values found in other population exposure groups mentioned above.

The other human population that is extensively used or rather misused by these standards setting bodies in determining the cancer risk coefficient is the group of ankylosing spondylitis (AS) patients that is treated with large local doses of x-rays to the spine. As shown in Fig. 7 the incidence of cancer per rem (A) in this AS group was

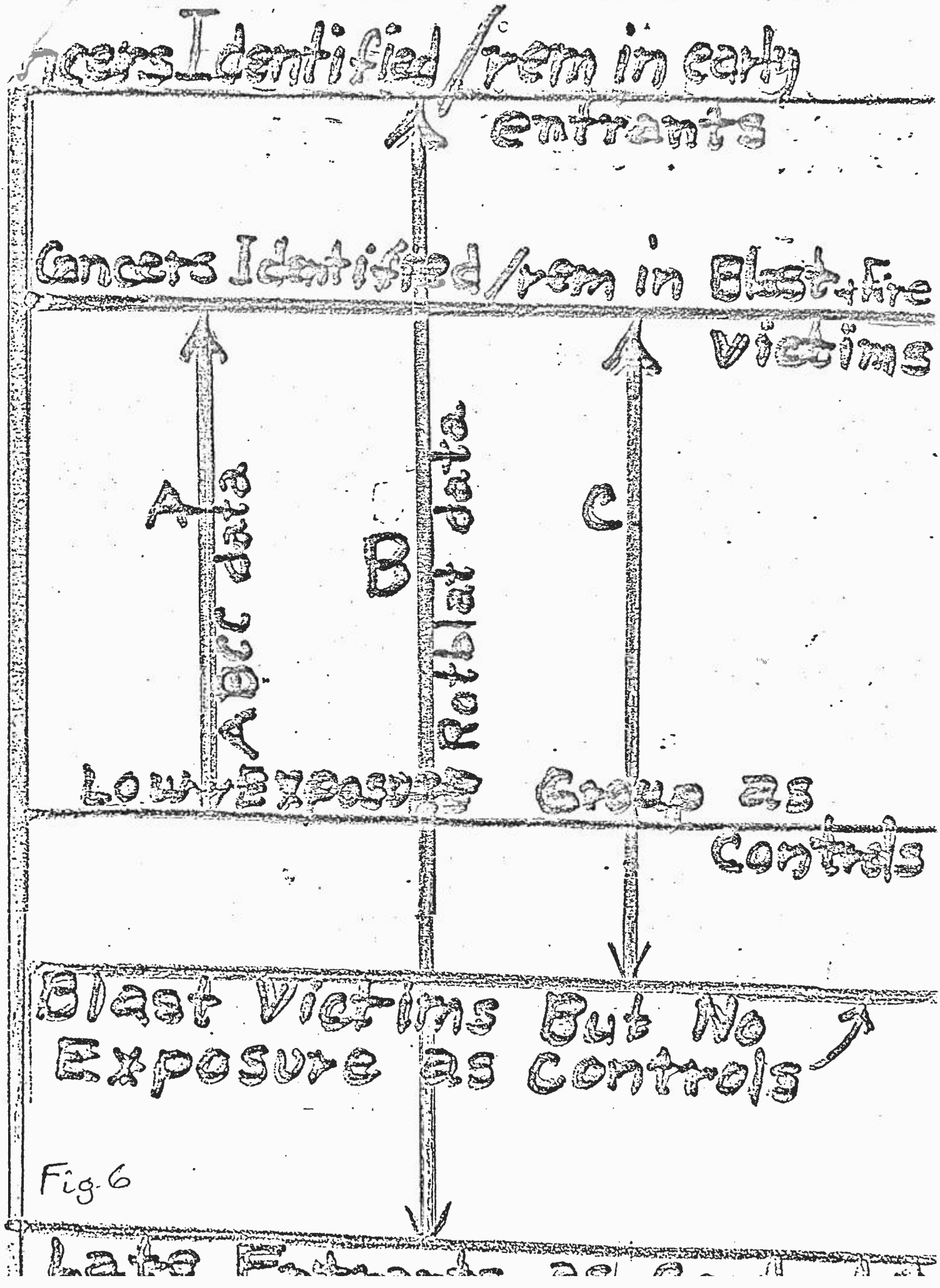
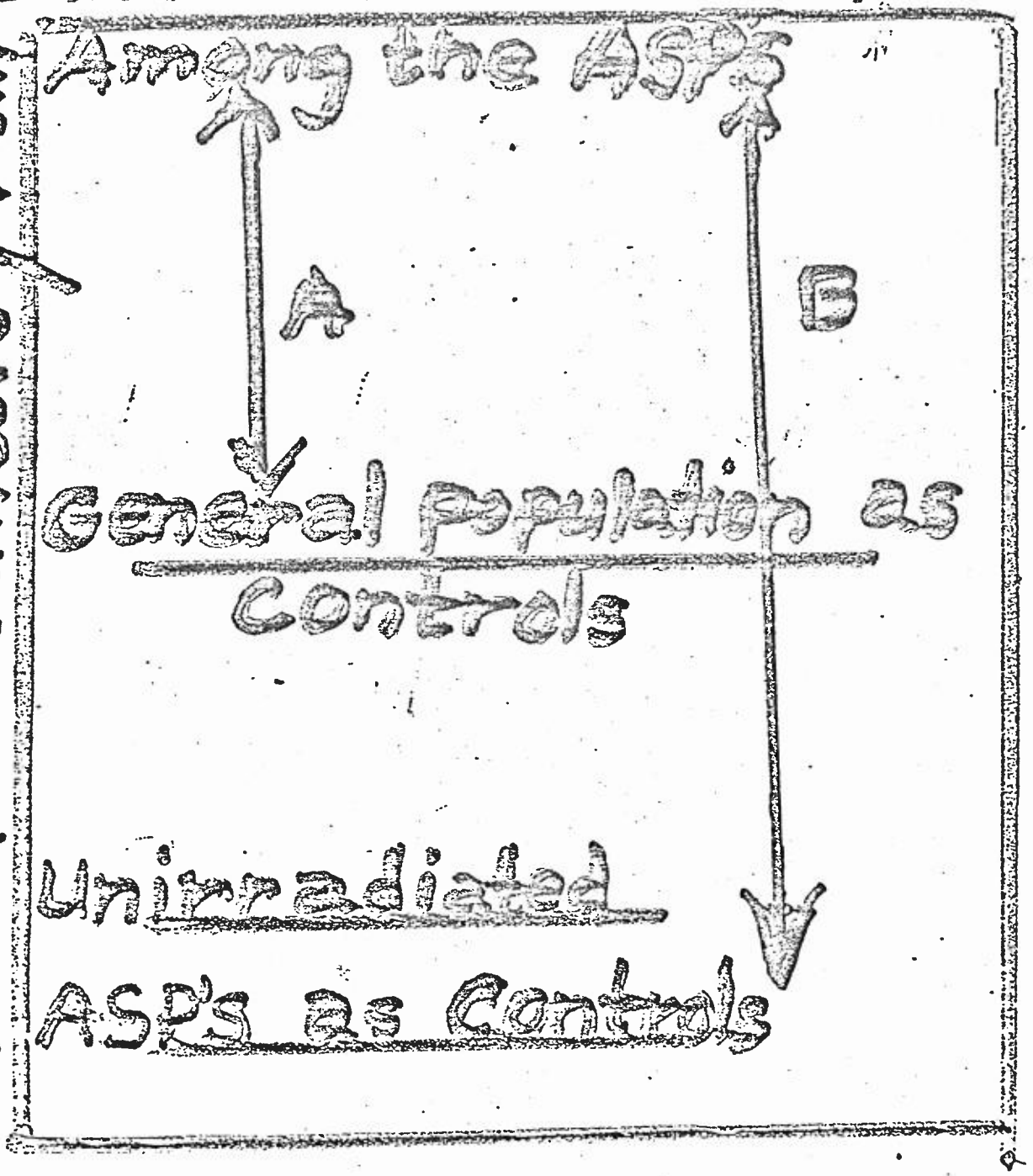

Cases Identified from early entrants
Cases Identified from Electronic Victims
A
Both data
B
Neither data
C
Low Exposure
Cases as Controls
Blast Victims But No Exposure
As Controls

Fig. 6

that which was above the incidence in the general population taken as controls. However, studies have shown that AS patients have a lower incidence of cancer than the general population because, as a result of the disease, they don't live as long as normal. An unirradiated AS group should be taken as controls (B in Fig. 7). Therefore, the studies of AS patients have led to a serious underestimate of the risk of radiation induced cancer.

Cancers identified / rem



Estimated cancers / 100

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