Anhang/Appendix I

The Role of Epidemiology in the Detection of Harmful Effects of Radiation and the Setting of Safety Standards

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Introduction

Among radiobiologists and epidemiologists there is widespread agreement on two points: for estimating cancer effects of ionizing radiation the best method is by linear extrapolation of the high dose effects observed in A-bomb survivors, and the risk is much greater for leukaemia than for other neoplasms. As a result of this consensus the cancer risk coefficients in BEIR V[1] and ICPR 60[2] are based on A-bomb data. They are also based on methods of risk analysis which require relations between cell death and mutational effects of radiation to be the same at all dose levels since they allow pooling of data from high, medium and low dose levels. Nevertheless, from clinical studies of persons suffering from acute effects of radiation, there has come evidence that, at high dose levels, cell death effects include both a shortlived leucocytosis and prolonged loss of immunological competence (Fig.1)[3,4].

In a lengthy follow-up of A-bomb survivors (where there were several study populations and constant pooling of data from all dose levels) there is no mention of the two exclusively high dose effects[4]. But they must have reduced the number of high dose survivors, and they probably left the source of the extra leucocytosis (i.e. the red marrow component of the RES or reticulo-endothelial system) with more mutant cells than other equally exposed tissues. Therefore, there is clearly a need to know how A-bomb data compare with data from exclusively low dose situations. Suitable for this purpose are two sets of A-bomb data: one describing the cohort which was assembled from census data five years after the bombing (life span study or LSS cohort), and one describing the survivors who feature in several studies of teratrogenic and carcinogenic effects of fetal irradiation (*in utero* cohorts)[4], and two sets of data from elsewhere: one describing the first survey to find evidence of a cancer risk at low dose levels (Oxford Survey of Childhood Cancers or OSCC data)[5]

and the other describing the first survey of nuclear workers to find evidence of a cancer risk at supposedly safe dose levels (Hanford data)[6].

LSS Cohort

The official position regarding late effects of the A-bomb radiation is largely the result of keeping five year survivors under continuous mortality or morbidity surveillance and repeatedly coming to the following conclusions: no late effects of the radiation apart from cancer; no cancer risk at the dose levels likely to be encountered by nuclear workers; a greater risk of leukaemia than of solid tumours (with relatively short intervals between exposure and death for the leukaemia cases) and higher levels of radiosensitivity at the beginning than the end of adult life[4].

On the strength of these findings it is widely assumed that A-bomb survivors, apart from their radiation dose, are representative human beings and, consequently, that levels of radiosensitivity were the same both for survivors and nonsurvivors, and for the high dose survivors who did and did not show any signs of acute radiation effects. Both in BEIR V and in ICRP 60 the cancer risk coefficients are based on 75,991 members of the LSS cohort with the latest DS86 dose estimates; and in neither report is there any mention of the fact that a massive epidemic of acute bone marrow depression[7] had evoked very different reactions from the lymph node and red marrow components of the RES (Fig.1).

Following identification of the persons who were still alive at the time of the first postwar census of Japan (October 1st, 1950) there was systematic recording of exposure positions, shielding and four types of acute radiation injuries, *viz:* flash burns, oropharyngeal lesions, purpura and epilation[8]. The exposure positions and shielding were needed for dose estimation and the epilation data were used by haematologists and cytologists to represent survivors with acute radiation effects[4].

But following a suggestion by Jablon *et al* that the injury data were not trustworthy'[9] there was no further mention of them in a long series of 4 yearly mortality reports.

For several years after the bombing, the only distinctive effect of marrow aplasia (aplastic anaemia) remained a common cause of death; and some survivors from the marrow damage epidemic were still showing signs of faulty leucopoiesis or erythropoiesis 8 to 11 years later[7]. But when the post-1950 death rate for "diseases of blood and blood forming tissues" was found to be higher than normal (and strongly dose related)[10] this was regarded by Beebe *et al*, not as evidence of late effects of the marrow damage, but as a further sign of an exceptionally strong association between leukaemia and radiation[11].

In 1982 there was a suggestion (based on published data) that the normal noncancer death rate of the LSS cohort might be an artifact caused by deaths from marrow damage continuing after 1950 and obliterating selection effects of deaths before this data[12], but no one who was in a position to test this hypothesis was at all interested. Nevertheless, following release of a limited amount of LSS data by RERF (in the form of *LSS data on disk*[13]) Stewart and Kneale succeeded in showing, first, that for all causes of death except cancer and cardiovascular diseases the death rate was negatively correlated with dose below the marrow damage threshold and positively correlated with dose above this level (Fig. 2)[14]; and, later, that among the survivors whose doses exceeded 1 Gy there were very few persons who were under 10 or over 50 in 1945 (Fig. 3)[15].

These findings favoured the artifact hypothesis and made it appropriate to be quite certain that there were no differences between the survivors with and without acute radiation injuries. The relevant tests were made possible by RERF adding to the *LSS data on disk* the little used injury data and thus disclosing the fact that among

the 75,991 survivors included in BEIR V, there were 63,042 who had denied all four of the injuries mentioned above (control group), and 2,601 who had claimed at least two injuries (test group)[16] (Table 1). The statistical analyses which followed this discovery are still awaiting publication in a peer reviewed journal. But from them has come evidence that levels of radiosensitivity were much higher for the test than the control group of survivors (Fig. 4). Furthermore, although in the control series there was no evidence of any late effects of the radiation apart from cancer (and levels of radiosensitivity were higher at the beginning than the end of adult life), in the test series, cancer was not the only cause of extra dose related deaths; and levels of radiosensitivity were highest for the youngest and oldest of six exposure ages (Fig. 4). Only 5 of the 6 age groups are shown in this figure, but for each cause of death the excess relative risk (ERR) was greatly in excess of 100 for the survivors with multiple injuries who were under 10 years of age when exposed. Finally, the 1998 report showed that it was only in the test group that the proportion of leukaemias among the cancer deaths was exceptionally high (Table 1).

Since acute effects of the A-bomb radiation were an important cause of death before 1950, we have in the latest independent analysis of LSS data both indirect evidence that levels of radiosensitivity were much lower for survivors than nonsurvivors, and direct evidence that it was only among survivors with no acute injuries that levels of radiosensitivity were higher at the beginning than the end of adult life (Fig. 4). This relationship between age and sensitivity to any harmful influence is a very unusual one, but it 'fits' not only with the fact that there were very few infants or old persons among the high dose survivors (Fig. 3), but also with the fact that selection effects of the early deaths were less obvious at high than low dose levels (Fig. 2) and with the fact that it was only among the survivors who had no acute injuries that levels of radiosensitivity were higher at the beginning than the end of adult life (Fig. 4).

OSCC Data

The survey which first found evidence of a cancer risk at low dose levels did so by comparing each dead child in a nationwide sample of early cancer deaths with a live child from the same 'regional birth cohort'[5]. When these comparisons showed that the dead children had been more often x-rayed before birth than the live children, new targets were set, and the Oxford survey gradually became an important source of information under various headings including cancer effects of fetal irradiation, and the etiology of childhood cancers[17].

The new targets necessitated a long period of data collection which eventually produced both *interview data* for a long series of case/control pairs (with supplementary data from family doctors, antenatal clinics and x-ray departments) and *regional data* for each 10 Km square of the national grid[18]. The latter included annual numbers of live births, stillbirths and infant deaths (1943-74); independent measurements of background radiation doses (supplied by the National Radiological Protection Board); annual numbers of cancer deaths before 16 years of age (1953-79), and *interview data* for most of these cases and their matched controls (who were now representing all members of the regional birth cohorts with cancer cases).

From numerous comparisons between the OSCC cases and their matched controls there have come the following observations: the usual time for x-raying pregnant women (third trimester) is later than the usual time for initiating a childhood cancer (first trimester) and, following these early, low dose exposures, the risk is no greater for leukaemia than for other neoplasms[19,20]. The risk is much greater for first than third trimester exposures[21] but even during the less dangerous period it only needs a dose of 10 mSv to double the normal risk of an early cancer death[19]. Besides the x-ray findings there is also evidence that during the latent phase of all childhood cancers, especially leukaemia, there is mounting sensitivity to infections[22]; and

evidence that in three countries this early effect of the cancer process was the cause of a strong negative correlation between the number of deaths ascribed to leukaemia and pneumonia[23].

From comparisons between the different regions there has come evidence that, in Britain, childhood cancers have a naturally clustered distribution, with higher death rates in rural areas than in large cities[18]. The *regional data* also showed that the causes of childhood cancers included *in utero* exposure to background radiation as well as prenatal x-rays, and that factors which increase the risk of an early cancer death include both pregnancy illnesses and postnatal infections. Still unexplained was the fact that the world wide increase in childhood leukaemias which followed the discovery of antibiotics was solely the result of lymphatic cases[24], but gradually surfacing was evidence that this might be the result of *in utero* mutations having a mixture of teratogenic and carcinogenic effects[25].

According to this suggestion, mutations in embryonic equivalents of lymph nodes simultaneously cause lymphatic leukaemia and prevent normal maturation of immunoglobins; and mutations in embryonic equivalents of red marrow simultaneously cause myeloid leukaemia and prevent normal maturation of haemoglobin and immunoglobins. As a result of this difference the principal competing cause of death for the lymphatic cases is infections. But for the myeloid cases there is also heightened sensitivity to low oxygen pressures which allows stillbirths during the second stage of labour (or deaths during the shallow breathing of deep sleep) to intervene. In favour of these suggestions are several observations: thus in children with myeloid leukaemia (and in cases of the sudden infant death syndrome) there are exceptionally high levels of fetal haemoglobin and other signs of faulty erythropoiesis[26,27]. In children with Downs syndrome and other congenital diseases where there is faulty maturation of the immune system there is an

exceptionally high risk of an early death from lymphatic leukaemia which only became obvious after antibiotics were discovered[17]. And since it is mainly in tissues which are not essential for *in utero* survival that cancers develop to the point of becoming clinically recognisable, the prime sites of childhood cancers are the brain, the RES, the autonomic nervous system, and the Woolfian Ridge.

In short, from the Oxford survey there has come both evidence of a cancer risk at low dose levels which is equally great for solid tumours and leukaemia (and is only obvious in populations with low rates of perinatal mortality) and evidence that childhood cancers are the result of mutations which have teratrogenic as well as carcinogenic effects. These observations have made it reasonable to assume that competing causes of death are necessarily different for childhood and adult cancers, and that background radiation is a relatively common cause of cancer at all ages.

In Utero Cohort

From studies of about 1,500 persons who survived *in utero* exposures to the A-bomb radiation there have come the following impressions: no teratogenic effects of the radiation apart from microcephaly and no risk of this following exposures before 8 weeks of fetal age[4]; no equivalent of the OSCC findings for prenatal x-rays[1]; and among 14 cancers which presented before 40 years of age no childhood leukaemias and only four male cases[28]. For the *in utero* cohorts there are no equivalents of *LSS data on disk*. But from published data it is possible to discover that in the *in utero* cohorts there is gross under-representation of births after March 1946 (and therefore gross under-representation of exposures before 8 weeks of fetal age)[15]. These deficits were clearly the result of young embryos being exceptionally sensitive to lethal effects of radiation, and abortion effects of this sensitivity leaving the *in utero* cohorts even more strongly biased in favour of low levels of radiosensitivity than the LSS cohort. Evidence of this bias includes the low sex ratio for the cancer deaths

(since male are more abortion prone than females) and the total absence of any childhood leukaemias (since deaths from devastation effects of the blast probably made a clean sweep of all preleukaemic children). Finally, although there was a long period when findings for A-bomb survivors were regarded as a reason for doubting the validity of OSCC data, it is now generally recognised that we have in OSCC data a valuable source of information about cancer effects of fetal irradiation[29].

Hanford Data

By having a maximum permissible dose and making it compulsory for nuclear workers to wear radiation badges, the nuclear establishment was reasonably certain that routine work in nuclear facilities would not be a cause of occupationally induced cancers. Additional support for this assumption (which was based on A-bomb data) was provided by Gilbert *et al* studies of workers in US nuclear facilities[30] since these both showed that the total number of cancer deaths was small by national standards and found no evidence of any extra dose related cancers. But meanwhile a survey of workers in one of these facilities (Hanford) had come to very different conclusions[6,31].

The rival survey by Mancuso, Stewart and Kneale (MSK) ascribed the small number of cancer deaths to selective recruitment of exceptionally healthy persons into the industry (so called 'healthy worker effect'). It also used 'new' methods of statistical analysis to show, first, that there was sufficient evidence of extra dose related cancer deaths to warrant further investigation[6], and later that, provided each annual dose of radiation was allowed to make a separate contribution to the result[31], it was possible a) to detect a cancer risk at supposedly safe dose levels and b) to show that this was largely the result of exposures after 50 years of age which (like the x-rays in the Oxford survey) showed no signs of a special association between leukaemia and radiation.

In 1996 a WHO survey (which pooled data from seven cohorts of nuclear workers in three countries) failed to find any evidence of a cancer risk at low dose levels[32]. But there are today, two surveys of workers in US nuclear facilities whose findings are in total agreement with the Kneale *et al* analysis of Hanford data (Oak Ridge[33] and Rocketdyne[34]) and one which showed that different standards of dose recording (or dose estimation) are making it unsafe to pool data from different locations[35].

Conclusions

The world wide increase in leukaemia mortality which made it appropriate to compare children who had recently died from malignant neoplasms with live children from the same regional birth cohorts (OSCC data) was largely the result of antibiotics greatly reducing the risk of dying from an infection during the latent phase of leukaemia. It had nothing to do with the nuclear industry or with the bombing of Hiroshima and Nagasaki. But it became a means of discovering that cancer risk coefficients were much lower when based on A-bomb data than when based on OSCC or Hanford data. For each data set the method of risk assessment assumed that the cancer risk was directly proportional to the radiation dose; and both in A-bomb data and in Hanford data there was pooling of data from all dose levels. But it was only in A-bomb data that this meant combining data from persons whose doses exceeded the threshold for two exclusively high dose effects (Fig. 1), with data from persons whose doses were too small to have any cell death effects. For A-bomb survivors there were also further complications caused by deaths from devastation effects of the blast as well as deaths from radiation injuries being dose related; and deaths from marrow damage continuing after 1950.

The long time which elapsed before there was any suspicion that early effects of the bombing had left the survivors with exceptionally low levels of radiosensitivity (and continuing resistance to this idea) are direct consequences of not recognising the epidemiological importance of the injury data. These data are needed to show that the LSS cohort is not a homogeneous population and to show that three of the survey findings (i.e. the early leucocytosis; the much later deaths from aplastic anaemia, and the seemingly normal noncancer death rate of the LSS cohort) were *all* the result of marrow damage.

We have been living with these mistakes for several decades and so far nothing untoward has happened. But it is high time that radiation protection committees realised that levels of radiosensitivity are much higher at the beginning and end of the life span than during the intervening period (Fig. 5), and also realised that a simple method for distinguishing between naturally occurring cancer and cancers caused by occupational exposures to radiation already exists[36]. This model has been used to settle compensation claims in the US[36] and something very like it is much needed if the nuclear industry is to steer clear of the expensive litigation which is currently crippling the asbestos industry. Also much needed is a) better representation of epidemiologists with no RERF associations on radiation protection committees, and b) better recognition of two facts of great public concern. Since a single *in utero* exposure to 10 mSv of radiation is sufficient to double the normal risk of an early cancer death, it is probable that even small leakages of radioactivity from nuclear power stations are causing extra childhood leukaemias. Furthermore, on the reasonable assumption that both for teratogenic and carcinogenic effects of fetal irradiation there are competing causes of death in the form of abortions, it is probable that brain damage is not the only teratogenic effect of radiation, and that even fetuses under 8 weeks of age are at risk of this and other cell death effects of radiation.

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Legend to Figures and Tables

Figures:

1. The changes with time following exposure to various doses of ionizing radiation in two hematologic parameters – lymphocytes and neutrophils. From Schull 1995[4] and Gerstner 1958[3]

2. Fitted Relative Risk for all Causes of Deaths Except Cardiovascular Disease and Cancer: 1950-1982 deaths of A-bomb survivors in four exposure age groups. From Stewart & Kneale 1990[14]

3. Ratio of Observed to Expected Numbers for Five Sets of LSS Data Classified by Exposure Age and T65 Dose. From Stewart & Kneale 1993[15]

4. Excess Mortality Risk/Gy. A-bomb survivors by injuries and exposure age. From Stewart & Kneale 1998[16]

5. Relations Between Exposure Age and Cancer Risk. Diagrammatic representation of three data sets. From Stewart 1999[37]

Tables:

1. Members of the LSS cohort included in tests of differences between survivors with and without acute radiation injuries

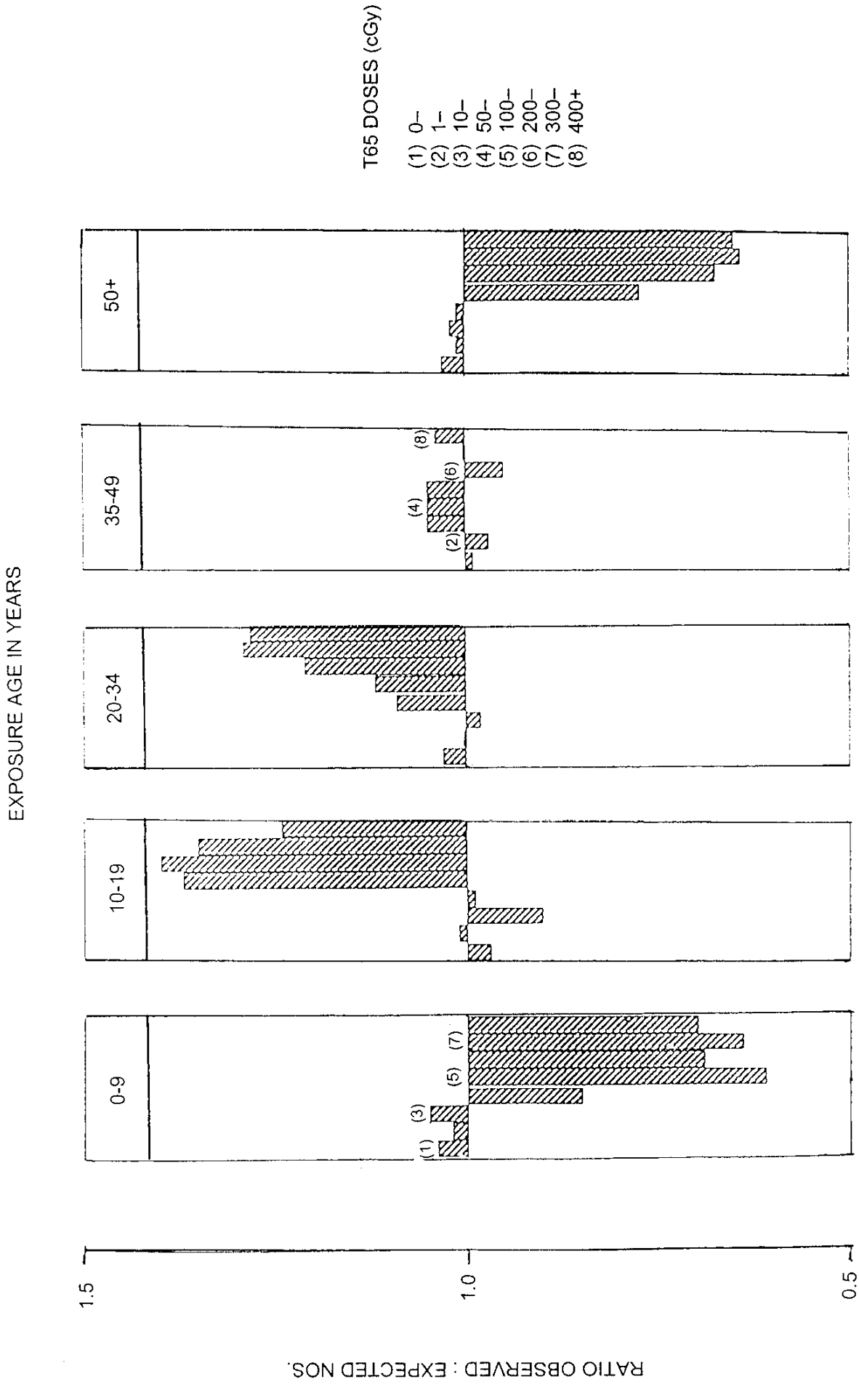
Table 1: Members of the LSS cohort included in tests of differences between survivors with and without acute radiation injuries

Specificactions	5 year survivors Nos:	Cancer deaths 1950-85 Nos: (Leukaemias)
Burns	5,551	
Purpura	3,613	
Oropharyngeal lesions	2,443	
Epilation	1,308	
2+ injuries claimed (Test group)	2,601	349 (41)
All four injuries denied (Control group)	63,072	4,832 (121)
Residue	10,318	755 (40)
Total LSS cohort**	75,991	5,936 (202)

* Including 6,683 survivors who claimed only 1 injury and 3,035 with incomplete data

** See BEIR V, p 183

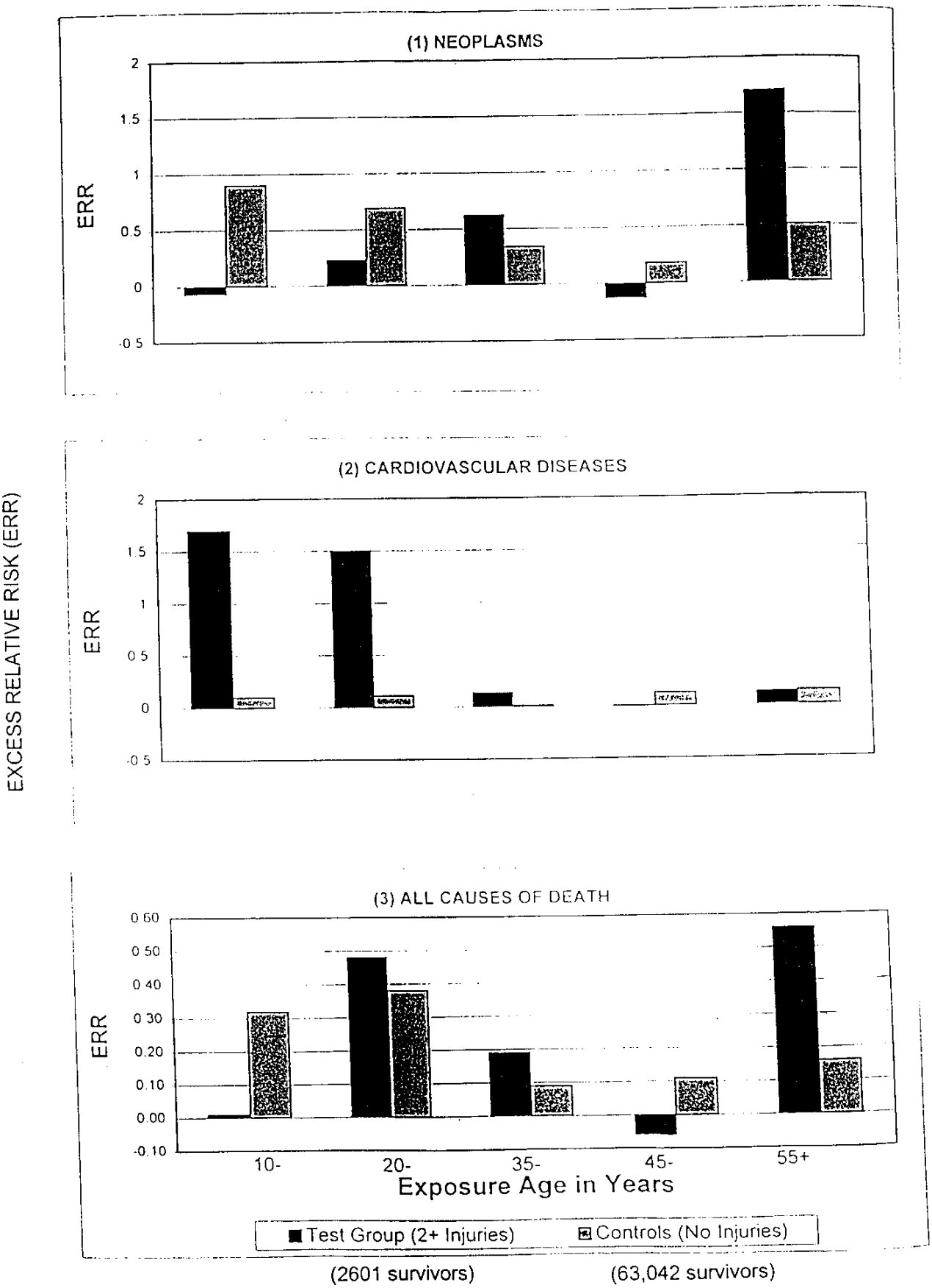
Anhang/Appendix I



Anhang/Appendix I

EXCESS MORTALITY RISK / Gy*

A-BOMB SURVIVORS BY INJURIES AND EXPOSURE AGE



* from Stewart & Kneale 1998[16]

Anhang/Appendix I

RELATIONS BETWEEN EXPOSURE AGE AND CANCER RISK
DIAGRAMMATIC REPRESENTATION OF THREE DATA SETS*

* from Gilman *et al* 1998[21], Schull 1995[4] and Kneale *et al* 1981[31]