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Discussant Paper on Professor T.D. Luckey's Paper

HORMESIS AND NURTURE WITH IONIZING RADIATION

by

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ON RADIATION HORMESIS -
An Appraisal of Professor T.D. Luckey's Paper

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The nature of health effects of low level radiation has been a problem of considrable controversy. Ionizing radiation has been confirmed to be carcinogenic within a certain dose range, and this has for many years been of concern to the public as well as to governmental organizations and expert bodies. Radiation carcinogenesis is considered to be a stochastic effect. It has been taken for granted by many that the risk of cancer due to low level ionizing radiation can simply be extrapolated from data obtained with large doses, using some mathematical models, whether linear, guadratic or linear-guadratic. Some radiation biologists believe that we should adopt the linear model which states that the risk is directly proportional to the radiation dose received, right down to zero dose. Actually there have been reports in the literature opposing such predictions. More than two decades ago, H.F. Henry presented the concept that low level radiation may be beneficial, stating that a significant and growing amount of experimental information indicated that the overall effects of chronic exposure at low levels might not be harmful (Henry, 1961). In recent years attention has been paid by many investigators to

the possible entirely different effets of low level ionizing radiation from those of high doses. In Professor T.D. Luckey's monograph "Hormesis with Ionizing Radiation" (Luckey, 1980) an extensive survey of literature was made. This has aroused vivid discussion since its publication (Hickey, 1983: Liu, 1985a; Conference on Radiation Hormesis at Oakland, C.A., Aug. 14-16, 1985). In his paper "Hormesis and Nurture with Ionizing radiation" presented to the present Conference more than 50 new references since 1980 were cited giving more support to the premise.

Professor Luckey has collected data on bacteria, plants, invertebrates and vertebrates, including mammals, to illustrate the stimulating effect of low level radiation on physiological functions, including immune competence. Special emphasis was given in this paper to radiation hormesis expressed in the immune system. The immune status of the popula tion and the individuals may be closely related to life span and to cancer induction and mortality. Though the theory of immune surveillance against the growth of transformed cells into malignant tumor has been doubted by some authors (Möller and Möller, 1975; Klein and Klein, 1977; Spärck, 1980), the consensus of opinion still holds that the nonspecific and specific components of host immune system constitute one of the most important defense mechanisms against the establishment and growth of tumor induced by various environmental agents. As it has been repeatedly disclosed in humans as well as in experimental animals in our laboratory, low dose radiation has a stimulatory effect on many para-

meters of the immune system. It was found that the morphologic transformation rate of peripheral blood lymphocytes in response to PHA stimulation was increased in inhabitants in an area of high natural radioactivity in Guangdong, China (Liu et al, 1982;1983;1985;1986), though the number of T lymphocytes might be somewhat lowered. In workers of nuclear industry engaged in processing of uranium compounds and metallic uranium, the reactivity of peripheral blood T lymphocytes to PHA may also be significantly heightened (Liu, 1986, to be published) in the presence of moderate decrease of the absolute number of the T lymphocytes. Animal experiments have confirmed these observations. Single whole body x-irradiation with 25 to 75 mGy caused a definite increase in the PFC reaction of the splenocytes in C57BL/6 mice (Liu et al, 1986; Liu and Liu, 1986). Continuous γ-irradiation with a dose rate of 5.4 mGy/6h/d also led to enhancement of PFC reaction of the spleen at a cumulative dose of 65 mGy (in 2 weeks) (Liu et al, 1986). The NK activity of the splenocytes in this same strain of mice showed marked increases at single whole body doses of 75 and 500 mGy when the effector to target cell ratio was 200:1, using YAC-1 cells labelled with ^{125}I-UdR. This increased NK activity was also noticed at single whole body x-irradiation with doses of 25 to 75 mGy when effector to target cell ratio was 50:1 and 100:1 (Fan and Liu, 1986, to be published). The enhancement of immunologic functions under such small doses could not be explained by a change of ratio of helper to suppressor T lymphocytes. In our laboratory acid α-naphthylacetyl esterase (ANAE) cytochemical staining was used as a cytoplasmic marker

to distinguish T and B lymphocytes and the subsets of T lymphocytes. The spot-granular pattern of ANAE stain was taken as a marker of the helper T cells and the scattered granular pattern for the suppressor T cells. Under single and continuous irradiation in doses causing stimulation of PFC reaction and NK activity, there was no statistically significant change in the percentage of these subsets (Liu et al, 1986; Liu and Liu, 1986, to be published). At the same time we looked at the reactivity of thymocytes and splenocytes to interleukin 1 and interleukin 2, respectively, under different radiation doses. It was found that the reactivity of the thymus to interleukin 1 and that of the spleen to interleukin 2 tended to increase under the above mentioned dose range. These experimental data point to the possibility of an increase in release of immunoenhancing lymphokines under low level radiation resulting in an amplification of the immunologic processes (Liu et al, 1986). Recent work in our laboratory also showed a tendency of the splenocytes from mice irradiated with low doses to produce more interleukin 2 in response to ConA stimulation. Therefore, under such small doses as 25 to 75 mGy the enhancement of immunologic functions could not be explained as the result of preferential damage to or killing of the suppressor T cells.

In his paper, Professor Luckey mentioned the so-called Hellström effect (Hellström and Hellström, 1979). It was demonstrated that a single whole body irradiation with 4.5 Gy would increase the tumor suppressing effect of the host previously immunized with the specific tumor antigen due to damage of the relatively radiosensitive suppressor T cells. However, in our experiments, 4 Gy whole body x-irradiation actually profoundly suppressed

the PFC reaction (Ju et al, 1985) as well as THE NK activity (Fan and Liu, 1986). It should be pointed out that the Hellström experiment was done under specific circumstances. The mice had been immunized with tumor antigen before the whole body irradiation with 4-4.5 Gy. That means all the T subsets, including the suppressor, helper and cytotoxic T lymphocytes had already been activated before irradiation. It is well known that activation of lymphocytes, either with antigens or with mitogens would markedly increase their radioresistance, though the relative radiosensitivity of the suppressor T cells might still be higher than that of the helper and cytotoxic T cells. Under such circumstances, a single acute dose of 4 Gy would result in a preferential damage to the suppressors manifesting in an enhancement of immune reaction against the tumor cells. However, without prior activation through immunization with the tumor antigen a medium dose such as 4-4.5 Gy would kill the suppressor as well as the helper and the killer T cells, resulting in an overall depression of the immune competence. There have been many reports on the enhancement of immune reactions by radiation. Both in vivo and in vitro experiments showed enhancement of immune reaction by medium radiation doses only when antigen stimulation preceded irradiation, and immunoenhancement occurred only with smaller doses (e.g. within 0.25 Gy) when irradiation preceded antitgen stimulation (Anderson et al, 1980; Liu, 1985a). Therefore, the experiment of Hellström and Hellström cannot be taken as a general phenomenon.

More than half of the space of Professor Luckey's paper

is devoted to hormesis in radiation induced cancer. Both experimental and epidemiological data were presented to illustrate the phenomenon of hormesis for a wide variety of radiation induced cancers. It is clear that the linear no-threshold model does not fit all cases. Many radiation induced cancers have an actual dose threshold, such as radium-induced osteosarcoma. Hormesis has been observed in some instances. Some remarks should be made on the "China study" which was cited in Professor Luckey's paper. According to the 1982 report (Zhai et al, 1982) with 531,972 man·years for the area of high natural radioactivity and 563,507 man·years for the control area, the standardized mortality rates for all cancers were $41.19/10^5$ and $49.86/10^5$ for the two areas respectively ($P < 0.05$). For specific cancers it was found that the mortality rates for liver and lung cancer were significantly lower in the area of high natural radioactivity ($P < 0.05$). However, in the 1985 report (He et al, 1985) with 764,696 man·years for the area of high natural radioactivity and 777,482 man·years for the control area, the standardized mortality rates for all cancers were $44.60/10^5$ and $51.00/10^5$ respectively ($P > 0.05$),being lower in the area of high natural radioactivity, though having not reached a significant level statistically. On the other hand the difference in mortality rates for all cancers in the female populations of the two areas was statistically significant, being $32.30/10^5$ for the area of high natural radioactivity and $41.90/10^5$ for the control area ($P< 0.05$). In conclusion, we can say that with the survey of 3 quarters of one million man·years, at least no increase of cancer mortality was found in an area with the

natural radioactivity 3 times as high as the control. This study has provided a rather stable human population under continuous low level irradiation for generations, which will undoubtedly yield valuable information when long enough follow-up observations are made.

Another human study is the Japan atomic bomb survivors which provides data of remote effects following acute exposure. The data were given in table 5 and Fig. 12 in Professor Luckey's paper (Kato and Schull, 1982) in which the 10-90 mGy (1-9 rad) group demonstrated a lower than control mortality rate for all cancers, especially for leukemia, malignant lymphoma and some other cancers. However, the authors considered the difference to be of no statistical significance.

The dose-response curves given in Fig. 8 and Fig 9 in Professor Luckey's paper deserve special consideration. The V shaped curve in Fig 8C may not be a universal phenomenon. As it has been pointed out in a previous paragraph, the so-called Hellström effect which occurs only under specific circumstances should be scrutinized more closely. Actually most animal and human data with acute radiation of 4-4.5 Gy did not show a marked drop of cancer mortality rate (Upton, 1961; Kato and Schull, 1982). I think the preferential killing of host suppressor T cells in the dose range around 4-4.5 Gy could not be considered as an inevitable constituent part of the dose-response curve for acute exposures, and it is even more doubtful for chronic irradiation. Therefore, for human cancer induction or mortality the hormesis phenomenon may only be manifest in the region of low doses confined to 10 to 100 times of the natural background. And further epidemiological data are needed even for such a generalization.

Another aspect worthwhile mentioning is the rate of chromosomal aberrations occurring under low level radiation. Most studies, including examination of the inhabitants living in the area of high natural radioactivity in China (Chen et al, 1985) and the atomic bomb survivors in Japan (Awa and Nakano, 1985) as well as other surveys (Wang et al, 1984) disclosed a definite increase of chromosomal aberrations in the peripheral blood lymphocytes. Although "chromosomal damage in an individual exposed to radiation has not been associated with subsequent illness" (Webster, 1981), anyway it stands for definite structural changes of genetic material. Some relate these damages with possible cell transformations. It has been confirmed that under conditions of low level radiation the repair synthesis of DNA might be stimulated, expressed in the form of an increase in unscheduled DNA synthesis (UDS) (Tuschl et al, 1983; Liu et al, 1985; 1986). This may be the result of activation of repair enzymes under low level radiation. The whole picture might be visualized as follows: With such adaptive mechanisms the host may still not be able to properly repair all damages of the genetic material caused by radiation and some transformed cells may appear. If the immune competence of the host is deranged by relatively large doses of radiation, the transformed cells may have a chance to develop into an established tumor. On the other hand, if the immune competence of the host is enhanced by low level radiation, such newly transformed cells may be eradicated or kept dormant by the defense mechanisms, preventing the establishment of a clone of cancer cells. Elucidation of the whole cascade of events

of such mechanisms will be of great importance in consolidating the thesis of hormesis with ionizing radiation and promoting its practical application in health sciences.

The experimental data presented in the paper have clearly demonstrated the "essentiality" of ionizing radiation for proper growth and reproduction of protozoa. If this is proven to be true also for mammals and humans, it could mean that ionizing radiation should be considered as an indispensable element for optimal health. At present such a tentative conclusion can only be drawn by inference.

In concluding, Professor Luckey's paper has clearly illustrated the phenomenon of radiation hormesis in its broad sense by an extensive review of the existing literature and has re-emphasized the concept that low level radiation reasonably above background may not be harmful to human health. The theory of radiation hormesis will undoubtedly promote research in radiation biology and radiation epidemiology. Further confirmation of this new concept with forthcoming radiobiologic and epidemiologic data would influence government standards and regulations and give great impetus to the theory and practice of radiological sciences.

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