

## **Pratzel, Deetjen: Radon in der Kurortmedizin**

Die Wirkung von Radon auf das Immunsystem

*Effects of Radon on the Immune System*

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### **Summary**

As an environmental agent that is toxic at high concentrations, radon can exert a beneficial effect on the immune system when it generates low radiation doses in man. This paper is a brief examination of this effect and considers in particular that produced by low radiation doses and their mechanisms of action. It also analyses the effects found in the study of human populations exposed to low radiation doses and those occurring in people living in areas with a high level of background radiation. Lastly, it deals with the effects on the immune system of patients treated in radioactive spas where radon is the main agent. The analysis of this set of data indicates that radon exerts an effect on the immune system and further experimental and clinical studies are needed to determine the mechanisms producing this effect.

### **Introduction**

Radon ( $^{222}\text{Rn}$ ) is considered the main source of natural radiation in man [UNSCEAR, 1993] with an average annual dose of about 1 mSv. Most of this figure is due to the irradiation produced in the lungs by its daughters, which are retained in respiration.

However, the gas itself may enter the body by several routes, mainly through the pulmonary alveoli, and, thereby, irradiate different bodily organs. This irradiation can be substantial, though always within the low dose range, in people living in areas with a high level of natural background radiation and in patients treated in radioactive spas.

Although the effects of radon, other than causing lung cancer, have received little attention, epidemiological studies [UNSCEAR, 1994] and the results of treatment of patients in radioactive spas suggest that the gas has an effect on the immune system. This effect would be the result of the disintegration of radon and its daughter products in different organs of the body where a dose, because of its low rate, would act indirectly on the cells [Bond et al., 1987; Nagasawa and Little, 1992], through its action on water.

This study will deal with the effects of radon on the immune system in relation to its role as an environmental agent and with a number of phenomena caused by low doses of ionizing radiation.

### **Adaptive response and immune response**

There are several environmental agents which are toxic at high concentrations but which, when acting at low doses, produce cellular responses aimed at improving the cell's ability for adaptation. The environmental agents used to produce this response include ionising radiation, heat, heavy metals and other oxidising agents. Their effect has been tested on a wide variety of cells including lymphocytes, bone marrow cells, spermatocytes, and fibroblasts. The adaptive response is reflected in an increased resistance of the cells to high doses of inducing agent [Shadley et al., 1987] or of others with a similar effect, the latter being termed cross-adaptation [Dominguez et al., 1993].

The first phase of the adaptive response by the cell to radiation includes a higher production

of the proteins involved in the regulation of the cell cycle, cyclins and kinases, greater synthesis of the enzymes responsible for DNA repair, and a greater expression of the genes that induce cell proliferation [Wiencke et al., 1986; Fornace, 1992]. This first phase of adaptive response is studied by using heat as the test agent in the so-called heat-shock model, the most widely used model of response to stress [Welch et al, 1989; Smith-Sonneborn, 1992].

The response to heat shock induces formation of a wide range of proteins, HSP70 and other more specific proteins for each stressor [Boothman et al., 1989]; these result in modifications in the cells, and are expressed as adaptive phenomena such as acclimatisation. The existence of other induced phenomena, such as increased cell division and life span, has led to response to stress being identified with hormesis [Smith-Sonneborn, 1994].

The immune system is responsible for maintaining the integrity of higher organisms by responding to external agents. The specific response of the immune system is based on the action of T cells, lymphocytes developed in the thymus. T lymphocytes include at least the following subtypes: cytotoxic T cells, which respond to cells infected by viruses or tumour cells; T helper cells, which secrete mediators to activate lymphocytes; B cells; macrophages; natural killer cells and the T cells themselves.

Certain phases of the activation process of T lymphocytes in response to recognition of an antigen are known. The binding of the antigen transported by the MHC molecules with the TCR/CD3 complex triggers a chain of bio-chemical processes leading to the creation of two second messengers, IP<sub>3</sub> and DG [Isakov et al., 1986]. These raise the intracellular Ca<sup>++</sup> concentration and active protein-kinases, which in turn leads to the early expression of c-fos gene and later to the expression c-myc, gamma interferon, interleukins 1 and 2 and transferrin, which are essential for T cell proliferation [Karanta et al., 1992].

Similar mechanisms appear to operate as a consequence of the action of low doses of radiation. Experimental studies characterising immune response to radiation implicate intracellular calcium and protein-kinase C, which cause transcription of the c-fox gene and production of interleukin-2 to activate T cells [Zhivotovsky et al., 1988; Ishinara et al., 1993].

### **Effects in animal experiments**

It is well known that high doses of radiation inhibit immune system response. Experiments in mice injected with antigenic sheep red blood cells and then exposed to doses of several Gy show a decrease in the number of splenic plaque-forming cells when compared to unexposed animals [Kennedy et al., 1965].

For low radiation doses, less than 0.1 Gy, there is basic agreement that the immune response is enhanced, and expressed as stimulation of the proliferation of plaque-forming cells [Anderson and Levkovits, 1970; Sado et al., 1988; De Ruyscher et al., 1989].

Interestingly, this stimulation depends on the caloric diet of irradiated animals [James and Makinodan, 1988; Kharazi et al., 1994]. Immune-depressed mice are more sensitive to changes in diet, which appears to support the hypothesis that stress due to continuous irradiation is consistent with an adaptive mechanism for cell renewal and maintenance of mitogen responsive cells.

The explanation of the effects of low radiation doses on T cells appears to lie in the different radiosensitivity of the cell subsets. Mitogen responsive T cells appear to be the main target of radiation, although their numbers are increased by expression of HSP70 [Liu

et al., 1987]. Interpretation is complicated by the metabolic status of the irradiated animals, which can influence response, and by the considerable differences in radiosensitivity between animal strains.

Studies have been performed in mice to determine the effects of X-rays on plague-forming cell ability, mixed lymphocyte reaction, mutagenic stimulation, antibody dependent cell mediated cytotoxicity, natural killer cell activity, interleukine-2 and interferon secretion; these indicators were highest at 0.075 Gy [Liu, 1992]. This type of response is related to a process involving more than one agent [Soto et al., 1996] and is explained by changes that take place in the transduction of signals in T lymphocytes. The process seems to be similar to that postulated for apoptosis, and studies are now investigating how it may be influenced by neuroendocrine factors, since radiation is known to result in decreased serum corticosterone accompanied by a decrease in the adrenocorticotrophic hormone [Liu et al., 1993].

In contrast, there are few experimental studies on the effects of radon on the immune system. Recently, Ma et al., 1996, studied the effect of radon inhalation on superoxide dismutase (SOD) activity in rats. SOD is an antioxidant that catalyses the reduction of superoxide radicals to hydrogen peroxide. It has been successfully administered in the treatment of rheumatoid arthritis [Goebel, 1981], and has an antitumor effect [Yamagushi et al., 1994]. Inhalation of radon significantly increases SOD activity in the liver and kidney four hours after exposure, with a decrease after 16 hours, which suggests that radon acts as a stimulus.

Equally interesting is the report by Nagarkatti et al., 1996, who studied radon inhalation in relation to changes in the immune system of mice. Exposure to high doses resulted in decreases to the total mass of cells in most lymphoid organs, thymus, peripheral lymph nodes and nodes associated with the lungs. The percentage of T cells increased whereas the proportion of all non-T cells decreased. At the same time, radon led to an increased response of T and B cells to mitogens in the spleen and peripheral lymph nodes, which the authors attributed to an indirect effect of irradiation.

### **Epidemiological effects in man**

Epidemiological studies on the effects of low radiation doses on the immune system in humans are numerous in the case of the Hiroshima and Nagasaki bomb survivors. Measurement in peripheral blood of mitogenic response to phytohemagglutinin, of mitogenic response to allogenic lymphocytes, and of interferon production do not differ significantly from control measurements, but a significant difference is seen in natural cell mediated toxicity [Bloom et al., 1988]. Results from other studies on this type of population are also inconclusive [Schull, 1996].

The effect on the immune system in workers exposed to radiation has been studied by Tucht et al., 1995, who measured a series of immunologic parameters in groups of subjects exposed to low doses of external gamma radiation and internal irradiation with tritium. The results confirmed a differential sensitivity in the different cell subsets, with CD8 positive suppressor T cells proving the most radiosensitive in peripheral blood. An inverse correlation was observed between the total number of T cells and the number of S phases occurring after stimulation. The results seem to agree with those of Makinodan and James, 1990, which would support the notion of a potentiality of the immune response by an effect of selective cell renewal.

Other epidemiological studies with radon as one of the main agents have been carried out

on inhabitants of regions with high background levels of natural radiation. In many such regions, radium ( $^{226}\text{Ra}$ ) is abundant in the soils. It causes external irradiation and internal irradiation due mainly to inhaled radon and that present in water supplies [Hanson, 1984]. Epidemiological studies of the effects of radon on populations in areas with high background radiation attempt to determine whether lung cancers is induced by retention of radon daughters in the lungs. The fact that this effect has been observed in populations of miners [ICRP, 1993] has largely overshadowed the study of other effects.

However, the relationships between radon and lung cancer and between radon and other types of cancer are, in many studies, contrary to that is expected. Thus, the study by Nambi and Soman, 1987, showed an inverse correlation between irradiation and the rate for lung cancer in an area with high background radiation in India. Similarly, the studies of Frigerio and Stowe, 1976, Zahi et al., and Cohen, 1987, reported increased resistance to infection, an increase in longevity, and a lower death rate for cancer in populations exposed to high natural background. Both Cohen, 1994, and Pollycove, 1994, have reviewed the effects in these regions and those due to indoor radon, and these authors question the established paradigm [Luckey, 1980; Sagan, 1994].

The above results appear to indicate an action by radon on the immune system. Although the role played by the immune system in the natural history of cancer is not known [Adams et al., 1992], leukocytes grown in vitro in the presence of the cytokine interleukin-2 are known to acquire the capacity to kill tumour cells. Low radiation doses have also been used in animal experiments to enhance the effect of immunisation in order to reduce tumour growth in induced fibrosarcoma or Lewis sarcoma [Miyamoto and Sakamoto, 1987; Li et al., 1993]. Low-dose radiation has also been used to treat patients with non-Hodgkin's lymphoma, with a high proportion of tumours showing partial or total remission [Takai, 1992].

The effects on the immune system of low radiation doses over a prolonged period of time have been measured in two areas in Guandong, China, one with low background radiation and the other with high background [Yao et al., 1993]. In both cases, the proportion of cells secreting interleukin-2 found in peripheral blood lymphocytes was measured in the inhabitants of the regions divided into age groups. The results indicate that the number of these cells is significantly higher in people living in the area with high background radiation, thus demonstrating the potential effect on the immune system.

### **Effects in radioactive spas**

The so-called radioactive spas provide an excellent opportunity to study the effects of radon on the immune system in man. Radon in the spas water is the main source of radiation for patients and for staff. The effects on these people must, therefore, be due to radon.

Radon in water supplies results in high radon concentrations in spa water and air [Kobal and Reiner, 1987; Soto et al., 1995]. By different routes, depending on the type of treatment, the radon enters the body and is dissolved in the bodily organs [Gosink et al., Pratzel, 1993]. The energy produced by the disintegration of radon and its short-lived daughters generates an ionisation with production of oxidising radicals that act on the cells of the organs.

There is general agreement on the effects produced in radioactive spas. Waters with radon are considered to have analgesic, anti-inflammatory properties and others regulating neurovegetative balance [Armijo and San Martin, 1994]. Therapy with these waters is indicated in a range of complaints affecting the cardiovascular, respiratory and digestive

systems, rheumatic processes, allergic conditions and skin diseases [Bogoljubow and Andrejew, 1994; Davydowa et al., 1994]. The action of radon on some of these conditions seems to be associated with the effect exerted by radiation from the radon dissolved in the endocrine organs, which results in modifications in hormone production.

Among the conditions that have been treated in radioactive spas with greatest success, several - rheumatoid arthritis, bronchial asthma, psoriasis - are described as being of autoimmune aetiology. They are characterised by an excessive response of the immune system, which is made to attack the individual's own cells. Many results of treatment of this type of condition demonstrate a recovery of the status of the immune system. This is the case with bronchial asthma [Marshalick and Fenko, 1991], the most effective being treatment of atopic asthma, and with intestinal dysbacteriosis [Marshalick and Shkolenko, 1993], where there is a long-term positive effect on the immune system affected.

There is no complete explanation of the effect of radon in spas on the immune system [Scheminzky, 1965; Gusarov and Obrosof, 1971]. However, the most favoured hypothesis is that it is mediated by the neuroendocrine system, stimulation of the suprarenal glands by the hypophysis, rather than a direct action of radiation on the T cells. According to this hypothesis, irradiation with radon inside the body would act on the neurosecretory cells and lead to hormonal changes, which would then act on the different T cell subsets. This explanation is consistent with the hypothesis of Liu et al., 1993, for the effect of the lymphoid tissue blood vessels, which are mediated by hypothalamic hormonal factors, and is conditioned by the role of previous caloric diet.

## **Conclusions**

From all this evidence we can deduce that radon does act on the immune system. At cell level, the action of radon appears to result in a certain adaptive response to the environmental agent whereas, at organ level, it produces a lymphocyte response. Although there are only a few studies on the subject, we consider that the existence of an immune response to radon is indicated by the fact that such a response is produced by low doses of other ionising radiation, as demonstrated both in animal experiments and in studies on irradiated human populations. The action of radon seems clear in the case of inhabitants of regions with high background radiation where radon is the main agent and where effects are observed that seem typical of immune system involvement. Finally, there is good evidence for the response of the immune system in patients treated in radioactive spas, in whom the response is restored, and treatment is indicated for a variety of conditions.

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