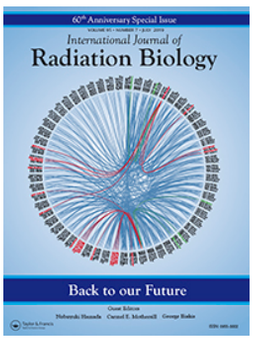

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REVIEW

Radiobiology at the forefront: Hanns Langendorff and two of his disciples

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ABSTRACT

Hanns Langendorff (1902–1974) was an eminent radiobiologist and a visionary, who not only helped found the field, but also made significant scientific contributions. He was a member of the first editorial board of IJRB and actually published a paper in its first issue about the radioprotector 5-hydroxytryptamine. Langendorff started working in the field of radiobiology in 1929 and became director of the 'Radiologisches Institut' of Freiburg University in 1936. His studies impressively show the development of radiobiology over decades in areas such as radiation-induced cell death at various stages of development, as well as radiosensitivity of sea urchin, yeast and mammals. Using mice, Langendorff made many early discoveries about spermatogenesis, hematopoiesis, prenatal development, chromosomal damage and metabolic pathways after exposures to X-rays and neutrons. He also investigated aspects of target theory and dosimetry and developed personal dosimeters using films. After the atomic bomb catastrophes in Japan, Langendorff and his collaborators soon began research in mice related to acute radiation sickness and stimulated the development of radioprotectors by studying their mechanisms of action associated with cell death, as well as cellular and metabolic changes involved. Langendorff also trained a cadre of young scientists who advanced the field and brought it to its golden age in the seventies and the eighties. Research activities of two of his disciples are reviewed: Ulrich Hagen and the author. Both made significant contributions: Hagen mainly studying DNA-damage and repair in vitro as well in cells and the author investigating metabolic processes, cellular and chromosomal damage, prenatal effects, genomic instability, individual radio-sensitivity and their connections to cancer therapy.

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Introduction

The letter of 'Invitation to contribute to the special 60th Anniversary Issue of IJRB' stated: 'We envision a Review paper from you covering the topic of the activities of Langendorff. … However, you have full freedom to divert regarding actual content as you deem appropriate!') Hanns Langendorff (1902–1974) has been an eminent radiobiologist of the last century. After completing radiological studies in 1929 at the Katharinenhospital in Stuttgart, Langendorff became director of the 'Radiologisches Institut', University of Freiburg im Breisgau in 1936, a position he held until 1971. He was member of the first Editorial Board of the 'International Journal of Radiation Biology and related studies in Physics, Chemistry and Medicine'. In fact, the Journal published in its very first issue a paper entitled '5-Hydroxytryptamine as a Radiation Protective Substance in Animals' by Langendorff et al. (1959a). This research on biogenic amines, especially 5-hydroxy-tryptamine, opened at that time a new field of study investigating very effective radioprotectors.

Hanns Langendorff took up earlier experimental radiological activities and founded the Radiological Institute at the University of Freiburg with high international reputation, staffed with scientists covering diverse disciplines related to radiation research. This environment fostered a broad spectrum of studies in radiobiology and radiological protection, very similar to the scope of IJRB. When reviewing the activities of individual scientists, it is always relevant to consider their legacy in the form of scientific continuity reflected in the activities of pupils. Thus, this article will take the reader back to studies of radiation research and radiological protection over several decades of the twentieth century using as compass the example of Hanns Langendorff.

The 60th Anniversary of a scientific journal is certainly an appropriate time to look back for the foundations on which our present understanding of the field is based. After this exciting journey, the activities of two disciples of Hanns Langendorff will be briefly described, who built on his legacy and made significant research advances in the field: Ulrich Hagen and the author.

Research of Hanns Langendorff in radiobiology and radiological protection

The beginnings in the field of radiobiology in Stuttgart

After studies of Botany and Genetics at the University Jena, Langendorff started, his radiobiological research in 1929 at

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the Roentgeninstitut of the TH Stuttgart under the directorship of the physicist Richard Glocker, a former assistant of Wilhelm Conrad Roentgen. The Institute had a strong collaboration with Otto Jüngling, surgeon and radiologist of the large Katharinenhospital in Stuttgart. Thus, Langendorff was soon confronted with problems of radiotherapy and dosimetry for radiological protection. He studied the effects of different X-ray doses on cell proliferation in Vicia faba equina (Jüngling and Langendorff 1930). The mitotic rate and the number of damaged mitoses were measured after X-ray exposure over a wide range of doses between 40 and 550 R[1]. Several 'mitotic waves' were observed up to 19 days after exposure. At low radiation doses the first wave of mitoses appeared early, but with increasing dose, significantly stronger delays were observed. Together with the clinician Jüngling, Langendorff also investigated the effects of dose fractionation on cell proliferation in Vicia faba equina. It was observed that the radiation effect was dependent on the mitotic cycle. Furthermore, it was observed that mitotic cells showed radiosensitivity widely different from resting cells (Jüngling and Langendorff 1932).

The germ cells of sea urchin, a very radiosensitive biological system, was studied by Langendorff together with his wife (Langendorff and Langendorff 1931). Margarethe Langendorff, also a biologist, had a very close scientific collaboration with Hanns Langendorff until his retirement in 1971 in Freiburg. During these years, biological effects were also investigated after exposure to X-rays of different wavelengths (energies). Thus, algae were irradiated with X-rays of wavelengths 0.56 Å and 1.54 Å and it was found that shorter wavelengths (higher LET) exert effects stronger by an almost factor of 2 (Langendorff et al. 1933).

During his time in Stuttgart, Hanns Langendorff also started his first experiments with mice. Again, he chose sensitive organs and organ systems in these studies of mammals: he investigated the effects of X-rays on spermatogenesis, where he studied the cellular behavior in the gonadal channels after doses between 20 and 500 R (Langendorff 1936a), as well as on the formation of reticulocytes after exposures to 100–200 R (Langendorff 1936b). These experiments were continued in Freiburg with fractionated irradiation and followed by studies of recovery processes (Langendorff 1937).

Thus, Langendorff focused during his early years of radiobiology research on questions of great scientific interest, many aspects of which remain unanswered even today: mechanisms of cell proliferation, mitotic (cell) cycle, dose fractionation, inherent radiosensitivity, biological consequences of radiation such as cell death, chromosomal damage, recovery from radiation damage and most importantly the dependence of many of these effects on radiation quality.

Starting as director of the 'Radiologisches Institut' in Freiburg

In 1936, Langendorff moved to Freiburg University as the director of the 'Radiologisches Institut', the oldest Institute for radiation research in Germany. Hanns Langendorff established there several strong working groups, as well as an inbred mouse colony. His wife Margarethe Langendorff took important responsibilities for the mouse colony. Langendorff continued to study reticulocytes in mice after X-ray exposures. He concentrated on the effects of dose fractionation (Langendorff 1937) and began histological investigations of bone marrow in mice (Langendorff and Papperitz 1939). During this period Langendorff also started to work with transplanted cancers on mice in order to improve cancer therapy. The tumors were treated with X-rays (2000 R) in combination with microwaves (Langendorff and Langendorff 1942). The increase of tumor temperature achieved with this microwave treatment was around 2 °C. The sequence of administration of microwave treatment and X-rays was also studied in detail and it was observed that microwave treatment directly before irradiation gives the strongest tumor response. These studies may be the first to demonstrate a strong radiosensitization by a combination of ionizing radiation with hyperthermia for the treatment of cancer. As we know, the field of hyperthermia was advanced through many stages by many radiobiologists in the seventies and the eighties and remains even today an option in the treatment of cancer in some centers, especially for palliative care.

Langendorff also investigated intensively the mechanisms of radiation action in different eukaryotic cell systems. In cells of Salamandra maculosa he investigated chromosomal damage and cell death and concluded:

> *Eine bestrahlte Zelle wird sich daher stets deutlich von einer unbestrahlten unterscheiden, selbst dann, wenn das Erscheinungsbild, wie z.B. bei der Ruhezelle, dem der normalen Zelle gleicht. Dieser Unterschied wird so lange bestehen bleiben, bis der Tod oder eine vollständige Erholung der Zelle vom Strahleninsult eingetreten ist, was unter gewissen Umständen möglich erscheint.* (An irradiated cell will always differ from a non-irradiated cell, even when it has the same appearance, e.g. in a resting cell. This difference will persist until cell death or full recovery from radiation damage has occurred; indeed the latter appears possible under certain circumstances.) (Langendorff 1943).

Thus, Langendorff postulated cell recovery on the basis of his experimental data already in 1943. He also observed bridges between chromosomes in metaphase and the formation of micronuclei. Langendorff discussed the radiation effect 'cell death' as a change or even loss of regulatory processes in the cell nucleus. In further experiments Langendorff (1949) studied the cellular radiosensitivity during the different mitotic phases and observed the highest sensitivity during the prophase, just at the moment when cells enter mitosis.

From the beginning of his studies in radiation research, Langendorff also showed strong interest to elucidate the primary processes of radiation action. To this end, dosimetric problems had to be solved. At the Institute in Freiburg, Langendorff met the theoretical physicist Kurt Sommermeyer with whom he collaborated on research about the question of how many ionizing radiation hits are required to generate measurable effects in the eggs of drosophila flies (Langendorff and Sommermeyer 1940). The

authors reported an exponential dose-effect curve for the killing of drosophila eggs after exposure to X-rays and concluded that one hit is sufficient. These studies were of great interest in the development and evolution of the target-theory.

In November 1944 intensive bombing completely ruined the Institute. Langendorff and a technician, Mrs. Seiter, collected the few surviving mice in the ruins and took them to Heiligenberg near Lake of Konstanz, where he founded, together with a biochemist and a biologist specializing in developmental biology, the 'Heiligenberg-Institut für Experimentelle Biologie'. The mouse strain 'Heiligenberger-Mice' was thus generated and used for several decades in many experiments in the Heiligenberg-Institut, as well as in the re-built Radiologisches Institut, Freiburg. This mouse strain was also used in the Institute for Medical Radiobiology at the University Essen later, as well as in several other laboratories as far away as Japan. All these activities demonstrate the enthusiasm of Hanns Langendorff for his work, as well as his determination to move things forward and succeed.

In a commemoration-lecture, which Hanns Langendorff gave on the occasion of Roentgen's 105th birthday (Langendorff 1950), he summarized some thoughts about the radiobiological knowledge on cellular effects, especially cell death after exposures to ionizing radiation. Langendorff came to the following conclusions:

- The nucleus is the most radio-sensitive structure of the cell. Significant changes of the 'protoplasma' (cytoplasm) occur only after much higher radiation doses. The highest radiosensitivity is observed in the phase of the preparation for mitotic cell division, especially during the prophase of mitosis. This is most important for clinical treatments.
- Quite often it can be seen that the radiation damage is not expressed directly in the irradiated cell. After exposure of sea urchin eggs the further development appears during the next cell generations apparently quite normal until, e.g. in the gastrula stage the development suddenly stops and the embryo dies.
- This radiation effect can be described as a 'somatic mutation'.
- After an exposure to smaller doses the effects can be reversible. This can be seen e.g. for the synthesis of ; 'Thymonukleinsäure' (DNA), which is inhibited for a limited time after such doses.

One has to realize these ideas were brought forward in 1950, three years before the helical DNA-structure was solved and several more years before any thoughts of DNA-repair, or even decades before data on genomic instability were published.

The atomic bomb catastrophes enhance the focus on radioprotectors

After the atomic bomb catastrophes in Japan, there was strong public and political pressure for the development of indicators of radiation damage, effective radioprotectors and adequate clinical management of the acute radiation syndrome. To this end, peripheral blood cells, especially lymphocytes, as well the spleen cells were studied as means to increase mouse survival after irradiation (Langendorff 1953; Langendorff et al. 1954a, 1954b; Langendorff, Koch, Sauer 1954). Further experiments investigated the effect on mouse survival of bone marrow transplantation after whole body irradiation. Surprisingly, it was shown that the therapeutic effect was quantitatively different in two mouse strains investigated (Langendorff et al. 1958).

In the field of radioprotectors chemical compounds with a sulfhydryl group generated enthusiasm in the fifties, mainly based on the results of radiochemical experiments performed with proteins, tested often in aqueous solutions. It was assumed that these substances protect sulfhydryl residues in proteins and that they generally act as radical scavengers (Patt 1953; Bacq and Alexander 1955; Eldjarn and Pihl 1956). The number of studies on the topic increased exponentially during that period. Thus, Kimball (1959) wrote in a report about the first International Congress of Radiation Research in Burlington 1958 in his report in the first issue of this journal: 'A considerable number of papers dealt with chemical protective agents.' Indeed, in the first issue of the Journal three of the nine original articles published, dealt with the topic of chemical radioprotectors. However, in contrast to the general trend towards sulfhydryl containing substances, two of the articles dealt with amines: van der Meer and van Bekkum (1959) with histamine and Langendorff et al. (1959a, 1959b) with 5-hydroxytryptamine. Amines and especially 5-hydroxytryptamine, gained particular interest in the field as they showed high radioprotective activity, despite the fact that they do not contain sulfhydryl-groups. In fact, regenerating processes were well protected by amines, as it was clearly shown for the recovery of DNA synthesis by 5-hydroxytryptamine injected into the mice just before irradiation.

In contrast to the general enthusiasm with sulfhydryl containing substances as radioprotectors, Langendorff's group showed that the radioprotective effect is limited only to a small group of sulfhydryl substances. The best protection was seen with cysteine and cysteamine, and a somewhat smaller effect was observed with homocysteine. A much larger group of sulfhydryl containing substances did not show radioprotection at all (Langendorff et al. 1954a, 1954b; Langendorff, Koch, Sauer 1954. The group concluded that physiological processes play an important role in radioprotection by these substances. Along these lines it was striking that splenectomy or gonadectomy significantly increased mouse survival after whole body irradiation. When mice were irradiated 3 months after gonadectomy and cysteamine was given just before irradiation, maximum radioprotection was found. As the effects of these treatments were additive, it was concluded that two different mechanisms were active (Langendorff et al. 1957). On the other hand, cysteamine was found much less efficient in combination with fractionated irradiation than with acute radiation exposure (Langendorff and Catsch 1956).

These observations and some preliminary studies showing radioprotective effects by central-nervous acting substances (Langendorff et al. 1957) led Langendorff to the idea that regulatory amines, especially 5-hydroxytryptamine (5-HT) (serotonin), might be good radio-protecting agents. Results of these studies are presented in the paper, which was published in the first issue of this Journal (Langendorff et al. 1959a, 1959b). Here, the survival of female mice was somewhat higher than that of male mice, but the dose modifying factor (DMF) for the $LD_{50/30}$ was the same for both genders (1.84 for female and 1.85 for male mice). The effect of 5-HT was higher than the effects of all other radioprotective agents known at that time. Therefore, further experimental work on radioprotective substances in the Institute was very much focused on 5-HT and the elucidation of the underlying mechanisms. For the best effects 5-HT had to be injected intraperitoneally 5–15 minutes before irradiation. When radiation exposures were repeated three times with an interval of 30 days in between, maximum radioprotection by 5-HT was always observed (Langendorff et al. 1959a, 1959b). On the other hand, oral administration of the substance showed no radioprotective effect.

A great challenge for the group was to elucidate the mechanism of 5-HT. 5-HT is formed from 5-hydroxytryptophan (5-HTP) by a decarboxylase which needs pyridoxal-5-phosphate (Pyr-5-P) as co-enzyme. Therefore, various substances participating in this enzymatic process were tested to determine whether they had radioprotective action. Indeed, it was observed that 5-HTP, Pyr-5-P as well as ATP, given alone, have only a weak protective effect. However, when these substances were injected together into mice before irradiation, a strong radioprotective effect was observed that was comparable to the effect by 5-HT alone (Langendorff et al. 1959b). The strongest protective effect was observed when 5-HT was included in the cocktail instead of 5-HTP. In these experiments the resulting DMF for the $LD_{50/30}$ was 2.2 after the irradiation of Heiligenberger mice (Langendorff et al.1960). Shortly before these observations were made, it was shown that the radioprotective effect of 5-HTP was inhibited when an inhibitor of the 5-HTP-decarboxylase was injected 60 minutes before the injection of 5-HTP. This experiment, elegantly demonstrated that 5-HT was the active principle for 5-HTP as a radioprotector (Langendorff et al. 1968).

An interesting development in the field was the observation that adenosine and all adenosine-mononucleotides had a radio-protective effect against X-rays, and that in combination with 5-HT this effect was increased. The combination of 5-HT plus 2-AMP showed the highest effect on mouse survival with a DMF of 2.36 (Langendorff et al. 1962). It was well-known at the time that X-ray exposures cause a strong decrease of lymphatic cells in the spleen and thymus. Notably, injection of 5-HT before the irradiation did not influence this initial decrease of the cell number in these organs, but promoted the regeneration of the tissue (Langendorff and Hagen 1962; Abe and Langendorff 1964). An analogous situation was observed with the mitotic rate and chromosomal aberrations in the bone marrow of mice. The number of mitoses decreased rapidly after X-irradiation alone, as well as in combination with 5-HT, but the regeneration occurred earlier when 5-HT was injected before irradiation. On the other hand, 5-HT showed no effect on chromosome damage in bone marrow cells (Langendorff and Shibata 1965), an effect which was in agreement with the investigations of Chaudhuri and Langendorff (1968). However, studies with bone marrow of rats showed that radiation-induced chromosomal aberrations could be suppressed by the injection of the protector AET (Chaudhuri and Langendorff 1968).

In victims of the atomic bombs in Japan, it was observed that the number of deaths was higher when radiation exposure was combined with skin burns or other wounds. In the fifties and sixties the public in Europe and especially in Germany, were very much concerned about a possible war using atomic weapons. Therefore, there was a strong desire to study, besides radio-protectors, also severe radiation damage including combined effects with other insults. Langendorff et al. (1964) had reported that the mortality of X-irradiated mice was considerably enhanced when a skin wound (removal of ~5% of the skin) followed the X-ray irradiation 2 days later. 5-HT had no protective effect against such combined damage, whereas histamine, cysteine and cysteamine did protect. These data clearly showed the different mechanisms of the latter compounds in comparison with 5-HT (Langendorff et al. 1965).

In the sixties, several groups investigated whether the injection of RNA after exposure to ionizing radiation would have a therapeutic effect. The results were contradictory and led Langendorff to start such experiments using yeast RNA preparations made available by JP Ebel, Laboratoire de Chimie Biologique de la Faculte des Sciences, Strasbourg, France. Such RNA preparations gave a protective effect when injected 3 h before X-irradiation and also when the RNA was injected 6 h after X-irradiation. These RNA preparations showed an effect with prophylactic, as well as with therapeutic treatments, which was quite extraordinary (Ebel et al. 1969).

The last experimental work with chemical radioprotectors carried out by Langendorff was connected to the radioprotective effect of cyclic-3-5-AMP. A good radio-protective effect was found with this interesting substance. Langendorff (1970) concluded:

> *Zwischen dem Zeitpunkt der Verabreichung einer Schutzsubstanz und dem ihrer größten Wirksamkeit liegt regelmäßig ein Zeitraum von wenigstens einigen Minuten bis zu mehreren Stunden. Wir schließen hieraus, dass während dieser Latenzzeit die Aktivierung der Rezeptoren, die Stimulierung des Adenylcyclase-Systems und die Umwandlung des ATP zu 3'-5'-AMP in verstärktem Maße erfolgt.* (Between the time of application of the radioprotective substance and its highest efficiency, there exists generally a time of several minutes up to several hours. We conclude therefore that during this latency period the activation of receptors, the stimulation of the adenylcyclase-system and the transformation of ATP to adenosine-mono-phosphates occurs at an increased rate.).

In his last paper in the International Journal of Radiation Biology Langendorff and Langendorff (1971) concluded:

> We assume that the protective substance is first transported to the effector cells. Here the drug interacts with regulatory sub-units or receptors (facing the extracellular fluid) of the membrane-bound adenyl-cyclase system, which has catalytic sub-units in the interior of the effector cell. This interaction between the receptors and the protective substance leads to an activation of the adenyl-cyclase system, the function of which is to convert ATP into adenosine 3′, 5′-monophosphate (c AMP). The activation of this enzyme system results in an increase of the level of c AMP in the effector cell.

This was written in 1971. It certainly sounds visionary for the time and is quite in line with current work on receptors localized on the cell membrane.

The intensive studies on radio-protective substances were mainly published in the journal 'Strahlentherapie' (today 'Strahlentherapie und Onkologie') in a series 'Untersuchungen über einen biologischen Strahlenschutz' (Investigations about a biological radiation protection). In total, 85 original papers were published in this Journal during the period 1954–1968 by members of the 'Radiologisches Institut'.

Further activities in embryology, dosimetry and education

Although work on radioprotectors occupied a large part of Langendorffs scientific activities, Langendorff was always fascinated by very radiosensitive processes in living organisms and devoted a considerable amount of effort. Thus, early on in the 1930s Langendorff studied sperm development in mouse testicle in corollation with the rhythmic changes of spermatozoa divisions (Langendorff 1935, 1936a, 1936b). Later the fertility of mice was studied after small radiation doses of 2.5 R per day. A decrease of fertility was observed after 200 days, but interestingly in those mice that remained fertile, the litter size was not decreased as compared to un-irradiated animals (Langendorff and Langendorff 1954).

His group also studied radiosensitivity during prenatal development in mice. These studies focused on the effects of radiation during organogenesis. The induction of anatomical malformations is extremely high during this prenatal phase and the types of malformations generated were studied in great detail. It was interesting that malformations of the eyes, the brain and the ventral fissure (gastroschisis) had their maximal occurrence after exposures during early organogenesis, while malformations of the limbs and tail were observed mainly at the later phase (Kriegel, Langendorff, Kunick 1962, Kriegel, Langendorff, Shibata 1962). In the fifties and sixties the environmental contamination with the radioactive nuclides of cesium (^{137}Cs) and of strontium (^{90}Sr) became considerable in Germany and other countries, from the fallout of atomic bomb tests in the atmosphere. Thus the uptake of these radionuclides through the drinking water was studied during prenatal development. The uptake of ^{90}Sr was especially critical, as its retention and biological half-lifetime are high owing to incorporation into the developing bone (Langendorff and Kriegel 1964). Such studies on the risks from environmental radioactive contaminations, generated strong public protest against the nuclear tests that culminated in the agreement between the Soviet Union, the United Kingdom and the United States of America in 1963 to abandon nuclear tests in the atmosphere.

With respect to radiological protection it was very important that Langendorff together with Wachsmann, developed the personal dosimeter with films, which was used for several decades to control the radiation exposure at the workplace for each individual worker. These film badges were and are still used in many countries (Langendorff et al. 1952; Langendorff and Wachsmann 1953, 1954). This methodology is now increasingly substituted by thermoluminescence dosimeters. Langendorff formed a working group in Freiburg assigned to the monthly evaluation/reading of these film dosimeters from many regions in Germany and extended their use to neutron exposures.

It has already been pointed out that besides familiar also a close scientific collaboration existed between Hans and Margarethe Langendorff. Further Margarethe Langendorff cared for the social life in the 'Radiologisches Institut'. She always tried to calm down the situation if any misunderstanding arose. The couple was a solid unity. Margarethe Langendorff was a strong supporter for her husband and a 'Mother of the Institute Family' (Figure 1). Besides Hanns Langendorff there lived two other prominent German radiobiologists/biophysicists at that time: Boris Rajewsky and Karl G. Zimmer. Rajewsky and Langendorff had very close contacts in advisory committees for the German government. Figure 2 shows these two scientists when Rajewsky visited Freiburg 1964 on the occasion of the 50th anniversary of the Radiologisches Institut. The contact with K. G. Zimmer who had to stay during the period 1945–1955 in the Sowjet Union was less. Boris Rajewsky had a very broad spectrum of scientific interests with many disciples, e.g. Otto Hug, Dietrich Harder, Wolfgang Pohlit. K. G. Zimmer was very well-known for his genetic studies together with Timofeev-Resovskij. A prominent disciple is Horst Jung.

Hanns Langendorff enjoyed very much to have excellent scientists visiting the institute. For many years the Nobel Laureate Georg Karl von Hevesy, Stockholm and the Regius Professor Joseph Mitchel, Cambridge came for several weeks during the summer to the Radiologisches Institut. Further visitors were Professores Hedi Fritz-Niggli (Figure 3), Zürich, Zenon Bacq, Liege, Michel Ebert Manchester. Langendorff always supported and promoted his younger coworkers. Indeed, eight young scientists of the 'Radiologisches Institut' received the academic degree of 'Habilitation', which vested them with the right to teach at a University and is an important step towards becoming University Professor. Besides his scientific merits Langendorff also could be a good communicator with a glass of wine and giving jokes in the typical Saxonian dialect which he, born in Dresden, had inherited perfectly.

When Hanns Langendorff died in January 1974 his wife Dr. Margarethe Langendorff continued with the evaluation of such dosimeters with a specialized working group outside the institute. She continued this work until 1986, when the

Figure 1. Margarethe and Hanns Langendorff in the ceremony for the 50th Anniversary of the Radiologisches Institut Freiburg.

Figure 2. Hanns Langendorff and Boris Rajewsky: Rajewsky after a speech at the ceremony for the 50th Anniversary of the Institute handing over a document to Langendorff.

German Government decided to assign these evaluations to state offices. With the money earned from this activity, the Hanns Langendorff Foundation was established, aiming to promote young radiation researchers. This was a special wish of Hanns Langendorff, who always promoted his younger coworkers. Indeed, eight young scientists of the 'Radiologisches Institut' received the academic degree of 'Habilitation', which vested them with the right to teach at a University and is an important step towards becoming University Professor.

After the atomic bombings of Hiroshima and Nagasaki, Hanns Langendorff felt it was his duty not only to perform basic scientific research on the effects of ionizing radiation, but also to distribute this knowledge to the public and to teach and train, especially medical doctors, on the medical aspects of radiological protection. Thus Langendorff initiated with the support of the German Red Cross courses for medical doctors in the 'Radiologisches Institut Freiburg' in order to educate them on the acute radiation effects, protection options, including de-corporation of incorporated radionuclides and several other therapeutic measures. These courses took place in the 'Radiologisches Institut', but faculty from internal medicine and surgery in Freiburg, as well as well-known scientists from abroad, like Professor Hedi Fritz-Niggli, radiobiologist, Zürich University, participated regularly. These courses were the first courses of this type in Germany.

Epilogue

Langendorff was a consultant to the German government and to EURATOM. In addition to his membership on the editorial board of International Journal of Radiation Biology, Langendorff was member of the editorial board for several other scientific journals. For his extraordinary achievements, Hanns Langendorff received several academic honors: the doctor degree honoris causa of the University Marburg, the governmental honor of 'Großes Verdienstkreuz des Verdienstordens der Bundesrepulik Deutschland' and numerous international distinctions. Although Hanns Langendorff was awarded the honorary citizenship of Tokyo, in the eyes of the Japanese, the invitation to a private audience by the Emperor Hirohito (to visit the private laboratory of the biologist Hirohito) was the greatest achievement of all.

The above outline abundantly demonstrates that Hanns Langendorff and the activities of the 'Radiologisches Institut Freiburg' covered a wide field of research topics from basic radiobiological mechanisms to cancer therapy (Figure 4) and radiological protection (Figure 5). In all these areas it achieved the highest scientific standards and reached an outstanding reputation. Langendorff was deeply engaged in his scientific work and felt privileged as the leader of an efficient and productive academic Institute (**his** Institute). From this position, he also demonstrated a strong sense of responsibility to translate the knowledge he helped generate to human well-being.

The research activities of Ulrich Hagen

After completing studies in biology and medicine, Ulrich Hagen started in 1953 radiobiological research in the 'Heiligenberg Institut' and joined in 1961 the re-built 'Radiologisches Institut' in Freiburg. Hagen joined the program of radioprotectors and focused on sulfhydryl compounds as outlined above (Langendorff et al. 1954a, 1954b; Langendorff, Koch, Sauer 1954). However, early on, Ulrich Hagen began to study biochemical processes like DNA-

Figure 3. Hedi Fritz-Niggli, Professor for Radiobiology, Zuerich Iniversity as a visitor in the Radilogisches Institut with Hanns Langendorff and two of his disciples (J. Berndt, left and C. Streffer, right).

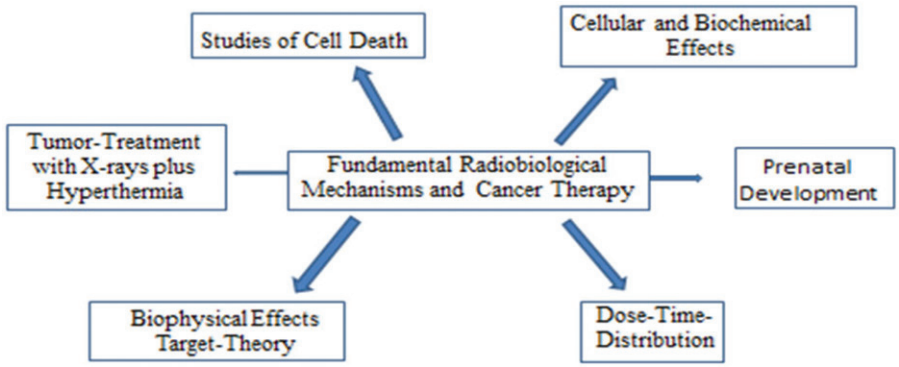

Figure 4. Topics of scientific investigations in the 'Radiologisches Institut' University of Freiburg (Director Professor Hanns Langendorff) 1936–1971 for fundamental radiobiological mechanisms and experimental cancer therapy.

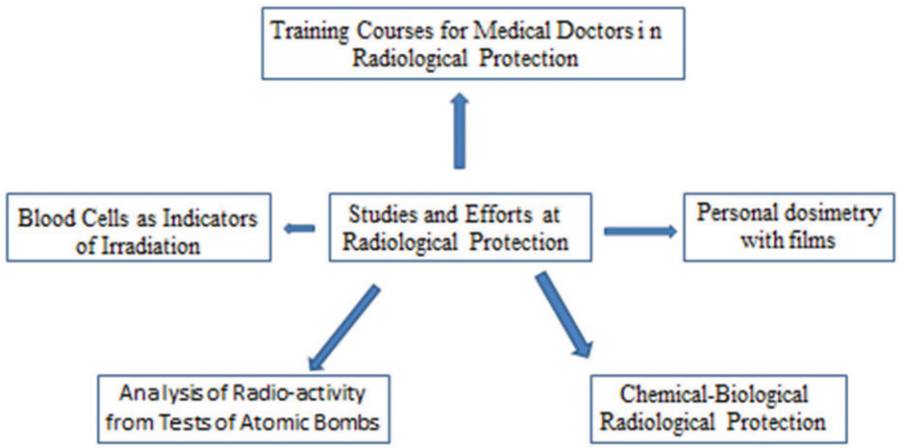

Figure 5. Topics of scientific investigations in the 'Radiologisches Institut' University of Freiburg (Director Professor Hanns Langendorff) 1936–1971 for studies and efforts at Radiological protection.

synthesis by measuring incorporation of ^{3}H-thymidine in spleen, liver and regenerating liver. Hagen et al. (1958) reported a rapid decrease of DNA-synthesis after X-irradiation, especially in spleen and regenerating liver. The effect was smaller in normal liver. In adult animals, normal liver protection against DNA synthesis inhibition could be

achieved by cysteamine. Surprisingly, cysteamine exerted no radioprotective effect in the spleen and or the regenerating lever. Hagen et al. (1958) came to the conclusion that cysteamine protects resting cells stronger than proliferating cells.

From these experiments Ulrich Hagen, as well as other investigators, concluded that DNA in the thymus was damaged after whole body irradiation of rats; indeed he observed that increasing amounts of DNA could be extracted several hours after irradiation from the organ with increasing radiation dose (in the range of 50–800 R) (Hagen 1960). In further investigations Hagen irradiated purified DNA after exposures to 70–420 kR and observed a shift of the UV-spectrum at 260 µm. Hagen interpreted his effect as 'breakage' of hydrogen bonds in the DNA (Hagen 1962). When an aqueous solution of calf thymus DNA was exposed to 500 R its viscosity decreased dramatically. This effect is apparently due to strand brakes in the DNA (Hagen 1963). It was consequent then to study the amount of mRNA, which was synthesized on DNA by RNA polymerase after radiation exposure and it was found that the amount of mRNA was reduced (Zimmermann et al. 1964). Further experiments of this kind resulted in the finding that the number of RNA molecules generated from γ-irradiated DNA was almost the same as that from un-irradiated DNA, whereas the chain length of the synthesized RNA was shorter (Hagen et al. 1969, 1970). Hagen et al. (1969) analyzed these data and came to the conclusion that breaks forming in the template DNA strand after irradiation reduce transcription. He could calculate that the number of transcription stopping places is about the same as the number of strand breaks. Notably, sites of base damage had apparently no influence on this process (Hagen et al. 1970). In 1965 Ulrich Hagen moved from Freiburg to the 'Institut für Strahlenbiologie' at the Nuclear Research Centre Karlsruhe under the directorship of K.G. Zimmer.

In Karlsruhe, Ulrich Hagen and his group developed methods to determine single strand breaks and double strand breaks in irradiated thymocytes from rat thymus (Lücke-Huhle et al. 1970). Linear dose-effect-relations were observed for the production of single strand breaks, as well as for double strand breaks in a dose range from 0.5 to 5 Mrad (Hagen 1973). From these data Hagen (1973) calculated that a radiation exposure of 100 rad induces in one cell about 340 single strand breaks and about 19 double strand breaks. Furthermore, Hagen estimated that the number of base damages was by a factor of about two to three higher than the number of strand breaks in the irradiated DNA. Notably, Hagen also concluded from these data that irradiated cells process single strand breaks very quickly (Hagen 1973). All these conclusions have been confirmed by other authors and are very well accepted today.

In further experiments using DNA in vitro, Hagen and his group showed that 30 percent of the breaks induced in aqueous solution are quickly repaired when polynucleotide ligase is added to the solution (Jacobs et al.1972). These damaged sites are apparently breaks with a 3′OH– group on one end of the broken DNA and 5′P-group on the other end (Bopp and Hagen 1970). Hagen (1973) summarized results available in the literature, as well as his own data in an excellent review, where he also drew exciting conclusions regarding the future importance of DNA repair.

In the following years Ulrich Hageńs research was very much focused on DNA damage characteristics and the ability of cells to repair the various types of DNA damage. In this respect radiation-induced clustered damage in DNA was of special interest and it turned out that the type of DNA damage induced was quite different depending upon whether the DNA was irradiated in vitro (in aqueous solution) or in situ (in λ phage particles or in living cells). For DNA irradiated in situ, the DNA strands matched complementarily, whereas after in vitro irradiation the DNA showed mismatch patterns the extent of which depended on radiation dose. It was assumed that DNA damage induced after in situ irradiation was mainly caused by direct energy absorption in the DNA (Martin-Bertram and Hagen 1979) and that clustered damage sites have characteristics that make them sensitive to S1-nuclease. S1-nuclease is an enzyme that splits these sites (S1-sites) to double strand breaks (DSB) (Hagen et al. 1989), a reaction that occurs even in DNA isolated from γ-irradiated yeast cells. It was thought that the enzyme cleaves DNA specifically at sites where localized denaturation has occurred and can therefore be used as a lesion probe to identify regions in the DNA where base-pairing has been disrupted. By analyzing the number of single strand breaks, double strand breaks and alkali-labile sites in the DNA before and after treatment with S1 nuclease, it has been possible to calculate the number of S1 nuclease-sensitive sites induced by ionizing radiation. It was found that these lesions occur at a frequency about twice that of the double strand breaks and are the result of direct radiation effect.

Notably, S1-sites could be detected only after irradiation of the DNA in situ – not after irradiation in solution. However, S1-sites were detected after irradiation of bacteriophages, in yeast and in mammalian cells (Andrews et al. 1984; Hagen et al. 1989). Repair of DSB and of S1-sites occurred within 20–30 h in diploid wild-type yeast cells, but not in haploid yeast cells. Repair of these DNA-changes was also not found in 'rad 50/2n mutated yeast', which is defective in recombination repair. In these cells no repair of DSBs or S1-sites occurred. Interestingly in 'rad 18/2n yeast cells', defective in mutagenic repair, only repair of DSB and not of S1-sites was affected (Hagen et al. 1989). The authors concluded that for the repair of S1-sites, recombination repair plus enzymatic processes for mutagenic repair are necessary. These 'denatured regions' not only gave rise to impaired reannealing of melted DNA, but also sensitized DNA for cleavage by the S1 nuclease of Aspergillus oryzae. As it is known that sensitivity to S1 nuclease derives from the ability of the enzyme to recognize single-stranded regions, it was suggested that the S1 nuclease-sensitive sites did in fact correspond to localized regions of disrupted base-pairing, which were in turn most probably caused by clusters of damaged bases.

Ulrich Hagen and his coworkers were at the forefront of molecular radiation biology over several decades. This was

nicely documented in two reviews, which he published at the end of his active career (Hagen 1990, 1994). Everyone interested in the status of the DNA damage and repair field 25 years ago, should read the review by Ulrich Hagen (1994) where the author offers not only a state-of-the-art overview, but also speculations and hypotheses on future directions.

Hagen (1994) stressed again in this review the differences between the DNA damages induced after radiation exposure of DNA in vitro, in aqueous solution, and in situ in living cells or animals. The direct radiation effects are more dominant after irradiation in situ than in vitro. Not only the structure of DNA itself but also the structure of the chromatin is important for the spectrum of lesions induced by ionizing radiation, with high LET radiation inducing more complex clustered DNA damages than low LET radiation. This leads to more protracted DNA repair and a higher amount of unrepaired DSBs. Hagen also pointed out that the 'enzymatic machinery' is most important for the biological outcome from the radiation insult, and there were many open questions regarding the organizational structure of the DNA in chromatin. Hagen ends the paper:

> Therefore, we have to develop a new model of DSB repair taking into consideration the aspects of molecular damage, microdosimetric analysis, enzymatic repair and the mechanisms of recombination. Perhaps the recombinational DSB repair is triggered by the DSB itself and the signal depends partly on the complexity of the radiation-induced damage. (Hagen 1994).

Besides these excellent scientific studies Ulrich Hagen was an admired academic teacher and he served in a number of offices in scientific societies representing Radiobiology in the German 'Röntgen-Gesellschaft', and as German Representative in the Council of the International Association for Radiation Research. He organized a number of scientific meetings and was the President of the 10th International Congress of Radiation Research in Würzburg, 1995, celebrating the discovery of X-rays by Röntgen 100 years ago. From 1980 until 1996 Ulrich Hagen served as Managing Editor of 'Radiation and Environmental Biophysics' and he was a Member of the Editorial Board until his death in 2007. Ulrich Hagen did everything with high competence, great care and admirable discipline.

The research activities of Christian Streffer

After having studied chemistry, I started with investigations in radiobiology in 1959 in the 'Radiologisches Institut Freiburg' under the leadership of Hanns Langendorff. In parallel I was working on the amino acid analysis of a large protein (β-galactosidase of *Echerichia coli*) and the kinetic interactions of sulfhydryl- with amino-groups in the active center of enzymes as part of PhD thesis that was completed in January 1963 (Streffer 1963; Wallenfels and Streffer 1964). Directly thereafter, I was able to get a grant for a six month leave to work in the Department of Biochemistry, Oxford University, under the leadership of Sir HA Krebs, where I received training in biochemical methodology and studied regulatory processes of the intermediary metabolism in rat liver (Streffer and Williamson 1965).

Metabolic studies of tryptophan and 5-HT

Langendorff and Melching had observed in 1959 that pyridoxal-5-phosphate (Pyr-5-P) had a protective effect against X-irradiation, when injected into mice together with 5-hydroxytryptophan. The combination of these substances together with ATP resulted into a radio-protective effect almost as strong as with 5-HT alone (see above). Pyr-5-P plays an important role as coenzyme in tryptophan metabolism. It is needed for the formation of 5-HT by a decarboxylase. It is also needed for the degradation of tryptophan to nicotinamide from which NAD is formed in liver. In this pathway Pyr-5-P is involved in several enzymatic steps. One cornerstone is the degradation of 3-HO-kynurenine to xanthurenic acid or 3-HO-anthranilic acid. Thus, we studied these metabolic pathways in mice after irradiation by determining the excretion of these metabolites in the urine (Langendorff et al. 1961). The results led us to study related enzymatic activities in the liver of mice (Streffer and Langendorff 1966; Streffer 1967). It turned out that the 'pacemaker' enzyme for NAD-synthesis was decreased in the liver after whole body irradiation with 690 R and that this process was critical when the animals developed severe radiation sickness – the kynurenine aminotransferase activity was not changed. Both enzymes need Pyr-5-P as coenzyme. The same situation was found for the synthesis of 5-HT (Langendorff et al. (1968). These data showed that not all Pyr-5-P dependent enzymatic activities were decreased after whole body X-irradiation, only those of regulating enzymes. One of the important findings in this set of experiments was that in metabolic chains the so-called pacemaker enzymes were most radiosensitive. Further, it could be shown that an appreciable amount of NAD in the liver is synthesized through the tryptophan–kynurenine pathway (Streffer 1967). In regenerating liver the DNA-synthesis can be modified by NAD in the reduced form. After irradiation this NADH has no influence on the rapid radiation-induced decrease of DNA-synthesis, while the regeneration of DNA-synthesis starts earlier than after irradiation alone (Streffer and Scholz 1972; Streffer 1974). This effect was similar as with the observations with 5-HT.

It was also observed that the protein synthesis of tryptophan pyrrolase is unexpectedly more radiosensitive than the synthesis of tyrosine aminotransferase, although the coding gene for tryptophan pyrrolase is smaller than that of the tyrosine aminotransferase (Streffer and Schafferus 1971). On the basis of target theory it should be the opposite. It was concluded that there are regions in the active DNA, which are more radiosensitive than others.

We also uncovered profound details of the mechanism of 5-hydroxytryptamine as a radio-protector in mice. The CNS is very important in this context and it was observed that 5-hydroxytryptamine is passing the blood-brain-barrier at around the third ventricle of the brain (Streffer and Konermann 1970). The direct injection of 5-HT into the

brain with a much smaller substance dose had the same effect as intraperitoneal application (Streffer and Flügel 1972).

Studies with mouse preimplantation embryos

After attending a lecture on the in vitro culture of mouse 2-cell embryos up to the blastocyst stage, I decided that this would be an excellent system for radiobiological investigations: One can follow cell division over several generations with synchronized cells without needing any physical or chemical manipulation. The system could be improved by our group by starting with the zygote (1-cell stage) instead of the 2-cell stage (Streffer et al. 1980). One can work with a synchronized cell population on a physiological basis. The embryos can be implanted after the in vitro culture into foster female mice and their development to new born mice can be followed.

Extensive studies investigated the effects of radiation on embryo development as a function of the cell cycle phase, and the formation of micronuclei was quantified after exposure to X-rays or neutrons (cyclotron 7 MeV). These studies were continued and intensified when I moved in 1974 from Freiburg to Essen, where I was appointed full Professor and Director of the Institute for Medical Radiobiology at the University Clinics Essen. Cell proliferation and cell cycle effects can be studied with this system very efficiently, as cell division can be clearly seen under the microscope and characterized for each individual embryo. In this way, radiation induced changes in cell cycle progression can be studied either in vivo or in vitro and the results directly compared (Streffer et al. 1980). The individual cell cycle phases as well as the alteration in their duration as induced by radiation exposure could be measured (Molls et al. 1982). Thus, the G_2-block generated after radiation exposure could be nicely documented and linked for the first time with cell recovery and DNA-repair (Molls and Streffer 1984).

For decades it was believed that malformations could not be induced by ionizing radiation exposure during the pre-implantation period. Embryo lethality was considered the only effect of ionizing radiation exposure, or exposure to other toxic agents during this period of prenatal development. Russell laid down the 'all-or-none rule' in 1956 for radiation damage in mammalian pre-implantation embryos (Russell, 1956, p. 378). It was generally accepted that during the pre-implantation period, the pluripotency of the blastomeres or the low degree of differentiation of the later stages could compensate for cell loss to a certain extent, while at the same time radiation damage was repaired. Therefore, no malformations were generally expected during this developmental stage (Streffer and Mueller 1996). However, from the experimental data of our group it now turned out that in a mouse strain with a genetic predisposition for a malformation (gastroschisis in our case) this malformation increased after exposure during the pre-implantation period (Pampfer and Streffer 1988). The highest radio-sensitivity was seen after exposure at the zygote stage briefly after conception (Mueller and Streffer 1990). Genetic and molecular studies led to the conclusion that three genes are responsible for this malformation (Hillebrandt et al. 1996). One of these three genes is located on chromosome 7 in a region where strong imprinting occurs (Hillebrandt et al. 1998). It is certainly exciting that imprinting is apparently an important process on the prenatal development.

This in vitro culture system is also suitable for studying combined effects of exposures to ionizing radiation and various toxic substances, such as heavy metals. The dose relationships and risks for several such combinations have been studied with pre-implantation mouse embryos. Lead and mercury were most effective in these combinations (Müller and Streffer 1987). These investigations led to my appointment as chairman of an ICRP task group on prenatal effects of ionizing radiation (ICRP 2003).

Experimental radiotherapy and 'individualization' of cancer therapy

Besides investigations on embryos, our institute studied several aspects of experimental radiotherapy with normal and human cancer cell systems, as well as with tumor systems on nude mice or cancer biopsies. The biological end points studied were: cell death, cell cycle distribution measured by flow cytometry, chromosomal aberrations, micronuclei formation and tumor growth. The following treatment modalities were used: X-rays, fast neutrons, hyperthermia, various cytostatic drugs and combined modality protocols.

The combination of X-rays with hyperthermia showed a very strong radiosensitizing effect when human cancer cells were heated to a temperature of 42 °C (Streffer and van Beuningen 1983). With the hyperthermia treatment administered directly after X-irradiation, the shoulder of the dose effect curve for cell survival was completely lost. Apparently, DNA-repair was inhibited by heat exposure and caused a strong radiosensitization, especially in those cancer cells, which had efficient DNA-repair and were therefore radioresistant (Streffer 1987). Metabolic studies also showed that hyperthermia induces strong changes in glucose metabolism and leads to a strong increase of the lactate/pyruvate ratio. This is a very similar situation as that found under hypoxic conditions (Streffer 1988). For the sake of brevity further interesting studies of this kind by our institute are not mentioned here but the interested reader can refer to our publications.

Many of the above investigations were carried out in close cooperation with clinicians of various disciplines, and one of the aims was to find indicators for the individualization of cancer therapy. The determination of micronuclei in biopsies from patients with head and neck cancers turned out to be a promising parameter in this context (Zamboglou et al. 1992). With rectal adenocarcinoma, it was demonstrated that the probability of cancer regression by cell repopulation could be predicted after a preoperative radiotherapy by the proportion of S-phase cells in cancer biopsies before the first and after the last radiation fraction (Streffer et al. 1988). An increase of S-phase cells after preoperative radiotherapy indicated high probability of cancer regression

due to repopulation. A wide inter-individual variability was found for S-phase cells, micronuclei and density of small blood vessels. The increase of micronuclei after radiotherapy frequently correlated with the vascularization index (Streffer et al. 1989).

However, the decision of our clinical partners to focus on large randomized studies rather than select patients on the basis of prognostic factors, reduced the priority of such investigations. Today 'personalized' or 'individualized' therapy is at the forefront of clinical practice again.

Cytogenetic studies and genomic instability

Cytogenetic studies have shown that radiation-induced chromosomal aberrations do not only occur in the first mitosis after a radiation exposure with 0.06 to 1.88 Gy X-rays (240 kVp) or 0.03 to 0.75 Gy neutrons (7 MeV), but also in the second and third mitosis after these radiation exposures (Weissenborn and Streffer 1988). From these data it could be clearly concluded that new chromosomal aberrations developed during the progression of cells through subsequent divisions. Also in fibroblasts from a fetus, which had been X-irradiated with 2 Gy at the zygote stage, the number of chromosomal aberrations was increased, although a normal mouse had developed and many cell divisions had occurred after the radiation exposure (Pampfer and Streffer 1989). Thus, new chromosomal aberrations developed many cell generations after the radiation exposure. In the publication in 1989 the increase of 'genomic instability' was discussed for the first time. Such an effect was not only observed, but also interpreted as 'increased instability of the genome'. The editor of this Journal and the reviewers were overall satisfied with the submitted paper, but questioned the interpretation of 'instability of the genome'. After some discussions with the Editor, who found this interpretation peculiar, it was agreed to use the term 'instability of the genome' only once and to shorten the discussion. In experiments with the Heiligenberger mice it was also observed that genomic instability is transmitted to the next mouse generation (Streffer 2006). Genomic instability is today one of the most prevalent concepts in cancer and the elucidation of its mechanisms one of the most pressing tasks of the field. Sometime views change quickly. Several years later many more publications reported the same phenomenon after radiation exposure (UNSCEAR 2006). Yet, the first publication on this topic appeared in this journal in 1989.

A comparatively simple method for measuring genomic instability was developed by analyzing micronuclei with centromeres separately from micronuclei without centromeres (Chang et al. 1999). Such studies were performed by counting micronuclei in combination with labelling of centromeres by the FISH technique in human lymphocytes. In non-irradiated cells, ~75% of the micronuclei have centromeres – mainly from whole chromosomes. After radiation exposure more micronuclei are observed, but the percentage of micronuclei with centromeres decreases as more acentric fragments are formed (Kryscio et al. 2001). With this method the ratio of micronuclei with centromeres versus without centromeres can be calculated. The ratio decreases after radiation exposure and can also be taken as a measure of genomic instability. Using this technique it was shown that in normal lymphocytes of individuals who had worked in uranium mines with high radiation exposures, an increased genomic instability developed decades after the radiation exposure. This effect was even higher in the lymphocytes of uranium miners with lung cancer (Kryscio et al. 2001; Müller et al. 2004).

Furthermore, patients with head and neck cancers showed with this method increased genomic instability in their lymphocytes as compared with normal individuals (Streffer 2010). From these observations and various other reports for increased genomic instability in individuals with genetic predispositions that render them radiosensitive, e.g. Ataxia Telangiectasia, Fanconi's anaemia, Li Fraumeni etc, it was concluded that increased genomic instability is a general occurrence in cancer development. This appears plausible, as a number of mutations are required for the development of cancer (Streffer 2010, 2015).

Epilogue

I served in a number of offices in scientific societies representing Radiobiology in the German 'Röntgen-Gesellschaft', as German Representative in the Council of the International Association for Radiation Research and as President of the European Society for Radiation Biology 1993/1994, 2002–2008 Honorary President of this Society. I organized a number of scientific meetings and was the Secretary-General of the 10th International Congress of Radiation Research in Würzburg, 1995 as well as Chairman of the Annual Meeting of the European Society for Radiobiology in Erfurt, two International Meetings on Hyperthermia in Essen.

I was Chairman of the 'Strahlenschutzkommission' for the German government 1984–85 and 1993–95, German Delegate to UNSCEAR (2000–2006); member of ICRP Main Commission (2000–2007) and was elected Emeritus Member of ICRP Main Commission.

Conclusions

It is gratefully acknowledged that a number of papers published in the International Journal of Radiation Biology opened new fields and discussions in radiobiology as examples:

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Note

1. R is the former so-called 'ion dose' or 'specific ionization' (mass ionization in air); 1 R = $2.58 \cdot 10^{-4}$ C/kg

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Disclosure statement

No potential conflict of interest was reported by the author.

Notes on contributor

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