The Life Span Study of Japanese atomic bomb survivors demonstrates that radiation exposure significantly increased the risk of developing ischemic heart disease, in particular myocardial infarction. Similarly, epidemiologic investigations in very large populations of patients who had received postoperative radiotherapy for breast cancer or for peptic ulcer demonstrate that radiation exposure of the heart with an average equivalent single dose of approximately 2 Gy significantly increased the risk of developing ischemic heart disease more than 10 years after irradiation. These epidemiologic findings are compatible with radiobiologic data on the pathogenesis of radiation-induced heart disease in experimental animals. The critical target structure appears to be the endothelial lining of blood vessels, in particular arteries, leading to early functional alterations such as pro-inflammatory responses and other changes, which are slowly progressive. Research should concentrate on the interaction of these radiation-induced endothelial changes with the early stages of age-related atherosclerosis to develop criteria for optimizing treatment plans in radiotherapy and also potential interventional strategies. © 2007 Elsevier Inc.

INTRODUCTION

The heart long had been regarded the prototype of a radioreistant organ. This notion was supported by its proliferative organization with postmitotic cardiac myocytes and extremely low proliferative activity of the endothelial cells and connective tissue cells. Yet, since the clinical and experimental studies of Fajardo and Stewart (1, 2), it has increasingly become apparent that the heart is actually one of the most critical dose-limiting organs in radiotherapy. Tolerance doses recommended today are approximately 40 Gy (in 2-Gy fractions) and thus similar to other radiosensitive organs.

Radiation-induced heart disease is generally regarded a classical “deterministic” radiation effect, which is only expected to occur if the radiation dose exceeds a well-defined threshold. It is therefore generally assumed to be associated with curative radiotherapy of cancer only and to be of no concern in radiation protection. Recent reports of a significant and dose-dependent increase of cardiac mortality after doses well below 10 Gy, however, require reconsideration.

In this article, we discuss the available radiobiologic data on the pathogenesis of radiation-induced heart disease in a wider context to explore whether the epidemiologic evidence is compatible with and supported by the radiobiologic evidence.
disease, when large volumes of the heart (i.e., the pericardium) were exposed to doses $>40$ Gy (4). The incidence rate of radiation pericarditis increased steeply with increasing dose. The median latency of symptomatic pericarditis (a total of 179 cases) was approximately 12 months. Most cases started as exudative pericarditis, but some progressed to constrictive pericarditis. Treatment methods have been altered considerably since 1970, and the volume of the heart exposed to the target dose has been very much reduced. Consequently, radiation pericarditis is rarely diagnosed in more recent years (4).

Cardiomyopathy

Symptomatic cardiomyopathy during or shortly after radiotherapy is only seen in combination with anthracycline chemotherapy. After radiotherapy without cardiotoxic chemotherapy, systematic long-term follow-up studies at $\geq 1$ year reveal subclinical changes in systolic and diastolic cardiac function (5, 7). Depending on investigational methods used, reduced left-ventricular function, myocardial perfusion defects, valve dysfunction, or conduction defects are observed. Incidence rates depend on the investigational methods used.

Coronary artery disease

After mediastinal radiotherapy of Hodgkin’s disease, an absolute excess risk of fatal cardiovascular disease—mainly from myocardial infarction—of between 0.1% and 0.5% per year has been reported. The risk is increasing with time after radiotherapy and becomes statistically significant after 10 years (6, 8, 9).

The awareness of the potential risk of late cardiovascular disease after exposure to low radiation doses was initiated by a recent analysis of mortality from cancer and nonmalignant diseases among the Japanese atomic bomb survivors (10). Mortality from myocardial infarction more than 40 years after radiation exposure was significantly increased in people who had received an acute single dose of 1–2 Gy. The excess relative risk could be fitted by a linear dose–response relationship with a slope of 0.17% per Sievert (Sv). A quadratic dose-dependence could be fitted to nonfatal heart disease incidence. Approximately 16% of the 117 myocardial infarctions could be attributed to radiation exposure from the bomb, most of which was due to doses $>1$ Gy (11).

The most important study to compare with the life span study (LSS) (10) is the peptic ulcer study (12). Between 1936 and 1965, 1859 patients suffering from peptic ulcer received radiotherapy with approximately 9 to 18 Gy to the stomach to reduce gastric secretion of hydrochloric acid. A similar number of patients suffering from the same disease, but treated with other means were selected as control group. After a latency of $>10$ years, the mortality from coronary heart disease was significantly increased in the radiation group by 24%. Moreover, a significant ($p = 0.01$) relationship between the mean cardiac dose and relative risk of mortality from coronary heart disease was determined. Thus the results of both studies, the LSS of the atomic bomb survivors (10) and the peptic ulcer radiotherapy study (12), which are the largest of their kind, appear to support each other. However, there is pronounced dose heterogeneity across the volume of the heart. Only the heart apex received the prescribed stomach dose, whereas the remainder of the organ was exposed to different doses from scatter. As extensively discussed by Carr (12), it is open to speculation whether it is the relatively high dose to the small volume of the apex or the much lower but still inhomogeneous dose (with a mean of around 2 Gy) to the main volume of the heart muscle and the major heart vessels which causes the damage to the heart.

An increase of the rate of myocardial infarctions was also recorded after postoperative radiotherapy of breast cancer (13–17). In these patients, part of the heart is exposed to the target dose of $\geq 40$ Gy, whereas the mean organ dose usually is only a few Gy given in very small dose fractions. After correction for fractionation effects using the linear quadratic model and the $\alpha/\beta$ ratio determined in experimental studies in the rat heart of 1–3 Gy (18, 19), equivalent single doses to the total heart are about 1–2 Gy and thus very similar to those in the atomic bomb survivor study (Fig. 1). Therefore the most relevant breast cancer studies will be considered in more detail.

The Surveillance, Epidemiology, and End-Results cancer registries database provided the first quantitatively convincing evidence of an increased rate of myocardial infarction after breast cancer radiotherapy (16). A first analysis in 1998 suggested a twofold, statistically significant increase in the rate of myocardial infarctions observed after postoperative radiotherapy for left-sided breast cancer (16). This analysis included only those patients who were $<60$ years old at the time of treatment. The risk of death from myocardial infarction after adjuvant radiotherapy was highest after more than 10 years follow-up.

The Surveillance, Epidemiology, and End-Results cancer registries cohort was reanalyzed recently (17), confirming and extending these earlier results. In the total cohort of 308,861 women treated for early breast cancer between 1973 and 2001, 115,165 received postoperative radiotherapy as part of the primary treatment. Of those 4130 women who died more than 10 years after radiotherapy, 1721 (42%) died from breast cancer and 894 (22%) died from heart disease. Whereas the risk of death from recurrent breast cancer was the same after left- or right-sided cancer, the risk of death from heart disease was higher by 44% in women with left-sided compared right-sided breast cancer. In absolute numbers, 359 women with right-sided breast cancer and 535 women with left-sided breast cancer died from heart disease, which is an excess of 176 deaths of which 44 are due to myocardial infarction, 72 from other ischemic heart disease, and the remainder from other heart disease. Although misclassifications may have occurred, these data suggest that it is not only myocardial infarction, but also other ischemic heart diseases that may be induced by the relatively low radiation dose. This risk is not significant in
the first 10 years after treatment but its significance increases progressively with follow-up time. Because both surgical and radiotherapy procedures changed dramatically over the analyzed period of time, the two periods between 1973 and 1982 and between 1983 and 1992 were also analyzed separately. Confidence limits for the later period are large, but there is little evidence that the advances in radiotherapy techniques decreased the excess relative risk of radiation-induced heart disease significantly.

The analysis of the Early Breast Cancer Trialists’ Collaborative Group (13, 14) on the cause specific mortality among 20,000 women at 10–20 years after primary treatment clearly demonstrated the effectiveness of adjuvant radiotherapy for the reduction of local recurrence by about a factor of 3. However, this benefit did not translate into any survival benefit because it was offset by a statistically significant increase (about 30%) in the annual death rate from cardiovascular deaths, which was ascribed to inadvertent irradiation of the coronary arteries, the carotid arteries, and other major arteries. With an additional follow-up of 5 years, the significance of these findings was strengthened.

In conclusion, there is convincing evidence that radiation doses lower than 10% of the doses usually noted as tolerance doses for the irradiated heart in radiotherapy are associated with a significant increase in cardiovascular morbidity after latencies of >10 years. On the other hand, most studies with shorter follow-up (20–22) fail to demonstrate a significant risk. The following open questions need to be critically analyzed.

- Is there a dose threshold of increased risk? Does the latency depend on dose as suggested by experimental data (Fig. 2)?
- What is the clinical nature of cardiovascular disease induced by low radiation doses and is it the same as after high radiation doses?
- In most described studies, there are significant dose inhomogeneities within the heart. Which part of the heart is the most radiosensitive and should be chosen as a reference point for tolerance doses?

![Fig. 1. Relative risk of heart disease increases with radiation dose: Preston et al. 2003 (10) and Yamada et al. (11) reported on cardiac mortality in atomic bomb survivors (life span study [LSS]); Carr et al. 2005 (12) reported on mortality from coronary heart disease at >10 years after radiation therapy of peptic ulcers; Darby et al. (14) and the Early Breast Cancer Trialists group (16) analyzed mortality from heart disease after radiotherapy for breast cancer.]

![Fig. 2. Average survival time ± SEM of rats after local heart irradiation (Schultz-Hector, unpublished).]
**The dose–response relationship of radiation-induced heart disease**

The first systematic experimental studies on radiation-induced heart disease were carried out by Fajardo and Stewart (2) in rabbits and by Lauk (23) and Yeung and Hopewell (24) in rats. After single doses of 16–20 Gy to the heart (with careful shielding of the lungs), exudative pericarditis developed in rabbits, rats, and dogs after about 70–100 days (23–25). The dose–response relationship was very steep, rising from 0% incidence at 15 Gy to 100% incidence at 20 Gy. After >20 Gy, pericarditis was so severe that animals had to be sacrificed within 100–120 days (23). In patients, an increase in total dose to the anterior pericardium from 50 Gy to 60 Gy increased the incidence of symptomatic pericarditis from <10% to >50%. In all experimental animals (i.e., rats, rabbits, and dogs), the maximum of exudative pericarditis was at 3 months after irradiation.

In rats, congestive heart failure was observed (23, 24) at dose dependent latency times (Fig. 2). A practical threshold of approximately 15 Gy was probably related to the short life span of rats of only about 2 years. If more subtle criteria of radiation injury were used, even a single dose of 10 Gy lead to significant effects such as focal loss of endothelial enzymes. In patients, reductions in left ventricular function are observed not only in older studies relating to radiation injury were used, even a single dose of 10 Gy lead to significant effects such as focal loss of endothelial enzymes. In patients, reductions in left ventricular function are observed not only in older studies relating to radiation injury, but also in experimental models, ultrastructural studies revealed endothelial alkaline phosphatase. Myocardial degeneration is invariably situated within enzyme negative areas and the maximum extent of these areas is dose dependent. Morphologically, enzyme loss is associated with signs of endothelial cell activation such as swelling, lymphocyte adhesion, and extravasation (30) as well as with increased endothelial cell proliferation (31).

These experimental findings suggest radiation injury to the capillary network as the underlying cause of ischemic myocardial degeneration and heart failure after heart irradiation. This is supported by several clinical studies reporting myocardial perfusion defects caused by breast cancer radiotherapy. In the most recent study (32), 114 patients underwent single photon emission computed tomography cardiac perfusion scans at 6, 12, 18, and 24 months after radiotherapy for left-sided breast cancer. New perfusion defect were observed in a both time- and volume-dependent manner: they increased with time from 27% after 6 months to 42% after 24 months, and they ranged from 10% to 20% less than 5% myocardium in the treatment field to 50–60% with more than 5% of the myocardium in the treatment field.

The pathophysiologic significance of the focal loss of endothelial cell alkaline phosphatase is unknown. Endothelial alkaline phosphatase is a membrane-bound endothelial marker enzyme that is involved in the regulation of endothelial cell proliferation and microvascular blood flow (33). A focal loss of myocardial alkaline phosphatase has been observed not only after heart irradiation, but also in experimental diabetes and hypertension (34). In all of these experimental models, ultrastructural studies revealed endothelial cell swelling and endothelial cell proliferation, indicating a relevant role of enzyme loss in the pathogenesis of cardiomyopathy. In experimental animals, local heart irradiation with single doses of >15 Gy causes clinical heart failure. Histologic appearance varies in different species: in rabbits, interstitial myocardial fibrosis is predominant (2), whereas in dogs, focal myocarditosis is surrounded by replacement fibrosis (25). In rats, on the other hand (26), focal myocardial degeneration occurs without interstitial fibrosis. Hemodynamic function is largely maintained until shortly before clinical failure is evident. In one experimental study, this was associated with an increase of β-adrenergic density and decreased myocardial catecholamine (27)—a finding that could explain functional compensation but is atypical for chronic heart failure in general. At the time of manifest heart failure, myocardial degeneration covers >20% of the entire myocardium without any distinct pattern of anatomic distribution.

In 1967, Morgenroth (28) demonstrated in rats that radiation-induced cardiomyocytolysis is preceded by alterations in capillary endothelial cells. Fajardo and Stewart (29) observed that these early, reversible ultrastructural alterations in endothelial cells are followed by a persistent decrease in capillary density. Extensive studies of dose- and time-related changes in rats (26) showed that capillary loss is associated with a focal loss of the endothelial cell marker enzyme alkaline phosphatase. Myocardial degeneration is invariably situated within enzyme negative areas and the maximum extent of these areas is dose dependent. Morphologically, enzyme loss is associated with signs of endothelial cell activation such as swelling, lymphocyte adhesion, and extravasation (30) as well as with increased endothelial cell proliferation (31).

**PATHOGENESIS**

**Experimental data on pathology and pathophysiology of radiation-induced heart disease**

**Pericarditis.** Pericarditis after heart irradiation is associated with edematous swelling, fibrotic thickening, and adhesions of epicardium and pericardium (23). This histopathologic picture, the dose-independent latency time, and the reversibility indicate that radiation-induced pericarditis is an acute radiation response of an actively proliferating cell population. Mesothelial cells are the most likely candidates for target cells, but systematic cell kinetic studies have not been performed.
myocardial degeneration that would well deserve further investigation.

**Radiation effects on capillaries and endothelial cells.** A number of pro-inflammatory molecules have been reported to be upregulated by endothelial cell irradiation *in vitro* and *in vivo*.

E-selectin is an endothelial cell adhesion molecule mediating leukocyte rolling. In endothelial cells *in vitro*, E-selectin mRNA and protein are upregulated at 2 h and 4 h after 0.5 Gy (35). In the mouse lung *in vivo*, E-selectin upregulation occurs at 6 h after 2 Gy (36). Gel shift analysis indicated activation of NF-κB to be involved. In larger blood vessels, P-selectin, another early pro-inflammatory factor promoting leukocyte rolling, was also increased on the luminal vessel surface.

Radiation-induction of intercellular adhesion molecule (ICAM), which is an important mediator of leukocyte arrest, has been observed in endothelial cell cultures of various origins (37, 38). *In vivo*, ICAM-1 was upregulated at 2–7 days after 8 Gy total body irradiation in mice (39) and ICAM-1 knockout was found to abrogate radiation pulmonary inflammation. ICAM-1 upregulation has been associated with a NF-κB–like binding site of the ICAM-1 promoter (37) and can be abrogated by introducing NF-κB–dominant negative gene constructs (40). Thus there is strong evidence of NF-κB–regulated ICAM-1 induction by radiation as an early key reaction of the endothelium.

Adhesion molecule PECAM-1 (CD31), which is involved in leukocyte transmigration was upregulated 3 days after endothelial cell irradiation *in vitro* in one study (41) and between 7 and 21 days after 10 Gy in another study (42). There are, however, no *in vivo* data yet published.

We consider these pro-inflammatory events as the molecular correlate of early radiation-induced ultrastructural changes observed in the microvessels of the myocardium (28, 29).

Besides induction of adhesion molecules, upregulation of cytokines, namely interleukin (IL)-6 and IL-8, have been observed after endothelial cell irradiation in a time- and dose-related fashion (41). Although IL-6 has anti-inflammatory properties and is known to induce endothelial cell alkaline phosphatase (42), IL-8 is a chemo-attractant for leukocytes and induces endothelial cell proliferation (43). As described previously, endothelial cell proliferation is a key event in the development of experimental radiation-induced cardiomyopathy (30). Proliferation, once triggered (e.g., by IL-8 induction), would be expected to lead to expression of radiation damage and mitotic death of irradiated endothelial cells. Furthermore, endothelial cell apoptosis has been observed after radiation *in vitro* (44) and *in vivo* (45). If the same mechanisms of endothelial cell loss and proliferation occurred in the endothelium of larger vessels, it would lead to focal endothelial denudation, which is known to be a potential trigger of arteriosclerotic lesions (46).

In addition to pro-inflammatory responses, there is evidence of prothrombotic effects of radiation: an increased deposition or release of von Willebrand factor has been observed after irradiation of endothelial cells *in vitro* (47), in capillaries and arteries of the rat myocardium (48), the mouse kidney glomerulum (49), and in the plasma of total-body irradiated monkeys (50). Observations covered a post-irradiation time span of 5 h after total body irradiation with 4 Gy to 16 months after heart irradiation with 15 Gy. Although *in vitro* studies indicated an increased transcriptional activity (51), this could not be confirmed in the mouse kidney *in vivo* (52). These findings are possibly indicating the cause of increased platelet adherence and thrombus formation observed in irradiated capillaries and arteries.

**Radiation-induced arteriosclerosis.** In studies using healthy rodents, coronary artery disease was not observed. Only in dogs, intimal thickening and perivascular fibrosis is associated with radiation-induced myocardial degeneration (25).

None of the rodent experimental models of radiation-induced heart disease explored coronary arteries systematically, however. Therefore, they may have underestimated the extent of late radiation injury in the arteries. Furthermore, normal rats and mice are known to be relatively resistant to arteriosclerosis from any cause (53) because of very low levels of low-density lipoprotein (LDL) in their plasma, which would explain negative findings. Therefore, more recent studies on radiation-induced arteriosclerosis focus on arteriosclerosis prone animal models, which combine one or more risk factors with radiation.

In spontaneously hypertensive rats (54), heart irradiation causes arteriosclerotic changes and arteriole obliterations as well as myocardial degeneration. Hypertension is more pronounced in male than in female spontaneously hypertensive rats and is associated with shorter survival times after heart irradiation. Although antihypertensive treatment of male rats had no effect on survival after irradiation, a synergistic action of hypertension and heart irradiation is suggested by these findings.

Stewart (55) irradiated the carotid arteries of apolipoprotein-negative mice (apoE–/–) with a single dose of 14 Gy and followed the development of atherosclerotic plaques for up to 34 weeks after irradiation. Irradiation of the carotid arteries had no influence on either cholesterol levels, markers of systemic inflammation, or atherosclerotic lesions in the nonirradiated renal arteries, but the onset of initial plaque formation was earlier and the rate of plaque growth was faster in irradiated carotid arteries. At histologic examination, these carotid arteries showed typical signs of plaque instability such as intraplaque hemorrhage or macrophage accumulation. Stewart (55) concluded that the interaction of radiation-induced changes in endothelial function with the initial events of atherosclerotic lesion formation in these animals resulted in chronic inflammation, favoring the development of a vulnerable plaque.

In summary, radiation appears to be an independent risk factor of arteriosclerosis that acts in concert with other known risk factors. The close association of intimal damage in larger vessels and focal myocardial degeneration may suggest a common pathogenetic pathway of radiation-in-
Pathogenesis of human cardiovascular disease unrelated to radiation

Radiation-induced arteriosclerotic lesions do not differ substantially in their anatomic distribution or their histologic appearance from age-related arteriosclerosis (4). Thus it appears reasonable to assume that both conditions may at least partly share common pathogenetic pathways. The typical sequence of initial events leading to coronary artery disease unrelated to radiation is briefly summarized in the following sections and in Fig. 3 to review possibilities of interaction between known radiation effects and age-related atherogenesis.

Human coronary artery disease is a chronic progressive disease, driven by many genetic and exogenous factors (56, 57). Inflammatory processes in combination with local shear stress and lipid accumulation in the vessel wall both play a key role in its initiation. A shear stress–dependent, NF-kB–mediated inflammatory response has been described as an initial event (58), triggering expression of a plethora of atherogenic genes. The role of NF-kB activation is confirmed by findings in human arteriosclerotic lesions (59).

The second initial key event is a systemic accumulation of LDL in the vascular intima, which is then transformed into pro-inflammatory lipids (58). These also induce leukocyte adhesion molecule expression in endothelial cells, leading to adhesion of platelets and leukocytes to endothelial cells and to cell migration into the subendothelial space. Monocytes transmigrate into the vessel wall and differentiate into macrophages. These internalize apoptotic cell fragments or oxidized LDL particles, thereby transforming into foam cells, the typical histologic marker of arteriosclerotic lesions. In this phase, macrophages and endothelial cells release pro-inflammatory signal molecules including inflammatory cytokines, proteases, cytotoxic oxygen, and nitrogen radical molecules. In addition, oxidized LDL activates innate immunity pathways in human atherosclerotic lesions, resulting in expression of proinflammatory cytokines (interferon-γ, tumor necrosis factor-α, IL-1), cell surface molecules, and enzymes by T-helper cells. As a consequence, increased levels of downstream molecules such as IL-6 or C-reactive protein, serum amyloid A, and fibrinogen may be found in the circulation. This complex cascade, much simplified in Fig. 3, leads to local plaque formation and eventually to plaque rupture. As indicated in Fig 3, several of these events can also be triggered by radiation; an acceleration of events by radiation is easily conceivable.

Anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β) as well as circulating endothelial cell stem cells (60) decelerate the development of arteriosclerosis. Their role after radiation remains to be elucidated.

Smooth muscle cells in human atherosclerotic plaques appear to be monoclonal in origin (61, 62). Because normal adult arterial intima also shows patches of monoclonality, it was hypothesized that atherosclerotic lesions arise by expansion of preexisting clones of smooth muscle cells (63). Therefore, if clonality of smooth muscle cells should occur in radiation-related atherosclerotic plaques, it is probably not from to an early radiation–inducible mutational event but rather from expansion of naturally preexisting clones.

Another feature of arteriosclerosis possibly relevant to radiation effects is genetic instability. At autopsy after myocardial infarction, Hatzistamou (64) found evidence of allelic imbalance in 7 of 30 (23%) atherosclerotic lesions and microsatellite instability in 10 of 30 (33%) lesions. The frequency of abnormal allelotypes did not follow a Poisson distribution, which was taken as evidence that genomic instability was associated with the formation of atherosclerotic plaques. Minisatellite instability was in all cases limited to one to three minisatellites suggesting the absence of true mutator phenotypes. The authors hypothesized that minisatellite instability in human atherosclerotic plaques could be involving genes actively involved in the formation of plaques. In a review, Andreassi and Botto (65) concluded that increasing evidence supported a role of genetic instability in human atherosclerosis, either as cause or consequence of disease progression. Radiobiologic research provides ample evidence that one of the most important effects of low radiation doses of ≤2 Gy is the induction of persistent genomic instability, indicating a possible pathway of synergistic action.

DISCUSSION

Although neither clinical nor experimental data on late cardiovascular radiation damage are entirely conclusive, some general conclusions may be drawn.

Radiation-induced heart disease appears to be a characteristic late radiation effect, characterized by progressive functional alterations such as conduction defects or reduced ventricular function. Both epidemiologic data and experimental
findings relate these late effects to vascular damage: epidemiology revealed an association of the mean dose to the heart with ischemic heart disease and myocardial infarction, clinical studies document perfusion defects in irradiated myocardium, and experimental studies documented early and persistent alterations in capillaries and endothelial cells. Thus information obtained in human and animal studies is complementary. Pro-inflammatory responses to radiation and loss of endothelial cells are presumably the driving events leading to both microvascular perfusion defects and arteriosclerosis.

Various abscopal mechanisms of cardiovascular radiation effects have been suggested in the Japanese atomic bomb survivors who received total body radiation exposure. Changes in the patterns of lymphocyte subpopulations (66) or increased levels of parathyroid hormone (67) might have contributed indirectly to the development of cardiovascular disease. Yet the evidence for radiation induced cardiovascular disease from localized exposure to the heart at similarly low mean heart doses strongly suggests that cardiovascular disease is the direct consequence of local irradiation of the heart.

Low radiation doses are known to induce cellular stress responses, but these usually are of short duration and their impact may be small compared with that of shear stress. Still, the hypothesis of interactions between the two different stress responses deserves thorough investigation, in particular with regard to the possibility of chronicification of the inflammatory process.

There is ample experimental evidence of pro-inflammatory signaling cascades being induced by radiation of endothelial cells in vitro. It has been suggested that pro-inflammatory radiation effects may be an independent risk factor promoting arteriosclerosis and microvascular dysfunction. In vivo data are still sparse, but are essentially supporting in vitro findings (55). Dose and time relationships need to be defined (i.e., more data on doses below 5 Gy and beyond 2 weeks are still needed to gain a full understanding). The pro-inflammatory hypothesis is supported by the effectiveness of strategies to block or prevent radiation-induced pro-inflammatory reactions (68–70).

Investigation of the functional changes of the endothelium which are related to the enzyme loss described above and which may affect the barrier function and the antithrombotic activity of the endothelium could be another promising approach for further research.

Radiobiologic research provided ample evidence that one of the most important effects of low radiation doses of \( \leq 1 \) Gy is the induction of persistent genomic instability. The observations of an increased level of genomic instability in atherosclerotic plaques unrelated to radiation might (64, 65) offer another attractive hypothesis of synergistic interaction between radiation-induced effects and pathogenetic events unrelated to radiation. This hypothesis is particularly attractive because there is evidence that radiation-induced genomic instability may persist many years after an acute radiation exposure.

Whichever hypothesis is favored, it should be clear that radiation is only one factor in a multifactorial process. An integrated research program to study the development of radiation-induced heart disease after low-dose irradiation needs to be based on animal experiments. One key aspect would be the elucidation of the potential interaction of focal radiation injury in the endothelial lining of arteries and of radiation-induced stress responses (such as inflammatory changes) with the pathogenetic processes that drive the development of age-related atheromatous plaques. Various gene knock-out strains of mice and rats have been developed that have been invaluable in identifying the roles of various gene products in the pathogenesis of cardiovascular diseases. It is expected that these models might also be of great importance in the analysis of the mechanisms involved in the pathogenesis of cardiovascular disease induced by low radiation doses.

Based on the findings of in vivo studies, in vitro models might be designed that permit, for example, the closer investigation of mechanisms of intercellular signaling between endothelial cells grown as monolayer sheets. We also see a role for the exploitation of the targeting possibilities of microbeam technology. On the other hand, “classical” molecular radiobiology of DNA strand breaks does not, at present, appear to play a significant part in the pathogenetic pathways.

A particular problem in the design of those studies is the observation that the rate of damage progression is dose dependent. This means that in vivo experiments with low radiation doses require a very long time because animals have to be followed for several years. In vitro experiments would, no doubt, yield interesting data in less time. The significance of their results, however, would be doubtful if they were not integrated into a program that reflects the complexity of the development of radiation-induced heart disease in irradiated people.

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