APPENDIX-J

Coronary Effects of Very High-Dose Medical Radiation

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• Part 1. Two Distinct Types of Radiation-Induced Damage

There are reports as early as 1899 to 1909 which examine the types of damage inflicted by high-dose xrays to small blood vessels, especially in the skin (Part 7). By 1922, reports began appearing on damage to the heart from high-dose medical radiation (Part 7). By 1942, occurrence of such damage was well established (Part 7). Starting in the 1960s, numerous reports related xray therapy --- for various Cancers in the chest --- to xray-induced damage to the heart and its vessels (Parts 3, 4, 5, and 6). Also, there have been some animal studies (rabbits, rats) which report synergism between xray exposure and elevated plasma-levels of atherogenic lipoproteins (Part 5c, for example).

The evidence described in this appendix has firmly established that exposure of the heart and the coronary arteries, to very high-dose medical radiation, can result in damage typically having results very different from atherosclerosis. What are such results?

The answer requires explanation of a few more terms. The heart muscle itself (the myocardium) is surrounded by a sac of tissue whose outer side (adjacent to other organs) is called the pericardium, and whose inner layer is called the epicardium. The lining of the four chambers of the heart is called endocardium.

1a. Types of "Non-Atherogenic High-Dose Radiogenic Damage"

Among various patients who have received a few thousand rads of radiation involving the chest, injuries of virtually every component of the heart and its coronary arteries have been observed. These include severe pericarditis (both of the pericardium and the epicardium), myocardial fibrosis, myocardial infarction, endocardial fibrosis, and a variety of injuries to the coronary arteries. When very high-dose radiation has injured a coronary artery, the observors typically (but not always) report that the resulting lesions DIFFER from the usual atherosclerotic plaques. Parts 3, 4, 5 and 6 provide the observations in great detail.

We can refer to all types of radiation-induced non-atherosclerotic injuries, to the heart and its vessels, as "non-atherogenic high-dose radiogenic damage." We found no reliable estimate of its frequency, per 1,000 patients whose hearts have received very high-dose irradiation.

An undisputed point deserves emphasis, here at the outset: Not every type of radiation-induced injury to the heart itself, and to the coronary arteries, is part of the ATHEROSCLEROTIC process --- the process which underlies Ischemic Heart Disease (Coronary Heart Disease, Coronary Artery Disease) in the human.

Nonetheless, the kinds of non-atherogenic damage described above have been called "heart disease" or "coronary heart disease" or "coronary artery disease" in the biomedical literature (Parts 4, 5, and 6). Unfortunately, these labels are almost certainly the basis of some confusion.

1b. The Atherogenic Damage from Xrays: Radiation-Induced Mutations

In contrast to the well-established "non-atherogenic high-dose radiogenic damage" described in this appendix, we have proposed that ionizing radiation is also a cause of atherogenic damage and fatal Ischemic Heart Disease --- as a result of radiation's undisputed power to cause mutations of virtually every type in the coronary arteries. Chapter 45 introduces our Unified Model of Atherogenesis and Acute IHD Death.

• Part 2. RadioTherapy and Angioplasty: Range of Xray Dosage

High-dose irradiation, of all or part of the heart and coronary arteries, can be unavoidable during radiation therapy for certain malignancies (for example, breast cancer, Hodgkin's disease or other lymphomas). Such therapies, received in a series of doses over a period of weeks, can amount to internal radiation doses (all exposures combined) in the range of 1,000 to 5,000 rads, and even higher, in parts of the chest (Part 4a). These are very high doses (Appendix-A). Tissues located adjacent to an xray beam (or "field") receive some dose too, from internally scattered photons. Of course, the amount of scattered radiation declines as distance from the edge of the field increases.

Cancer therapy is not the only cause, in modern medicine, of high-dose heart irradiation. Heart patients who receive MULTIPLE cardiac catheterizations and angioplasties can accumulate skin doses from fluoroscopic xrays in the range of 1,000 to 3,500 rads (Lichtenstein 1996), which could mean accumulated doses of a few hundred rads --- even 1,000 rads --- to parts of the heart and the coronary vessels. These are very high doses, too. Under ordinary circumstances, however, the estimated average dose from angioplasty is about 60 rads per procedure to the skin (less to the heart) if one stenosis is dilated, and about 130 rads to the skin if two are dilated (NCRP 1989, p.31). Because of self-shielding, the side of the heart which is proximal, to the source of the xray beam, receives a higher dose than the distal side of the heart.

• Part 3. Autopsy Reports in 1965 on Two Very Interesting Patients

On July 31, 1965, the Lancet published a three-paragraph letter entitled "Myocardial Infarction Following Radiation," by Dollinger, Lavine, and Foye of the San Francisco Veterans Adminstration Hospital (Dollinger 1965). They reported on what "appears to be the first case of acute myocardial infarction secondary to radiation therapy to be studied histologically" [by pathologists]. The next year, they reported at length on the case in JAMA, under the title "Myocardial Infarction due to Post-Irradiation Fibrosis of the Coronary Arteries" (Dollinger 1966).

3a. Lesions Observed by Dollinger: Not the Usual Atherosclerosis

The case was a man diagnosed with Hodgkin's disease at age 23. However, he did not receive radiation therapy until he was age 31. Two months later, he experienced an acute but nonfatal myocardial infarction. In subsequent years, he developed angina pectoris, congestive heart failure, and several other afflictions. He died of pulmonary impairment in 1961, eighteen years after his initial diagnosis. When he died, autopsy revealed "extensive infarction of the right ventricle and posterior septum" (1965, p246). And how did his coronary arteries look? Dollinger reports (1966, p.317):

"The left coronary arteries showed only a few plaques and were widely patent [unobstructed]. However, the right coronary artery, 2 cm distal to its origin, abruptly changed to a pliable fibrous cord with a pinpoint lumen. This obliteration extended the full length of the right circumflex coronary artery down into the beginning of the posterior descending coronary artery, which was patent and thin-walled ... Multiple sections of the right coronary artery showed a marked degree of fibro-muscular proliferation interior to a well-preserved internal elastic membrane. This fibrous tissue was rather dense and contained a small number of fibroblasts with very scanty cytoplasm. No foam cells were present, and there was no evidence of cholesterol clefting, which was found to a minimal degree in areas of the left coronary artery ... The small branches of the right coronary artery in this area also showed intimal fibrous proliferation. The aorta and its major branches showed only minimal atherosclerosis." And in the "Comments" section (p.318):

"... it appears that the fibrous muscular proliferation of the right coronary artery was due to radiation. The patient was 31 years of age at the time of his myocardial infarction, two months after

completion of radiation therapy. There was no significant atheromatous change in the coronary arteries or other major arteries, there was no family history of coronary artery disease, and the serum cholesterol value was normal."

Dollinger and co-workers characterize the radiation-induced damage as "fibrosis of the coronary arteries" (their title), they never describe the lesions as atherosclerotic, and they specifically emphasize that "there was no atheromatous change in the coronary arteries." So the high-dose radiogenic lesions did not look to THEM like the "usual" atherosclerotic lesions.

3b. Lesions Observed by Prentice: Typical Atheromatous Change

Only three weeks after Dollinger's 1965 letter, Lancet published a comment on it, provided by R.T.W. Prentice of the Western Infirmary in Glasgow. Prentice had a case of his/her own (Prentice 1965). In the Glasgow hospital, a young man had recently died at age 19 from "acute left ventricular failure." At age 15, he had received chest irradiation (3,250 Roentgens) after diagnosis of probable lymphoma of the Hodgkin group. For a few years, he seemed "generally well" until he developed angina pectoris, which could not be relieved. "There was no family history of premature coronary-artery disease ... His serum-cholesterol was within normal limits." After his death, his coronary arteries were studied:

"Histological examination confirmed the presence of typical atheromatous change in all three main branches of the coronary vessels; there was no evidence of deposits of Hodgkin's tissue in the vessels, serial sectioning of which showed extensive fibrin deposition in the intima of the left descending artery, but no evidence of ante-mortem thrombus formation. There was recent extensive myocardial infarction of the left ventricle and septum. There was no atheroma of the vessels elsewhere." And Prentice added that the histological findings fail to resemble "those described by Dr. Dollinger and his colleagues ..." And Prentice ends by saying:

"While it is not possible to postulate a direct causal relation between radiotherapy and severe coronary-artery disease in this case, it is felt that the association of these two events in a young man of this age should be reported." Indeed.

3c. One Agent and Two Different Responses

Dollinger's case appears to have developed severe "non-atherogenic high-dose radiogenic damage" in his right coronary artery, and no apparent radiation-induced atherosclerosis. Prentice's case appears to have developed radiation-induced atherosclerosis in the three main branches of the coronary arteries, and no severe "non-atherogenic high-dose radiogenic damage." These two cases are consistent with our point (Part 1) that ionizing radiation can induce two DIFFERENT kinds of heart-related damage.

• Part 4. Distinctions Found and Emphasized by Cohn, Fajardo, Stewart

In 1967 and 1968, the California team of Cohn (medicine), Fajardo (pathology), and Stewart (radiology) published three papers on "radiation-induced heart disease" (Cohn 1967; Stewart 1967; Fajardo 1968). These papers report on some or all of 25 patients in whom "significant heart disease followed radiation therapy to the chest for a variety of malignant tumors" (Stewart 1967, p.302). Those tumors included cancers of the lung, breast, esophagus, thymus, and Hodgkin's disease. None of the patients had evidence of "heart disease" before they received radiation therapy.

4a. Radiation Dosage, and Its Consequences

Dose to all or part of the heart ranged from 3,000 to 9,800 rads per patient, administered at 1,100 rads per week (Fajardo 1968, p.512). The interval of time, between initiation of radiation and taking of the tissue for study, ranged from 6 to 84 months (Fajardo 1967, tabulation on p.513 for 16 patients). The discussion in Stewart 1967 begins (p.307):

"Scattered case reports have described radiation-induced heart disease of essentially all the types seen in this series. Acute pericarditis (Jones 1960; Portioli 1963; Spodick 1959), chronic pericardial and myocardial fibrosis (Rubin 1963; Gimlette 1959; Hurst 1959), and myocardial

infarction (Prentice 1965) have been noted following thoracic irradiation. The present series of cases from a single institution [Stanford University School of Medicine] is unique in that the number of reported cases is high ...It is our contention that many similar cases could be found in other institutions where large numbers of patients are treated with irradiation." And the summary on all 25 patients states (Stewart 1967, p.308):

"Acute pericarditis, often with pericardial effusion [presence of escaped fluid] and tamponade [acute compression of the heart], chronic pericardial effusion, and chronic constrictive pericarditis sometimes associated with myocardial and/or endocardial fibrosis or fibroelastosis were most commonly seen. Five of these cases were fatal. An additional patient [Case 21] died at the age of fifteen of myocardial infarction sixteen months after irradiation. In the majority of patients, detectable heart disease developed after a delay of several months. Most had received at least 4,000 rads to a sizable portion of the heart, and the more severe cases occurred among patients who had received the highest radiation doses to the heart (up to 8,950 rads) ... Radiation-induced heart disease, particularly pericarditis, is apparently more frequent and important than is commonly appreciated ..."

Reporting on 16 of the 25 patients, the Fajardo 1968 paper begins (p.512):

"Connective tissue proliferation is the hallmark of these late radiation lesions wherever located in the heart. Organizing pericarditis with extensive fibrosis is the most frequent alteration ... Diffuse interstitial myocardial fibrosis is commonly present. Endocardial and vascular changes are much less frequent. The diffuse nature of the myocardial fibrosis makes it difficult to detect grossly, and pathologists should be aware of its deceivingly innocent appearance."

4b. One Anomalous Case in the Series

In both Stewart 1967 and Fajardo 1968, the authors emphatically differentiate between one non-typical case in their series (Case 21) and all the other cases. Stewart 1967 describes the "spectrum of heart disease" observed in the 25 cases, and when the authors reach "Coronary Artery Disease and Myocardial Infarction," only ONE patient fits the category (p.305):

"A 15-year-old boy died of myocardial infarction sixteen months after receiving 4,000 rads to the 'mantle' for Hodgkin's disease. There was no known familial or metabolic predisposition to atherosclerosis, and an autopsy showed intimal proliferation and atheromatous deposits in the coronary arteries with a fresh myocardial infarction." In Fajardo 1968, the authors organize the results in anatomical groups, and when they reach "Vessels," they report (p.516):

"The vessels did not show consistent changes. However, proliferation of endothelial cells was observed in six of the 12 cases where large, medium, and small vessels could be examined. Case 21 was a remarkable exception. This 15-year-old boy, who absorbed 4,400 rads in the heart during treatment for Hodgkin's disease, developed severe coronary atherosclerosis. There was marked thickening of the intima by fibroblasts, collagen, endothelial cells, and histiocytes, some with large foamy cytoplasm. This thickening resulted in severe narrowing of the lumen of the left anterior descending branch to less than one eighth of its expected cross sectional area. Thrombosis was found at necropsy [autopsy] with an extensive area of ischemic necrosis of myocardium. No evidence of atherosclerosis was found in other vessels at necropsy and there was no history of familial hyperlipemia or severe juvenile atherosclerosis."

So, these investigators find that the damage from very high-dose radiation typically is NOT atherogenic damage --- which is why they comment so clearly on this single, apparent exception.

4c. Myocardial Fibrosis: Due to Radiation-Damaged Micro-Circulation

In 1973 and 1977, Fajardo proposed that closure of small irradiated vessels, resulting in "insufficient micro-circulation," is the cause of the myocardial fibrosis observed after high-dose irradiation of the heart (Fajardo 1973 and 1977).

In 1984, Stewart and Fajardo jointly proposed that existing evidence is "consistent with the following explanation of the pathogenesis of radiation-induced myocardial fibrosis. Radiation injures capillary endothelial cells leading to destruction or obstruction of capillaries. A compensatory mechanism of endothelial cell renewal is set in motion, but is inadequate to reconstruct the damaged

capillary network. Ischemia [deficiency of blood supply] results from the insufficient micro-circulation and leads finally to fibrosis."

4d. Harmony between Hypothesis-2 and the California Studies

In 1977, Fajardo wrote an editorial in the journal Chest, in which he says (Fajardo 1977, p.564): "As far as I know, typical coronary atherosclerosis, of the type seen in man, has not been produced experimentally [in animals] by the administration of radiation alone."

We are not surprised. Our Unified Model of Atherogenesis and Acute IHD Death requires BOTH mutation-induced dysfunctional clones in the coronary arteries AND elevated levels of atherogenic lipoproteins in flux through the intima of those arteries (Chapter 45; see also Part 5c, below, on synergism).

In 1984, Stewart and Fajardo published a 21-page paper entitled "Radiation-Induced Heart Disease: An Update," in which they again draw the distinction between Coronary Artery Disease (CAD) and the heart troubles they observe after very high-dose radiation. Unfortunately, because they say "radiation" without specifying "very high-dose," their text may appear to be in conflict with Hypothesis-2 --- although there is no conflict at all. For example (Stewart 1984, p.175):

"... one must conclude that the evidence for an important role of radiation in the pathogenesis of CAD is weak (Stewart 1978)."

What they studied was damage to the heart and its vessels after very high-dose radiation. If they had written what they meant --- which was surely that "the role of VERY HIGH-DOSE radiation in the pathogenesis of CAD is weak" --- then our position would be like theirs. Such a statement would be fully compatible with Hypothesis-2 and with a highly consequential role of medical radiation in the etiology of fatal Ischemic Heart Disease. After all, the number of people whose hearts ever accumulate very high-dose radiation, is very small by comparison with the number whose hearts accumulate low to moderate doses of radiation from medical procedures.

On another point, agreement clearly exists between Stewart, Fajardo, and us. We agree that the so-called "radiation-induced heart disease" on which they report, with elegance, is NOT THE SAME DISORDER as atherosclerosis --- the disorder which causes the overwhelming share of Ischemic Heart Disease.

• Part 5. Distinctions Found and Emphasized by McReynolds

Before describing the McReynolds' case, we will describe the Huff case, which was reported four years earlier.

5a. The Huff Case, 1972: Infarction Followed by Cardiogenic Shock

Harry Huff and E. Max Sanders reported (Huff 1972, p.780) on a patient, age 21, who had an acute myocardial infarction about nine months after receiving 3,500 Roentgens to the left cervical region (of the heart) for Stage 1a Hodgkin's disease. Huff and Sanders do not report whether any of the heart was directly in the xray field.

Following complications of the infarct, the patient died of cardiogenic shock (circulatory failure due to sudden decrease in cardiac output). The patient's prior records showed "normal average serum cholesterol," normal blood pressure and fasting blood sugars. He lacked a family history of arteriosclerotic heart disease, hyperlipidemia, or hypertension. They state (Huff 1972):

"At autopsy, adhesive pericarditis with loculated areas of pericardial fluid and an anterior infarction with definite extension into the ventricular septum were found. The proximal 2 cm of the left anterior descending coronary artery was completely occluded by organizing thrombus superimposed on an atherosclerotic plaque. The right coronary, left coronary and posterior circumflex arteries were grossly normal, but microscopical observation revealed atheromatous changes here as well. No residual Hodgkin's disease was found." And (Huff 1972):

"Myocardial and pericardial disease secondary to radiation is widely acknowledged. Since many patients subject to radiation therapy are also candidates for coronary-vessel occlusion, the independent effect of radiation on the coronary vessels is difficult to evaluate clinically ... We should be interested in knowing whether other cases exist ..."

5b. The McReynolds' Case 1976: "Adventitial Scarring" of the Coronaries

In January 1976, McReynolds and co-workers began a paper as follows (McReynolds 1976, p.39):

"Attention is called to the development of coronary heart disease in two patients several years after they received mediastinal irradiation [mid-chest irradiation] for Hodgkin's disease. One patient, a 33-year old man, died suddenly eight years after irradiation; necropsy disclosed marked narrowing of all three major coronary arteries. In addition to severe intimal fibrous thickening, there also was considerable adventitial scarring of the coronary arteries. This type of coronary sclerosis is different from that seen in the usual patient with coronary heart disease." They present no autopsy data on the second patient, age 42, because he was RECOVERING in 1976 from his second acute myocardial infarction (p.42).

Details of the Observed Differences

In the "Comments" section of the paper, McReynolds and co-workers say (McReynolds 1976, p.43):

"Several factors support the view that the coronary disease in Case 1 [deceased] was the result of mediastinal irradiation rather than the result of atherosclerosis of the usual type: (1) The patient had received large doses of irradiation to the mediastinal tissues eight years earlier. (2) He was young (age 33 years) at the time of sudden coronary death. (3) The patient had other lesions which were readily attributable to the effects of irradiation, including pericardial adhesions and thickening, interstitial myocardial fibrosis of the right ventricle and focal thickening of the mural endocardium of both ventricles. (4) The patient had coronary arterial lesions of a type uncommonly observed in the usual type of coronary atherosclerosis, including severe coronary adventitial fibrosis, usually in continuity with overlying epicardial fibrous tissue, and marked paucity of lipid in the intimal lesions." And (McReynolds 1976, p.43):

"In our experience (Roberts 1972, 1973, 1974, 1975) the dominant component of atherosclerotic plaques large enough to be fatal is fibrous tissue (collagen), but lipid, primarily extracellular, is present in most plaques and constitutes a significant proportion of them (at least 25 per cent, occasionally much more). In the present patient, the amount of lipid in the plaques examined was minute, and this probably is particularly unusual for such a young patient. Furthermore, the collection of cells in the adventitia of the coronary arteries included large numbers of plasma cells and fewer lymphocytes. In the usual type of coronary atherosclerosis, lymphocytes are dominant and plasma cells are infrequent ('adventitial lymphocytosis'). (5) The patient had relatively 'low level' risk factors to the development of accelerated atherosclerosis ... (6) He had virtually no atherosclerosis in other systemic arteries, including the aorta."

5c. Observations of Synergism between Radiation and Cholesterol

In the same paper, McReynolds and co-workers allude to the experimental animal evidence on synergism between very high-dose xrays ("ballpark" of 2,000 rads in these studies) and cholesterol (McReynolds 1976, p.44-45):

"Experimental studies also support the thesis that therapeutic levels of irradiation can produce or hasten coronary atherosclerosis (Gold 1961 and 1962; Amromin 1964; Lamberts 1964). The effects of radiation alone, however, are minimal, but when irradiation is given to animals (rabbits or rats) on high cholesterol diets, severe coronary atherosclerosis results, far more severe degrees of atherosclerosis than that resulting from the hypercholesterolemia alone. Irradiation and hypercholesterolemia appear to act synergistically to produce considerably more atherosclerosis than that produced by either radiation or hypercholesterolemia alone."

Very similar comments on synergism, citing the same sources, are found also in Fajardo 1977 and Stewart 1984 (who adds Artom 1965 to the list of sources for such observations).

• Part 6. Distinctions Found and Emphasized by Brosius and by Dunsmore

6a. The work of Brosius, Waller, and Roberts

In 1981, Brosius and co-workers (at the National Heart, Lung, and Blood Institute) published a study entitled "Radiation Heart Disease: Analysis of 16 Young (Aged 15 to 33 Years) Necropsy Patients Who Received over 3,500 Rads to the Heart." Their study reported in parallel manner on findings from 10 control patients. "Although only six of our 16 patients had clinical evidence of cardiac dysfunction, at necropsy, all had anatomic evidence of cardiac abnormality. All but one had fibrous thickening of the pericardium ..." (p.526). We will omit the now-familiar details. The authors themselves say (Brosius 1981, p.527):

"The most important contribution of the present study is the detailed information regarding the epicardial [extramural] coronary arteries. Damage to these vessels by high-dose irradiation has been reported previously [many references cited], but the extent of, and the type of, damage to these arteries have not been described. It is now clear that high-dose irradiation can cause damage to the epicardial coronary arteries and allow intimal proliferation of mainly fibrous tissue to produce luminal narrowing." And (Brosius 1981, p.527-528):

"Of our 16 patients, 16 of the 64 major (right, left main, left anterior descending and left circumflex) epicardial coronary arteries were narrowed >75 percent in cross-sectional area, primarily by fibrous plaques. In contrast, of 10 control subjects of similar age and sex, only one of 40 major epicardial coronary arteries was similarly narrowed ... Thus, our study-patients clearly had more coronary narrowing than did the control subjects, and none had pronounced recognized risk factors to premature atherosclerosis." And (Brosius 1981, p.528):

"The dominant component of the atherosclerotic plaques in both our study patients and in the control subjects was fibrous tissue; very little lipid was present in either." Even though this is not the "usual" atherosclerotic plaque, the authors call it by the usual name. They continue by describing additional non-typical findings (Brosius 1981, p.528):

"The study patients, however, had a striking loss of smooth muscle cells from the media (76 percent of sections versus 10 percent of sections in the controls). Furthermore, adventitial fibrosis was noted in 49 percent of the coronary sections in the study patients and in only 3 percent of the sections in the control subjects. Thus, high dose radiation causes coronary luminal narrowing ... adventitial scarring and damage to the smooth muscle cells in the media."

6b. Case Reported by the Dunsmores, 1986 and 1996

In 1986, Dunsmore, LoPonte, and Dunsmore authored a paper entitled "Radiation-Induced Coronary Artery Disease" (Dunsmore 1986). It is inevitable that a large proportion of physicians reading that title would assume the disorder under study to be no different from atherosclerotic disease of the coronary arteries. But in 1996, the Dunsmores made a special effort to correct that assumption, as we shall show.

The 1986 paper reports on three patients with Hodgkin's disease who received radiation therapy at ages 19, 19, and 32, respectively --- exposing "large areas of the heart" to 4,000 rads of dosage in 1965, 1966, and 1970 respectively. None received adjunctive chemotherapy. All developed "coronary artery disease," after 8, 12, and 4 years, respectively. All "succumbed" to their heart problems before age 40 (Dunsmore 1996). In Dunsmore 1986, there are autopsy findings only from Case 2.

Case 2, male, was age 19 when he was diagnosed with Stage IIB Hodgkin's disease in 1974. He received 4,000 rads of mediastinal midplane radiation dose. In 1978, he suffered two acute myocardial infarcts, but survived. At that time, he quit smoking two packs of cigarettes per day. In 1983, he was hospitalized with a large pleural effusion. He had 80% stenosis of the left mainstem coronary artery, and "the left anterior descending artery was totally occluded near its midpoint and the distal segment was thin and irregular and not bypassable. The main circumflex artery was occluded.

The right coronary artery had extensive luminal irregularity without critical obstruction." Coronary bypass surgery was performed. "The patient had a stormy post-operative course and died 48 hours later" (p.240). The Dunsmore paper presents four photos of coronary artery samples from Case 2, with the following captions:

Figure 1: "Case 2. Coronary artery showing compromise of the lumen by thickened intima. Intima and media are replaced by dense hyalinized tissue with only a peripheral rim of adventitia discernible." Hyalinization means conversion into amorphous tissue lacking definite and specialized structure.

Figure 2. "Case 2. Medium power view of a coronary artery showing dense areas of sclerotic hyalinization with focal calcification replacing the bulk of the coronary wall."

Figure 3. "Case 2. Medium power view of the coronary artery wall showing clusters of fibroblasts in dense hyalinized tissue."

Figure 4. "Close-up of wall of coronary artery showing fibroblasts in an area of dense fibrotic hyalinization."

In the summary of Dunsmore 1986 (p.243), the authors state: "... a striking difference in the pathologic features of the coronary arteries has been noted in those patients exposed to [therapeutic] radiation, as in our Case 2, compared with the typical atherosclerotic lesions of non-irradiated patients."

1996: Emphasis Again on Distinction from "Typical" Atherosclerosis

On February 27, 1996, the Wall Street Journal (p.B-1, B-6, "Can Radiation Help Fight Heart Disease?") reported on some small trials in which coronary angioplasty patients receive radioactive stents, as a potential method for preventing re-stenosis. The article elicited a cautionary response from Doctors Richard and Lillian Dunsmore, whose letter to the editor was printed on April 1, 1996. They warn:

"... the long-term results of coronary-artery radiation may terminate in further heart damage, inability to perform bypass surgery and even untimely deaths in patients treated with radiation. For decades the teaching had been that the heart was resistant to radiation. However, in 1986, we presented data suggesting to the contrary ... Our data showed that coronary arteries, exposed to radiation, resulted in fibrosis of the walls of the vessels with resultant narrowing in contrast to the atherosclerosis present in the typical cases of coronary-artery disease."

The Dunsmores clearly emphasize that the arterial fibrosis induced by the patient's high-dose irradiation DIFFERS from "the atherosclerosis present in typical cases of coronary-artery disease."

• Part 7. A Little History: Some Interesting Observations in 1899-1909

In 1942 and 1943, the eminent pathologist, Shields Warren, published a series of articles, in the Archives of Pathology, covering the effects of ionizing radiation on normal tissues. This was quite a comprehensive set of publications. The December 1942 article (Warren 1942, p.1070) is entitled "Effects of Radiation on the Cardiovascular System." It contains a section entitled "The Heart" which begins as follows (Warren 1942, p.1070):

"Relatively little attention has been paid to the effects of radiation on the heart." After reviewing some studies (earliest: 1922), Warren summarizes (p.1074): "The various forms of cardiac damage secondary to radiation therapy cannot be recognized as specific in themselves, but the aseptic necrosis, hyaline fibrosis, and obliterative vascular changes combine to form a fairly characteristic lesion."

The next section is entitled "The Blood Vessels." The evidence cited therein deals largely with blood vessels of the skin, and Warren draws no inferences about radiogenic responses in the coronary arteries. Nonetheless, the very old observations cited by Warren may be relevant to the explanation proposed by Fajardo and Stewart for radiation-induced myocardial fibrosis (Part 4c, above).

Unfortunately, the magnitude of the skin-doses in the old work is unknown, but we doubt that such doses could have been comparable with heart-doses in the Fajardo and Stewart series.

Warren documents that, very quickly after discovery of the xray ("roentgen ray"), researchers had ascertained that high doses injured the small cutaneous vessels (blood and lymph vessels in the skin). Indeed, xray-induced skin damage was rather common in the years before xray operators understood the need to control dosage (Chapter 2, Part 2b). Some very detailed studies of damaged skin were published between 1899 and 1909. (However, one should be doubtful whether, in those years, the investigators could really distinguish reliably between the types of cells they observed. Even today, it is a matter of sophistication to prove that certain cells are really certain types.)

7a. Narrowing, and Even Closure, of Small Irradiated Vessels

A prominent consequence, in vessels which received high-dose radiation, was proliferation of cells and of connective tissue, resulting in the narrowing and sometimes permanent CLOSURE of the small irradiated vessels. Warren relates the following (1942, p.1074):

"The early observations (Baermann 1904, + Gassmann 1899, 1904) established that although no element of the blood vessel is immune to radiation injury, the endothelium is the most susceptible; consequently, the major changes are seen in those vessels in which the endothelium makes up a proportionately large part of the wall. Injury to large vessels is rare with doses below 500 Roentgens..." And (Warren 1942, p.1075):

"As early as 1899 the intimal thickening, the swelling and proliferation of the endothelium and the vacuolation of the smooth muscle were noted by Gassmann, who stated these alterations would lead to 'starvation of the surrounding tissues' and hence explained the intractable character of the roentgen ulcer [xray-induced skin-ulcer]. He later (1904) treated rabbits with roentgen rays and sectioned the resulting cutaneous ulcers one month after their development. He found obliteration of lymphatics [lymphatic channels] by endothelial proliferation as well as endothelial proliferation in the arteries and vacuolation of their smooth muscle cells ..." And (Warren 1942, p.1075):

7b. Delayed Consequences: "The Progressive Character of Vascular Lesions"

"In human skin treated with roentgen rays of low voltage, Linser (1904) noted, at the end of four days, fissuring of the media of vessels, occlusion of vessels by thrombi and slight perivascular round cell infiltration [round cells are lymphocytes], reaching its peak at eight days. After twenty days, intimal thickening by connective tissue was marked, with obliteration of some vessels ..." And (Warren 1942, p.1076):

"The importance of vascular changes in the cutaneous radiation effects was clearly presented by Wolbach (1909). He gave detailed descriptions of the walls of the blood vessels in the later radiation changes and defined the changes occurring in the endothelium and the supporting tissues of the walls. If the endothelium was not killed, proliferation often recurred, even to the point of obliteration of the capillaries. Sometimes the swollen or vacuolated endothelial cells formed tufts projecting into the lumen. In the veins and arteries subintimal fibrosis, with the collagen often showing some degree of hyalinization, resulted in thickening of the wall at the expense of the lumen." And (Warren 1942, p.1076):

"In the media, the elastic tissue degenerated and the smooth muscle cells showed vacuolation, hyalinization or atrophy. This coat was thickened as well by the presence of large, sometimes branching fibroblasts with abundant collagen. The degeneration of elastic lamellas was sometimes complete with substitution of fibrous tissue or bands of hyalinized collagen. He [Wolbach 1909] also emphasized the progressive character of the vascular lesions and cited the proliferation of fibroblasts in the media of arteries as late as four years after the last exposure to roentgen rays. However, even in severe damage, some normal blood vessels may be seen."

• Part 8: Summary, and a Recommendation

Existence of severe injury to the heart and its coronary arteries, inflicted by medical irradiation at very high doses, has been acknowledged for at least five decades. However, the number of people

who accumulate only low and moderate doses, of heart irradiation, far exceeds the number of cancer patients whose hearts receive very high-dose irradiation. This was true in the past, and is likely to remain so in the future.

The dose-response evidence in Chapters 40 and 41, combined with collateral circumstantial evidence, is persuasive that routine medical radiation was and continues to be a highly consequential "player" in the etiology of coronary atherosclerosis and fatal Ischemic Heart Disease.

In light of such evidence and the pathologic evidence in this appendix, we are confident that xrays can cause TWO types of heart-related damage: a) Atherogenic lesions and b) Non-atherogenic high-dose radiogenic damage to the heart and its coronary arteries.

We have found no dispute over the evidence that the damage to the heart and the coronary arteries, from very high-dose xrays, typically (not always) DIFFERS from atherosclerotic lesions. Therefore, we urge that distinct labels be used in the literature, whenever lesions have different characteristics and different etiologies.

If investigators and journal editors persist in referring to non-atherogenic high-dose radiogenic damage as "heart disease," or "atherosclerotic plaque," or "Coronary Artery Disease," the practice can badly obscure what is really going on, and even can introduce unnecessary bickering among investigators, to no good end.

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