Initial clinical reaction to therapeutic whole-body x-radiation

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Abstract

Early clinical events displayed by 11 cancer patients after whole-body roentgen treatment in one single large dose are compared with previous reports on "radiation sickness" and with acute sequelae observed in nuclear accidents. From this comparison, the typical initial reaction to penetrating radiation emerges as follows: signs and symptoms—essentially in form of fatigue, nausea, and vomiting—begin to develop within 2 to 4 hours postexposure; they reach a climax somewhere between 5 and 8 hours; and they completely subside on the second or third day. During the intense phase of the disturbance, approximately extending from 4 to 10 hours postexposure, about 60 percent of the irradiated persons experience various degrees of disability. Despite its transitory nature, the reaction may present a major medical problem in civil defense situations because of coincidence and, thereby, of interference with evacuation plans and first-aid procedures. Therefore, the early sequelae of exposure to penetrating radiation require the attention of all physicans who may have to manage such emergencies.

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Introduction

Medical application of Roentgen's discovery of the "x-rays" soon led to the observation that cancerocidal doses of the new agent frequently elicited an early systemic reaction characterized by dizziness, fatigue, anorexia, nausea, and vomiting. This clinical complex—termed "radiation sickness"—developed into a more and more serious problem as intensity and penetration of radiation increased with technical advancement of x-ray equipment (1-3). The radiotherapist then learned to minimize the irksome side-effect by dividing the total dose into fractions delivered at intervals; size of each fraction and length of intervals between exposures were determined by the patient's disease and general condition. This procedure, together with closer restriction of radiation to the desired body part, proved so effective that "radiation sickness" lost its significance for modern radiotherapy. Renewed interest in the early clinical reaction, however, arose with advent of the atomic age. Ever accelerating utilization of nuclear energy, for military and industrial purposes alike, created the hazard of deliberate or, to a much lesser degree, of accidental disasters exposing large populations to significant amounts of penetrating radiation. Under these circumstances, early clinical sequelae constituting the initial reaction to such exposure have left the exclusive realm of radiotherapy and have entered a sphere of concern to all physicians

who, in an emergency, might be confronted with radiation casualties. This atomic age also brought about the need for more precise terminology based upon the time relationship between the various phases in the clinical response to penetrating radiation. To specify the early burst of signs and symptoms, the broad term "radiation sickness" should be replaced by the more restricted and more striking denotations "initial reaction" or "prodromal reaction" (4-6).

Although almost extinguished as sequel of routine therapy, the initial reaction still can be seen and studied in the exceptional instances requiring treatment with single high doses to the entire body (7). Observations on such patients merit particular interest because they represent the only human data for which type of radiation, dose distribution, and total dose are known with certainty; therefore, they are indispensable for establishing correlations between physical parameters and clinical consequences of radiation. Based on 11 additional case histories, the present report describes the early radiation-induced response, and evaluates its potential role in nuclear disasters.

Method

Previous studies (7,8) had shown that whole-body irradiation might be eligible as a tool for inducing palliation, or even temporary remission, in cancer patients inaccessible to more promising kinds of treatment. Accordingly, the 11 patients selected for the present series suffered from malignant neoplasms that were so widely disseminated and so far advanced—predominantly stage-III lymphomas of various histological types (table I)—that any other mode of

management appeared hopeless. The antecedent clinical history varied; in most instances, records revealed futile attempts at controlling the disease either by local x-radiation, or by steroid administration, or by chemotherapy.

Hospital admission preceded irradiation by at least one week; during this period, each particular patient was seen daily by the same resident physician who, in addition to the usual examinations, recorded activity, behavior, and mental attitude. Having retained relatively good general condition, 7 of the 11 patients were allowed to walk freely about the ward and to participate in moderate physical activities; for the remaining 4, however, confinement to bed became necessary because of weakness, weight loss, and a tendency toward both nausea and temperature elevations. The 1-week adaptation phase was followed by the radiation treatment and, then, by a postexposure period of observation usually exceeding 10 days. At all times, even on the day of treatment, the initially established routine persisted—examination by the same physician, normal meal schedule, and liberty of movement for ambulatory patients. Administration of radiation, as a rule, occurred during the interval between breakfast and lunch (table I); only occasionally, antiemetic prophylaxis appeared indicated.

The radiation source was a conventional x-ray apparatus under the following conditions of operation: 250 kvp; 30 ma; filtration added to beryllium window of tube, 1 mm aluminum and 0.5 mm copper; half-value layer, 1.2 mm copper; open portal; and distance from target to midcoronal plane of the patient, 200 cm. At that distance, the dose

rate in air averaged9 r/min. Multiplication of this value with exposure time yielded the "nominal air dose" (9) that has been adopted for dosimetry throughout the present analysis. As verified by radiographic check-films, the entire body remained well within the primary beam directed horizontally toward the patient who, with hips and knees flexed, lay sideways on a treatment table; first facing the x-ray machine he received one-half of the prescribed dose, then presenting his posterior aspect to the source he obtained the remaining half-dose. In this manner, whole-body doses of either 150 r or 200 r (table I) were administered during one single session approximately lasting 20 min. for 150 r, and 25 min. for 200 r.

Results

As its most striking feature, the initial reaction displays wide variability among persons exposed to similar, or even identical, doses. Corroborating previous findings (7), the present series comprises degrees ranging from complete absence of symptoms to severe prostration. This dramatic individual difference of unknown origin, together with the difficulty of assessing complications possibly caused by the preradiation disease, render the number of 11 patients much too small for derivation of a typical clinical picture. Yet, from a comparison of present findings with previous reports on early consequences of both therapeutic (7) and accidental (5) whole-body exposure, the typical initial reaction emerges with reasonable accuracy (10).

Typical clinical picture. Throughout the time of exposure, radiation induces no sensations, and the patient remains completely

asymptomatic. After completion of treatment, this freedom from symptoms continues for about one or two hours—"delay period" (10). Then, rather abruptly, the reaction starts with the onset of fatigue, listlessness, and apathy. Usual activities are discontinued; lying down on his bed, the patient withdraws more and more from his environment and appears depressed. Not infrequently, he describes his condition as "washed-out" or "worn-out," and complains about dizziness, dullness, and headache. This "fatigue complex" (11), as a rule, is accompanied by concurrently developing signs and symptoms pointing to the gastrointestinal tract. Loss of appetite and complaints about an "upset stomach" suddenly enter the scene around 2 hours postexposure. Nausea, frequently associated with spells of frank vomiting, soon supervenes and increases in intensity until it reaches a climax somewhere between 5 and 8 hours postirradiation. At that time, the combination of "fatigue complex" and "vomiting complex" may lead occasionally to pronounced weakness or even to prostration. After passage through the climax, the reaction steadily recedes; intervals between bouts of vomiting lengthen, emeses decrease in number as well as in volume until they disappear completely, then, nausea, anorexia, and fatigue subside in this order. Due to gradual ebbing of the waves caused by the succession of exacerbations and remissions, duration of the initial reaction cannot be defined accurately; yet, the following course is the rule: on the second day, moderate nausea and occasional spells of vomiting still persist but the general condition is markedly improved; on the third day, the patient becomes asymptomatic.

Special observations. Two factors are of decisive importance for both nuclear accidents and atomic disasters (12): First, the delay time elapsing between exposure and onset of the initial reaction represents the period during which an exposed group remains in full possession of fitness and alertness—two properties so vitally necessary for well-organized active evacuation of disaster areas. Second, both duration and extent of disability occurring after onset of the initial reaction determine the degree of reduction evidenced by the exposed group's work potential—e.g., capability for active participation in evacuation procedures and rescue efforts. To arrive at reasonably accurate assessments of these two factors, the present findings again must be supplemented by previous data (7,13).

The delay time is known most reliably for the 7 patients who experienced reactions leading to vomiting. Owing to its occurrence shortly after onset of symptoms, the first emesis strikingly and dependably marks beginning of the initial reaction and, thereby, length of the delay period. To enable assessment of this important factor, table II contains, first, the present findings; second, a part of the M. D. Anderson results (7)—out of 30 patients exposed to 200 r, observations are presented only for those who vomited during the first 24 hours after treatment; and third, data reported for the Y-12 accident (13). Most conspicuously, the table demonstrates three points: a.—when vomiting develops at all during the first day, the initial emesis consistently occurs in the interval between 1 and 5 hours postexposure; b.—in the several-hundred-roentgen range, length of the delay period barely is affected by dose; and c.—agreement between

therapy and accident data suggests irrelevance of radiation type (roentgen, gamma, neutron, or any mixture of these penetrating rays). Validity of the three points has been established by a comprehensive analysis covering additional therapy evidence and all known nuclear accidents (10). Hence, it must be anticipated that a population exposed in the several-hundred-roentgen range will remain completely asymptomatic for one hour, and will experience a negligible incidence of initial reactions until two hours postirradiation. Consequently, for all practical purposes, the 2-hour time limit represents the delay period applicable to a large group of persons because, after transgression of this limit, incidence of prodromal reactions rapidly grows to reach a maximum between the fourth and fifth hours postexposure. That, occasionally, vomiting may start on the second or even third day has been reported for all groups —radiotherapy patients, individuals involved in nuclear accidents, and Japanese bomb casualties; these rare atypically-timed manifestations probably must be explained as reactions to psychogenic stresses or to other complications (10).

Duration and extent of disability displayed an extraordinary variability. Among the present series, two patients remained completely asymptomatic and, as a consequence, retained full possession of both mental and physical faculties existing prior to exposure. In two other patients, the reaction assumed the form of a mild indisposition characterized by fatigue, anorexia, and episodes of nausea, headache, and dizziness. Even during the period of definite discomfort, approximately ranging from 2 to 8 hours postexposure, almost any degree of activity probably could have been performed when required

by necessity. Quite a different appraisal, however, emerged for the seven patients who developed initial reactions associated with vomiting. Here, during their most intense phase usually extending from 2 to 10 hours postradiation, prodromal effects distinctly impaired mental and physical capabilities alike. Apathy and depressed mood combined with weakness and malaise created incapacitation of such a degree as to seriously hamper execution of any task surpassing well-drilled actions. Although too evasive for objective assessment, clinical impression suggested that, in most instances, disability attained an extent too great to be overcome, or alleviated decisively, by psychologic factors—probably, even not by the strong motivations inherent in disaster situations. Beyond any doubt, such a conclusion could be drawn especially for one patient who, throughout 24 hours, exhibited complete prostration and absolute inability to walk. In summary: extent of disability among the 11 patients ranged rather evenly from unnoticeable impairment to absolute physical incapacitation; when occurring, disability generally occupied the interval between 2 and 10 hours postexposure. How do these findings compare with previous data?

According to severity of reaction, comparison of the present series (G) with both the M. D. Anderson group (MDA) and the Y-12 patients (Y) yields the following incidences: completely asymptomatic—G, 18%; MDA, 21%; Y, 20%; mild reaction not exceeding nausea—G, 18%; MDA, 18%; Y, 20%; marked reaction associated with vomiting—G, 64%; MDA 61%; Y, 60%. Between therapy and accident data, this close conformity with respect to distribution of severity probably is

paralleled by a similar agreement as to duration and extent of disability. Hempelmann's case reports (5) contain several striking examples of the initial reaction and its various degrees of incapacitation occurring most conspicuously during an interval ranging from 2 to 10 hours after the accident. One additional point requires brief mentioning. Despite the fact that, in general, accidental doses by far exceed the therapeutic range used in the present series, the initial reactions closely correspond in degree and duration. Most likely, this surprising relationship is the result of two contributing factors: first, because of their spontaneous tendency toward nausea, cancer patients react at lower doses more vehemently than healthy persons; and second, within the several-hundred-roentgen range, severity of the initial reaction does not increase materially as dose exceeds the 200 to 300 r level (10).

Other findings on the present series were surprisingly inconspicuous and equivocal. At the height of the reaction—between the fifth and the eighth hour postexposure—5 patients showed a slight elevation of temperature, a trivial acceleration in the rate of both pulse and respiration, and a just noticeable drop in blood pressure. That these changes might represent true components of the initial reaction, despite their failure to occur in the remaining 6 patients, is suggested by the development of similar effects in persons exposed to much higher doses during nuclear accidents (5).

Case reports. To illustrate the points discussed thus far and to demonstrate the various types and degrees of clinical picture, three case histories have been selected according to a step-wise increase in severity of the initial reaction.

1. Mild initial reaction, patient N.C., case number 3 of present report. Throughout one year prior to admission this 61-year-old woman had suffered from recurrent pleural effusions of unknown origin necessitating two thoracenteses. During the last few months of that period, she experienced a 25-pound weight loss, shortness of breath with "fluttering" of heart, and enlargement of lymph nodes—particularly conspicuous in both supraclavicular and axillary regions. After admission, biopsy of a scalene lymph node revealed malignant lymphoma—Hodgkin's granuloma.

During the pre-exposure observation period, the patient was found to be in fair physical condition; throughout most of the daytime, she walked about the ward and performed light work. Her morale was good; she liked to converse with patients, nurses, and physicians alike, and she displayed a positive attitude toward both her disease and her new environment. On 29 August 1957, she had breakfast as usual around 8:00 a.m. Later that morning, total-body radiation (150 r) was administered as follows: first half-dose, 11:08 a.m. to 11:25; repositioning, 11:25 to 11:30, and second half-dose, 11:30 to 11:47 a.m. Completely unaffected by the radiation procedure, the patient resumed her usual activities soon after return to the ward; however, some resentment about the frequent close examinations was expressed. Temperature, pulse, respiratory rate, and blood pressure showed normal values. At 12:30 p.m., she ate lunch with fair appetite. Around 1:30 p.m.—2-1/2 hours after start of exposure—a spell of ill-being erupted suddenly; fatigue, headache, and anorexia appeared as chief complaints over which were superimposed brief episodes of nausea

associated with regurgitations causing "sour" taste but no frank emesis. After a 1-hour duration, this wave of discomfort largely subsided, and was followed by resumption of usual activities; however, listlessness and a somewhat subdued behavior persisted. Althouth the 3:30 examination revealed a small rise in temperature associated with trivial fall of both blood pressure and pulse rate, the patient expressed no complaints. This practically asymptomatic state was interrupted by a second wave of apathy, anorexia, and nausea arising around 5:30— 6-1/2 hours postexposure. The period of discomfort approximately lasted two hours; thereafter, the patient returned to a completely asymptomatic state. During the following days, a few periods of poor appetite were the only complaints that, possibly, could have been caused by the irradiation treatment.

Comment: The initial reaction of this patient stands out as two waves of mild indisposition, with no appreciable impairment of mental and physical capabilities.

2. Moderate initial reaction, patient J.H., case number 10 of present report. Since several months prior to hospitalization, this 25-year-old man progressively experienced general weakness, exertional dyspnea, epigastric as well as substernal pain, and loss of body weight. On admission, the most prominent findings were generalized adenopathy and a marked reduction of both capacity and distensibility of the stomach displaying large gastric rugae. Biopsy of the right lacrimal gland revealed infiltrations of small lymphocytes consistent with the diagnosis of lymphosarcoma.

During the pre-exposure observation period, the patient complained about weakness, nasal congestion, and night sweats; however, he was able to ambulate and to participate in some activities. On 5 November 1957, the patient had his usual breakfast around 8:00 a.m., and received total-body radiation (200 r) between 9:30 and 10:00 a.m. He, then, walked about the ward and conversed with other patients. This period of obviously unimpaired condition suddenly terminated at noon—2-1/2 hours after start of radiation—with the abrupt onset of marked anorexia and severe nausea that were swiftly followed by a bout of vomiting. Lunch could not be eaten. Although vomiting failed to recur, anorexia and nausea unabatedly persisted until 4:00 p.m. and, then, gradually subsided. During the intense phase of discomfort—extending from 2-1/2 through 6 hours postexposure—the patient appeared apathetic, weak, and too listless for ambulation. At the height of the reaction, temperature rose to 100 degrees, while pulse rate, respiratory rate, and blood pressure practically remained unchanged. Late in the afternoon, improvement became clearly evident; some supper was eaten at 5:00 p.m. and, thereafter, ambulation could be resumed, although slight listlessness still persisted. On the next morning, the patient appeared asymptomatic, and ate his entire breakfast with good appetite. Comment: The initial reaction of this patient causes a moderate impairment of mental and physical fitness, prominently, during a 5-hour period starting at 2-1/2 hours postirradiation.

3. Severe initial reaction, patient V.A., case number 5 of present report. Approximately 3 months prior to admission, this 69-year-old man noticed development of a tumor in the epigastrium. Growth of the mass was

paralleled by increasing polydipsia, polyphagia, polyuria, and weight loss. Examination on admission revealed lymphadenopathy, particularly prominent in the left parietal and left axillary regions. Exploratory laparotomy and biopsy disclosed the large abdominal mass as malignant giant-follicle-lymphoma.

During the pre-exposure observation period, the patient's physical condition was fair; he liked to roam about the ward and to assist in little tasks. Displaying a bright and cheerful attitude, he easily and swiftly established friendly relations with other patients as well as with hospital personnel. On 9 April 1957, he had his usual breakfast around 8:00 a.m. Total-body radiation (150 r) was started at noon and was completed by 12:40 p.m. After return to the ward, the patient displayed his normal cheerful attitude in explaining to others the procedure through which he had just passed. Subsequent to the 1 o'clock lunch, eaten with perfect appetite, he slept for one hour as was his custom. This completely asymptomatic period ended sharply at 3:20 p.m. when vomiting suddenly started. Concomitant with the onset of repetitive emeses—producing large amounts of undigested food and watery fluid—increasing lethargy developed. Muscle strength, particularly in the lower extremities, was distinctly reduced, and the gait appeared unsteady and atactic. The distress reached a climax between 5 and 6 p.m. At that time, the patient became prostrated and mentally depressed; the temperature rose from 98 to 101.2 degrees while pulse, respiratory rate, and blood pressure remained unchanged; attempts at eating supper were answered immediately by such severe bouts of vomiting to necessitate peroral administration of 25 milligrams of

chlorpromazine hydrochloride. The period of intense disability lasted about 5 hours. Around 8:30 p.m., marked improvement already made its appearance as indicated by resumption of ambulation and consumption of a small meal consisting in corn chips, oranges, and the drinking of some water. On the next morning, the patient appeared asymptomatic; muscle strength had completely returned; and breakfast was eaten with normal appetite. During the following days, no complaints related to the radiation treatment were expressed; however, some waves of anorexia, extending into the fourth postradiation day, perhaps must be regarded as last remnants of the initial reaction.

Comment: The initial reaction of this patient appears as a transitory severe depression of both mental and physical capabilities; the period of disability begins at 3-1/4 hours after start of irradiation and lasts for about 5 hours.

Discussion

The subsequent discussion of the initial reaction will center around two aspects—namely, first, its potential significance in the atomic age and, second, its therapeutic management.

Civil defense aspects. When medical assistance is available as readily as in both radiotherapy and reactor accidents involving small numbers of persons, the initial reaction represents a bothersome but insignificant side effect that, due to its short duration, rarely poses serious problems. Yet, that this harmless disorder may assume quite a different role ensues from an analysis of certain civil defense situations (12). Obviously, nuclear disasters can assume such dimensions that exposed persons, in order to reach medical facilities, may have

to endure several hours of driving or walking through streets congested by vehicles and panic-stricken people. Thus, while on their way, they become affected by the disturbance and, thereby, suffer reduction of fitness at a time when ultimate physical and mental efforts are necessary for survival. In a small group of hypersensitive persons, reactions probably will attain such severity as to imperil escape from the disaster area without aid. Therefore, the disturbance must be taken into account by authorities designing evacuation plans and other emergency measures which require active participation of exposed populations. The several-hour delay between exposure and arrival at medical facilities also has another implication demanding the physician's attention: on admission, casualties already may display initial reactions. Radiation-induced dizziness, nausea, and vomiting—when occurring in patients with mechanical or thermal lesions, particularly of head and abdomen—easily can be mistaken as sequelae of these other injuries. Thus, unrecognized, the initial reaction may jeopardize proper diagnosis, prognosis, and classification of casualties (12).

Therapy. Owing to its unsolved pathogenesis, the reaction can neither be prevented nor treated with specific remedies. Nevertheless, clinical experience has firmly established several principles of management which, when properly applied, enable alleviation or even suppression of overt manifestations in many instances. Among these principles, psychologic reassurance demands the leading role because, similar to motion sickness, the initial reaction frequently is aggravated by apprehension or introspection. Such reassurance becomes especially important in civil defense situations where uncertainty

and fear, triggered by onset of nausea and vomiting, may grow so powerful as to induce outbreak of mass hysteria in an uninformed exposed population. Education must center around two characteristic peculiarities of the initial reaction—namely, first, its brief transient course and, second, its relative insignificance as indicator of received doses; in a wide dose range, severity of clinical manifestations is determined much more by individual susceptibility than by amount of radiation (10). Radiotherapy experience demonstrates that proper psychologic preparation and treatment frequently suffice for controlling the distress. When these measures prove insufficient, however, additional steps must be taken. Among the drugs, probably all sedatives are beneficial; by contributing to the restoration of equanimity they support psychologic measures, and by depressing the excitability of autonomic centers they raise the threshold for nausea and vomiting. Selection of type and dose of medication is determined by the given situation; often, the drug of choice will be one that acts almost exclusively on the medullary autonomic centers but does not affect cortical functions. Since barbiturates possess certain deficiencies in this regard, they are replaced increasingly by more effective chemicals developed during recent years—e.g., meclizine, prochlorperazine, and chlorpromazine. According to clinical experience, the combination of psychologic measures and drug medication leads to a satisfactory alleviation of the initial reaction in the vast majority of cases. Only the occasional hypersensitive patient will develop disturbances of such a degree as to necessitate parenteral supply of fluid, glucose, and protein.

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TABLE I

Survey of patients treated with whole-body x-radiation

Patient No.	Sex	Age years	Diagnosis	Nominal air dose r	Start of radiation; time of day
1	f*	62	Hodgkin's disease	150	0915
2	m**	57	Adenocarcinoma	150	1235
3	f	61	Hodgkin's disease	150	1115
4	m	39	Hodgkin's disease	150	0930
5	m	69	Giant follicle lymphoma	150	1200
6	f	15	Ewing's sarcoma	150	1310
7	m	5	Acute lymphocytic leukemia	150	0930
8	m	48	Carcinoma of kidney	200	1010
9	m	13	Malignant lymphoma	200	0900
10	m	25	Lymphosarcoma	200	0930
11	m	52	Malignant lymphoma	200	0900

*f: female; **m: male

TABLE II

Delay time elapsing between start of total-body irradiation and onset of vomiting on the day of exposure; observations on cancer patients—present series, and M. D. Anderson series (reference 7)—are compared with findings on healthy persons involved in a typical nuclear accident (reference 13)

Patient No.	Present series first emesis hours	Present series air dose r	M.D.Anderson series first emesis hours	M.D.Anderson series air dose r	Nuclear accident first emesis hours	Nuclear accident body dose rad
1	nausea only	150	2	200	2	365
2	4.5	150	2	200	4	270
3	nausea only	150	2	200	asymptomatic	339
4	asymptomatic	150	3	200	2	327
5	3.3	150	3	200	nausea only	236
6	1	150	3.5	200		
7	3.5	150	4.5	200		
8	1.8	200	5	200		
9	1.5	200				
10	2.5	200				
11	asymptomatic	200				