SYMPTOMATIC DISTURBANCE AFTER SINGLE THERAPEUTIC DOSE OF X RAYS

ITS RELATIONSHIP TO THE GENERAL RADIATION SYNDROME

BY

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The development of atomic power and the consequent dangers, both in war and in peace, of exposure to the radiations produced by nuclear fission have instigated extensive research into the effects of whole-body irradiation on many animal species. This research, together with the observations made on the populations of Hiroshima and Nagasaki following their exposure to the radiations of the atomic bombs, has shown that such irradiation produces a fairly well defined pattern of signs and symptoms, collectively known as the general radiation syndrome (Fig. 1). This syndrome has been reproduced following whole-body irradiation given to a wide range of mammals such as rats, mice, monkeys, dogs, swine, etc., and, although there are certain species differences, particularly concerning the critical dose of x rays required to produce the full syndrome in each instance, the overall picture of the syndrome is sur-

The position to-day regarding the aetiology of these symptoms is only a little less confused. Progress has been hampered by the lack of any clear-cut definition in the medical literature of what has come to be known to radiotherapists as radiation sickness, and the apparent absence of any correlation with the disturbances found after the experimental whole-body irradiation of animals.

It is the object of this communication to describe the pattern of symptoms which occurs in human beings shortly after a single exposure to a dose of x rays within therapeutic limits, and to demonstrate the place of this pattern within the general radiation syndrome.

Clinical Material

Concurrently with the supervision of the x-ray therapy of certain patients referred to the Radiotherapy Department of Hammersmith Hospital, detailed clinical observations were made before and after a single dose of x rays. Fifty such patients have now been observed, and they were selected for these studies because their general health was good and the nature of their disease necessitated the irradiation of a large volume of tissue. The primary diseases of these patients are as follows:

Ankylosing spondylitis	20
Reticulosis	20
Carcinoma of ovary (post-operative)	5
" " testis "	2
" " thyroid "	1
Malignant melanoma (recurrent)	2

It will be seen that the majority suffered either from ankylosing spondylitis or from various forms of reticulosis.

In the latter group all patients except one have been early or moderately early cases of Hodgkin's disease, follicular reticulosis, and reticulum-cell sarcoma, the single exception being a case of multiple myeloma. The patients suffering from carcinoma of the ovary, testis, and thyroid had been referred for radiotherapy following surgical excision of the primary tumour. Both cases of melanoma demonstrated metastases after surgical treatment of the primary tumour at an earlier date, the recurrences being widespread.

To provide a control series of observations, sham irradiations were also given to 34 of the 50 patients. The conditions of the sham irradiation exactly resembled those of the actual irradiation in respect of the positioning of the

patient under the x-ray tube, the number of fields apparently irradiated, and the delineation of the fields of irradiation on the skin. The patient believed that irradiation was being carried out, and was in position under the tube for the correct period of time. The x-ray tube, however, was not energized.

Irradiation

Sites.—The main sites of irradiation are shown in the Table. The sacro-iliac joints and whole length of the spine were irradiated in patients suffering from ankylosing spondylitis and also in the one patient with multiple myeloma. In the patients with reticulosis, irradiation was given either to the upper half of the trunk or to the abdomen, depending upon the main sites of distribution of the lesions, the only exceptions being one individual with reticulum-cell sarcoma in whom radiation was directed to the lower part of the left half of the pelvis and upper half of the left thigh, and three

FIG. 1.—Diagrammatic representation of the general radiation syndrome in man. (Adapted from Liebow, Warren, and De Coursey, 1949.)

prisingly comparable throughout the range of mammals investigated. The fact that such a reproducible syndrome exists is of great value and importance in furthering basic research work into physiological disturbances produced by x rays.

Walsh (1897) first described acute constitutional symptoms in an x-ray worker, and since that time many reports have appeared concerning the production of such symptoms as nausea and vomiting in patients undergoing radium and x-ray therapy. Early workers held several factors to be responsible for these symptoms, among which may be mentioned poor ventilation of the treatment rooms, electrical charging of the patient's body, psychological disturbances, and the release into the circulation of the toxic products of protein breakdown.

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Incidence of Symptoms After a Single Dose of X Rays to Various Sites

Radiation Given		No. of Patients		
Site	Mean Integral Dose	Irradiated	Developing Symptoms of Any Type	Developing Vomiting
Whole spine and sacro-iliac joints	4.0	21	20 (97%)	12 (57%)
Whole abdomen	3.4	10	9 (90%)	6 (60%)
Upper half of trunk	3.9	13	11 (84.5%)	4 (31%)
Whole body	2.9	4	2 (50%)	1 (25%)
Lower abdomen and thigh	4.2	1	0	—
Both thighs	3.8	1	0	—

patients to whom whole-body irradiation was given. Whole-abdominal irradiation was employed in those patients who had had testicular and ovarian tumours excised. One patient with an undifferentiated carcinoma of the thyroid was given wide-field irradiation of the upper half of the trunk; and of the two patients with melanoma metastases one was given whole-body irradiation and the other had both thighs irradiated.

Dosimetry.—All patients were irradiated with x-ray tubes operating at 250 kV. the tube current being 18 mA. In each instance dosage has not been expressed in terms of the number of conventional r units received on the skin or at some defined point deep to the skin, but in terms of the total amount of energy absorbed within the body, calculated in megagram-roentgens. The estimate of total energy absorption is known as the "integral" dose, and from the biological standpoint it carries greater significance than an estimate of dose in r units, allowing, with certain reservations, comparisons to be made between results obtained following irradiation in differing sites of the body. In the calculation of integral doses, valuable help has been given by Mr. J. W. Boag, of the M.R.C. Radiotherapeutic Research Unit, and the figures for whole-body irradiation have been derived from the observations of Mayneord and Clarkson (1944). The Table demonstrates the mean integral dose given in the various sites irradiated.

Results

The General Symptom Pattern

Symptoms developed in 42 out of 50 patients irradiated (84%), and the chief symptoms were found to be fatigue, anorexia, nausea, and vomiting. The pattern of symptoms in each instance was found to be very similar (Fig. 2), and

FIG. 2.—Diagrammatic representation of symptom pattern after a single therapeutic dose of x rays.

differed in degree only from one patient to another. The time interval which elapses from the beginning of irradiation until the disappearance of all symptoms can be divided into three main periods: the latent period, the period of acute disturbance, and the period of recovery.

Control Sham Irradiation

Information was obtained from the control sham irradiations concerning the part played by psychological and emotional disturbances in determining the incidence of symptoms. Eight out of the 34 patients developed symptoms from their sham irradiations (23.5%), but in no instance did the pattern of symptoms resemble that following the actual irradiation. It was characteristic that in these circumstances the patient complained of symptoms, chiefly headache and fatigue, either during the period of apparent irradiation or immediately after leaving the treatment room. The emotionally or psychologically disturbed patient failed to demonstrate any latent period—in complete contrast to the symptom pattern following actual irradiation. In the great majority of instances the sham irradiation was given some days before the actual irradiation, and it was noticeable that those who developed symptoms after their sham exposures did not develop any symptoms at comparable times after their actual irradiation.

Detailed Analysis of Symptom Pattern :

1. Latent Period

The mean time lapse from the beginning of irradiation to the development of symptoms was 2.7 hours. It appeared that the latent period was shorter in those patients who were generally more severely upset and who developed vomiting. A comparison made between these two groups showed that there was a difference of nearly three-quarters of an hour between the mean values of the latent periods, a difference which was found to be statistically significant (see appendix). The lengths of these two latent periods have been examined for possible influences upon them of sex distribution, dosage, disease, and site of irradiation, but no evidence has been found that these factors were responsible for the significant difference observed. It seems fair to conclude that, following a given dose of x rays, the more sensitive an individual is to the effects of irradiation the earlier are the symptoms likely to appear.

It will be realized that the latent period as calculated includes the period of time occupied by the positioning of the patient under the x-ray tube and in most instances by the irradiation of several fields. On an average this period is approximately half an hour, so that the absolute value of the latent period, assuming irradiation to have been given in an instantaneous period of time, is approximately 2.25 hours for all the patients in the series.

2. Period of Acute Disturbance

The usual complaints are of a sudden bout of nausea or of a sudden feeling of severe fatigue. Less frequent initial symptoms are headache of no particularly characteristic distribution, a feeling of dizziness or "muzziness" in the head, and an emotional disturbance taking the form of acute mental depression, in a few instances accompanied by actual weeping. Whatever the initial symptoms may be, the predominant symptoms which establish themselves in the early part of this period are fatigue, anorexia, and nausea. Objective assessment of these symptoms is practically impossible, but it appears that, after being present for a time interval varying approximately from half an hour to an hour and a half, three developments may occur, depending on the severity of the patient's upset. In the mild case the symptoms gradually subside; in the moderately severe case either the fatigue element or the feeling of nausea, or both, become accentuated for a further period of about one hour before subsiding; and in the severe case vomiting and retching supervene. Only one bout of vomiting may occur, but in the more severe cases there may be vomiting at intervals for a period of two to three hours. After the cessation of vomiting the recovery period ensues.

In studying the incidence of the various symptoms in this period of acute disturbance it is clear, both from

impressions of the observer and from the descriptions given by the patients, that fatigue appears to be dissociated from nausea and vomiting. Thus in some individuals the outstanding complaint is one of fatigue, nausea being a mild transitory symptom and vomiting not occurring at all. In rare instances the patient has never complained of nausea but solely of fatigue. On the other hand, at least four patients were encountered whose presenting symptom was nausea, which was rapidly followed by vomiting, but in whom fatigue, apart from slight tiredness apparently consequent upon the act of vomiting, did not occur at all. It was a striking observation that these latter patients remained perfectly well between their bouts of vomiting, and as soon as their vomiting ceased had no further symptoms. This suggests that two aetiological disorders may underlie the development of these symptoms—one associated with fatigue and the other with nausea and vomiting.

A detailed analysis of the incidence of symptoms for each site irradiated, and in particular for the incidence of vomiting, is shown in the Table. The incidence of vomiting when irradiation was confined to the upper half of the trunk was 31%, as opposed to an incidence of 60% when the abdomen alone was irradiated. However, the total numbers in each group are small, and, by considering all instances in which radiation was not directed to the abdomen in contrast to all those in which the abdomen was irradiated, irrespective of whether radiation was directed to other sites as well, the relevant figures are 29% and 53%. Statistically these two sets of figures are not significant, but in the larger group the difference approaches much nearer to a significant level than in the smaller group. It is possible that with an even larger series of patients a significant difference may be found in the incidence of vomiting, depending on whether the abdomen is irradiated or not.

During this period of acute disturbance no consistent changes have been noted in the pulse rate, blood pressure, body temperature, and respiration rate up to the act of vomiting.

3. Recovery Period

An accurate estimation of the recovery period is difficult, but it is possible to make an approximate estimate to the nearest day. With the subsidence of the period of acute disturbance the patient is left with a feeling of mild fatigue, nausea, and anorexia. Depending on the degree of acute disturbance, these symptoms either persist for one day or less, or extend in the most severe instances over a period of up to five days. In the most severely upset patients nausea may persist for two to three days, but of the three outstanding symptoms it is the first to disappear. Its disappearance is followed by the gradual subsidence of fatigue and anorexia, in that order.

The General Radiation Syndrome

The pattern of symptoms following a single dose of x rays within therapeutic limits having been demonstrated, the basic pattern of the general radiation syndrome, observed after the exposure of both animals and man to high levels of radiation, must now be considered.

The main features of the general radiation syndrome are depicted in Fig. 1. This diagram was derived from the observations made upon Japanese necropsy material and from the histories and clinical features of the survivors (Liebow, Warren, and De Coursey, 1949). It will be seen that there are four main periods in which clinical disturbances and death may or do occur, which may be designated: the period of initial reaction, the period of acute reaction, the period of subacute reaction, and the period of chronic reaction.

Period of Initial Reaction.—This supervenes after a brief latent period following exposure, and is characterized by nausea, vomiting, and fatigue. It is probable that the mean length of this latent period is approximately two hours, although species differences and the level of dosage received

may well determine its actual length. In the Japanese cases the latent period is said to have been in some instances as short as half an hour. On the other hand, Painter and Brues (1949) state that the initial signs and symptoms occur within the first six hours in man, the dog, rat, mouse, guinea-pig, and goat. Theoretically it is possible for a human being to die during this stage, as it has been shown that animals subjected to radiation of very high intensity may die either during the period of irradiation or within a few hours of its cessation (Henshaw, 1944). It is generally stated that in most instances the duration of the initial reaction is approximately two to three days and that following its disappearance a period of comparative well-being ensues before the next stage of the general radiation syndrome supervenes. It appears likely, however, that in some of the Japanese casualties and also in some rats and dogs (Painter and Brues, 1949) this period of initial reaction is prolonged towards the end of the first week after exposure, and terminates in death. The human beings showing this developed high fever, thirst, diarrhoea, and delirium before they died. At the time of death clinical evidence of bone-marrow damage was not prominent, and it seems likely that death at this stage is the outcome of an extremely severe form of damage inflicted during the original irradiation.

Period of Acute Reaction.—This stage becomes apparent towards the end of the second week, and is characterized by the clinical features of acute marrow failure, of ulceration of the mucous membrane of the gastro-intestinal tract, of acute secondary infections, and also by epilation.

Period of Subacute Reaction.—This stage occurs at about the end of the sixth week, at which time the marrow damage, clinically obvious in the preceding phase, is becoming less marked. At this stage death may result from lung or brain abscess, persistent ulceration of the large bowel, an exacerbation of a pre-existing focus of infection, and malnutrition.

Period of Chronic Reaction.—The preceding period of subacute reaction probably merges insensibly into the period of chronic reaction, where the presenting features and causes of death are malnutrition, chronic anaemia, chronic infections, premature senility, and possibly leukaemia.

It will be realized that in the majority of patients the complete syndrome will not be shown. In these patients, depending on the amount of radiation received during the original exposure and the inherent radiosensitivity of the individual, one or more of the acute manifestations may develop, resulting in some instances in death. On the other hand, there may only be evidence of mild upset, probably in the form of a minor degree of suppression of marrow function and some epilation. Finally, a proportion of individuals will show no clinical features of the syndrome, but haematological investigation will demonstrate an abnormally low total white-cell count.

Conclusion

It has been shown that, following a single dose of x rays within therapeutic limits and of the order of 3–4 megagram-roentgens, there is a well-defined latent period which terminates in the sudden onset of symptoms, and that the period of acute disturbance, after lasting for a variable number of hours, passes into a recovery phase. The total duration of the symptomatic disturbances has been shown to vary from one to five days, depending on the radiosensitivity of the individual and the actual dose given. The similarity of the symptom pattern following the therapeutic dose of x rays to the period of initial reaction, the first manifestation of the general radiation syndrome, is evident. The close agreement in the length of the latent periods and the similarity of the symptoms justifies the conclusion that after therapeutic x-ray doses the symptom pattern is a milder version of the symptom pattern of the period of initial reaction seen in animals after mid-lethal doses. This conclusion indicates that it is justifiable to utilize observations made

after a single therapeutic dose of x rays in the interpretation of the consequences of exposure to irradiation of greater and possibly lethal proportions.

Summary

The pattern of symptoms following a single therapeutic dose of x rays has been described, based on the findings in a group of 50 patients. The pattern was found to consist of three well-defined phases: a latent period extending from the administration of the x rays to the onset of symptoms; a period of acute disturbance which persisted for approximately between one and a half and four hours after the onset of symptoms, depending on the degree of upset; and a recovery period which in the most acutely disturbed patients extended over four to five days. In those patients in whom the period of acute disturbance was not associated with vomiting the latent period was found to be significantly longer than in those who vomited.

A brief description has been given of the general radiation syndrome produced in man and in many types of mammals following a single mid-lethal dose of x rays, in which four general periods of reaction can be discerned: the periods of initial reaction, acute reaction, subacute reaction, and chronic reaction.

The similarity between the pattern of symptoms following therapeutic doses of x rays and the symptoms of the period of initial reaction of the general radiation syndrome has been stressed, and attention has been drawn to the possible value of using clinical studies based on single therapeutic doses of x rays to interpret what may occur when, either accidentally or under conditions of war, much higher doses are received.

No account has been given of the physiological disturbances produced by therapeutic doses of x rays, which will form the subject of a later communication.

I wish to thank Professor J. McMichael and Dr. Russell Fraser, of the Department of Medicine, Dr. J. F. Loutit, of the M.R.C. Radiobiological Research Unit, A.E.R.E., and Dr. C. A. P. Wood, Director of the M.R.C. Radiotherapeutic Research Unit, for their advice and criticism.

APPENDIX

The mean length of the latent period in the less severely upset group of patients (Group A) has been compared with that in the more severely upset group (Group B). The distribution of the different lengths of the latent periods within each group, the value of the mean and t and P values of the difference of the means are shown below.

	Length of Latent Period (Hours)							
	1-1.49	1.50-1.99	2.0-2.49	2.5-2.99	3.0-3.49	3.5-3.99	4.0-4.49	4.5-4.99
Group A (19 patients)	0	1	2	7	0	7	2	0
Group B (23 patients)	5	4	4	4	1	2	1	2

Mean length of Group A = 3.06 hours } Difference of mean
Mean length of Group B = 2.44 hours } lengths = 0.62 hr.
The t value of the difference is 2.10, indicating that $P < 0.05$ and that the difference is significant.

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ORAL N,N'-DIBENZYLETHYLENE-DIAMINE PENICILLIN IN CHILDREN

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The greatest drawback to the use of oral penicillin has been, in our experience, the variability with which it is absorbed into the blood stream. Several penicillin derivatives have been tried in different dosages, with and without antacids, before and after meals, and scaling the dosage according to body weight. While in a good proportion of cases therapeutic blood levels have been obtained by the oral route, with no preparation have consistent levels been observed; this has meant that, when any case has been treated with oral penicillin, blood-level estimations have been essential to confirm that the antibiotic was being absorbed.

Recently a new salt N,N'-dibenzylethylenediamine penicillin has been available (Szabo, Edwards, and Bruce, 1951); this is referred to here as "penidural." It has been the subject of a recent report by Fletcher and Knappett (1953) as a long-acting repository penicillin following intramuscular injection; we have investigated it from the point of view of reliability of absorption following oral administration.

Side-effects.—Several adults have complained of borborrygmi and urgency at stool during the first 24 hours of treatment but not subsequently. No children of any age have been disturbed, and the palatability of the product has made its administration easy.

Material and Methods

Penicillin blood levels were estimated, using a dilution technique with a strain of *Staphylococcus aureus* of sensitivity to 0.03 µg. of penicillin per ml. A total of 101 children of all ages were given 300,000 units of penidural and their blood levels were estimated three to four hours after administration for reliability of absorption. In addition a small series of 17 adult volunteers were investigated with the same preparation.

The penidural was given irrespective of the times of meals and whether the stomach might be full or not.

Results

Fig. 1 shows that the antibiotic was reliably absorbed in all of the 118 cases in which it was administered, and Table I shows the levels obtained in the 101 children. In several

TABLE I.—Serum Penicillin Levels in 101 Children Three Hours After 300,000 Units of Penidural

Weight in lb.	0.06 unit per ml.	0.125 unit per ml.	0.25 unit per ml.	0.5 unit per ml.	Total Cases
0-10	—	1	4	—	5
11-20	—	5	2	1	8
21-30	7	4	6	1	18
31-40	10	13	—	2	25
41-50	8	8	1	—	17
51-60	5	7	—	—	12
61-70	5	5	1	—	11
71 and over	1	4	—	—	5
TOTALS	36	47	14	4	101