RADIATION SICKNESS

AN ANALYSIS OF OVER 1,000 CONTROLLED
DRUG TRIALS

BY

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The multiplicity of drugs recommended for the treatment of radiation sickness accords with our ignorance of the precise somatic causes of the condition. It also reflects a confusion aptly summarized in an editorial comment on anti-emetic trials: "Of the many reports through the years, most are of little value because the design of the experiments has been poor and statistical treatment of the data either suspect or not carried out" (*Brit. med. J.*, 1954). It should therefore be possible to derive some information concerning the basic causes of radiation sickness from a controlled statistical assessment of its response to drug therapy.

There are two main drugs in general use and of accepted value in the palliation of symptoms from radiation sickness—pyridoxine and the phenothiazines. Even with the best drugs, however, until the last year or two, relief in approximately two out of three cases of radiation sickness was the best that could be expected (Finney, 1961). The value of corticoids in the condition has also been demonstrated (Jenkinson and Brown, 1944; Ellinger, 1948; Taber, 1951; Finney, 1958), but the incomplete palliation of symptoms has not justified their possible side-effects. Similarly, cysteamine is of value (Patt *et al.*, 1950; Bacq and Hervé, 1951) but its action is of short duration.

This report of 1,042 randomized drug trials conducted personally by me in radiation sickness attempts to assess the relative value of the central sedatives (mainly phenothiazines) as compared with pyridoxine and a relatively inert group of drugs. An attempt has been made to throw light on the underlying basis of the condition, by associating with the drug trial an investigation of pyridoxine metabolism in radiation sickness. It covers the periods 1948 to 1961 and incorporates the results of two previous papers (Ellis and Stoll, 1952; Stoll, 1957a) together with over 500 drug trials carried out since then.

The vitamins of the B complex, particularly pyridoxine, were the first group to show undoubted efficacy in the treatment of radiation sickness (Maxfield *et al.*, 1943; Oppenheim and Bjorn, 1946; Van Haltern, 1946; Shorvon, 1949) and are still widely used. The anti-histamines, having been proved useful in motion sickness, were advocated for radiation sickness (Lofstrom and Nurnberger, 1946), but, although still used by some radiotherapists, neither cyclizine hydrochloride ("marzine") nor diphenhydramine hydrochloride ("benadryl") is significantly better than inert tablets (Ellis and Stoll, 1952; Stoll, 1957a). In 1954 the value of chlorpromazine ("largactil") in this condition was reported (Marks, 1954). Since then the phenothiazine series has expanded widely and has been tried extensively in the treatment of radiation sickness, and new types of central sedatives of the vomiting centre have been developed.

Recording of Results

The record sheet used for each patient is the same as that used in the previous investigations (Fig. 1). The

drugs under trial were randomized in a sequential method—that is, they were changed weekly in order to avoid selection of cases. All drugs were given orally, but we did not attempt to make them up in tablets of the same size, shape, or colour. One week after a drug was prescribed the patient was questioned and a form completed concerning the relief of each individual symptom. If satisfactory the drug was continued till the end of treatment, but, if not, the drug of the second week was prescribed and recorded as a new drug trial. From the information so collected the following data are presented: the cases were divided into four groups.

The first group, comprising 199 patients, were treated by "relatively inert" drugs (Ellis and Stoll, 1952; Stoll, 1957a):

Cyclizine hydrochloride ("marzine")	50 mg. t.d.s.
Amphetamine sulphate ("benzedrine")	5 mg. b.d.
Diphenhydramine hydrochloride ("benadryl")	50 mg. t.d.s.
Acid hydrochlor. dil. (7%)	20 min. (1.2 ml.) t.d.s.
Lactose	300 mg. t.d.s.

The second group, comprising 255 patients, were treated by oral administration of pyridoxine hydrochloride 10 mg. q.i.d. (in a small proportion with the addition of acid hydrochlor. dil.).

The third group consisted of 336 patients who were treated by the following older phenothiazines orally:

Chlorpromazine (largactil)	25 mg. q.i.d.
Prochlorperazine ("stemetil")	10 mg. q.i.d.
Thiopropazate ("daltalan")	10 mg. t.d.s.
Fluopromazine ("vespral," "siquil")	25 mg. t.d.s.
Pecazine ("pacatal")	50 mg. t.d.s.

RADIATION REACTIONS

INITIAL DRUG DOSE For Week
AND ROUTE Beginning
NAME No. Age Disease
Region treated Size of fields
Date of starting treatment
Use symbols ++, +, or —

Date	Initial Symptoms	1 Week Later	Continued if successful			
Control Symptoms						
Nausea						
Vomiting						
Anorexia						
Listlessness						
Toxic Effects						
Note type						

First drug failed after 1 week trial.

NEW DRUG.....

Date	Initial Symptoms	1 Week Later	Continued if successful			
Control Symptoms						
Nausea						
Vomiting						
Anorexia						
Listlessness						
Toxic Effects						
Note type						

Second drug failed after 1 week trial.

NEW DRUG.....

Date	Initial Symptoms	1 Week Later	Continued if successful			
Control Symptoms						
Nausea						
Vomiting						
Anorexia						
Listlessness						
Toxic Effects						
Note type						

FIG. 1.—Record sheet used for details of the equipment.

The fourth group consisted of 252 cases treated more recently by oral administration of newer tranquillizers:

Trifluoperazine ("stelazine")	...	1 mg. t.d.s.
Haloperidol ("serenace") combined with cinnarizine ("mitronal")	...	2 mg. t.d.s.

Analysis of Results

In order to distinguish the more efficacious group of drugs, data are taken from the two preceding papers and added to the data more recently acquired. The proportion of relief for each symptom separately is assessed for each main class of drug—that is, pyridoxine, older phenothiazines, and newer tranquillizers—as against the relatively inert drugs (Table I and II).

TABLE I.—Evaluation of Drug Groups on Nausea. Numbers of Cases Relieved by Each Drug, Percentage for Group, and Limits of 95% Confidence

Group 1, Relatively Inert		Group 2, Pyridoxine		Group 3, Older Phenothiazines		Group 4, Newer Tranquillizers	
Inert	22/58	Pyridoxine group	157/225	Chlorpromazine	48/71	Trifluoperazine	163/179
Others	80/141			Pecazine	82/126	Haloperidol	66/73
	102/199			Prochlorperazine	26/40		229/252
				Thiopropazate	50/65		
				Fluopromazine	27/34		
					233/336		
	51% (44–58)		62% (55–69)		69% (64–74)		91% (87–95)

TABLE II.—Evaluation of Drug Groups on Symptoms Other than Nausea. Numbers of Cases Relieved by Each Group, Percentage for Group, and Limits of 95% Confidence

	Group 1	Group 2	Group 3	Group 4
Vomiting	58/102 57% (48–66)	80/120 66% (58–74)	106/154 69% (61–77)	98/115 84% (77–91)
Anorexia	46/129 36% (28–44)	74/135 55% (47–63)	81/148 55% (47–63)	53/148 36% (29–43)
Listlessness	33/116 29% (20–38)	40/107 37% (28–46)	67/131 51% (42–50)	70/101 69% (60–78)

In the case of nausea, where the number of cases is largest, pyridoxine, the older phenothiazines, and the newer tranquillizer groups are all significantly superior to the inert drugs (Table III). The newer tranquillizers

TABLE III.—Comparison of Drug Groups When Significance Examined by Chi-Square Test

	Group 4 v. Groups 2 and 3	Group 2 v. Group 3	Group 2 v. Group 1
Nausea	50.31 P < 0.01	0.0002 NS	14.47 P < 0.01
Anorexia	7.98 P < 0.01	0.01 NS	9.00 P < 0.01
Vomiting	15.08 P < 0.01	0.06 N.S.	1.86 NS
Listlessness	16.66 P < 0.01	3.97 P < 0.05	1.63 NS

P=Probability level. NS=No significant difference.

are superior to all others, but there is no statistical difference between pyridoxine and the older phenothiazines in the relief of nausea. In the case of vomiting and listlessness, a similar superiority of the newer tranquillizers is shown (Table III). In the case of anorexia, however, it is remarkable that while pyridoxine and the older phenothiazine series are shown as superior to the inert group the newer tranquillizers are relatively less effective in this symptom (Table II).

It should be noted that for all drugs used in radiation sickness anorexia is the most difficult symptom to relieve (Ellis and Stoll, 1952; Stoll, 1957a), possibly because its control lies in the "appetite centre" separate from the "vomiting centre." Possibly also some other factor enters into its control, such as the loss of taste associated with radiation sickness and assessed by Finney (1961) as a separate symptom. Haloperidol and trifluoperazine are assessed separately (Table IV) for their relief of symptoms, and no statistical difference can be shown in

their relative efficacy in any symptom including anorexia.

It is well established that radiation of the abdomen and pelvis causes more severe radiation sickness, and inert drugs give, in general, less relief of symptoms arising from radiation of this area than of other parts

TABLE IV.—Trifluoperazine and Haloperidol. Numbers of Cases Relieved by Each Drug. Evaluated Separately for Each Symptom, as Against the Inert Group

	Inert Group	Trifluoperazine	Haloperidol
Nausea	102/189 51%	163/179 91%	66/73 90%
Vomiting	58/102 57%	70/84 83%	28/31 90%
Anorexia	46/129 36%	44/116 38%	9/32 28%
Listlessness	33/116 29%	55/79 70%	15/22 68%

(Ellis and Stoll, 1952). For this reason an attempt is made to assess the efficacy of each group of drugs on the symptom of nausea, depending on whether radiation was given above or below the diaphragm (Table V).

TABLE V.—Evaluation of Drug Groups on Nausea. Numbers of Cases Relieved by Each Group, According to Whether Radiation Given Above Diaphragm, Below Diaphragm, or Uniform Breast Series. Percentage and Limits of 95% Confidence

	Group 1	Group 2	Group 3	Group 4
Above diaphragm	51/97 53% (43–63)	94/146 65% (58–72)	127/180 70% (63–77)	135/144 94% (90–98)
Below diaphragm	51/102 50% (40–60)	59/101 58% (48–68)	95/139 69% (61–77)	94/108 87% (81–93)
Breast	23/45 51% (36–66)	44/69 64% (53–75)	52/77 68% (58–78)	70/74 95% (90–100)

As in previous papers, it is noted that all the drugs assessed appear somewhat less efficacious when radiation is given to the abdomen and pelvis, although not at a significantly statistical level. Comparing the efficacy of each group for irradiation both above and below the diaphragm, it is noted that the newer tranquillizer group appears significantly superior to all other groups (Table VI).

TABLE VI.—Comparison of Drug Groups According to Site Irradiated, When Significance Examined by Chi-Square Test

	Group 4 v. Groups 2 and 3	Group 2 v. Group 3	Group 2 v. Group 1
Above diaphragm	42.02 P < 0.01	1.14 NS	2.90 NS
Below	20.44 P < 0.01	2.10 NS	1.13 NS
Breast	24.42 P < 0.01	0.09 NS	1.32 NS

P=Probability level. NS=No significant difference.

Finally, nausea arising in a uniform series of 265 cases of breast irradiation is considered (Table V). A uniform series is of especial importance in an investigation of this nature, in that a host of variables in technique, dose, site, and size of field are eliminated. Again, the newer tranquillizers are found significantly superior to all others (Table VI). For simpler visualization a different method of assessment (Wood and Boag, 1950) has been used. The percentage relief by each group of drugs at the 95% level of confidence has been

graphed separately in Fig. 2 from the data presented in Table V.

For the first time, therefore, a group of drugs capable of relieving the nausea of irradiation in 9 out of 10 cases have been significantly evaluated (Table I), although a surprising finding is that the same drugs have relatively little effect on the symptom of anorexia.

FIG. 2.—Percentage relief of nausea by each group according to site irradiated (limits of 95% confidence).

Origin of Symptoms of Radiation Sickness

Contrary to popular belief, radiation sickness requiring the prescription of anti-emetic drugs is not common. It is noted in only about 10% of patients treated by modern techniques of x-ray therapy. Earlier hopes that its incidence would decrease even further with the development of supervoltage x-ray therapy (Ellinger, 1957) have not been sustained. In the past 18 months our incidence of radiation sickness requiring drugs was 10.4% in 894 cases treated by megavoltage, as against 10.8% in 1,407 cases treated by orthodox x-ray therapy. It is obviously not statistically different.

The symptoms of nausea, vomiting, anorexia, and lassitude noted after therapeutic exposure to x rays are identical with those observed a few hours after exposure to atomic radiation. Nevertheless the origin of these symptoms is not clear. Whereas whole-body irradiation causes early vomiting in man, monkeys, and dogs, yet, in the rat, early anorexia is the prominent symptom (Patt and Brues, 1954). Also, whereas in most animals anorexia and vomiting follow only if the abdomen is irradiated, yet in the rat anorexia will follow irradiation of the head alone (Smith *et al.*, 1951). It has therefore been suggested that anorexia may have a different origin, possibly from the delayed gastric emptying and pyloric spasm which have been noted after irradiation (Mead *et al.*, 1951).

Since anorexia and vomiting are noted clinically after extra-abdominal irradiation and with much lower doses

than those used experimentally, other factors have been suggested as predisposing to radiation sickness in men. The most likely are anxiety and a poor nutritional status. Animals appear to show increased susceptibility to radiation injury in the presence of vitamin deficiency or after a low-fat diet (Van Bekkum, 1960). With regard to the clinical observation that symptoms may develop after extra-abdominal irradiation, there is good experimental and clinical evidence that local irradiation causes biological change in distant organs (Leblond and Segal, 1942; Stoll, 1957b). In fact, Bloom and Bloom (1954) suggest that the manifestation of radiation sickness is one of the strong arguments in favour of an indirect effect of radiation.

That the emetic action of irradiation is mediated by the emetic chemoreceptor zone in the brain-stem was demonstrated by Chinn and Wang (1954) in dogs and later confirmed in monkeys. Destruction of this centre in the brain completely prevents vomiting after whole-body irradiation. The symptom of anorexia after irradiation may, however, originate in the appetite centre or have a different cause such as the delayed gastric emptying previously mentioned. Separate origins for vomiting and for anorexia may account for the superior effect noted in our series by the newer tranquillizers on the symptoms of nausea and vomiting and the greatly inferior effect on the symptom of anorexia.

Mode of Action of Drugs Used in Radiation Sickness

The causes of vomiting and nausea are numerous, and whereas treatment in the past was based upon an attempt to distinguish the individual aetiological factor, in recent years there has been a tendency to prescribe our new armamentarium of anti-emetic drugs without regard to the cause of vomiting.

Similar drugs have thus been prescribed for radiation sickness, pregnancy sickness, post-operative vomiting, motion sickness, etc. All these conditions have, it is true, anxiety as a common factor, and this explains why placebos will claim a percentage of success, and tranquilizer drugs a further percentage, in all these conditions. Nevertheless it is established that motion sickness (as measured by vomiting) is best relieved by antihistamines, while pyridoxine and the tranquillizers are relatively ineffective (Chinn, 1956). Pregnancy sickness is relieved by tranquillizers and almost not at all by pyridoxine and antihistamines (A.M.A. Council on Pharmacy and Chemistry, 1956). Finally, from this report it would appear that radiation sickness is best relieved by tranquillizers, less so by pyridoxine, and not at all by antihistamines.

The tranquillizer group may act by sedating the vomiting centre (Chinn and Wang, 1954). Drugs with a selective action on this centre may relieve this specific symptom, but may have no effect on the symptom of anorexia. The sulphhydryl compounds such as cysteamine may relieve radiation symptoms by inactivating the free hydroxy radicals liberated in the cell after radiation (Bacq and Hervé, 1951). The action of cortisone may be explained in terms of damping down the "stress action" of x rays (Taber, 1951). In this connexion it is of interest that Edelmann (1951) noted that shielding the relatively small adrenal gland area in rats will decrease the mortality from irradiation.

Because the origin of clinical radiation sickness is not clear we should be able to derive some conclusions from this assessment of its drug-response. In particular

instances, however, account must be taken of size of area and the region irradiated (as, for example, the upper abdomen as compared with a peripheral area), because different factors may operate with different sites of irradiation.

Pyridoxine in Radiation Sickness

After radiation there is a reduced level of excretion of certain members of the vitamin-B complex (Jarvis and Cayer, 1949). Interference with the bacterial and enzyme content of the bowel, and possibly interference with absorption after irradiation, may account for this deficiency. That radiation causes inactivation of enzymes and of co-enzymes is well established (Barron, 1952). Pyridoxal-5-phosphate acts as a coenzyme in the breakdown of amino-acids and in many other systems, particularly decarboxylation, transamination, deamination, and desulphydration. Its wide participation in metabolism makes possible its inactivation by small doses of irradiation. That this does occur is shown by the observed accumulation of metabolic products such as xanthurenic acid after irradiation (Langendorff *et al.*, 1961).

Tryptophan requires the presence of pyridoxal to yield nicotinic acid, and in the absence of pyridoxal gives rise to xanthurenic acid instead. The measurement of urinary xanthurenic acid after tryptophan loading is therefore an accurate measure of the pyridoxal level of the blood (Lepkovsky *et al.*, 1943; Glazer *et al.*, 1951). Pyridoxal phosphate is the active form of pyridoxine in the body.

It has been suggested that when a specific deficiency of pyridoxine can be shown associated with severe vomiting, then the administration of vitamin B₆ may be of value (A.M.A. Council, 1956). For this reason an investigation of xanthurenic-acid excretion after tryptophan loading was carried out in 20 patients complaining of nausea or vomiting as a result of abdominal irradiation by wide fields. In three cases the xanthurenic-acid excretion was well beyond the normal range, suggesting the presence of pyridoxine deficiency. Nevertheless, in two of the cases the patients' symptoms responded to the administration of tranquillizer drugs. The third case is worth recording in detail.

A woman aged 47, receiving wide-field abdominal irradiation for carcinoma of the ovary, complained of severe vomiting, nausea, and anorexia. A week's trial of haloperidol gave no relief, nor did a trial of trifluoromazine for a further week. At this stage the xanthurenic-acid excretion after tryptophan loading was found to be 99 mg. in the 24 hours (normal maximum level 40 mg.). Treatment with pyridoxine 50 mg. intramuscularly daily was then instituted, and was immediately followed by complete relief of symptoms.

There is thus evidence of a specific deficiency of pyridoxine in the body in some cases of radiation sickness. Whether this is a direct effect on enzymes, an effect on the bowel, or a result of metabolic changes associated with vomiting is uncertain. Nevertheless there is a suggestion that pyridoxine will be of value in these cases, even if other anti-emetic drugs fail to control the symptoms of radiation sickness.

Summary

This is a report of 1,042 randomized drug trials in radiation sickness, with separate assessment of the response of nausea, vomiting, anorexia, and listlessness. For the first time in the literature a group of new drugs capable of relieving the nausea of irradiation in about

90% of cases has been statistically evaluated. Nevertheless both pyridoxine and the older phenothiazines are confirmed as statistically superior to inert drugs in relieving this symptom. It is noteworthy that the two new tranquillizers, although highly effective in relieving the vomiting and listlessness of radiation sickness, are nevertheless comparatively ineffective in relieving the symptom of anorexia. It is suggested that anorexia may have a different control from nausea and vomiting in this condition. An investigation of pyridoxine metabolism in patients with radiation sickness suggests that pyridoxine deficiency may be present in some cases. This may account for the statistically significant relief of symptoms resulting from pyridoxine administration in this condition.

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