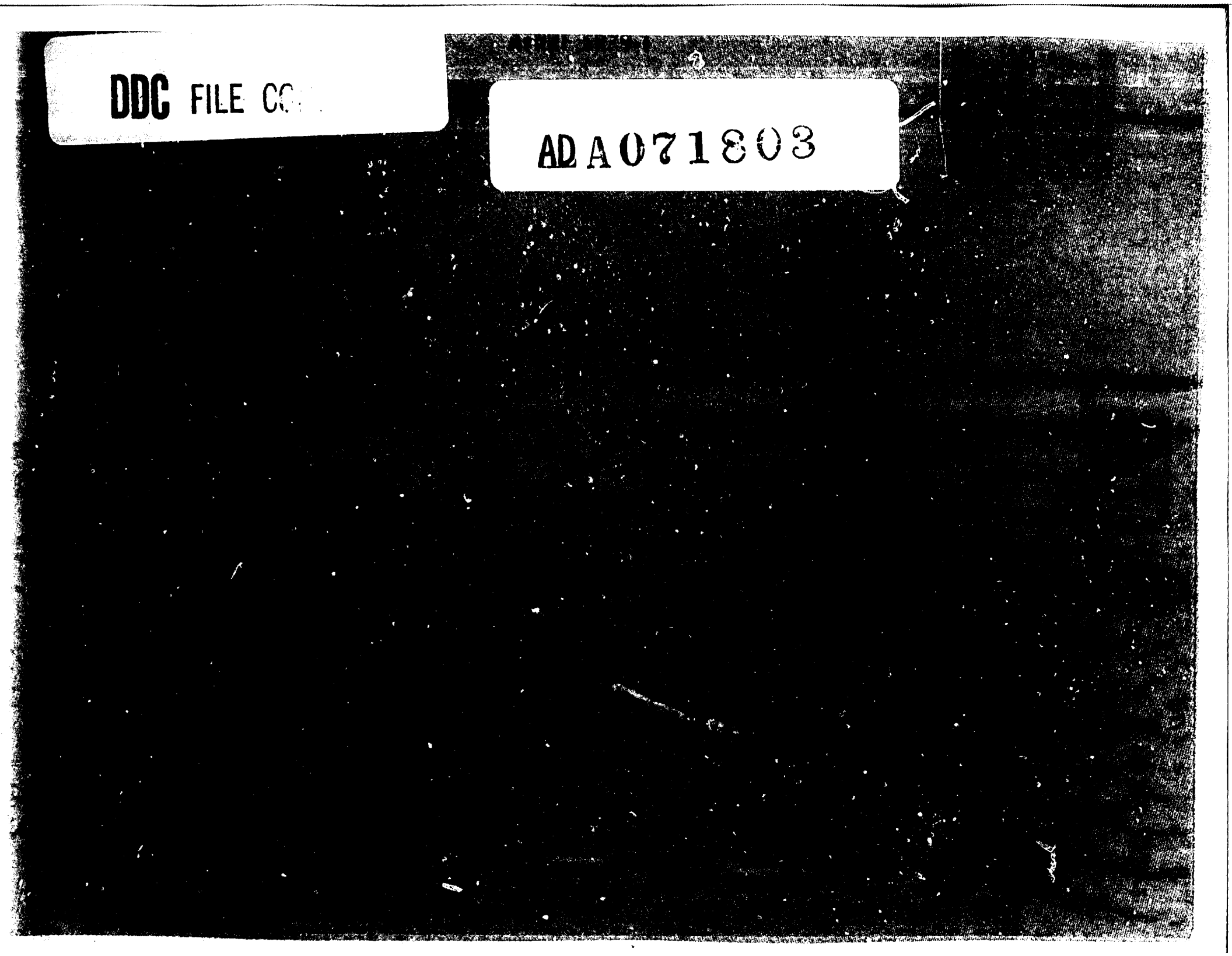

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Research was conducted according to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals," prepared by the Institute of Laboratory Animal Resources, National Research Council.

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Early transient incapacitation (ETI), which is a decrement in the performance of a specified task resulting from the effects of supralethal ionizing radiation exposures, has been observed in a number of animal species. Since nuclear weapons result in radiation fields sufficient to cause ETI in personnel that may be exposed, an understanding of the mechanism of this phenomenon is essential for the development of a rational plan for preventing or reversing the effect. This report is a

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20. ABSTRACT (continued)

A review of the behavioral experiments concerning ETI and presents a critical analysis of available experimental information as to the cause of the phenomenon. It appears that the primary cause of ETI in experimental animals is probably faintness resulting from a fall in cerebral blood flow due to the direct action of histamine on blood vessel smooth muscle cells.

INTRODUCTION

The performance of personnel after exposure to supralethal levels of ionizing radiation is of significant interest to the Department of Defense. Many studies with animal models have attempted to define and evaluate the expected human response to radiation from nuclear weapons and especially to assess the effects of supralethal exposures on performance capabilities. It has been shown that exposure to ionizing radiation at high doses does affect nerve cell activity and, at sufficiently high doses, leads to death from central nervous system (CNS) depression within hours to a few days.

In subhuman primates trained to perform various physical and visual tasks, several CNS-associated responses have been described following exposure to large levels of radiation. The responses are somewhat dependent on the total dose, as is the time period in which they occur. Generally, there are three levels of recognizable events: (a) ability to perform at or near control level for some relatively lengthy period, then total inability to perform; (b) ability to perform for a relatively short period, then total inability to perform for some period, followed by recovery to control level; and (c) ability to perform for a relatively short period followed by total inability to perform. These are usually referred to as delayed, transient, and immediate incapacitation.

It is obvious that the success (or failure) of many military operations could depend on the type of incapacitation experienced. Further, a method of preventing, delaying, or even reversing these phenomena would increase the probability of successfully carrying out various duties and functions. To develop means of interfering with these incapacitation syndromes, an understanding of the underlying mechanisms is necessary. In particular, more information is needed to define the syndromes as a function of task, radiation quality, and dose, and to define the relation of these parameters to expected human responses. In this report, the behavioral experiments relating to early transient incapacitation are reviewed, and a critical analysis of available experimental information on the cause of the effect is presented.

Early transient incapacitation (ETI) is defined as a decrement in performance of a trained task, occurring transiently and within minutes of exposure to supralethal doses of ionizing radiation.[33] In monkeys, ETI will vary widely in groups of animals similarly exposed. Table 1 divides monkeys from seven AFRRI studies into three groups on the basis of their responses to varying doses of ionizing radiation. The first group, No Effects (NE), continued to perform at or near control levels for at least 2 hr postirradiation. The second group (ETI) showed some period of incapacitation or performance decrement, followed by a return to performance. The third group, Incapacitation (Incap), became incapacitated within 10 min and did not recover. Although 70 6 of the animals at the highest dose (15,000 rads) were totally incapacitated, the other distributions among the three groups of responses show that degree of incapacitation is only roughly dose-related. Some animals in those studied showed a second

period of performance decrement, often at about 45 min postirradiation, but this was not a consistent observation.

Table 1. Behavioral Decrements Following Exposure to Ionizing Radiation*

Dose (rads)	Task	NE	ETI†	Incap‡	Reference
1,100	VD§	9/10	1/10	0/10	20
1,760	VD	2/12	10/12	0/12	20
2,000	VD	5/14	5/14	4/14	19
2,500	VD	1/6	4/6	1/6	30
2,600	VD	9/39	23/39	7/39	20
4,200	SB§	2/6	3/6	1/6	51
4,900	VD	1/15	12/15	2/15	20
5,000	VD	2/6	4/6	0/6	21
8,900	VD	0/5	2/5	3/5	20
10,000	VD	1/6	5/6	0/6	31
15,000	VD	0/7	2/7	5/7	52

* Each set of numbers under NE (no effects), ETI (early transient incapacitation), and Incap (incapacitation) denotes number of animals showing that response over total number irradiated.

† Performance below 80% within first 30 min; recovery to above 80% within 1 hr.

‡ Performance below 50% within 20 min and no recovery within 60 min.

§ VD indicates a visual discrimination task; SB indicates a shuttlebox task.

The tasks used to test monkeys in the experiments summarized in Table 1 were either simple visual discrimination or shock-avoidance shuttlebox tests. Bruner et al.[6] used a more demanding delayed match-to-sample task and demonstrated

considerable performance decrement at doses as low as 1000 rads for cobalt-60 irradiation. They compared effects on a simpler visual memorization task and saw much less decrement even after higher doses of irradiation.

ETI does not occur with equal frequency in all species. No ETI was found over a dose range of 1000-17,600 rads in dogs.[14,39] However, ETI was readily elicited in miniature swine, although differing from that in monkeys by the frequent accompaniment of convulsions and spasms of extremities.[15]

Since ETI is a deficit of functioning of the nervous system, it is of crucial importance to determine if it occurs only after irradiation of the head (in which case it might reflect a direct damage to the nervous system) or if it can also be elicited by irradiation of only the trunk. Table 2 summarizes results from partial body shielding in monkeys and pigs. These results show that for monkeys there is no clear benefit of head shielding, although the pig data suggest a very significant benefit of head shielding compared to trunk shielding. The differences in monkeys and pigs suggest that ETI is not identical in the two preparations. This has already been suggested by the fact that convulsions, incoordination, and muscle spasms are very prominent in the pig but not in the monkey.

Table 2. Effects of Partial Body Shielding on Occurrence of ETI*

Species	Dose (rads)	Unshielded	Trunk Shielded	Head Shielded	Reference
Monkey	2,500	8/10 (1)	10/10	9/10 (1)	44
Monkey	4,500	10/10	7/10	6/10	43
Monkey	4,500	5/10 (3)	9/10	6/10	44
Monkey	10,000	2/3 (3)	3/3	1/3 (2)	44
Pig	3,000		1/4		42
Pig	6,000		4/4		42
Pig	13,000	2/2	7/8	1/3	42

* Each set of numbers under Unshielded, Trunk Shielded, and Head Shielded denotes number of animals showing ETI over total number exposed. Numbers in parentheses are numbers of animals incapacitated without recovery, which therefore are not considered to have shown ETI.

Although total shielding cannot be obtained under conditions of reactor irradiation, the failure to find any significant protective effect of head

shielding argues strongly that ETI is not a result of a direct effect of radiation on nervous tissue. This conclusion is already suggested by the studies on Aplysia nervous tissue in isolation[10] as well as by other older observations on isolated nervous tissue.

If ETI does not result from irradiation of only the head, then its effect must be mediated by a humoral factor. In agreement with this conclusion are results from experiments with both monkeys[36] and pigs[13] showing that ETI is shorter, if present at all, when the same amount of radiation is given in two parts rather than in a single dose. This would be expected if, after radiation exposure, a substance were released in the body that could be dealt with in moderate amounts, but which the body would find overwhelming in too great a concentration.

BLOOD PRESSURE AND CEREBRAL BLOOD FLOW IN ETI

One obvious possible explanation for cerebral dysfunction is an inadequate supply of oxygen. Since blood pressure falls dramatically following irradiation, this is a possible explanation for ETI. In a recent study, Bruner et al.[5] carefully compared the time course of the fall in blood pressure to the occurrence of ETI. Using cobalt-60 irradiations at 50, 75, and 180 rads/min (for a total dose of about 1000 rads), they found that for all three groups the blood pressures fell to about 50% of control, with the smallest drop being to 70% of control. Not all animals showed a performance decrement in these studies, and the presence of a performance decrement did not highly correlate to the magnitude of the hypotension. Some animals showed a fall in pressure to 35% of control without showing a performance decrement. However, when it occurred, the performance decrement always tended to closely correlate to the hypotension, usually following within a few minutes the initial fall in blood pressure, but often appearing before blood pressure reached its lowest value. Usually the performance began to recover within a few minutes after the initial rise in blood pressure, and often was fully reversed by the time the blood pressure reached 75% of control. These authors showed that this depth of hypotension was significantly correlated to the occurrence of a performance decrement for two of the dose groups but not the third (180 rads/min).

If ETI results from hypotension, it should be prevented by maintenance of blood pressure. Turns et al.[47] infused either saline or norepinephrine after irradiation in order to attempt to block the fall in pressure. They reported no significant difference between the performance of animals in which the blood pressure was maintained with norepinephrine and the performance of animals that were injected with saline. However, their results do suggest a beneficial effect between 4 and 6 min postirradiation, which is the most usual time for ETI. Such experiments should be repeated.

Bruner et al.[7] studied the effect of 1000 rads of cobalt-60 exposure on the baroreflex function in conscious monkeys. They found a depressed sensitivity

for 8-15 min postirradiation but could not demonstrate any permanent loss of function. A depressed sensitivity could contribute to the lowered blood pressure. However, the depressed baroreceptor reflex could also result from a humoral agent's direct effect, with the latter producing still other effects on blood pressure and flow.

Another important control experiment was done by Bruner,[3] who studied ETI and blood pressure in animals performing a task with positive rather than negative reinforcement, using electrical self-stimulation of several brain sites. In the normal animal the self-stimulation had a direct effect on blood pressure. But after exposure to about 1000 rads of cobalt-60 irradiation, the self-stimulation ceased within minutes and the blood pressure returned to normal minutes later. In most animals, the time course of decrement paralleled the time course of hypotension, which was usually to 40-60 mm Hg. Furthermore, the direct effect of self-stimulation in raising blood pressure was reduced or abolished during ETI.

Bruner[4] recently expanded his studies on the cardiovascular changes after exposure to 1000 rads of cobalt-60 in the rhesus monkey to include measurement of aortic blood flow velocity, blood pressure, and heart rate, and also included calculation of peripheral vascular resistance. He found tachycardia and hypotension beginning within 3-4 min of the onset of exposure, and a lowest value of cardiac output at 10-20 min, by which time the blood pressure and vascular resistance were already beginning to recover.

Defects in CNS function following hypotension must result from a decreased cerebral blood flow (CBF). Through its very important system of autoregulation, the CNS can often maintain CBF under conditions of severe hypotension. Thus it is of crucial importance to measure CBF directly in irradiated animals. This has been done in several studies. In a careful study using a single 2500-rad dose of cobalt-60, Chapman and Young[11] demonstrated a dramatic fall of CBF immediately following exposure. They measured CBF with an electromagnetic flow meter in one common or internal carotid, with the other common carotid ligated. Under these circumstances the flow to be measured would not be exclusively to the brain. They found in 18 animals that the blood pressure fell from 117 to 43 mm Hg and was lowest at 5 min postirradiation. CBF fell with a similar time course, falling to only 30% of its preirradiation value at 5 min, with recovery similar to the peripheral blood pressure toward control values at about 25 min.

In a later study, Chapman and Young[12] measured CBF after head-only irradiation with X rays to monkeys. CBF was measured by using the inert krypton-85 desaturation technique. This head-only irradiation of 2500 rads produced only a small drop in blood pressure (16 mm Hg) and no significant change in CBF. On the basis of these results, the authors concluded that the hypotension and lowered CBF characteristic of high-exposure radiation to whole animals do not result from direct effects on the CNS.

Two other studies have attempted measurement of CBF. Nathan and Craig[37] used a magnetic flow probe in the common carotid (following ligation of external vessels). They reported that whereas the CBF fell after 2100 rads of X irradiation (whole body, monkey), it increased after 2500 rads of gamma-neutron irradiation, even though hypotension ensued. Turbyfill et al.[45] used monkeys trained for visual discrimination tasks that were exposed to 2500 rads of mixed gamma-neutron radiation. They found dramatic hypotension and ETI in five of six animals, but did not see a change in common carotid blood flow. They proposed that CBF was maintained following irradiation and that it was not correlated to ETI. However, in light of the much more carefully performed previous studies, this conclusion appears unwarranted.

There have been no studies of CBF attempting to maintain blood pressure pharmacologically after exposure to radiation. As indicated above, Turns et al.[47] maintain there is no beneficial effect of postirradiation maintenance of blood pressure with norepinephrine, although their data suggest some benefit. Turbyfill et al.[46] studied the effects of 2-(n-decylamino)-ethanethiosulfuric acid on ETI in trained monkeys. This drug is a β-adrenergic receptor blocker, and it did prevent or reduce the occurrence of ETI. Although it did not prevent hypotension following irradiation, it reduced it considerably. Because of the very distinct innervation pattern of cerebral blood vessels, one cannot generalize about effects of such an agent on CBF when one knows only the effect on blood pressure. It is perhaps likely that the radioprotective effects of this drug are secondary to its maintenance of CBF.

ROLE OF HISTAMINE IN ETI

Since in the monkey the ETI does not appear to result from a direct effect of radiation on the brain (as indicated by the shielding experiments) and since the hypotension also is not of cerebral origin,[12] it appears very likely that both result from a release by radiation of some agent that travels in blood and affects blood pressure and CBF and has consequent or perhaps direct effects on cerebral function. The best candidate for such a humoral agent is histamine.

Histamine is a bogenic amine primarily stored in mast cells throughout the body. It may have a function as a neurotransmitter in the CNS.[8] Histamine can be released from mast cells by a number of mechanisms, including radiation. There is a depletion of local and mast cell histamine following irradiation,[16,26,32] although at doses of X irradiation up to 4000 rads, as many as 50% of mast cells show no morphological injury.[48] Furthermore, the level of circulating histamine is raised over a period of days in humans undergoing radiation therapy.[34] Rats exposed to X irradiation show an increase in blood histamine measured at 2 hr and 5 days postirradiation.[49]

Doyle and Strike[23] studied blood histamine in monkeys exposed to 4000 rads of mixed neutron-gamma radiation, using animals pretreated with an inhibitor of

the enzyme that degrade. histamine. They found under these circumstances that histamine rose from 28 to 235 ng/ml blood following irradiation, and this peak amount was reached 3 min after exposure. The concentration fell with time, even with the major catabolic pathway blocked, and was significantly different from control at 22 min. When pretreated with chlorpheniramine, a blocker of H_1 receptor sites the level following radiation rose from 28 to 460 ng/mL. If animals were pretreated with compound 48/80 which causes a release mast cell histamine, there was no measurable release of histamine on irradiation. Thus the time course of histamine release by irradiation correlates very well to the time courses of ETI and hypotension.

Histamine has dramatic effects on most smooth muscle cells, and most of its biologic effects are probably mediated by receptors on smooth muscle cells. Histamine has several direct effects on the heart-lung preparations, including a decrease in heart rate, bronchoconstriction, and pulmonary artery vasoconstriction. In addition, it causes release of catecholamines at high concentrations that have other effects on the heart and vessels.[27] Histamine causes a dramatic drop in blood pressure. With 48/80 injection, which causes a release of natural histamine, Doyle and Strike found blood pressure fell to 30% of control values. Edvinsson and Owman[25] showed that activation of one type of histamine receptor (H_1) in cat causes a contraction of extracranial arteries, while another receptor (H_2) causes a vasodilation of both pial and extracranial arteries. In addition, there was a nonspecific contraction of pial arteries produced by histamine. These results are to be compared to direct observations of the effects of histamine on the cerebral vasculature by Forbes et al.,[28] who observed that histamine caused a vasodilation of cerebral vessels by 40%-50%! They report dilation of dural and pial vessels as well, but not of the large systemic vessels.

The only reported measurements of effects of histamine on CBF are unpublished experiments of H. G. Wolff and M. Cattrell reported by Wolff[50] They measured CBF in the cat after I.V. histamine infusion. They found that hypotension followed immediately after infusion was begun and that it continued for the duration. CBF also fell after the onset of peripheral hypotension.

In two studies, antihistamines have been used in an attempt to determine if a blockade of the effects of radiation-released histamine would prevent ETI. Doyle et al.[24] used chlorpheniramine, an H_1 receptor blocker. He treated one group of animals with 10 mg at 30 min before irradiation and another group with 10 mg at 60 min before plus another 10 mg at 30 min before. In all animals they recorded a sharp rise in blood pressure within a few seconds of exposure, but a fall beginning at 1 min. Since the blood pressure rise is blocked by the α-adrenergic blocker, dibenzyline, this effect is probably mediated by a release of norepinephrine from sympathetic nerves. For all animals, the blood pressure fall reached a maximum at 2-5 min, but whereas the fall for untreated animals was to less than 50% of control values, for those with 20 mg chlorpheniramine it was to about 75% of control. Of eight control animals, all but one became unresponsive for 5-30 min. Of 10 animals treated with 10 mg

and 7 animals given 20 mg chlorpheniramine, only 1 became unresponsive, and the rest were apparently alert. Even more dramatically, the mean survival times of the 20-mg animals (23.2 hr) was almost ten times greater than that for controls (2.9 hr). The 10-mg animals had a mean survival of 13.1 hr.

In a further study, Doyle et al.[22] repeated the same test using animals trained to a visual discrimination task. They irradiated with 4000 rads and confirmed the previous results on the partial protective effect of chlorpheniramine against hypotension. Most of the 10 control animals they used were totally incapacitated or dead before 60 min, while 5 animals receiving 20 mg of chlorpheniramine showed no ETI and very little decrement in performance over 2 hr. Animals receiving 40 mg, for some unexplained reason, did not differ from controls.

In total, these results on histamine and radiation strongly suggest that histamine, released by radiation from stores in mast cells all over the body, acts on H_1 and H_2 receptors on the heart and blood vessels to cause a fall of systemic blood pressure. There is, in addition, a dramatic fall in CBF that may be due only to the fall in systemic blood pressure, leading to a failure of autoregulation of the cerebral vasculature, and may be further due to direct vasodilatory effects of histamine on extracranial and intracranial cerebral vessels. A fall in CBF will compromise cerebral function because of inadequate oxygenation, and will result in light-headedness and faintness in both humans and monkeys. The appearance of a monkey experiencing ETI is identical to that of a monkey who is feeling faint and very weak. The animals usually are not unconscious but are very inactive. They usually lie listlessly on the floor and display a greatly diminished responsiveness to shock.

There is yet another effect of histamine that may also contribute to ETI: the acute production of severe headache. It has long been known that I.V. injection of 0.1 mg histamine causes a generalized, throbbing headache.[9,38,40,50] The headache is thought to result from stimulation of afferent fibers in cerebral blood vessels that are contained in the trigeminal nerve. The stimulation results from the vasodilation and stretching caused by histamine.[50] The histamine headache usually has a latency of about 1 min and lasts from 2 to 12 min. It leaves no sequelae. If histamine is injected on one side only, there is a homolateral headache. Since the effect is not blocked by anesthesia of scalp blood vessels, it must be from only intracranial vessels. Furthermore, an increase of intracranial pressure decreases the headache, and this manipulation would be expected to decrease the stretch of vessels. At least one type of clinical headache syndrome is associated with an increase in circulating histamine, which is assumed to be causative.[1]

Headache has been a symptom in only some of the accidental radiation exposures in man. It was reported to be a prominent symptom in the Lockport, NY accident in 1960, in which pulsed X irradiation exposures in doses up to 1500 R to the head were sustained by nine workers. It was also reported as a symptom by the Japanese fishermen exposed to fallout from the Pacific test location in 1954.[2]

An observation of major importance on the variability of occurrence of ETI postirradiation was made by Wolff.[50] He found that humans show great variability in their responses to injected histamine. As is apparent from the results of Table 1, the occurrence of ETI is vaguely dose-dependent, but it never occurs in 100% of the animals. This is compatible with individual variability in susceptibility to histamines.

If ETI is indeed caused by a sudden release of histamine by mast cells and is mediated by some combination of headache and reduced CBF, then one should be able to reproduce ETI by injection of adequate amounts of histamine. These experiments are presently being performed and, in at least one trained animal, histamine injection has shown development of an ETI-like response (Doyle and Young, unpublished observations).

Of particular interest regarding histamine and radiation of the CNS is a series of studies on taste aversion in rats. Rats will show a taste aversion for a long period of time if exposed to an unpleasant experience within a few hours after intake of a new food. Radiation exposure will elicit taste aversion.[29] Neurons in the olfactory bulb have been shown to respond electrically to beta radiation[17] and X rays.[18] However, this is apparently not due to a direct effect of the radiation on these neurons, since the taste aversion response is blocked by antihistamines.[35]

It is not clear if humans exposed to a massive dose of radiation will undergo ETI. In a case reported by Shipman,[41] a man exposed to 12,000 rads of neutron-gamma radiation showed a total collapse beginning within seconds and lasting 20-25 min, followed by recovery for about 25 hr. The early response was characterized by severe hypotension, restlessness, disorientation, and apparently severe pain; this may be similar to ETI. It has not been seen, however, in several other lethal exposures summarized by Bond et al.[2]

(Note: This review of the AFRRI program was completed in late 1976.)

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