

FACTORS ASSOCIATED WITH PROTECTION AGAINST EXPERIMENTAL SHOCK

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A VARIETY of pharmacologic agents and techniques have been shown to protect animals against otherwise lethal injury (1-5). These studies conclusively indicate that experimentally induced protection against stress is a valid, reproducible entity. Review of the diverse experimental contingencies, however, does not reveal any obvious pattern which is common to each, and to which the physiological mechanisms producing resistance to stress could be attributed. As a step toward elucidating the basic mechanisms in the etiology of the shock syndrome, our laboratory has recently been concerned with the identification of discrete aspects of the phenomenon of protection.

Screening experiments have demonstrated that a number of drugs with autonomic blocking properties were effective in either attenuating or eliminating the deleterious effects of severe hemorrhage and trauma (2, 4). Among the protective drugs, chlorpromazine was found to be especially effective and has been utilized extensively as an experimental tool in subsequent investigations. Animals pretreated with chlorpromazine which survive normally lethal stress situations consistently present functional and pathological differences when compared with untreated controls (6).

The present report deals with a series of experiments in the rat intended to delineate some of the characteristics of the protected state. The experiments were concerned with: (a) the capacity of chlorpromazine to generate protection against graded degrees of hemorrhage, (b) the effectiveness of chlorpromazine protection when the drug is administered at different stages of the shock syndrome and in combination with different forms of supportive therapy, (c) the role of bacteremia in breaking down spontaneous and induced resistance, and (d) the carry-over of protection against one form of stress (that is, hemorrhage) to other forms (trauma, x-radiation).

CAPACITY OF CHLORPROMAZINE TO PROTECT AGAINST HEMORRHAGE

Methods and Observations. Normal female Wistar strain rats (120-150 Gm.) were subjected to various degrees of hemorrhagic hypo-

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tension by bleeding through a cannulated carotid artery leading via a T-tube to a conventional mercury manometer and a self regulating bleed-out re-infusion reservoir. This setup permits the maintenance of preselected blood pressure levels for several hours with accurate measurement of bleed-out and spontaneous uptake of blood. Controls were anesthetized with intramuscular pentobarbital (3.5 mg. per 100 Gm. of body weight) thirty minutes prior to the onset of hemorrhage. Experimental animals received intramuscular chlorpromazine (2.0 mg. per 100 Gm. of body weight) twenty minutes prior to a reduced dose of pentobarbital (2.0 mg. per 100 Gm. of body weight).^{*} Parallel control

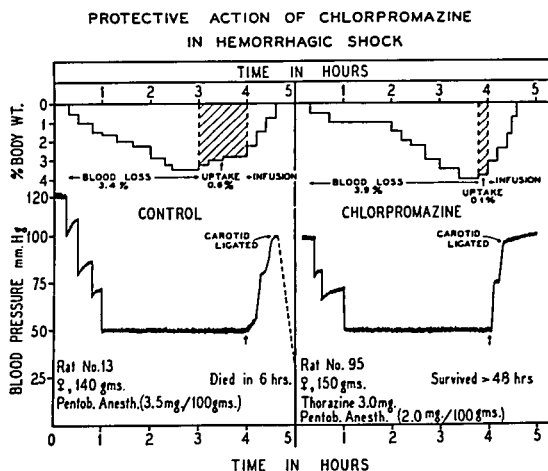


FIG. 1. Typical protocols of one set of paired experiments in the Group IV series. Autopsy of chlorpromazine-treated rat did not show congested, hemorrhagic bowel and liver seen in control.

experiments were run in conjunction with each of the chlorpromazine treated rats. Five groups of animals were recorded according to the pattern of hemorrhagic hypotension to which they were subjected: Group I. Blood loss and take-up adjusted to maintain a mean blood pressure of 75 mm. of mercury for two hours. Group II. Blood pressure maintained at 50 mm. for two hours. Group III. Blood pressure maintained at 65 mm. for one hour, followed by two hours at 50 mm. Group IV. Blood pressure adjusted to 50 mm. for three hours. Group V. Blood pressure maintained at 65 mm. for one hour followed by two

^{*} Chlorpromazine (Thorazine®, Smith, Kline and French) treated animals with the reduced dose of pentobarbital develop a degree of narcosis equivalent to that obtained in the controls.

hours at 40 mm. At the end of the acute portion of each experiment, the blood remaining in the reservoir was completely re-infused, the incision was closed and the animal observed for forty-eight hours, the period arbitrarily designated to determine death or survival. Animals which did not survive the acute portion of the experiment were not included in the tabulation of the data. Gross autopsies were routinely performed at the time of death or at sacrifice after forty-eight hours.

Figure 1 shows typical protocols of one set of paired experiments in the Group IV series. It is significant that while both rats were subjected to identical hypotensive episodes and had lost a comparable volume of blood, the chlorpromazine treated rat survived, required very little re-infusion of blood to sustain the selected blood pressure level and, at autopsy, did not show the usual congested, hemorrhagic bowel and liver consistently encountered in irreversible shock in the rat.

TABLE 1
EFFECT OF CHLORPROMAZINE ON GRADED LEVELS OF HEMORRHAGIC STRESS

Group		Survival		Blood Takeup*		Blood Output	
		Control	CPZ†	Control	CPZ	Control	CPZ
I	75 mm./Hg—2 hrs.	7/12, 58%	11/12, 92%	0.2	0.01	3.2	3.7
	50 mm./Hg—2 hrs.	6/14, 43%	12/14, 86%	0.4	0.2	3.7	3.0
III	65 mm./Hg—1 hr.,	4/12, 33%	11/12, 92%	0.7	0.02	3.9	3.6
	50 mm./Hg—2 hrs.						
IV	50 mm./Hg—3 hrs.	8/14, 57%	8/9, 89%	0.8	0.1	3.7	3.2
	65 mm./Hg—1 hr.,	10/23, 43%	11/21, 52%	0.9	0.3	4.0	3.8
V	40 mm./Hg—2 hrs.						

* Blood values indicated as % of body wt.

† CPZ, Chlorpromazine (Thorazine®, S.K.F.)—2.5 mg./100 Gm. body wt.

Table 1 summarizes the data for the five groups of rats subjected to varying degrees of hemorrhagic hypotension. Based on survival rates, Groups I to IV are considered to be protected whereas Group V, subjected to the most drastic hypotensive episode, cannot be considered significantly protected. In comparing the data on the control and experimental animals in each of the four protected groups the most striking differences, aside from survival rates, are the unusually small blood uptake values in the treated rats and the uniform protection afforded by chlorpromazine pretreatment in the presence of varying degrees of hemorrhagic hypotension.

Other observations are pertinent. During the period of hypotension, in contrast with controls, protected animals showed more favorable respiratory patterns, pale, pink skin color with sustained refill of the superficial vessels, and almost total absence of hemorrhage into the intestine and congestion of the liver and lungs. These data, as a whole, by providing information on an anatomic and functional level, establish tentative characteristics of the protected animal.

EFFECTIVENESS OF CHLORPROMAZINE WHEN FACTORS OF REPLACEMENT THERAPY, DRUG DOSAGE AND TIMING ARE MODIFIED

Methods and Observations. 1. Rats were prepared as controls and chlorpromazine pretreated animals as described for Group IV (BP: 50 mm. for 3 hrs.) with the exception that re-infusion of whole blood in the final stage of the acute experiments was omitted. In these "no replacement" experiments all of the animals died within a few hours. 2. Instead of whole blood as the infusion medium, some of the controls and chlorpromazine pretreated rats received gelatin † in volume equal to the whole blood left in the reservoir. 3. Others received a suspension ‡ of their own red cells in gelatin, the suspension again in volume

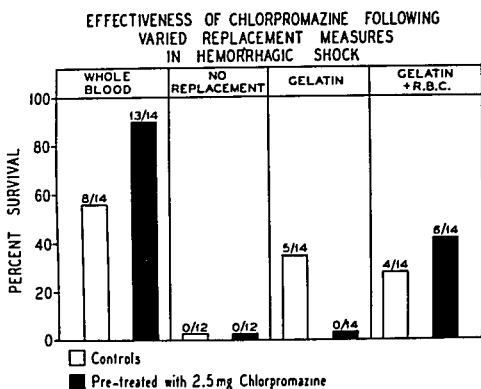


FIG. 2. Comparison of survival rate in control and chlorpromazine-pretreated rats receiving whole blood, gelatin or gelatin-red cell suspension as replacement therapy after three hours of hemorrhagic hypotension (50 mm. Hg).

equal to the remaining, whole blood. The results of these three groups of experiments are summarized in figure 2.

In considering these findings it is evident that chlorpromazine pretreatment was not, of itself, significantly protective in the absence of replacement therapy. In regard to the latter, when gelatin alone was substituted for whole blood, chlorpromazine pretreatment seemed to increase the incidence of irreversibility. For in this group the gelatin

† The gelatin used in this study was generously supplied by the Atlantic Gelatin Co. (Intravenous Gelatin. Lot No. P1-29).

‡ The gelatin red-cell suspension was prepared by centrifuging the whole blood remaining in the reservoir, discarding the plasma, washing the cells in Ringer's solution, re-centrifuging and adding gelatin in equal volume to the discarded plasma. During its reinfusion it was kept as a suspension by gentle agitation with a continuous stream of fine oxygen bubbles. The set-up contained a trap to avoid gas embolus.

controls had a 33 per cent survival as opposed to 100 per cent mortality in the gelatin-chlorpromazine treated animals.

Several other experiments were undertaken in which the treatment with chlorpromazine was modified. In one group, animals were prepared as untreated controls up to the end of the third hour of hypotension (50 mm. Hg). Some of these rats received 0.6 mg. per 100 Gm. body wt. of chlorpromazine dissolved in the final whole blood transfusion from the reservoir. Others were given 1.25 mg. per 100 Gm. body weight in the same way. Similarly prepared animals received 0.6 mg. per 100 Gm. at the end of the first-hour period of hypotension or at the end of each hour of the three-hour period of hypotension. The results of these experiments in which treatment with chlorpro-

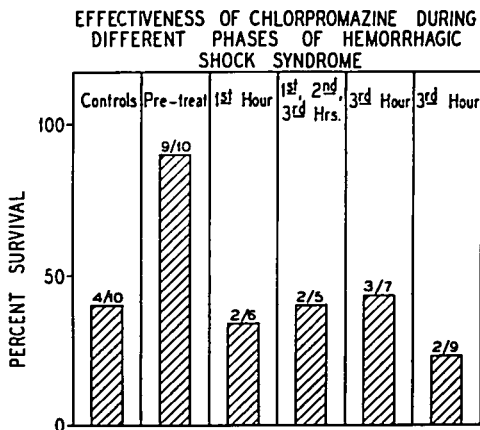


FIG. 3. Survival rates when chlorpromazine is given at various intervals after the onset of hemorrhage. The last column represents approximately twice the drug dose used in the animals represented by the fifth column. (See text for drug dosages.)

mazine after the onset of stress was substituted for pretreatment with the drug are shown in figure 3. These data indicate that treatment with chlorpromazine instituted after the onset of stress did not appreciably alter the survival rate in these animals.

ROLE OF BACTERIAL FACTORS IN RESISTANCE TO HEMORRHAGIC HYPOTENSION

In this series, the rats were divided into two groups; one group was prepared as the previously described untreated controls. These experiments were carried out under conventional laboratory conditions with the usual measure of cleanliness but no real provision for abso-

lute sterility of the apparatus. The second group was similarly prepared, except that these experiments were performed under completely aseptic conditions. Blood, liver, spleen and bowel of both groups were cultured at time of death or sacrifice.

The first group subjected to this pattern of graded hemorrhage under standard laboratory conditions showed positive bacterial findings which became increasingly evident in the liver, spleen, and bloodstream. *E. coli*, *lactus bacilli*, *paracolon bacilli* and occasionally *enterococci* appeared in the bloodstream and liver. The spleen was less regularly found to be infected. When some of these animals were sacrificed after being anesthetized, but prior to surgery and hemorrhagic stress, no organisms could be cultured. Pretreatment with chlorpromazine of some of the animals in this group, although protective, did not change the incidence or magnitude of the bacteriological findings.

In the second group of animals prepared similarly except for the use of aseptic technique, no organisms could be cultured. This ab-

TABLE 2
BACTERIOLOGICAL FINDINGS IN RATS SUBJECTED TO HEMORRHAGE
UNDER STANDARD AND ASEPTIC CONDITIONS

	Positive Bact. Cultures*	Survival†
Standard Conditions		
Controls	2/13	—
Shock	20/20	8/20
Shock & chlorpromazine	5/5	4/5
Aseptic Conditions		
Controls	0/5	1/5
Shock	0/6	5/6

* Blood, liver and spleen.

† Blood replacement after 1 hr. at 65 mm. Hg and 2 hrs. at 40 mm. Hg.

sence of infection was seen in animals sacrificed at intervals during the hypotensive episode, immediately after transfusion and twenty-four and seventy-two hours after transfusion. Further investigation indicated that the source of contamination noted in the first group was introduced by handling the rats which had been exposed to their own fecal deposits. The major source of contamination was the blood pressure measuring apparatus. It was of particular interest that in these shock experiments under aseptic conditions, the survival rate was higher than in rats bled under standard conditions. Furthermore, in the sterile experiments the severe congestion of the gastrointestinal tract, invariably associated with irreversibility under standard conditions, was completely absent. This occurred despite the fact that the gastrointestinal tract was shown to contain all the usual bacterial strains. Table 2 summarizes the findings in these bacteriologic studies.

It should be noted that the tissues and bloodstream of the rat, which under normal conditions are completely free of bacterial elements, do not show bacterial contamination following the stress of hemorrhage

or drum trauma unless the contaminant is introduced from the apparatus. Although bacterial infection clearly serves as a deleterious factor during the readjustment to hemorrhagic hypotension, it does not represent a critical factor since pretreatment with chlorpromazine serves to protect the rat in the face of bacterial contamination of the blood, liver and spleen following loss of blood.

CARRY-OVER OF PROTECTION AGAINST HEMORRHAGE TO OTHER FORMS OF STRESS

Trauma. Untreated rats were subjected to a lethal trauma of 650 revolutions in the Noble-Collip drum. Eighty-nine per cent of these animals went into shock and died within two to four hours. In no instance, in these drummed animals that were cultured, was any positive culture observed. Autopsy studies revealed extensive injury and hemorrhage in all viscera. However, because of the possibility of direct injury to the viscera from the tumbling trauma, these findings could not be correlated with the visceral congestion observed after simple hemorrhage.

TABLE 3
BACTERIOLOGICAL FINDINGS IN CONTROL AND CHLORPROMAZINE
TREATED RATS FOLLOWING DRUM TRAUMA *

Untreated		Chlorpromazine	
Survival	Positive Bact. Cultures	Survival	Bact. Cultures
3/12	0/12	11/12	0/5

* 650 revolutions in the Noble-Collip drum.

A comparable series of rats were pretreated with chlorpromazine in the same dose (2.5 mg. per 100 gm. of body weight) that would protect them against hemorrhage prior to exposure to drumming of 650 revolutions. As in the hemorrhage experiments, these animals now showed a high incidence of twenty-four-hour survival after this usually fatal trauma. At autopsy, the intestinal tract showed no evidence of engorgement or mucosal congestion, despite the considerable direct trauma inherent in the drum procedure. Bacteriological cultures of blood, liver and spleen were negative (table 3).

Radiation. Untreated female rats were subjected to 920 roentgens of total body x-radiation. This dose of x-ray is an LD₅₀ value within thirty days. Examination at four and twelve days revealed bacterial contamination (chiefly of the *Klebsiella* and *E. coli* type) in the blood and liver and considerable congestion of the intestinal wall.

Six rats were pretreated with chlorpromazine (2.5 mg./100 Gm.) prior to exposure to a similar dose of x-radiation. The bacteriological findings were identical with untreated controls. No effect on the LD₅₀ was introduced by the chlorpromazine.

In another series of experiments a study was made of the pre-

disposing action of x-radiation on the subsequent response to drum trauma. It was found that doses of radiation from 500 to 920 *r* increased the susceptibility of rats to drum trauma within four days and for a period extending to fifty days after x-ray exposure. The possibility was explored that chlorpromazine might counteract the lethal tendency in response to drum trauma in x-radiated rats. These rats were therefore exposed to 500 to 900 *r* of x-radiation as before and just prior to drum trauma received 2.5 mg. of chlorpromazine per 100 Gm. of body weight. The incidence of survival was not favorably influenced by this procedure.

DISCUSSION

These studies have presented a number of pertinent observations on the mechanism of resistance to severe injury and have thereby made it possible to delineate some of the characteristics of this entity. The data also direct attention to possible areas for more critical investigation of the subject.

The first group of experiments dealing with hemorrhagic stress of various intensities indicate that pretreatment with a specific pharmacologic agent, chlorpromazine, exerts a favorable influence on survival rate. This drug does not, however, afford complete protection in that it does not significantly alter the incidence of survival in those rats subject to the most severe patterns of hemorrhage. Furthermore, drug protected animals still take up a small volume of blood during the hypotensive episode, indicating the existence of a limited but definite decompensatory tendency. This lack of absolute protection after chlorpromazine pretreatment suggests that, in severe stress situations, the decompensatory factors may progress to such intensity that they cannot be effectively counteracted by the drug. It may further imply that in such profound shock decompensatory factors continue to be generated which are not susceptible to the influence of chlorpromazine. This drug, while it is an effective protective agent, cannot of itself completely counteract the irreversible tendency during shock.

Some of the observations relating to chlorpromazine protection are of special interest in that they suggest fairly specific functional and anatomical characteristics associated with the capacity to survive after severe stress. According to Fine (8) and others (9) the rate and volume of uptake of blood from the reservoir is a better index of the degree of vascular decompensation than the total volume of blood lost in a shock experiment. The small values of such uptake in drug-protected rats indicates the existence of good compensation and is an objective favorable sign of ultimate survival. This attenuation of vascular decompensation may be related to the more recent observation (10) that while chlorpromazine blocks neurogenic peripheral vascular control, it also serves to render the small blood vessels (arterioles and venules) hyper-reactive to circulating vasoactive materials. Such humoral

hyper-reactivity tends to sustain regional blood flow in the presence of a decreased circulating blood volume more effectively than the sympathetic overcompensation seen in the unblocked peripheral circulation in response to stress. This effect is not limited to the visceral circulation alone but is noted also in the skin, which retains a pink pallor rather than developing the cyanosed gray color typical of the shocked animal.

The absence of visceral congestion and intestinal bleeding further differentiates the chlorpromazine protected from the control animal. This contingency is a favorable sign for it indicates the elimination of much of the deleterious pooling of blood in the splanchnic area, a feature commonly implicated in irreversible shock. The protective effect of this drug is probably not limited entirely to the elimination of visceral vascular pooling alone. A previous report (7) demonstrated that eviscerate animals (without liver and bowel), anatomically without a splanchnic vascular bed in which blood can be pooled, when pre-treated with chlorpromazine and then subjected to hemorrhage show a higher survival rate than unmedicated bled eviscerates.

Resistance to stress must also involve adjustments in central nervous system responses to injury in that the animal with induced protection does not show the agonal gasping respiration or excessive tachycardia resulting reflexly from a stress stimulus. The more favorable cardio-respiratory sequelae could be due to better blood flow within the central nervous system or in the peripheral neurohumoral receptor areas. However, as indicated by other reports (11), a direct neural effect of the drug may be implicated since relatively normal respiratory patterns continue to be present in animals deliberately bled to extreme hypotensive levels (below 30 mm. of mercury) at which tissue perfusion is clearly inadequate.

Two other circumstances were investigated: the administration of chlorpromazine in conjunction with blood substitutes (gelatin and gelatin-red cell suspensions) and the use of chlorpromazine after the onset of hemorrhage. With extensive loss of blood it is not surprising that survival requires blood replacement therapy even when a normally effective dose of the drug is used. The observations with gelatin and gelatin-red cell replacement indicate that, as replacement therapy, these fluids are not adequate substitutes for whole blood. The incidence of irreversibility with gelatin alone may be due to the fact that, in these experiments, up to the time of infusion, the drug treated animals have taken up little or no whole blood from the reservoir and, as a result, at the end of the experiment, are left with an unusually large red cell deficit. The poor response resembles that of the uninfused chlorpromazine group in this respect. It would appear that protection against protracted hemorrhagic hypotension with chlorpromazine pre-treatment requires additional therapy with whole blood. The relative

volume of whole blood needed as replacement in relation to the total blood loss is not determined by these studies.

The experiments in which chlorpromazine was administered, not as pretreatment but subsequent to the onset of hemorrhage, indicate that these animals respond to stress very much as though they did not receive the drug at all. It would appear that whatever favorable factors are generated by chlorpromazine when given before the onset of stress, they cannot be effectively mobilized in already established stress situations. There still exists, of course, the possibility that some form of co-treatment could be effective but these studies do not sufficiently explore this aspect of its use. In regard to time of administration, it is interesting to note that reports from this and other laboratories (1-5, 10) dealing with protective agents and techniques indicate that protection against stress is achieved by prior exposure or conditioning to the protective modality. These data seem to show that chlorpromazine is apparently also in this category of protective modality.

The bacteriological studies in one sense yielded the most provocative observations in as much as they contributed information about the controversial subject of the role of the enteric bacterial flora in irreversible shock. In most laboratories, including our own, the surgery included in shock experiments is performed with precautions of cleanliness but not with rigidly aseptic technique. Under these circumstances bacterial invasion is apparently common. The fact that the organisms found in the blood and viscera are always of the same groups as those cultured from the animals' intestinal tract at first glance supports the thesis that the shock procedure broke down certain normal defense barriers and led to bloodstream invasion from the rat's own bowel. However, the experiments done under sterile conditions, in which no bacterial invasion occurred, point to the apparatus rather than the bowel as the source of contamination. Furthermore, under sterile precautions, animals do not develop the typical bowel congestion observed in the standard experiments despite the observation that their bowel contained all the usual bacterial strains. In addition, they showed better survival rates than those bled with non-sterile precautions. Experimental precaution against bacterial contamination therefore eliminates the hemorrhagic bowel, one of the factors ordinarily present in animal experiments leading to irreversible shock. The findings of bacterial invasion *per se* neither implicate nor negate the influence of the normal intestinal flora in many shock experiments. In considering the nature of chlorpromazine as a protective agent, it is apparently effective in attenuating whatever deleterious influence bacterial invasion produces since in the standard, nonsterile experiments the drug does protect rats having the same bacteriological findings as unprotected controls. In the chlorpromazine experiments, it is of interest to note that bacterial contamination during stress was not accompanied by bowel congestion or hemorrhage.

The evaluation of chlorpromazine, in a dosage that is effective in hemorrhagic stress in terms of its influence on other forms of stress, indicates a similarity of end-result in trauma but not in x-radiation. It is of significance, however, that the beneficial action of this drug is not limited to hemorrhagic shock alone. This observation is important since it suggests the concept that a variety of barriers of resistance are probably broken down or impaired depending upon differences in the type of stress situations that are created. The positive bacteriological findings in the radiated rats and the negative findings in the traumatized rats, both groups showing a high incidence of irreversibility, are also indicative of this probability. The protective effect of chlorpromazine must therefore be related to more than a single pharmacodynamic property of the drug.

SUMMARY AND CONCLUSIONS

This series of experiments in the rat delineates some of the characteristics of the phenomenon of protection against stress. The data indicate that: 1. Pretreatment with chlorpromazine increases the survival rate in rats subjected to various degrees of hemorrhagic hypotension except when the latter is unusually severe. 2. Protected animals require little re-infusion of blood during the hypotensive episode, do not develop hemorrhagic congestion of the bowel, liver or lungs, and do not show the gray cyanosed skin or gasping respiration observed in controls. 3. Drug-treated rats re-infused with gelatin and gelatin-red blood cell suspension instead of whole blood are not protected. 4. Administration of chlorpromazine after the onset of hemorrhage does not afford protection. 5. Bacterial invasion of blood, liver and spleen is related to contamination of the experimental apparatus. 6. Bowel congestion is eliminated by aseptic surgery. 7. Doses of chlorpromazine which protect against hemorrhage are also effective in trauma but not in x-radiation.

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