red blood cells. Resuspension of the cells would be effected either by raising the ionic strength, splitting the γ-globulin–γ-globulin bond, or by raising the *p*H, breaking the γ-globulin–lipoprotein bond.

To examine this hypothesis, two red cell lots of the same blood were washed centrifugally with saline solutions buffered at *p*H's of 5.5 and 7.2. Under my hypothesis, the γ-globulins responsible for reversible agglomeration would be expected to remain complexed to the cells washed at *p*H 5.5 and to be removed from those washed at *p*H 7.2. Those cells washed at *p*H 5.5 agglomerated and settled after dilution with 10-percent glucose, while those washed at *p*H 7.2 did not. Addition of minute amounts of human immune γ-globulin to the cells washed at *p*H 7.2 restored their ability to clump together and settle. Human serum albumin, fibrinogen, and egg white were ineffective in restoring the ability to agglomerate.

Collateral evidence to support my hypothesis was obtained when I found a patient with severe hypogammaglobulinemia (E.S. MGH No. 88-80-75). Her packed blood cells in acid citrate dextrose solution (ACD) anticoagulant settled poorly; however, another 1-ml sample to which had been added 20 mg of human immune γ-globulin settled normally when diluted with 10-percent dextrose in water. Neither the *p*H nor the electrical conductivity of the supernatant was altered by the addition of the γ-globulin.

The mechanism of action of reversible agglomeration of human erythrocytes may well prove more complex than my simple hypothesis would suggest. It does, however, explain observed facts and has been found useful in the development of a simple technique for washing dimethylsulfoxide from thawed human blood.

Clinical units of blood (500 ± 100 ml) from healthy donors were drawn into standard plastic bags containing ACD anticoagulant. The blood was separated centrifugally. The packed cells thus obtained were diluted with an equal volume of either autoclaved 5-percent glucose or 8-percent sucrose made up in 8.6*M* dimethylsulfoxide (*2*). The treated cells were reconcentrated by centrifugation and their plastic container placed horizontally in an electrical deepfreeze at −88°C. The frozen cells were completely thawed in 5 to 8 minutes by placing their plastic bags in a vigorously stirred water bath at 40° ± 0.5°C. Hemolysis was less than 5 percent, and generally less than 2 percent, for a consecutive series of 67 units stored for periods up to 42 days (*3*).

The thawed blood was transferred from its plastic bag to the bottom of a glass cylinder (48.5 cm long by 8.5 cm in diameter), and stirred with a magnetic stirrer. Sterile 10-percent glucose at a temperature of 20°C was added slowly to effect dilution from 300 to 2000 ml. The clumped cells settled, the supernatant was discarded, and the washing by dilution repeated twice. No attempt was made to resuspend the cells between dilutions. The supernatant-free agglomerated cells were finally resuspended by the addition of the thawed plasma from the original donor. The reconstituted blood was drawn off into a sterile plastic bag and stored at 5°C.

Recovery of 75 to 85 percent of the originally donated cells may be easily accomplished in 45 to 60 minutes after thawing. It is fortuitous that the *p*H of ACD anticoagulated blood and 10-percent glucose are optimal for reversible agglomeration of the cells. Dimethylsulfoxide concentration of the reconstituted blood, as measured by gas chromatography, is less than 0.2 percent (*4*).

Clinical units of human blood have been treated with dimethylsulfoxide, stored at −88°C, and administered without apparent ill effect. Reversible agglomeration of the red blood cells, possibly mediated by erythrocyte-γ-globulin coprecipitation, has proved a simple, effective, and inexpensive method for rapidly removing dimethylsulfoxide from thawed blood. Further studies to perfect this method for clinical preservation of blood by freezing are in progress.

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Disinhibition after Prefrontal Lesions as a Function of Duration of Intertrial Intervals

Abstract. *Dogs were trained preoperatively in both positive and inhibitory conditioned food reflexes on a schedule of either a 15-second or 1-minute intertrial interval. After lesions had been made in the medial surface of the prefrontal cortex, errors of disinhibition occurred in both schedules and in association with an increased "drive" for food. In contrast, lesions of the dorsolateral prefrontal cortex produced the disinhibition syndrome only in the group which was tested at short intertrial intervals, and no increase in food-directed activity was noticed. In each instance the postoperative recovery was very rapid. It is suggested that the quality of disinhibition in prefrontal animals is different, depending on the placement of the lesion.*

This study was undertaken to delineate further the role of the prefrontal cortex in inhibitory activity (*1*) by investigating the effect of partial lesions on conditioned reflexes (CR's) in dogs.

The animals were prepared as previously described (*2*). Briefly, the procedure consisted of training the dogs to place their right forelegs on a food tray to obtain food reinforcement when a 1000-cy/sec tone (positive conditioned stimulus) was presented, and to refrain from this response when a 700-cy/sec tone (inhibitory conditioned stimulus) was presented. No food was given on the inhibitory trials. Errors

Table 1. Scores of pre- and postoperative inhibitory trials and errors, including the criterion, in group 1 animals (15-second intertrial interval). *T*, trials; *E*, errors.

Dog No.	Preoperative		Postoperative	
	T	E	T	E
Dorsolateral prefrontal lesions				
30	360	195	270	92
31	520	346	270	64
32	830	395	140	22
33	200	120	155	41
Medial prefrontal lesions				
34	520	263	125	60
35	360	172	115	32
36	605	451	215	94
37	280	143	245	85
Posterior cingulate lesions				
26	420	291	50	5
27	295	171	55	7
28	435	273	50	3
Unoperated controls				
47	440	230	50	4
48	290	120	50	5

Table 2. Scores of pre- and postoperative inhibitory trials and errors, including the criterion, in group 2 animals (1-minute intertrial interval). *T*, trials; *E*, errors.

Dog No.	Preoperative		Postoperative	
	T	E	T	E
Dorsolateral prefrontal lesions				
38	305	163	50	3
39	135	75	60	8
40	150	81	50	5
Medial prefrontal lesions				
41	100	48	105	36
42	170	63	130	57
43	220	76	95	35

of disinhibition were scored if the animal responded positively to the presentation of an inhibitory conditioned stimulus. Fifteen positive and 15 inhibitory trials were presented daily to each animal. In group 1 ($N = 13$), trials were separated by 15 seconds, while in group 2 ($N = 6$) they were separated by 1 minute. Training continued until the animals attained the criterion of 50 correct positive responses and 45 correct inhibitory responses in 100 consecutive trials. Upon completion of training, two animals in group 1 were retested after a 10-day interval; these served as unoperated controls. The remaining dogs were retested 7 days after the following cortical areas were ablated: (i) the dorsolateral portion of the proreal gyrus and the anterior part of the orbital gyrus, which, taken together, constitute the dorsolateral aspect of the dog's prefrontal cortex; (ii) the cortex of the upper medial wall of the prefrontal lobe, that is, sparing the subgenual and subproreal regions; (iii) the posterior cingulate cortex.

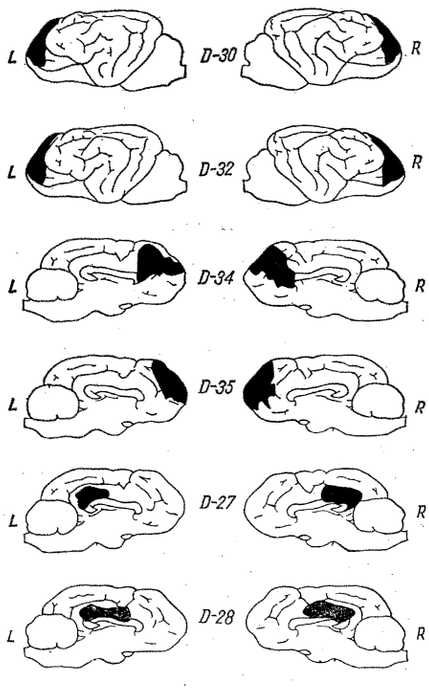

Fig. 1. Representative reconstructions of the prefrontal lesions described in the text. (Top two) Lateral reconstructions of bilateral ablation of the proreal and anterior orbital gyri in dogs Nos. 30 and 32. (Middle two) Medial reconstructions of bilateral ablation of the medial prefrontal cortex in dogs Nos. 34 and 35. (Bottom two) medial reconstructions of bilateral ablation of the posterior cingulate cortex in dogs Nos. 27 and 28.

Three months after operation the animals were killed and their brains were fixed in formalin, sectioned at 20 μ, and stained with thionine. Representative reconstructions of each type of lesion are shown in Fig. 1.

Since responses on positive trials were generally unaffected, the results are shown for all the dogs on the inhibitory trials only. In Table 1 data are given for dogs in group 1. It is seen that both the unoperated animals and the animals in which the posterior cingulate area was removed were not impaired, whereas lesions of both the dorsolateral and medial prefrontal cortex produced temporary disinhibition of inhibitory CR's. In contrast, in dogs in group 2 the impairment on inhibitory trials followed only the medial lesions. Ablation of the dorsolateral prefrontal cortex was without effect (Table 2).

Examination of other aspects of the behavior indicates that, in the initial postoperative period, the dogs with medial lesions displayed marked food-oriented behavior characterized by sniffing, licking, and gazing at the cup throughout the testing session. In addition, they scratched the food tray and performed many intertrial CR's. On the other hand, the dogs with dorsolateral prefrontal lesions were not affected by a similar increased "drive" for food. Their impairment on the 15-second-interval schedule seems to be a reflection of somatoperseverative tendencies which have been described previously in animals with prefrontal lesions (*3*). Short intervals between trials appear to produce an increase of this type of error in animals in which the dorsolateral prefrontal cortex is ablated.

The findings in the present study add support to the conclusion derived earlier from studies on monkeys (*4*) that different "inhibitory" defects follow selective lesions restricted to the orbital and dorsolateral frontal cortex. Future research in this area must involve testing procedures other than instrumental conditioning in order to permit a more precise evaluation of the view that different types of disinhibition result from different prefrontal lesions (*5*).

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Xenon Hydroxide: An Experimental Hazard

An ~ 0.39-g sample of xenon tetrafluoride in an evacuated silica bulb equipped with a Hoke valve was dissolved in 1.5 ml of distilled water. The solid reacted vigorously and the fumes of hydrogen fluoride were pumped off immediately. Evaporation of the resulting clear solution at ambient temperature left a white solid. Previous runs in nickel weighing bottles indicated that this residue had a composition of $Xe(OH)_4$ or $XeO_2{,}2H_2O$. This solid detonated when warmed under vacuum above 30° or 40°C and completely shattered the enclosing vessel (*1*).

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