preincubation of serum with this primer before addition of enzyme were necessary to demonstrate marked inhibition. Seven normal sera and 5 from multiple myeloma and neutropenias not associated with collagen disease did not inhibit after preincubation of serum and primer. Without preincubation, the normal sera were stimulatory. Incubation of enzyme with primer before addition of inhibitory serum markedly reduced the inhibition. Results indicate that the combination of serum factor(s) with DNA covers up at least part of the active site for the polymerase.

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Disposition of S^{35}-Prochlorperazine in the Jaundiced Rat.* (28146)

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We have recently reported on the excretion of S^{35}-prochlorperazine in experimentally stressed rats(1) and the disposition of this agent in normal as well as chronically-treated rats(2). These studies revealed that information derived from certain investigations in normal animals may be misleading when applied to agents which will be used in abnormal physiological states. They also demonstrated the major importance of the fecal route of excretion of prochlorperazine and the contribution of the biliary route to elimination in the feces. For this reason we felt it of interest to investigate the distribution and excretion of this agent in rats subjected to ligation of the bile duct.

Methods. Male albino Holtzman rats having an initial weight of 250 to 350 g were employed. All animals were allowed food and water *ad libitum* up to the time of drug administration. Rats employed in excretion studies were allowed free access to food and water during the entire period. Each rat received 25 mg/kg of prochlorperazine base (as the dimaleate) as a 1.2% suspension in 4% acacia intraperitoneally. Within the separate studies, all animals were dosed from the same freshly prepared drug suspension. Each rat received 10 μc of S^{35} per 275 g of body weight.

Rats to be made jaundiced were anesthetized with ether and the bile duct was ligated with a single suture placed at about one-third of the length of the duct from the liver. Rats prepared in this manner were used 12 hours later. Preliminary studies revealed that rats operated on as above lived longer than 96 hours, the maximum duration employed in this investigation.

Distribution and excretion studies were conducted as previously described(2).

Results. Fig. 1 and 2 represent S^{35} levels in cerebrum, liver, kidney, fat, muscle, and blood of jaundiced and control rats, respectively, following administration of S^{35}-prochlorperazine. With the exception of fat, S^{35} levels one hour after drug administration were higher in all tissues in jaundiced than in control rats. Despite the higher initial levels,

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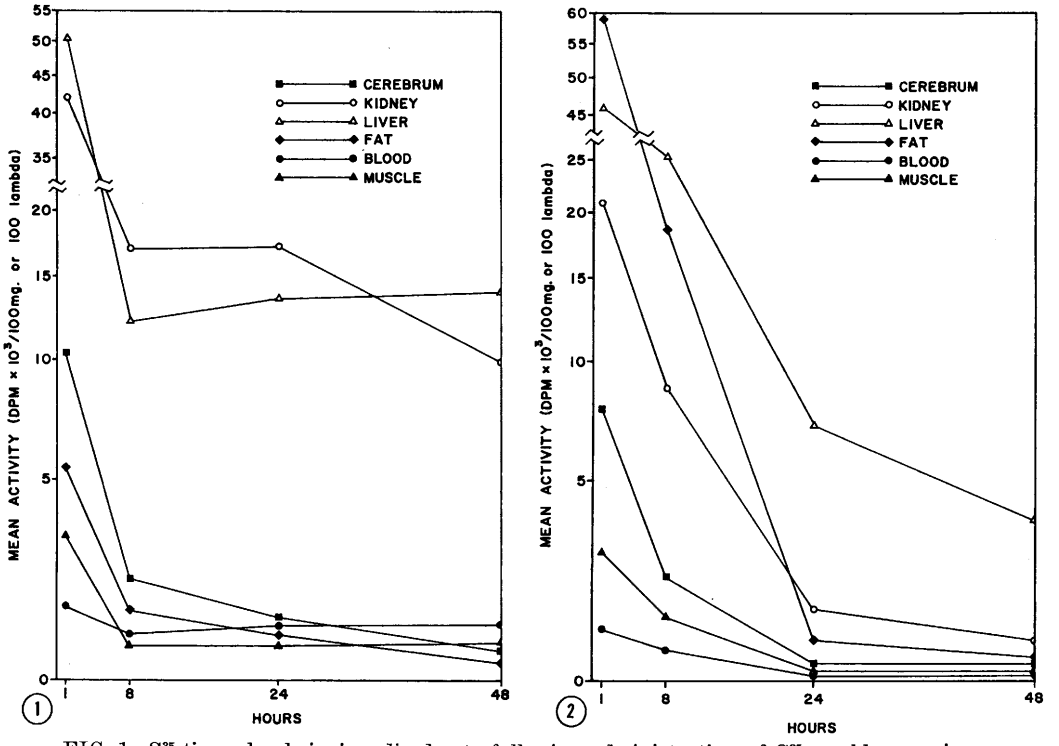

FIG. 1. S^{35} tissue levels in jaundiced rats following administration of S^{35}-prochlorperazine.
FIG. 2. S^{35} tissue levels in control rats following administration of S^{35}-prochlorperazine.

tissue S^{35} levels at 8 hours, with the exception of blood, were lower in jaundiced than in control animals. After 8 hours, however, tissue levels fell very slowly and at 48 hours all tissue levels were higher in jaundiced rats than those observed in control animals.

Table I contains the percent of the originally administered dose excreted in urine and feces of jaundiced and control rats at various time intervals. A much greater portion of the dose was excreted in the urine of jaundiced rats, while very little was excreted in the feces. Both total excretion and excretion at the end of 48 hours are decreased in jaundiced rats. It is of interest that only about one-third of the radioactivity in the urine of jaundiced rats is extractable with chloroform at pH 11, while nearly two-thirds of the radioactivity in the urine of control rats is extractable.

Discussion. The low S^{35} levels observed in fat of jaundiced rats were not anticipated since preliminary studies indicated that bile accumulated in fat. These low levels may be the result of the 12 hour waiting period be-

TABLE I. Mean Cumulative Percent of Original Dose of S^{35} Excreted in Urine and Feces Following Administration of S^{35}-Prochlorperazine to Rats.

Route of excretion	Control	Jaundiced*
Urine		
4†	.94	3.58
8	6.98	12.19
12	9.08	19.81
24	17.87	40.08
36	21.49	50.29
48	22.64	55.83
60	22.85	58.04
72	22.98	59.39
84	23.04	60.57
96	23.20	61.91
	± .61‡	
Feces		
24	2.75	2.38
48	56.39	5.93
72	68.10	8.16
96	71.51	9.53
	3.45‡	
Total	94.71	71.44
	± 3.59	

* Six rats were dosed; however, one died at 24 hours, 2 more at 36 hours, a fourth at 60 hours, and a fifth at 72 hours. At each time interval the mean cumulative amount was calculated for number of animals alive. Five control rats were used.

† Hours after drug administration.

‡ ± Standard error. This term could not be calculated with the jaundiced data.

tween ligation of the bile duct and drug administration, during which time fat may have become saturated with bile. Subsequent exchange would then take place slowly. Tissue levels of S^{35} in jaundiced rats implied that initially, excretion by another route was increased to compensate for the lack of biliary excretion. Apparently at later time intervals this route became saturated or in some manner failed to continue the accelerated excretion of S^{35} thus accounting for the increased tissue levels observed at 48 hours. These findings illustrate the changes which might occur in the patient suffering from severe obstructive jaundice, following treatment with prochlorperazine. The initial rapid urinary excretion of S^{35} in jaundiced rats explains the prompt decline of S^{35} tissue levels from the high peak levels seen in the distribution study. The observation that rate of urinary excretion is decreased considerably after 24 hours is consistent with the finding that after the initial rapid fall S^{35} tissue levels declined much more slowly.

The unusual toxicity of prochlorperazine in jaundiced rats in this study is apparently the result of the alteration in disposition of the drug. The unusual feature of this toxicity is that deaths all occurred at a time when brain levels of the drug were much lower than initial peak brain levels, indicating a delayed death phenomenon. These findings suggest that the intensity of pharmacological response may be related to the initial drug levels attained at the active site. The findings are similar to those of Plaa *et al.*(3) who found that in animals in which liver damage had been induced by carbon tetrachloride the N-substituted phenothiazine, thioridazine, produced delayed death. In addition, they found that thioridazine tissue levels were higher in animals with liver damage than in controls. Thus, it is probable that the delayed death seen with prochlorperazine in jaundiced rats is due to liver damage resulting from obstructive jaundice.

The extraction studies indicate that much larger quantities of some apparently bound metabolite(s) are excreted in the urine of jaundiced rats. This probably represents the appearance in the urine of a conjugated metabolite(s) normally excreted in the bile.

Summary. Initial S^{35} tissue levels were higher in jaundiced than in control rats following S^{35}-prochlorperazine administration. However, 8 hours later tissue levels were lower in jaundiced rats. After this time tissue levels decreased very slowly in jaundiced rats and at 48 hours were considerably higher than in control animals. A major portion of the dose administered to jaundiced rats was excreted in the urine, while fecal excretion is the predominant route in control rats. In view of findings by other investigators it is likely that the altered drug disposition observed in jaundiced rats is the cause of the delayed death phenomenon observed in these animals.

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