tions to blood protein production and utilization. Thus, it has been demonstrated recently[18] that although the antibody level in the *blood* of immunized, normal and adrenalectomized rats may be at similar levels, the *tissues* of the adrenalectomized rats are producing antibody at a rate which is distinctly less than that of the unoperated animals. This suggests that the adrenalectomized animals are also removing antibody from the circulation at a rate which is less than normal. Thus, although the blood titer is similar in the two groups of animals, the presence of the adrenal does appear to influence the rate at which the antibody globulin enters and leaves the circulation. It may also be of significance that Mondolfo and DeLerner[10] reported recently that whereas relatively small doses of adrenal cortical extract may augment the rate of antibody production, significantly larger amounts of the same extract produced a suppression of antibody production as compared to the rate seen in animals receiving antigen alone.

Summary. Normal mice, or mice bearing a transplantable lymphosarcoma, were given single injections of adrenal cortical extract or exposed to a single radiation dose of 200 r (total body radiation). Examination of the serum protein patterns of these mice at 3 and at 6 hours after hormone injection, or at 6 hours after exposure to X-rays, revealed a striking increase in total serum protein levels. However, electrophoretic examination did not reveal significant alterations in the relative distribution of the serum proteins.

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18 Roberts, S., and White, A., unpublished results.

Cinchophen Choleresis and Production of Peptic Ulcer in Various Species. (17457)

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Brugsch and Horsters[1] were the first to show that cinchophen, in both dogs and man caused an increase in the bile flow. Stransky[2] carried this study to rabbits and was unable to detect any choleretic effect of cinchophen in this species. Berman and Ivy[3] confirmed this finding and found in addition that the excretion of cinchophen in the bile of rabbits was very small.

Churchill and Van Wagoner[4] demonstrated that dogs receiving 20 to 30 times the human dose of cinchophen developed gastric or duodenal ulcers. This finding has since been confirmed very many times.[5-7] Shoji[8] found that rabbits were very resistant to the ulcerogenic action of this drug. Okada[9] likewise failed to produce cinchophen ulcers in either rabbits or guinea pigs. Schwarz and Simmonds[10] were unable to induce cinchophen gastric, or duodenal ulceration in rabbits or guinea pigs, but found cats very susceptible. The ability of cinchophen to cause liver damage in rats[11] has been noticed but there has been no report of its effect upon the gastrointestinal tract.

1 Brugsch, W., and Horsters, H., *Z. ges. Exp. Med.*, 1923, **38**, 367.

2 Stransky, E., *Biochem. Z.*, 1925, **155**, 256.

3 Berman, A. L., and Ivy, J. H., PROC. SOC. EXP. BIOL. AND MED., 1940, **45**, 853.

4 Churchill, T. P., and Van Wagoner, F. H., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 581.

5 Stalker, L. K., Bollman, J. L., and Mann, F. C., *Arch. Surg.*, 1937, **34**, 1172.

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7 Nasio, J., *Rev. Gastroenterol.*, 1946, **13**, 195.

8 Shoji, A., *Trans. Soc. Path. Jap.*, 1933, **23**, 520.

9 Okada, S., *Trans. Soc. Path. Jap.*, 1933, **23**, 522.

10 Schwarz, S. O., and Simmonds, J. P., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1133.

11 Barbour, H. G., and Fisk, M. E., *J. Pharm. and Exp. Therap.*, 1933, **48**, 341.

TABLE I.
Effect of Cinchophen Upon Bile Output in Various Animals and Its Excretion in the Bile.

No. of animals	Species	Avg wt, g	Cinchophen administered, mg/kg	Bile output: Control, ml in 30 min.	Bile output: Control, ml/kg hr	Bile output: 1st 30 min. after cinchophen	Bile output: Increase, %	% recovery of cinchophen in bile in 1st 2 hr
4	Rabbits	2,400	100	4.5	3.74	4.25	0	1.75
13	Rats	241	100	0.266	2.2	0.239	0	5.1
14	Guinea pigs	569	100	2.2	7.2	3.0	36.3*	27.7
11	Cats	2,850	100	0.77	0.54	0.95	23	2.18

* This figure only is statistically significant ($P = <0.01$).

Except in the case of the rabbit and dog, it has not previously been shown whether or not any relationship exists between the susceptibility of an animal to cinchophen peptic ulcer and the animal's choleretic response to this drug.

Methods. Two series of experiments were conducted, acute experiments to determine the effect of cinchophen upon the bile flow and chronic feeding experiments to determine the susceptibility of the various animals to cinchophen ulceration.

Acute experiments. Cats, rabbits, guinea pigs and rats were used in this study. Dogs were not used as they have been adequately studied by others.[1,12] The animals having been fasted for the preceding 12 hours were anesthetized with "Nembutal". The gallbladder, where present, was tied off and the common duct cannulated using plastic tubing. In rats, a glass cannula of near-capillary dimensions attached by rubber tubing to a horizontal graduated 1 ml pipette was used. In the other species the bile was collected in 10 ml graduated cylinders. The volume was measured half-hourly. After a steady control output had been reached, cinchophen dissolved in $\frac{N}{10}$ NaOH was administered intravenously. In those animals failing to respond, the reactability was tested with sodium dehydrocholate ("Decholin"). Animals failing to give a response to sodium dehydrocholate were discarded.

Chronic Feeding Experiments. In these studies the same four species were used with the addition of dogs. The latter were used to determine the ulcerogenic potency of the cinchophen. The drug was administered to cats, dogs, guinea pigs and rabbits daily in gelatin capsules. It was in addition administered subcutaneously to another series as an aqueous solution of the sodium salt to guinea pigs, rabbits and rats. To still another series of rabbits and rats a suspension of the free acid in tragacanth was administered by stomach tube. In these species this mode of administration was found more convenient than gelatin capsules. As it was observed that the animals most susceptible to cinchophen ulcer were carnivora, a series of rabbits, rats and guinea pigs was fed the same proprietary meat dog food as were the dogs and cats. In all cases control animals were fed the same diet without cinchophen as the test animals.

It is now well known that choleresis results from the administration of cinchophen both

TABLE II.
Apparent Relationship Between Cinchophen Excretion in Cats' Bile and Choleresis Induced by Cinchophen.

Cat. no.	% cinchophen recovery in bile in 1st 2 hr.	% increase in bile flow
1	0.13	0
2	1.13	0
3	1.7	16.75
4	2.5	100
5	5.65	117.5

[12] Bradley, W. B., and Ivy, A. C., PROC. SOC. EXP. BIOL. AND MED., 1940, **45**, 143.

TABLE III.
Incidence of Ulceration in Various Animals Resulting from Cinchophen Feeding.

No. of animals	Species	Dose range, mg/kg	Diet	Survival time, days	No. of animals showing	
					Ulcers	Erosions
21	Rabbits	100-600	Normal	12-32	0	0
11	''	100-200	Meat	12	0	2
20	Guinea	100-230	Normal	16.5	1	0
10	pigs	300	''	7.1	6	0
6	''	400	''	5	1	0
24	Rats	100-400	Meat and normal	S 42-56	0	0
11*	''	500 and 1500	Normal	S 15	2	5
12	''	600-700	''	S 10	10	1
6	Cats	100	''	9	3	1
4	''	200	''	6	3	0
1	Dogs	100	''	S 62	0	0
6	''	200	''	14	6	0

* These animals were fed 500 mg/kg for 13 days and given 1,500 mg/kg on the 14th, and killed on the 15th.
S = Sacrificed.

by vein and orally to acute and chronic biliary fistula dogs.[12]

Results. It will be seen from Table I that guinea pigs show both the greatest choleretic response to cinchophen and also the greatest secretion of cinchophen in the bile. Rats and rabbits show no choleretic response. The rats, however, secreted appreciable quantities of cinchophen in the bile whereas the rabbits as was previously shown by Berman and Ivy[3] did not. Our results in cats were not clear cut. The average figures show a slight increase, but this was not statistically significant, many of the animals failed to respond to sodium dehydrocholate and were therefore not included in the results. It will be seen from Table II that the cinchophen output in the cats' bile shows individual variation, but nevertheless the magnitude of the choleretic effect appears to vary directly as the cinchophen output.

It was found (Table III) that among the species studied rabbits alone failed to develop cinchophen ulcers. Two gastric erosions occurred amongst the meat fed animals, but as these appeared with equal frequency in the controls fed meat without cinchophen the causative factor was thought to be the presence of fragments of bone in the meat.

The only ulceration seen in rats occurred in a series fed 500 mg/kg cinchophen daily for 13 days. On the 14th day, 1,500 mg/kg was administered. Two ulcers and a number of erosions (Table III) were observed at autopsy on the 15th day, and in another series in which 10 of one dozen rats, fed 600-700 mg/kg developed ulcers within 10 days (Fig. 1). The stomachs of all were full of food thus excluding starvation as a possible cause of the gastric lesions. All the ulcers seen occurred in the glandular part of the stomach. The meat diet seemed to be without effect.

Ulcers occurred in guinea pigs more frequently than in rats, but still with less frequency than in cats or dogs. They occurred only when doses in the neighborhood of 300 mg/kg were given daily. Above and below this dose level cinchophen killed the animals but ulcers were not seen. Meat feeding to guinea pigs over long periods of time was found impossible as the animals would starve rather than eat the diet. In our earlier investigation,[13] doses of 200 mg/kg were used and ulcers were not produced. A group of control animals fasted for one week without being given cinchophen developed the charac-

[13] Magee, D. F., Kim, K. S., and Ivy, A. C., *Fed. Proc.*, 1949, **8**, 103.

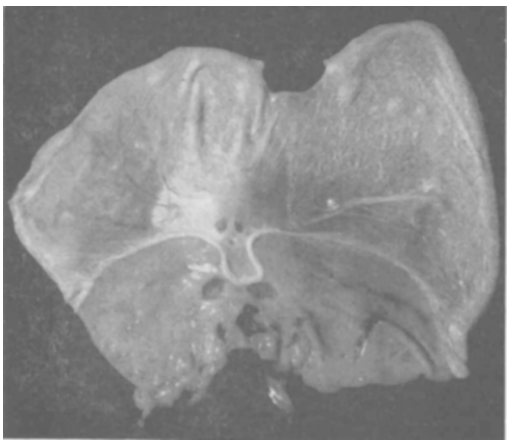

FIG. 1.
Ulcers produced in the rat's stomach by feeding 600 mg/kg cinchophen for 10 days.

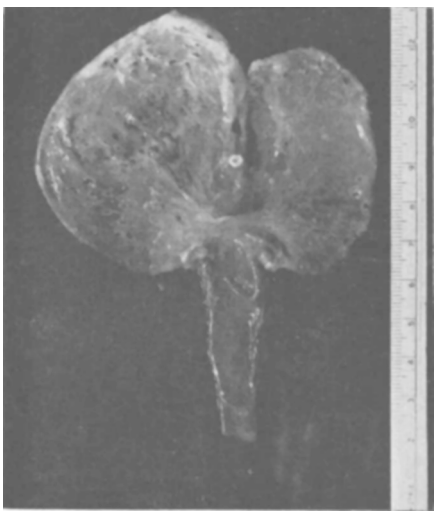

FIG. 2.
Typical gastric ulceration resulting from feeding 300 mg/kg cinchophen to guinea pigs.

teristic mottled yellow liver, seen in all animals except dogs, but no ulcers appeared. This excludes the possibility that cinchophen produced ulceration is secondary to loss of appetite and subsequent starvation.

The ulcers seen in guinea pigs were quite unlike those seen in other animals. They were almost always multiple and were confined almost exclusively to the fundic part of the stomach (Fig. 2) whereas in cats and dogs, in both of which ulcers occurred easily, they were pyloric, usually single, occasionally 3 or 4 were observed in cats. In guinea pigs there were seldom less than 20.

Similar ulcers were produced in guinea pigs using sodium dehydrocholate in doses of 200 mg/kg/day orally or subcutaneously often within 24 hours. Sellards[14] and Tsuruta[15] have produced this characteristic guinea pig type of ulceration with sodium glycocholate and the sodium salts of conjugated cholic acids obtained from ox bile.

Discussion. It appears, at least superficially, that cinchophen ulceration can be produced most easily in those species which show a choleresis, but the choleretic response in cats to cinchophen is so small and variable as to be statistically insignificant, and moreover it is not certain that the ulcers in the guinea pig are of the same origin as those occurring in cats and dogs. Sodium dehydrocholate administered to guinea pigs will produce ulcers almost identical in site and appearance with those resulting from cinchophen. This has not been seen in the other animals. The ulcers produced in rats were in response to such enormous doses of cinchophen that a direct effect upon the mucosa cannot be excluded.

No correlation appears to exist between the cinchophen output in the bile and the species susceptibility to cinchophen ulceration. Rats and especially guinea pigs secrete very much more cinchophen in their bile than do cats and yet cats were the most ulcer susceptible animals studied.

The only factor which is common to all ulcer resisting species is that they have a high control output of bile. However, the most susceptible of the resisting species, the guinea pig, has the highest basal bile flow (Table I). Cats and dogs, both of which secrete approximatey 0.5 ml per kg/hr are very susceptible. It is well known that dogs totally deprived of bile often develop spontaneous ulcers. A possibility which must be considered is that cinchophen has a different metabolic pathway in the more resistant group of animals from that in the less resistant species.

[14] Sellards, A. W., *Arch. Int. Med.*, 1909, **4**, 502.
[15] Tsuruta, T., *Cincinnati Med. Bull.*, 1931, **6**, 110.

Summary and conclusions. A choleretic response to cinchophen was observed in guinea pigs.

The cinchophen output in the bile was found to be greatest in guinea pigs and to decrease in the following order: rats, cats and rabbits.

The following is the order found for susceptibility to cinchophen ulceration: cat, dog, guinea pig and rat. Rabbits were found completely resistant.

There appears to be no obvious relationship between the species susceptibility to cinchophen ulceration and the choleretic response of that species to cinchophen or to the concentration of cinchophen in the bile after intravenous administration.

It would appear that the ulcer susceptible animals investigated have a low basal bile flow whilst the unsusceptible have a high flow.

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Focal Neurological Lesions Produced by Microwave Irradiation. (17458)

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Prewar and wartime research allowed the development of electronic equipment capable of efficiently producing large quantities of radiation above 1000 megacycles (microwaves). Notable among these advances was the development of the magnetron tube which is used in radar equipment[1] and has been incorporated recently in a microwave diathermy machine.* The frequency at which this machine operates (2450 megacycles, 12.2 cm) allows good penetration of animal tissue and even of bone, as demonstrated by Osborne and Fredericks[2] and Krusen, Herrick and Wakim.[3] These findings and the fact that radiation at this frequency travels in substantially straight lines suggests that the application of toxic doses of this radiation to a small area of the cerebral cortex is possible without injury to the scalp and skull.

However, a review of the literature reveals no report of the utilization of microwave radiation for the artificial production of focal neurological lesions. With the technic to be described focal lesions were produced in rabbit brains without surgical procedure. The site of the cortical lesion, moreover, was accurately determined before the irradiation.

Method. Adult rabbits weighing about 3 kg were utilized. Under intravenous pentothal anesthesia sufficient to immobilize the animal (80-100 mg) the animal's head was placed on a wooden block approximately 7 cm in thickness. The area of the scalp over the proposed site of irradiation was shaved. A thin copper shield with an oval hole 2 x 3 cm was then placed with the long axis of the hole parallel to the rabbit and over the proposed site, in the present cases the right cerebral hemisphere. It was found convenient to braze a guide on the upper surface of the shield to maintain the intersection of the lead-in conductor and dipole directly over the hole in the shield. In the "C" type of director, which was used throughout, the point of maximum radiation was directly underneath the small screw which held the dipole in place.

The plastic protector of the radiating elements was then placed in contact with the shield and the shield in contact with the scalp over the proposed site. It was found convenient to mark the site lightly with a dot of colored crayon before putting the shield

1 Argento, H. F., Centimeter-wave Magnetrons. QST, Dec. 1945.

* Available as the "Microtherm" from the Raytheon Mfg. Co., Waltham, Mass., who courteously supplied the machine with which this work was done.

2 Osborne, Stafford L., and Frederick, Jesse N., *J.A.M.A.*, 1948.

3 Krusen, F. H., Herrick, J. F., and Wakim, K. G., *Proc. Staff Meet. Mayo Clin.*, 1947, **22**, 209.