Brit. J. Pharmacol. (1951), **6**, 89.

THE ENHANCEMENT OF THE EFFECT OF ORAL PENICILLIN IN LABORATORY ANIMALS BY THE USE OF OIL CONTAINING ALUMINIUM RESINATE

BY

Y. C. HSU AND G. A. H. BUTTLE

From the Department of Pharmacology, School of Pharmacy, University of London

(Received October 31, 1950)

Libby (1945) and many other workers (McDermott, Bunn, Benoit, Dubois, and Haynes, 1945; Perlstein, Kluener, and Liebmann, 1945; Finland, Meads, and Dry, 1945; Rake and Richardson, 1946) employed vegetable oils alone or with other substances as suspending media for penicillin given orally. As oils are not miscible with water, they might well form an ideal protection for the penicillin in the stomach. As the oil is absorbed in the small intestines, the site where the maximum absorption of oral penicillin occurs, penicillin might be carried there by the oil and both might be absorbed at the same time. Thomas, Lyons, Romansky, Rein, and Kitchen (1948) reported the use of a water-repelling substance, aluminium stearate, with oil in delaying the absorption of intramuscular penicillin. It was therefore thought that a water-repelling agent might increase the protective effect of the oil on oral penicillin.

Among many water-repellents tested aluminium resinate was found to be the most effective in mice, rats, guinea-pigs, and rabbits. The present paper gives an account of experimental results in the course of an investigation of this effect of aluminium resinate.

METHODS

Blood penicillin levels.—Five species of laboratory animals, viz., mouse, rat, guinea-pig, rabbit, and cat, were used. Doses were given by means of a stomach tube. The " oral dose " referred to in this paper was given by this method. Blood samples were withdrawn at different intervals by heart puncture in all species except the rabbit, in which blood samples were obtained from the ear veins. In the mouse, 0.3 ml. of blood was withdrawn from each of three animals and the specimens were then pooled. In the rat, successive blood samples for a test were obtained from each of the same three animals. In a similar manner, in the guinea-pig, blood samples were obtained from each of the same two animals and in the cat or rabbit from the same one animal. The potencies of penicillin in different blood samples were compared by the Agar-cup plate method.

Infection test.—Mice (18–22 g.) of either sex were used. Tests were designed to compare the degree of protection given by various penicillin preparations against a haemolytic streptococcal infection. The mice were infected intraperitoneally by an inoculum of 0.2 ml. of a 1: 10,000 dilution of a 6-hour blood-broth culture of the Richards strain of *Streptococcus haemolyticus*. The doses of the various penicillin preparations were all of a potency equivalent to 10 units of penicillin. Other methods will be described later.

RESULTS

Effect of oil on oral penicillin in mice

In order to confirm Libby's theory of the beneficial action of an absorbable oil as a protective agent, the effects of various oils were compared. It was found (Table I) that if penicillin was given orally together with an absorbable oil such as cod-liver oil, olive oil, or arachis oil, an increased blood level was obtained; if on the other hand it was given with the non-absorbable liquid paraffin the levels were no better than those in the control animals.

TABLE I

BLOOD PENICILLIN LEVELS IN GROUPS OF MICE AFTER ORAL PENICILLIN IN VARIOUS OILS

9 mice in each group. Penicillin levels estimated by Agar-cup plate method. D = diameter of inhibition zone in mm. U./ml. = units of penicillin per ml. of blood

Oral dose: (500 u. calcium penicillin in 0.2 ml. oil)	Blood penicillin level at various times after dose				
	1 hr.		2 hr.		4 hr.
	D	U./ml.	D	U./ml.	
Cod-liver oil ..	16	0.48	17	0.50	0
Olive oil	17	0.53	14	0.39	0
Arachis oil	18	0.58	15	0.44	0
Liquid paraffin ..	12	0.32	0	0	0
Control (water) ..	13	0.35	0	0	0

Arachis oil (later referred to as oil) was used throughout the experiments to be described as a medium in which calcium penicillin was to be suspended; 0.2 ml. of this oil was used to suspend 500 units of calcium penicillin. This preparation was found to give as good blood levels in mice as an aqueous preparation containing 50 mg. sodium citrate and 500 units of sodium penicillin (Table II).

TABLE II

BLOOD PENICILLIN LEVELS IN GROUPS OF MICE AFTER ORAL PENICILLIN IN VARIOUS AMOUNTS OF ARACHIS OIL

9 mice in each group. Symbols as in Table I

Oral dose	Blood penicillin level after				
	1 hr.		2 hr.		4 hr.
500 u. Ca penicillin in :	D	U./ml.	D	U./ml.	
0.1 ml. arachis oil ..	15	0.44	0	0	0
0.2 ml. arachis oil ..	20	0.70	14	0.39	0
0.5 ml. arachis oil ..	22	0.85	14	0.39	0
500 u. Na penicillin with 50 mg. Na citrate ..	18	0.58	15	0.44	0

Aluminium resinate

Aluminium resinate, derived from colophony resin, is widely used in paint and paper industries. It was tested because of its water-repelling property.

(*a*) *Acute toxicity of aluminium resinate in mice.*—Doses of 5, 10, 20, 50, 100, 200, and 400 mg. of aluminium resinate per 20 g. mouse were given by mouth to

different groups of mice. Doses of 5, 10, or 20 mg. per 20 g. mouse were non-toxic and the LD50 by mouth was found to be 8.75 g. per kg.

(*b*) *The effect of aluminium resinate in oil on oral penicillin in mice.*—20 mg. aluminium resinate in 0.2 ml. oil per 20 g. mouse was found to enhance the blood penicillin level after oral penicillin. A number of tests were carried out in mice in which the blood levels after the administration of various preparations of penicillin were compared. These included the following:

1. Al resinate (20 mg.) and calcium penicillin (500 units) in 0.2 ml. oil given orally.
2. Procaine penicillin (500 units) in 0.1 ml. oil containing 2 per cent Al stearate given intramuscularly.
3. Sodium citrate (50 mg.) and sodium penicillin (500 units) in 0.2 ml water given orally.
4. Calcium penicillin (500 units) in 0.2 ml. oil given orally.

The results are shown in Table III.

At equivalent dose levels the mice receiving oral penicillin with aluminium resinate in oil gave even higher blood penicillin levels than those receiving intramuscular procaine-penicillin. Oral penicillin with sodium citrate or oil alone both gave lower figures (Fig. 1).

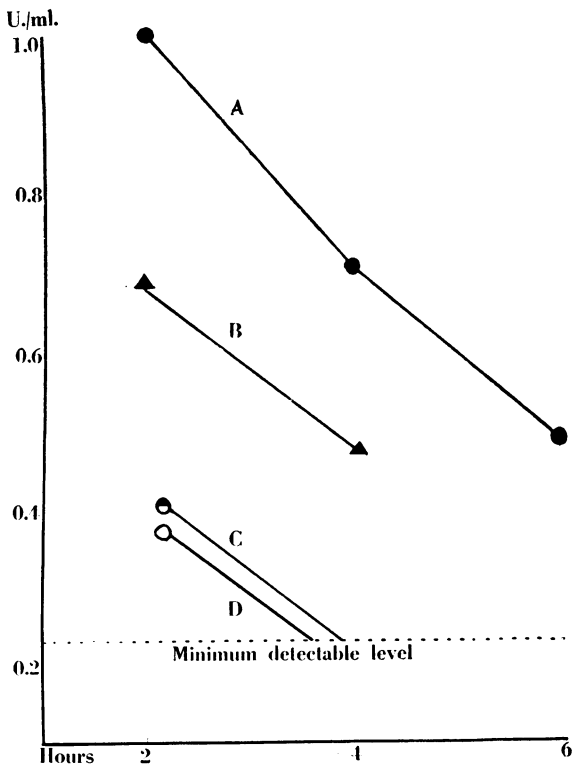


FIG. 1.—A comparison of the blood penicillin levels in mice after (A) oral penicillin (500 u.) in 0.2 ml. oil with 20 mg. Al resinate; (B) intramuscular procaine-penicillin (500 u.); (C) oral penicillin (500 u.) with 50 mg. Na citrate; and (D) oral penicillin (500 u.) in 0.2 ml. oil. Doses are quoted per 20 g. mouse.

TABLE III

BLOOD PENICILLIN LEVELS IN GROUPS OF MICE AFTER ORAL PENICILLIN PREPARATIONS AND INTRAMUSCULAR PROCAINE PENICILLIN

9 mice in each group. Symbols as in Table I, except that a dash means zero level

Dose	Group No.	Blood penicillin level after					
		2 hr.		4 hr.		6 hr.	
		D	U./ml.	D	U./ml.	D	U./ml.
Oral: Ca penicillin, 500 u. Al resinate, 20 mg. Oil, 0.2 ml.	1	26	1.25	20	0.70	13	0.35
	2	26	1.25	23	0.94	14	0.39
	3	26	1.25	17	0.53	19	0.63
	4	20	0.70	19	0.63	17	0.53
	5	26	1.25	13	0.35	18	0.58
	6	22	0.85	21	0.77	19	0.63
	7	20	0.70	22	0.85	13	0.35
	8	20	0.70	23	0.94	17	0.53
	Mean		1.00		0.71		0.50
I.M.: Procaine penicillin, 500 u. Oil, 0.1 ml. (containing 2% Al stearate)	1	22	0.85	17	0.53	—	—
	2	21	0.77	15	0.44	—	—
	3	20	0.70	17	0.53	—	—
	4	17	0.53	14	0.39	—	—
	5	18	0.58	18	0.58	14	0.39
	6	19	0.63	18	0.58	—	—
	7	19	0.63	14	0.39	—	—
	8	21	0.77	14	0.39	—	—
	Mean		0.68		0.48		
Oral: Ca penicillin, 500 u. Na citrate, 50 mg. Water, 0.2 ml.	1	17	0.53	—	—	—	—
	2	12	0.32	—	—	—	—
	3	16	0.48	—	—	—	—
	4	15	0.44	—	—	—	—
	5	14	0.39	—	—	—	—
	6	12	0.32	—	—	—	—
	7	13	0.35	—	—	—	—
	Mean		0.40		—		—
Oral: Ca penicillin, 500 u. Oil, 0.2 ml.	1	11	0.29	—	—	—	—
	2	12	0.32	—	—	—	—
	3	12	0.32	—	—	—	—
	4	15	0.44	12	0.32	—	—
	5	13	0.35	—	—	—	—
	6	15	0.44	—	—	—	—
	7	17	0.53	—	—	—	—
	8	12	0.32	—	—	—	—
	9	12	0.32	—	—	—	—
	Mean		0.38		—		—

(*c*) *The effect of aluminium resinate on oral penicillin in the rat, guinea-pig, rabbit, and cat.*—In a series of experiments (Table IV) it was found that the rat and guinea-pig responded to aluminium resinate in the same way as the mouse; the rabbit did not give such consistent results, but five out of six cross-over experiments gave a positive result; the cats used for cross-over experiments showed no effect.

(*d*) *Oral aluminium resinate and subcutaneous penicillin.*—Many substances, e.g., caronamide (Crosson, Boger, Shaw, and Miller, 1947) and benzoic acid (Waldo and Lee, 1948), enhance penicillin blood levels by delaying the excretion of penicillin

TABLE IV

BLOOD PENICILLIN LEVELS IN RATS AND GUINEA-PIGS AFTER ORAL PENICILLIN IN OIL WITH AL RESINATE

Species and body weight	Dose: g. or u. per kg. body weight	No. of test	Blood penicillin level (as inhibition zone in mm.) after			
			1 hr.	2 hr.	4 hr.	6 hr.
Rats:	Test:					
150±10 g.	Al resinate ,1 g.	(1)		15	14	13
3 in each group	Ca penicillin, 25,000 u.	(2)		18	18	14
	Oil, 5 ml.	(3)		16	13	—
	Control:					
	Ca penicillin, 25,000 u.	(1)		12	—	—
	Oil, 5 ml.	(2)		11	—	—
		(3)		13	—	—
Guinea-pigs:	Test:					
(1) 250 g.	Al resinate, 1 g.					
260 g.	Ca penicillin, 25,000 u.	(1)	22	18	13	
(2) 270 g.	Oil, 5 ml.	(2)	18	17	11	
280 g.						
(1) 220 g.	Control:					
280 g.	Ca penicillin, 25,000 u.	(1)	14	11	—	
(2) 235 g.	Oil, 5 ml.	(2)	14	13	—	
265 g.						
Rabbits:						
No. wt. (kg.)						
1 2.05	Test:	(1)		15	—	—
2 2.20	Al resinate, 1 g.	(2)		19	15	10
3 1.37	Ca penicillin, 50,000 u.	(3)		14	13	—
4 1.43	Oil, 5 ml.	(4)		13	—	—
5 2.10		(5)		13	—	—
6 2.10		(6)		11	—	—
2 2.20		(1)		—	—	—
1 2.05	Control:	(2)		—	—	—
4 1.43	Ca penicillin, 50,000 u.	(3)		—	—	—
3 1.37	Oil, 5 ml.	(4)		—	—	—
6 2.10		(5)		19	15	—
5 2.10		(6)		17	—	—
Cats:						
No. wt. (g.)	Test:					
1 650	Al resinate, 1 g.	(1)		15	16	15
2 600	Ca penicillin, 25,000 u.	(2)		22	21	20
1 650	Oil, 5 ml.	(3)		19	18	14
2 600	Control:	(1)		22	17	15
1 650	Ca penicillin, 25,000 u.	(2)		16	—	16
2 600	Oil, 5 ml.	(3)		20	17	16

through competition with it in tubular excretion. Tests were made to try to find any indication of this sort of action by aluminium resinate. Four groups of three mice, A, B, C, and D, were treated as follows: (A) oral penicillin in oil with aluminium resinate; (B) subcutaneous penicillin in saline and oral aluminium resinate in oil;

(C) oral penicillin in oil; (D) subcutaneous penicillin in saline. Blood levels were estimated as usual.

Fig. 2 shows the result of this test. Comparison of curves B and D will show that the blood level after subcutaneous penicillin was enhanced by oral aluminium resinate; this suggests that aluminium resinate may possess a " caronamide-like " action. Comparison of curves A and B will reveal that in these two groups both with oral aluminium resinate, the group with oral penicillin gave consistent and longer blood penicillin levels, whereas the group with subcutaneous penicillin gave higher blood penicillin levels at the start which decreased rapidly afterwards. From a comparison of the two pairs of curves A, C and B, D, it appears that aluminium resinate increased the effect of penicillin given orally more than it increased the effect of penicillin given subcutaneously.

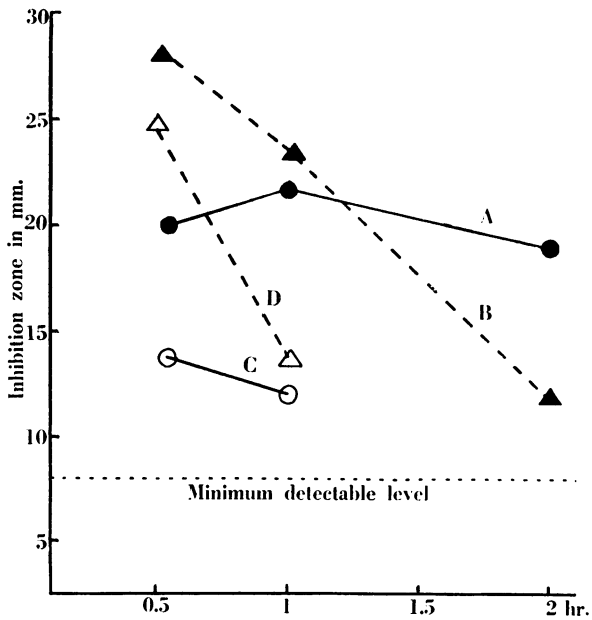


FIG. 2.—A comparison of blood penicillin levels in mice after (A) oral Ca penicillin (250 u). in 0.2 ml. oil with 10 mg. Al resinate; (B) subcutaneous Ca penicillin (250 u.) in 0.1 ml. saline and oral Al resinate (10 mg. in 0.2 ml. oil); (C) oral Ca penicillin (250 u.) in 0.2 ml. oil; and (D) subcutaneous Ca penicillin (250 u.) in 0.1 ml. saline. Doses per 20 g. mouse. Experiment repeated 3 times so that each point represents the average value for nine mice.

(*e*) *Protection of mice against a haemolytic streptococcal infection by oral penicillin with aluminium resinate in oil.*—A series of tests were performed to see whether the enhancement in blood penicillin levels caused by the use of aluminium resinate would induce a higher percentage of survivors in mice infected with haemolytic streptococci.

The effect of treatment with oral penicillin and aluminium resinate was compared with the effects of treatments with intramuscular procaine-penicillin and with oral penicillin and sodium citrate. Three groups, each of 26 mice, were treated immediately after infection with one of the following agents:

A—Oral calcium penicillin (10 units) in 0.2 ml. oil containing aluminium resinate (20 mg.).

B—Intramuscular procaine-penicillin (10 units) in 0.1 ml. oil containing 2 per cent aluminium stearate.

C—Oral sodium penicillin (10 units) with sodium citrate (50 mg.) in 0.2 ml. water.

Three other groups of mice were included as various controls:

D—Oral calcium penicillin (10 units) in 0.2 ml. oil (30 mice).

E—Oral aluminium resinate (20 mg.) in 0.2 ml. oil (10 mice).

F—Untreated (20 mice).

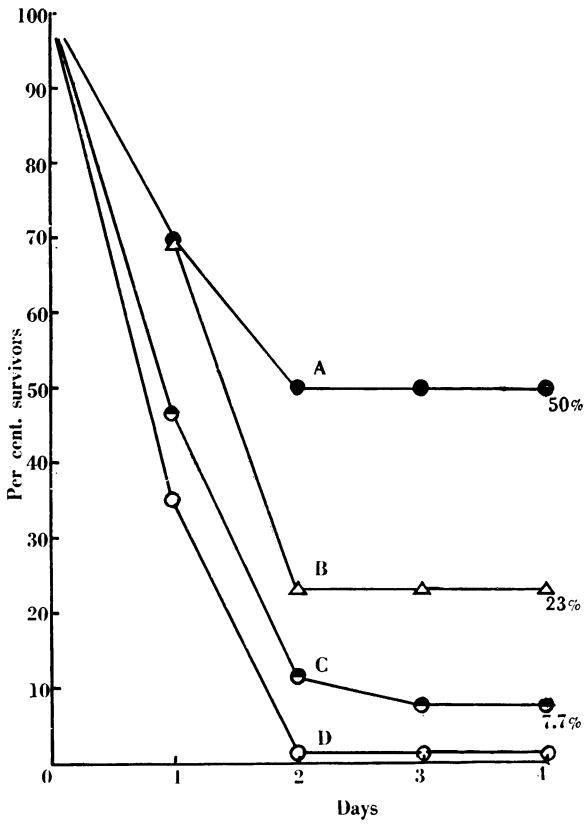


FIG. 3.—Protection of mice against haemolytic streptococcal infection. Survival curves: (A) after oral penicillin (10 u.) in 0.2 ml. oil with 20 mg. Al resinate; (B) after intramuscular procaine-penicillin (10 u.); (C) after oral penicillin (10 u.) with 50 mg. Na citrate; and (D) after oral penicillin (10 u.) in 0.2 ml. oil. Doses per 20 g. mouse. All infected mice, untreated or given an oral dose of aluminium resinate (20 mg.), died on the first day of infection. All infected mice given oral penicillin in oil alone (D) dead within two days.

Fig. 3 gives the percentages of survivors each day after the infection. It will be noticed that oral aluminium resinate with penicillin in oil gave the highest degree of protection (50 per cent), that intramuscular procaine-penicillin was the second best (23 per cent), and that aqueous penicillin with sodium citrate gave the lowest figure (7.7 per cent). In the control groups, all the mice treated with oral penicillin in oil died within three days and those untreated or receiving oral aluminium resinate in oil died within twenty-four hours after infection.

(*f*) *Effect of aluminium resinate on the kidneys.*—Two groups of mice (6 in each group) were fed with normal diet and with diet containing 2 per cent of aluminium

resinate respectively for 14 days. Two mice from each group were killed by use of ether. The kidneys were then dissected out and sectioned. Microscopical examination showed no obvious difference between the kidneys of the mice receiving normal diet and those of the mice receiving diet containing Al resinate. No sign of epithelial degeneration in the tubules was observed.

Three groups of rats (5 in each group, approximately 200 g. each) were fed respectively with normal diet and with diet containing 2 and 5 per cent of Al resinate for 13 days. On the 14th day, 0.1 g. albumin was added to every 10 g. of the various kinds of diet. The next day, a urine sample from each group was collected. The urine was tested for the presence of albumin both with sulphosalicylic acid reagent and with glacial acetic acid. On addition of the reagent, slight cloudiness was observed in the urine passed by the rats with normal diet. Voluminous precipitates were obtained in the samples of urine passed by rats with diet containing Al resinate. Al resinate therefore increased albuminuria in rats.

(*g*) *Test for any* in vitro *effect of aluminium resinate.*—It was found that the addition of 20 mg. aluminium resinate to 4.5 ml. nutrient broth had no influence on the growth of either *Staphylococcus aureus* or *Escherichia coli.* The addition of this quantity of resinate did not influence the point at which penicillin would inhibit the growth of either of these organisms.

(*h*) *Estimation of urinary penicillin in animals after an oral dose of penicillin with Al resinate.*—As an increase of urinary excretion of penicillin is a good indication of increased absorption or of increased stability of penicillin, an estimation of the urinary penicillin was made in rats and rabbits. Rats, 4 in each group, were kept in metabolism cages the bottom parts of which were waxed to prevent the direct contact of urinary penicillin with metals. The urine was collected at intervals for five hours after the dose. The collections were immediately Seitz-filtered and then made up to a definite volume. The potency of penicillin was estimated by the serial dilution method. It was found that the group receiving oral penicillin with Al resinate excreted twice as much penicillin as the control group (Table V).

TABLE V

THE URINARY PENICILLIN IN RATS AFTER ORAL PENICILLIN IN OIL WITH AND WITHOUT AL RESINATE

4 rats in each group. Weight 200±10 g.

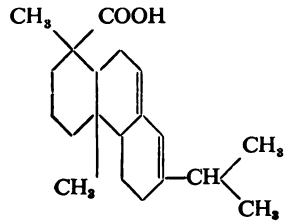
Dose (per rat)	Time (hr.) of collection of urine after dose	Volume (ml.) of urine collected	Total urinary penicillin (u.)	Percentage recovery
Control: Ca penicillin, 3,000 u. Oil, 0.5 ml.	2	14	200	5
	5	8	400	
Test: Al resinate, 0.2 g. Ca penicillin, 3,000 u. Oil, 0.5 ml.	2	17	400	10
	5	12	800	

Urine was also collected from two groups of rabbits which received oral doses of penicillin in oil and penicillin in oil with aluminium resinate respectively. No

significant difference was found in the urinary recoveries between the control and the test groups.

(*i*) *Abietic acid derivatives and copals.*—In view of the activity of Al resinate in mice, the study was extended to allied compounds. Many metallic resinates are available commercially, but as ions of most heavy metals are toxic only calcium resinate was tried. It was found to be as effective as Al resinate both in enhancing blood penicillin levels in mice and in protecting mice against a haemolytic streptococcal infection.

The substance colophony resin, from which Al resinate is prepared, contains about 85 per cent resinic acid which is chiefly abietic acid. The structural formula of abietic acid is shown as follows:



Tests on blood penicillin levels in mice showed that this compound was effective. The abietic acid molecule seemed therefore to be responsible for the activity of Al and Ca resinates. To follow up the research, four classes of abietic acid derivatives were examined. These were as follows:

(1) *Salt.*—Al abietate; a salt (composition unknown) prepared by treating alum with abietic acid.

(2) *Esters.*—Methyl abietate, glyceryl abietate, and pentaerythritol abietate.

(3) *Alcohol.*—Hydroabietyl alcohol; this is a partially hydrogenated abietic acid with the carboxyl group reduced to a primary alcohol group.

(4) *Derivatives with changed cyclic structures*

(*a*) Hydrogenated: " Stayblite "; this is a hydrogenated abietic acid in which one of the two double bonds has been saturated by catalytic hydrogenation.

(*b*) Dehydrogenated: " Resin 731 "; this is a partially dehydrogenated abietic acid so that an additional double bond has been introduced.

(*c*) Polymerized: " Polypale resin "; this is the dimer of abietic acid.

(*d*) Addition compound: " Fumaric modified rosin " (lewisol 40); this is the simple combination of fumaric acid and abietic acid so that it is, in effect, a tricarboxylic acid.

These compounds were tested for their activity in enhancing blood penicillin levels in mice after oral penicillin. In this respect, Al abietate was found to be as effective as Al resinate. Three other derivatives, Stayblite, Resin 731, and Polypale resin, were also found effective but more toxic than Al resinate.

It is interesting to note that the metallic salt and those derivatives in which the carboxyl group is free were active with the sole exception of " Fumaric modified rosin," and that the esters and the alcohol derived from abietic acid were inactive.

Copals are of diverse botanical origins. As they are strongly water repelling, five samples of copal were tested. These were as follows:

Congo copal; Kauri (candle bush); Zanzibar (goose skin); Manila (half-hard); and fused Congo copal.

The first four resins are natural products composed of mixtures of acids and non-acids. Their composition has not been established with any certainty, but the acids contained therein, while bearing some structural relationship to abietic acid, are polycarboxylic and mainly of higher molecular weight. Fused Congo copal is Congo copal which has been destructively heated to render it soluble in glyceride oils.

Tests were made on each of these compounds. It was found that there were enhanced blood penicillin levels in mice after an oral dose of penicillin and fused Congo copal in arachis oil.

As fused Congo copal is a mixture, different organic solvent fractions were tested. It was found that the ether fraction enhanced oral penicillin in mice to a greater extent than any of the other fractions, namely, the petroleum ether fraction, the ether-ethanol fraction, and the ether-methanol fraction.

Discussion

The use of absorbable oils as protective agents for oral penicillin was supported by the experiment in this paper in which oral penicillin given in liquid paraffin, a non-absorbable oil, did not give as good a result as when it was given in arachis oil, olive oil, or cod-liver oil. It might be true, as Rake and Richardson (1946) pointed out, that the salts of penicillin being highly water-soluble would not remain in the oil phase for more than a short period of time after mixing with gastric contents. The addition of aluminium resinate, a water-repellent, to the oil might be able to keep penicillin in the oil phase so that the oil could carry it to the site of its absorption. The water-repelling property of aluminium resinate is abolished in an alkaline medium; it is probable that in the small intestine owing to the relatively alkaline *p*H there is not sufficient water-repelling action to interfere with absorption.

Aluminium resinate in oil not only induces a high blood level in mice after oral penicillin but also enhances the protective effect of oral penicillin in mice against a haemolytic streptococcal infection. The mechanism of action of aluminium resinate is not fully known. Orally administered aluminium resinate also enhanced the effect of subcutaneous penicillin in mice, and this might suggest that as with caronamide this substance caused a delayed renal clearance of penicillin. Experiments on the urinary output of penicillin given with the resinate and oil in rats (but not in rabbits) showed that the total urinary penicillin was doubled; this suggests that there was increased absorption or increased stability rather than delayed excretion. That the principal action was due to increased absorption of oral penicillin was also suggested by the following experiments: (*a*) aluminium resinate increased the effect of oral penicillin more than it increased the effect of subcutaneous penicillin, and (*b*) treatment of a haemolytic streptococcal infection in mice with oral penicillin and aluminium resinate gave a much higher percentage of protection than treatment with oral penicillin and a dose of caronamide of the same weight as the aluminium resinate. (Note: the molecular weight of Al resinate calculated as Al abietate is 328.4 and that of caronamide 291.)

The activity of aluminium resinate in mice may be threefold; firstly, it may increase the protective effect of oil on penicillin in the stomach by acting as a water-repelling substance; secondly, it may promote absorption of penicillin in the intestine; and thirdly, it may delay excretion of penicillin through the kidney. There is, so far, no evidence that aluminium resinate itself shows any antibacterial activity either *in vivo* or *in vitro*.

Species differences were seen. The resinate is effective in mice, rats, and guinea-pigs. In rabbits it gave inconsistent results, while in cats no enhancement was obtained.

Abietic acid derivatives and other resins

The investigation was extended to include the essential component of aluminium resinate, *abietic acid*, and some of its simple derivatives in order to correlate the molecular structure with the activity of enhancing oral penicillin in mice. That the activity and the toxicity of aluminium abietate are of the same order as that of aluminium resinate suggests that it is the abietic acid molecule which is essential.

Copals

In the study of copals, not all raw copals have been found to be of use, but fused Congo copal showed some activity which was, however, not as high as that of aluminium resinate. It is hoped that fractionation or degradation of fused Congo copal or better still the determination of the chemical identities of the constituents of this highly complex mixture might reveal the essential feature with regard to its activity.

SUMMARY

1. Aluminium resinate, when given orally to mice with penicillin in oil, is effective in increasing the blood penicillin levels. This effect is also shown in rats, guinea-pigs, and rabbits, but not in cats.

2. Aluminium resinate increases the effect of oral penicillin in protecting mice infected with a strain of haemolytic streptococci, and in this respect oral penicillin with aluminium resinate was found to be somewhat more effective than an equivalent amount of procaine penicillin injected intramuscularly.

3. The experimental results suggest that this action of aluminium resinate is due to the absorption of penicillin being increased and to its excretion being delayed.

4. Several derivatives of abietic acid (the essential component of aluminium resinate) and various copals were tested. Although these are all water-repelling agents, only a few of them showed an activity in enhancing blood penicillin levels in mice after oral penicillin.

5. The acute toxicity of aluminium resinate to mice is low, the LD50 by mouth being 8.75 grammes per kilogram.

One of the authors (Y.C.H.) would like to express his gratitude to Messrs. Allen & Hanburys, Ltd., for their generous financial assistance to make possible the present study. We wish to thank Messrs. A. Boake Roberts & Co., Ltd., for kindly supplying metallic abietates and abietic esters; Messrs. Hercules Powder Company for kindly supplying many other abietic acid derivatives ; the Research Association of British Paint, Colour, and Varnish Manufacturers for kindly supplying all the copals tested; and the Distillers Company for advice and assistance.

We should like to acknowledge a grant from the Medical Research Council to one of us (G.A.H.B.).

REFERENCES

Crosson, J. W., Boger, W. P., Shaw, C. C., and Miller, A. K. (1947). *J. Amer. med. Ass.*, **134**, 1528.
Finland, M., Meads, M., and Dry, E. M. (1945). *J. Amer. med. Ass.*, **129**, 315.
Libby, R. L. (1945). *Science*, **101**, 178.
McDermott, W., Bunn, P. A., Benoit, M., Dubois, R., and Haynes, W. (1945). *Science*, **101**, 228.
Perlstein, D., Kluener, R. G., and Liebmann, A. J. (1945). *Science*, **102**, 66.
Rake, G., and Richardson, A. P. (1946). *Ann. N.Y. Acad. Sci.*, **48**, 165.
Thomas, E. W., Lyons, R. H., Romansky, M. J., Rein, C. R., and Kitchen, D. K. (1948). *J. Amer. med. Ass.*, **137**, 1517.
Waldo, J. F., and Lee, W. C. (1948). *Amer. J. Med.*, **4**, 621.

Note added in proof.—Since this paper was written Dr. B. N. Halpern has kindly informed us that he has been able to obtain enhanced blood levels of penicillin administered orally in dogs and in human patients by using aluminium resinate in arachis oil.