TECHNICAL PAPERS

A New Penicillin for Prolonged Blood Levels[1]

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The advantages of prolonged therapeutic blood levels of penicillin following a single injection have been well proven with penicillin in oil and wax (Romansky formula) (*2–6*). However, the necessity of wax in this vehicle has been the apparent cause of a number of unfavorable local reactions.

In our laboratories, a sparingly soluble penicillin has been developed which may be administered in various vehicles, such as oil, oil and water emulsion, or physiological saline. This new crystalline penicillin complex was produced by chemically combining procaine with penicillin G. These crystals have a solubility of approximately 7,000 units/cc in the above vehicles. They contain not less than 90% penicillin G, with a potency of 940 units/mg (1,040 units/mg, theoretical). In the oil suspension, at least 50% of the total weight of the particles are 50 μ or more in length.

The importance of particle size for the slow absorption of penicillin has been demonstrated by Dowling, *et al.* (*1*) and Welch, *et al.* (*7*). In preliminary experiments with laboratory animals, it was shown that the administration of a suspension of procaine penicillin crystals resulted in the slow release of penicillin G over prolonged periods. The blood levels reported in Table 1 were obtained in 21 hospitalized patients receiving the material suspended in cottonseed oil. Blood level determinations were made, using Kolmer's method.

TABLE 1

BLOOD LEVELS OF PROCAINE PENICILLIN IN COTTONSEED OIL*

Patient	Date	Amount administered (cc)†	Blood levels						
			1 hr	2 hrs	12 hrs	18 hrs	24 hrs	36 hrs	48 hrs
1	8–17–47	1		0.496		0.124	0.248		
2	8–18–47	1	0.248		0.124	0.124	0.124		
3	8–18–47	1	0.992		0.248	0.124	0.124		
4	8–18–47	1	0.496		0.248	0.124	0.124		
5	8–19–47	1		0.124	0.124	0.124	0.124		
6	8–19–47	1		0.124	0.124	0.062	0.062		
7	8–20–47	1	1.984		0.124	0.062	0.062		
8	8–20–47	1	0.248		0.124	0.062	0.062		
9	8–24–47	1	0.062		0.062	0.062	0.062		
10	9– 3–47	1	0.496		0.124	0.062	0.062		
11	9–15–47	1	0.248		0.496	0.248	0.124		
12	9–15–47	1	0.496		0.248	0.031	0		
13	9–16–47	1	0.062		0.124	0.124	0.062		
14	9–16–47	1	0.992		Not drawn	0.124	0.124		
15	9–17–47	1	0.496		0.248	0.124	0.062		
16	9–17–47	1	1.984		3.968	0.496	0.124		
17	9–20–47	1	0.824		0.824	0.659	0.329		
18	9– 3–47	2	0.124		0.124	0.124	0.124		
19	9–16–47	2	1.984		0.496	0.496	0.062		
20	9– 8–47	3	0.992		0.248	0.248	0.248	0.031	0
21	9– 8–47	4	0.496		0.496	0.496	0.496	0.248	0.124

* Control blood level determinations on all patients were 0.
† 1 cc contains 300,000 units.

It will be noted that in only one individual were there blood levels lower than 0.062 at the 24th hr. Many of the patients showed levels of 0.124. One patient receiving 3 cc (900,000 units) had a therapeutic blood level at the 36th hr, and a second patient receiving 4 cc (1,200,000 units) had a blood level of 0.124 at the 48th hr. In none of the cases were there any local or systemic reactions.

[1] Since submitting this manuscript for publication, it has been brought to our attention that Charles J. Salivar, F. H. Hedger (Chas. Pfizer and Co., Inc.), and E. V. Brown (Department of Chemistry, Fordham University) have in the press (Note to the Editor Section, *Journal of the American Chemical Society*) a manuscript dealing with the chemical characterization of the procaine salt of benzyl penicillin.

Further studies are now being conducted, using various other vehicles.

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Delayed Maturity of Bean Plants Sprayed With Solutions of 2,4-Dichlorophenoxyacetic Acid of Nonherbicidal Concentrations[1]

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In a study (*2*) of the effect of 2,4-D on the growth and development of bean plants it was found that their maturity was markedly delayed by concentrations of 10 ppm applied just prior to flowering. Since this response from 2,4-D has not been found in the literature and since it is thought to be of practical interest, a report on the conditions under which it was observed is presented here.

A certified strain of red kidney bean was used in experiments which were carried out under greenhouse conditions during the spring and under field conditions during the summer. The plants were sprayed when the first trifoliate leaf was expanding, using an aqueous solution of a commercial herbicide (70% 2,4-D and 30% sodium bicarbonate) acidified with 1 gm of citric acid/liter to increase activity (*1*). The solutions were applied as a fine mist by means of an atomizing nozzle, the leaves being wet on both sides.

In the greenhouse study, a stand of uniform plants was obtained in pots containing equal amounts of soil and at intervals receiving an equal amount of a dilute, complete nutrient solution. On April 7 (1 week after germination) half the plants were sprayed with a solution of 2,4-D at 10 ppm. The treatment caused slight epinasty of stem and petioles, and inhibited temporarily the rate of top growth, while the root growth seemed to be accelerated.

Flowering began about May 1. At this time the top growth of treated plants was as vigorous as that of untreated plants, although the former were somewhat greener, and some of the younger leaves of the treated plants showed toxicity symptoms. Affected leaves became dark green, dwarfed, and lanceolate and felt thicker and stiffer than leaves on untreated plants. By the end of May there was a definite, more vigorous growth of treated than of untreated plants. At harvest time, the middle of June, the treated plants carried a significantly higher number of leaves per plant (an average of 11.2 leaves per treated plant and only 6.6 leaves per untreated plant). This difference reflects the more extensive lateral growth of treated plants. Fig. 1 shows representative plants, treated and untreated, from which all leaves and petioles were removed to indicate this development of lateral branches from the second node of the treated plants.

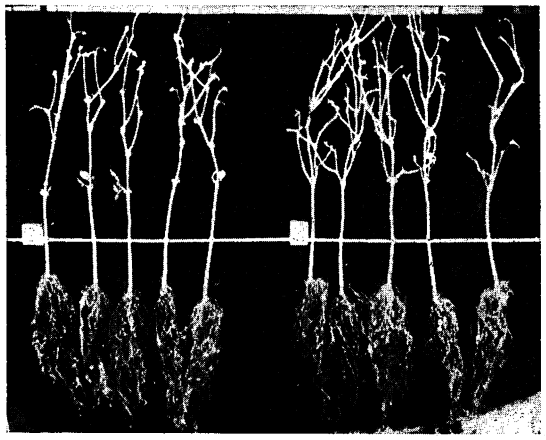

FIG. 1. Development of lateral branches from the second node of plants treated with 2,4-D at 10 ppm just prior to flowering (*right*) as compared with untreated plants (*left*).

TABLE 1

AVERAGE NUMBER AND WEIGHT PER PLANT OF PODS AND SEEDS OF 14 UNTREATED PLANTS AND 12 PLANTS SPRAYED WITH A SOLUTION OF 10 PPM OF THE SODIUM SALT OF 2,4-D

Plants	No. of pods	Wt. of pods (gm)	No. of seeds	Wt. of seeds (gm)
Untreated	3.2	9.6	10.2	7.4
Treated	4.1	10.6	11.6	7.6

On June 2, counts showed a greater set of fruits on treated than on untreated plants. Of fruits which actually developed, however, there were not significantly more on treated than on untreated plants (Table 1).

While the untreated plants turned yellow at the beginning of June, the treated ones remained green for about two weeks longer. The pods were not harvested until

[1] Journal article No. 911 (m.s.) of the Michigan Agricultural Experiment Station.