or collectively at plasma concentrations sufficient to inhibit maximally the tubular excretion of penicillin. Effects produced at excessive elevations of blood levels of the compound sufficient to be toxic in the customary sense of the word are, of course, beyond the intent of this principle. (5) If the agent acts by competitive inhibition of an enzymatic reaction, in accordance with this concept, the process should be reversible. (6) Such a compound should not necessarily influence either renal blood flow or glomerular filtration rate. However, it would vitiate the use of PAH for the measurement of renal plasma flow or normal PAH_{Tm}, for PAH is excreted in a manner similar to that for penicillin. (7) The agent should not have a high order of systemic toxicity. (8) The compound need not necessarily influence any properties peculiar to penicillin, such as its bacteriostatic action, inactivation, etc. (9) It follows from (2) and (3) that the dosage of the compound would be quite practical. (10) It was anticipated that these properties might be contained in a compound or compounds having the additional advantage of oral efficacy at reasonable dosage.

Of the compounds synthesized for this research by the Department of Organic Chemistry of these Laboratories, 4′-carboxyphenylmethanesulfonanilide incorporates essentially the properties listed above.

In the experiment summarized in Table 1, penicillin was infused at a rate and in an amount that would permit a falling penicillin plasma concentration if the drug were not effective. Duplicate control penicillin and creatinine clearances were obtained. The drug then was injected as a priming and maintenance dose, its distribution in the body allowed to equilibrate, and additional penicillin clearances obtained. It may be seen that the tubular excretion of penicillin was completely suppressed, as indicated by the rising penicillin plasma concentration, decreased penicillin clearance, and increased filtration fraction.

Fig. 1 illustrates two experiments wherein dogs were administered 100,000 units of penicillin by stomach tube every 4 hours for 16 hours, including the 4-hour period wherein the control curves for penicillin plasma concentration were obtained. Immediately after the 4-hour control blood samples were taken, each dog was given 100,000 units of penicillin plus 60 mg./kg. of the drug by stomach tube, another curve for plasma concentration of penicillin being obtained over the next 4-hour period. It may be seen that in the control phase the maximal penicillin plasma concentrations were 0.8 and 1.2 units/cc. and at 2 hours the values were less than the lower limits of the Florey cup-plate assay, 0.24 units/cc. Following administration of drug and penicillin the maximal penicillin plasma concentrations were 2.85 and 3.6 units/cc. In one instance the peak occurred at 2 hours following oral administration. At 4 hours the plasma concentration was still somewhat above 0.5 units/cc.

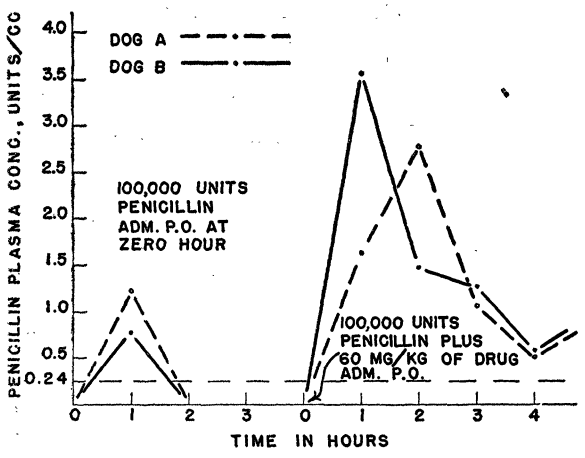

FIG. 1. The blood level response to equivalent oral dosages of penicillin alone and with the coadministration of 4′-carboxyphenylmethanesulfonanilide.

Summary. It has been found that the excretion of penicillin by a renal tubular transport mechanism could be physiologically inhibited reversibly. The basis for this effect is thought to be one of substrate competition between penicillin, which is excreted by the tubules, and 4′-carboxyphenylmethanesulfonanilide, which is essentially refractory to excretion by that transport mechanism.

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Some Effects of O-Isopropyl N-Phenyl Carbamate Upon Cereals[1]

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Most of the reports in the literature concerning the use of chemicals as plant-growth regulators indicate that application of such substances in some form to the aerial portions of plants is the most common practice. In the instance of O-isopropyl N-phenyl carbamate, however, greatest success appears to have been achieved through applications to the soil in a suitable diluent or carrier, and the results of applications in sprays to the plant itself have been inconclusive (*1*, *2*). To test further the herbicidal activity of sprays of this compound, several experiments have been carried out using oats and barley as test plants.

To insure thorough wetting of the leaves, young oat and barley plants were exposed by immersion of the aerial plant portions for intervals of 2–4 seconds up to 10 minutes in isopropyl alcohol-water solutions containing 500, 250, or 100

[1] These studies were conducted from March 1946 to August 1946 under the supervision of Dr. C. E. Minarik.

ppm of O-isopropyl N-phenyl carbamate and a wetting agent. Care was exercised to prevent contamination of the soil by the growth regulator. The subsequent plant growth appeared normal, and there was no reduction in yield of grain. These results indicated that O-isopropyl N-phenyl carbamate does not influence the growth of such plants when applied to the

TABLE 1

EFFECT UPON OATS OF EXPOSING SOIL TO SPRAYS OF O-ISOPROPYL N-PHENYL CARBAMATE

Rate of O-isopropyl N-phenyl carbamate in grams/sq. yd.	Mean grain yield per pot (grams)	
	Soil exposed	Soil not exposed
0.5	0.55	4.00
1.5	0.04	2.31
0.0 (10% TBP*)	4.25	—
0.0 (30% TBP*)	4.05	—
0.0	6.05	—

Minimum significant difference between means at the 5 per cent level of probability is 2.0 grams; at the 1 per cent level, 2.68 grams.

* 10% or 30% tributyl phosphate in oil applied in same proportion as in the 0.5-and 1.5-gram rates of O-isopropyl N-phenyl carbamate, respectively.

leaves at these concentrations. In order to establish that these preparations possessed herbicidal activity, applications were made to the soil of similar plants, each application being equivalent to 5 mg. of compound/4-inch pot. This treatment was lethal.

To test the effects of sprays of this compound when allowed to contaminate the soil, potted oat plants approximately 15 inches in height were sprayed in quadruplicate with O-isopropyl N-phenyl carbamate in an oil spray. Tributyl phosphate was used as a cosolvent at the rate of 2 ml./gram of the growth regulator. The desired concentrations were made by diluting with No. 2 fuel oil. The rates of application were 0.5 and 1.5 gram/square yard in 10 ml. of solution. The plant-growth regulator was applied to plants at each rate, the soil being

TABLE 2

EFFECT UPON OATS OF EXPOSING SOIL TO SPRAYS OF O-ISOPROPYL N-PHENYL CARBAMATE

Treatment	Mean grain yield per pot (grams)	
	Soil exposed	Soil not exposed
O-isopropyl N-phenyl carbamate	0.63	1.45
Acetone-water (1:2) control	1.18	1.26
Untreated control	1.51	1.51

Minimum significant difference between means at the 5 per cent level of probability is 0.36 gram; at the 1 per cent level, 0.48 gram.

protected from the spray in one instance and exposed in another. It is to be noted (Table 1) that the yield of grain from the plants where the soil was exposed to the spray was significantly less than that from the corresponding protected series. This suggests that much of the effect from such sprays of this substance results from soil contamination.

Since considerable injury to the plants was caused by tributyl phosphate in the above spray, a further experiment was carried out using acetone as a cosolvent. Oats 12–15 inches in height were sprayed with acetone-water (1:2) solutions of O-isopropyl N-phenyl carbamate with the soil protected from the spray in one case and exposed in another. The carbamate was applied at the rate of 0.5 gram/square yard in 20 ml. of solution. The plants making up the series in which the soil was protected from the spray were not noticeably affected, whereas the series having the soil exposed to the spray yielded highly significantly less grain (Table 2).

Practical implications of these findings are that spraying O-isopropyl N-phenyl carbamate may not be the most efficient method of application, since in these studies inhibitory effects were not induced in young oat and barley plants by exposing the aerial plant portions to sprays or solutions of this compound. Should sprays be used for application of this plant-growth regulator as a herbicide, it appears that emphasis should possibly be directed toward actual soil treatment. It is suggested that this may be achieved by applying the carbamate with a suitable diluent or as an impregnated material. Since it has been reported (*1*) that young cereals are more susceptible to O-isopropyl N-phenyl carbamate than older plants, it is further suggested that for most efficient use it should be applied when the plants are in a young stage of development, or even prior to seedling emergence.

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Is Sterility Induced in Growing Rats on a Tryptophane-deficient Diet?

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Some months ago Keller (*3*) reported that permanent sterility was induced in albino rats which, at the age of 28–48 days, had been placed on a tryptophane-deficient diet for 3–18 days. According to him, male and female pairs of such rats failed to show sexual interest upon reaching maturity, and did not produce litters, even when mated to control animals of proven fertility.

Because there were several possible complicating factors in Keller's experiments, we undertook to test his claim. As a tryptophane-deficient source of nitrogen, Keller used gelatin, which, unfortunately, is a notoriously poor protein, possibly lacking valine (*4*) as well as tryptophane and being low in other essential amino acids and very high in glycine, proline, and hydroxyproline. Keller presented no evidence that his animals had been provided with vitamin E or with factors of the vitamin B complex during the deficiency period. We assume that the 5 grams of "castor oil" recorded as a dietary component was an error and that cod-liver oil was meant.

In planning our tests we tried to avoid as many complicating factors as possible. Three types of tryptophane-deficient diets were used. In one (G), bacto-gelatin served as the sole source of amino-acid nitrogen; in a second (Hy), acid-hydrolyzed casein (*1*) was employed; and in the third (Pr-free), there was no protein. The compositions of these diets, the control diets (Gt, Gvt, Hyt), and the stock diet are recorded in Table 1. A synthetic mixture of the factors associated with the vitamin