puric acid. In order to obtain and maintain levels between 30 and 45 mg %, it is necessary to administer the drug at a rate of 150 mg/kg/hr.[1] For an average individual weighing 150 lb (68 kg), this necessitates a daily dosage of 245 g per 24 hr period. Since the daily dosage in our experiments varied between 60 and 100 g of sodium para-aminohippurate, it is not surprising that augmentation of penicillin serum levels was not consistently maintained. On the other hand, such exaggerated serum penicillin levels which were obtained take on added significance when found in conjunction with heightened para-aminohippuric acid levels.

When priming doses of sodium para-aminohippurate were administered, the same smooth muscle effects noted by Beyer and his coworkers[1] ensued. There was a feeling of restlessness and warmth. The face and neck became flushed and there was a sense of cardiac palpitation. The patients noted a burning sensation at the injection site. Several moments later there was a desire for urination and defecation. If the injection was given immediately prior to alimentation there was complete loss of appetite. These symptoms were all mild in character, evanescent, and could be prevented by slowing the rate of injection of sodium para-aminohippurate.

There were no untoward effects noted during the simultaneous administration of sodium para-aminohippurate and penicillin by continuous venoclysis except for an immediate, occasional, slight sense of warmth along the course of the veins which disappeared in a short time. This was more likely to occur with higher concentrations of sodium para-aminohippurate. No cumulative toxic effects were observed after continuous administration of sodium para-aminohippurate for periods up to eight days.

Conclusions. 1. When the plasma para-aminohippuric acid concentration was maintained at or above 10 mg/100 ml a 3 to 6 fold elevation in penicillin plasma concentration was obtained except in two instances. 2. When the para-aminohippuric acid plasma levels were allowed to fall below 10 mg/100 ml there was no effect of that compound on the plasma concentration of penicillin. 3. The para-aminohippuric acid was non-toxic in the dosage given even when administered over a period of 8 days.

14932

Metabolism of Vitamin D in the Chick.

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In a previous publication dealing with the hypercalcemic effects of activated sterols in the chick[1] some attention was given to the metabolism of vitamin D in this species. It was found that there was excreted in the feces a larger proportion (49%) of an oral dosage of vitamin D_2 than there was of vitamin D_3 (36%). However, in the carcasses of chicks killed 48 hr after the administration of the vitamins, a larger proportion of the vitamin D_3 was found (27% as against 12%). The general purpose of other papers of this series[2,3] has been to obtain information which would serve to explain the remarkably low sensitivity of the chick to vitamin D_2,[4] a characteristic which seems to be shared by turkey poults.[5]

It has been suggested[1] that there appear to be 3 possible causes for the low activity of vitamin D_2 in the chick. One of these, namely, differences in the extent of absorption from the digestive tract, has been dealt with in other papers,[2,3] and it has been shown that such differences can account for no more than half

[1] McChesney, E. W., PROC. SOC. EXP. BIOL. AND MED., 1943, **52**, 147.

[2] McChesney, E. W., *J. Nutrition*, 1943, **26**, 81.

[3] McChesney, E. W., *ibid.*, 1943, **26**, 487.

[4] Hess, A. F., and Supplee, G. C., PROC. SOC. EXP. BIOL. AND MED., 1930, **27**, 609.

[5] Willgeroth, G. B., Halpin, J. L., Halloran, H. R., and Fritz, J. C., *J. Assoc. Off. Agr. Chem.*, 1944, **27**, 289.

of the observed difference in activity. The purpose of the present work is to study the second suggested cause; namely, possible differences in the rates at which the 2 vitamins are inactivated in the tissues.

The metabolism of vitamin D in animal species has not been extensively studied. Knudsen, Remp, and Barlow[6] have studied the metabolism of several forms of vitamin D in the albino rat. They found that the inactivation of the vitamin in the tissues proceeds very rapidly. The metabolism of prophylactic dosages of vitamin D_2 in the chick has been studied by McChesney and Giacomino.[7]

Methods. The chicks used as experimental subjects were raised as previously described.[1] When they were 32 days of age and averaged about 250 g in body weight, the actual experiment was begun. The chicks were divided into 14 groups of 4 birds each such that each group weighed between 980 and 1020 g. Half of these groups were designated for the study of vitamin D_2 metabolism, and the remainder for vitamin D_3.

The vitamin dosages were now administered orally according to the following plan: Each of the vitamin D_2 birds received, per kg body weight, 2.5 cc of a corn oil solution containing 50 mg of calciferol per cc; each of the vitamin D_3 birds received, per kg, a similar volume of a corn oil solution containing 3 mg of crystalline vitamin D_3 per cc. These doses were chosen on the basis of previous work[1] which indicated that they would produce the same degree of hypercalcemia (serum calcium elevated to 12 mg % three days after administration). On the first, second, third, fourth, fifth, seventh, and tenth days after the administration of the vitamins, a group of 4 chicks from each main group was taken for sacrifice. The birds were killed by decapitation and were immediately transferred to 2 separate flasks, each containing one liter of boiling 20% alcoholic KOH. The remainder of the procedure for the preparation of extracts for bioassay has already been described in detail.[1]

Feces were collected from the vitamin D_2 and D_3 groups for the first 24 hr after the administration of the vitamins D. The excreta were thoroughly dried and then prepared for bioassay by the methods which have been described. These methods, and those used for the animals, were used by Knudsen, Remp, and Barlow in their work and were found by them[8] to give quantitative recoveries. For this reason the present work does not include recovery experiments.

When the results of the assays* became available, it was evident that studies of the vitamin content of chicks killed at intervals less than 24 hr after the vitamin administration would be of interest. For this purpose other chicks were raised as before, but the procedure was changed slightly as follows: When the chicks were killed the entire digestive tracts and their contents were dissected out, then the remainders of the carcasses were treated as previously described. In all cases care was taken that practically all of the blood should be included in the digest.

The results have been calculated in terms of the percentage (recovered) of the dosage given, and the data are given in Fig. 1. Since the values for the amounts found in the feces cannot be represented on the graph, they are given below.

Vitamin D_2 (2 separate experiments were run): dosage given, 34,000,000 units; recovered, 17,900,000 units, or 52.6%; dosage given 12,000,000 units; recovered, 6,400,000 units, or 53.3%.

Vitamin D_3: dosage given, 2,175,000 units; recovered, 980,000 units, or 45%.

Discussion. The percentage of vitamin D_3 found in the feces in these experiments is somewhat higher than previously reported.[1,9] The amounts of vitamin D_2 found in the feces are in good agreement, and also slightly higher than previously reported. In the chicks which were killed 8 hr after the administration of the vitamin D_3, 57% of the dosage given was recovered. This value, together with the amount found in the feces, accounts for all of

6 Knudsen, A., Remp, D. G., and Barlow, O. W., *Proc. Am. Chem. Soc.*, 1941, Sept., 20B.

7 McChesney, E. W., and Giacomino, N. J., *J. Nutrition*, 1945, **29**, 229.

8 Personal communication from Dr. A. Knudsen.

* The author is indebted to Mr. Donald Sepplin and Mrs. Charles Miller for the bioassays.

9 Klein, D., and Russell, W. C., *J. Biol. Chem.*, 1931, **93**, 693.

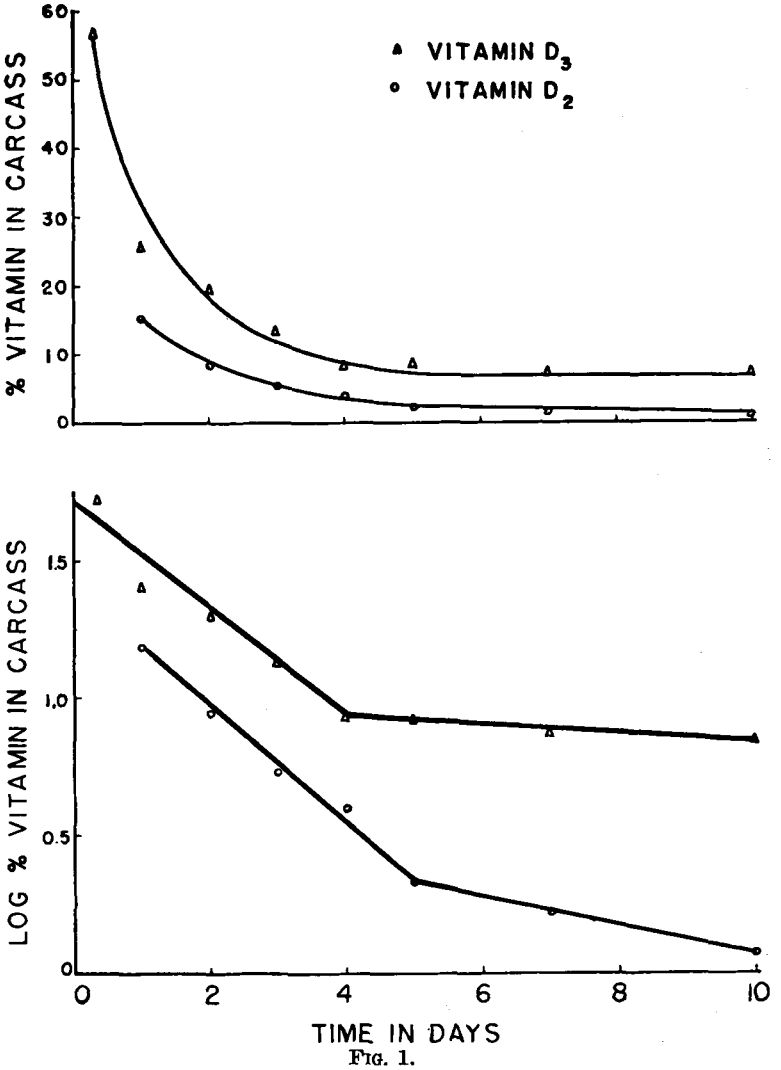

FIG. 1.

Metabolism of vitamin D in the chick. Percentage and log % of oral dose remaining in the body at various time intervals after administration.

the dose which was given. However, in the case of vitamin D_2 the recovery was not quantitative. It was never possible to recover more than 10 to 15% of the dose given from the carcasses of the chicks, even when they were killed at 8 or 16 hr after medication. This amount, together with the 52% found in the feces, leaves one-third of the dosage unaccounted for. It would be logical to suppose that the missing fraction is inactivated in the digestive tract.

The curves which result, when per cent vitamin recovered from carcasses is plotted against time after medication, reveal little more than the fact that there remains at any given time a much larger residue of the vitamin D_3 than of the vitamin D_2. In comparison with the dose given there remains on the tenth day about 5 times as much of the vitamin D_3 as of the vitamin D_2. The kinetics of the disappearance of the vitamin D activity becomes more apparent when the data are plotted as log percentage-vitamin-remaining in carcasses against time after medication. The curves do not seem to represent simple first-order reactions since each is apparently made up of two distinct parts or phases. In the first phase the destruction of the vitamins is quite rapid and parallel, with a half-life period for both of about 1.4 days. In the second the

destruction is much slower, and a difference between the 2 vitamins is apparent. The half-life period of vitamin D_2 during this phase is 2.7 days, while the half-life period for vitamin D_3 is 3.9 days. The destruction of vitamin D_2 is, therefore, proceeding at a rate exceeding that of vitamin D_3 by approximately 50%.

Summary. The metabolism of large (hypercalcemic) dosages of vitamins D_2 and D_3 has been studied in the chick. The chick evidently does not absorb vitamin D_2 as well as it does vitamin D_3, at least in the doses given; a larger proportion of it is found in the feces, and less is found in the carcasses. The amounts of vitamin D_3 found in carcasses and feces account for all of the dosage given, but about 35% of the vitamin D_2 cannot be accounted for. Analysis of the data indicated that there are two phases of inactivation of the vitamins. In the first both are inactivated at about the same rate, but in the second phase the rate of destruction of vitamin D_2 is about 50% greater. The generally more rapid inactivation of vitamin D_2 in the tissues may have a bearing on the fact that it is less effective in the chick than is vitamin D_3.

14933

Supplemental Use of Ergotamine in Eliciting Transient Disturbances of Rhythm in Acute Rheumatic Fever.

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The diagnosis of acute rheumatic fever has frequently been found, among soldiers, to be less dependent on the elicitation of significant cardiac murmurs than on the registration of transient aberrations in sequential electrocardiographic curves.[1] For the most part, these aberrations have consisted of various types of disturbances in rhythm due to a temporary hypervagotonic state excited by the acute rheumatic process.[1,2] However, in a significant number of instances, such electrocardiographic alterations, presumably because of their very brief duration[1] may never be apparent even in repeated tracings. Therefore, in an attempt to improve the usefulness of the electrocardiograph in such circumstances, the author undertook a clinical study in which this diagnostic aid was employed, following the administration of a sympatholytic preparation such as ergotamine tartrate (Gynergen). The results obtained by this method would seem to justify this brief preliminary report concerning the utility of such a simple supplementary procedure.

Material and Method. The observations were made in a random group of 8 soldiers suffering from acute migratory polyarthritis. In most instances no clinical evidence of cardiac disease was discernible. A routine electrocardiogram, in all cases, was obtained with the patient in the recumbent position shortly after his admission to the hospital. If the tracing revealed no significant changes, a control curve was obtained immediately preceding the intravenous administration of 0.5 mg of ergotamine tartrate, followed by comparable sequential records at 30 and 60 min intervals after the exhibition of the drug. Each of the 8 patients was under close medical surveillance during the convalescent stage of his illness and in 5 of them, a similar type of study was repeated after the usual manifestations of activity of the infection had disappeared.

Results. In each of the 8 patients, the initial electrocardiogram, before the administration of the ergotamine tartrate, was within normal limits. In 6 of the cases, comparative tracings obtained after the exhibition of this drug revealed significant disturbances in rhythm of a type usually associated with acute rheumatic fever, and consisted of first degree A-V heart block in 4 instances, second degree

1 Wendkos, M. H., and Noll, J., *Med. Clin. N. A.*, 1944, **2**, 124.

2 Wendkos, M. H., unpublished data.