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(CALCIFEROL) IN CHRONIC PARATHYROID TETANY**

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# ON THE ACTIONS OF CRYSTALLINE VITAMIN D<sub>2</sub> (CALCIFEROL)<sup>1</sup> IN CHRONIC PARATHYROID TETANY

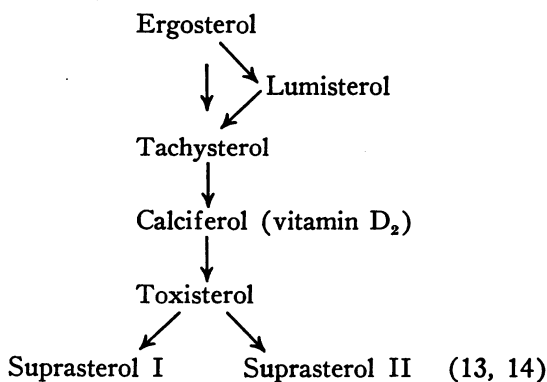
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Vitamin D has proved effective in raising the serum calcium and alleviating the symptoms of chronic parathyroprivic tetany in experimental animals (1, 2) and man (3, 4, 5). A number of factors including dosage (6, 7), and calcium-phosphorus content of the diet (8), have been found to influence its effect, and where these have not been taken into consideration vitamin D has failed (9, 10). The possibility of toxicity and the point made by Shelling and his associates that it raises the serum inorganic phosphorus, has led some workers to question the advisability of using vitamin D in tetany (11, 12).

In most studies on the actions of vitamin D, irradiated ergosterol (viosterol) has been used. In dealing with its physiological and toxic effects it must be borne in mind that irradiated ergosterol is not a simple solution of synthetic vitamin D but rather, a complex mixture of irradiated sterols, only one of which has antirachitic activity. Undoubtedly, some of the conflicting results obtained have been owing to the presence of sterols other than vitamin D. By means of newer chemical and physical methods, it has been possible to study the individual products of ergosterol irradiation. During the course of irradiation ergosterol undergoes a series of changes schematically represented below:



Commercially available viosterol contains 40 to 50 per cent calciferol, 50 to 60 per cent lumisterol plus tachysterol, but no toxisterol or suprasterol (15). Tachysterol and lumisterol have no antirachitic activity. Although their presence in ordinary therapeutic doses of viosterol is probably insignificant, it is conceivable that they might modify the effects of vitamin D when large doses, such as are recommended in the treatment of tetany, are used (15). Toxisterol and the suprasterols, on the other hand, are definitely toxic and represent the end products of over-irradiation. They are usually not present in commercially available irradiated ergosterol but at least one variety (Vigantol), which was the material used in a number of studies on vitamin D action (4, 7, 16), is known to have contained considerable quantities of toxisterol (13).

In 1932 Askew and his associates succeeded in isolating pure vitamin D from crude irradiated ergosterol and named it "calciferol" (17). Their product was crystalline and had a potency of 40,000 international vitamin D units per milligram. At about the same time Windaus isolated two distinct forms of crystalline vitamin D and designated them vitamins D<sub>1</sub> and D<sub>2</sub> (18). Vitamin D<sub>2</sub> proved to be identical with calciferol, while vitamin D<sub>1</sub> was found to be a loose molecular combination of calciferol and lumisterol.

Since pure crystalline vitamin D<sub>2</sub> (calciferol) has recently become available for clinical use it was felt worth while to study its actions in two cases of parathyroid tetany who have been under our care for some time, and whose long past records offered an opportunity to compare the efficiency of calciferol with other antitetanic agents. We have been particularly interested in the serum

<sup>1</sup> Calciferol was furnished by the Winthrop Chemical Co., Inc., New York, in the form of a sesame oil solution containing 1,000,000 international vitamin D units per gram.

calcium and phosphate response, the significance of the calcium intake, and the possible toxic effects of vitamin D<sub>2</sub> therapy. Unfortunately, calcium and phosphorus balance studies were not possible, but the patients were observed closely with frequent blood analyses.

Several favorable reports on the use of calciferol in tetany have appeared in the English literature (19, 20) but none in the American, so far as we have been able to determine.

#### CASE REPORTS

##### Case 1

H. B., a 39-year old white American widow, was admitted to the Strong Memorial Hospital on December 1, 1935, with an acute nonspecific salpingitis of six days' duration.

In 1926, nine years prior to her admission, she had undergone a two-stage subtotal thyroidectomy for thyrotoxicosis at another hospital. The operation failed to relieve her symptoms and it was found necessary, therefore, to re-operate in 1927 and again in 1929. Shortly after the last operation she developed severe tetany, requiring continuous treatment with large doses of calcium, viosterol and parathormone for a period of six months. During the last six years she had had only occasional attacks of mild tetany, relieved by moderate doses of calcium lactate.

Although the thyrotoxicosis was relieved by the last operation, the left eye had continued to grow more prominent while the right had receded. During the past two years the patient had again been troubled with nervousness, fatigability, and slight weight loss. There had been no increase in appetite, excessive sweating, tremor, sensitivity to heat, or palpitation.

*Physical examination.*—The patient was a well developed middle-aged woman, weighing 64.6 kgm., who appeared acutely ill. The temperature was 38.2° C., pulse rate 120, respirations 22; blood pressure 145/72. The skin was warm and moist and the face deeply flushed. There was bilateral exophthalmos and lid-lag, more pronounced on the left. Pupils were equal, round, regular, and reacted to light and accommodation. No evidence of cataract was present, and the fundi were normal. The teeth were normal save for a moderate amount of dental repair. The tongue was coated and protruded in the midline without tremor. There was a thick postoperative scar at the base of the neck, but no thyroid tissue was palpable. Percussion failed to reveal evidence of a retro-manubrial thyroid. The lungs were clear to auscultation and percussion. The heart was normal in all respects save for tachycardia and a soft blowing, non-transmitted systolic murmur at the apex. Abdominal examination revealed marked tenderness and spasm in both lower quadrants but no masses or palpable solid viscera. On pelvic examination the cervix was found to be painful on motion and the uterus normal in size and position. The left

adnexae felt normal but were tender, while on the right an exquisitely tender mass 5 cm. in diameter was present. Except for a fine tremor of the extended fingers the extremities were normal. The deep reflexes were all diminished and the abdominals and Babinski physiological. Trousseau's and Chvostek's signs were negative. The scalp and body hair appeared normal in texture, abundance, and distribution, but there was premature greying. The finger and toenails were all present and without trophic changes.

*Laboratory data.*—Blood: Red blood cells 4,090,000, hemoglobin 12 grams per 100 cc. (Sahli), white blood cells 16,250. Urine: yellow, cloudy, specific gravity 1.012, albumin trace, sugar absent, microscopic examination revealed rare leukocytes. Subsequent urinalyses were entirely negative. Blood Wassermann and Kahn tests negative. Gonococcus complement fixation negative. Smears and cultures on two occasions from the cervix, urethra, and rectum failed to demonstrate the presence of gonococci. Basal metabolic rate on December 5, 1935, was 34 per cent above average normal (Aub-DuBois). This test was not entirely satisfactory, but a successful determination on November 20, 1936, proved to be 48 per cent above average normal. Urea clearance (June 4, 1937) 69.7 cc. per minute = 92 per cent. Creatinine clearance (June 4, 1937) 139.8 cc. per minute. X-ray of both tibiae and femurs (June 16, 1937) revealed a slight degree of decalcification. Frequent determinations of the serum total proteins, albumin:globulin ratios, carbon dioxide combining power, chlorides, and nonprotein nitrogen were within normal limits. Serum calcium was determined by Clark and Collip's method (21); serum inorganic phosphorus by Kuttner and Cohen's method (22). Normal values by these methods in this laboratory: Calcium = 9 to 11 mgm. per cent, phosphorus = 3.0 to 4.5 mgm. per cent.

*Course.*—Under symptomatic treatment and bed rest the salpingitis subsided and the temperature fell to a normal level by the end of the first week. The day after admission the serum calcium was found to be 5.5 mgm. per cent and the serum inorganic phosphorus 6.4 mgm. per cent, but there were no signs or symptoms of tetany. On December 4, three days after admission, generalized spasticity of the musculature and marked carpal spasm appeared. During the following eleven months latent or manifest tetany was present at all times despite intensive therapy. Since November 1936 the patient has received calciferol intermittently and has been free from tetany. The details of treatment will be discussed below.

The patient was discharged from the hospital on December 17, 1935, and has since been followed in the Out-patient Department. There have been several brief readmissions to the hospital for injections of parathormone, trial of special diets, and parathyroid gland transplantation.

*Treatment* (Figures 1 and 2).—*Period I* (approximately 11 months). Despite the use of large quantities of calcium, viosterol, and parathormone, it was found impossible to raise the serum calcium or lower the serum inorganic phosphorus to normal levels. On one occasion

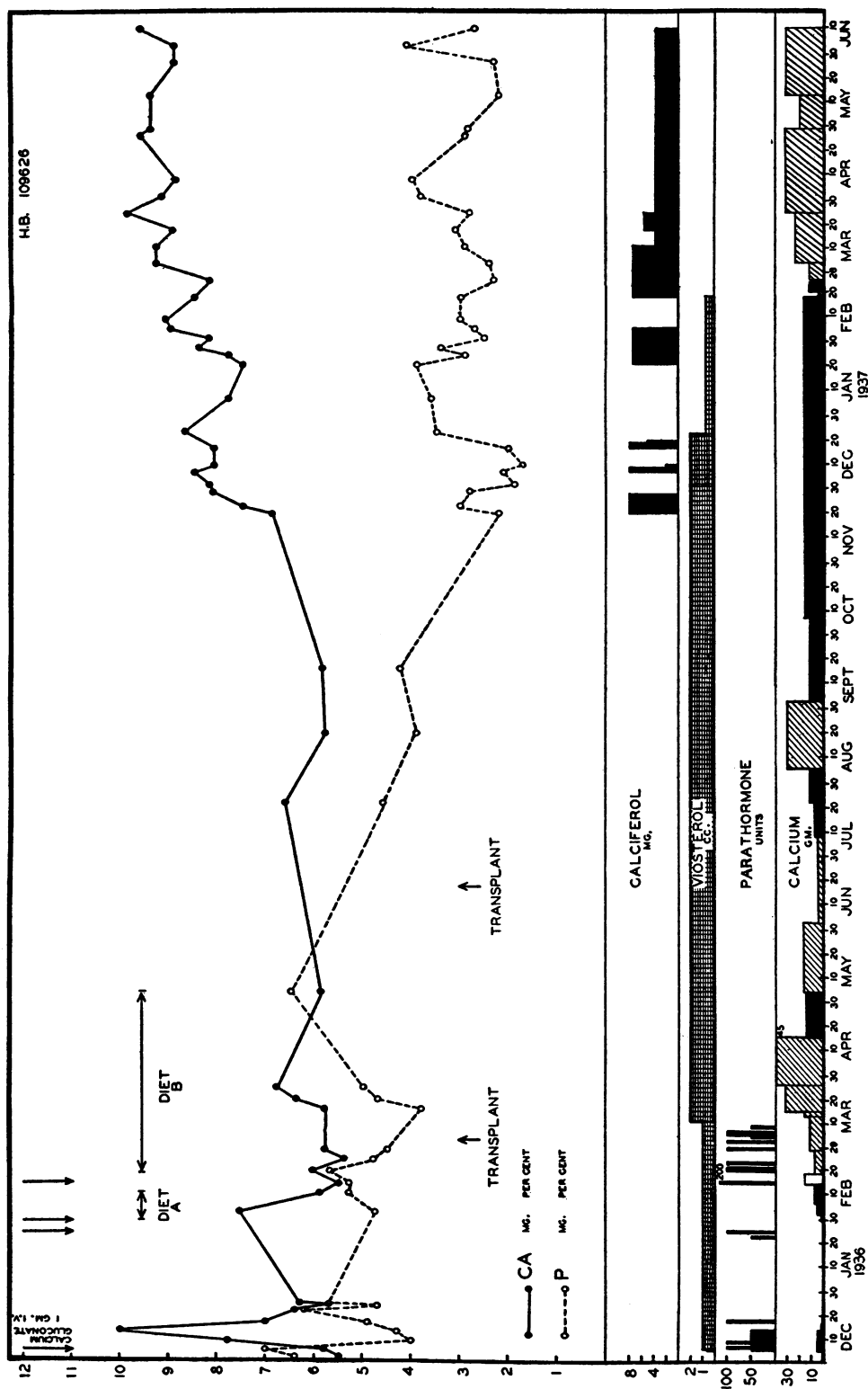


FIG. 1. CASE I, H. B. POSTOPERATIVE PARATHYROID TETANY

Calciferol: 1 mgm. equivalent to 40,000 international vitamin D units. Calcium salts: Solid blocking = calcium chloride; shaded blocking = calcium lactate; open blocking = calcium gluconate.

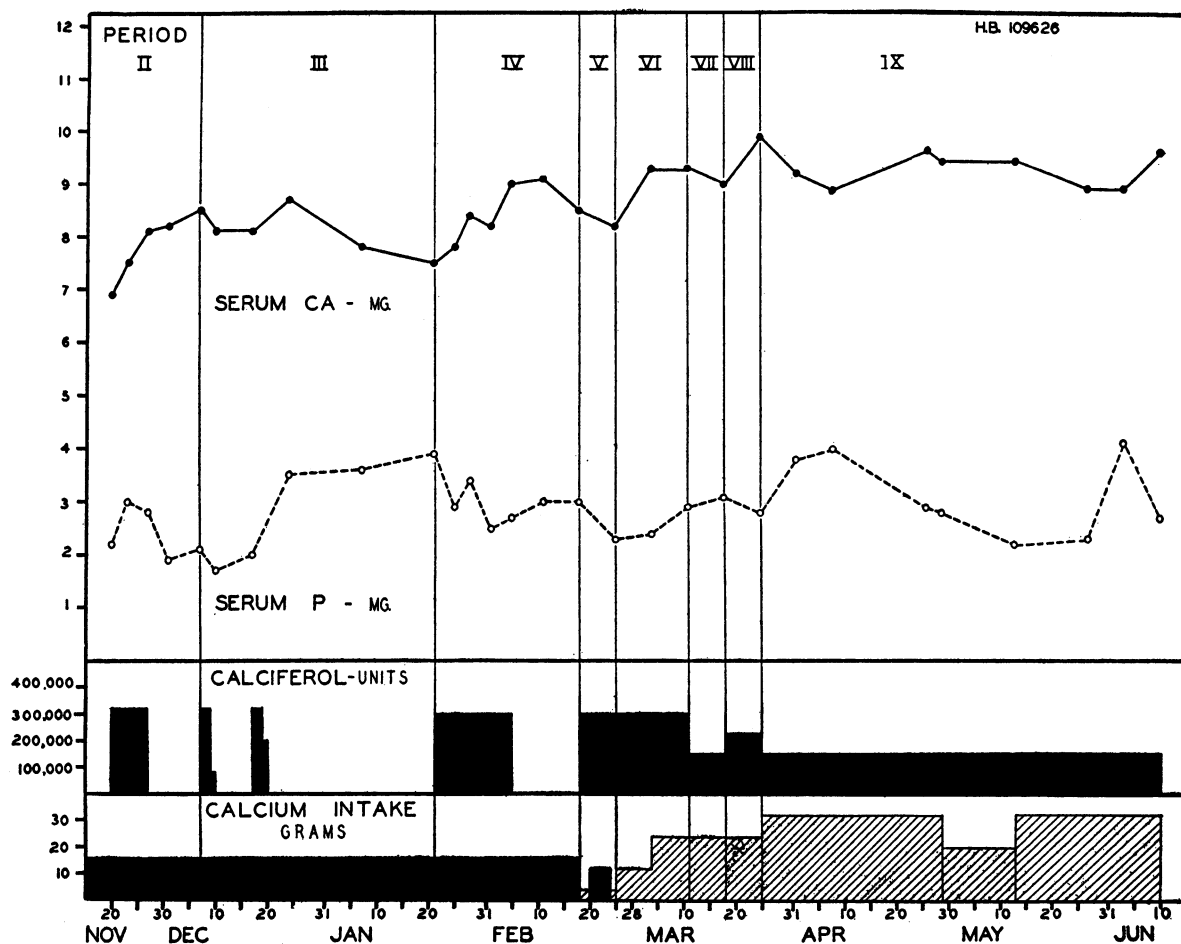


FIG. 2. CASE I, H. B. POSTOPERATIVE PARATHYROID TETANY

Calciferol: 1 mgm. equivalent to 40,000 international vitamin D units. Calcium salts: Solid blocking = calcium chloride; shaded blocking = calcium lactate.

only (December 13, 1935) was the serum calcium normal, but within a few days it had dropped again. For a two-week period the patient was given a diet containing daily 2.0 grams of calcium and 0.6 gram of phosphorus (Diet A). There was a temporary rise in the serum calcium to 7.5 mgm. per cent and a concomitant fall in the serum phosphorus to 4.8 but these promptly returned to their former levels at the end of a week. Following this, a high acid-ash diet (Diet B) was tried for a period of three months. As a result, there was a transient but small rise in the serum calcium and a fall in the serum inorganic phosphorus.

On March 3, 1936, two parathyroid glands of pin-head size were removed from a still-born baby ( $3\frac{1}{2}$  hours) and injected into the region of the left deltoid through a trocar with about 3 cc. of Ringer's solution. On June 17, 1936, a small parathyroid gland removed at operation was transplanted over the right femoral vein through a small incision in the skin. No appreciable effect upon the clinical course or serum calcium was noted. Five months af-

ter the second transplantation the serum inorganic phosphorus had fallen to 2.2 mgm. per cent. Since all the preceding and subsequent determinations were higher (*i.e.*, when the patient was not taking calciferol), there is reason to question the accuracy of this determination.

The average values for the entire period were: serum calcium 6.4 mgm. per cent, serum inorganic phosphorus 4.9 mgm. per cent.

*Period II* (17 days). For one week, daily doses of 320,000 vitamin D units of calciferol were administered. The daily intake of calcium ( $\text{CaCl}_2$ , 16 grams) and viosterol (2.0 cc.) was the same as in Period I. Within three days the serum calcium had reached 8.2 mgm. per cent, the highest it had ever been, except on the one occasion mentioned above. The serum phosphorus at first rose slightly and then fell, but all determinations remained within normal limits during this period. Calciferol was discontinued at the end of a week but during the next eleven days the serum calcium continued to rise, the phosphorus to fall.

*Period III* (45 days). The viosterol and calcium intake remaining the same as in Period II, calciferol was given for three days (total 720,000 units). Eight days later a similar dose was given. There was no change in the serum calcium after the first block of calciferol, but following the second block there was a definite rise to a level of 8.7 mgm. per cent. Following the last dose of calciferol there was a gradual fall in the serum calcium, but even at the end of thirty-three days it had not reached the average level of Period I. The serum inorganic phosphorus fell slightly after the first block of calciferol and rose after the second, although not to an abnormal level.

*Period IV* (28 days). The calcium intake remaining the same as in Periods I, II, and III, a daily dose of 300,000 vitamin D units was given for fourteen days, twice as long as in either Period II or III. There was a correspondingly greater rise in the serum calcium, reaching a maximum of 9.0 mgm. per cent. The serum inorganic phosphorus fell abruptly to 2.5 mgm. per cent. During the following week the serum calcium remained about the same and then fell, reaching a level of 8.5 mgm. per cent two weeks after the last dose of calciferol. The serum inorganic phosphorus rose slightly (to 3.0 mgm. per cent).

*Period V* (7 days). Keeping the calciferol intake at the same level as in Period IV (300,000 units daily), the calcium intake was reduced to 4 grams of the lactate daily. Within two days the patient developed acute tetany. Unfortunately, she was unable to come into the clinic, but increased her calcium intake to 12 grams of the chloride, with diminution in her tetany. Despite the fact that similar doses of calciferol had previously resulted in a rise in the serum calcium, at the end of one week there was no rise but, in fact, a slight fall. Had a blood calcium been determined on the third day of the period, when the patient was in active tetany, it would undoubtedly have been considerably lower. This appears to demonstrate the dependence of calciferol activity on the calcium intake.

*Period VI* (14 days). With the same calciferol intake as in Period V, and 12 grams of calcium lactate daily, there was a prompt rise in the serum calcium to 9.3 mgm. per cent. Doubling the calcium intake resulted in no further rise. At any given dose of calciferol, there appears to be an optimal calcium intake above which additions will cause no further rise in the serum calcium.

*Periods VII and VIII* (7 days each). The calcium intake was kept the same as in Period VI. The calciferol dosage, however, was reduced to one-half (150,000 units daily). At the end of one week there was a slight fall in the serum calcium. By increasing the dose to 225,000 units per day it was possible to raise the serum calcium again to 9.9 mgm. per cent. This response was of the same order of magnitude as that which resulted from a daily dose of 300,000 vitamin D units. There appears, therefore, to be an optimal dose of calciferol, at any given intake of calcium, which will raise the serum calcium level.

*Period IX* (77 days). It was possible to maintain the

serum calcium at approximately 9.0 mgm. per cent and to keep the patient free from tetany for a period of eleven weeks on 150,000 units of calciferol and 20 to 32 grams of calcium lactate daily.

During the periods in which calciferol was administered, a total of 202 days, manifest tetany was absent at all times, except in Period V when the calcium intake was greatly reduced. The only evidence of latent tetany which could be occasionally demonstrated, was a slightly positive Trousseau's sign after application of a tight tourniquet for a period of more than one minute, a finding of questionable significance. The patient felt perfectly well during this period and exhibited no signs or symptoms of vitamin D intoxication. The nervousness, tremor, and exophthalmos which were undoubtedly related to a state of hyperthyroidism, remained unchanged. There was slight persistent tachycardia, but no loss of weight. In December 1936, a small nodule appeared in the region of the left lobe of the thyroid. This increased somewhat in size during the ensuing three months and then remained stationary. No iodine was administered to avoid complicating these studies. A fluoroscopic examination of the chest in November 1936 failed to demonstrate a substernal thyroid.

Except for three months during Period I, the patient ate a well balanced diet of her own choosing. Since no effort had been made to control its calcium or phosphorus content, the diet for a sample period of one week during June 1937 was recorded and analyzed. The average daily calcium intake (exclusive of added salts) was 0.566 gram; the average daily phosphorus was 0.855 gram.

#### Case 2

J. La P., a 39-year old Italian para iii, gravida iv, was delivered on August 9, 1936, of a normal full term male child, weighing 2710 grams, after a labor of 6½ hours. The last week of pregnancy had been complicated by a severe pyelitis. On the seventh day postpartum, the symptoms of pyelitis having already subsided, the patient developed excruciating pain, numbness, and spasm of the right hand and wrist. Examination of the blood revealed hypocalcemia and hyperphosphatemia, and Chvostek's and Trousseau's signs were positive, confirming the diagnosis of idiopathic parathyroprivic tetany.

The patient's first two pregnancies (1927 and 1929) had been uneventful. The last, in 1933, had been followed by a similar attack of tetany lasting six months and incorrectly diagnosed as arthritis, as subsequent events proved. Since then she had had monthly attacks of tetany, characterized by tingling and twitching of the thenar eminences, coinciding with the menstrual periods. The attacks were always mild, involved the right hand more than the left, and usually appeared two or three days before, and subsided immediately after the onset of menstrual flow. There was nothing else of note in the past or family history.

*Physical examination* (three weeks after delivery, August 29, 1936).—The patient was a well developed obese Italian woman who did not appear ill. The vital signs were normal. Scalp hair was abundant and of normal

texture. The skin was dark, warm, and moist. The nails were all present and showed no trophic changes. Examination of the eyes revealed no evidence of cataract; the pupils and fundi were normal. The teeth were in good repair and exhibited no unusual pitting or ridging. The thyroid gland was of normal size and consistency and there were no eye signs, tremor, tachycardia, or excessive sweating to suggest thyroid disease. The heart and lungs were normal, the blood pressure 120/80. Abdominal examination revealed right costovertebral angle tenderness but the kidneys were not palpable. There was a mild cervicitis and a relaxed pelvic floor. Slight pitting edema was demonstrable over the left ankle. Chvostek, Trousseau, and peroneal signs were markedly positive. All the reflexes were hypoactive and equal, the Babinski physiological.

*Laboratory data.*—Blood: Red blood cells 4,300,000, hemoglobin 11.4 grams (Sahli), white blood cells 13,600. On subsequent examination the red blood count, white blood count, and hemoglobin fell to 3,560,000, 7,900, and 10.4 respectively. Urine: yellow, cloudy, albumin 2+,

sugar absent. Microscopic: loaded with clumped white blood cells, no red blood cells or casts. Urine culture: *B. coli communior*. Wassermann and Kahn blood tests negative. Abdominal x-ray on September 2, 1936: kidney shadows of normal size and shape, no evidence of calcification in the kidneys or along the course of the ureters. Phenolsulphonphthalein excretion test on June 5, 1937 (1 cc. intravenously): 15 minutes 25 per cent, 30 minutes 20 per cent, 1 hour 20 per cent, 2 hours 15 per cent. Total excretion 80 per cent. Urea clearance: 52.2 cc. per minute or 69.6 per cent. Creatinine clearance: 92.8 cc. per minute.

Several determinations of the serum total proteins, albumin:globulin ratios, carbon dioxide combining power, chlorides, and nonprotein nitrogen were within normal limits.

*Course* (Figures 3 and 4).—The patient ran a hectic temperature with marked pyuria for one week. These subsided under a régime of forced fluids, sodium acid phosphate, and hexamethylenamine. Subsequently, in the Outpatient Department, the latter was alternated with

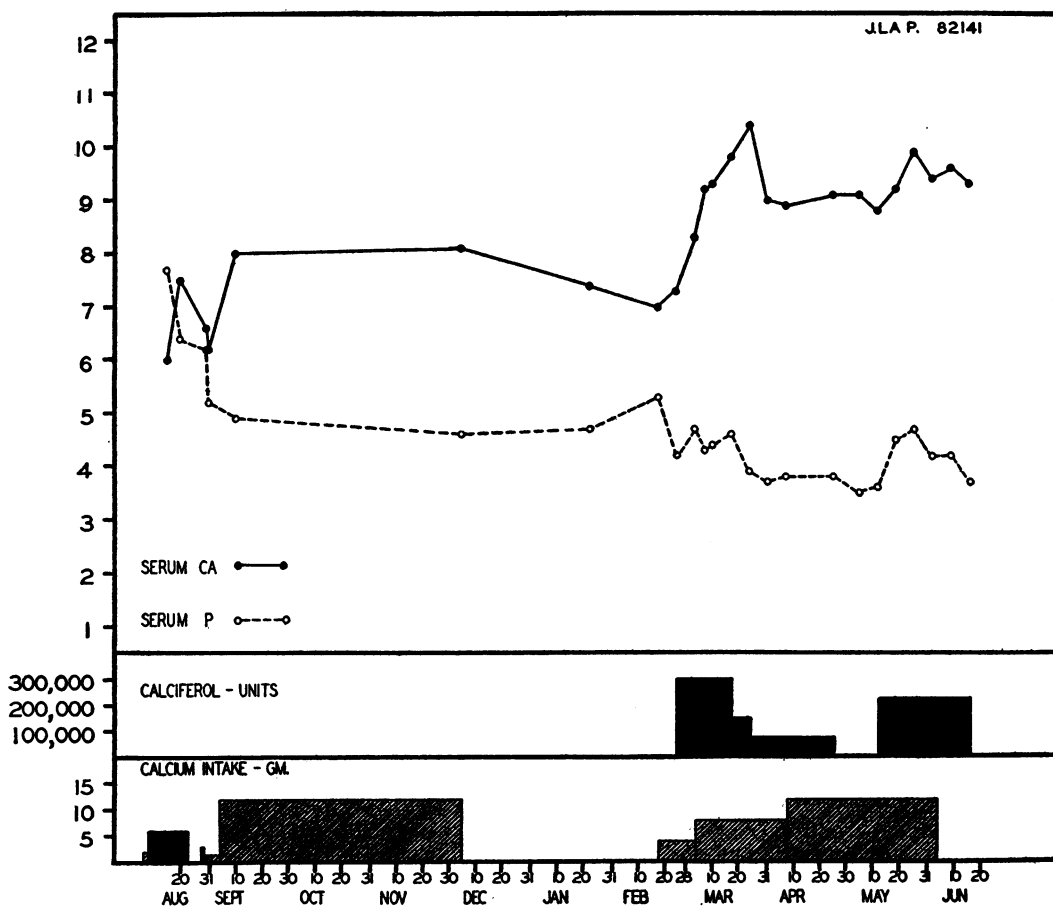


FIG. 3. CASE II, J. LA P. IDIOPATHIC PARATHYROID TETANY

Calciferol: 1 mgm. equivalent to 40,000 international vitamin D units. Calcium salts: Solid blocking = calcium chloride; shaded blocking = calcium lactate.

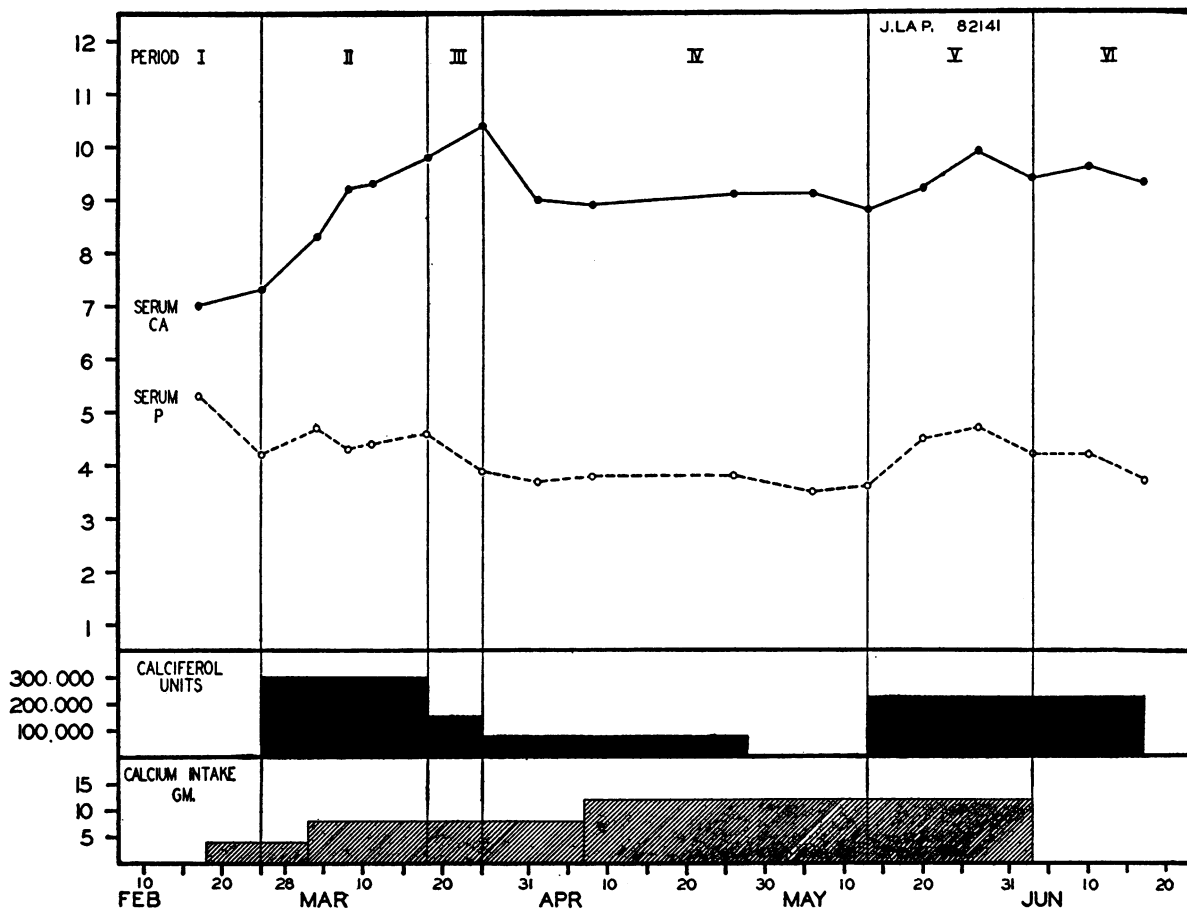


FIG. 4. CASE II, J. LA P. IDIOPATHIC PARATHYROID TETANY

Calciferol: 1 mgm. equivalent to 40,000 international vitamin D units. Calcium salts: Solid blocking = calcium chloride; shaded blocking = calcium lactate.

neutral acriflavine and alkali for a period of five months, when all urinary symptoms disappeared. Although the urine no longer contained pus cells, culture yielded *B. coli* as late as March 1937.

*Period I* (6½ months). The initial attack of tetany (August 15, 1936) was promptly relieved by the intravenous injection of 1 gram of calcium gluconate. Moderate amounts of calcium were then administered orally. Although there was no further active tetany, Trousseau's sign remained positive. The patient was discharged from the hospital on August 22, 1936, without medication. Six days later she was readmitted in acute tetany. This promptly responded to calcium therapy. The patient was discharged on September 5, 1936, and advised to take 16 cc. of cod liver oil and 12 grams of calcium lactate daily. Hypocalcemia and hyperphosphatemia persisted but manifest tetany did not reappear until February 17, 1937. The average serum values for the entire period were calcium 7.1 mgm. per cent; phosphorus 5.6 mgm. per cent.

*Period II* (21 days). Doses of 300,000 vitamin D

units of calciferol with 4 and then 8 grams of calcium lactate were administered daily. The serum calcium rose steadily to 9.8 mgm. per cent, but the serum phosphate remained constant between 4.2 and 4.7 mgm. per cent. Signs of latent tetany disappeared when the serum calcium reached a level of 8.3 mgm. per cent.

*Period III* (7 days). The daily calciferol intake was reduced to 150,000 units but the serum calcium continued to rise and the serum phosphate to fall, reaching new levels of 10.4 and 3.9 mgm. per cent, respectively.

*Period IV* (49 days). The daily calciferol intake was reduced still further (to 75,000 units) and the calcium intake increased to 12 grams of the lactate. Serum calcium fell to and remained fairly constant at 9 mgm. per cent. The serum inorganic phosphorus fell to 3.5 mgm. per cent. At the end of four weeks calciferol administration was discontinued, but the serum calcium remained elevated for the following three weeks.

*Period V* (21 days). Calciferol therapy was resumed at a somewhat higher level, 225,000 units daily. There



was a gradual rise in the serum calcium to 9.9 mgm. per cent and in the serum inorganic phosphorus to 4.7 mgm. per cent.

*Period VI* (14 days). Calciferol was administered as in Period V but calcium lactate was omitted. The serum calcium remained at essentially the same level for two weeks, in contrast to the rise of serum calcium which followed the continued administration of comparable doses of calciferol supplemented by calcium lactate (Periods II, III, V).

Except for the lapse of three weeks in Period IV, calciferol was administered continuously for 106 days. At no time were there any signs or symptoms of tetany, and the serum values for calcium and phosphorus remained within normal limits. There was no evidence of hypervitaminosis D and the weight remained constant.

The patient ate a well balanced diet of her own choosing during the entire period of observation. Its average daily calcium and phosphorus content was determined as for Case 1 and found to contain 0.434 gram and 0.829 gram respectively.

#### DISCUSSION

The results of this study confirm Elliott's (19) and Stacey's (20) conclusion that crystalline vitamin D<sub>2</sub> (calciferol) is an effective agent in the treatment of parathyroid tetany. Case 1 had suffered from severe tetany for at least one year preceding the use of calciferol and had failed to respond to parathormone, low phosphorus-high calcium diet, two parathyroid gland transplants, moderate doses of viosterol, and calcium salts in amounts suggested by Boothby and Davis (23). Large doses of calciferol, in the presence of an adequate calcium intake, maintained the patient in a normal state during the succeeding six months. Case 2, on the other hand, had suffered from mild tetany for a period of six months preceding the use of calciferol. Although moderate doses of calcium and cod liver oil prevented severe tetany, there were mild attacks at each menstrual period and hypocalcemia was constantly present. By the use of calciferol and an adequate calcium intake, it was possible to maintain the patient in a normal state with respect to her tetany and blood chemistry during the succeeding four months. It must be granted, however, that larger doses of calcium and viosterol, such as were used in Case 1, might have been equally effective.

*Serum calcium.*—The effect of calciferol on the serum calcium was found to be dependent on the daily dose, duration of dosage, and the calcium intake. Moreover, there appeared to be individual differences between the two patients.

Daily doses of 225,000 to 300,000 vitamin D units resulted in a progressive rise in the serum calcium in both patients, when the calcium intake was adequate. Doses of 150,000 units daily resulted in a rise in Case 2 (Period III), but merely maintained the serum calcium at its initial level in Case 1 (Period IX). In Case 2 (Period V), 75,000 units daily were inadequate to maintain a serum calcium of 10.4 mgm. per cent.

When adequate amounts of calciferol were administered, there was an appreciable rise in the serum calcium at the end of a week, often at the end of three days. A daily dose of 300,000 units of calciferol was ineffective when given for less than one week. A similar dose given ten days later, however, resulted in a very definite rise in the serum calcium, apparent evidence of cumulative action (Case 1, Period III). The continued rise in the serum calcium after cessation of calciferol administration also suggested cumulative action (Case 1, Period II).

Calciferol was administered uninterruptedly to Case 1 for four months without the development of hypercalcemia. Since an effort was made to maintain the serum calcium at the lower limits of normal, to avoid toxic manifestations, daily doses as large as 300,000 units were not administered for longer than three weeks, so that it is impossible to say whether the serum calcium would have continued to rise at the end of that time. Crimm's work (24), however, on the effects of viosterol in tuberculous patients, seems to indicate that continued administration of large doses of vitamin D does result in hypercalcemia and a prolonged cumulative effect. He administered the daily equivalent of 500,000 vitamin D units for eight to thirty-two days. The serum calcium reached abnormal levels (13.8 to 18.5 mgm. per cent) within five days, increased with the continued administration of viosterol, continued to rise after viosterol was discontinued, and remained abnormally high for as long as 213 days.

When the calcium intake was reduced to 4 grams of the lactate in Case 1, the serum calcium fell sharply and the patient developed severe tetany, even though 300,000 units of calciferol were being administered daily (Period V). Similarly, in Case 2, daily administrations of 225,000 units of calciferol without added calcium salts failed to raise the serum calcium, even though

comparable doses supplemented by calcium lactate had previously effected very definite rises (compare Period VI with Periods III and V).

Bauer, Marble, and Claffin (4) were among the first to demonstrate the direct relationship between the calcium intake and the effectiveness of irradiated ergosterol in raising the serum calcium. Five milligrams of irradiated ergosterol daily (equivalent to approximately 100,000 vitamin D units) raised the serum calcium to normal levels in a case of hypoparathyroidism, when the calcium intake was adequate, but was ineffective when the calcium intake was greatly reduced. In experimental animals, on the other hand, Harris and Innes (25) and Shelling (2) were able to induce viosterol hypercalcemia in the absence of calcium from the diet. The doses used, however, were tremendous and not comparable to those used in the present or other studies on humans.

The failure of some workers (9, 10) to demonstrate a rise in the serum calcium after the administration of vitamin D to parathyroprivic patients can probably be explained on the basis of inadequate dosage and the failure to include adequate available calcium in the diet.

The larger calcium requirement of Case 1, as compared to Case 2, may have been related to the presence of hyperthyroidism, since, as Aub and his associates (26) have demonstrated, there is an increased excretion of calcium in hyperthyroidism.

*Serum inorganic phosphorus.*—Shelling and his coworkers (11, 12) have questioned the advisability of using vitamin D in parathyroid tetany since it primarily increases the concentration of the inorganic phosphorus in the blood and favors phosphate retention. Other investigators have not confirmed these findings. Bauer, Marble, and Claffin (4) found that a daily dose of 5 mgm. of irradiated ergosterol, supplemented by a high calcium intake, resulted in a decreased serum phosphate and a negative phosphorus balance in a case of parathyroid tetany. Similarly, Crimm (24) demonstrated in tuberculous patients, fed large doses of viosterol, a transient rise followed by a sustained fall in the serum inorganic phosphorus. This transient rise in the serum phosphate may be the explanation for Shelling and Goodman's controversial results (11). In their first patient the serum phosphate rose on the third day of viosterol

administration but had started to fall by the sixth day when viosterol administration was discontinued. Had viosterol been continued, there is reason to believe from Crimm's work that the serum phosphate would have fallen further and the serum calcium could have risen to normal levels.

Although the effect of calciferol on the serum inorganic phosphorus was not as constant as on the serum calcium, there was, in general, a reciprocal relationship between the serum calcium and serum phosphate in the present study. In both Cases 1 and 2, the serum phosphate was lowered to and remained at normal levels during the entire period of calciferol administration. This is strikingly illustrated in the divergence of the serum calcium and phosphorus curves in Figures 1 and 3. Similarly, in the four cases of tetany treated with calciferol by Stacey (20) and Elliott (19), there was a reciprocal fall in the serum phosphate as the serum calcium rose.

The diet is no less important in its effect on the serum phosphate than it is on the serum calcium level. As has been demonstrated by Shelling and Goodman (11) and others (10, 27), high phosphorus diets predispose to hyperphosphatemia, whereas low phosphorus diets result in a reduction of the serum phosphate. The use of high calcium-low phosphorus diets in parathyroid tetany is to be commended as a logical procedure. Both subjects of this investigation were on a relatively low phosphorus (less than 1.0 gram) and high calcium intake. The diet undoubtedly played some rôle in lowering the serum phosphate but the major effect must have been due to vitamin D, since the average serum phosphate level on the diet alone was 4.9 mgm. per cent in Case 1 and 5.6 mgm. per cent in Case 2, whereas the averages for the calciferol periods were 2.8 mgm. per cent and 4.1 mgm. per cent respectively.

*Mode of vitamin D action.*—Since they were able to protect monkeys against dietary tetany with irradiated ergosterol when the parathyroids were intact but not after they had been removed, Hess and Lewis (28) concluded that irradiated ergosterol acted by stimulating the parathyroids. Greenwald and Gross (29) came to a similar conclusion and suggested the presence of accessory parathyroid tissue to explain the activity of vitamin D in parathyroidectomized animals.

Bauer and his associates (4, 7) and others (30), on the other hand, have refuted the "parathyroid theory" of vitamin D action and have demonstrated that, both in normals and patients suffering from hypoparathyroidism, the essential action of irradiated ergosterol is to increase absorption of calcium and phosphorus from the intestine. In normals, the excess calcium and phosphorus absorbed is rapidly excreted so that there is very little change in the lime salt balance (7). Where there is a deficiency of calcium and phosphorus in the serum and bones, as in osteoporosis and osteomalacia, the extra calcium and phosphorus absorbed are retained in the serum and then deposited in the bones (31). In hypoparathyroidism the action of vitamin D appears to be somewhat different. There is an increased absorption of calcium from the intestine, some retention in the serum, and an increased excretion in the urine. Phosphorus, on the other hand, appears to be excreted in increased quantity through the bowel, while the serum content falls (4). This apparent loss of phosphorus in the feces does not preclude, however, the possibility of increased absorption, since, as Shelling (32) has pointed out, the excretion of phosphorus through the bowel is an important mechanism when the kidneys are no longer able to handle an excess.

Although the theory that vitamin D increases the absorption of calcium and phosphorus from the gut explains the effects of moderate doses, it cannot explain the development of the hypercalcemia and negative calcium balance that occurs when large doses of viosterol are administered to animals on calcium-free diets (2). Taylor and his associates (33) feel that excessive doses reverse the usual effects of viosterol, resulting in decalcification of the bones and a negative calcium balance, by stimulation of the parathyroids. Shelling (12) has analyzed Taylor's experiments and pointed out that they "neither prove nor disprove that the parathyroids regulate the activity of vitamin D."

The present study of pure crystalline vitamin D<sub>2</sub> (calciferol) adds but little to the solution of this problem, since calcium and phosphorus balance studies were not carried out. In general, the response was similar to that seen with crude irradiated ergosterol in parathyroid tetany (4). The dependence of calciferol on an adequate cal-

cium intake in raising the serum calcium, suggested increased absorption or possibly decreased excretion in the gut. The reduction of phosphatemia could have been due to deposition of phosphorus in the bones, increased excretion into the intestine, or increased phosphaturia. In the light of Bauer's work (4) on irradiated ergosterol, the last would appear to be the most likely.

Crimm and Strayer (34), using doses of viosterol large enough to induce hypercalcemia in tuberculous patients, noted an increase in the serum total proteins, the albumin fraction and the pH, and a decrease in the globulin fraction and the chlorides. The carbon dioxide content remained constant. In the present study no significant changes were noted in the concentrations in the serum of any of these substances.

*Toxicity of vitamin D.*—Excessive doses of irradiated ergosterol have been shown to be toxic for man (35) and experimental animals (6, 8, 25). Shohl, Goldblatt, and Brown (16) found that rats fed 4 mgm. of irradiated ergosterol (Vigantol) daily, lost weight and died in from 5 to 14 days with hypercalcemia, decalcification of the bones, parenchymatous lesions and metastatic calcification of the kidneys, heart, blood vessels, and gastric mucosa. In two infants who died of hypervitaminosis D, Thatcher (36) described pathological calcification and cellular infiltration of the kidneys, fatty degeneration of the liver, but no calcification of the blood vessels or soft tissues. That toxic manifestations may occur without pathological calcifications has been demonstrated by Shelling (32) and others (25). The arterial calcifications seen in experimental hypervitaminosis D do not appear to be related to the arteriosclerosis of man, but represent a deposition of calcium limited to the media, similar to that seen in Mönckeberg's sclerosis (8).

The pathogenesis of metastatic calcification is unknown, but it appears to be related to the presence of hypercalcemia and/or hyperphosphatemia (30). Ham and Portuondo (37), however, were not able to demonstrate a direct relationship between the level of the serum calcium and pathological calcification, and suggested that the precipitation of calcium in the tissues was due to a change in the state of the serum calcium rather than its level. Smith and Elvove (6) believed that hyperphosphatemia was the determining fac-

tor, since they found that hyperphosphatemia, in the presence of even a slight increase in the serum calcium, resulted in metastatic calcification, while hypercalcemia in the presence of a normal or low serum phosphate never gave rise to abnormal calcifications. That the phosphatase content of the tissues may play a rôle in the deposition of calcium has been suggested by Harris (30), on the basis of Martland and Robinson's studies on ossification (38).

The toxicity of vitamin D is dependent, at least in part, on the diet and renal function (8, 39). High phosphorus intake and renal impairment, which result in phosphate retention, predispose to greater metastatic calcification.

The toxic symptoms of viosterol overdosage in man have been best described by Reed (35), who studied the effects of tremendous doses in patients with hay fever and related conditions. Of the 300 patients studied, 43 developed one or more of the following symptoms: urinary frequency, anorexia, nausea, vomiting, diarrhea, loss of weight, muscle weakness, muscular incoordination and disturbed equilibrium. Reed feels, however, that "there need be little apprehension about the administration of amounts up to 150,000 international units daily for indefinite periods" and that doses equivalent to those given dogs to produce medial sclerosis have never been given to man. In the elderly patients he studied, there did not appear to be any evidence of increased arteriosclerosis or hypertension. Crimm (24) was unable to demonstrate any evidence of decalcification, such as is seen in experimental animals, in patients with hypercalcemia of long duration.

Many of the studies on hypervitaminosis are open to question since the vitamin products used (chiefly Vigantol) have been shown to contain toxisterol (13). That vitamin D itself, however, is toxic when given in large enough amounts, is borne out by the fact that the pure crystalline vitamin D<sub>2</sub> (calciferol) has been shown to be toxic for experimental animals (17) and man (20).

The two subjects of this report exhibited none of the usual symptoms of vitamin D toxicity during the administration of calciferol. There was no direct evidence of metastatic calcification and, since the serum calcium and serum phosphate were kept within normal limits, there was no rea-

son to suspect that it occurred. The mild degree of decalcification of the bones in Case 1 was probably related to the long standing state of hyperthyroidism, and the diminished renal function in Case 2 can probably be attributed to the presence of pyelitis.

*Advantages of calciferol over parathormone in chronic tetany.*—The transient effect, the necessity for repeated subcutaneous injections, the tendency toward a negative calcium balance, and the possible deleterious effects on the remaining parathyroid tissue (12) make the prolonged use of parathormone in chronic tetany objectionable. Calciferol, on the other hand, has a prolonged effect, may be given orally, tends to increase calcium retention, and if Shelling's theory (12) is correct, may lead to a hypertrophy of the remaining parathyroid tissue. The objection raised by Shelling and Goodman (11, 12) that vitamin D raises the serum phosphate in addition to the calcium and is, therefore, not effective, has been shown to be invalid. The necessity for frequent determinations of serum calcium and phosphate, to control dosage, is equally true of parathormone and calciferol. The danger of toxic effects did not appear to be any greater with calciferol than with parathormone administration.

Since calciferol is relatively slow in its action, there appears to be a place for parathormone therapy where a rapid rise in serum calcium is desired. Thereafter, the use of calciferol would appear to be advantageous. Calciferol is not advocated as a universal therapeutic agent in tetany but is recommended in those cases of chronic parathyroid tetany which do not respond to high calcium-low phosphorus diets, and in which satisfactory parathyroid gland transplants are not possible.

#### SUMMARY AND CONCLUSIONS

1. Two cases of chronic parathyroid tetany were presented which failed to respond to the usual therapeutic agents used in such cases.
2. Calciferol (crystalline vitamin D<sub>2</sub>) satisfactorily controlled the tetany and maintained the serum calcium and phosphate at normal levels in both patients for periods of four and six months respectively.
3. The action of calciferol appeared to be dependent upon an adequate calcium intake.

4. No toxic manifestations were demonstrable with the doses of calciferol used.

5. Calciferol is recommended as a valuable therapeutic agent in cases of chronic parathyroid tetany which do not respond to high calcium-low phosphorus diets and in whom satisfactory transplants of parathyroid gland are not possible.

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