ANNALS OF
INTERNAL MEDICINE

VOLUME 10 JANUARY, 1937 NUMBER 7

FURTHER STUDIES ON INTOXICATION WITH VITAMIN D * †

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WITH the extensive application of massive doses of vitamin D as a therapeutic agent in various clinical conditions [1, 2, 3, 4, 5, 6, 7] numerous criticisms have arisen which may be summarized as follows:

1. Hypervitaminosis D may produce symptoms of hyperparathyroidism.
2. The therapeutic use of vitamin D is rational only in conditions of known deficiency.
3. Animals experimentally treated with vitamin D concentrates have shown extensive calcium deposits in various tissues, and other pathological changes have been found. There is, thus, danger of permanent injury to human subjects.

It is not the purpose of this paper to discuss the therapeutic value of concentrated vitamin D in any clinical condition. Only by more extensive clinical investigation can its therapeutic value be established finally.

That vitamin D in massive doses may be toxic to any individual, animal or human, has been recognized in all stages of this series of investigations which was begun early in 1929, and its administration to human subjects has been governed accordingly. It is the purpose of this paper to present evidence bearing on these questions. The first of these questions has been discussed very thoroughly by Shelling,[8] who concluded that the preponderance of evidence is against the view that the activity of vitamin D is dependent upon the functional integrity of the parathyroids and in favor of the existence of an antagonism between the two. The second criticism is purely speculative. If this idea held true very few therapeutic procedures now in use could be justified.

* Received for publication September 26, 1936.
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† This investigation at various stages has been supported in part by grants from Mead Johnson and Company; the Graduate School Research Fund, University of Illinois; the American Academy of Arts and Sciences; the Wisconsin Alumni Research Foundation; the Committee on Therapeutics of the American Medical Association; and the Phi Rho Sigma Medical Fraternity.

In considering the nature of the action of massive doses of vitamin D it is assumed that the action is very different from the physiological effects of small doses. It is so different, in fact, that the concentrated material may be considered tentatively as a different substance. At the same time there is some legitimate doubt as to the justification for this attitude.

TABLE I

Observations on Dogs Receiving Vitamin D

No.	1000 units/ K/day	Days	Kidney Mg Ca/ 100 gm. Dry Tissue	Max. Blood Ca	Microscopic		Wt. Loss Per Cent	Other Symptoms of Toxicity	
					Cell. Degen.	Ca Stain			
1	500	8	671	19.90	5	5	40	Severe	Died in coma
2	500	9	212	21.60	5	5	32	Severe	Died in coma
3	500	9	—	—	—	—	28	Severe	Died in coma
4	500	11	—	—	—	—	38	Severe	Died in coma
5	200	18	—	—	—	—	44	Severe	Died in coma
6	200	10	—	—	—	—	34	Severe	Died in coma
7	130	7	598	16.36	4	3	30	Severe	Died in coma
8	125	12	52	23.30	1	0	23	Mild	Died of distemper
9	100	30	110	16.30	0	0	7	Mild	Died of distemper
10	100	6	676	14.98	3	1	19	Severe	Died of distemper
11	100	20	—	—	—	—	23	Severe	Died in coma
12	100	13	—	—	—	—	17	Moderate	Found dead
13	60	7	340	23.36	?	0	24	Severe	Died of distemper
14	60	13	540	23.29	1	1	20	Severe	Died in coma
15	60	8	685	18.16	—	—	9	Severe	Found dead
16	60	7	800	19.56	4	2	+17	Mild	Found dead
17	60	12	865	24.50	—	—	0	Severe	Found dead
18	60	13	1221	31.06	5	5	37	Severe	Died in coma
19	60	20	—	—	—	—	42	Severe	Died in coma
20	60	10	—	—	—	—	30	Severe	Died in coma
21	50	17	3464	27.00	5+	5+	15	Severe	Died in coma
22	50	43	119	18.90	1	0	21	Moderate	Found dead
23	50	35	—	—	—	—	10	Moderate	Allowed to recover
24	50	12	—	—	—	—	28	Severe	Died in coma
25	50	24	—	—	—	—	19	Severe	Died in coma
26	48	35	47	21.50	0	0	6	Mild	Fair condition when killed
27	38	10	2200	16.02	5	5	18	Severe	Died in coma
28	37	47	115	23.16	?	0	48	Mild	Good condition when killed except emaciate
29	35	73	1148	19.30	5	5	60	Severe	Died in coma
30	35	33	693	15.60	5	5	—	Severe	Poor condition when killed
31	35	23	597	16.47	5	5	35	Severe	Poor condition when killed
32	35	8	407	22.74	1	?	17	Mild	Died of distemper
33	35	60	—	—	—	—	26	Mild	Fair condition when killed
34	35	54	—	—	—	—	40	Moderate	Found dead
35	35	30	—	—	—	—	29	Severe	Found dead
36	35	26	—	—	—	—	42	Severe	Found dead
37	25	33	1214	19.38	4	4	13	Moderate	Good condition when killed
38	25	62	131	15.80	1	1	15	Mild	Good condition when killed

TABLE I—*Continued*

No.	1000 units/ K/day	Days	Kidney Mg Ca/ 100 gm. Dry Tissue	Max. Blood Ca	Microscopic		Wt. Loss Per Cent	Other Symptoms of Toxicity	
					Cell. Degen.	Ca Stain			
39	25	70	—	—	—	—	18	?	Good condition when killed
40	25	79	—	—	—	—	8	Moderate	Found dead
41	25	50	—	—	—	—	22	Severe	Died in coma
42	25	56	—	—	—	—	5	Severe	Died in coma
43	25	16	—	—	—	—	20	Severe	Died of distemper
44	20	38	228	13.26	0	0	0	0	Good condition when killed
45	20	41	186	12.90	0	0	3	0	Good condition when killed
46	20	67	174	11.78	0	0	5	Mild	Good condition when killed
47	20	83	203	12.02	0	0	0	0	Good condition when killed
48	20	120	93	11.00	0	0	+7	0	Good condition when killed
49	20	60	—	—	—	—	0	Mild	Died of distemper
50	20	93	—	—	—	—	0	0	Good condition when killed
51	20	80	—	—	—	—	7	?	Allowed to recover
52	20	55	—	—	—	—	0	0	Good condition when killed
53	20	40	—	—	—	—	0	0	Good condition when killed
54	15	62	212	16.85	?	0	5	Slight	Died from distemper
55	15	136	147	11.83	0	0	0	Slight	Good condition when killed
56	15	70	86	12.15	0	0	0	0	Good condition when killed
57	15	153	262	10.80	0	0	+16	0	Good condition when killed
58	15	56	248	11.50	0	0	0	0	Good condition when killed
59	15	61	—	—	—	—	+12	0	Good condition when killed
60	15	61	—	—	—	—	0	0	Good condition when killed
61	15	67	—	—	—	—	0	0	Good condition when killed
62	15	90	—	—	—	—	+10	0	Good condition when killed
63	15	47	—	—	—	—	0	0	Good condition when killed
64	15	30	—	—	—	—	5	0	Good condition when killed

Early experience with impure preparations of vitamin D, particularly abroad, has led to a great deal of misunderstanding and fear of overdosage on the part of those who have had little acquaintance with the fundamental mechanisms involved. This point has been adequately discussed by Bills.[9] Suffice it to say that most of this earlier work must be disregarded when considering the effects produced by the highly purified preparations now available.

Experiments on Toxicity of Vitamin D for Dogs

The effects of massive doses of vitamin D must be judged on the basis of the dose per unit body weight and not on the absolute size of the dose. When considered in this light the order of increasing susceptibility appears to run as follows: rat, dog, human, rabbit, with little difference between the dog and human, while the rat is very much more resistant, and the rabbit much less so.

In the experiments on dogs, vitamin D was administered in the form of a solution of activated ergosterol in corn oil * (1,000,000 units per gm.) or of calciferol † dissolved in corn oil. Most of the administration was done orally. A few animals received intravenous injections in which form the material is slightly more effective. The results of experiments on 64 adult healthy dogs are shown in table 1. The daily dose ranged from 15,000 to 500,000 units per kilogram of body weight as shown in the first column. An effort was made to adjust the dose to decreasing body weight so that the ratio between the dose and the weight of metabolising tissue remained fairly constant.

The figures in the second column represent the actual number of days of administration of the vitamin D and, therefore, the number of days the animals *survived the treatment*. Usually those that did not die were killed on the day following the last dose, others within two to three days. With amounts greater than 50,000 units daily the average survival period was 12 days; with amounts between 20,000 and 50,000, 39 days; and with 20,000 units or less, 68 days.

At death, tissues were taken for chemical analysis and for microscopic examination. In an earlier report [10] on analyses of 13 different tissues in a series of dogs, it was shown that the kidney is the most vulnerable of any tissue to the calcifying action of vitamin D. In order to conserve space, only the figures for the calcium content of the kidney are included. In all other tissues the findings were very inconstant. Analyses of tissues of normal dogs have shown a calcium content in the kidneys ranging from 29 to 301 mg. per 100 gm. of dried tissue with a mean of 85 mg. The calcium content in the kidneys of 33 of the 64 dogs is shown in the third column of table 1.

With a daily dose above 50,000 units per kg. the average content of calcium in the kidney was 564 mg. per 100 gm. of dried tissue; between 20,000 and 50,000, 921 mg.; and with 20,000 units or less, 183 mg. The lower average in the first group may possibly be related to the shorter period of survival. The average in the third group is obviously lower because the dose was not great enough to cause as much deposition.

In the fourth column the figures represent the maximum concentration of

* Supplied mainly by Mead Johnson and Company, also by Abbott Laboratories, Parke Davis and Company, and Winthrop Chemical Company.

† Supplied by Mead Johnson and Company, Winthrop Chemical Company, and Glaxo Laboratories.

plasma calcium found at any time. The level was not constant in any group. Very high levels were seldom constantly maintained. In figure 1 is shown the distribution of the figures observed in dogs in relation to the daily dose of vitamin D. It is obvious that there is little correlation between the two factors. With daily doses greater than 20,000 units per kg. every animal at some time showed very high concentrations, but the level fluctuated greatly in each animal. With lower doses the figures are within the normal range for heparinized plasma.

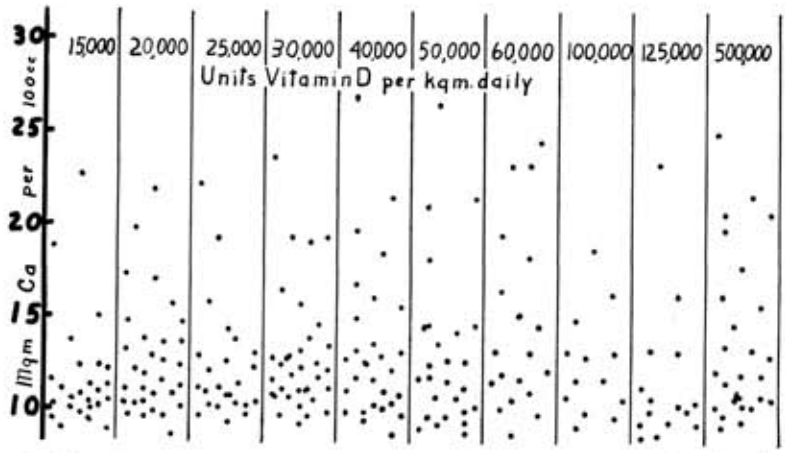

FIG. 1. The blood calcium in 43 normal dogs under treatment with vitamin D. In each column are shown the total number of determinations made on all in each dosage group. Successive determinations on the same dog appear on the same ordinate.

For purposes of simplicity of recording and comparing the microscopic findings, a scale of 1 to 5 arbitrary units was used, although this method is open to some objection. The only striking microscopic findings were degeneration of individual cells and the presence of deeply stained areas of calcium deposition. In recording the degree of cell injury, a unit of 1 indicates the presence of only occasional degenerated cells, two or three in a single field. A unit of 5 indicates a stage in which considerable masses of contiguous cells had undergone degeneration. However, this stage always occurred in conjunction with a comparable stage of calcium deposition. It will be seen that the relationship between the degrees of cell destruction, calcium deposition and calcium content of the tissue varies considerably, but that in general those tissues having the higher calcium content by analysis showed the more extensive injury. These injuries appeared first and were most numerous in the collecting tubules but later were extended quite generally throughout the organ. In only one animal were calculi found in the tubules (No. 21, table 1).

It appears that cellular injury occurs first and that calcium deposition then takes place at the sites of these injuries. In four animals (Nos. 7, 18, 27, 31) showing extensive damage to the kidney, there was no evidence of

cellular injury nor of excessive calcium deposition in any other tissue examined.

From evidence obtained on 12 other animals not included in the table, it appears that considerable loss of weight may occur before there is any evidence of injury to cells, but this was not invariably the case.

Our observations do not confirm those of Appelrot [11] to the effect that hypervitaminosis D produces medial thickening in arteries. In only four of the 64 dogs examined, i.e., numbers 18, 21, 27 and 29, was this observed. In each case there was some medial thickening in the aorta and occasionally in smaller arteries.

Loss of weight was marked in 36 out of the 43 dogs receiving more than 20,000 units per kg. per day. One retained constant weight, one gained 17 per cent. As previously suggested,[12] the early weight loss appears to be due mainly to impoverishment of fat depots. When dog No. 28 was examined at autopsy it was almost impossible to find any macroscopic fat deposits. This dog lost 48 per cent of the original weight, yet showed only mild objective symptoms of toxicity and was lively and active at the termination of the experiment. There was practically no microscopic evidence of cell injury. The plasma calcium was maintained at a higher average level over the period of the experiment than in any other animal in our experience.

On the other hand, dog No. 21 lost only 15 per cent of the initial weight, although the kidney content of calcium was higher than in any other animal. These two animals serve to show clearly that weight loss is not an inevitable accompaniment of fatal intoxication in dogs.

One of the characteristic features of fatal hypervitaminosis D is the premortal coma. This condition is usually, though not always, preceded by partial paralysis, slow, shallow respiration, fine, thready, rapid pulse, salivation, and often by psychic changes of such a nature that a previously tame, friendly dog may become unmanageable and even vicious. Very often the symptoms resemble those following an injection of oil of wormwood. This condition may persist for several days but usually appears from two to three hours before death. It is probable that all of the dogs labelled " found dead " passed through this stage during the night, but the actual train of symptoms could not be observed. None of the animals that were killed were in this stage.

The objective symptoms of toxicity were much the same as those previously described for the human,[4] such as weakness and lassitude, anorexia, polydipsia, polyuria, psychic disturbances, diarrhea. Bloody feces were passed by 11 of the 64 dogs. In addition, petechial hemorrhages were found in the mucosa of the stomach and intestines at autopsy.

With eight exceptions all of the 43 dogs receiving more than 20,000 units per kg. per day died spontaneously. Nine of these died from distemper. Of the nine, three were in such a condition that early death in coma was predictable. Of the eight exceptions, one was allowed to recover. Of

the seven that were killed, two would probably have died. The other five would probably have recovered with cessation of the treatment.

Among the 20 dogs receiving 20,000 units or less per kg. there were no evidences of cell injury, insignificant weight loss, very little evidence of toxic symptoms, and with the exception of two dogs that died from distemper and one that was allowed to recover all were in good condition when killed.

Thus, it may be concluded that vitamin D up to 20,000 units per kg. per day for periods ranging up to 153 days is not seriously injurious to normal dogs. In greater amounts there is a wide range of susceptibility entirely unpredictable from any data at present available.

That the toxic effects may be characterized as true hypervitaminosis D is proved by the fact that in four instances (numbers 7, 17, 29, 34) the vitamin preparation administered was crystalline calciferol (40,000,000 units per gm.) in solution in corn oil. This preparation contained *no* toxic by-products and yet the results were quite comparable with those from the same dose of activated ergosterol which may contain some inert material but practically no toxisterol.

In another series of experiments the dogs were brought to a stage of extreme toxicity with vitamin D and the administration was then discontinued. The state of toxicity was manifested by loss of weight, anorexia, listlessness and paralysis, and, in six animals, prostration. After varying intervals, when there was objective evidence of complete recovery, the animals were killed and subjected to the same examination as in the other series. The results are shown in table 2. In the first column are shown the periods

TABLE II

No.	Days	Recovery Days	Units/K/Day	Kidney Ca	Max. Blood Ca	Microscopy		Wt. Loss Per Cent	
						Cell. Degen.	Ca Stain		
1	24	126	15,000	257	18.59	0	0	6	Good condition
2	15	9	20,000	48	19.89	0	0	13	Good condition
3	80	102	20,000	212	17.41	0	0	7	Good condition
4	10	48	25,000	323	22.13	0	0	30	Good condition
5	5	113	30,000	240	19.14	0	0	43	Good condition
6	5	107	35,000	242	19.43	0	0	30	Good condition
7	35	20	50,000	151	16.87	0	0	10	Good condition
8	18	115	50,000	272	14.62	0	0	29	Good condition
9	26	38	50,000	300	19.30	0	?	45	Fair condition. Still 15 per cent under weight
10	15	8	105,000	218	18.72	—	—	30	Fair condition. 10 per cent under weight

of administration of the vitamin, in the second the daily dose per kg., and in the third the recovery interval allowed. Actually in the dogs No. 4, 6, 7 and 8 complete recovery of weight was accomplished in 53, 86, 73 and 60 days respectively. Animals No. 9 and 10 were killed before weight

recovery was complete because both were definitely overweight when the experiments were begun.

Eight additional dogs were originally included in this series but all of these were in the terminal stages of toxicity described above when the treatment was discontinued, and all died within two to seven days. Six of these were already prostrate when administration was discontinued.

In all but one (dog No. 4) the kidney content of calcium was within the normal range, although all showed figures in the higher limits of the normal range except Nos. 2 and 7. The average weight loss approximated that in comparable dosage ranges in the first series.

The maximum concentrations of plasma calcium observed were all high. Microscopic examination of the tissues showed no definite evidence of calcium deposition and no cellular injury. In Nos. 2 and 5 there was some distortion of the collecting tubules in the kidney by fibrosis. No vascular lesions were found.

From these experiments it appears that dogs may recover from extreme stages of toxicity and that whatever tissue injury occurs may be reparable. In extremes the result may be fatal before repair can be effected.

In the experiments on animals reported by others, so far as the potency of the dose can be calculated, toxicity has occurred only with doses above 20,000 units per kg. per day. Since the relation of dosage to weight has not been stressed before, many other workers have failed to record data which would make it possible to calculate the dose in terms of units per kilogram.

In both of our series it is apparent that the total amount of vitamin administered is not the most important determinant of the degree of toxicity since large doses have been tolerated well over long periods while smaller doses have produced drastic effects in a few days. Nor is the magnitude of the daily dose the sole factor. In general both dogs and human subjects appeared to be less sensitive during winter months.

TABLE III

Dog No.	1	2
Units/kg./day	60,000	30,000
Initial plasma Ca	11.60	10.89
5th day	12.03	14.62
7th day	12.00	13.90
14th day	14.00	12.44
15th day	11.30	11.79
16th day	12.57	11.12
21st day	12.10	12.15
22nd day	11.34	—
23rd day	12.00	13.25
24th day	dead	—
26th day		12.24
30th day		9.70
31st day		13.00
32nd day		11.93
33rd day		dead

It has been emphasized many times that the diet is a very important factor in conditioning toxicity. All of these animals were kept on the stock kennel diet throughout and no variations were introduced at any time.

It is also apparent that the concentration of plasma calcium is not closely correlated with toxicity. Many investigators have been inclined to use the terms "hypercalcemia" and "toxicity" interchangeably. Many experiments have been done which clearly disprove a causal relation between these conditions but the two experiments reported in table 3 will serve to illustrate the point. Both of the animals showed some hypercalcemia, but it was by no means pronounced. Number 1 received twice the dose of number 2, but except for the earlier death there was no striking difference. When one contrasts these figures with the high figures for some of the animals that survived as in tables 1 and 2, it is a fair assumption that hypercalcemia per se is not the cause of toxicity.

Observations on Human Subjects

The enormous absolute doses of vitamin D that have been administered to human subjects have naturally aroused some question. If, however, one bears in mind that human and canine susceptibility seem closely approximated, and if one gives due consideration to the weight/dosage relationship, it appears that few of the human subjects have ever received amounts comparable to the highest doses tolerated by the dogs of this series.

Table IV

	Male			Female		
	Total No.	No. Toxic	Per Cent	Total No.	No. Toxic	Per Cent
Postoperative tetany	2	0	0	15	4	26.4
Hay fever and asthma	178	13	7.3	322	24	7.4
Arthritis	43	5	11.6	107	11	9.4
Miscellaneous	12	1	8.3	23	3	13
Normal subjects	63	1	1.5	8	1	12.5
	298	20	6.7	475	43	9

Total subjects.....773
Number toxic..... 63
Per cent toxic..... 8

Table 4 shows the status of 773 human subjects who have received amounts of vitamin D above 100,000 units daily. The doses *routinely* given ranged upward from 200,000 units total daily dose for periods ranging from seven days to five years. With such a dose a 50 kilo subject would receive only 4,000 units per kg. per day. With 300,000 units a 60 kg. subject would receive 5,000 units per kg. per day. This table, of course, does not take into account the *varying* dosages, so that one cannot draw conclusions as to comparative susceptibility in the various groups of subjects. However, it ap-

pears, from other statistics too voluminous to include here, that the order of decreasing susceptibility among the different groups of patients is: arthritis, normal subjects, hay fever alone, hay fever with asthma, tetany.

TABLE V

Units/kg./day	No.	No. Toxic at any Stage	Per Cent Toxic
1500–3000	5	5	100
3000–5000	555	25	4.5
6000–7000	123	18	14.6
8000–15,000	70	11	15.7
15,000–25,000	16	3	18.8
25,000–35,000	4	1	25
	773	63	8+

In table 5 the incidence of toxicity at each range of dosage is shown. This analysis does not take into account the duration of administration since, as was indicated by the experiments on dogs, the total amount does not seem to be the most important factor. Nor does it take into account the effect of simultaneous administration of yeast as a protective measure which was done with many human subjects. This procedure has already been discussed rather fully.[4, 5] The first five subjects may be disregarded since they became nauseated from corn oil as readily as from viosterol, so that they do not represent true hypervitaminosis D, but rather some kind of sensitivity not related to the vitamin. It is probable that some of those subjects included in the toxic groups at higher dosage were of this type. The shortest period of administration that produced intoxication in the group on 3,000 to 5,000 units per kg. per day, was 87 days. Since the condition in this instance developed very suddenly and without any weight loss, it is possible that some unrecognized disturbance rendered the subject temporarily more susceptible. On discontinuance of administration of vitamin D prompt recovery occurred, and four days later the treatment was resumed and continued four months without further disturbance.

In the group on 6,000 to 7,000 units per kg. per day the shortest period for development of toxicity was 60 days. In this instance there was a loss of four pounds in two days. The condition was abated sufficiently to resume only after eight days without treatment. A second mild intoxication occurred three months later.

In the last two groups the high doses were not continued beyond 10 days except in one case, regardless of whether intoxication occurred. In this case one of the authors, a normal subject, took 35,000 units per kg. per day (3,000,000 units total daily) for 15 days without any evidence of disturbance of any kind.

Vrtiak and Lang [7] have recently reported 100 per cent incidence of toxicity in a series of 22 human subjects to whom massive doses of vitamin D

were administered. The discrepancy between this high incidence and the relatively low incidence in our series is difficult to explain at present.

The symptoms of hypervitaminosis D in human subjects were described fully in an earlier paper.[4] It remains now to correlate these findings with the experimental results on animals. Tentatively we suggest that the course of events is as follows: First, cellular degeneration occurs, more commonly in the kidney. Concurrently there may be loss of weight and other objective symptoms. If weight loss occurs before other symptoms it is probably due solely or mainly to increased fat catabolism. Second, deposition of calcium occurs at the sites of cell injury; apparently this does not occur except as a secondary result of such injury. Third, up to advanced stages of toxicity these processes may be reparable in dogs if the vitamin D administration is discontinued.

From the results of previously reported work [10, 12] it appears that the calcium removed from the tissues during recovery is excreted in the urine. At least, repair is not complete until the urine calcium excretion becomes normal.

The increased excretion of calcium that usually takes place [12, 13] under massive administration of vitamin D in both human subjects and dogs is not, however, due solely to removal of the microscopic deposits in the soft tissues, because the increase in the urine begins before there is any microscopic or chemical evidence of excessive deposition in soft tissues. The source of this initial increase in the urine has not yet been determined, but from Shelling's discussion it probably comes from the trabeculae of the bones. Generally the average level of blood calcium is decreased after the excretion is increased.

We have made no examination of blood pressure in dogs, but a large number of the human subjects were examined at frequent intervals over long periods. Since there have been no significant changes the data are omitted. In most instances there seems to be some tendency to a slight decrease in the general level. This, of course, does not eliminate the possibility of medial proliferation in the arterioles.

Our human subjects ranged in age from 17 to 76 years. Older subjects were generally less readily intoxicated but recovered less readily when intoxication did occur, and seemed to be somewhat more sensitive thereafter.

There are on record only two instances of death in human subjects, certainly due to hypervitaminosis D, since the more highly purified preparations became available. One of these, recently reported by Thatcher,[14] was probably a case of idiosyncrasy to vitamin D. It is difficult to determine from the report the unit dosage. However, it *is* clear that the administration was continued after intoxication was markedly developed.

We wish to stress that administration of vitamin D should be discontinued at once when the symptoms of intoxication appear. Neither animal nor human subjects in our experience have ever recovered from the toxic condition while administration continued.

The other case has not yet been reported in detail in the literature, but the reports of the coroner and the attending physician [15] reveal the following facts. A physician, aged 74, weight 290 pounds, undertook self medication with a concentrated solution of activated ergosterol. Owing to an *error* in calculation of the dosage he received 2,300,000 units daily for 18 days or approximately 18,000 units per kg. per day, a dose 10 times that intended. Since he was very obese the dose per kilogram of actively metabolizing tissue was much greater. The symptoms described were quite typical of hypervitaminosis D, with hypercalcemia, so that there is no doubt that in this case the treatment was the immediate cause of death. However, the presence of generalized arteriosclerosis suggests that this was a fundamental handicap to his recovery after discontinuing the treatment.

The administration of similar or larger amounts in our series without serious disturbance should not be interpreted to mean that such treatment can be undertaken without caution. In fact, our experience indicates clearly that administration of massive doses of vitamin D should not be undertaken for any cause except under the careful supervision of a physician who can and will carefully check the patient's condition at frequent intervals and who will see to it that the treatment is discontinued promptly on the appearance of the first signs suggestive of toxicity.

It is probable that any suggestion of kidney dysfunction should constitute an absolute contraindication. Until further information is available arteriosclerosis also should probably be considered a contraindication. Consequently, this form of treatment should be administered to older subjects only with extreme caution.

Nevertheless, if these precautions are observed, massive doses of vitamin D may be utilized therapeutically as safely as many other agents administered daily. That its misuse has resulted in death should not prejudice its controlled use under circumstances of possible value.

In view of the extensive experience in administration of vitamin D to human subjects with a relatively low incidence of toxicity, and the correlation of the results of animal experiments with the observations on human subjects, we believe that the burden of proof now rests on those who maintain the undesirability of the use of this form of therapy. Its actual practical value in particular clinical conditions will, of course, be determined only by more extensive clinical experience.

It must be admitted that the mechanism of toxicity is still unexplained. Our findings do not agree entirely with those of Ham and Lewis.[16] It is possible that the dose of approximately 600,000 per kg. per day or more, which these observers administered to rats, was a factor in producing a different type of lesion. Up to the present time conceptions of the physiology of vitamin D have perhaps been too circumscribed because of its striking effect on calcium metabolism. That the thyroid plays an important part in the action of vitamin D is indicated by the results of another investigation.[17]

Also, it appears that the pathologic effects are greatly accentuated in a hypothyroid state. This *may* be an important factor in the variability in sensitivity to intoxication.

The results obtained by Gelfan [18] on isolated frog muscle suggest that vitamin D exercises a catalytic effect in peripheral tissues. If this should be confirmed, it might serve as a forward step in explaining the injury to isolated cells in peripheral tissues. It is conceivable that the metabolism of individual cells might be accentuated to such a point as to result in the disintegration of the cells themselves. We have not been able to recognize the cellular changes preliminary to disintegration so that we can offer no explanation of the actual nature of this process.

Summary and Conclusions

1. Observations on 64 dogs and 773 human subjects receiving massive doses of vitamin D have been made and data recorded as to dose per unit of body weight, and on the nature of the process of intoxication.

2. Both human subjects and dogs generally survive the administration of 20,000 units per kilogram per day for indefinite periods without intoxication.

3. Hypervitaminosis D first produces cell injury followed by calcium deposition. This process is reversible and reparable if administration is discontinued promptly.

4. Intoxication for short periods does not result in any permanent injury that can be recognized by the methods employed in this investigation.

Addendum. After this manuscript was written there came to our attention a very comprehensive study by Cowdry and Scott [19] on normal monkeys under treatment with vitamin D in which it was suggested that pathological changes may occur in tissues without clinical symptoms. However it was also suggested that there might be a species peculiarity.

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