



VITAMIN D IN MASSIVE DOSES AS AN ADJUVANT TO THE SULFONES IN THE TREATMENT OF TUBERCULOID LEPROSY¹

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Vitamin D in massive doses is often used in certain skin diseases such as lupus vulgaris, pemphigus, sclerodermia and psoriasis, and it has been advocated in the treatment of leprosy. Some authors have found it advantageous to use, for injections, mixtures of chaulmoogra and shark oils because of the richness of the latter in vitamin.

Capurro and Guillot, of Argentina, presented at the Havana Congress a brief report on the treatment of tuberculoid reaction with vitamin D₂ in high dosage (1). As compared with the results obtained with similar treatment without the vitamin, their observations in thirteen cases led them to believe that the use of that substance shortened and favorably modified the clinical characters of that condition. They stated that, with that medication, the plaques lose their characteristic form and color and show a parallel lessening of infiltration and epithelial desquamation, all indicative of improvement of those lesions, and that at the same time the symptoms of neuritis improve without the use of any special antineuralgic or antineuritic drugs.

Encouraged by Dr. Capurro, I undertook to try this treatment in our patients, with a view to modifying the method heretofore used in order if possible to accelerate the rate of improvement. Although ignorant of the doses, daily and total, which he had used in oral medication, I first experimented with massive doses given in that way to four patients with reactional and four with quiescent (*tórpida*) tuberculoid leprosy. In the quiescent cases no improvement could be seen. In the reactional ones there was epidermal desquamation of the plaques and diminution of their infiltration, but those favorable changes did not continue to progress with further administration of this drug. The limited benefit obtained with it alone led to its trial as an adjuvant in the previously established sulfone (promin) treatment.

¹ Translation from the Spanish manuscript, approved by the author.

Although there are conflicting opinions among different workers regarding the efficacy of the sulfones in tuberculoid leprosy, it is certain that in our cases of that type treated with them exclusively they have not been without effect. Among these there were three of the reactional form and two quiescent ones whose lesions showed no benefit for more than six months, but which later on started to show noteworthy improvement and finally disappeared completely. In two other cases the disappearance of lesions was limited to certain regions of the body; in still another two there were only alterations as to size and elevation of the lesions. On the other hand, in some cases the changes were insignificant despite promin treatment given regularly for months.

Such cases, which showed various degrees of resistance to the sulfone treatment, were selected for this experimental study of a combined sulfone-vitamin D treatment of tuberculoid leprosy. This report presents the data of the three reactional and five quiescent tuberculoid cases which have been so treated for the longest period of time, though in our evaluation of this method consideration has also been given to the results obtained in five new cases treated for only two months. This study is to be considered as a preliminary one, made in an attempt to determine the efficacy of this method of treatment and not with the expectation of obtaining definite therapeutic results in all of the cases.

EXPERIMENTAL TREATMENT

In this experiment the vitamin D was given by the subcutaneous route, rather than by mouth, concurrently with a sulfone (promin). The eight patients chosen for the treatment were organically sound children, adolescents or young adults under 25 years of age, this choice being made to avoid the production of arteriosclerosis as a result of the massive doses of the vitamin to be given, which were much larger than we have administered orally.

An attempt was made to establish a dose which would be effective without provoking symptoms of hypervitaminosis which might cause interruption of the treatment. Although tolerance for this vitamin varies with individual susceptibility, it was borne in mind that it takes a daily dose of approximately 20,000 International Units per kilogram of body weight to produce intoxication. The dose selected was one ampule containing

500,000 I. U. of synthetically pure vitamin, a derivative of irradiated ergosterol, in 1 cc. of refined vegetable oil.²

The injections were made in series, with intervening rest periods, the first six cases of the following report according to one schedule and the other two cases according to another one which was essentially the reverse of the former. These schedules were as follows:

Cases 1 to 6.—First series, 3 ampules at 4-day intervals; one week of rest. Second series, the same. Third series, 6 ampules at 2-day intervals; 1 week rest. Fourth series, 6 ampules given one per day; 10 days rest. Final series, increased dose (750,000 I. U.) every 6 days, the number of doses varying in different cases. (In Case 3 the second series was omitted.)

Cases 7 and 8.—First series, 5 ampules given one per day; 4 days rest. Second series, 5 ampules at 2-day intervals; 4 days rest. Third series, 3 ampules at 4-day intervals; 10 days rest. Final series, as in the first group.

In all cases promin was administered in the usual way, and entirely independently of the vitamin series. In consequence the rest periods of the latter courses might or might not coincide with the regular interruptions in the course of the sulfone treatment.

CASE REPORTS

CASE 1.—A boy, 13 years old, mestizo, with reactional tuberculoid leprosy, who after 13 months of exclusive treatment with promin still showed several plaques on the cheeks and nose, one of them 10 cm. in diameter, and others in the posterior region of the forearm.

Even during the first series of injections the plaques began to decrease in thickness, and at the end of the second series those on the cheeks and nose had become fragmentated, broken up into secondary plaques. During the third series some of the secondary plaques (earlobe, dorsum of the nose, and forehead) became less noticeable, while the zones of healthy skin between the secondary plaques on the cheeks became wider; but at the end of this series some of these lesions had increased in prominence, while those of the forearm started to show desquamation and decreased in thickness. At this stage the erythrocyte sedimentation rate was 20 mm., and the serum calcium level, which had been 8.5 mgm. per cent before starting the vitamin treatment, had increased to 12.0 mgm. per cent (examinations made at the Juan Pablo Pina Hospital).

During the fourth series the lesions continued to improve, and some of the secondary plaques disappeared. The sedimentation rate remained the same,³ while the serum calcium had risen further, to 15.0 mgm. per

² The product used, known commercially as "decolake," was supplied free of charge by the Lakeside Laboratories for this study. Unless otherwise stated subsequent reference to "doses" or "ampules" refer to this unit of 500,000 I. U.

³ The same statement holds true for all the other cases when re-examined at this stage, but it will not be repeated in other reports.

cent. After an interruption of 10 days, however, it had dropped to 10.8 mgm. per cent (examination by the Public Health Laboratory). For this reason 4 doses of 750,000 I. U. were given at 6-day intervals. By that time other lesions had disappeared, and those still persisting had further diminished.

During the period of 110 days this patient received a total of 12,000,000 I. U. of the vitamin. The results of this combined treatment, which is being continued, can so far be considered satisfactory.

CASE 2.—A boy, 12 years old, mestizo, with reactional tuberculoid leprosy, who after 12 months of promin treatment still showed, on the external surface of the lower third of the left arm, a plaque 8 cm. in diameter, and another one extending from the lower third of the external surface of the right arm to the upper third of the forearm. The forearm was semi-flexed and subject occasionally to intense neuritic pain. Covering the external half of the left external supraciliary region there was also a plaque 2 cm. thick.

After the first injection there was slight desquamation on all of the plaques followed by lessening of the infiltration, and at the end of the second series all of the plaques had disappeared leaving achromic spots. The right forearm could now be bent and extended with ease, and the neuritic pains had become less severe. During the third series it was observed that in none of the spots could infiltration be felt by palpation, and the eyebrow lesion was now of a clear brownish color. The arm could be flexed and extended normally, and the neuritic pains had completely disappeared. At this time the sedimentation rate was 22 mm.; and the serum calcium increased from 8.5 to 11.5 mgm. per cent.

During the fourth series the lesions continued to improve at the same rate as before. After the 10-day interruption the serum calcium had dropped to 9.6 mgm. per cent. Four 750,000 I. U. doses were then given, with no ill effects, and all of the lesions became dark brown, approaching the normal color of the patient.

During the period of 110 days this patient received a total of 12,000,000 I. U. of vitamin D. The results obtained so far may be considered satisfactory.

CASE 3.—A girl, 11 years old, colored, with reactional tuberculoid leprosy, who had been treated with promin for 24 months but still showed, on the back and the external surfaces of the arms, large numbers of achromic spots from 2 to 5 cm. in diameter which remained after the disappearance of the plaques.

She was given only one of the usual first two series (i.e., those of 3 ampules at 4-day intervals), the second series in her case being the one comprising 6 ampules given at two-day intervals. Only a slight change of the color of the spots was observed at the completion of that series. The sedimentation rate was then 57 mm. and the serum calcium 10.0 mgm. per cent, up from 8.0.

After the series of 6 daily injections and the subsequent 10-day rest the serum calcium had dropped to 9.0 mgm. per cent. A series of five large doses was then given, after which the spots on the external surfaces of the arms and on the back disappeared.

During the period of 100 days this patient received a total of 11,250,000 I. U. and the results obtained were complete.

CASE 4.—A young adult, mestizo, with quiescent tuberculoid leprosy,

who after 13 months of promin treatment still showed large numbers of achromic spots from 2 to 5 cm. in diameter on the anterior and posterior regions of the chest, on the abdomen, and in the lumbar region.

After the second ampule of the first series of injections the spots on the chest and abdomen began to become less noticeable. The improvement increased during the rest period, and by the end of the second series all of those spots had disappeared. During the third series those on the lumbar region became less noticeable, and many of those in the upper part of that region disappeared. The sedimentation rate was then 4 mm. and the serum calcium had increased from 9.0 to 12.5 mgm. per cent.

After the fourth series and the subsequent rest, during which time the spots continued to lessen, the serum calcium had dropped to 11.1 mgm. per cent. Two large doses were then given with the usual 6-day interval, and after them the spots on the lower part of the lumbar region completely disappeared.

During the period of 90 days the patient received a total of 10,500,000 I. U., with complete results.

CASE 5.—A young adult, mestizo, with quiescent tuberculoid leprosy, who after 16 months of promin treatment still showed a large number of achromic spots from 1 to 5 cm. in diameter on the anterior and posterior regions of the chest and abdomen. In both lumbar regions there were rows of achromic spots running below the costal border down to the abdominal region on the same sides.

By the end of the first vitamin series all the spots had shown favorable changes as regards color, and this became more marked during the second series. During the third one many of the small spots on the chest and abdomen disappeared, while the large ones became dark brown. The sedimentation rate was then 9 mm., and the serum calcium had increased from 9.2 to 13.0 mgm. per cent.

By the end of the fourth series the remaining spots on the chest and on the abdomen had disappeared. Ten days later the serum calcium had dropped to 12.0 mgm. per cent, and four large doses were given on the usual schedule. By the time that was finished the large spots of the lumbar region had disappeared.

During the period of 120 days this patient received a total of 12,000,000 I. U., and the results obtained were complete.

CASE 6.—A young adult, mestizo, with quiescent tuberculoid leprosy, who after 14 months of promin treatment still showed on both sides of the lumbar region zones of achromic patches extending up to the abdominal region, running below the costal border almost to the umbilicus. In the scapular regions on both sides there were similar patches 10 cm. in diameter. A large one extended from the upper third of the posterior-external surface of the left arm to the deltoid region, and there was another of the same color in the right deltoid region.

After the completion of the first vitamin series the macules began to improve in color, and by the end of the third series they had turned brown. At this time the sedimentation rate was 45 mm., and the serum calcium had risen from 8.7 to 11.5 mgm. per cent.

The lesions continued to improve, at the same rate, during the fourth series. Ten days later the serum calcium had dropped to 11.1 mgm. per cent, and two large doses were then given. By that time the spots on the posterior-external region of the left arm, the right deltoid region, and

the right scapular region had disappeared, while the remaining spots had become dark brown, approaching the patient's normal color.

In the period of 90 days—after which time he escaped from the institution—this man had received a total of 10,500,000 I. U., with results which can be considered satisfactory.

CASE 7.—A girl, 13 years old, with quiescent tuberculoid leprosy, who after 14 months of promin treatment still showed one achromic area 25 cm. in diameter on the anterior surface of the right thigh, and another one 2 cm. in diameter on the left lateral region of the chin.

During the first series of injections of the reversed schedule used in this and the next case, the color of those areas turned to a clear brown. After the second series the sedimentation rate was 20 mm., and the serum calcium had risen from 8.3 to 8.5 mgm. per cent. The spots had become less noticeable by the end of the third series, and after the four final larger doses they had completely disappeared.

During the period of 90 days this patient received 9,500,000 I. U., with complete results.

CASE 8.—A boy, 14 years old, mestizo, with quiescent tuberculoid leprosy who, after 24 months of promin treatment, still showed a large number of achromic spots from 1 to 2 cm. in diameter, scattered over the cheeks and jaws.

During the first series these spots turned to a clear brown color, and there was slight desquamation which became more marked during the second series. The sedimentation rate at this time was 15 mm., and the serum calcium had increased from 8.8 to 13.4 mgm. per cent. After the third series only three spots remained, and they were hardly noticeable. They, too, had gone by the time the final (large-dose) series had been completed.

During the period of 100 days this patient received 9,500,000 I. U., with results which were complete.

In summary, Cases 3, 4, 5, 7 and 8 are regarded as having become totally improved under the combined treatment, and Cases 1, 2 and 6 are satisfactorily improved. Attention is called to Case 2, which is of special interest because of the clearing up of the neuritic pains and the complete restoration of mobility of the elbow joint.

DISCUSSION

In spite of the administration of massive doses of vitamin D in these cases, in no instance did any sign of hypervitaminosis appear. The serum calcium, which is usually low in this class of patients, became normal in all cases receiving approximately 5,000,000 I. U. of the vitamin. In those in which the level went beyond the maximum normal limit, 10 days of interruption of the injections was sufficient to restore it to the normal level. There is no indication of any relationship between the erythrocyte sedimentation rate and the calcemia.

The limited number of cases so far treated does not permit the establishing of a relation between the improvement or in-

crease of serum calcium and the objective improvement of the lesions, but it is worthy of note that the latter change began from the first administration of high doses of the vitamin, at which time the serum calcium had not yet evidenced any appreciable increase. This fact suggests that the improvement of the general condition of the patient, which occurred from the first dose of the vitamin, aided the promin to act with greater efficacy.

The rate at which the objective improvement of the lesions was produced was the same whether the doses were given daily or at longer intervals. This fact has led to the adoption of a schedule of injections in series of three given every four days with interruption of a week after each series, the interruptions preferably coinciding with those of the regular promin treatment. The usual dose is as used in this experimentation, 500,000 I. U., but in cases requiring larger amounts it is increased to 750,000 I. U. and the interval between doses is increased to 6 days. In these schedules the risk of sudden hypervitaminosis is reduced to a minimum.

In the period of about four months during which this method of combined treatment of tuberculoid leprosy has been used, the most frequently observed changes of the lesions which characterize this clinical type, both the plaques and the achromic spots, were desquamation paralleled by gradual lessening of the infiltration of the skin, and this process often ended in disappearance of the lesions. At other times the plaques broke up into secondary ones, which afterwards gradually disappeared one after another. In most cases the plaque, in disappearing, leaves in its place an achromic spot which, as with all other such spots under this combined treatment, usually improves in color until the normal color of the healthy skin of the patient is regained and the spot disappears. As yet, not all plaques and macular spots in our patients have disappeared, but, considering the slow and continuous progress of the regressive process of those which still remain, it is to be expected that they will do so ultimately.

From what has been observed in three more recent cases, which so far have given satisfactory results, the vitiligoid spots are particularly stubborn to this combined treatment. It has been started in our private clinic with two adult patients with tuberculoid leprosy who had not had any previous antileprosy treatment, and the results obtained in two months' time may also be considered satisfactory.

CONCLUSION

Massive doses of vitamin D, used according to the method employed by us, have proved harmless. On the other hand material benefit has been derived from their systematic use as an adjunct to the antileprosy treatment with sulfone (promin), not only in tuberculoid leprosy but also in neuritis and arthralgia which may occur during the course of the treatment with the sulfones. It has also been found to improve the general condition of certain patients of the lepromatous type, thus permitting the sulfones to act more effectively in such cases.

SUMMARY

Having learned of the use of vitamin D in the treatment of reactional tuberculoid leprosy by Capurro, I have made a trial of that substance as an adjuvant to sulfone (promin) therapy in tuberculoid leprosy. To avoid causing arteriosclerosis, only young patients were so treated. It was found that single doses of 500,000 I.U. administered subcutaneously every four days gave satisfactory results, although after a certain time a short series of 750,000 I.U. doses every six days was given. The total amounts administered varied from 9,000,000 to 12,000,000 I.U., in periods of from 90 to 120 days.

Of the three reactional cases, one was completely cleared of lesions, the other two partly so; in the latter the neuritic pains disappeared and mobility of joints was restored. Of the five nonreactional cases, four were completely cleared of their lesions, the other one partly so. No relation has been seen between the objective improvement of the lesions and changes in the blood calcium levels.

REFERENCE

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