THE SOLAR IRRADIATION OF CHILDREN WITH SPECIAL REFERENCE TO HYPERVITAMINOSIS D.

BY

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Various aspects of solar irradiation have been studied and many important discoveries have been made during the past few years. Probably the most significant was that made by Huldshinsky when he discovered the beneficial effect which followed exposure in infantile rickets. His work was quickly followed up by other workers and the subject investigated in considerable detail. Not only natural sunlight, but artificial sunlight was used during these investigations.

In 1921, Powers, Park, Shipley, McCollum and Simmonds¹ showed that by irradiating with a mercury quartz vapour lamp rats which had been fed on a rickets producing diet, the occurrence of rickets could be prevented. Hess and Unger² exposed rachitic children to natural sunlight, and found that the condition improved as evidenced by a deposition of lime salts at the wrist epiphyses. That the effect was general and not local was demonstrated by the fact that increased calcification occurred at both wrists although only one arm had been irradiated. Hess, Pappenheimer and Weinstock³ showed that the beneficial effect was due to the ultra-violet rays and was lost when plain glass was interposed. In the same paper they showed that protection against rickets is effected by rays of a wavelength of 313 $\mu\mu$ or less. Hess and Gutman⁴ showed that after exposure of rachitic children to natural sunlight the blood inorganic phosphorus, previously low, as is usual in rickets, increased to normal figures, the rickets subsiding at the same time. Kramer, Casparis and Howland⁵, using a mercury quartz vapour lamp raised the blood phosphorus of rachitic children from 2.7 to 6.0 milligrammes per 100 c.c. blood. Hess and Gutman⁴ noted that these results are comparable to those obtained by the administration of cod-liver oil in rickets.

For some time it was difficult to understand the mode of action of sunlight in its effect on rickets, and why the results should be similar to those obtained with cod-liver oil. Vitamin D was known to be the substance in cod-liver oil which cured rickets. But why should vitamin D result from irradiation of the skin? It was found that the exposure of lipoid-containing foods to ultra-violet rays caused them to assume anti-rachitic properties. A sterol was suspected as being the vehicle for the vitamin D and the evidence pointed towards cholesterol. This stage of the investigation has been summarised by Pfannensteil⁶: Hess succeeded in irradiating cholesterol. Rosenheim, and Pohl, showed by spectral absorption tests that cholesterol was not the pro-vitamin, but found that absorption bands in the spectrum pointed to ergosterol. Irradiation of this substance proved it to be the substance which provided the vitamin D.

Ergosterol is present as an impurity in cholesterol. It can normally be obtained from fungi, principally ergot, and from yeast. The cod probably gets it from the plankton of marine algae in which it is said to be present. This accounts for the presence of vitamin D in cod-liver oil. Hess and Lewis⁷ mention the beneficial effect in rickets which followed the administration of irradiated ergosterol. Hess⁸ and Hess and Weinstock⁹ showed that pieces of irradiated skin from infants and calves were anti-rachitic when eaten by rats. Hume, Lucas and Smith¹⁰ showed that vitamin D could be absorbed through the skin.

The chain of evidence appears to be complete. The beneficial effect of ultra-violet rays in rickets is due to the activation in the skin of ergosterol and the liberation and absorption of vitamin D.

Another aspect now presents itself in considering the effect of prolonged solar irradiation. Is it possible to activate vitamin D in injurious quantities? It is manifestly impossible to assay the quantities being liberated and absorbed except by their remote effects.

During experimental work with irradiated ergosterol it was found that the doses necessary to procure protection against and to cure rickets were minute. Rosenheim and Webster¹¹ found that 1/10,000 mgm. daily cured rickets in rats, and prevented the occurrence of rickets in rats fed on a rachitogenic diet. They suggest that the smallest protective dose is probably about 1/50,000 mgm. daily. This dosage is agreed upon by many workers on the subject. Harris and Moore¹² draw attention to the very small dosage and suggest the need for determining whether or not an injurious overdosage is likely to occur readily. They point out that in the cases of fat soluble vitamins instances of hypervitaminosis have been recorded. They found in experiments that young rats lost weight rapidly and died when receiving a synthetic diet containing 0.1 per cent. irradiated ergosterol. This is equivalent to 100,000 times the minimal protective dose. The animals suffered from anorexia, diarrhoea, inanition and bad condition of coat prior to death. These results occurred only when activated ergosterol was given and did not follow when the ergosterol was non-irradiated or had been inactivated by over-irradiation. Pfannenstiel¹⁶ states that overdosage of vitamin D led to death of rabbits, and that Kreitmar and Moll verified this. According to Rosenheim and Webster¹¹ a dose of 10,000 times the minimal effective dose produced no ill effects in rats.

Harris and Moore¹³ suggest that there are two threshold values for vitamin D, a minimum and a maximum. Below the minimum altered calcium and phosphorus metabolism results with deficient calcification. Above the maximum threshold signs of toxicity occur.

The question of the specificity of vitamin D in producing toxicity and the possibility that the toxicity might vary with the means of extraction has been raised. Dixon and Hoyle¹⁵ using irradiated ergosterol extracted in oil failed to produce toxicity. Harris and Moore¹³ have investigated this point and show that toxicity can be produced using both alcoholic and oily extracts of vitamin D. They realise that it is impossible to deny the existence of hypothetical toxic by-products, but suggest that the characteristic calcium-phosphorus disturbance points to the vitamin. They suggest that possibly Dixon and Hoyle gave doses which fell short of the threshold necessary to produce toxicity.

The signs of toxicity have been described by many workers, and there is general agreement that there is anorexia, loss of weight, diarrhoea and cachexia. In addition to these Harris and Moore¹³ include a rise in blood phosphorus, and urine saturated with calcium salts.

These writers record the post-mortem findings: emaciation, atrophy of the spleen and thymus, calculi in the bladder, and deposits of calcium salts in the kidneys, heart-muscle, pyloric end of the stomach, aorta and colon. Microscopic examination revealed extensive deposition of calcium salts in the tunica

media of the aorta, in the medulla, cortex and pelvis of the kidneys, and in the duodenum and small intestine. Hypercalcaemia and the deposition of calcium salts has been found to have occurred by all workers who produced signs of toxicity with irradiated ergosterol (Harris and Stewart¹⁴; Pfannensteil⁶; Smith and Elvove¹⁵; Policard, Paupert-Revault and Barral¹⁶; Taylor, Weld, Brannion and Kay¹⁷; Ashford¹⁸; Levaditi and Li Yuan Po¹⁹; Klein²⁰).

The symptoms and signs of toxicity all point to a gross disturbance of the calcium-phosphorus metabolism, but the huge doses apparently necessary in rats and rabbits would indicate that a large margin of safety exists. Taylor, Weld, Brannion and Kay¹⁷, however, show that in dogs this margin of safety is not so high, and suggest that human tolerance is about the same.

It has already been pointed out that the calcium-phosphorus metabolism in rickets is stimulated by the administration of a limited amount of sunlight. The administration of an unlimited quantity of sunlight may cause excessive stimulation. This is one of the points to be decided in this paper.

Present investigation.

In making these observations two series of children were used. With three exceptions they were between the ages of six and fifteen years. All were patients receiving treatment for various orthopaedic conditions at the Country Branch of the Royal National Orthopaedic Hospital. The conditions for which they were receiving treatment are stated in Table 1.

TABLE 1.

CLASSIFICATION OF DISEASES.				No. of Patients.
SERIES I.				
Tuberculous disease of spine	...	...	...	4
„ „ hip-joint	...	...	...	6
„ „ knee-joint	...	...	...	2
„ „ ankle	...	...	...	1
Deformities of spine—non-tuberculous	...	...	...	2
Diseases of hip-joints „ „	...	...	...	5
Osteomyelitis of metatarsal bone	...	...	...	1
Epiphysitis „ „	...	...	...	1
Poliomyelitis—deformity	...	...	...	1
Spastic paraplegia	...	...	...	1
Peroneal muscular atrophy	...	...	...	1
Infective arthritis in knee-joint	...	...	...	2
Bone abscess—tuberculous	...	...	...	1
SERIES II.				
Tuberculous disease of spine	...	...	...	6
„ „ hip-joint	...	...	...	6
„ „ knee-joint	...	...	...	2
„ „ ankle-joint	...	...	...	1
„ „ shoulder	...	...	...	1
„ abscess of tibia	...	...	...	1
Rickets—old-standing, healed	...	...	...	1
Anterior poliomyelitis	...	...	...	1
Malunited fracture	...	...	...	1

In Series I the children were new admissions, the majority being from congested districts in which they would not have obtained much pure sunshine.

A preliminary clinical examination was made on admission and specimens of blood, urine and faeces were collected. The children were then exposed to sunlight. These examinations were repeated at intervals of three or four weeks during the period of observation. The examinations were divided into two groups, clinical and biochemical. An enquiry was made into previous clinical history, with special regard to any condition which might cause abnormal findings. Cases in which there was a possibility of previously damaged renal function were rejected.

The clinical examination consisted of an investigation of the various systems. The condition for which the patient was admitted to the hospital was noted as such and was not described in detail. Special mention was made of the reaction to the sun as shown by the degree of pigmentation attained. The weight was noted and the blood pressure taken with a mercury manometer. The systolic pressure was taken as the measurement of the mercury in the tube at the moment of reappearance of the pulse sounds in the brachial artery at the elbow after the artery had been obliterated by a higher pressure. The diastolic pressure was taken as being the measurement at which soft sounds followed the appearance of short, sharp knocks. Bearing in mind the possibility of calcification of the arteries, a special clinical note was made as to the condition of the radial artery at the wrist as far as could be determined by digital pressure. Examination of the abdomen consisted only of palpation, special attention being given to the kidney areas in an effort to elicit tenderness such as might be caused by renal stone. No renal x-rays were made.

The technique for collection of specimens for biochemical examination was as follows :—

BLOOD. Twenty c.c. of blood were withdrawn from the median cephalic or basilic vein into a Record syringe. The analyses carried out on blood were estimations of non-protein nitrogen, urea, calcium, inorganic phosphates, cholesterol, haemoglobin, total solids, and alkali reserve.

URINE. A twenty-four hour specimen was collected, usually from 8 a.m. to 8 a.m. The analyses consisted of the volume output in 24 hours, specific gravity, reaction, estimation of urea, and examination of the centrifuged deposit. All specimens were also examined for abnormal constituents such as sugar, albumen, blood and acetone bodies.

FAECES. No aperient was given for at least forty-eight hours before the specimen was obtained. Specimens of faeces were examined for the presence of occult blood by the benzidine and guaiacum test. A microscopical examination was also carried out. A complete analysis on the fat content was done which included estimating total and neutral fat and the free fatty acid content.

After the first clinical examination and collection of the first specimens the children were exposed to natural sunlight. In the majority of cases, exposure was given while the children were recumbent. A few were up and about. The length of the exposure was limited during the early stages in order to prevent too severe a skin reaction, but once an immunity had been established, as much natural sunlight as was available was administered. The hours of sunshine recorded at Greenwich during

the period of observation are given in Table 2. The entire body surface was exposed where possible. In many cases only one aspect could be insolated. The degree of reaction to the early doses, and the degree of pigmentation obtained, were noted. For purposes of comparison the degrees of pigmentation are divided into: erythema, light brown, golden brown and dark brown. No artificial sunlight was used.

TABLE 2.
HOURS OF SUNSHINE RECORDED AT GREENWICH.
April to October, 1930.

April	...	...	107.0
May	...	...	136.4
June	...	...	227.4
July	...	...	157.7
August	...	...	227.2
September	...	...	119.4
October	...	...	104.5

Diet.—The diet received was the customary full hospital diet with a sufficiency of all essentials, well balanced, with possibly a slightly greater amount of fat than is usual. Plenty of fluids were administered, mostly in the form of water. Extra quantities were given on hot days when the children were exposed to sunlight.

The period during which these observations were carried out was from May to October.

Series II consisted of twenty cases who had had insolation either before admission or during previous summers. Similar examinations to those stated above were made in this series at the end of the summer, and were not repeated.

Commentary.

The results of clinical observations in Series I are not given in tabulated form in view of space requirements. The number of examinations recorded is greater in the earlier than in the later cases. The reason for this is that there was no object in continuing the observations later than October, and the number of new admissions was not sufficiently large to enable all the cases to be examined over a similar period of time. The earliest cases were those admitted in May. Observations were not made on any cases admitted after July.

The degree of pigmentation attained a maximum at about the period from the end of June to the middle of July. This can be attributed to two reasons, (1) the greater amount of sunlight during the preceding two or three weeks, and (2) the greater inclination of the sun, giving a larger number of ultra-violet rays. After this period the degree of pigmentation diminished in intensity.

The general condition improved steadily in all cases, the most marked improvement being that noted soon after admission. In no case was any marked loss of appetite noted even during the periods giving the greatest hours of sunshine. In all but one an increase in weight occurred and the

general condition showed improvement. With regard to the local condition, in most cases an improvement was shown, but in three cases it was no better.

The heart was normal in every case except one. In this child a doubtful aortic diastolic murmur was thought to have been present at the fourth examination, but the heart sounds had previously been normal.

The blood-pressure readings fell within normal limits. In some cases they were on the low side. In fifteen cases the pressures at the end of the observation period were higher than those noted at the beginning; in eleven cases the reverse occurred. Intermediate readings did not show any progressive change.

Digital examination of the radial artery at the wrist failed to show any definite change except in one case where a note was made that the artery 'feels harder than before.'

Examination of the abdomen revealed no abnormality, either on admission or during the period of observation.

BLOOD. The non-protein nitrogen, urea and cholesterol fell for the most part within normal limits, and any marked variation which occurred in one or two of these constituents were unconfirmed by abnormal readings in the remaining one or two. Thus, the cholesterol was as high as 260 mgms. per 100 c.c. blood in two cases without there being any indication of pathological change. In twenty-two cases the blood cholesterol was higher at the end of the experiment than at the beginning, and this rise was in most cases progressive. Haemoglobin and total solids showed results which are normal or lower than normal. There was apparently no tendency towards dehydration. The alkali reserve showed a general tendency to fall slightly in twenty-one cases, against a rise in six. Here, again, the figures are normal.

The blood calcium and phosphorus figures are those which show definite and progressive changes. In the majority of cases the serum calcium showed a tendency to rise during the period of observation. This occurred in seventeen patients as against a fall in six. Although most of the terminal readings may be taken as higher than is usual they do not lie outside normal limits. It is interesting to note that the highest serum calcium levels do not necessarily follow the sunniest periods.

The blood inorganic phosphorus shows an increase during the period of observation in all but two cases. In the main the increase is a gradual one, but a few cases show a drop in the second or third readings followed by a rise. The majority of cases shows that the increase continues up to the end of the period, and that the terminal values are the highest.

URINE. The quantity of urine passed in twenty-four hours was a little below normal in most instances, and definitely low in a few. It was sufficiently high, however, to show that there had been no gross dehydration and that the quantity of fluids taken had been adequate. The specific gravity fell within normal limits and bears out the observation that there had been no undue concentration. The reaction of the urine was usually acid. Occasionally a neutral or alkaline urine was noted without any apparent significance.

The urinary urea figures were definitely low in the greater number of cases. There does not appear to have been any progressive failure of excretion of urea during the period of observation. When taken in conjunction with the blood urea the combined observations show that there can be no suggestion of diminished renal function. Again, the low figures have less significance in view of the fact that no attempt has been made to measure the nitrogenous intake.

In seven cases a trace of sugar was found in one or two of the specimens which have been examined. These are apparently instances of alimentary glycosuria.

Rothera's and Gerhardt's tests show the absence of any ketosis.

A large number of cases showed albuminuria. In twenty-three cases albumen was present, though always in small amounts. Its appearance varied, sometimes being present in the first or second, but more often in the later specimens. Albumen was constantly present in only one case. In ten cases the patients were boys and in thirteen girls.

In six cases a trace of blood was detected in the urine. In two of these pus was also present.

The deposit showed pus cells in five cases, red blood corpuscles in three, epithelial cells in nine. The crystalline deposit was usually calcium oxalate, the next most frequent being phosphates, with a few uric acids and urates.

FAECES. In the greater number of cases the total amount of fat excreted was about normal, and the results of the fat digestion are within normal limits. In a few instances in which the total amount of fat excreted was high the increase was usually most marked in the neutral fat.

Microscopic examination revealed the presence of starch granules or striped muscle fibres in one or more specimens from all but six cases. The scarcity of these substances and the normal, or almost normal fat metabolism deprives them of any significance.

Discussion.

The literature which has been read in connection with the subject under review deals mostly with the effect of insolation on the calcium-phosphorus metabolism, and in particular with the effect of insolation in infantile rickets. Within our knowledge a complete report of the effects of exposure to sunlight such as has been made in this paper has not been previously recorded.

The general sense of comfort and lazy well-being which results from solar irradiation, and the pleasant effect of lying exposed to a warm sun are well known and much sought after by those to whom they are available.

Rollier²¹ in his book 'Heliotherapy' gives a detailed review of the historical and biological aspects of solar insolation, and stresses the necessity for control of the quantity administered. He also mentions the individual response and susceptibility to exposure as shown by general reactions and by the degree of pigmentation attained. The ultra-violet ray value of the sun, and probably also the actual heat of the sun to which his patients were exposed are considerably in excess of those which are obtained in the district in which the present observations were made. As a result one might expect that individual and general reactions would not be so marked in the present cases. This was found to be the case within certain limits. Some of the patients developed an earlier and a more severe erythema than others, and the degree of pigmentation attained showed individual variations to the same amount of sunlight. The degree of pigmentation has been regarded by Rollier as of prognostic value in his treatment of tuberculous patients, those pigmenting most being likely to respond to treatment more readily than those in whom the pigmentation is less marked. In this connection it cannot be said that any difference in healing was noted in the tuberculous patients with differing degrees of pigmentation in this series. Apart from the reaction as evidenced by degree of pigmentation no general reactions were found to occur. The patients seemed to enjoy insolation and did not suffer from undue drowsiness or from loss of appetite.

The response of the calcium-phosphorus metabolism to sunlight through the medium of vitamin D has already been briefly referred to in the opening section of this paper in relation to its effect on rickets (Kramer, Casparis and Howland⁵). In rickets, however, one is dealing with patients in whom there is a pathological depletion of calcium and phosphorus and the result of treatment is to restore to the blood the normal quantities of these substances.

Can the normal amounts of blood calcium and phosphorus be increased by the action of sunlight, and if so can this increase amount to injurious proportions? Other factors than the quantity of sunlight administered must be taken into account, the most important being the balance of the mineral intake in the diet. This is referred to by Orr as a necessity for the maintenance of general health. Henderson²² in his experiments on the effect of ultra-violet irradiation on calcium and phosphorus retention in pigs stresses this point, and notes that on a well-adjusted diet the influence of light is at a minimum. The importance of the subject is also referred to by Harris²³ in his work on hypervitaminosis D with irradiated ergosterol. Hart, Steenbock and Elvehjem²⁴ found that the blood phosphorus showed a marked and persistent increase when goats with a negative calcium balance was irradiated daily for twenty minutes.

Granted a normal diet, however, what variations in the blood calcium and phosphorus levels can occur apart from the action of vitamin D? Havard and Reay²⁵ showed that variations in the levels of blood phosphorus occur during the course of the day. Differences up to 14 per cent. occurred between the first and second estimations made in a man who had just walked a short distance in the morning. A definite rise up to 16 per cent. above morning levels occurred at times in midday specimens. During sleep a rise of 20—50 per cent. was noted with a rapid fall on awakening.

As a result of the action of sunlight the same observers note a rise in blood phosphorus figures between January and August. The values were lowest in the first month, an average of 2.9 mgm. per 100 c.c. blood, which rose to 4 mgm. in August. Hess and Lundagen²⁶ showed the occurrence of a seasonal rise in the blood phosphorus in infants. Sixty infants between the ages of six months and eighteen months, fed on an adequate diet, were used. The blood phosphorus was found to be lowest in March, average about 3.85 mgms. per 100 c.c. blood and highest in June, when the readings averaged 4.22 mgms. The phosphorus intake was fairly rich in these cases. The children were not exposed to the sun to any marked extent, normal clothing being worn. In a series of ten older children the change was less marked. In adults, members of the medical staff, no change was noted. Hess⁸ showed that not only phosphorus but calcium was raised in the blood by ultra-violet rays. The calcium was more stable. He mentions the seasonal incidence of tetany. The blood phosphorus rise as a result of irradiation is also reported by Grant and Gates³². Havard and Hoyle³⁴, however, failed to produce a rise in the blood calcium and phosphorus winter levels by irradiating two adults for sixteen days with a mercury quartz vapour lamp. The substances are evidently more stable in adults than in children. (Hess and Lundagen²⁶.) In one case of the present series this point is further illustrated. This was a youth aged 19 years. The blood phosphorus figures showed no increase during the period of insolation.

From the above it can be seen that the normal calcium-phosphorus metabolism is affected by sunlight. In the observations made above, however, the amount of irradiation was limited either by the length of exposure or by the extent of body surface insolated. With unlimited exposure to the sunlight in this country and the greater extent of body surface exposed, would the calcium-phosphorus metabolism be still further affected, and if so in sufficient amount to constitute hypervitaminosis D?

Hypervitaminosis D.—In dealing with this subject recourse must be had to the work done in connection with the action of large doses of irradiated ergosterol. That the mode of action of sunlight and of irradiated ergosterol is through the same mechanism has been shown earlier in this paper. It is reasonable to assume, therefore, that the signs and symptoms of overdosage will be similar.

Basing their estimates on the results of animal experiments most observers consider that the doses necessary to cause injurious effects would be so large as to render the possibility of overdosage impracticable. Thus Light, Miller and Frey²⁷ from their experience gained by experiments on rats suggest that for infants a harmful dose of irradiated ergosterol would be 1.5 litres per diem of a solution with a potency one hundred times as great as that of cod-liver oil. Hess, Lewis and Rivkin²⁸ think that the importance of these investigations has been over-rated.

The degree of the susceptibility of various animals to vitamin D has been studied by Taylor, Weld, Brannion and Kay¹⁷. They found that the degree of resistance diminishes in mice, chickens, rabbits, cats, dogs successively. In the case of dogs the susceptibility is marked and an instance is given in which death followed the administration of irradiated ergosterol when the amount given had a potency only twenty times the maximal therapeutic dose for an infant. They found that puppies were more susceptible than adult dogs. The symptoms of toxicity were general depression and lethargy, weakness, diarrhoea and vomiting. Hypercalcaemia was present. Hess and Lewis⁷ describe two cases of toxicity in infants receiving five milligrammes of irradiated ergosterol daily. The symptoms in dogs and infants are strangely similar. Both are typical of overdose of vitamin D and were caused by amounts not much in excess of therapeutic doses. Levaditi and Li Yuan Po¹⁹, however, found that monkeys appeared to be less susceptible to overdosage than other animals.

The amount of ergosterol which can be stored and irradiated in the skin is not known. Nor is the rate or extent of its absorption from the skin capable of accurate measurement. It has been previously mentioned that Hume, Lucas and Smith¹⁰ were able to prove absorption of vitamin D through the skin in rabbits by painting on a small depilated area, inaccessible to the mouths of the animals, a solution of irradiated cholesterol, and so preventing the onset of rickets although the diet given was a rickets-producing one. Evidently the power of absorption from the skin is fairly high.

Taylor, Weld, Brannion and Kay¹⁷ have studied the effects of administration of irradiated ergosterol by various routes. The conclusions they arrive at are that when given intravenously the therapeutic effect and toxicity are the same as when given orally. When injected subcutaneously, however, the vitamin was found to be less effective in producing

hypercalcaemia or other signs of overdosage. In comparative tests on six puppies, using oral, intramuscular and subcutaneous routes, two puppies for each method, and giving those in which the oral administration was used only half the dose of the other two, it was found that the 'oral' pups showed symptoms in forty-eight hours, and died in five to eight days. The 'subcutaneous' pups lived for twelve and eight days, and were bright after a week, while the 'intramuscular' group took a middle course. In the animals receiving the vitamin by the subcutaneous and intramuscular routes an initial depression of serum calcium was found to have occurred. The writers suggest that the comparative ineffectiveness of irradiated ergosterol when given subcutaneously may be of physiological importance. It may be that over-irradiation of the body surface will result in storage of vitamin D and that some mechanism exists whereby quantities of the vitamin excessive to the body's needs are rendered inert. Also they suggest the probability that the pigment found in the skin is a protective mechanism designed to prevent excessive activation of ergosterol. Hess⁸, and Hess, Pappenheim and Weinstock³ have found that black rats require more irradiation to be protected against rickets than do white rats. In support of their hypothesis that there is some mechanism regulating the quantity of irradiated ergosterol absorbed, Taylor, Weld, Brannion and Kay¹⁷ suggest that pigmentation alone could not protect against the absorption of ergosterol secreted and irradiated on the surface of the skin or in the layers of the epidermis superficial to the pigment layer.

The above factors would tend to suggest that the activation and absorption of excessive amounts of vitamin D by irradiation of the body surface is unlikely to occur.

Before discussing the results of the observations and examinations made in this series of cases, it would be well to set out the signs and symptoms of hypervitaminosis D. In the cases of animals these have already been mentioned and the pathological findings outlined. Cases have been reported in children, however, three of which will be detailed here.

Hess and Lewis' report two cases occurring in infants. One infant, after five milligrammes of irradiated ergosterol daily, developed moderate fever, vomiting, drowsiness, and loss of weight. The serum calcium was 16.2 mgm. per 100 c.c. blood. The blood phosphorus was about normal. The other case was similar and the condition resembled dehydration. In one of these patients hypercalcaemia recurred after three weeks further dosage, a month having elapsed since the previous trouble. Here the serum-calcium rose to 14.7 mgm. per 100 c.c. blood. Gain in weight continued till the twenty-fifth day when the serum calcium rose to 17.6 mgm. per 100 c.c. blood. Then vomiting and loss of weight occurred. The coagulation time of the blood was shortened. Electric muscular reactions were sluggish. A trace of albumen and granular casts were present in the urine.

A fatal case of hypervitaminosis D is reported by Thatcher²⁹ which is worth describing in detail.

In this case the patient was a boy aged eighteen months, weighing 15½ lb., and in length 29 inches. The child was pale, puny, and thin. There was no evidence of rickets. Albuminuria was present and the infant developed pyuria and acetonuria. The mentality was dull; vomiting occurred. The blood urea was

90 mgm. per 100 c.c. blood. The systolic blood pressure 78 mm. of mercury. The urine was acid and contained pus, red blood corpuscles and granular casts. The condition was diagnosed as a case of pyelo-nephritis. Death ensued and at post-mortem examination the kidneys were large, firm, pale yellow, with tiny gritty particles in medulla, especially at bases of pyramids. Microscopically, deposits of calcium were found in the medulla and in the lumen of the collecting tubules. Fibrous tissue had formed about some of the calcium deposits. There were no calcium deposits in other organs. The spleen was healthy, the thymus small and the liver showed some fatty degeneration. The bones were well calcified, though some demineralization was present. The comment made was that the changes resembled hypervitaminosis D. Subsequent investigation revealed the fact that 3iv of irradiated ergosterol emulsion had been given daily from May to September. This amounted to twice the curative dose. The diet which this patient had been receiving was half to three quarters of a pint of cow's milk daily, some thin farinaceous food, orange-juice and a proprietary meat-juice.

Thatcher suggests that the demineralization may have been due to deficient diet, but it may have been due to excess of blood phosphorus, apt to occur in babies a few weeks after administration of vitamin D has begun. In this case the serum calcium and phosphorus have not been recorded although the deposition of calcium in the renal tissues suggests that hypercalcaemia was present. The two cases reported by Hess and Lewis showed definite hypercalcaemia and in one the blood phosphorus was 'about normal.'

It has been seen that the predominant feature of hypervitaminosis D is a severe disturbance in the calcium-phosphorus metabolism, most marked in the case of calcium. Hypercalcaemia and the laying down of calcium salts form a constant feature. It is interesting to note the mechanism through which this occurs. Although the subject has been controversial it seems to be fairly well established that vitamin D acts on the calcium-phosphorus metabolism through the medium of the parathyroid glands. The signs and symptoms of parathyroid overdosage have been found to agree accurately with those caused by overdosage with irradiated ergosterol. (Taylor, Weld, Brannion and Kay¹⁷; Collip and Clarke³⁰; Jones, Rapoport and Hodes³¹.) Smith and Elvove¹⁵ point out the possibility of calcium precipitation through lowered carbon dioxide tension. Calcium deposition is most likely to occur in the lungs, kidney and aorta.

In the cases under review symptoms and signs which could be attributed to hypervitaminosis D have not occurred. The general health of the patients remained good throughout the period of observation. Mentally they were bright and cheerful. No instance of undue drowsiness was observed. No case of anorexia can be recalled. There was no diarrhoea. The state of nutrition was good. No vomiting occurred which could not be readily accounted for.

SERUM CALCIUM. The slight increase in serum calcium which has been noted in many cases is within normal limits, and bears out the observation made by Hess⁸. In one case the serum calcium rose as high as 12.5 mgm. per 100 c.c. blood, but no symptoms were observed. In the

remainder of the cases the calcium figures were between 9 and 12 mgm. per 100 c.c. blood.

BLOOD PHOSPHORUS. The definite and progressive increase in the inorganic blood phosphorus which has occurred during the period of insolation also corroborates the findings already recorded (Havard and Reay²⁵; Hess⁸; Hess and Gutman⁴; Grant and Gates³²). The figures are actually higher than those mentioned by these workers. Few of the initial estimations are lower than 4 mgm. per 100 c.c. of blood, and many rise to levels above 6 mgm. A mild hyperphosphataemia has occurred as a result of the insolation. There is no apparent reason for the drop in the blood phosphorus which was seen in two cases.

Other constituents of the blood in this series of cases show normal figures.

HAEMOGLOBIN. The haemoglobin value of the blood was found by Hess, Poncher, Klein and Dale³³ to be lower in twelve infants receiving maximum doses of irradiated ergosterol than in those receiving lesser doses. Jones, Rapoport and Hodes³² found the haemoglobin value was normal in dogs receiving large doses.

NON-PROTEIN NITROGEN. Collip and Clarke³⁰ noted a terminal rise in non-protein nitrogen in dogs receiving large doses of parathyroid extract.

CARBON-DIOXIDE TENSION. Smith and Elvove¹⁵ suggest that lowered carbon-dioxide tension might cause precipitation of calcium salts.

URINE. The occurrence of albuminuria in such a large number of cases is difficult to explain. In six instances it was associated with the presence of pus cells, evidently the result of a mild pyelitis or cystitis, or due to tuberculous infection of the kidney. On five occasions red blood cells were present, with or without pus cells. Tuberculous infection is the more likely in the latter cases. The presence of epithelial cells does not call for any special interpretation. The absence of casts excludes an interstitial nephritis such as has been described by some investigators of hypervitaminosis D as being present in that condition (Smith and Elvove¹⁵).

FAECES. Apart from the remarks already made no interpretations can be made as a result of the examinations.

Series II.—Observations made on the cases in this series, and the results of the biochemical examinations do not differ from those in Series I. Exposure during successive summers evidently does not produce cumulative effects.

Conclusions.

As a result of the exposure of the present series of children suffering from various orthopaedic conditions to all the available sunlight between the months of May and August, 1930, it has been found that no clinical ill-effects occurred. In no case can it be said that the progress of the

patient was retarded as a result of the insolation. The marked improvement in the general condition which followed admission might be attributed partly to a beneficial effect resulting from exposure to the sun.

Although the amount of insolation obtained was not the maximum possible it was sufficient to demonstrate that there is little or no likelihood of producing ill-effects due to excessive liberation of vitamin D which had been produced by irradiation of the ergosterol contained in the skin. The increase in the serum calcium and phosphorus which was found to have occurred was within physiological limits. No signs of toxicity such as have been reported by investigators of hypervitaminosis D have been demonstrated.

Taking the combined calcium-phosphorous metabolism into consideration it appears that on a normal diet doses of vitamin D such as are produced by irradiation cause a greater increase in the blood phosphorus than in serum calcium.

Summary.

1. A series of twenty-eight children has been exposed to solar irradiation during the summer months. Clinical examinations and biochemical investigations have been made periodically during the period of observation. A further series of twenty children has had similar tests made at the end of the summer.

2. No ill-effects have been observed as a result of the insolation.

3. An increase in the blood calcium and phosphorus values has been demonstrated during insolation.

4. No evidence of excess production of vitamin D has occurred.

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