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Hypervitaminosis A

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I. Introduction.

The increasing reports in the literature of a man-made disease resulting from overdosage of vitamin A has prompted the author to consider at some length this little understood entity. It is especially fascinating that one of the vitamins, absolutely essential in rather minute quantities, should result in toxicosis when given in excess.

A thorough consideration of the topic through an exhausting survey of the literature has been made. The outline of the study is considered the best possible, because, though it adds burdensome length to consider the normal physiology, it is the obvious requisite which is basic to a study of the pathologic physiology; furthermore, without an elaboration of the standard values, meanings are lost to the reader. The past and present uses of vitamin A in therapy is considered especially integral to the discussion, for herein lies the pitfall of <u>vitamin A toxicity</u>.

II. Historical Material.

A review of the literature on the vitamins discloses that most of our knowledge concerning this subject has been gained through a study of deficiency states; the earlier work with vitamins was concerned almost solely with this aspect.

A. Development of the concept of vitamins.

At about the turn of the century, students of nutrition considered that a well-balanced diet need contain only a suitable amount of each of the following "proximate principles," proteins, fats, carbohydrates, salts, and water. Casimir Funk (1) accounts that in the older literature there were no lack of statements which of themselves should have given rise to an eager search for additional dietary components necessary to life.

The scientific research leading to the conception of the vitamin theory proceeded through many intermediate stages, many investigations being based on the aforestated premise that only certain basic constituents of diet were necessary for the complete nutrition of an animal organism. Funk (1) believed the earliest of these investigations to be the work of Lunin (2), who reported experiments with mice which were fed on casein, fat, and cane sugar. Out of five animals used, one lived eleven days; the others thirteen, fourteen, fifteen, and twenty-one days, respectively, while starving animals lived only from three to four

days. He explained the results as being due to lack of lecithin, and to a disturbance in the balance between the inorganic and organic food components. Lunin made the important observation that mice thrived very well on milk powder, and concluded that milk contained, besides the known elements, other unknown substances essential to life. Thus we have, in 1881, the first concept of what came to be known as the vitamins. Socin (3), working in the same laboratory, repeated Lunin's observations.

In 1897, Eijkman (4), concerned with beriberi, found that the disease was brought about by a long continued consumption of white rice, since polishing removed a substance which was protective against the outbreak of beriberi. Takaki (5) had observed in 1882 that beriberi could be eliminated in the Japanese Navy by the addition of meat, bread, fruit, and vegetables to the diet. The Dutch investigators at the time were of the opinion that white rice contained a toxin which could be neutralized by the "silver skin" of unpolished rice. Grijns (6) in 1901 took up Eijkman's investigations and showed that there was actually a protective and curative substance in the polishings and also in other foods. Grijns was probably the first to have a clear concept of a deficiency disease and to attempt to isolate the active principle from foods.

Osborne and Mendel (8) in 1911 described experiments with a fat-free mixture fed to white rats which led to their

eventual death without any plausible explanation. Hopkins and Neville (9) and McCollum and Davis (10) confirmed these findings. These experiments reiterated the existence of a specific growth substance in certain fats, like butter, egg-yolk, and others. It was also in 1911 that Funk (11) isolated from rice polishings a crystalline substance which was efficacious in preventing or curing polyneuritis in pigeons. Funk's (12) analyses indicated that it contained nitrogen in a basic form and that it was probably an amine. Since it appeared to be essential to life, he named it "vitamine."

Osborne and Mendel (13) in 1913 attempted to disprove the amine structure of the "growth substance," and by separation of butter into three fractions, were able to cure ophthalmia in rats on pure butter fat which was supposedly nitrogen and phosphorus-free.

In 1912 Holst and Frölich (14) published the results of several years of systematic work upon experimental scurvy. They found that the guinea pig, when kept upon a diet of polished rice, developed the symptoms of scurvy instead of beriberi, and that scurvy also developed when whole grains, such as would have ensured protection against beriberi, were fed. The results of their work indicated clearly that scurvy is due to the deficiency of a substance in the diet theretofore unknown.

Thus observations upon disease led to the conception of

the existence of several substances of the vitamin type, needed for the prevention of deficiency diseases and for the maintenance of that condition of healthy resistance which safeguards against susceptibility to infections in other ways than through the ordinary immunological mechanism.

In order to avoid the difficulties of classification which had arisen out of the newly discovered nutritional essentials, the "antineuritic," the "antiscorbutic," and the "anti-ophthalmic" substances, McCollum and Kennedy (15) suggested alphabetic designations qualified by a statement of solubilities where necessary. Thus the fat-soluble substance of butter was "fat-soluble A," and the next substance which they recognized as essential was designated "water-soluble B." Drummond (16) in 1919 used "water-soluble C" for the antiscorbutic vitamin.

Drummond (17) suggested in a later paper that the designations then most common, those of Funk and McCollum, be combined and simplified both for convenience and to free them from questionable implications, as follows: That the familiar alphabetical designations be retained in part but without the antecedent statements of solubility; and that the original designation of Funk be retained in part but the final "e" be dropped, so that the resulting word vitamin shall carry no implication as to the chemical constitution of the substance. The three substances then recognized as belonging to this group thus became

vitamins A, B, and C, respectively, and the way was left open for any others whose existence might be demonstrated before they were chemically identified, to be added in chronological order and in alphabetical sequence, regardless of solubilities.

B. Isolation of vitamin A.

The separation of vitamin D from vitamin A was not complete before 1925. As early as 1909 Stepp (18) had found that there was some unrecognized factor in fats necessary for growth, and in 1913 McCollum and Davis (10) and Osborne and Mendel (8) confirmed this, the latter workers stressing that different fats varied in their value for growth. Mellanby (19) in his work from 1918 onwards on rickets, originally believed that the antirachitic factor, whose existence he discovered, was the same as the fat-soluble A factor of McCollum and Davis (10). But in 1922 and the following years several very important papers appeared, all showing that there were two separate factors in fats—the growth promoting or anti-xerophthalmic factor and the antirachitic factor. Thus Hume (20) and Goldblatt and Soames (21) found that ultra-violet irradiation, while it cured rickets, would not prevent xerophthalmia or maintain growth in animals on fat deficient diets. A year later in 1923, Goldblatt and Zilva (22) found that the growth-promoting and antirachitic functions of cod-liver oil were destroyed by heat and oxidation at different rates, and they also observed that spinach was excellent for

growth but not for preventing rickets. Mellanby (19) in 1926, comparing the diets of a series of puppies who had died or survived an epidemic of bronchopneumonia, reported that the protective value of the diet against infection was not related to its protective value against rickets.

The carotene content of plants was observed by Rosenheim and Drummond (23) in 1920 and by Coward (24) in 1923 to vary with their vitamin A potency, a relationship which was further emphasized by Rosenheim and Drummond's earlier observations on the similarity of the color reactions of the two. Between 1920 and 1930 Moore (25) and Capper (27) were largely responsible for showing that carotene could be used by animals as a source of vitamin A, into which it is converted in the body.

The chemistry, isolation and synthesis of vitamin A, and its relationship to carotene was settled chiefly by the work of Karrer (28) and Heilbron (29) and their co-workers, and of Holmes and Corbett (30) between 1930 and 1937. Karrer and his collaborators (28) worked out the formulas for vitamin A and the most important of the carotene plant sources, beta-carotene, showing that vitamin A is a complex primary alcohol, containing a beta-ionone ring, and beta-carotene having two such rings and no alcohol groups.

The synthesis of vitamin A was achieved in 1937 by Kuhn and Morris (32) though they did not obtain it in a pure form.

Holmes and Corbett (30) isolated the crystalline vitamin from fish liver oil.

The synthesis of vitamin A did not stop the investigations into the chemistry of vitamin A--the vast literature covering the subject is formidable, but for the interested reader, Hume and Kon of the Lister Institute of Preventive Medicine, London, and National Institute for Research in Dairying, University of Reading, respectively, have undertaken to discuss the modern knowledge of vitamin A-active substances (33).

C. Standardization of vitamin A.

Hume has undertaken in an excellent and thorough review of the developments and significance of "units" of vitamin A, to tell the story of standardization in full (34). For purposes of this writing, only enough of her review has been abstracted to clarify the significance of units, as these have varied chronologically, and accurate interpretation of dosage is necessary elsewhere in this writing.

It was in 1931 that the Health Organization of the League of Nations held its first conference, aimed at setting up international standards for certain of the vitamins; the carotene standard of 1931 was a crystalline mixture of carotenes, and the vitamin A activity of one microgram of it was the unit of vitamin

A. At a second international conference in 1934 (Permanent Commission on Biological Standardization; League of Nations, 1934), the preparation of mixed carotenes was changed to one of pure crystalline beta-carotene. By collaborative biological test, it was established that the amount of the pure substance that had the same activity as one microgram of the mixture was 0.6 micrograms, which was accordingly established as the new international unit. The same 1934 conference decided it would be well to have a subsidiary standard, namely, a cod-liver oil sample. The United States Pharmacopoeia Advisory Commission had some time before issued a sample of Reference Cod-Liver Oil to be used in the United States as a standard, so the Board of Trustees of the U. S. P. were asked to and did place a quantity of their oil at the disposal of the Health Organization of the League of Nations. The Reference Oil was tested in twelve laboratories and the value ascribed to it was 3,000 international units per gram. The U. S. P. unit was, in terms of the cod-liver oil, to have the same activity as the international unit of beta-carotene. During World War II, the U. S. P. Vitamin Advisory Board announced a solution of vitamin A acetate as their new Reference Preparation to replace the Reference Cod-Liver Oil. The amount of the acetate found equivalent to one international unit (0.6 micrograms) of beta-carotene was 0.344 micrograms, (or 0.3 micrograms of vitamin A alcohol), so that one gram of the

pure substance must contain

$$1/0.3 \times 10^6 = 3.3 \text{ million international units.}$$

The World Health Organization finally came into being, and its Expert Committee on Biological Standardization created a Subcommittee on Fat-Soluble Vitamins. On April 26-29, 1949, the Subcommittee met in London and recommended the acceptance of vitamin A acetate as the international standard for vitamin A, with the activity of 0.34 micrograms of it, or 0.3 micrograms of vitamin A alcohol, as the new international unit.

Then, with regard to the International Unit and the United States Pharmacopoiea Unit, there is no difference in meaning at the present time.

III. Physiology of vitamin A.

A. Conversion of provitamins to vitamin A.

Current literature indicates a diversity of opinions concerning the site of conversion of carotene to vitamin A, with much evidence in favor of species difference. The manner in which animals convert the provitamins into vitamin A is presumably an enzymatic process (36). Until recently it was thought that the liver was the main site of this transformation, and the idea remains in many quarters that the liver does play an important part in the vitamin A synthesis (37). Thompson et al (38) came to the conclusion that in dogs, at least, beta-carotene is largely converted to vitamin A in the mucosa of the intestine, but participation of the liver in the process is not rigidly excluded, and this view seems to be largely accepted for human beings at the present time (36). Conversion is rapid, but absorption is slow. Thompson (38) found that vitamin A appeared in the intestinal wall within five minutes of oral administration of beta-carotene, but was not found in the flowing lymph in less than one hour. It was apparently not absorbed by way of the blood stream, since concentrations in the systemic and portal blood during absorption were essentially the same. The vitamin was found in high concentration in the intestinal lymph one to two hours after feeding. In the lymph it appeared exclusively in the ester form, but in the wall of the intestine and in the in-

testinal contents both the alcohol and ester were present. Only traces of beta-carotene were ever found in the portal or systemic blood, indicating that conversion in the intestine is fairly complete. Sexton, Mehl, and Deuel (39) injected carotene intravenously into rats. Carotene but not vitamin A was deposited in the liver. These workers came to the conclusion that the conversion of carotene to vitamin A in the rat was an extrahepatic function and suggested the wall of the intestine as a site for this species.

Koehn (40) has recently compared highly purified beta-carotene, vitamin A alcohol, and vitamin A acetate, as to their growth-promoting properties in rats. The data point unequivocally to the fact that on a weight basis, beta-carotene and vitamin A have equal growth promoting properties for the rat. This indicates that *in vivo* the beta-carotene molecule is converted quantitatively into the two possible vitamin A molecules by symmetrical scission.

B. Absorption.

The transfer of vitamin A across the gut-wall is in the form of the alcohol, the naturally occurring vitamin A esters being first hydrolyzed by the enzymes of the gut (41). The re-esterification and lymphatic transport have been discussed above.

C. Storage and distribution; plasma levels.

Sharman and Moore (42) state that experiments on rats and other animals have established that the body's main stores of vitamin A are usually located in the liver, being concentrated in both the liver cells and Kupffer cells. Bauman and Johnson (43) have shown in their experiments that rats given vitamin A in doses of about thirty i. u. store vitamin A in the kidney in excess of the amount stored in the liver. Eden and Moore (44) have confirmed this observation, and have drawn attention to the failure of the concentration of vitamin A in the kidneys to increase parallel with that in the liver when large doses of vitamin A were given; with liberal intakes of vitamin A, substantial amounts appear in the lungs, adrenal glands and fat deposits.

Although more is known about the metabolism of vitamin A in the eye than in any other organ, it is important to realize that the retina normally contains only a very minute fraction of the total amount present in the body (42).

Moore (45) gives the following figures, in i. u. of vitamin A per gram of wet liver, for adults dying of various diseases: Thyrotoxicosis, 310; diabetes, 300; poisoning, 170; hypertension, 120; gall-bladder disease, 110; gastric ulcer, 110; coronary thrombosis, 110; tuberculosis, 96; syphilis, 96; endocarditis, 90; bronchiectasis and bronchitis, 80; subacute nephritis, 75; pneumonia, 63; empyema, 60; valvular disease of the

heart, 60; septic diseases, 51; prostate, 40; chronic nephritis, 25; kidney and bladder infections, 19. In children under the age of fifteen, the values were (46): Tuberculosis, 140; measles, 110; pneumonia, 78, meningitis, 68; septic diseases, 47, and heart disease, 15. Bicknell and Prescott (35) would explain these effects as given by Moore (45, 46): 1) That all the diseases where low storage occurs would tend to decrease absorption by a poor appetite, fever, and an unhealthy gut; 2) that the low figures found in heart disease are partly due to anoxemia interfering with conversion, and partly to the engorgement of the liver with blood which decreases the proportion of vitamin A to liver weight; 3) that the yellow liver found in patients dying from the uremia of chronic nephritis is due to the presence of carotene, which presumably could not be converted to vitamin A because of the toxic condition of the body; 4) that though many of the pulmonary infections with a low storage are similar to those from which vitamin A deficient animals die, yet the low storage is not the cause of the infections, but the result of poor absorption or poor conversion, and increased renal secretion, all of which might then tend to set up a vicious cycle by decreasing the power of resistance of the lungs.

Investigations of the levels of vitamin A and of carotenoids in the plasma of normal individuals have been made by many investigators, and a table is furnished as a composite of

some of these figures established by various investigators:

Table 1

Values for vitamin A and carotenoids in adult blood plasma

Authority	Country	No. of Subjects	Carotenoids (IU/100 ml)	Vitamin A (IU/100 ml)
Moore & Leitner 1940 (47)	Great Britain	195	150	120
Campbell & Tonks 1949 (48)	Great Britain	110	133	108
Kimble 1949 (49)	United States	64	294	109
Abels et al 1941 (50)	United States	124	325	160
Murrill 1941 (51)	United States	45	343	104
Lahiri & Scandrett-1952 (52)	Great Britain	114	68	187

Some uncertainty in the comparison of the British and American results for vitamin A must arise from unintentional differences in the magnitude of the units, judging from Hume's 1951 discussion (34) of the long-standing differences in direction of standardizations on different sides of the Atlantic Ocean, but the figures of Murrill and Kimble in the United States do not differ greatly from the figures established by Campbell and Tonks and by Moore and Leitner in Great Britain, for vitamin A.

Differences in technics of plasma assay, and dietary differences may have been responsible for some of the larger variations.

Szymanski and Longwell (53) have recently undertaken plasma Vitamin A determinations in a group of normal children. The trends of their results for varying ages are listed in an abstract of table 1 of their publication:

Table 1 (53)

Plasma Vitamin A Levels by Age

Age (years--months)	No. of Children	Vitamin A in micrograms per cent				
		Minimum	Percentile(1)			Maximum
			25	50	75	
2 days	13	5	13	23	38	46
0 - 1(mo.)	20	11	20	29	45	72
0 - 2	20	18	27	36	52	213
0 - 3	20	21	32	42	58	120
0 - 6	17	17	37	47	62	100
0 - 9	22	23	39	56	68	125
1 - 0 (1 yr.)	21	32	42	52	74	113
1-3 to 1-6 (2)	18	19	38	47	64	143
1-9 to 2-0	19	17	36	44	58	113
2-3 to 3-0	15	27	32	41	53	102
3-3 to 4-9	17	14	31	39	50	62
5-0 to 6-0	23	18	28	36	46	96
6-6 to 16-0	56	14	28	35	42	110

(1) The 50th percentile is the median value for each age group. For example, at one month of age, half of the children had vitamin A levels equal to or below 29 microgram %, one-fourth had levels equal to or below 20 microgram %, one-fourth had levels above 45 microgram %.
(2) In the age groups from 1-3 up, the number of determinations on each child ranged from one to eight, depending on the age span. In the 6-6 to 16-0 group, there were 278 separate analyses on the 56 children.

The authors point out that a peak in the median occurs

at nine months to one year of age, after which the values drop gradually to level off at about six years of age. The authors point out further that this peak was almost entirely due to the girls in the group. This is interesting in the light of the observation by Lahiri and Scandrett (52) whose analyses for adults showed a higher carotene value for females, as did the other workers mentioned.

1. Physiological factors affecting the level of vitamin A in the plasma.

Our knowledge of the factors which control the mobilization of vitamin A from the liver into the blood plasma is still very limited (42). According to Clausen and his co-workers (54), the administration of alcohol to dogs or human beings causes a rise in the vitamin A level of the plasma. This is disputed by Hume and Krebs (55) in their 1949 report of experiments with volunteers.

Sex is obviously an important factor in influencing the plasma level, as observed by Kimble (49), Moore and Leitner (47), and Szymanski and Longwell (53). Sharman and Moore (42) found in experiments with rats differences in the same direction. Chapman, Gluck, Common and Maw (56), in experiments utilizing immature pullets, found that with combined injections of oestradiol and testosterone, the vitamin A content of the plasma was about doubled. According to Bodansky, Lewis, and Lillienfeld (57),

pregnancy has a slight effect on the plasma level of vitamin A in human subjects, causing decreased values in the later stages. In this connection, it has been found by Argonz and Abinzano (58) that therapeutic vitamin A has relieved the syndrome called "premenstrual tension," in many of his patients, such state being ascribed by the authors to an excess of circulating estrogen.

The level of vitamin A in the plasma may be influenced by disease in various ways. Sharman and Moore (42) state that in diseases such as sprue, celiac disease, and infectious hepatitis, flattened absorption curves (in contradistinction to the sharp rise observed in normal subjects) are observed, because of the defective absorption of fat. Kagan, Thomas, Jordan and Abt (59) observed in 1950 that children suffering from nephrosis had a very high resting level of vitamin A, showing a much greater increase after dosing. They concluded that in nephrosis, the power of the liver to absorb or utilize vitamin A is seriously impaired.

The effects of fever were extensively investigated by Lindqvist (60) who in 1938 found greatly reduced levels of vitamin A in the plasma in pneumonia, influenza, tuberculosis, and other infections. The levels returned to the normal range promptly on recovery. It is interesting that Moore (45) found low liver reserves in fatal cases of pneumonia, suggesting that the decline in the plasma level in this disease indicates not

only a failure in mobilization, but the actual loss of a large fraction of the vitamin A reserves of the body. Clear evidence that a very low level of vitamin A in the plasma does not necessarily imply exhaustion of the liver reserves was obtained by Harris and Moore (61) in 1947 in a fatal case of infectious hepatitis. A specimen of plasma collected a few days before death contained only 19 i. u. per 100 ml., whereas the liver contained no less than 900 i. u. per gram, or about three times the average level.

D. Mobilization.

The mobilization of vitamin A from the stores in the liver and its liberation into the blood is not yet clearly understood. The liver under normal conditions apparently maintains the level in the blood until its own stores are exhausted (42) and can be stimulated to liberate vitamin A by alcohol (54), epinephrine and sympathetic stimulation (62). There is an hepatic esterase which maintains a normal ratio of vitamin A alcohol-ester in the blood, the alcohol being the active form. The mechanism by which the balance is maintained between the liver, the blood, and the urine, is altered in favor of the urine and sometimes the blood in renal disease (63) and in conditions where the level of lipoids in the blood is high (64). During the first few days of life (53), and during fever (59), and in hepatic disease (60), the mobilization is poor or virtually does not

occur.

E. Excretion and destruction.

Lawrie, Moore, and Rajagopal (65) in 1941 reviewed the work on excretion of vitamin A by the kidney and also gave the results of their own research. The following is based chiefly on their paper. Vitamin A is never excreted by man during good health, but it may appear in the urine during illness, being first noted in pneumonia. A daily output of 3,200 i. u. has been recorded, which is said to cease abruptly with the crisis. In chronic nephritis, vitamin A is common in the urine though in smaller amounts than in pneumonia. Still smaller amounts have occasionally been reported in chronic infections, rheumatic fever, skin diseases, diabetes mellitus, pernicious anemia, asthma, cancer, and normal pregnancy.

How vitamin A is dissolved in human urine is obscure. It is always associated with protein, but not all urines containing protein contain the vitamin, even though they are capable, unlike normal urines, of taking it up from halibut liver oil. Apparently the excretion of vitamin A in the urine is dependent on a functional abnormality of the liver causing a diminished capacity for absorbing or retaining the vitamin. This alters the equilibrium between the liver and the blood, vitamin A passing to the latter. But the blood and kidneys will yield up the vitamin to the urine only if their capacity to retain vitamin A is

impaired. In pneumonia this is frequently so to a marked degree. In nephritis, the damage to the kidney probably leads to an accumulation in the blood of substances which increase the solubility of vitamin A and so partially hold it back from excretion.

The healthy dog constantly excretes vitamin A. Rats never excrete vitamin A, even when taken in toxic amounts, and rabbits only when diseased.

The large stores which accumulate during a diet rich in vitamin A are depleted with great rapidity if the diet becomes deficient in the vitamin (67) or in vitamin E (68), the depletion being greater than can be accounted for by the needs of the body. Davies and Moore (69) suggest that there are two ways in which vitamin A is destroyed, one depending on the normal and economical physiological use of vitamin A in the processes of the body, and the other depending on some mechanism for destroying vitamin A when it is stored in excessive amounts.

F. Action of vitamin A in the body.

Not much is definitely known about what is the fundamental part played by vitamin A in the metabolic processes of the body. All that can be said is that its structure containing five unsaturated bonds suggests its probable function as an oxidation-reduction catalyst (35). Mason (69) has suggested that it is necessary for some particular metabolic process peculiar to all

epithelial cells in varying degrees, but not to other tissues. There is also evidence that the vitamin has a specific effect on growth of animals, and quickens the growth and prolongs the life of tissue cultures (70), which is reminiscent of Batchelder's (71) work, where she found that a very plentiful supply of vitamin A throughout the life of the rat increased longevity and delayed the onset of senility.

The action of vitamin A has been studied mostly in relation to deficiency and excess, more having been learned from deficiency studies than any other way, and it is perhaps best discussed in the light of the effects of deficiency for the present discussion of "normal physiology."

1. Growth.

Patterson et al (72) have shown that in the absence of a Vitamin A source, animals fail to grow and may die before body stores are completely exhausted, and often before typical deficiency symptoms develop. The mechanism of the cooperation of vitamin A in the growth processes is not understood. In the presence of subminimal amounts of dietary vitamin A, life is prolonged, with or without growth, and a variety of deficiency symptoms develop. It is to be understood that symptoms may appear even in the presence of normal growth.

2. Effect on epithelial tissues.

Wolbach and Howe (73) have said that the specific tissue change due to deprivation of fat-soluble vitamin A is replacement of various epithelia by stratified squamous keratinizing epithelium. Regarding this phenomenon, Bicknell and Prescott (35) have to say: "If this statement is broadened to include all tissues of epithelial origin be they from entoderm, or ectoderm like the skin, nervous system and retina, a valuable generalization is made which harmonizes all the more important functions of vitamin A, always remembering that some tissues are damaged earlier than others by a deficiency." These changes occur in man and presumably all the vertebrates, even in the foetus (74). Mainly affected are epithelia with secretory function, such as the salivary glands, including the tongue and pharynx, the respiratory tract with the trachea and bronchi, the eyes including the cornea, conjunctivas, and intra-and extra-orbital glands, the genito-urinary tract with the renal pelvis, ureters and bladder, and the sex glands (75). In man, the skin may also be involved. Keratinization in the secretory cells may produce severe obstruction in the gland ducts with cystic dilatation and accumulation of debris leading to severe infection of the surrounding tissues (76). On the other hand, epithelial cells with chemical function and capable of division, such as those of the liver, do not show marked atrophy, and do not exhibit keratinizing metaplasia (75). Wolbach and Howe (77) have shown

that after vitamin A administration, each individual epithelium reassumes its normal structure and function, when the keratinized cells have been removed by autolysis and leucocytic infiltration.

3. Eyes.

There are various eye conditions resulting from vitamin deficiency (36). Early symptoms in rats and other species are enlargement of the eyelids and inflammation of the conjunctiva. This is followed by corneal changes leading to blindness. In man, nyctalopia is one of the early symptoms of deficiency. If the deficiency is slight, further changes may not be seen, but with a more severe deficiency, especially in children, xerosis and keratomalacia develop. The eyelids stick together as a result of a purulent discharge. Small ulcers may appear on the cornea and blindness may ensue. Metaplasia of the corneal epithelium and vascularization of the substantia propria are typical findings and generally lead to infection and obstruction of the ducts of the ocular glands. Wald (78), as early as 1935, indicated a mechanism involving vitamin A in vision. A pigment in the retinal cones (also in the rods) called rhodopsin is a protein complex with vitamin A. Under the influence of light, this pigment breaks down to form protein plus retinene, the vitamin A aldehyde. This breakdown may be associated with a nerve impulse. Resynthesis of rhodopsin from vitamin A and protein must keep pace with its photochemical breakdown under the influence of

light in order to maintain normal vision. Bright light markedly depletes the stores of rhodopsin in the rods. Rhodopsin synthesis is associated with vision in dim light and is the reverse of the photochemical breakdown. If the blood is not well supplied with vitamin A, the time required for rhodopsin synthesis is lengthened or the total synthesis may not reach optimum quantities. Under such circumstances, dark adaptation is subnormal. The original hypothesis of Wald has gone essentially unchallenged. It may be summarized as follows:

retinal rhodopsin $\xrightarrow{\text{light}}$ retinene + protein

retinene $\longrightarrow$ vitamin A

vitamin A + protein $\xrightarrow{\text{dark}}$ rhodopsin

Hubbard and Wald (79) discuss the mechanism in great detail in the light of modern knowledge of enzymes, etc., but any detailed discussion is felt not to be integral to this paper.

4. Gums and teeth.

In man, lack of vitamin A causes the gums to become hyperplastic and keratinized (80), while the developing teeth both in infants and animals (81) are severely damaged, since the enamel organs being of epithelial origin, shrink, or are replaced by keratinizing epithelium, thus apparently removing from the odontoblasts some controlling influence over their growth. They

therefore form poor or deformed dentine, which in prolonged mild deficiencies leads to the formation of odontomas and tooth reduplication in the perpetually growing incisors of rodents(82). Bicknell and Prescott (35) concluded that vitamin A is the most important vitamin for the structure of the dentine and enamel of the tooth, in spite of the commonly and "quite erroneously" held belief that lack of vitamin D is the main cause of dental degeneration.

5. Olfactory epithelium.

LeMagnen and Rapaport (83) found the existence of a carotenoid pigment in the olfactory epithelium of several mammals and undertook to investigate the possible role of vitamin A in the process of olfaction. White rats were fed a vitamin A-deficient diet and lost their olfactory ability only in the far advanced stages of deficiency just prior to death, and the authors concluded that vitamin A did not play a specific role in the mechanism of olfaction, as suggested by Milas (84) who had found that the olfactory area in the steer was rich in carotenoids and vitamin A.

6. Digestive tract.

In man severe deficiencies often cause diarrhea and there is some evidence that vitamin A is important for the function, if not the structure, of the gastric glands and pancreas.

Földes and Vajda (85) report that in twenty cases with deficient or absent hydrochloric acid, twelve improved both as regards their symptoms and the amount of acid in their test meals after two weeks on 16,000 i. u. of vitamin A thrice daily. The patients who benefited and improved had chronic gastritis, neurasthenia, gastroptosis, diabetes, thyrotoxicosis, or renal lithiasis. The eight patients who did not benefit had gastric carcinoma, pernicious anemia, or gall stones. Seelig (86) purported to show that large amounts of vitamin A rapidly removed both the symptoms and radiological or gastroscopic evidence of gastric ulcers, but work by Douthwaite (87) failed to confirm this.

7. Genital ducts and epithelium.

Mason (69) in a very careful study has shown that vitamin A is essential for the germinal epithelium of the testes; the earliest changes are sloughing of germinal cells into the lumen of the tubules, with a gradual reduction in the latter's size. As the degeneration becomes more advanced only three or four layers of cells are left lining the tubules, but these still are capable of forming an occasional sperm, and at no time can the testis be so damaged that it cannot return to normal when the vitamin A deficient diet is stopped. These changes are due to a direct effect on the cells themselves and not an indirect one from vitamin A acting on the pituitary, since neither pituitary transplants nor injections of pregnancy urine hastened recovery,

and also because the degeneration caused by removal of the pituitary is unlike that caused by a lack of vitamin A.

In females the normal oestrus cycle is not maintained. In slight deficiencies, fairly normal reproduction is possible, but with a severe deficiency, few if any live young are born. Alterations in the lining of the reproductive tract appear to interfere with the nutrition of the embryo.

8. Endocrine glands.

The structure, as apart from function (35), is said to maintain its normalcy; no change beyond decrease in size was noted in the rat's anterior pituitary, thyroid, thymus, parathyroids, suprarenals, islets of Langerhans, ovaries, Graafian follicles, corpora lutea, and interstitial tissue of the testes. In a human infant dying from lack of vitamin A, Hassall's corpuscles were found to be enlarged (88).

9. Skin.

Only comparatively recently has a vitamin A deficiency been associated with specific lesions of the skin in man. Perhaps the earliest description of this condition was reported in 1931 by Frazier and Hu in China (89). The lesions vary considerably in different individuals (36). The general features of the deficiency involve dryness and roughness of the skin. This appears early in the deficiency and is due to a suppression of

the sweat glands. A keratosis, especially of the hair follicles, is a prominent feature. Papules, masses of keratinized epithelium, develop. The sides and backs of the thighs and the lateral parts of the forearm are most frequently involved, although the condition is often more extensive.

Another skin condition resembling acne vulgaris, common on the face, is apparently a vitamin A deficiency. Straumfjord (90) has made a critical study of a number of such cases.

Leitner (75) discusses a "congenital" disease of the skin, which is characterized by a low level of vitamin A in the blood and by generalized keratinizing metaplasia, called pityriasis rubra pilaris.

10. Osseous system.

Bone growth is markedly impaired in vitamin A deficiency. Cessation of growth in parts of the body as well as abnormal growths are encountered (36). Mellanby (91) has shown that changes in morphology of bone from compact to cancellous leads to overgrowth and an increase in thickness though not in the calcium content, resulting in compression of the brain, cranial and spinal nerves, in young puppies.

11. Renal function.

In a long-standing vitamin A deficiency in rats, Higgins (92) found that a high percentage of his animals devel-

oped urolithiasis. The calculi were composed primarily of calcium phosphate. According to this worker, the deficiency allows keratinization of the genitourinary tract epithelium followed by bacterial invasion and alkalinuria. These factors predispose to calcium phosphate precipitation. Vitamin A therapy and an acid-ash diet are alleged by Higgins to be effective in alleviating the condition, and in a number of human beings this regimen was supposedly effective in bringing about dissolution of urinary calculi. Higgins does not assume that a vitamin deficiency is involved in the production of all urinary calculi.

The role of the kidney in storage, excretion, and destruction of vitamin A has been discussed earlier, as have the plasma levels in renal disease.

Herrin (93) found that in rats on a vitamin A deficient diet, the urea clearance fell by twenty-three to twenty-seven per cent, this being a purely functional effect, since not only was the urine normal, but histologically no structural changes were found in the kidneys. In further studies on human subjects, Herrin (94) found that doses of 50,000 to 75,000 i. u. daily, two out of thirteen showed no response, four had an increase in their urea clearance of from eleven to fifteen per cent, and seven had an increase of from twenty-four to ninety-one per cent. The last group belonged to the type whose body weight fluctuates widely and rapidly. It is apparent that there is a definite effect

on the kidney's excretory power, exerted by vitamin A, although Bicknell and Prescott (35), in confirming this action, found it to be transitory in their experience.

12. Endocrine function and vitamin A metabolism.

Attention has been focused on the thyroid gland, especially in regard to control of absorption and metabolism of vitamin A and carotene, since Kunde (95) in 1926 reported the appearance of vitamin A deficiency in thyroidectomized goats. In man the importance of the thyroid for converting carotene to vitamin A is shown by the occurrence of nyctalopia in hypothyroidism (97) and by the low level of vitamin A in the blood of cretins (98). That over-action of the thyroid actually increases the conversion of carotene above the normal, appears to be borne out by Moore (45) finding in the livers of patients dying from thyrotoxicosis, larger stores of vitamin A than were present in any other human livers. Johnson and Baumann (43) in 1947, using the storage of vitamin A in the liver as the criterion of carotene conversion, found that the same dose of carotene produced less liver vitamin A in the thiourea-treated animals than in controls, and that control rats stored less than did rats dosed with dessicated thyroid, while administration of thyroxine and thiourea together produced normal liver storage, indicating that the action exerted by thiourea was antithyroid, and that it

did not reduce liver storage of vitamin A by virtue of any other pharmacological action. Belasco and Murlin (99) have found that the metabolism of thyroid tissue from animals taking large amounts of vitamin A is decreased, compared to that of controls, this decrease being even greater if the animals have been given thyroxine as well.

Cama and Goodwin (100) in 1949 did experiments to prove that the thyroid plays a part in the metabolism of carotenoids, not by stimulating the conversion of carotene, but by controlling the intestinal absorption of carotene. The antithyroid action of thiouracil was also demonstrated by the fact that it inhibits absorption of the pigment and that this effect is counteracted by the simultaneous feeding of dessicated thyroid. The authors further state that neither dessicated thyroid nor thiouracil, even in large doses, has a significant effect on the plasma-vitamin A levels of rabbits, which would indicate that the liver factors controlling the plasma-liver equilibrium are unaffected.

Drill observed (101) in 1943 that the simultaneous administration of vitamin A and thyroxine prevents a rise in the basal metabolic rate. Sadhu and Brody (102), following this lead, demonstrated that in rats, large doses of vitamin A cause a decrease in thyroid size and reduce the basal metabolic rate while allowing normal growth. In 1948, Sadhu (103) postulated that the thyrotropic hormone is counteracted in some manner by part of the

vitamin A, as is the action of the injected thyroxine on end organs and enzyme systems.

All changes in the endocrine glands due to lack of Vitamin A have been thought by some workers to be a secondary effect of a primary change in the pituitary (35). It is stated that the amount of thyrotropic hormones in the anterior pituitary is low in rats on a high vitamin A diet, and high in rats on a deficient diet. It has also been found that the factor in the anterior pituitary which stimulates the growth of the female genital system is increased in vitamin A deficient male rats, but Mason (69) has pointed out that this is a purely secondary effect due to the virtual castration of the male rats by the degeneration of the vitamin A deficient testes, since deficient female rats showed no such changes in the pituitary's secretion.

Williams (104) found that the amount of milk secreted by nursing mothers was not altered by varying their intake of vitamin A, seeming to indicate that the pituitary principle controlling lactation is not affected by vitamin A. Kepinov (105) found that adrenaline did not accelerate the hydrolysis of liver glycogen to glucose unless vitamin A was previously given, the vitamin having no effect on glycogenolysis after removal of the pituitary.

The adrenal glands have been shown by Davies and Moore (106) to store vitamin A, which may indicate a direct relation

between vitamin A and their function. Bicknell and Prescott (35) feel that the difficulty diabetics have in converting carotene to vitamin A is probably due to their impaired liver function and not to any pituitary effect. In this connection, Kimble and his associates (107) have listed a number of reasons, other than pituitary effect, why diabetics could show low plasma levels of vitamin A.

Sex hormone relationships to vitamin A are not well established. Mason and Ellison (108) observed that in rats, oestrus is not stopped by a deficiency, but becomes delayed and irregular. This is interesting in the light of the menstrual pattern of the one human adult case of hypervitaminosis A on record, where the periods became shorter and the flow less (109). Cannon found (110) that in severe deficiencies, rats refused to mate; that with decreasing degrees of deficiency, there was mating but no conception, conception but the fetuses were resorbed, death of the fetuses, prolonged gestation. Moore, Sharman, and Ward (111) observed differences in body distribution of vitamin A, the storage in liver and kidney varying consistently and significantly in different groups of castrated rats which were given male hormone, female hormone, or no hormone at all, as compared to each other and normal rats. Beher and Gaebler (112), in studying female adult dogs in a state of induced anabolism, observed that testosterone propionate caused a marked drop in

plasma vitamin A concentration. Of interest is the therapy with vitamin A in conditions alleged to be due to estrogenic disorders. Argonz and Abinzano (58) claim successful treatment of "premenstrual tension" (supposedly due to excessive circulating estrogen) with large doses of vitamin A. Schneider (113) observed marked improvement in seven of eight patients during the premenstrual period who usually suffered exacerbations of Raynaud's syndrome, these having been treated with large doses of vitamin A. Keddie (114) suggests estrogen imbalance as a possible cause in certain skin diseases, namely keratosis follicularis, ichthyosis, and pityriasis rubra pilaris, which have often been successfully treated with heavy doses of vitamin A.

13. Vitamin A and fat metabolism.

For many years it has been noticed that lipemia was associated with high carotene levels in the blood, and Josephs (64) has shown a definite correlation between carotenemia and lipemia. It has been thought that vitamin A may be necessary for transfer of fat across the gut wall in fish (115); this is apparently not so in animals (116). But the converse, that fat and lecithin aid the absorption of vitamin A, is satisfactorily proved (117).

Josephs (116), besides reporting the effect of vitamin A in raising the serum lipoids, the more important observations by himself and others being essentially the same in man and

animals, has also reviewed the literature on the effect of vitamin A on serum lipoids. Serum cholesterol varies in the same way as that of the serum lipoids and the raised levels of both following the administration of vitamin A ultimately fall even though vitamin A is still given. In the reported cases of hypervitaminosis A, where serum lipoid levels have been determined, high lipoid levels have been found, and most authors share Josephs' opinion that vitamin A has an important and specific, though poorly understood, effect on the metabolism of lipoids.

14. Vitamin A and the nervous system.

The effect of deprivation of vitamin A on the nervous system is still uncertain in animals, while in man all that can be said is that in some nervous diseases, such as lathyrism, a deficiency of vitamin A appears to be one of their most important causes. Some workers with animals have found no degeneration of the nervous system when other signs of a vitamin A deficiency were already severe (118); others working with dogs (119), rabbits (120), and rats (121) have reported a widespread degeneration of the medullary sheaths of the peripheral nerves, the optic and auditory nerves, the retina, and the tracts in the medulla and spinal cord. This degeneration is considered by some to be irreversible (120), although it can be prevented from progressing further with vitamin A (122).

Of interest is the current work in treatment of various

forms of deafness with large doses of vitamin A. Mellanby's experiments on dogs (123) depleted of vitamin A has shown: 1) nerve degeneration, more especially of the cochlear neurons; 2) new bony growth in the modiolus; 3) overgrowth of the internal periosteal layer of the labyrinthine capsule; 4) degenerative changes in the organs of Corti and sensory epithelium of the semicircular canals. Similar observations have been made in rabbits by Perlman (124), who also noted that a vitamin A-rich diet did not result in restoration of the labyrinthine capsule to a normal state, and that the degeneration in the nerve fibers and ganglion cells were also not reversed. Baron (125) reported the results of treatment of various types of deafness with large doses of vitamin A in 36 patients, and critically reviewed the results of other investigations. Her conclusions were that the optimism concerning the effects of vitamin A on deafness expressed by earlier investigations conducted by Lobel (126), Anderson and coworkers (127), and Bau and Savitt (128) was unwarranted, and that intramuscular injections of vitamin A, according to the method outlined by Lobel (126) was no better than other forms of therapy. Hers is the first dissident note in the investigation of treatment of deafness and tinnitus with vitamin A therapy, and it must be considered that the series of patients were in all cases small and the value of such therapy awaits further investigations before judgment can be pronounced.

G. Physical requirements of vitamin A and carotene.

The latest and now widely accepted broad statement on the requirements of vitamin A was made by the Food and Nutrition Board of the National Research Council in 1948 (129). The Board recommended a daily intake, as a mixture of vitamin A and carotene, of 5,000 i. u. for adults of both sexes, whatever their occupation, of 6,000 i. u. for women in the latter half of pregnancy, and of 8,000 i. u. during lactation. For boys between the ages of sixteen and twenty years, 6,000 i. u. were recommended; for children of both sexes between thirteen and fifteen years, 5,000 i. u.; ages ten to twelve, 4,500 i. u.; seven to nine, 3,500 i. u.; four to six, 2,500 i. u.; one to three, 2,000 i. u.; and for the first year of life, 1,500 i. u. These recommendations are based on the needs during normal good health, and on the premise that two-thirds of the vitamin A value in this country is contributed by carotene and that the latter has half or less than half the value of vitamin A.

Bicknell and Prescott (35) have reviewed the diseased states where the need for supplementation may exist. Those mentioned are: Diabetes mellitus; all diseases which interfere with the digestion of fat; fever; hepatic disease; parasitic infestations of the small intestine.

Caffey, who has contributed much in the way of diagnosis of hypervitaminosis A, and whose experience in observation

of children who have been poisoned by excessive intake of vitamin A is considerable, considers that vitamin A concentrates are probably superfluous (130), certainly expensive, and potentially toxic preparations which should not be placed in the hands of mothers for daily feeding to healthy children. Caffey refers to the statements of Butt (131) who regards the minimal requirement for vitamin A as unknown, and believes that in practice the vitamin A needs of the body are usually taken care of by the mixture of vitamin A and provitamin A in the diet. Caffey decries the commercial advertising of the "magic of vitamins" by pharmaceutical houses, which is designed to create public belief that there is a wide-spread need for daily supplementary intake of vitamin A, that daily supplements prevent and cure a host of indefinite common complaints, and that vitamin A concentrate is harmless.

H. Interaction of other vitamins with vitamin A.

Excessive doses of vitamin A have been found to produce hypoprothrombinemia in some species. Quick and Stefanini (132) reviewed the subject in 1948 and suggested that the cause is likely to be due to the interference in the synthesis of vitamin K in the gut by intestinal flora.

Vedder and Rosenberg (133) in 1938 wrote concerning the toxicity of vitamin A and pointed out that certain features of hypervitaminosis A in rats resemble scurvy due to lack of

vitamin C, and also concluded that supplementation of ascorbic acid prevented much of the pathology due to vitamin A poisoning. Moore and Wang (134) also noted the similarity of scurvy and hypervitaminosis A, but failed to obtain any protection by ascorbic acid against the toxic effects of hypervitaminosis A. Rodahl (135) in 1949 reviewed the subject, and produced a scorbutic picture with excessive vitamin A in guinea pigs and a dog, and noted that the effects of hypervitaminosis A in a guinea pig fed a scorbutic diet were greater. He also observed a drop in blood levels of ascorbic acid of the dog. He concluded, however, that abnormality in the vitamin C metabolism cannot be considered the sole causative factor in hypervitaminosis A. Van Bruggen and Straumfjord in 1948 (136) compared the vitamin C blood levels in 36 patients fed 100,000 units of vitamin A as against 36 control patients. After 36 months, there were no changes in vitamin C levels; in this connection, it will be observed later that this dosage has not been found toxic in adults, however. The effect of hypervitaminosis A on the blood levels of vitamin C is especially interesting in view of the evidence that the synthesis of vitamin C in those animals which are able to synthesize it, depends upon adequate vitamin A. Jonsson (137) stated that deprivation of vitamin A causes a gradual disappearance of vitamin C from the blood, while at the same time changes occur in the incisor teeth which are said to be similar to those seen in the

teeth of scorbutic guinea pigs. Mitolo (138) reports that scurvy reduces the amount of vitamin A in the livers of guinea pigs. Rubin and Bird (139) could not confirm that lack of vitamin A prevents chickens from synthesizing vitamin C.

Moore (140) found that the storage of vitamin A—given weekly as halibut liver oil—in vitamin E deficient rats, was increased from two to ten times when the deficiency of vitamin E was removed. Hickman and his collaborators (141) investigated the subject further. The chief conclusions of their extensive work were: Vitamin E increases the growth-promoting power of vitamin A and carotene and the survival and depletion times of vitamin A deficient rats; there is an optimum ratio between vitamins A and E in the diet; vitamin E is most effective when fed together with vitamin A; injections of vitamin E are ineffective; the effect of injected vitamin A is enhanced by oral vitamin E; a mixture of the three naturally occurring tocopherols is slightly more effective than alpha-tocopherol alone and much more effective than tocopherol esters; the action of vitamin E is enhanced by reducing agents such as vitamin C. Hickman (142) believes that vitamin A in vitamin E deficient animals is drained away from the liver to replenish the blood vitamin A which is lost through oxidation within the blood vessels of the gut. These oxidants diffuse from within the lumen of the gut; normally such oxidants are destroyed within the gut by the vitamin E of the food, which thus preserves vitamin A before absorption.

IV. Past and present uses of vitamin A in therapy.

The purpose of this section is not to evaluate in particular any therapeutic use of vitamin A, except in the light of its future use, as this vitamin in massive doses in therapy has with it the pitfall of toxicosis.

A. Treatment of tinnitus and hearing loss.

The use of vitamin A in massive intramuscular doses in attempted therapy of hearing defects has been discussed. All of the clinical studies have been well controlled and worthy attempts, and have followed the pattern established by Lobel (126) who presented a new injectable vitamin A preparation consisting of olive oil, terpins, and 50,000 units of vitamin A per cc. He gave 50,000 units intramuscularly twice weekly for six weeks, and if he observed favorable progress, the treatment was extended twenty-two weeks, or until the tests showed that maximum improvement had taken place. Such a dose is probably not toxic for adults, but it is interesting to note that Baron (125) in her discussion of the use of the vitamin in this respect, referred to a 1934 report on the innocuous nature of vitamin A and was apparently unaware that sixteen cases of poisoning had been reported up to the year in which she published her work, 1951.

B. Vitamin A in vascular disease.

Vitamin A enjoyed a brief consideration as a possible therapeutic agent in the treatment of arterial hypertension after Villaverde made his first report of a dramatic response of a hypertensive patient to large doses of the vitamin (143); the enthusiasm of Villaverde's article stimulated Wakerlin and Moss (144) to obtain rather irrefutable proof that the hypotensive factor was not vitamin A but some unknown constituent in the sesame oil solvent.

Schneider (113) in Berlin has reported that in seven of eight patients treated for Raynaud's disease, a marked improvement was obtained with 300,000 units of vitamin A daily. The symptoms in three cases were especially severe in the premenstrual period and their disappearance after therapy suggested an antagonism between vitamin A and estrogen, for which idea he obtained support from earlier literature.

C. Use of vitamin A in premenstrual tension.

Argonz and Abinzano (58) recently described the syndrome of "premenstrual tension," which was said to appear from seven to fourteen days before menstruation, vanishing on the first or second day of menstrual flow, and consists of variable symptoms such as nervousness, emotional instability, insomnia, headaches, depression, physical asthenia, neuralgia, fainting, tenderness of the abdomen, and rapid weight gain due to fluid retention which is followed by a fall to the previous level

following menstruation, cyclomastopathies of all sorts from simple painful distension to the actual formation of nodules and glandular cysts. They observed considerable improvement in thirty patients by oral administration of 200,000 units per day in two doses after meals. They found it necessary to treat for three or four months. The authors cite Frank (145) and the fact that most other authors agree with the latter in that the cause of premenstrual tension is an excess of circulating estrogen. Argonz and Abinzano contend that vitamin A acts by modifying a disorder in the metabolism of estrogen; this view is shared by Schneider (113) whose article, already referred to, appeared later. It can be expected that vitamin A will be used in the treatment of premenstrual tension in the future.

D. Vitamin A in visual disorders.

Aside from the long established virtue of treating nyctalopia with prophylactic amounts of vitamin A, there have been one or two suggestions that vitamin A was of further use in visual disorders. The Staff of the Aligarh Eye Hospital in India (146) have reported briefly of their success in treating certain cases of "asthenopia" which had resisted correction of refractive errors, by administration of vitamin A.

Feldman (147) cites the theory for the cause of myopia which involves avitaminosis A and hypocalcemia, and believes it

possible that some myopes may have been benefited by treatment with vitamin A.

E. Vitamin A and the respiratory system.

Frequent respiratory infections have been frequently reported as occurring with a deficiency of vitamin A (148), but this is not of much concern to this paper in view of the fact that normal prophylactic doses or simply a normal diet (149) have been shown to be as preventive to the degree that nutritional adequacy can be, and supplemental increases are of no value in this respect. Of greater interest is the report from Scandinavia by Strandbygard (150) of cure of all cases of ozaena, or atrophic rhinitis, a disease of the nasal mucosa characterized by mucosal crusting and a foul, offensive odor, which have come under his supervision. In the typical case, the disease yielded to about ten to fifteen injections of "Arovit," an injectable vitamin preparation, of 300,000 units per injection, combined with a daily dose of four to six "Arovit" tablets, or about 50,000 units orally. The author states that the vitamin is also capable of giving good results in chronic rhinitis sicca, a disease characterized by chronic congestion, diminution of secretions and abnormal dryness of the nose and pharynx—there is no atrophy of the mucosa though there is crusting, and the secretions have a musty odor—which distinguishes it from atrophic rhinitis.

F. Vitamin A and kidney stones.

Higgins of Cleveland reported in 1935 (92) on eighteen cases of renal calculus which were treated with high doses of vitamin A and an acid ash diet. He claimed that all stones disappeared roentgenographically under this regimen. West and Todd (36) give credibility to this idea, but there is a dearth of information in the literature showing success of others in using this treatment, and belief in the efficacy of this regimen or any other method of dissolution of kidney stones is not shared by midwest urologists (151).

G. Treatment of fissured nipples.

Vitamin A and vitamin D combined in ointment for use in local application was first used by Weissberg in 1940 in Russia with success in the treatment of fissured nipples, according to Brougher (152). The latter reports that this ointment is valuable in preventing and treating painful and tender post-partum nipples, with and without gross fissures, and indicates a preference for this mode of treatment over any other method. Ointments containing vitamins A and D for this purpose have come into wide use today.

H. Vitamin A and skin disease.

The literature concerning use of vitamin A in diseases of the skin is voluminous, but in examination of the many ac-

counts of successful employment of vitamin A, one is led to the observation made by Sainz de Aja (153) who stated that, in general, vitamin A is indicated in hyperkeratotic states.

Darier's disease, or keratosis follicularis, is one condition which responds at least in part to dosages of 100,000 to 200,000 units per day (154, 114). This disease is characterized by small, uniform, firm, reddish-brown, greasy keratinous papules which subsequently become coalescent, papillomatous, crusted, and acquire an offensive odor. Tye (154) reports that the above treatment when used with local ointments of vitamins A and D is helpful, but not in all cases.

Acanthosis Nigricans is another skin lesion which has been reported to be benefited by the oral administration of 24,000 units of vitamin A per day for an indefinite time; the disease appears as patches of gray-black warty hyperkeratosis in the absence of vitamin A deficiency. The vitamin therapy does not affect the pigmentation, but benefits only the hyperkeratotic element of the disease (155).

Acrodermatitis pustulosa perstans has long been recognized as a difficult disease to treat. It is characterized by hyperkeratotic and recalcitrant pustular eruptions of the palms and soles. Fishman (156) describes three typical cases which have showed clinical clearing on a regimen of 150,000 units of vitamin A orally per day, frequent application of 5% coal tar

solutions, and weekly suberythema doses of radiation from a cold quartz lamp. Clearing took two to ten weeks.

Fisher and Chamberlain (157) described treatment of all kinds of plantar warts with 100,000 units of vitamin A per day orally in addition to mechanical filing. They reported a cure rate of 35.6% in treatment varying from four weeks to nine months; it is conceivable that this modality may be used further due to the well-known hazards of irradiation and surgery in treatment of these lesions.

Vulvar leukoplakia are of unknown etiology and treatment has always been empirical. Hyans and Gallagher (158) consider 42 cases seen and treated with vitamin A alone or in combination with another agent. The daily oral dose varied from 250,000 to 500,000 units and intramuscular injections of 50,000 units twice weekly. Fourteen of the 42 patients treated for varying periods from 4 months to 5 years had subsidence of symptoms and were histologically normal at the end of therapy. Thirteen patients treated at irregular intervals for the same variable periods had subsidence of symptoms but recurrences. The remainder of their patients showed less encouraging results. The improvement seen warrants further study and trial of vitamin A, and it seems likely that such will ensue.

Porter (159) wrote a recent paper to present evidence that certain defects of the skin, often hereditary, are commonly

accompanied by low plasma levels of vitamin A, and showed evidence that keratosis palmaris et plantaris, ichthyosis, and pachyonychia were benefited in some cases on 100,000 units of vitamin A daily for three months or longer. He believes the etiology in some of these cases is a vitamin A "dysmetabolism" incidental to faulty ectodermal development.

Webster and Falk (160) mention the agreement of many investigators that some disturbance of vitamin A metabolism is important in the causation of another skin disease, pityriasis rubra pilaris. They recognize that very little is known concerning the mechanism of utilization of vitamin A by the skin in the normal person, or how it is interfered with in this disease. They used 50,000 U. S. P. units of vitamin A in combination with corticotropin (15 mgm. q.i.d.) daily for 20 days, after which vitamin A alone was continued for 67 days. The authors report 90 to 100% improvement at the end of this therapy; however, signs of recurrence showed after one month without therapy. Other clinicians (161, 162, 163) have reported marked improvements with doses ranging from 50,000 to 150,000 units per day, with or without various additional agents. There is little doubt of the value of vitamin A in therapy of this rare disease.

Another skin condition resembling acne vulgaris is apparently a vitamin A "deficiency." Straumfjord (90) has made critical studies of a number of such cases. The acne cases which

were successfully treated responded only to large doses (100,000 U. S. P. units) daily over long periods of time. Of 100 acne cases studied, 79 became free or nearly free of the eruption, while only three were unimproved.

Lobitz and Kierland (164) state that many authors are in agreement that miliaria rubra (prickly heat), a phenomenon of sweat retention resulting from hyperkeratotic plugging of the orifices of sweat glands, is related to subnormal utilization of vitamin A. These authors and Tolmach (165) report cases in which miliaria have subsided and sweating has been produced on treatment with 50,000 to 200,000 units of vitamin A daily.

Chalazion is a chronic infection of the meibomian gland, forming a hard swelling which gradually develops in the eyelid. Hickey (166) likens the pathology of chalazion to the effects of vitamin A deficiency. He cites the action of the liver in vitamin A synthesis, the inhibition of Kupffer's cells in diabetes, and the frequent occurrence of chalazion in diabetics. He uses 50,000 to 100,000 units for several weeks in the treatment of early chalazion, and as a preventive following surgical removal of large, long-standing chalazia. Vitamin A alone is of no value in treating long-standing chalazia. He is convinced of the efficacy in early chalazia, and mentions that his therapy has been innocuous except for transient diarrhea which developed in a few patients.

V. Vitamin A toxicosis.

As is suggested in the title, this section incorporates the main emphasis of this writing. Previous sections have been quite long, but it is perhaps unwise to consider the pathologic physiology of excessive vitamin A without a consideration of such prerequisites.

A. First reports of toxic effects of vitamin A.

Rodahl and Moore (167) wrote in 1943 that Eskimos and Arctic travelers have long been acquainted with the fact that ingestion of polar-bear liver by man dogs resulted in severe illness. They cite the early accounts of the phenomenon and in particular the writings of Lindhard in 1913 who reported poisoning among members of an expedition to Franz Joseph Land, after eating a stew prepared from the liver of a bear. The first signs of distress occurred in two victims two to four hours after the meal, and most of the others became ill during the night. The symptoms described were drowsiness, sluggishness, irritability, irresistible desire to sleep, severe headache, and vomiting. During the second twenty-four hours, the skin of ten of the nineteen men began to peel around the mouth, beginning in spots and gradually spreading over larger areas. In some cases the peeling was confined to the face, but in others it was general. The authors state further that one of them made a then recent expedition to northeast Greenland in 1939-40, and collected specimens

of polar-bear liver with a view to identifying the toxic substance. On chemical and biological examination these specimens were found to be very rich in vitamin A, as was a specimen of liver from a seal, Phoca barbata, which had also been reported to have a poisonous liver. The bear livers contained about 20,000 i. u. of vitamin A per gram of wet liver, which would be 7,500,000 units in three-fourths of a pound of liver, presumably enough to cause a reaction, not being an excessive portion to be eaten at a single meal.

Prior to Rodahl and Moore's investigations, Drigalski and Laubman (168) in 1933 administered 0.5 and 1.0 cc. daily of a concentrate of fish liver oil called "Vogan"(which contained 40,000 rat units of vitamin A per cc.) to rats weighing 100 grams. Their coats became rough; cachexia, catarrhal conjunctivitis, hemorrhagic rhinitis, and diarrhea developed. Death occurred within five to eight days in the animals receiving the larger dose, and within seven to nineteen days in those receiving the small dose. At autopsy they found degeneration of the renal glomeruli and tubules, proliferation of the reticulo-endothelial cells of the spleen, absence of striations in some of the cardiac muscle fibers, degeneration of the testes, and only slight changes in the liver. Moll, Domagk and Laquer (169) reported similar injuries in mice in the same year. At the same time Collazo and Rodriguez (170) conducted similar experiments with

rats. In addition to trophic changes of the skin and loss of hair, they noted inflammatory changes of the eyes, bilateral exophthalmos, cessation of growth and spontaneous fractures of bones. When the overdosage was stopped, the animals recovered and gained weight. Fasold (171) in 1934 added to the list of pathologic lesions fatty infiltration in the Kupffer cells of the liver.

B. Clinical reports of vitamin A poisoning.

Josephs in 1944 (64) published the first clinical account of vitamin A poisoning in a child, and summarized the experimental data up to that time. Toomey and Morissette (172) in 1947 published the second recorded case, which was followed in 1948 by a report of two cases seen by Rothman and Leon (173) and one by Dickey and Bradley (174). By 1950, an increasing awareness of the entity of vitamin A poisoning resulted in the report of two cases by Fried and Grand (175), seven cases by Caffey (176), several of which were re-evaluated cases which had not been correctly diagnosed in the past, another case by Berrey (177), and one by Wyatt, Carabello, and Fletcher (178). Since 1950, ten more cases have been reported, and pertinent data from case records have been tabulated in Table 2 in all of the twenty-six cases reported at the time of this writing.

All cases reported have occurred in the United States.

TABLE 2

TABULATION OF CLINICAL DATA IN ALL CASES OF HYPERVITAMINOSIS A REPORTED TO DATE

Author & Ref.	Age at Onset & at Diagnosed	Symptoms and progress before diagnosis	Amount of Vitamin A	Physical Examination	Plasma Vit.A Level per 100ml	Serum Ca Mg.%	Serum P Mg.%	Serum Alk. Phosphatase Bod.u.	Roentgenographic Findings	Course after discontinuing vitamin A
Josephs 1944 (64)	Onset-18 mo. Diagnosed at 3 yrs.	Appetite decreased; disinclined to play; hemorrhage after tonsillectomy 8 mo. after onset; diagnosed Gaucher's dis. at 16 mos. of illness	Since age of 2-3 mo., 1 tsp. halibut liver oil daily (240,000 USP units q.d.)	Increasing anemia at 8 mo.; thinning, dry, coarse hair at 8 mo (after onset); hepatosplenomegaly at 8 mo.; slightly clubbed digits	910 USP units	10.1	4.5	19.3	Thin cortex and vacuolated medullary cavities in phalanges & metacarpals; epiphyses of upper ends of humeri and tibiae were mottled	Within 2 mo., appetite improved, gained weight, hair began to grow back
Toomey & Morissette 1947 (172)	Onset-17 mo. Diagnosed at 23 mos.	Intense itching--became severe; intermittent swelling & tenderness of fore arms & lower extremities until 2 yrs old; irritability; anorexia; constipation; craved butter	1-2 tsp. cod liver oil q.d. plus 1-2 tsp. Oleum Percomorphum daily since newborn period (250-500,000 u/d)	Hair dry, coarse, sparse; lips dry, cracked, bleeding; tender over femur, both radii and tibiae	700 IU	11.0	4.5	.62 mg.	Periosteal line on right femur and left tibia; pronounced periosteal thickening of ulnae; broad growth lines, all long bones	Within 5 days periosteal pain and tenderness disappeared
Rothman & Leon 1948 (173)	Onset-5 mo.; Diagnosed at 14 mos	Pruritus without rash at 5 mos., accompanied by irritability & anorexia; wrist pain since 9 mos.; Sparse hair since 1 yr.; cracked, bleeding lips for a few weeks	Oleum Percomorphum since 3-4 wks old; 1 tsp since 9 mos; 10 gtts. Vifort added at 6 mos. (130,000 units per day)	Yellow skin; fine scars; hair sparse; liver palpable; unable to stand; irritable	2,081 IU	7.6	4.1	11.9	Periosteal reaction on both clavicles and ulnae	Within 24 hr., child stood and physical activity increased; bone tenderness disappeared; appetite better and irritability decreased
Ibid.	Onset at 6 mos.; Diagnosed 22 mos	Painful extremities; irritability; erythematous rash with pruritus; difficulty walking	O.P.* since 1 mo.; At 10 mo., 12-20 gtts./d., plus 250,000 u. Squibbs Vit. A; at 16 mo., 20-25 gtts OP/d & 50-100,000 u. Vit. A (100-200,000 u./d.	Hair fine, dry, and coarse; lips dry & cracked; pruritic marks on trunk; hepatomegaly	600 IU	12	5	8	Periosteal proliferation of ulnae and left clavicle	Within 1 wk., pain in extremities and tenderness gone; by 1 mo., symptom-free
Dickey & Bradley 1948 (174)	Onset at 18 mos; Diagnosed 3 yrs.	Intense pruritus at 18 mos.; painful extremities for 2 mos.; difficult to walk; lump on head for 6; Restless sleeper-phenobarbital necessary	Since newborn 3 tsp Navitol & large amounts cod-liver oil plus 10 gtts. ViPenta, large amts butter (total: 400,000 u. for 1½ yrs.)	Thin, coarse hair; erythema of left arm & leg; dry, excoriated skin; hepatomegaly; irritability; tender arms and left leg	943 IU	10.2	5	17	Periosteal elevation of forearm bones; irregular left femoral epiphysis; slight calcification extending into interosseous membranes, both forearms	Improvement within few days; stopped limping, appetite better; mother repeated cycle 3 more times

Author & Ref. No.	Age at Onset & at Diagnosis	Symptoms and progress before diagnosis	Amount of Vitamin A ingested	Physical Examination	Plasma Vit. A Level	Serum Ca Mg.%	Serum P Mg.%	Serum Alk. Phosphatase Bod.u	Roentgenographic Findings	Course after discontinuing Vitamin A
Fried & Grand 1950 (175)	Onset-5-6 mo. Diagnosed 3 yrs.	At 5-6 mo., constant state of irritability and itching; periods of remission & relapse; extreme irritability & tender extremities short period prior to diagnosis; 10 days " to hosp., vomiting & anorexia; reddish desquamating rash since onset; diarrhea & dark urine at time of hospitalization	Since 2 wks of age 30 gtts. O.P. q.d.; gradually increased in few mos to 2 tsp. q.d. for a year (500,000 u.)	Tender upper & lower extremities; swellings of upper extremities; excoriated, erythematous, brawny, desquamating rash; hepatomegaly; chose supine, immobile, outstretched posture; nonpitting edema	1,630 IU	10.3	4.6	35	Thickened periosteal areas of mid-ulnae; lateral bowing of shafts of bones of lower extremities, with widening of bone ends and slight sclerosis	Improvement within days; RG studies in 3 wks. showed evidence of healing (smoother epiphyseal surfaces)
Ibid.	Onset-22 mos & diagnosed at 2 yrs.	Protracted severe pain & tenderness of all 4 extremities, since 2 mos.; Slight rash over forearms; generalized itching; Irritability, crying, anorexia with wt. loss, same duration; craved butter	½ to 3/4 tsp. O.P. daily for "many" mos. (120-180,000 u./d.); ¼-½ lb. of butter on many occasions	Sparse, coarse hair; Hepatomegaly; excoriations; tender extremities; pinched, anxious facies; brawny, scaly, eczematoid skin over mid-extremities; swollen extremities	700 IU; 1600 IU; 2500 IU	10.4	4.8	26	Periosteal thickening involving middle 1/3 of tibiae, left ulna, & lower right ulna	Slowly made a complete recovery.
Caffey 1950 (176)	Onset-19 mos Diagnosed 25 mos	Anorexia for 6 mos; pain in legs for 4 mos; painful swollen left shank & foot-could not wear shoe; refused to walk; heavy night sweats; fatigueability since onset	O. P. in amount of 150,000 u/d of Vitamin A for "several months" before onset of symptoms.	Cracked lips; tender swellings in occiput, forearms, ventral surface of rt. shank; lateral aspects both feet	not done	10.6	4.3	18	Cortical hyperostoses of clavicles, right & left 7th ribs, right femur, left tibia, rt. fibula, all save first metatarsals	Appetite returned in few days; pain & tenderness mostly gone in 4 days although swellings persisted; discharged asymptomatic in 22 days
Ibid.	Onset-19 mos Diagnosed 21 mos	Restless, "whiny" at 19 mos.; painful, tender lump on rt. shin at onset; refused to eat and walk 3 wks before hosp.; marked insomnia & heavy sweats for 3 wks before hosp.; could not bear heavy bedclothing, resisted handling; hard lump on occiput-1 wk. dur.; tender rt. foot & left arm, 2 wks.	One tsp. O.P. q.d. for 7 mos. before and 2 mos after onset (250,000 u/d)	Dry, cracked lips; bilateral clavicular swelling, swelling of anterior left tibia; exceedingly irritable & apprehensive of being touched; lump on occiput; tender swellings left forearm, dorsum of rt. foot	330 IU	Not done	Not done	Not done	Multiple cortical hyperostoses on both ulnae, both clavicles, left tibia, and both 5th metatarsals	Asymptomatic in 4 days though swelling still present---these gone in 2 weeks; hyperostoses barely visible in films at 6 wks.

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Berrey 1950 (177)	Onset-28 mos diagnosed at 29 mos.	Pain in shoulder for 4 wks; limp due to painful feet 2 wks; enlargement of head for 3 days; coarse thinning hair; constant pain in the ears; irritability since onset; 3 days before admission, increased irritability, photophobia, and extreme lassitude with fever of 38.2°C.	37,500 i.u. vit. A per day since 1 yr. of age (for 14 mons before age of onset of symptoms)	Temp.: 38.2°C. on admission; hyperirritable; mild photophobia, positive MacCewen's sign; seborrheic placques over rt. shoulder & thighs; hair dry and coarse; bilateral non-pitting soft-tissue swelling from zygoma to temporomandibular junction	Not done	17.6	3.6	15.4	Skull showed enlarged posterior fossa and a scaphocephalic contour; periosteal thickening of distal right ulna; similar fusiform calcification of clavicles, rt. 7th rib, and shaft of left 5th metatarsal.	In 2 wks., all symptoms except disinclination to walk were absent; in 4 wks., still some pain in feet, lasting 8 more weeks; RGs at 12 weeks showed resolution in hyperostotic areas and at 8½ mos. all abnormalities had disappeared.
Gribetz, Silverman & Sobel 1951 (182)	Onset-27 mos diagnosed 30 mos	At 27 mos., a pruritic rash on buttocks, back, & abdomen. Fissures of lips, sores in corners of mouth, same time. Ten days later, crying on handling, rt. leg tender to touch. 2 mos. before admission, became less active and preferred not to walk. Two weeks later arms became painful. Patient remained in bed, very irritable.	Ten gtts. O.P. daily 1st yr. of life; at 1 yr. O.P. discontinued and 1 tsp. Infadol given. (more than 100,000 USP units daily for 1½ years)	Irritable; thin; slight bony protuberances over temporal areas; immobile, ill-appearing; coarse, sparse hair; fissured lips hepatomegaly; meatitis; tender extremities	2,790	11.5	2.9	12	Thinning of bony structures of forearms and lower extremities with slight thickening of cortex in midportion of left ulna and lateral aspect of right tibia; increase in density of epiphyseal lines	Within 3 days, the extremities were less painful; began to stand and walk. Perioral lesions disappeared and patient discharged in 9 days. In 9 mos., RGs showed less dense epiphyses and decreased periosteal change
Ibid.	Onset-10(?) mos.; Diagnosed 17 mos	Hospitalized at 10 mos. with diagnosis of rickets and early hydrocephalus. 2 mos. later, refused all foods except water and fruit juices; became irritable, slept poorly, did not walk well because of "weakness." Lost weight.	At 10 mos., total intake was 240,000 u/d., since 4 mos. of age (prescribed because of earlier diagnosis of celiac disease)	Irritability; refused to walk; regression in development; thin; enlarged head, with prominent forehead with asymmetrical anterior fontanelle and paucity of scalp hair	Not done	12.4	4.6	16.3	Slightly dilated ventricles on pneumoencephalogram and ventriculogram at 10 mos. At 17 mos., cortical thickening (subperiosteal) of the tibiae and ulnae	Patient did well immediately, with increased appetite and weight gain; physical examination at 4 mos. revealed a normal child

Author & Ref. No.	Age at Onset & at Diagnosis	Symptoms and progress before diagnosis	Amount of Vitamin A Ingested	Physical Examination	Plasma Vit.A Level per 100ml	Serum Ca Mg.%	Serum P Mg.%	Serum Alk. Phos-phatase Bod.U	Roentgenographic Findings	Course after discontinuing vitamin A
Ibid.	Onset-11 mos; diagnosis-12 mos.	Soreness of left shoulder, swelling and failure to use left arm, 3 wks. duration; no constitutional symptoms	Two tsp. O.P. q.d. for 6 mos.(400,000 to 600,000 units per day)	Pruritic areas on body; left forearm had tender swelling	1,384 IU	9.9	4.8	19	Bilateral cortical hyperostoses of ulnae	Asymptomatic in 4 days
Ibid.	Onset-31 mos.; diagnosed-32 mos.	Painful feet-3 wks. duration; tender swellings of left hand, arm & shin of 12 days duration; generally irritable; several nosebleeds in past ten days	Ten gtts.O.P. q.d. from 6th wk. of life until 17 mos, then increased to 1 tsp.daily for 15 mos.	Long,hard, tender swelling over ulna of left arm, left thumb, left 2nd metacarpal, & left tibia; feet & left wrist swollen	Not done	10.7	4.9	19	Hyperostoses in 2nd left metacarpal, both ulnae & tibiae & fibulae	Hospital course uneventful
Ibid.	Onset-a few wks. before admission at 18½ mos.	Pain in bones of a few weeks' duration; appetite had always been poor; fell and bruised leg 2 weeks before and had leg pain since	Drisdol with Vit.A 1 dropperful daily from 1 wk. till 1 yr., then increased to ½ & then 3/4 tsp. After 13th mo, 1 tsp q.d.(250,000 units of Vitamin A)	Both hands and forearms, and left shank swollen and tender; hepatomegaly	1,395 units	10.5	3.6	9.7	Cortical hyperostoses of both clavicles, 6th & 7th right ribs, both ulnae, rt.radius, left tibia, rt.fibula, 4th & 5th rt. metatarsals, both 4th metacarpals	Clinical recovery rapid
Ibid.	Onset-22 mos.; diagnosed-2 yrs.	Pain, tenderness, and swellings of the extremities for 2 mos.	100,000 u.q.d. for 7 mos before admission (for 5 mos. before onset of symptoms)	Short periods of fever, soon disappearing completely; swollen, tender feet and ankles	Not done	Not done	Not done	Not done	Cortical thickenings of ulnae and 5th metatarsal	Rapid recovery-a few days became remained asymptomatic
Ibid.	Onset-32 mos.; diagnosed-37 mos.	Pruritic rash on back for 6 mos.; arms & legs tender-2 mos.; frequent limping; refused to bend due to pain	One tsp.Navitol q.d.for 17 mo.(12 mos.prior to onset of symptoms	Tender extremities and dry, excoriated skin; hepatomegaly	Not done	10.8	5.2	22	Cortical hyperostoses of clavicles & ulnae	Recovered quickly the hospital and mained well for th ensuing 4 years
Wyatt, Carabello and Fletcher 1950 (178)	Age-2 yrs.; 2 weeks of symptoms	Anorexia, tenderness of extremities, low grade fever, weakness, irritability, severe generalized pruritus; sensation of walking on stones; cried on handling	400,000 to 600,000 units per day since 14 mos. old, as O. P.	Skin pale yellow; severe excoriations on back and legs; weakness; arms tender, gait unsteady; extreme irritability; cervical adenopathy	423 units	Not done	Not done	Not done	RGs of long bones showed cortical hyperostoses along medial aspect of midportions of shafts	Pruritus subsided a few days; recove apparently complet in 1 month; RGs at mos showed both ul nae to be normal

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Arena, Sarazen, & Baylin 1941 (191)	Onset-6 mos.; diagnosed at 6½ mos.	Born with large anterior fontanelle--because of this, supplementary vitamins prescribed; at 6 mos of age, a swelling appeared on rt.foot; softening of skull noted at same time; feet and arms tender; so irritable, had to be carried on pillow.	O.P., gtts.10 twice daily from birth to 4 mos., plus ABDEC gtts.10 once daily; at 4 mos., O.P. increased to 20 gtts.t.i.d., plus ABDEC as before (From 4 mos., 80,000 USP U./d.	Temp.38°C., pulse 160/min.; entire skull of ping-pong ball resistance of craniotabes; bony fusiform swelling distal end of 5th rt.metatarsal; pain on moving upper left extremity; liver down 2 cm.	860 IU	10	5.9	17.9	Skull bones thin; mandible normal; hyperostosis of both clavicles; irregular metaphyseal plates of femurs, tibae, fibulae; hyperostoses of left ulna and right 4th & 5th metatarsals	Rapidly became less irritable, ate better; pain decreased and skull became firmer; at 2 mos., gain in wt., ulnar hyperostosis not obvious to RG; normal metaphyseal details, no craniotabes
Bair 1951 (190)	Onset-2½ weeks before admitted at age 28 mos.	Painful swellings of left foot, right forearm, & temporal regions; itching of back & forearms; ceased to walk few days after onset; preferred butter & carotene vegetables until onset-then rejected food	240,000 u./d. as O.P. for at least 3 mos.; ate sizeable amounts of butter & carotene-vegetables	Appeared sick & in pain; stiff neck; irritable; puffy face; fissured lips; bilateral temporal swellings; swelling along 5th metatarsal; rt.forearm swollen	1,040 IU	Not done	Not done	Not done	Cortical hyperostoses of distal left radius and middle right ulna middle 1/3 rt. femur; middle 1/3 rt.fibula; 5th left metatarsal and skull bones	Walked within 3 days; appeared happy and improved. Foot swelling gone in 1 mo.; head swellings persisted but nontender; all other hyperostoses gone; Blood Vit.A: 750 IU
Rineberg & Gross 1951 (183)	Onset-34 mos.; diagnosed at 35 mos.	At 34 mos, pain, limp, swelling of left ankle--persisted; in few weeks hard mass developed on lateral surface of left leg; had become intensely irritable; wrists swollen and skin dusky; refused to eat; hospitalized 1 mo. later lacking sleep	185,000 u/d for 9 mos. before onset, as Navitol (advised to use 5 drops/d for rickets--used rather 1 tsp. daily)	Intensely irritable; cried when attempted to pick up objects or eat; swollen wrists, left leg & ankle; mandible swollen; tender soft tissue lumps on the calvarium	marked increase	Not done	Not done	Not done	Subperiosteal calcification of left lateral distal fibula, left ulna; thickened mandible; biopsy of left fibula showed changes of "productive periostitis."	Recovery
Salzberger & Lazar 1951 (180)	44 yrs. at diagnosis; onset 6 mos. earlier	Night sweats for 6 mos.; fissured lips 5 mos.; hypomenorrhea 5 mos.; excessive hair loss & generalized pruritus 2 mos; brawny desquamation of skin 2 mos.; migratory joint & bone pain-2 mos-never severe enough to prevent housework	600,000 u./d for 18 mos., supplemented by doses of 1-2,000,000 units on suspicion of oncoming colds or dry throat; took no vitamin D	Tender large joints and long bones & spine; slight exophthalmos; skin dry; hair dry, loose coarse & sparse; chloasma-like pigmentation on face & neck; pruritic, scaly dermatosis	60 blue units **	9.2	3.5	4.0	No abnormality	Bone & joint pains gone in 10 days; hair began to return in 4 weeks; skin normal by 4 mos., except for residual pigmentation); night sweats gone; menstrual cycle normal at 6 mos; pigment grad. fading

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Naz & Edwards 1952 (186)	Onset-2½ mos.; diagnosed at 9 mos	Parieto-occipital alopecia at 2½ mos.; maculopapular dermatitis of neck & scalp at 3 mos.; frontal bossing at 6 mos. at 8½ mos., irritability and tender forearms and wrists following a fall	8 droppersful given (instead of 8 gtts. as advised) q.d. since 2 wks. of age (200-300,000 units/d. for 8½ months)	Swollen & tender distal forearms; head enlarged with frontal bossing; liver palpable 2½ finger-widths below right costal margin	1,121 IU	11.5	3.0	3.4	Cortical hyperostosis of clavicle, radii, ulnae, fibulae and ribs	Rapid regression of complaints
Reyersbach, Hanelin, & Joplin 1952 (184)	Onset-33 mos.; diagnosed at 3 yrs	At 33 mos., a pruritic rash appeared on back of head & soon spread all over body; at same time, lips cracked & bled; 3 wks. before admission, developed soreness of rt. forearm & hip, & falling hair. Irritable since onset; cried on handling	O.P. increased to 1 tsp. (240,000 u.) per day since 2 yrs. of age on suspicion of rickets by MD	Irritable; thick skin with consistency of edema; diffuse erythema of trunk & extremities; lips dry and cracked; genu valgum; limped; tender swellings on right leg	2,670 IU	10.3	3.6	3.8	Periosteal new bone formation of clavicles, rt. 2nd & 7th ribs, left 2nd, 8th to 10th ribs, ulnae, fibulae, right femur & tibia, left 4th & 5th and right 5th metatarsals	Improvement within days; became active and rash gone in 1 week; walked in 3 weeks, developed a ravenous appetite; X-ray of skeleton at 8 wks. showed increased density of lesions
Kane 1952 (181)	Age: 8 years; onset 1 mo. before admission	Pains in calves & thighs since infancy--increased recently; skin rash 1 mo., scattered, discrete macular lesions of face, neck, & interscapular area--quite pruritic	50-100,000 u. per day as Theragran capsules for 1 yr.; also consumed considerable milk, butter, & carotene vegetables	Excoriated macular skin lesions; palpable nontender liver (not present 1 yr. previously); faint aortic systolic murmur	413 IU	Not done	Not done	Not done	No abnormal skeletal findings	Liver receded one finger-width in 2 mos.; myalgia remained--felt not due to vitamin A
Goldzier Pisacano & Wald 1952 (185)	Onset-18 mos.; diagnosed at 24 mos.	Became bowlegged at 14 mos.; at 18 mos., generalized itchy rash, worse on extensor surfaces; hyperirritability at 21 mos.; suspected early tibia vara, advised to "give adequate vitamins"-at this time, legs & feet exquisitely tender	O.P. 4 drops per day from 3 wks. to 3 mos. of age; then increased to 6 drops/d.; 10 to 18 mos., 10 drops/d.; then increased to 4 droppersful (120 drops) daily; at 22 mos, 8 droppersful daily (1 drop has (1250 units Vit.A)	Irritable and uncooperative; undernourished; complained at being touched; skin dry, scaly & scratched; forearms swollen; tibiae bowed; liver down 1 finger-width	**100 blue units	8.6	4.6	6.8	Bilateral symmetrical cortical thickenings of ulnae, anterior surfaces of tibiae, & 2nd to 5th metatarsals, corresponding to tender areas in arms	Improvement within 48 hours--hyperirritability, bone tenderness & pruritus diminished; after 14 days, child asymptomatic, rash almost cleared

*O. P. = Oleum Percomorphum

**Blue Units are the method of reporting used by Clausen and McCoord (210), where 10-20 units are normal

It is interesting to note that none have occurred in Great Britain, where much of our knowledge concerning vitamins has been gained. It is possible that cases of toxicity have occurred elsewhere, judging from titles of several indexed articles which are not available to the writer. Caffey, in an editorial on the subject written in 1952 (179), states: "Personal correspondence indicates that there are many more unrecognized cases of severe chronic vitamin A poisoning in practically all parts of the country."

Caffey deplores the lack of understanding on the part of the layman, and believes that until the whole truth concerning vitamin supplementation becomes available to the public, all authentic cases of toxicity should be carefully recorded and widely published in the medical literature.

Judging, then, from the increasing recent reports, and the demonstrated lack of knowledge among laymen, nurses, and even physicians, the matter of vitamin A toxicity is a timely subject.

D. Methods of Poisoning.

It is believed that it may be worthwhile to discuss the factors which led to excessive ingestion of vitamin A. The most obvious and frequent of these is the zeal of a person who is "sold" on vitamins. In considering the case reports, this

was the single factor in thirteen of the twenty-six cases. The typical example is that reported by Salzberger (180) of an adult woman who listened to a "nutrition commentator" on the radio and "got the point" that vitamin A was good for alleviating dry throats and as a prophylactic against colds. In another case, Kane (181) relates that the mother was a Registered Nurse who suddenly decided that her child needed more vitamins, indicating what has become obvious to the writer, that vitamin A toxicity as an entity is unknown to exist among most nurses and many physicians, and certainly has not been, in the experience of the writer, stressed in medical education.

Another factor that seems to have shown with frequency is the mistaken concept that Oleum Percomorphum, a Mead-Johnson proprietary fish liver oil vitamin concentrate, is equal in content to cod-liver oil. This concentrate figured in seventeen cases. In several, this preparation was furnished by druggists when the mother was of the belief that she was getting cod-liver oil (176).

Three cases were induced therapeutically because of diagnoses of celiac disease (182) , and rickets (182, 183, 184). These diagnoses resulted in the increase of vitamin supplements.

Misinterpretation of toxicity symptoms has compounded the error in dosage in several cases. Dickey reports (174) in one case that originally, zeal for vitamins resulted in excessive

dosage, and that when symptoms of chronic poisoning first appeared, the mother increased the dosage because she feared a vitamin deficiency. A similar case is reported by Goldzier (185), where the signs and symptoms of toxicity were misinterpreted by an orthopedic surgeon, who told the mother to "give the youngster an adequate vitamin intake." This occurred in 1950.

Other factors have been: 1) Eagerness to make up an established deficiency of vitamins, and 2) mistake in dosage, as in the case reported by Naz (186), where eight droppersful were given instead of the prescribed eight drops.

A point worthy of mention is that parents may not be convinced that excessive vitamin intake is the etiology of the syndrome. Dickey reports (174) that the mother repeated the cycle of poisoning three times before she was impressed, even though told at the time of diagnosis.

Yet another feature is the seeming reluctance of some mothers to admit that they have been dosing their children excessively. Toomey and Morissette (172) met with persistent denials until they confronted the mother with irrefutable laboratory proof of excessive intake.

E. Ages and groups affected.

Examination of the case reports reveals that there is

exactly equal sex distribution in the incidence of vitamin A poisoning, counting the one adult case. It appears that there is no reason to believe any peculiar susceptibility on the basis of sex difference.

Until the single adult case was reported (180), it was presumed that vitamin A poisoning was peculiar to children, but it now appears that any age can be affected. If one is to judge by this single adult case, then the picture in adults is different and may be termed milder, perhaps. One other case, seen by Kane (181), occurred in a child of eight years, and here too, signs and symptoms were "milder." Neither of these cases showed abnormal roentgenologic findings. In all of the other cases, a diagnosis was made at about three years of age, or younger. It may be concluded that it is still a pediatric problem. Salzberger and Lazar (180) logically interpret the differences in the clinical picture between the adult and young child or infant to the differences in physiological, chemical, and general body economy. Apparently the mature structure of bone is not so labile as a child's in its response to outside influences. Wolbach (187) made the following statement in connection with his extensive studies in laboratory animals: "It should be kept in mind that the results on bone of excessive vitamin A administration are exhibited only in the growing animal and only in regions undergoing growth." Moore and Wang (188) in

1945 noted the same findings and wrote: "In adult rats, the bones are probably more resistant to fractures, since we detected no breakages in our older animals."

Many authors have expressed wonderment at the paucity of clinical reports of vitamin A toxicity. Fried and Grand (175) believe that this is due to the lack of recognition rather than lack of existence. They also express their belief that some metabolic function involving vitamin A storage is impaired in some individuals, resulting in poisoning. Kane (181) expressed a similar belief, with somewhat more basis for his belief, however, his patient having a younger brother, age 6, who ingested approximately the same amounts of vitamin A without developing signs or symptoms. Perhaps the case of Berrey (177) where 37,500 i. u. were ingested daily, yet resulted in a toxic effect, provides additional evidence of a "threshold of toxicity" peculiar to the individual, this being considerably smaller than dosages in the other cases of toxicity. Concerning the matter of individual susceptibility, many other factors need consideration, such as impaired absorption in disease, ability of absorption at different ages, etc., and the question of individual thresholds will remain one of speculation until more controlled experimental work with human beings is done and reported on.

Analysis of the data concerning poisonous dosages, ages affected, etc., is somewhat difficult because of lack of

detail given in some accounts, and it is suspected that vitamin intake history is not precise in some cases. From the data in table 2, one sees that in the age group of 0 - 6 months, there were 4 cases which showed onset of symptoms; ages 7 - 12 months, 3 cases; 13 - 18 months, 5 cases; 19 - 24 months, 4 cases; 25 - 30 months, 3 cases; 31 - 36 mos., 5 cases; ages 3 years to 8 years, 1 case; and one adult of 44 years. It is readily apparent that there is an even spread across the first three years of life. The youngest case was 2½ months at onset of symptoms, and the oldest was 44 years.

It also becomes apparent that there is a lag period in all cases between the beginning of the period of ingestion of large doses of the vitamin, and the onset of symptoms. It is difficult to assess the lag period in view of the different dosages used in different cases, and one might expect the length of the lag period to be related to the size of the dosage, but this has not been the pattern. In the age group 0 - 6 months, the lag varied between 2 and 5 months; age group 7 - 12 months, a lag of 2 to 6 months is seen; age group 13 to 18 months, a lag of 6 to 17 months; age group 19 to 24 months, a lag of "several" to "many" months; ages 24 to 30 months, a lag of 3 to 18 months; ages 30 to 36 months, a lag of 9 to 14 months; the one 8 year old case showed a lag of 11 months, and the one adult showed a lag of 12 months. From these figures one may see a

general increase in the lag period as the age groups progress, but this is difficult to correlate with dosages, in view of the few cases reported.

The question arises: What is a toxic dose? If one were to judge from the fact that the greatest number of cases have occurred in the first three years of life, it becomes almost conclusive that sensitivity to excessive doses decreases markedly after this period. This hypothesis is confused by Kane's case (181) where from 50,000 to 100,000 units per day were ingested for 12 months by an 8-year old when symptoms occurred, although such symptoms were definitely milder. This can be seen, by comparison with the other cases, to be a relatively small dosage. Perhaps all that can be concluded should be judged from Berrey's case (177) where as little as 37, 500 units were ingested daily and were toxic, although a considerable lag (14 months) occurred before signs of toxicity manifested themselves, and for future guidance be it remembered that in some individuals this small dose is toxic. Certainly this does not prevail for adults; judging from the therapeutic trials with vitamin A, and the massive doses used, considerable leeway exists between prophylactic doses and toxic doses in older individuals. Straumfjord (136) administered 100,000 units per day to 36 normal adults for 3 years without discernible effect.

F. The clinical syndrome of vitamin A toxicosis.

Acute poisoning, in contrast to chronic poisoning, from excessive vitamin A ingestion, is all but unknown. According to Caffey (179), children have occasionally swallowed as much as 50 cc., a whole bottle, of Oleum Percomorphum containing 3,000,000 units of vitamin A, at one sitting and without harm, save for transient nausea and vomiting. As will be noted in the section on therapeutic uses of vitamin A, large doses of vitamin A have been well tolerated, there being occasionally noted regurgitation and diarrhea, and one author proposes to consider excessive ingestion of vitamin A as a cause of "food poisoning" because of such symptoms (189). It is well to recall the experiences of Arctic explorers and Eskimos as related by Rodahl (page 51), which have in some cases resulted in death from ingestion of vitamin A-loaded bear or seal liver.

Chronic poisoning presents some early features which are not particularly distinctive. A study of the case reports reveals in most such generalized signs and symptoms as: Decrease in appetite with consequent failure to gain weight and constipation; disinclination to play and increasing irritability; restless sleep and fatigueability; pruritus, usually over the back and extensor surfaces of the extremities, which may or may not be accompanied by a rash which has been variously described as erythematous, dusky, macular, papular, maculopapular, discrete,

scattered, desquamating, brawny, excoriated, or simply, dry, rough skin; a preference for butter and carotene-containing vegetables has been noted in some reports (174, 175, 181, 190); less commonly enlargement of the head or beginning hydrocephalus has been among the early signs noted. Dry, coarse, or sparse, thinning hair has been noted somewhat later in a majority of cases, after a lag of weeks to months, in addition to cheilosis or cracked, bleeding, and fissured lips. Jaundice has been noted in at least one (173) patient, and hepatomegaly is a fairly common finding at examination. Splenomegaly was noted in one case (64) which may have been related to the severe anemia noted in that patient. In most cases at least six months have elapsed between the beginning of excessive intake and the appearance of hard, tender, bony swellings in the extremities and skull bones, these tender swellings usually bringing the patient in for consultation, if such has not occurred already. The irritability is ever-increasing, and in the case of Arena's patient (191), the child had to be carried about on a pillow. Tenderness of bones and joints is a dominant late feature—the tenderness is usually associated with the swellings which are bony changes, but in the older child (181) and in the adult (180), there may be no gross bony changes to explain the tenderness and pains. If bony changes involve the feet, there may be a disinclination to stand or walk, or there may be a limp, and if the child is old enough

to talk, he may complain of a sensation of "walking on stones." Diarrhea and dark urine has been noted in the advanced state of toxicity (175).

Experiences with experimental animals (132) would lead one to expect bleeding tendencies, but only three cases have been observed where any suspicion of hemorrhagic tendency could be entertained: Josephs' case (64), where tonsillectomy was followed by hemorrhage, this occurring eight months after onset of symptoms and the child being therefore in long-standing toxicosis; one of Caffey's patients (176) had severe nosebleeds which occurred at about the time of appearance of bony swellings; and Berrey's report (177) of a case of subdural hematoma concomitant with vitamin A toxicosis. To be sure, many of the cases suffered from bleeding of the cracked or fissured areas of the lips and corners of the mouth, but this seems rather due to loss of skin continuity than a blood change.

G. Roentgenologic findings in vitamin A toxicosis.

The x-ray findings in vitamin A toxicosis are not specific for this state, as will be shown in the section on problems of diagnosis. In the main, they consist of what has been called "cortical hyperostoses." The hyperostotic process seems to show a preference for certain skeletal parts in this diseased state, which has become a point of differential diagnosis.

Caffey (176) in 1950, in addition to describing seven clinical cases, discussed the roentgenographic observations in those cases on record, and the most of the following has been taken from his excellent account. In every case except an older child and an adult, some of the tubular bones have been thickened with both ulnas and some of the metatarsals being consistently affected. Early, the hyperostoses have a shell-like appearance with a zone of diminished density between the subperiosteal thin layer of bone and the external surface of the old cortex, which may be wavy in outline when first seen. Berrey (177), described a typical case in which the zone of periosteal thickening "could have been the result of an old greenstick fracture." After the withdrawal of vitamin A, this intermediate clear zone disappears; the hyperostosis then shrinks onto the old cortex and fuses with it. These solid, sclerotic cortical thickenings are in turn gradually resorbed from within, but remain visible for many months after complete clinical recovery. During the reparative phase some of the hyperostoses become lamellated.

Caffey (130), in a later editorial on the subject of hypervitaminosis A, states that the metaphyses and epiphyseal ossification centers are characteristically normal, but other authors have noted changes; Wolbach (187), in observation of the effects of hypervitaminosis A on his experimental animals, considers that the mechanism of bony disturbance is one of

speeded growth and development, and Moore and Wang (188) noted detachment of the epiphyses in their experimental animals. In view of this, one would expect to find disturbances of epiphyses and metaphyses in clinical cases. This has been the case in a significant number of patients, and one finds allusions to these roentgenologic changes in the case reports as follows: Josephs (64) described "mottled" epiphyses; Dickey and Bradley (174) saw "irregular" epiphyseal lines; growth lines were "widened" in the cases reported by Fried and Grand (175) and Toomey and Morissette (172); increased density or sclerotic changes were noted by Fried and Grand (175) and by Gribetz and co-workers; Arena and Sarazen (191) described irregularity of the metaphyseal plates of the long bones of the legs; and Naz (186) reported epiphyseal cupping at the ends of long bones. It appears, then, that disturbances of metaphyses and epiphyses may be expected as part of the roentgenologic picture.

Perhaps the least often reported change, but not the most illogical in view of Wolbach's observation (187) of speeded growth processes, is that of advanced bone age. Josephs (64) reported that in a child of three years, there were five carpal centers of ossification, indicating that skeletal development was in advance of the child's age in years. This is the only such example reported, and it can be concluded that it is not a prominent feature of the roentgenologic picture in hypervitaminosis A, if indeed, it is part of the picture at all.

H. Laboratory findings in hypervitaminosis A.

Laboratory studies have in most cases been characteristic in vitamin A toxicosis. The patterns noted are hereinafter discussed.

1. Hemogram.

With regard to the hemogram, one finds reports of the blood picture in 21 of 26 cases, five cases not furnishing this report. Nine of the 21 were normal with regard to hemoglobin and erythrocyte count. Josephs' case (64) was severely anemic, understandably in view of a hemorrhagic episode following tonsillectomy. Of the remaining 12 cases, two can be called moderately severe, and ten mildly anemic. Standards for comparison have been taken from Mitchell-Nelson Textbook of Pediatrics, fifth edition, 1950, table 91, page 1093. Considering that the figures for various ages as reported by Mitchell-Nelson are averages, it may be that some of the mildly anemic cases in this series could be eliminated from consideration; however, it is to be noted that those cases showing normal hemograms did not include any high levels such as would be expected in a survey of normal individuals. The type of anemia seen is either hypochromic-normocytic or normochromic-normocytic. No author has attempted to explain the anemic tendency (seen here in 50% of cases). Anorexia may well play a part in the production of a

hypochromic anemia, this symptom being prominent in the syndrome. The anemia, on the other hand, may explain the common symptom of fatigueability. It is perhaps unwise to speculate that since excess vitamin A has a prominent effect on bone, the hematopoietic function is also disturbed.

Leucocyte counts were reported in eighteen cases. Seven show elevations at some time in the course of their toxicosis, four being very slightly elevated (10,800 to 11,800), two moderately elevated (14,900 and 15,400 cells/cu. mm.), and one high count (30,800 cells/cu. mm.) with 74% lymphocytes. The differential pattern seen is, by and large, normal throughout for the remainder of cases. The various authors have not emphasized this phenomenon and case records indicate that these elevated counts have not been consistent in the same individuals; therefore, it is doubted that an elevation in total leucocyte count is a significant feature of hypervitaminosis A.

One feature which looms large is the increase in sedimentation rate. The erythrocyte sedimentation rate has been reported in 18 of 26 cases, and was within normal limits in only 3 of these 18 cases. An explanation might lie in the fact that 50% are anemic in some degree, except that an elevation occurs in 5 cases where anemia is shown not to exist. It appears that this is a distinctive feature of hypervitaminosis A. The degree of elevation was quite variable; for example, in ten cases the

Westergren method was used (15 mm. per hour is the upper limit of normal) and elevations ranging from 7 to 63 mm. in the first hour were observed.

2. Blood non-protein-nitrogen.

Blood non-protein-nitrogen, where reported, has been normal.

3. Mineral studies.

Calcium and phosphorus determinations have been made in most cases. Kolmer (192, p. 128) gives normal values ranging between 8.5 and 12 mg. % for calcium and 4 to 6 mg. % for phosphorus, for children. Twenty of 26 cases reported calcium determinations, with 3 variations from normal, two of which were increased with values of 12.4 and 17.6 mg. %, and one decreased value of 7.6 mg. %. One of these aberrations is so slight as to be of questionable significance. It is believed that it can be assumed that calcium levels are normal in hypervitaminosis A. The question of concomitant hypervitaminosis D arises in those cases of significant elevation, inasmuch as excessive ingestion of vitamin D has occurred in the majority of cases of hypervitaminosis A, and high serum levels of calcium are a diagnostic point in hypervitaminosis D (193), as are high phosphorus levels. The phosphorus value for the adult case of hypervitaminosis A is within normal limits. Most of the 19 remaining reports are

within normal limits, with the exception of 5 low values, reported as 2.9, 3.0, 3.6, 3.6, and 3.8 mg. %. The decrease is not marked, and it becomes obvious that phosphorus levels in serum in hypervitaminosis A are not significantly affected, which, incidentally, tends to eliminate hypervitaminosis D as a complicating factor.

4. Serum vitamin levels.

Examination of the data in table 2 showed the serum level of vitamin A to be markedly elevated in all cases where it was determined. The determination of serum vitamin A is the essential point of diagnosis of hypervitaminosis A.

Vedder and Rosenberg (133) first noticed that excessive doses of vitamin A caused a decrease in serum vitamin C levels in rats. This has been confirmed by Morehouse and co-workers (194) and Rodahl (135). Vitamin C levels have been determined in only 3 cases under discussion, and findings were normal. Von Bruggen and Straumfjord (136) administered 100,000 units of vitamin A to 36 normal adults every day for three years, and found no characteristic aberration of vitamin C serum levels. Rodahl (135) is of the opinion that the scorbutic process is involved in the physiopathology of hypervitaminosis A, but does not think that it in any way explains the whole picture. From the evidence offered, in particular that of Von Bruggen and Straumfjord (136), it seems probable that exceedingly high doses

of vitamin A are necessary to depress serum ascorbic acid levels.

5. Liver function tests.

Serum alkaline phosphatase has been determined in 22 cases. Kolmer (192, p. 134) allows a normal range of 1.5 to 4 Bodansky units per 100 cc. of blood for adults, and 3 to 14 units for children. In the light of the osteogenetic process seen in hypervitaminosis A, one would expect increased blood values for alkaline phosphatase. Furthermore, it has long been noted that alkaline phosphatase levels rise somewhat in hypervitaminosis D (193), and the possibility of concurrent vitamin D poisoning in these cases has been considered. Ten of the 22 cases reported increased values ranging from 15.4 to 35 Bodansky units. It is noted that in every case where elevation occurred, excesses of vitamin D were also ingested. However, the same holds true where elevations were not observed. Toomey and Morissette (172) recreated the syndrome in their patient with pure vitamin A excess, indicating that the syndrome, including the bone picture, is due to excess of vitamin A and not vitamin D. They did not report a phosphatase level with their experiment, but it would probably have been valueless anyway, in view of the fact that high phosphatase levels have been shown to persist for many months after withdrawal of vitamin A (64). The only possible conclusion regarding elevation of serum alkaline

phosphatase is that it, in a significant number of cases, has been shown to be elevated, but that this might be due to excessive vitamin D, but in the light of the evidence given by Toomey and Morissette (172), it is probably an effect of hypervitaminosis A.

Serum protein studies have been done in 10 cases, and appear normal with 3 exceptions. Considering that a range of 6.5 to 7.5 gms. % is normal for children (195, p. 1606), two were slightly low, and one was somewhat elevated. Possibly anorexia may have led to hypoproteinemia in these two cases, but it is doubted that the slight variations are of great significance as regards the picture of hypervitaminosis A, and it should probably be considered that normoproteinemia prevails.

Icterus index has been determined in 3 cases, and was found to be slightly elevated in one case (10 units, taking 6 units as the upper limit of normal (192, p. 117), but this determination was made along with a battery of liver function tests which all yielded normal results. The patient was noted to have a mild carotenemia (181).

Prothrombin time and activity determinations have been made in four patients. Prothrombin time was within normal limits in all 4 cases, and prothrombin activity was reduced to 97% in one case (172), 85% in a second case (182), and 82.5% in a third, (177) it being 100% of normal in the 4th case. Though it has not been shown to be reduced to dangerous levels, these results indic-

ate that perhaps in the human case of hypervitaminosis A, the response is similar to that observed in rats by Light, Alscher, and Frey (196) in 1944, Walker, Eylenburg, and Moore (197) in 1947, and Quick and Stefanini (132) in 1948. The mechanism of this reduction is not understood (132), but is discussed further under the later section on "mechanism of toxicity."

Bleeding and clotting times were determined in four patients. In Berrey's patient the bleeding time (method of Duke) was 5 minutes and 45 seconds, the normal being 1 to 3 minutes and anything over 5 minutes being considered prolonged. In the other studies done, all values were normal. This single abnormality is not marked, and is worthy of consideration only as it should reflect a decreased fibrinogen as seen in hepatic disease (192, p. 36), but Kolmer considers that recent studies by MacFarlane have shown that the chief cause may be a defective capillary contractility in explanation of the paradox of a prolonged bleeding time with a normal coagulation time, as is seen in this case. If decreased fibrinogen were the cause, one might interpret this as evidence of hepatic damage by excessive vitamin A, the evidence of hepatic damage in hypervitaminosis A being rather meager.

The other common liver function tests, i. e., the cephalin-cholesterol flocculation test, bilirubin determinations by the van den Bergh test, thymol turbidity test, bromsulfalein

excretion, stool and urine urobilinogen, have in the few cases where applied, been normal.

6. Serum lipoids.

Many authors have stressed the fact that a rise in serum lipids has been noted in hypervitaminosis A. The normal relationships of vitamin A and carotene to serum lipids have been discussed on page 35. Normal values for total serum lipids are given for children by Mitchell-Nelson (195, p. 1606) as 500 to 700 mg. %, and 170-200 mg. %, respectively. Authors have reported total serum cholesterol determinations in seven cases, five of these showing elevated levels ranging from 217 to 368 mg. %. As regards total serum lipids, five cases reported determinations, all being elevated, ranging from 714 to 1,140 mg. %. As is apparent, a rise in serum total cholesterol and total serum lipids may be expected in hypervitaminosis A. Cholesterol metabolism is not well understood, but Brown, Philips, and Kazan (198) impaired the function of the reticulo-endothelial system of guinea-pigs and noted a rise in serum cholesterol levels similar to that seen in vitamin A poisoning, and expressed a belief that the integrity of the reticulo-endothelial system, principally the Kupffer cells of the liver, is important in the metabolism of vitamin A and cholesterol.

7. Urine studies.

Urinalyses have in all cases been consistently normal, with the exception of one case (185) where on one occasion, a trace of albumin and 8-10 leucocytes per high power field were noted. Urinary creatine and creatinine studies done on two patients by Fried and Grand (175) were normal.

8. Muscle studies.

Muscle potential studies were done by Fried and Grand (175) on two patients and were reported to be normal.

9. Biopsies.

Bone biopsies were done in two cases. Josephs (64) unfortunately took his specimen from an unaffected area, and found it to be noncontributory except as it reflected the anemic status of the patient. Rineberg and Gross (183) examined a specimen from an affected area and described it as follows: "Microscopic examination showed a strip of newly formed, poorly calcified bone of coarse fibered structure such as is seen in ordinary productive periostitis. The marrow spaces were filled with fibrous marrow containing thin-walled blood vessels and many osteoclasts. Much osteoblastic activity was seen along the bone surfaces. Pathological diagnosis was 'productive periostitis.'" It appears, then, that the histological picture is one of increased bone production and resorption which is not specific for hypervitaminosis A.

I. The mechanism of toxicity.

Little is known of the pathologic physiology of hypervitaminosis A. Lewis and Cohlan (199) and others believe that the liver is first saturated with vitamin A following excessive intake. These authors infer the vitamin A saturation of the liver from the observations that it takes weeks in rats and months in human subjects before signs and symptoms of toxicosis are evident. Fasold in 1934 (171) reported fatty infiltration of the Kupffer cells in the livers of rats poisoned with excessive vitamin A. Unfortunately, no liver biopsy specimens have been obtained in human hypervitaminosis A. Hepatomegaly would seem to be an inexorable evidence of liver damage in these cases. However, no consistent damage to any specific function of the liver has been demonstrated. Kane (181) believed that the vitamin A storage mechanism in these individuals was impaired--his belief stemmed from observation of the hypervitaminotic process with hepatomegaly in one member of a family while a younger brother who received the same vitamin dosage was apparently not affected. Brown, Philips, and Kazan (198) impaired the Kupffer cells of the livers of guinea-pigs and observed a rise in serum cholesterol and vitamin A similar to that seen in hypervitaminosis A. But the hepatic esterase which maintains the alcohol-ester relationship is apparently not disturbed, if one accepts Gribetz' evidence (182) of a normal

alcohol-ester ratio in the blood of hypervitaminotic patients. With regard to the matter of saturation of the liver and tissues before symptoms develop, Davies and Moore (106) noted that signs of intoxication developed in rats before storage capacity was used up. It was their opinion that the syndrome in rats does not depend on the absolute amount of vitamin A present in the body, but rather on the ingestion of the vitamin at a greater rate than that at which the vitamin could be stored or eliminated by the organism. It seems probable that both this factor and exhaustion of storage resources both are important. Sobel et al (200) in 1948 gave evidence that the transfer of vitamin A to the tissues was a function of the concentration in the plasma. This was shown by the following means: higher values of vitamin A were obtained both in the blood and the milk of lactating mothers when they were given aqueous rather than oily vitamin A preparations; it had already been shown by Kramer and co-workers (201) in 1947 that administration of vitamin A in an aqueous medium resulted in higher blood levels than when the same dosage was given in an oily menstruum. On the basis of the preceding biochemical evidence suggesting saturation of storage depots in hypervitaminosis A and the controlled clinical evidence that high plasma levels of vitamin A will pass various tissue barriers in the body, it is suggested that high permanent plasma levels may alter the metabolism of certain tissues resulting in the signs

and symptoms seen in clinical and experimental results of hypervitaminosis A.

How, then, does the vitamin act to produce the localized lesions noted? Several suggestions have been made, and this has been worked out best in the case of bone. Arena and Sarazen (191) state: "The elevated phosphatase level, which is probably responsible for the bone changes, may be secondary to hepatic damage produced by excess intake of vitamin A." This explanation is reasonable, but there is evidence that the effect of vitamin A on bone is a direct one. Wolbach (187) in 1947 had speculated this, because he found no cause for the histologic changes observed in rats and guinea pigs from any change in the parathyroids, thyroids, adrenals or pituitaries of his animals. He also discussed the histologic findings in hypervitaminosis A in this classic article. His investigations indicated that there was a speeding up of the metabolism of epiphyseal cartilage cells, resulting in their rapid maturation, degeneration, and death. There was increased epiphyseal bone formation, and at the same time, the shafts of the bones were being remodelled with bone from the epiphyses and from appositional bone growth. The resorption of bone, however, was greater than its formation and therefore there was an apparent lag in calcification. Fractures then occurred because the newly deposited bone did not have the requisite firmness to meet the varied

stresses ordinarily withstood by normal bones. The support of Wolbach's suspicions regarding local exertion of effect was shortly forthcoming. Barnicot in 1948 (202) reported the effects of grafting chips of vitamin A acetate onto small, excised pieces of parietal bone of young mice. There was intense and sharply localized resorption after 14 days, and the sharp edges of the resorbed areas demonstrated osteoclastic activity with supra-vital staining. Fell and Mellanby (203) in 1950 reported on similar work. They grew the bones of fetal mice in tissue culture, meanwhile observing the effects of altering the concentration of vitamin A. They concluded that the effect of vitamin A on bone is a direct one. They state: "The control bones in normal media did not lengthen much during cultivation but deposition and absorption continued in vitro.....the effect of the vitamin A acetate on the experimental bone was remarkable. In a concentration of 2,000-4,000 i. u. per milliliter, the soft tissue grew as richly as the controls, but in three days the bone of the shaft began to be absorbed and the entire bone rudiment seemed to melt away like a 'lump of sugar in hot water.' In extreme cases by the tenth day only a few crumbs of bone were left scattered in the sheet of actively growing soft tissue. Histological sections of the experimental bones showed that the cartilage matrix soon lost its basophilia and at the same time shrank, while the cells appeared normal. Finally, the matrix of

the epiphyses vanished completely, leaving only a compact mass of chondroblasts, while the diaphysial cartilage was rapidly invaded and raplaced by the highly cellular connective tissue of the marrow cavity. Exactly how the bone was absorbed was not clear, and although osteoclasts were fairly numerous, it was doubtful whether they accounted for all the destruction." Except for the severity of the action of the highly concentrated vitamin A acetate, such concentrations being impossible to match in vivo, the descriptions are surprisingly like Wolbach's observations, and there is little doubt left of the concept of direct action on bone.

Wolbach and Maddock (204), in an attempt to close another gap of evidence for the direct action hypothesis, repeated the earlier work of Wolbach, this time on hypophysectomized rats. The purpose of the study was to ascertain if the anterior pituitary is an intermediator in the production of the skeletal response to excessive administration of vitamin A. The authors, allowing for the retardation of bone growth resulting from hypophysectomy in growing rats, found no differences in the responses as compared to those in normal rats, and concluded that skeletal responses to excessive vitamin A are not mediated through the pituitary gland.

One hesitates to transpose results of in vitro and animal experiments to human physiology, but the description of

the biopsied material in Rineberg's case (183) is worthy of reconsideration at this point: "Microscopic examination showed a strip of newly formed, poorly calcified bone of coarse fibered structure such as is seen in ordinary productive periostitis. The marrow spaces were filled with fibrous marrow containing thin-walled blood vessels and many osteoclasts. Much osteoblastic activity was seen along the bone surfaces....." The process of remodelling and poor calcification as seen here is not unlike Wolbach's description. However, it is apparent that bone resorption has not proceeded in human beings at the rate observed in experimental animals. Gribetz (182), on the basis of a negative calcium balance produced in one of his patients six days after he was placed on a low-calcium-phosphorus diet, hypothesized that bone resorption in human beings takes place more rapidly than deposition in hypervitaminosis A. He realized, however, that his balance study was performed during one particular phase of the disease, and recognized that further studies are necessary to determine whether a negative calcium balance is characteristic of all stages of hypervitaminosis A. It is believed that the roentgenologic picture of thinned cortices covered by less dense newly-formed periosteal bone is compatible with the hypothesis. One might speculate that if patients with hypervitaminosis A were to go undetected and the high doses of vitamin A were to be continued for a sufficient length of time, the changes found

in animal experiments might occur.

The role of the elevated alkaline phosphatase is not yet explained--it may occur on the basis of hypervitaminosis D existing in some degree as a complication. Whether hypervitaminosis D has compounded the pathologic physiology of vitamin A toxicosis is not clear, but Toomey and Morissette's recreation of the syndrome in their patient tends to exonerate vitamin D. The similarity between the clinical picture of hypervitaminosis A in rats and that of scurvy as seen in humans, has been pointed out by Vedder and Rosenberg (133), who found that ascorbic acid offered protection against excess of vitamin A. These similarities were also noted by Moore and Wang (134) who failed, however, to detect any abnormality in the ascorbic acid metabolism in their hypervitaminotic rats. Rodahl (135) found that the toxic effects and the post-mortem findings in guinea pigs given excess of vitamin A, and in those given a scorbutic diet, were very similar. Thus, in both cases there was absence in normal gain in weight, hyperemia and hemorrhages--particularly muscular hemorrhages in the hind legs, as well as bleeding in the knee joints. The bone abnormalities were similar, as judged by roentgenograms and microscopic examination, and in both cases the bones were brittle. Finally, the same low content of ascorbic acid in the liver and in the serum was detected in both cases. Furthermore, similar gross doses of vitamin A proved more toxic to

guinea pigs given a scorbutic diet than to those given the usual basal diet. In a dog given 380 i. u. of vitamin A per gram of body weight during a period of 57 days, bleeding from the gums and swellings of the gingiva were also observed in addition to the symptoms which had been described for rats. The ascorbic acid content of the blood was 0.7 mg. % at the commencement of the experiment, and 0.0 mg. % at the end of the 57 days. It is thus evident that prolonged administration of excess vitamin A in experimental animals produces a condition which resembles scurvy, although Rodahl did not conclude that abnormality in vitamin C metabolism was in any way considered as the sole causative factor in hypervitaminosis A. The meager evidence of 3 normal vitamin C serum determinations in the reported cases tends to eliminate scurvy from the picture, and judging from the results of Von Bruggen and Straumfjord's experiment with 36 human subjects, it would probably take exceedingly high and prolonged doses of vitamin A to depress vitamin C levels to a scorbutic level—if indeed, it would be depressed at all in the human being. Nevertheless, in view of the inadequate studies done so far, it must be considered that the scorbutic process might have played a part in the production of the hypervitaminotic syndrome under discussion.

Quick (132) relates that the action of vitamin A in

producing hypoprothrombinemia is not understood. Whether it inhibits the synthesis of vitamin K by the intestinal flora or interferes in the absorption or utilization of vitamin K cannot be determined by using rats which normally depend on bacterial action for part of their vitamin K requirement. Quick found that by feeding chicks a vitamin K-free diet supplemented by a daily amount of vitamin K which was slightly less than the dose needed to maintain the prothrombin level, the effect of excessive doses of vitamin A could be determined. Large doses had no effect on the prothrombin time, and the authors concluded that in the chick, vitamin A excess does not interfere with either the absorption or utilization of vitamin K. They suggest that the hypoprothrombinemic action of vitamin A in the rat is likely due to its interference in the synthesis of vitamin K by the intestinal flora. It is an easy step to infer a similar cause of hypoprothrombinemia in the human hypervitaminotic subject.

Salzberger (180) was impressed with the resemblance of the skin in his adult patient to the hyperkeratotic state seen in hypovitaminosis A. He suspects that the latter state would have been the first diagnosis of any dermatologist from inspection alone, and hypothyroidism as the second most likely diagnosis. Hypothyroidism would well have explained several aspects of the clinical picture in that case, and he alludes

to the relationships of vitamin A to thyroid effect. On the basis of Drill's (101) statement to the effect that excessive dosing with vitamin A lowers the basal metabolism in toxic hyperthyroidism, he implies that hypervitaminosis A exerts its effect through this mechanism. It is an interesting speculation, but does not explain the intense pruritus which is almost a universal feature of vitamin A toxicosis; furthermore, the brawny edema which has been described in the latter state is related to bony swellings and is unlike the myxedematous state. There is no satisfactory explanation of many of the changes seen in hypervitaminosis A, but the most reasonable explanation could be concluded from the explanation of bony changes, which leads to the suspicion that the skin, too, is changed by a local saturation with vitamin A, and perhaps interference with local skin--metabolism in some unknown way occurs.

J. Approach to the study of the hypervitaminotic patient.

The syndrome of hypervitaminosis A presents diagnostic problems in several respects. Caffey (179) states that he has knowledge of many unreported cases, and it is probable that many cases are unrecognized.

To begin, most of the cases on record have been shown to have ingested excessive amounts of vitamin D. It is not clear how much of the pathology of vitamin A toxicosis is due to the added effect of excessive vitamin D. The signs and symptoms of bony swellings and exquisite tenderness inevitably results in roentgenologic study of the affected parts. The resulting roentgenographic picture has caused the following diseased states to be considered, in the past: Traumatic injury, infantile cortical hyperostosis, periostitis of congenital syphilis and other infections, leukemia, scurvy, rickets, and vitamin D poisoning. Acrodynia has been considered because of the exquisite pain, irritability, and pruritic rash. Hemorrhagic tendencies have not been common in hypervitaminosis A, but until further studies show them to be nonexistent, they must be considered possible and would perhaps arouse investigation into the hematologic picture; it remains to diagnose the cause of hypoprothrombinemia.

There are two essential points in the diagnosis of

hypervitaminosis A: 1) History of excessive ingestion of vitamin A, and 2) Detection of markedly elevated blood levels of vitamin A. These essential points, in addition to the clinical syndrome, the roentgenologic findings of cortical hyperostoses, and typical laboratory findings, establish the diagnosis. The determination of serum vitamin A levels is a procedure which may be done in the average laboratory, and the techniques and significance of the various tests are discussed hereinafter, to be followed by a differential diagnosis of the diseased states with which hypervitaminosis A may be confused.

1. Determination of vitamin A levels in serum.

a. The Carr-Price color reaction.

In 1926 Carr and Price (205) introduced a new means of assessing the vitamin A activity of different cod-liver oils, which was to be a practical method, whereas the long and difficult biological test was not. They selected a 30% solution of antimony trichloride in chloroform as their reagent. They observed that vitamin A or carotene reacted with this reagent to form a brilliant blue color which was stable for at least three minutes, and direct readings of the intensity of the color could be measured against standards with the help of a Lovibond tintometer. Their results compared well with biological tests, and this method has been widely used.

Sobel and Werbin in 1945 (206) substituted activated glycerol dichlorhydrin for the Carr-Price reagent, which technique was improved by Sobel and Snow in 1947 (207), and has the advantage of producing a color reaction which is stable for ten minutes, and therefore much more easily measured.

Lindqvist in 1938 (60) had advised saponification (incubation with alkali) as a preliminary to the extraction of vitamin A, since this treatment yielded higher results. All modern applications of determination techniques have adopted this feature. Bessey, Lowry, Brock, and Lopez in 1948 (208) demonstrated that the color development of the Carr-Price method was inhibited or delayed by unknown agents present in serum and stressed the importance of saponification as a means of aiding extraction. They also noted that their method (207) gave results equivalent to the Carr-Price test when saponification was added to the latter method.

Lahiri and Scandrett (52) have refined the glycerol dichlorhydrin technic with saponification, and apparently have obtained better or higher results than other techniques. All the modern methods employ a spectrophotometer and standard calibration curve.

2. The vitamin A tolerance test.

Ruch, Brunsting, and Osterberg (209) considered in

1946 that single determinations of vitamin A, or of its parent substance, carotene, would not furnish a true indication of the amount of this substance that reaches the tissues or of the requirements in this respect. In order to study the absorbability and utilization of this vitamin, they devised the vitamin A tolerance test. The method of study was as follows: The concentration of carotene and vitamin A in the serum was determined after all food had been withheld for 12 hours. At the end of this phase, a massive dose of vitamin A, that is, 7,500 i. u. per kilogram of body weight, was administered orally. Samples of blood were collected at intervals of two, four, six, nine, twelve, and twenty-four hours. During the study, the diet was restricted to avoid vitamin A and carotene-containing substances, and no mineral oil was ingested. The carotene and vitamin A in the specimens were extracted by the method of Clausen and McCoord (210), and quantitative determinations were made with the Coleman Junior Clinical Spectrophotometer. The carotene in the petroleum ether was determined by the spectral transmission at 440 millimicrons, and vitamin A was determined by spectral transmission at 620 millimicrons. Regarding the significance of this test, the authors point out that the amount of vitamin A present in blood serum at intervals after ingestion of large doses may be an index of that which has been pushed out

of the liver. Therefore, blood levels after such ingestion are a rough indication of liver content, since a liver with low content would remove more from the circulating blood than would one which was, so to speak, saturated. Thus, so-called absorption curves may be an index not only of the efficiency of this nutritional factor, but also of the state of liver storage, and their significance in demonstrating a fault in metabolism is greater than that of simple blood vitamin A levels, which tend to remain within normal range until gross depletion of the depot in the liver has taken place.

The authors have graphically represented the average, maximal, and minimal concentrations of vitamin A in the serum in normal individuals. The graph illustrates that in normal persons there is a sharp rise over a period of 6 hours to reach a peak, then a sharp drop within 9 to 12 hours, and a gradual sloping off to normal within 24 hours. Gribetz and co-workers (182) demonstrated in a case of clinical hypervitaminosis A that despite an initial high level of vitamin A, there occurred a marked rise in the plasma level. This increase was more than one finds in normal children, and there was only a slight drop after 12 hours. Since the liver appeared to be normal as measured by function tests, the authors interpreted the results to mean that the body stores must have been saturated with vitamin A and therefore deposition of vitamin A could have proceeded only at a slower rate. It becomes

apparent that the vitamin A tolerance test lends itself to a use as a diagnostic procedure in hypervitaminosis A, the one objection being that a massive dose must be given an already poisoned patient. It is believed that the diagnosis is not so difficult using the single determination as to warrant the use of the tolerance test, unless a single determination yields questionable results. The graph for normal individuals by Ruch and co-workers (209) has been reproduced below:

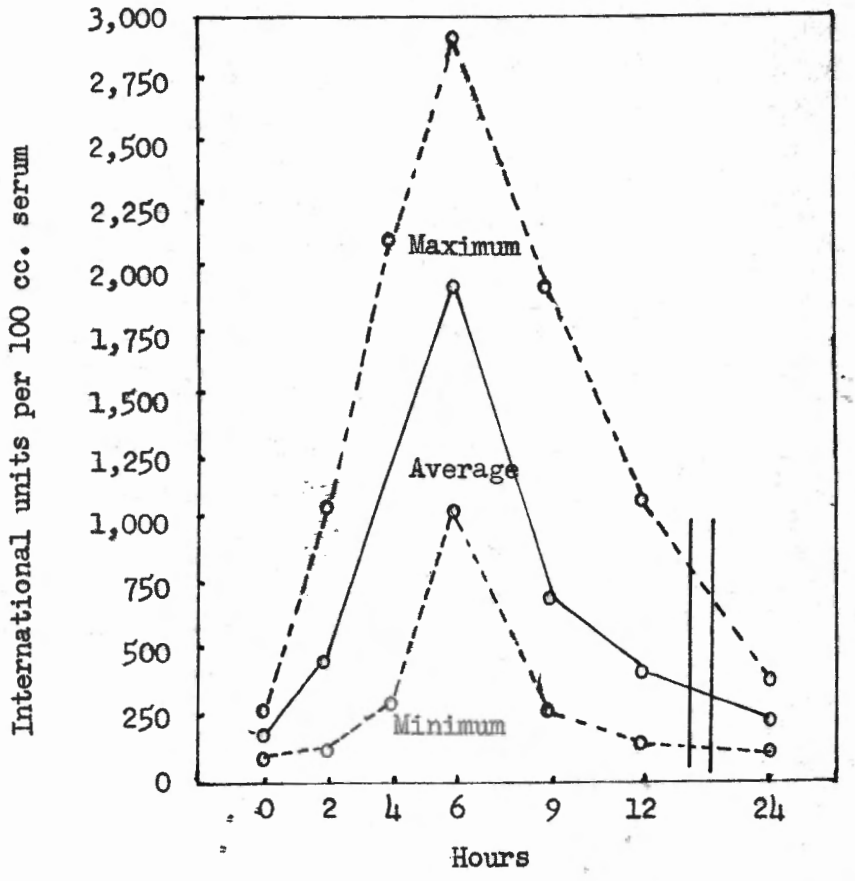

Fig. 1. Average concentrations of vitamin A in the serum of eight normal persons. (209)

3. Blood vitamin A alcohol levels.

Clausen and his collaborators (211) and Hoch and Hoch (212) have shown that vitamin A is transported in esterified form from the intestine to the liver where it is stored in this form. The Hochs also demonstrated that the vitamin was released to the plasma as the alcohol from the liver stores. The alcohol normally represents about 80% of the total plasma vitamin A in the normal fasting human being and in several animals studied (182, 211, 212, 213). Glover (214) observed that an increase in post-absorptive free vitamin can be obtained only by massive dosing, which, by virtue of the alcohol-ester equilibrium in the liver, increases the blood vitamin alcohol. Popper and his associates (213) found that the rise in his subjects fed massive doses was due entirely to the ester fraction, whereas the vitamin A alcohol showed little in the way of a characteristic variation. Popper concluded that the blood vitamin A alcohol was a better index of vitamin A nutrition because it reflects much better the storage in and release from the liver and is independent of solubility and postprandial rise. Popper applied this index to the study of nephrosis and liver disease, and Gribetz and his associates (182), following this lead, applied partition studies to a clinical case of hypervitaminosis A. The fasting blood level (total) was 675 micrograms per cent in their patient. They found that 454 micrograms or 67.3 per cent was in the form of the

alcohol and only 221 micrograms or 32.7 per cent was present as the ester, in contrast to that obtained in clinical studies in the laboratory when high levels of vitamin A in the blood were produced in normal infants after administration of an aqueous concentrate of vitamin A, the main portion of the rise in such children being found in the ester fraction, while the alcohol constituted but 20 per cent of the total, in agreement with Hoch and Hoch (212) and others (182, 211). Gribetz concluded that the vitamin A alcohol determination was a better index of hypervitaminosis A than the total vitamin A level, though more tedious a procedure. His opinion seems to have been founded on the concept that the liver is saturated in hypervitaminosis A and the blood vitamin A alcohol level rises accordingly, according to the mechanism suggested by Ruch and his associates (209), i. e., a "pushing out" of vitamin A alcohol.

Popper et al (213) have described a method of ester separation for this procedure.

It would appear that the method of ester separation is a more precise index of hypervitaminosis A, but it will be noted that only Gribetz (182) has applied this method, yet the diagnosis was possible in all the remaining cases using the total vitamin A determination. Levels have been sufficiently high to indicate hypervitaminosis, and it is believed that this latter procedure is adequate. Several modifications of the

Carr-Price color reaction have been mentioned. For diagnostic purposes, the methods discussed probably have no virtue over those outlined by Clausen and McCoord (210), Bessey and co-workers (208), or Sobel and Snow (214). The essential point is the determination of marked elevation of serum vitamin A levels.

2. Differential diagnosis of Hypervitaminosis A.

There are many conditions which have been or should be considered in the differential diagnosis. One of these is traumatic injury. The tendency of the layman to attribute many symptoms to the effects of trauma is illustrated in several cases under discussion (176, 183), and this factor might be misleading. It has also been noted that one case was treated as a fracture of the clavicle (173), and in another case, the roentgenographic picture was described to be like a healing greenstick fracture (177). It is doubted that a diagnosis of fracture could be entertained for long in view of the varied features of the syndrome and the tendency for wide bony involvment. Perhaps trauma is involved in the process, after all. It has been noted that exposed bones, and weight bearing bones are most often involved. If one accepts the concept of Wolbach (187) of greater resorption than deposition in this disease, then perhaps ordinary stresses or slight trauma might result in

loosening of periosteal fibers with hemorrhage, callus formation, etc., and the cortical hyperostoses which are seen could represent healing areas. While this concept seems within the realm of possibility, it remains a speculation by the author, inasmuch as no experimental work has been done to support it.

Periostitis of infectious origin usually follows a sequence of events involving penetration outward from marrow cavities following necrosis of the marrow and cortex. The process extends to the periosteum and elevates it from the cortex. The x-ray picture is usually typical with evidence of necrosis and sequestration, but in a small localized abscess the periosteum overlying the abscess may be irritated sufficiently to cause bone proliferation that results in considerable thickening of the cortex, which is similar to the picture in hypervitaminosis A. Occasionally the infection localizes in the periosteum or beneath the periosteal covering of the cortex and spreads only slightly into the interior of bone (215). This could present a confusing picture, but such processes usually follow trauma with penetration, and a history of such event should be obtained in such a case. Pain and tenderness would further complicate the picture, but leucocytic response, systemic picture of toxicity with fever, positive blood cultures, and favorable reaction to antibiotics eliminate the possibility of

The periostitis of congenital syphilis resembles the roentgenographic picture of hypervitaminosis A (182). However, the initial difficulty in differentiation is resolved by routine clinical and serologic studies.

The greatest problem in differentiation is in the case of the relatively new syndrome, "infantile cortical hyperostosis," which was first described by Caffey in 1945 (216) and again by Smyth in 1946 (217). The two conditions resemble one another, and it has been considered that they are but variations of the same pathologic process (183). As more and more cases of hypervitaminosis A are seen, the diagnostic criteria become less and less rigid, but the essential distinguishing points are: 1) preliminary history of excessive vitamin A intake (such a history may be hard to obtain); 2) age of onset is usually before six months in infantile cortical hyperostosis and rare before six months in hypervitaminosis A because of the "lag" period between the beginning of excessive dosage and the onset of symptoms; 3) fever is usually present in infantile cortical hyperostosis, but is rare in hypervitaminosis and if present, probably associated with some concomitant infectious process; 4) leucocytosis is said to accompany infantile cortical hyperostosis, but this is apt to occur in children in the hypervitaminotic state (though far from a universal feature); 5) respiratory infections and pleural effusions have been noted with consistency in infantile cortical hyperostosis; 6) the mandible is always involved in

infantile cortical hyperostosis, but has been shown to be involved in but one case of hypervitaminosis A; a similar relationship is noted for the metacarpals; 7) an anemia has been noted in 50% of cases of hypervitaminosis A; 8) plasma levels for vitamin A are normal in infantile cortical hyperostosis, while they are markedly elevated in hypervitaminosis A; 9) infantile cortical hyperostosis shows typically exacerbations and remissions, while lesions of hypervitaminosis A persist while vitamin A dosage continues, and withdraw rapidly when vitamin A is discontinued; 10) finally, the pruritic rash is not part of the picture of infantile cortical hyperostosis, but usually is prominent in hypervitaminosis A.

The nonspecific symptoms of anorexia, irritability, weight loss, painful extremities, and disturbances in gait, accompanied at times by subperiosteal elevations may suggest leukemia (218). The differential points with respect to the radiographic changes include the findings in leukemia of transverse bands of diminished density in the metaphyses of long bones, osteolysis and osteosclerosis (219), all of which are lacking in hypervitaminosis A.

Immediate aid in the differentiation of scurvy and rickets should be forthcoming from the dietary history, but then one must recall that hypervitaminosis A was induced in several cases when rickets was suspected, and has been worsened by

treatment for rickets. Certain aspects of the clinical and roentgenographic pictures may be confusing. In scurvy, one of the most prominent symptoms is marked tenderness of extremities; this, together with subperiosteal calcification seen during the healing stages may cause confusion (182). The following points may be helpful: presence of swelling, redness, and sponginess of gums; tendency towards hemorrhage; and characteristic roentgenographic changes in the ossification centers and metaphyses during the active stages of the disease. Of course, as has been discussed, it is entirely possible that the scorbutic process may in some cases be involved in hypervitaminosis A, and one would in that case see more of the specific epiphyseal changes of scurvy, but the total picture of vitamin A toxicity cannot be explained by this process (135). Healing rickets occasionally present subperiosteal bone proliferation. However, the characteristic roentgenographic changes in this disease are, of course, located at the epiphyseal plates (182).

Hypervitaminosis D should not be overlooked in the differential diagnosis since patients who are taking excessive vitamin A are usually ingesting proportionate increases in vitamin D. The literature concerning the quantities of vitamin D necessary for intoxication of infants and children is scanty. Conducting experiments with dogs and human adults, Steck (220) concluded that in both the minimum toxic dose was 20,000 i. u.

per kilogram per day. Hess et al (221) administered 21 to 52 times the prophylactic dose for periods of six to eight months and observed no deleterious effects. Wolfe (222) gave large doses of the vitamin to an infant with spina bifida and meningocoele in order to determine his tolerance. He concluded that 85,000 U. S. P. units per kilogram per day for 12 consecutive days was probably the toxic dose. It is of particular interest to note the short "lag" period here. Chaplin (223) relates that some patients have displayed toxic symptoms on as little as 50,000 units per day for a few weeks, whereas others may tolerate 10 times that dosage for 6 to 12 months before manifesting toxic effects of the medication. There is obviously a wide variation in individual susceptibility to excesses of vitamin D, just as there is to excesses of vitamin A. The chief occurrence of vitamin D intoxication is in those patients who are receiving massive doses prescribed by their physician in attempted treatment of some particular disease condition, i. e., deficiency states, pulmonary and cutaneous tuberculosis, scleroderma, various allergic states, and especially, rheumatoid arthritis.

There are a few similarities and some marked differences in the clinical and laboratory picture. Debre (224), in summarizing his findings in 21 cases of hypervitaminosis D in children, points out that there is usually a sudden appearance

of anorexia, nausea, vomiting, thirst and constipation. The children become progressively dehydrated, irritable and depressed, and gradually sink into a stupor. The laboratory data reveal a constant high blood pressure, an almost always greatly elevated calcium and phosphorus and signs of renal damage: albumin and formed elements in the urine, a high urea nitrogen, and abnormal kidney function tests. The pathology which is responsible for this syndrome consists of widespread metastatic calcification involving the kidney tubules, heart and blood vessels, gastric mucosa, lungs and pancreas (223).

Although the ingestion of vitamin D cannot be definitely ruled out as contributing partly to the clinical picture in the cases under discussion, it is the author's opinion that the vitamin, if anything, played a minor role. The doses were usually lower than what has been observed to be toxic in most cases; the clinical pictures, except for anorexia and irritability, were almost entirely different. Chaplin (223) states that a normocytic, normochromic anemia is part of the picture of vitamin D poisoning, as is slightly elevated alkaline phosphatase. In the 26 cases of hypervitaminosis A, there were no signs of metastatic calcification, high blood pressure, rarely an alteration of calcium-phosphorus levels, and no evidence of renal dysfunction.

Irritability, restlessness, and painful extremities, along with pruritus, may point to the possibility of acrodynia.

Certain features of acrodynia serve to differentiate the two conditions: pink coloration of hands and feet; profuse perspiration; extreme hypotonia; hypertension; loss of teeth and nails; absence of evidence of bone change on the roentgenogram, and presence of abnormal amounts of mercury in the urine. There are few clinical conditions in which extreme and persistent misery is such a prominent part of the clinical picture. Recent observations (225) suggest that chronic mercury poisoning or a sensitivity reaction to mercury may be the etiologic factor. Bivings (226) has reported that good results with BAL have been obtained in such a patient.

Hypoprothrombinemia below "therapeutic levels," which have been defined as 30 to 60% (227) of prothrombin activity, has not been shown to occur in human beings with hypervitaminosis A. Several hemorrhagic episodes have occurred which were not understood at the time. Conceivably, hemorrhagic episodes on the basis of hypoprothrombinemia due to hypervitaminosis A would be investigated in routine hematologic study and this factor found--it remains but to consider the list of conditions in which hypoprothrombinemia occurs, all of which are glaringly obvious in other respects and share no other features of hypervitaminosis A: Icterus neonatorum, biliary fistula with loss of bile and bile salts required in the small intestine for absorption; intestinal diseases interfering with absorption, defective digestion and

and absorption of fats due to deficiency in lipases (192, p.120). Differential diagnosis on the basis of hypoprothrombinemia would probably be unlikely to occur in view of the distinctive features of hypervitaminosis A.

K. Management after diagnosis.

All cases have been shown to respond immediately to withdrawal of vitamin A, with regression of signs and symptoms and eventual return to normalcy with no reported long term residual effects.

Since the hypoprothrombinemia appears to be on the basis of interference with vitamin K synthesis in the intestinal tract, administration of vitamin K should result in immediate remedy of this deficiency, however, this series of cases has not demonstrated a proved hypoprothrombinemia severe enough to warrant therapy.

L. Vitamin preparations involved.

Reference has been made, where known, to the vitamin preparation involved. The following list of such preparations with their vitamin content is furnished:

No. of Cases	Vitamin Preparation
17	Oleum Percomorphum--contains 1,250 units of vitamin A and 180 units of Vitamin D per drop, or 60,000 units of A and 8500 units of D per gram. A Mead-Johnson product.
3	Navitol--contains (in sesame oil) 65,000 units of vitamin A and 13,000 units of D per gram. Squibb & Sons.
2	Vifort--a water-soluble polyvitamin preparation. Each 0.6 cc. contains 5,000 u. of Vitamin A and 1,200 units of vitamin D, in addition to vitamins of the B group. Endo product.
2	Drisdol with Vitamin A--a solution in sesame oil containing 50,000 units of vitamin A and 10,000 units of vitamin D per gram.
1	Theragran--administered in capsules containing 25,000 units of vitamin A. Squibb & Sons.
1	ABDEC Drops--each 0.6 cc. contains 5,000 units of vitamin A, 1,000 units of vitamin D, 50 mg. of vitamin C, plus vitamins of the B group. Parke-Davis product.
1	Infadol--Each 3 drops contains 5,000 u. of vitamin A and 1,000 u. of vitamin D. I.V.C.
1	ViPenta--Each 0.6 cc. contains 5,000 u. of vitamin A and 1,000 u. of vitamin D. Hoffman-LaRoche product.

VI. Summary.

The earliest observation of the necessity for something more than the basic constituents of diet was made by Lunin (2), working in the laboratory of Bunge at Basel. Takaki (5) observed in 1882 that beriberi could be eliminated in the Japanese Navy by the addition of meat, bread, etc., to the basic diet of polished rice. The Dutch investigators showed, at the turn of the century, that there was something protective and curative of beriberi in rice polishings, having the first clear concept of beriberi as a deficiency disease (4,6). Many investigations (8, 9, 10, 11, 20, 21, 22) resulted in the problem of classification of the "growth factor," the "antineuritic," the "anti-scorbutic," and "anti-ophthalmic" accessory food factors which had been determined to exist, and "vitamines" was the original name given these substances by Funk (12). Drummond (17) suggested a compromise with modification of "vitamine" to "vitamin" and the addition of alphabetical designation as used by McCollum (15), leaving the way clear to add new accessory food factors by this system of designation. Vitamin A was originally confused with vitamin D, and the functions of both were ascribed to one vitamin. Mellanby separated the two in 1925 (19) and is credited with the discovery of vitamin D. In 1920, the carotene content of plants was observed (23) and Moore (25) showed that carotene

was a source of vitamin A for animals. The chemistry, isolation and synthesis of vitamin A was settled chiefly by the work of Karrer (28), Heilbron (29), and Holmes and Corbett (30) between 1930 and 1937. Hume and Kon (33) have summarized and discussed the chemistry of vitamin A in the light of modern knowledge. Hume has reviewed the sequence of events concerning standardization of vitamin A and carotene; the modern U. S. P. unit and the international unit are identical, having a value of 0.34 micrograms of the acetate or 0.3 micrograms of the alcohol.

Thompson (38) has shown that most of the carotene is converted to vitamin A in the mucosa of the intestine and absorbed slowly via the lymphatic system, which transports the re-esterified alcohol to its main storage depot in the parenchymal and Kupffer cells of the liver (41, 42). Some carotene, however, is absorbed as such and stored in the liver; the liver furthermore has the ability to convert carotene to vitamin A. Koehn (40) has shown the conversion of carotene to be quantitative and complete, under normal conditions. The vitamin is released to the blood in its active form, the alcohol, maintaining a fairly constant plasma level and alcohol-ester ratio in the blood, i. e., 80% alcohol and 20% esters (213), and blood levels tend to remain fairly constant regardless of the amount stored in the liver, until the liver is depleted of its stores. The mobilization of vitamin A from the liver is poorly understood, but apparently

involves a hepatic esterase which releases the vitamin to the plasma in the form of the alcohol (213). The administration of alcohol causes a rise in the vitamin A level of the plasma (54). Sex is apparently important in influencing the plasma level—Most investigators have reported higher levels for adult women than men, and Szymanski and Longwell (53) show that female infants around one year of age have a significantly higher level. Certain diseases which affect absorption will result in lower levels, such as sprue, celiac disease, and infectious hepatitis (42). In nephrosis the power of the liver to absorb or utilize vitamin A is impaired (59). Lindqvist has shown that the effect of fever results in greatly reduced plasma levels. Epinephrine and sympathetic stimulation will result in the mobilization of the vitamin from the liver into the plasma (62).

Vitamin A is never excreted by man during good health, but it may appear in the urine during certain disease states (65), especially pneumonia. It is common in the urine in chronic nephritis, and very small amounts have occasionally been reported in chronic infections, rheumatic fever, diabetes, pernicious anemia, asthma, cancer, skin diseases, and normal pregnancy. How the vitamin is dissolved in the urine is obscure (66).

Very little is definitely known about the fundamental part played by vitamin A in the metabolic processes of the body. Its structure with five unsaturated bonds suggests a function as

an oxidation-reduction catalyst (35). Mason (69) has suggested that it is necessary for some particular metabolic function peculiar to all epithelial cells. Patterson (72) has shown that in the absence of a vitamin A source, animals fail to grow and may die before body stores are completely exhausted. The specific tissue change due to deprivation of the vitamin is replacement of various epithelia by stratified squamous keratinizing epithelium (73). Mainly affected are epithelia with secretory function, the respiratory tract, the eyes, the genito-urinary tract, and the sex-glands, and in man, the skin is also involved (35), and these changes may occur even in the foetus (74). In man, nyctalopia is one of the early symptoms of deficiency; if deficiency becomes more severe, xerosis and keratomalacia develop, small ulcers appear on the cornea due to infection, and blindness may ensue. Metaplasia of the corneal epithelium and vascularization of the substantia propria are typical findings and generally lead to infection and obstruction of the ocular glands. In man, lack of vitamin A causes the gums to become hyperplastic and keratinized (80), while the developing teeth in infants are severely damaged (81), since the enamel organs, being of epithelial origin, shrink, and some controlling influence of the odontoblasts over their growth is disturbed; in prolonged mild deficiencies, the poor or deformed dentine leads to the formation of odontomas and tooth reduplication (82).

No function has been determined for vitamin A relative to the olfactory epithelium (83, 84).

Severe deficiencies often cause diarrhea in man, and there is some evidence that vitamin A is important for the function, and perhaps the structure, of the gastric glands and pancreas (85). Seelig (86) purported to show that large amounts of vitamin A resulted in healing of gastric ulcers, but this has been disputed (87).

Vitamin A is essential for the germinal epithelium of the testes (69); deficiency results in sloughing of the germinal cells, with a gradual reduction in the size of the tubules—at no time can the deficiency be so great as to lead to irreversible changes in the testes, however. In the female, alterations in the lining of the reproductive tract result in interference in the nutrition of the embryo, in deficiency.

No change in the histological structure of the endocrine glands has been noted in deficiency states (35).

The general features of deficiency as regards the skin in deficiency involve dryness and roughness of the skin early; later a keratosis, especially of the hair follicles, is a prominent feature. Papules, which are masses of keratinized epithelium, develop.

Another skin condition resembling acne vulgaris is

apparently a vitamin A deficiency (90). Pityriasis rubra pilaris, a congenital skin disease, is also characterized by a low level of vitamin A in the blood and generalized keratinizing metaplasia (75).

Bone growth is markedly impaired in vitamin A deficiency. Cessation of growth in parts of the body as well as abnormal growths are encountered (36).

Higgins (92) showed that a long-standing vitamin A deficiency results in the development of urolithiasis. Herrin (93) observed that in deficiency the urea clearance drops, and Bicknell and Prescott (35) account that massive dosing of the vitamin results in a transitory diuretic effect.

Cama and Goodwin (100) have shown that the thyroid plays a part in control of the absorption of carotene by the intestinal mucosa. Drill observed (101) in 1943 that the administration of vitamin A and thyroxine together prevents a rise in the basal metabolic rate. No relation has been shown between vitamin A and the pituitary gland. In vitamin A-depleted animals, adrenalin will not accelerate the hydrolysis of glycogen to glucose unless vitamin A is previously given (105). The adrenal glands have been shown by Moore (106) to store the vitamin, but no further relationship is known. Sex hormonal relationships to vitamin A are not well established; in rats

estrus becomes delayed and irregular in deficiency; Beher and Gaebler (112) observed that testosterone propionate caused a marked drop in plasma vitamin A concentration in female dogs while in a state of induced anabolism; premenstrual tension and exacerbations of Raynaud's syndrome in the premenstrual period have been attributed to excess of circulating estrogen and are allegedly relieved by massive dosing with vitamin A (58, 113), and Keddie (114) suggests estrogen imbalance as a cause in certain of the skin diseases which respond to vitamin A.

It has been noted for many years (116) that plasma lipoids and cholesterol rise and fall with vitamin A concentration in the plasma; the effect is poorly understood.

Severe deficiency results in widespread degeneration of the medullary sheaths of the peripheral nerves, which is irreversible (118, 119, 120, 121).

Physical requirements, as best known, vary with age and growth rate, and are greater in pregnancy and lactation. Requirements as set forth by the National Research Council in 1948 are given on page 48.

Vitamin A has certain important interactions with other vitamins. Quick (132) has shown that hypoprothrombinemia in certain species has been produced by the interference with vitamin K synthesis in the gut, by excessive vitamin A. Rodahl

(135) and others (133, 134) have shown that excessive vitamin A reduces liver storage and plasma levels of vitamin C in experimental animals, but this has not been shown to occur in man. Vitamin E in optimal relation with vitamin A in the gut and blood vessels prevents the oxidation of vitamin A (140, 141, 142).

It has been shown that vitamin A has certain therapeutic uses, and will beyond doubt be continued in certain states in massive doses; this is important in the light of the pitfall of possible toxicosis. Those diseases in which benefit from massive dosing is claimed are: Deafness and tinnitus, Raynaud's disease, premenstrual tension, atrophic rhinitis, and especially certain skin diseases, namely Darier's disease (follicular keratosis), acanthosis nigricans, acrodermatitis pustulosa perstans, plantar warts, vulvar leukoplakia, keratosis palmaris et plantaris, ichthyosis, pachyonychia, pityriasis rubra pilaris, and acne vulgaris; its usefulness in miliaria rubra and chalazion have also been demonstrated.

Rodahl and Moore (167) have written of the experiences of Arctic explorers and Eskimos who were poisoned by ingestion of polar bear and seal liver. The signs and symptoms of distress had their onset in from 2 to 4 hours after ingestion of the liver. Drowsiness, sluggishness, irritability, and irresistible desire to sleep were first noted, followed by severe headache and

vomiting. During the second 24 hours, some of the men began to have peeling of the skin in varying degrees. These authors have shown the toxic factor to be vitamin A existing in extremely high concentration in these livers. Drigalski and Laubman (168) and others (169, 170, 171) reported the earliest descriptions of the effects of excessive vitamin A on experimental animals. Drigalski and Laubman reported that rats were effected as follows: Their coats became rough; cachexia, catarrhal conjunctivitis, hemorrhagic rhinitis and diarrhea developed. Death occurred in from 5 to 18 days, depending on the dosage. At autopsy, these animals were observed to have degeneration of the renal glomeruli and tubules, proliferation of the reticulo-endothelial cells of the spleen, absence of striations in some of the cardiac muscle fibers, degeneration of the testes, and slight changes in the liver. Collazo and Rodriguez (170) after similar work, noted inflammatory changes of the eyes, bilateral exophthalmos, cessation of growth and spontaneous fractures of bones. Fasold (171) added to the list of pathology fatty infiltration in the Kupffer cells of the liver.

The first case reported in human beings was that published in 1944 by Josephs (64). Toomey and Morissette (172) in 1947 followed with a report of the second case. By 1950, an increasing awareness of the entity of hypervitaminosis A had

come to be, and to date there have been 26 cases reported in the United States medical literature. The clinical data in the reported cases have been summarized in tabular form (table 2).

As regards methods of poisoning, it will be observed that the zeal of a person who is "sold on vitamins" is the greatest factor leading to poisoning. Other factors are: belief that oily concentrates are equivalent to cod-liver oil; therapeutic induction of toxicosis secondary to treatment for celiac disease, rickets, and craniotabes; confusion of the symptoms of toxicosis with those of deficiency; eagerness by parents to make up an established deficiency; and mistakes in dosage. Case reports have shown that some parents will not admit of excessive dosing of their children, and others are slow to believe in the folly of overdosage.

The sexes have been shown to be equally affected; the vast majority of cases have occurred between the ages of 6 months and 36th months, with just one case in an older child of 8 years, and one adult woman, aged 44. There is a variable "lag" between the beginning of excessive dosage and the appearance of symptoms, which appears to be related to the size of dosage, individual thresholds of toxicity, and the physiological economy of the individual as reflected by age. The lag has varied from 2 to 18 months. The smallest toxic dose yet established was calculated to be 37,500 units daily for 14 months (177).

Acute poisoning, in contrast to chronic poisoning, is all but unknown to exist. Chronic poisoning presents the early generalized signs and symptoms of: Decrease in appetite with failure to gain weight and "constipation"; disinclination to play and progressive irritability; pruritus, usually over the back and extensor surfaces of the extremities; there may or may not be a rash which has been variously described as: dusky, erythematous, macular, papular, maculopapular, desquamating, discrete, scattered, brawny, excoriated, or simply dry, rough skin; a preference for butter and carotene-containing vegetables has been frequently noted; benign hydrocephalus is an infrequent observation. Somewhat later, dry, coarse, or falling hair is seen, along with dry, cracked, fissured and bleeding lips. Jaundice has been noted in 1 case, and hepatomegaly is almost the rule at examination. In most cases 6 months have elapsed between the start of excessive dosage and the appearance of hard, exquisitely tender, bony swellings in the extremities and skull bones. These have usually resulted in roentgenologic study and eventual diagnosis. Hemorrhagic tendencies have been noted in a few cases, but were not investigated for a cause.

The radiographic findings are not specific for this disease, but consist of cortical hyperostoses which show a preference for long bones and weight-bearing bones, these being

more exposed to trauma. Epiphyseal centers have been affected in a number of cases, but a consistent picture has not been demonstrated, the changes being described in a few cases as "mottling," "irregular epiphyseal lines," "widened" epiphyses, sclerotic epiphyses, and epiphyseal "cupping" at the ends of long bones. Advanced bone age was reported in one individual (64).

Laboratory findings have been usually characteristic. Anemia of the normocytic-normochromic or hypochromic-normocytic types has been noted in 50% of cases in some degree, usually mild. This may be due to excessive ingestion of vitamin D. Leucocytosis has been reported in a few cases, the differential pattern being usually normal. Increase in erythrocyte sedimentation rate is almost the rule. Blood non-protein-nitrogen and urine findings have been normal. As regards mineral studies, calcium and phosphorus serum levels have been shown to be consistently normal. Serum vitamin levels have shown normal vitamin C levels where determined, and markedly elevated vitamin A levels. Liver function tests are remarkably normal, in view of the common occurrence of hepatomegaly. The serum alkaline phosphatase is usually elevated (may be related to hypervitaminosis D). Serum protein studies show that a disturbance of this function of the liver is not common. Icterus Index is usually normal, and prothrombin activity may be slightly reduced. Bleeding and clotting times have been shown to be normal in

most cases where done. Other tests of liver function have yielded normal results, and the evidence of liver damage in this disease is rare. Muscle potential studies have been normal in the two cases where these were done, and the single worthwhile biopsy of bone showed that a process of accelerated remodelling characteristic of "productive periostitis" was going on.

The mechanism of toxicity is not well understood, but it is believed that the liver is first saturated with vitamin A (199), after which time high serum levels result in saturation of individual tissues which respond with altered metabolism in varying degree, producing the signs and symptoms noted. The evidence for this lies mostly in the work of Wolbach (187, 204), who has shown the effect on bone to be a local one, and one of accelerated growth and remodelling, with greater resorption than deposition of bone in experimental animals. A similar process has been hypothesized for human beings (182). The possible role of the scorbutic process in the mechanism of vitamin A toxicosis must be considered, because it has been shown (135) that high dosage with vitamin A produces a drop in liver and serum content of vitamin C, and a scorbutic picture, in experimental animals, though this has not been shown to be true for human beings. Quick's explanation for the hypoprothrombinemia in rats fed excessive vitamin A, as being related

to interference in the synthesis of vitamin K in the intestine, may explain the hypoprothrombinemia seen in a few of the cases of clinical hypervitaminosis A.

The diagnosis of hypervitaminosis A presents certain problems. Such diagnosis depends essentially on two points: 1) History of ingestion of excessive vitamin A, and 2) the determination of elevated serum vitamin A levels. It is believed that single fasting determinations of serum vitamin A levels are adequate, and any of the methods may be used. The vitamin A tolerance test may yield conclusive information in questionable serum level determinations, but is otherwise superfluous. The alcohol-ester separation is a more precise index of hypervitaminosis A, but is tedious and unnecessary.

There are several diseased states which may resemble hypervitaminosis A. Traumatic injury may be claimed by the patient's parents as the cause, and the roentgenologic picture may resemble a healing fracture, except that in hypervitaminosis A the lesions are widespread, and more than bony involvement exists. Trauma may in fact be involved in the process, if one accepts the concept of greater resorption of bone than deposition, and in such a case, slight trauma could result in periosteal loosening, hematoma, and callus formation to give the x-ray picture of cortical hyperostoses.

Periostitis of infectious origin may resemble the

roentgenographic picture, where periostitis results in bone production. However, this is usually secondary to penetration, and a history of the latter should be obtainable, or is resultant to outward penetration of an infectious process which would be hematogenous in origin and reflected in the systemic reaction to such infection. The periostitis of congenital syphilis also resembles the roentgenologic picture of hypervitaminosis A, but the differentiation is resolved by routine serology.

The greatest difficulty in differentiation is between vitamin A toxicosis and "infantile cortical hyperostosis." The latter disease resembles hypervitaminosis markedly, as regards the roentgenographic picture and some of the signs and symptoms. The distinguishing features are: 1) no history of excessive vitamin A intake; 2) normal serum vitamin A levels; 3) usually the onset is before the age of 6 months, and the disease shows exacerbations and remissions; 4) fever is usually present in this disease; 5) leucocytosis is common in this disease; 6) respiratory infections and pleural effusions are often seen; 7) the mandible is always involved and the metacarpals commonly involved, in contradistinction to hypervitaminosis A, where these sites are seldom effected; 8) anemia has not been reported as a distinguishing feature.

The nonspecific symptoms of anorexia, irritability, and weight loss, painful extremities and disturbances in gait

accompanied by subperiosteal elevations may suggest leukemia. However, in the latter state, transverse bands of diminished density in the metaphyses of long bones, osteolysis, and osteosclerosis are seen, all of which are lacking in vitamin A poisoning.

Scurvy is marked by tenderness of extremities, and subperiosteal calcification in the healing stages. Here, a dietary history, together with the presence of swelling, redness, and sponginess of gums, tendency towards hemorrhage, and characteristic changes in the ossification centers and metaphyses will aid in the differential diagnosis.

Healing rickets occasionally present subperiosteal bone proliferation. However, the characteristic roentgenographic changes in this disease are located at the epiphyseal plates.

Hypervitaminosis D should not be overlooked in the differential diagnosis, and may in fact be present, inasmuch as most cases reported have also ingested excessive amounts of vitamin D. The chief occurrence of vitamin D intoxication has been in patients who have been treated for some particular diseased condition, i. e., deficiency states, pulmonary and cutaneous tuberculosis, scleroderma, various allergic states, and rheumatoid arthritis. Hypervitaminosis D is marked by a sudden onset of anorexia, nausea, vomiting, thirst and constip-

ation. The children become progressively dehydrated, irritable and depressed, and gradually sink into a stupor. The laboratory data reveal a constant high blood pressure, an elevated calcium and phosphorus blood level, and signs of renal damage. The pathology which is responsible consists of widespread metastatic calcification.

The picture of irritability, restlessness, and painful extremities, along with pruritus, is seen in acrodynia, a disease of children which is apparently due to excessive ingestion of or a sensitivity reaction to mercury, and is characterized by lack of bony involvement to the roentgenogram and abnormally high levels of mercury in the urine, as well as pink coloration of hands and feet, extreme hypotonia, hypertension, and loss of teeth and nails.

Hypoprothrombinemia has never been shown to be below therapeutic levels in hypervitaminosis A, but conceivably might be. It is doubted that diagnosis of hypervitaminosis A would ever rest on the differentiation of the causes of hypoprothrombinemia, but the other conditions which cause it, all glaringly different from the clinical picture of hypervitaminosis A, are: Icterus neonatorum, biliary fistula with loss of bile required for absorption, intestinal diseases interfering with absorption, defective digestion and absorption of fats due to deficiency in lipases.

All cases have been shown to respond immediately to withdrawal of vitamin A, and none have shown any long-range residual effect. Vitamin K may be administered in case of serious hypoprothrombinemia.

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VII. Conclusions.

1. The increasing reports in the literature of a new syndrome called "Hypervitaminosis A" demonstrates the following facts:

A. There is a widespread lack of knowledge of the toxic effects of excessive intake of vitamin A among physicians, nurses, and lay people alike.

B. Present methods of dispensing vitamins are inadequately controlled, and these substances should be dispensed only by prescription of a physician.

C. Vitamin A poisoning is not apt to occur among the lower economic strata of society, in view of the prohibitive cost of vitamin preparations.

D. Every case of vitamin A toxicosis should be reported in the literature until knowledge of the existence of this entity is commonplace; the study of each case should not be slighted, rather, the opportunity for consideration of the following features should be exploited and carefully recorded until they are completely understood:

(1) Effects on the liver.

(2) Roles of vitamins C and D.

(3) Tissue biopsies and histological studies.

(4) Mineral balance studies.

(5) Effects on the blood.

(6) Effects on the endocrine system.

By careful study, the mechanism of toxicity will be better understood, as well as the normal physiology of vitamin A.

2. The existence of the entity should not stifle the use of vitamin A in therapy where this substance has been demonstrated to be of value, but the physician who administers vitamin A in massive doses should be fully apprised of the pitfall of toxicity of this essential factor, and guard the health of his patients with careful scrutiny.

3. There is no safeguard against the zeal of persons who have been indoctrinated with the "virtue" of vitamin supplements, but physicians should issue advice concerning toxicity with vitamin prescriptions.

4. Acute vitamin A poisoning is almost non-existent.

5. Chronic vitamin A poisoning has been reported in 26 patients in the United States, and presents the following distinctive features:

A. There is no peculiar susceptibility on the basis of sex difference.

B. The disease is essentially a pediatric problem, with greatest incidence between the ages of 6 months and three years of age.

C. A variable lag between commencement of overdosage

and onset of symptoms is a universal feature; this has been shown to be not shorter than 2 months and not longer than 18 months, and is apparently related to the size of the dosage, individual variations in susceptibility, and the physiological economy of the individual as reflected by age and body size.

D. There is a wide variation in individual susceptibility.

E. Poisoning has occurred with as little as 37,500 units per day; such a dose may therefore be considered potentially toxic in certain individuals.

F. A clinical syndrome comprising any or all of the following features is seen, depending on the severity of the case:

(1) History of decreased appetite, failure to gain weight, constipation, disinclination to play, irritability, restlessness, fatigueability, pruritis, rash of variable sorts, and dry, coarse, falling hair, in addition to swollen, tender extremities.

(2) Physical findings of enlargement of the head, cheilosis or cracked lips, jaundice, hepatomegaly, dry, coarse, or falling hair, irritability, rash, hard bony swellings which are exquisitely tender, crying on handling, standing, or walking.

(3) Roentgenographic picture of cortical hyperostoses of exposed long bones, and weight-bearing bones.

(4) Laboratory findings of anemia, possible leucocytosis, increased sedimentation rate, normal non-protein nitrogen and urine, normal mineral studies, elevated serum vitamin A and lipids, elevated serum alkaline phosphatase with otherwise normal liver function tests, except possibly slightly lowered prothrombin activity.

5. Diagnosis is based on two essential points: 1) History of excessive ingestion of the vitamin, and 2) Finding of elevated serum vitamin A levels. Other conditions which may present similar clinical pictures are: Traumatic injury, infantile cortical hyperostosis, periostitis, leukemia, scurvy, rickets, vitamin D poisoning, acrodynia, and blood dyscrasias which cause hemorrhage.

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