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Editorials

Hypervitaminosis A: Its Broadening Spectrum

THE AMERICAN medical literature concerned with the clinical aspects of vitamin A appears to have completed a full turn from concern with vitamin A deficiency in humans solely to papers predominantly related to hypervitaminosis A. In fact, if one excludes vitamin A deficiency produced secondarily by some disease process of the pancreas, intestine, etc., more instances of hypervitaminosis A seem to have been reported in the past 12 years than severe forms of vitamin A deficiency.

General improvement in the American diet, a better understanding of nutrition generally, and widely increased use of potent and readily available vitamin preparations, have made severe primary vitamin A deficiency an unusual disorder in this country. The circumstances for taking excess amounts of vitamin A, the frequent delay in clinical recognition, instances of multiple cases in one report, and circumscribed geographic areas of case location all indicate that the disorder is more common than reported. These factors strongly suggest that the laity, and for that matter, many physicians, are not fully aware that excess ingestion of vitamin A in very large doses for a short period (days), or in lesser excess amounts for longer periods (weeks to months) may produce toxic effects, not only in infants, but in older children and adults.

Careful studies of patients with vitamin A overdose have been reported with increasing frequency, and with such consistency of findings, that several well-defined and readily recognizable clinical syndromes have been delineated which can be classified, as suggested by Knudson and Rothman[1] into acute and chronic types in both infants and adults.

Recent reviews of the clinical aspects of hypervitaminosis A by Oliver,[2] Breslau,[3] and Gerber, Raab, and Sobel[4] and others; of the biochemical and pathologic aspects by Nieman and Klein Obbink;[5] inclusion of discussions of this disorder for the first time in recent editions of general textbooks; the detailed discussion of it in a monograph on vitamin A by Moore,[6] and editorial comment[3,7] all attest to the growing importance of this subject. Reference to these sources will be useful for those not familiar with the clinical recognition of the syndrome.

CHRONIC HYPERVITAMINOSIS A

Following Joseph's original description of chronic hypervitaminosis A in a three-year-old male in 1944,[8] 36 well-documented cases, mostly infants and young children, plus six adults, have been reported.[2] The onset is insidious, following a variable latent period of weeks to many months (average 10 months) of daily ingestion of vitamin A in doses of the magnitude of 100,000 units (occasionally more, rarely less). The correct diagnosis was often not made for long periods after onset of symptoms.

Infants and young children with this disorder insidiously and commonly develop constitutional symptoms, anorexia, dry, itchy skin (often followed by a seborrhea-like rash or desquamation), alopecia and sparse, coarse hair, angular fissures or cracking of the lips and a palpable hepatomegaly.[2] Particularly constant and characteristic, after a latent period, are painful swellings of the extremities over such bones as the tibia, fibula, clavicles, ulna and metatarsals (areas not well protected by muscle mass) which may produce a protective limp, refusal to stand, or disturbed sleep. The characteristic subperiosteal new bone growth and cortical thickening of the involved bones responsible have been ably described by Caffey.[9] Of diagnostic help and interest is the frequently elevated blood alkaline phosphatase value and the almost invariable normal calcium and phosphorus serum level. There may be constipation, weight loss, and rarely a peculiar craving for butter.

In adults, the clinical picture differs in the greater severity of the alopecia, skin involvement, and nail changes contrasted with the relative mildness of bone and joint pain, rarity of radiographic bone changes, relatively normal blood alkaline phosphate values and lesser size and incidence of hepatomegaly. Unique in adults have been exophthalmos, menstrual disturbances, and skin pigmentation.

Some cases, in both children and adults, may manifest clinical evidence of increased spinal fluid pressure which will be commented on elsewhere. Hemorrhagic phenomena, common in experimental animals, are rare in humans except for occasional epistaxis.

The rapid and complete recovery following treatment, which consists simply of cessation of the excessive vitamin A intake is particularly impressive and diagnostically significant. The effects are manifest within three to ten days for such features as anorexia, bone pain, headache, limps, pruritus, and weight loss, and somewhat longer for others due to tissue changes.[3] Permanent sequelae are unusual.

In infants and children the clinical picture may be confused with infantile cortical hyperostosis (Caffey's Disease), acute rheumatic fever, scurvy, rickets, arthritis; and in adults, with some of these and hypothyroidism or Addison's disease.

In both children and adults, the features of avitaminosis A may be confusingly similar to hypervitaminosis A.

ACUTE HYPERVITAMINOSIS A

The acute form of the disease in infants as described in 1951 by Marie and Sée,[10] and adult cases represented by many examples in arctic explorers, presents primarily with central nervous system manifestations due primarily to an abrupt and marked elevation in spinal fluid pressure. This is evident within hours after ingestion of a single large dose of vitamin A in the magnitude of 300,000 units for infants, and of one to several million units for adults.

In infants, the clinical picture (known as the Marie-Sée syndrome) is one of acute hydrocephalus, with marked bulging of the fontanelles (often as mushroom-like protuberances on the child's head), accompanied by vomiting and agitation or drowsiness, but without evidence of meningeal irritation or focal neurologic signs. Vitamin A is absent from the spinal fluid but blood levels are elevated. This is followed by a delayed but rough correlation of the increase in spinal fluid pressure to the blood level.

Reports of adults with the acute form emanate chiefly from arctic regions and are related to ingestion of polar-bear liver, an edible portion of which may contain several million units of vitamin A. Similar effects have also been noted from a comparable single dose of medicinal vitamin A.

The symptom complex occurs within hours after ingestion, manifested chiefly by a violent headache, accompanied often by nausea, vomiting, drowsiness, etc., all supposedly related to a marked increase in spinal fluid pressure. In addition, many of those afflicted noted desquamation of the skin either generalized or localized about the lips or to the exposed surfaces, evident on the second day.

In acute intoxication, manifestations appear to result from direct toxic effects on specific tissues, and are not dependent on supersaturation of liver stores.[3] It is of interest that some

patients manifest features of both the acute and chronic form.

Laboratory studies indicate that the blood vitamin A level is markedly elevated in all chronic cases thus studied, with variations from a normal fasting range of 50 to 150 i.u. per 100 ml of serum to values most frequently ranging from 800 to 2,000 i.u. per 100 ml, with a record high of 6,660 i.u. per 100 ml. Elevated values were also noted in the acute form. This determination is, therefore, diagnostically very helpful.

One study[4] indicated that the elevated vitamin A level was predominantly in the alcohol rather than ester form, a point of possible diagnostic value as indicated by the more rapid drop in this fraction as compared to the ester form.

The severity of most chronic cases on record in the literature, coupled with the long delay in diagnosis following onset of symptoms, indicates a low clinical suspicion for this disorder and suggests that milder (subclinical) forms may exist which are not recognized at all. Few physicians query patients on excess ingestion of vitamins compared to a possible deficient intake. Blood-vitamin A determinations are not readily available.

In one report, unexplained headache in two patients with a slightly elevated blood-vitamin A level, taking moderate excess daily doses of vitamin A, cleared when its ingestion was stopped. These may be representative of the subclinical form which, unfortunately, has not been delineated.

Suspicion of mild hypervitaminosis A may be warranted in instances where dryness, itching or desquamation of skin, fissured lips, chronic headache, vague bone and joint pains, constipation, anorexia or elevated alkaline phosphatase in various combinations are chronically present and unexplained. An elevation of blood-vitamin A level, history of excess intake, bone changes by roentgenogram and prompt cessation of these clinical phenomena with a low vitamin A intake would confirm the diagnosis. A careful study of this type would be particularly helpful. The minimal aspects of the clinical spectrum of hypervitaminosis A is hazy and poorly delineated in contrast to the sharp definition of the severe forms.

The clinical picture of hypervitaminosis A rests not only on the consistency with which certain signs and symptoms have been present in published material, but by its reproduction experimentally in humans. Experimental studies of hypervitaminosis A in animals are too well documented to require further comment.

In humans, experimental studies have taken two forms. In several reported instances of human hypervitaminosis A,[3] many of the clinical features which disappeared when excessive vitamin A intake was stopped, promptly reappeared when the excessive doses of vitamin A were again administered. The blood-vitamin A level, after an initial sharp fall, tapers off more slowly for many weeks. Prompt reacerbation of symptoms is apparently possible if excess vitamin A is further ingested before the saturated liver stores are depleted. This holds true with the use of pure vitamin A as well as fish liver oil concentrates, indicating the excessive intake of vitamin A as the specific cause of the clinical phenomena.[11]

Even more important is the recent report by Hillman,[12] in which hypervitaminosis A was induced experimentally, on two separate occasions, in a healthy human male, age 40, given excess quantities of this vitamin during two periods; one of 14 days' duration; the other of 25 days' duration (spaced many months apart). The dose was in the magnitude of 1,000,000 units per day. Striking rises in blood-vitamin A levels were noted rather promptly during each test period accompanied by such clinical features as severe headache, skin changes (dryness, rash, desquamation, itching), various constitutional symptoms, polyarthralgia and bone pain, etc., in variable sequence and combinations, duplicating many of the important clinical phenomena of both the acute and chronic forms of hypervitaminosis A documented in published case reports. This important work is worth reading in the original.

A particularly unique and intriguing manifestation of human hypervitaminosis A, more common in the acute than the chronic form, is a striking increase in cerebro-spinal fluid pressure. This subject was recently reviewed

by Bass.[13] All the more puzzling have been reports that this same phenomenon may result from avitaminosis A in humans,[14,15] and that either hypervitaminosis A or avitaminosis A during early pregnancy in rats may produce hydrocephalus in the fetal offspring.

The mechanism is unknown, but excess formation of spinal fluid has been suggested. Vitamin A does not enter the spinal fluid which has been normal in cytologic and chemical characteristics, but under high pressure, as indicated by manometric readings. Equally mysterious are indications of a similar increase in spinal fluid pressure at times with use of certain of the tetracycline antibiotics in children.[16] Investigation of the mechanism of the acute hydrocephalus in these several conditions appears highly desirable with particular attention to whether a common mechanism is responsible.

The acute hydrocephalus has been manifest clinically by bulging fontanelles in infants, elevated cerebro-spinal fluid pressure readings, occasionally as papilledema, and rarely by enlargement of the head. It could explain the headache, vomiting, stupor, and vertigo noted with acute poisoning in infants from excess intake of vitamin A preparations; and in adults acutely ill from ingesting livers of certain fish and arctic mammals (particularly polar bears) known to contain millions of units of vitamin A in a consumed portion. Internal hydrocephalus could explain the exophthalmos noted in experimental animals and (rarely) in humans.[3]

Published reports indicate a paucity of localizing neurologic signs and suggest that the process is generalized. The acute hydrocephalus rapidly subsides with cessation of the excess intake, or with drainage via lumbar puncture.

The implication of hypervitaminosis A was greatly broadened when Cohlan,[17,18] successfully demonstrated the frequent production of congenital anomalies in baby rats whose mothers received excessive doses of vitamin A during the early phase of pregnancy. The reader is referred to recent reviews[3,6] for further comment and references to several confirmatory studies. Cohlan's experiments indicate that the congenital defects noted in offspring in rat litters are dependent on the days of gestation during which the overload with vitamin A is performed.[18] From the fifth to the eighth day, the vitamin overload commonly terminated pregnancy with fetus resorption, but with anencephaly in a small percentage of the survivors. From the eighth to the tenth day, anencephaly was noted in 53 per cent of the offspring: spina bifida, cleft palate, microphthalmia or anophthalmia were noted to a lesser extent. From the 11th to the 13th day, 92 per cent exhibited cleft palate and occasionally cataracts. Between the 14th and 16th day, cleft palate was observed in 49 per cent with more manifesting cataract. From the 18th to the 20th day, cataracts were the main defect. Rarely, other anomalies such as hare lip, macroglossia and other eye defects were noted. Fetal hydrocephalus was noted and has been commented upon elsewhere.

It is well to recall that maternal avitaminosis A in rats, in early pregnancy, has similar teratogenic effects, often resulting in birth of young with anomalies of the brain, its calvaria, and production of congenital hydrocephalus. Apparently both avitaminosis A and hypervitaminosis A are hazardous in the early rat pregnancy.

Recently, Millen and Woollam[19] reported that cortisone administered during early pregnancy potentiated the teratogenic effect of maternal hypervitaminosis A in rats as regards gross malformations of the brain and calvaria; and in another study[20] they demonstrated a striking increased incidence of cleft palate with this combination. It was suggested that cortisone acts by increasing the sensitivity of the developing tissues which enhanced the teratogenic effect of hypervitaminosis A.

There is no available information as to whether hypervitaminosis A exerts a similar teratogenic effect in human pregnancy, but the subject is one worthy of critical investigation. It also is not known whether cortisone has a similar potentiating effect.

The general caution about excess use of vitamin A in patients may well deserve double emphasis when pregnancy exists. The steadily increasing literature on hypervitaminosis A indicates an established wide spectrum of its

effects and carries the implication of still further broadening.

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Nutrition and a State Medical Society

THE ultimate goal of all research and clinical investigation in nutrition is the improvement of the health of the people. To this end several progressive state medical societies have established programs which vary in scope and objectives but which have as their fundamental philosophy the "practical application" of our newer knowledge of nutrition.

One of the leading examples of such a progressive viewpoint may be found in the report of the Commission on Nutrition of the Medical Society of Pennsylvania (*Pennsylvania M. J.* 60:1113,1957). The Commission's report may well be studied by appropriate commissions of other state medical societies for it represents an admirable example of what can and should be done.

In brief, the Commission has had two objectives: (1) The stimulation of interest in clinical nutrition at state and county levels; and (2) the dissemination of factual information on nutrition to both practicing physicians and the laity.