Chronic Vitamin A Intoxication in Adults

Hepatic, Neurologic and Dermatologic Complications

MANFRED D. MUENTER, M.D.
HAROLD O. PERRY, M.D.
JURGEN LUDWIG, M.D.

Rochester, Minnesota

Two cases of chronic vitamin A intoxication in adults are described, and the literature is reviewed. Hepatocellular damage, portal fibrosis and eventual cirrhosis may result from chronic vitamin A intoxication in man. Neurologic complications are frequent and consist predominantly of increased intracranial pressure, muscle stiffness aggravated by exercise, and mental changes. Teratogenic effects have been documented in animal experiments and affect primarily the development of the central nervous system. Large doses of vitamin A, if prescribed at all for dermatologic conditions, should be given only for limited periods under close medical supervision and should not be given during pregnancy.

Vitamin A intoxication is a well recognized clinical entity. The acute form is self-limited and rarely presents a diagnostic problem. The chronic form has been observed predominantly in children, but an increasing number of cases have been described in adults. We report two cases of chronic vitamin A intoxication because of some findings hitherto undescribed.

CASE REPORTS

Case 1. An eighteen year old white women presented in November 1967 complaining of tiredness, dry and cracking skin, soreness and stiffness of muscles after exercise, and infected toe and finger nails. A diagnosis of McArdle's disease had been made elsewhere.

Her illness began in March 1966 as a flu-like syndrome with a skin eruption which was treated with vitamin A (Aquasol A), 300,000 IU daily. She had continued this medication beyond the recommended period of one month, taking 100,000 to 200,000 IU daily because of its favorable effect on her dry skin.

In July 1966 she noticed painful muscular stiffness and fatigue after exercise, more marked in the lower than in the upper extremities, which would subside within half an hour of rest; for example, after riding a bicycle she would be unable to walk because of muscle stiffness in both legs. She also complained of pain in bones and joints, nosebleeds, anorexia, swollen feet, cold forearms and generalized pruritus which was followed within two days by scaling. Severe generalized headache of one week's duration occurred in August 1966. A generalized maculoerythematous eruption, scaling and dryness of the skin were noted. A diagnosis of Stevens-Johnson syndrome was considered. Severe infections of ingrown toe and finger nails then occurred and were resistant to medical and surgical therapy. A diagnosis of McArdle's disease was made in

From the Sections of Neurology, Dermatology and Experimental and Anatomic Pathology. Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901. Requests for reprints should be addressed to Section of Publications, Mayo Clinic, Rochester, Minnesota 55901. Manuscript received January 23, 1970.

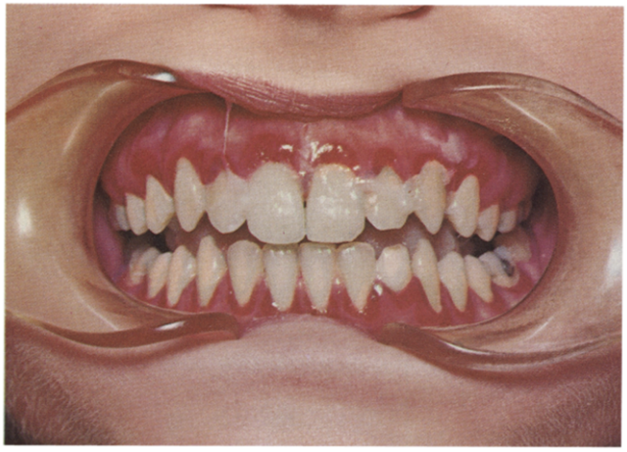

Figure 1. Case 1. Marginal discoloration (bright red) of gingiva.

September 1966. In March 1967 a bright red discoloration of the gingival margin was noted. In summer 1967 the maculoerythematous skin eruption cleared but recurred again for several weeks in the fall. For one year the patient had had an intense craving for carrots and eggs.

The medical and family histories were noncontributory.

Examination in November 1967 disclosed a healthy appearing woman in no distress (temperature 98.7°F, pulse 72/minute, respiration 17/minute, blood pressure 130/90 mm Hg). The skin was dry and scaly. An angular stomatitis and bleeding fissures of the paronychial tissues were noted. Several ingrown toe and finger nails had produced excessive granulation tissue. The gingiva was brightly red at its margin (Figure 1). Café-au-lait spots were noted on the left mid-abdomen and the anterior right thigh. The liver was palpable 4 to 5 cm below the xiphoid in the midline and 3 cm below the right costal margin; it was soft, smooth and not tender. The spleen descended 2 cm with deep inspiration. Neurologic examination showed bilateral subacute papilledema with less than 1 diopter elevation of the disk margins, confirmed by fluorescein studies. The myotatic reflexes were symmetrically increased to a moderate degree, but no pathologic reflexes could be elicited. The remainder of the examination disclosed no abnormalities.

Laboratory data included hemoglobin 11.3 gm/100 ml, leukocytes 4,100/cu mm, erythrocyte sedimentation rate 64 mm in one hour (Westergren), alkaline phosphatase 129 International Units/L, serum glutamic oxalacetic transaminase (SGOT) 80 units/L, sulfobromophthalein retention 32 per cent after one hour, urinalysis grade 1 protein, grade 1 white blood cell count, serum vitamin A 737 μg/100 ml (normal 37 to 45 μg/100 ml), serum carotene 88 μg/100 ml, cholesterol 178 mg/100 ml, cholesterol esters 127 mg/100 ml, phospholipids 173 mg/100 ml, fatty acids 355 mg/100 ml, triglycerides 64 mg/100 ml. Other laboratory tests giving normal results were differential leukocyte count; blood sugar; serum bilirubin, sodium, calcium, phosphorus and creatinine; protein-bound iodine, creatinine phosphokinase; glucose tolerance test; serologic test for syphilis (VDRL); urine screening test for inborn errors of metabolism; twenty-four hour urinary creatinine; electroencephalogram; echoencephalogram; electromyogram; ischemic exercise tolerance test. Roentgenograms of the head showed increased diploic vascular channels in the right frontal area and calcification of the choroid plexus. Roentgenograms of the thorax, lumbar and thoracic spinal regions, feet, right hand and both legs did not disclose any abnormalities.

A bone biopsy specimen was taken from the left ninth rib; the results have been reported elsewhere [1].

The diagnosis of chronic vitamin A intoxication was made, and all intake of supplementary vitamin A was discontinued.

When seen again in January 1968, the patient had recovered from all symptoms. The subacute papilledema was unchanged. Spleen and liver were unchanged in size. Ingrown nails continued to be inflamed, infected and resistant to therapy. Laboratory data were hemoglobin 10.8 gm/100 ml, red blood cell count 3.44×10^6/cu mm, sedimentation rate 87 mm in one hour, alkaline phosphatase 105 units/L, SGOT 55 units/L, prothrombin time twenty-nine seconds; bromsulfalein retention 24 per cent, serum total protein 7.2 gm/100 ml, albumin 3.3 gm/100 ml, serum iron 48 μg/100 ml, serum vitamin A 155 μg/100 ml, serum carotene 251 μg/100 ml. Vitamin K (Synkamin®), 4 mg daily, was prescribed.

In March 1968 the patient still felt well. The liver was palpable 4.5 cm below the xiphoid and the spleen, 2 cm with inspiration. One spider nevus was noted on the dorsum of the right wrist. The subacute papilledema was unchanged. The intraocular pressure was 12 mm in each eye as measured by applanation. Laboratory data included hemoglobin 11.0 gm/100 ml, sedimentation rate 80 mm in one hour, alkaline phosphatase 117 units/L, SGOT 49 units/L, prothrombin time 25 seconds, thymol turbidity 3 units, cephalin flocculation 4+, bromsulfalein retention 34 per cent, total serum protein 7.58 gm/100 ml, albumin 3.42 gm/100 ml, serum vitamin A 119.7 μg/100 ml. Urinalysis disclosed protein 1+, white blood cells 1+, red blood cells 1+. Treatment with vitamin K was continued. The patient was instructed to adhere to a low vitamin A diet with high protein and low fat content.

In July 1968 the optic disks were normal. The liver was palpable 6 cm below the xiphoid and the right costal margin, and the spleen, 3 cm below the costal margin with inspiration. Several spider nevi were noted. The gingival discoloration was barely visible.

Paronychia and infected toenails had healed. Laboratory data included sedimentation rate 82 mm in one hour, alkaline phosphatase 129 units/L, SGOT 53 units/L, prothrombin time twenty-nine seconds, bromsulfalein retention 32 per cent, serum total protein 7.46 gm/100 ml, albumin 3.44 gm/100 ml, serum vitamin A 97.2 μg/100 ml. Urinalysis disclosed protein 1+, white blood cells 1+. In view of persistent signs of active inflammatory liver disease, steroid therapy was recommended, 30 mg of prednisone daily for three weeks followed by 20 mg daily for four weeks and 15 mg daily for one week. However, the patient took only approximately half of the recommended dosage spread over a two month period.

In September 1968, she reported nosebleeds on eight occasions and fatigue. The liver was no longer enlarged; the spleen was palpable 2 cm with inspiration. Four spider nevi were noted on the hands. Laboratory data included a sedimentation rate of 72 mm in one hour, bromsulfalein retention 36 per cent, thymol turbidity 4 units, cephalin flocculation 4+, alkaline phosphatase 94 units/L, bilirubin direct negative, indirect 2.0 mg/100 ml, SGOT 50 units/L, serum total protein 7.65 gm/100 ml, albumin 3.41 gm/100 ml, prothrombin time twenty-one seconds. Needle biopsy of the liver (Figure 2) showed marked periportal and centrilobular fibrosis. Ill defined bands of connective tissue subdivided the lobules and caused distortion of the normal hepatic architecture. There was proliferation of the Kupffer cells and fibroblasts. Small groups of hepatic cells were encased by connective tissue fibers which had formed in the walls of the sinusoids. There was fibrosis of the portal fields. Some of the portal vein branches were markedly dilated. The walls of these veins were thin, and there were no signs of thrombosis. There was some atypical bile duct proliferation. A moderate number of polymorphonuclear leukocytes were found in the areas of intralobular fibrosis. The Prussian blue method (Perl) failed to demonstrate reactive ferric iron. Frozen sections of the specimen showed marked fatty changes with small and large isotropic Sudan IV-positive droplets, predominantly in the hepatic cells and to a lesser degree in the Kupffer cells. The fat showed a marked vitamin A fluorescence, fading from green to blue after about fifteen seconds [2]. The histologic diagnosis was severe hepatic fibrosis and fatty changes of the liver, secondary to vitamin A intoxication.

In March 1969 the patient was feeling well. The liver was palpable 3 cm below the costal margin and the spleen, 3 cm with inspiration. Several spider nevi were unchanged. Laboratory data included hemoglobin 12.6 gm/100 ml, sedimentation rate 85 mm in one hour, bilirubin direct negative, indirect 2.5 mg/100 ml, alkaline phosphatase 71 units/L, SGOT 53 units/L, serum total protein 6.94 gm/100 ml, albumin 3.12 gm/100 ml, bromsulfalein retention 26 per cent, thymol turbidity 4 units, cephalin flocculation 4+, prothrombin time twenty-seven seconds, serum vitamin A 92.1 μg/100 ml, carotene 216 μg/100 ml, cholesterol 454 mg/100 ml, cholesterol esters 295 mg/100 ml, triglycerides 164 mg/100 ml, phospholipids 392 mg/100 ml, total lipids 1,010 mg/100 ml.

Case 2. A 52 year old woman was first seen at the Mayo Clinic in June 1947 complaining of severe gen-

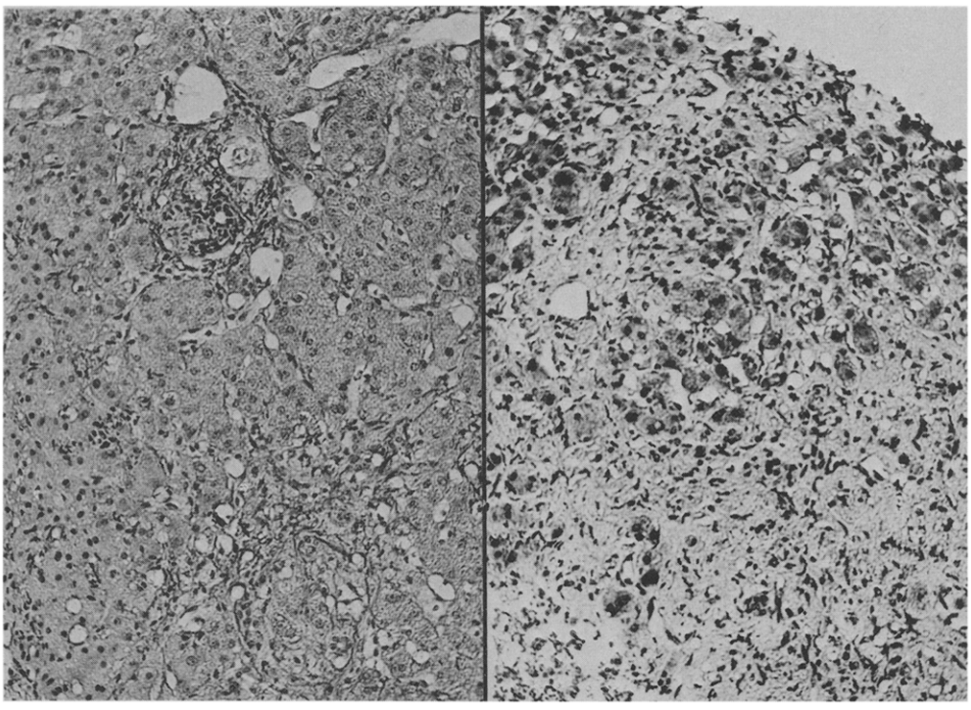

Figure 2. *Case 1. Liver biopsy specimen. Left, periportal, intralobular and centrilobular fibrosis; fatty changes, predominantly of hepatic cells; inflammation of portal tracts; proliferation of Kupffer cells; clusters of polymorphonuclear leukocytes. Van Gieson stain, original magnification × 150. Right, hepatic fibrosis with lymphohistiocytic and granulocytic inflammatory infiltrates; small cluster of partly degenerating hepatic cells with fatty changes; loss of normal hepatic architecture. Hematoxylin and eosin stain, original magnification × 165.*

eralized pruritus, predominantly of the scalp, shoulders and nuchal area, which had developed in September 1946. The skin had become rough and dry, and she had lost hair. The diagnosis of pityriasis rubra pilaris was made after a skin biopsy. Laboratory data were normal, including sedimentation rate 10 mm in one hour, serum vitamin A 35 μg/100 ml and carotene 131 μg/100 ml. The patient was treated with 3 per cent ichthammol (Ichthyol®) ointment, aluminum subacetate wet dressings, tripelennamine (Pyribenzamine®), and vitamin A (100,000 IU daily); the vitamin A was to be discontinued after three months. She was dismissed to the care of her local dermatologist. Her condition improved approximately 50 per cent. Because symptoms recurred whenever she discontinued vitamin A, she increased the vitamin A intake to 400,000 IU daily for one year and took 200,000 to 300,000 IU/day thereafter for the ensuing eight years.

The family history was noncontributory. The medical history included a hysterectomy in 1945. The patient had never had symptoms of hepatitis nor was there a history of exposure to known hepatotoxins. She had received one blood transfusion in 1950 without complication. In 1949 she had been treated for cystitis with sulfonamides. In 1950 cholecystectomy was performed because of cholelithiasis. In 1952 a deep vein phlebitis healed after conservative therapy. In 1952 she was hospitalized for severe low back pain which subsided with traction. In 1954 she had "low grade arthritis" for which she was treated with phenylbutazone (Butazolidin®) and thyroid preparations.

In September 1954 she experienced pain in the dorsal spinal region. In early summer of 1955, anorexia, nausea and a 16 pound weight loss occurred. At this time the liver was found to be tender and enlarged to the umbilicus. Laboratory data included hemoglobin 11.7 gm/100 ml, red blood cells 3.91 × 10^6/cu mm, bromsulfalein retention 45 per cent after thirty minutes, icteric index 13.9 units, prothrombin time twenty-four seconds, serum total protein 7.6 gm/100 ml, albumin 2.03 gm/100 ml, globulin 5.57 gm/100 ml, sedimentation rate 20 mm in one hour, basal metabolic rate −11 per cent, glucose tolerance test indicative of mild diabetes mellitus. Leukocyte count, urinalysis and plasma cholesterol levels were within normal limits.

An open liver biopsy was performed in October 1955 (in Denver). When the slides were later reviewed at this clinic, the histologic diagnosis was cirrhosis of the liver, probably postnecrotic and cause unknown. No fluorescence studies were carried out. (The paraffin sections were not available for study.) According to the original description by Dr. S. K. Kurland, Denver, the biopsy specimen was firm and gray-yellow; the sectioned surface was lobulated, nodular and varied in color from gray-brown to gray-yellow. Histologically there was marked disorganization of individual lobules with, in many instances, complete loss of the normal central vein and portal triad relationship. The fibrous tissue around the portal triads was increased and contained proliferating bile ducts, focal accumulation of lymphocytes and occasional histiocytes. The histiocytes in many instances were lipoid laden. The fibrous tissue was increased both between portal triads and occasionally between hepatic cell plates. The hepatic cells were finely reticulated. Within some of the liver cells and bile canaliculi was inspissated bile. Regenerative and degenerative changes of hepatic cells were evident in some areas. The diagnosis was cirrhosis, moderately advanced. Subsequent to this biopsy, a high protein, low fat diet was prescribed, and crude liver injections were given intramuscularly twice weekly.

The patient returned to the Mayo Clinic in March 1956, for the first time since 1947, complaining of increasingly severe, nonradiating, midthoracic back pain, anorexia, fatigue, somnolence and yellowish discoloration of the skin.

On examination the vital signs were normal; there was slight generalized icterus, pallor of the face and erythema of the fingers and palms. The liver was palpable at the umbilicus, firm and not tender. The spleen was slightly enlarged. Mild pitting edema of the legs was noted. Neck motions were moderately limited. A mild static and movement tremor of the head, lips, tongue and arms was present. The gait was stiff and slightly unsteady; all muscle groups showed moderately increased tone. The myotatic reflexes were symmetrically hyperactive, but no pathologic reflexes were found. Axillary hair was absent and pubic hair was sparse. The nails were spooned and dystrophic. The remainder of the examination was noncontributory.

Laboratory data included hemoglobin 11.2 gm/100 ml, red blood cells 3.9 × 10^6/cu mm, sedimentation rate 66 mm in one hour, bilirubin direct negative, indirect 1.16, alkaline phosphatase 14.8 Bodansky units, prothrombin time 22 seconds, thymol turbidity 3 units, cephalin flocculation 3+, bromsulfalein retention 26 per cent in one hour, serum total protein 6.66 gm/100 ml, albumin 3.79 gm/100 ml, serum vitamin A 250 μg/100 ml, serum carotene 90 μg/100 ml, cholesterol 234 mg/100 ml, cholesterol esters 167 mg/100 ml, phospholipids 240 mg/100 ml, fatty acids 359 mg/100 ml, total lipids 593 mg/100 ml. A roentgenogram of the thorax showed narrowing of the eighth and ninth thoracic intervertebral spaces.

The diagnosis of chronic vitamin A intoxication was made. Vitamin A intake was discontinued and, within four weeks, the back pain disappeared; the patient's level of energy, alertness and appetite returned to normal, she gained 4 pounds, and there was no abnormality of the skin. She was dismissed on a regimen consisting of a high protein, low fat diet and vitamin K. The vitamin A level four weeks after discontinuation of vitamin A intake was 85.8 μg/100 ml.

On follow-up examination in August 1956 the patient complained of fatigability but otherwise felt well. The scalp hair had become thicker, and the skin was less dry. The liver size was unchanged; the spleen was no longer palpable. One spider nevus was present on the forehead. Laboratory data included hemoglobin 12.1 gm/100 ml, red blood cell count 3.91 × 10^6/cu mm, sedimentation rate 63 mm in one hour, bilirubin direct negative, indirect 1.4 mg/100 ml, prothrombin time twenty-three seconds, thymol turbidity 3 units, cephalin flocculation 3+, bromsulfalein retention 26 per cent, serum total protein 6.5 gm/100 ml, albumin 3.8 gm/100 ml, serum vitamin A 75.0 μg/100 ml, plasma cholesterol 333 mg/100 ml, cholesterol esters 217 mg/100 ml, phospholipids 313 mg/100 ml, fatty acids 527 mg/100 ml, total lipids 860 mg/100 ml.

In September 1957 the patient had no complaints and looked well. The liver was unchanged in size and palpable at the umbilicus; the spleen was not palpable. The myotatic reflexes remained hyperactive. Laboratory data included hemoglobin 13.4 gm/100 ml, sedimentation rate 42 mm in one hour, bilirubin direct negative, indirect 1.34 mg/100 ml, prothrombin time 22 seconds, thymol turbidity 4 units, cephalin flocculation 4+, bromsulfalein retention 36 per cent, serum total protein 6.8 gm/100 ml, albumin 4.1 gm/100 ml, serum vitamin A 31.5 μg/100 ml, serum carotene 181 μg/100 ml, plasma cholesterol 311 mg/100 ml, cholesterol esters 200 mg/100 ml, phospholipids 333 mg/100 ml, fatty acids 507 mg/100 ml, total lipids 818 mg/100 ml.

In December 1961 bromsulfalein retention was 31.3 per cent in one hour cephalin flocculation 4+. In December 1963 bromsulfalein retention was 18.7 per cent in one hour.

In October 1968 the patient felt well and had no complaints. On reexamination by her local physician, the liver was no longer palpable; a roentgenogram of the abdomen showed a normal liver outline. Laboratory data included a hemoglobin of 16.0 gm/100 ml, sedimentation rate 7 mm in one hour, bilirubin direct negative, indirect 1.0 mg/100 ml, alkaline phosphatase 60 units/L, cephalin flocculation 2+, bromsulfalein retention 17.3 per cent after forty-five minutes, serum total protein 6.3 gm/100 ml, albumin 4.03 gm/100 ml, SGOT 38 units/L, cholesterol 257 mg/100 ml.

COMMENTS

The literature contains seventeen case reports of chronic vitamin A intoxication in adolescents or adults, including those reported in this paper [3–15]. They are summarized in Tables I and II.

Sixteen patients were female, and one was male. The age range was fourteen to sixty-two years. The daily vitamin A intake ranged from 41,000 to 600,000 IU, and the duration was two months to nine years. The smallest daily dose leading to intoxication was 41,000 IU taken for eight years [12]. Intoxication after a two-month period of vitamin A intake occurred on a daily dose of 200,000 to 275,000 IU [4].

In the past, vitamin A has been used in large doses over protracted periods for the management of a wide variety of dermatologic conditions, but without adequate therapeutic basis. The reason for vitamin A therapy in the cases reviewed was acne in eight cases, "cold prevention" in two and pityriasis rubra pilaris, nonspecific skin eruption, ichthyosis, food fadism, "to improve vision" and for "dry skin" in one case each.

Our cases confirm the clinical picture characteristic of chronic vitamin A intoxication in adults: the invariably present skin changes, increased intracranial pressure, bone and joint pain, fatigue and anorexia. In addition they exemplify clinical features which have not been emphasized in the past.

Both patients showed marked impairment of liver function, one and a half and twelve years, respectively, after vitamin A intake was discontinued. In

TABLE I Symptoms and Signs in Seventeen Cases of Chronic Vitamin A Intoxication in Adults and Adolescents

Symptom or Sign	Cases (no.)
Skin (dryness, maculopapular rash, fissures, desquamation, pigmentation, pruritus)	17
Hair loss	14
Generalized weakness and fatigue	14
Pain in bones and joints	13
Marked tenderness of bones to palpation	11
Anorexia	9
Headache	9
Hepatomegaly	8
Muscle stiffness	7
Endocrine (absent or decreased menorrhea)	7
Papilledema	6
Diplopia	6
Weight loss	6
Splenomegaly	6
Polyuria, polydipsia, urinary frequency	6
Psychiatric symptoms	6
Edema of lower extremities	6
Insomnia	5
Bleeding (nose and lips)	5
Brittle nails	4
Somnolence	3
Exophthalmus	2
Yellow discoloration of skin	2
Other neurologic symptoms	2
Gingivitis	1*
Lymphadenopathy	1

*A similar case of gingivitis in vitamin A intoxication has been described by Smith [16] but was not included in this review of seventeen cases.

TABLE II Laboratory Findings in Seventeen Cases of Chronic Vitamin A Intoxication in Adults and Adolescents

Test	Cases (no.)	
	Normal	Abnormal
Sedimentation rate (mm in one hr)	1	7 (range: 22-87)
Sulfobromophthalein retention (%)	3	3 (17, 26, 32)
Alkaline phosphatase	3	7 (increased)
Serum total protein	8	1 (decreased)
Serum total albumin	1	7 (decreased)
Serum bilirubin: total	7	5 (increased)
direct	7	1 (increased)
indirect	7	1 (increased)
Prothrombin time	4	3 (increased)
Thymol turbidity	9	1 (increased)
Cephalin flocculation	9	2 (increased)
Hemoglobin (gm/100 ml)	8	6 (decreased; range 10.2-12.0)
Leukocyte count (per cu mm)	8	3 (3,200, 4,100, 4,300)
Protein-bound iodine (μg/100 ml)	4	2 (1.8, 10.8)
Cholesterol	6	2 (decreased)
Urinalysis	6	3 (protein 1+)
Cerebrospinal fluid: Pressure (cm water)	3*	3 (35, 60 "increased")
Cells, protein	5	0
Roentgenogram of long bones and spine	11	2 (demineralization)
Electroencephalogram	4	2 (diffuse abnormality, projected type)
Serum vitamin A (μg/100 ml)	0	17 (range, 83-2,000)
Serum carotene (μg/100 ml)	6	3 (slightly increased; range 264-375)

*These normal values were 13/13, and 7 cm water.

Case 2, liver size returned to normal, and liver function improved slowly. Neither patient gave any history of hepatitis or exposure to hepatotoxic substances other than vitamin A. This, the fluorescence microscopic findings in Case 1 and the improvement after discontinuation of vitamin A intake in Case 2 suggest strongly that the impaired liver function and the morphologic changes in hepatic tissue were a result of the hepatotoxic effect of vitamin A. Hepatomegaly has been noted in six other cases of chronic vitamin A intoxication [4,6,7,10,11,15]. A liver biopsy was normal in one case [11]. Hepatic cell necrosis, fatty changes and other pathologic findings in the liver of experimental animals reported by numerous investigators seem to confirm the hepatotoxic effects of excess vitamin A [17]; the cause of death in these animals frequently was widespread hemorrhage due to hypoprothrombinemia secondary to marked loss and impairment of hepatic parenchyma. These experimental findings, however, refer to results of acute intoxication. The biopsy findings in our two cases suggest that, in man, chronic hypervitaminosis A may lead to hepatocellular damage, portal fibrosis and eventual cirrhosis.

A marked increase in plasma lipid levels was noted in both of our cases after discontinuation of vitamin A therapy and may be related to impaired liver function. However, it is of interest that the increase occurred shortly after vitamin A intake was discontinued. Misra [18] reported an increase in total brain lipids and cholesterol in vitamin A intoxication.

The cerebrospinal fluid pressure was measured in six of the cases reported in the literature; it was increased in three [6,8,14] and normal in three [9,12,13]. In the three cases in which pressure was increased, it was associated with papilledema twice, diplopia three times and headache twice. In the three cases in which the pressure was found to be normal, it was measured several weeks after vitamin A therapy was discontinued in one case, was not associated with papilledema or diplopia in the second case, and was measured after pneumoencephalography in the third case. In the case reported by Gerber and associates [6] the cerebrospinal fluid was found to be under increased pressure when ventriculography was performed. A craniotomy was carried out on this patient; she continued to take vitamin A, and the craniotomy site was repeatedly found to be tense and markedly bulging. Jennekens and Van Veelen [13] reported a case of subacute vitamin A intoxication (not included in our review of chronic cases) in a nineteen year old patient with diplopia, papilledema and headache; an elevated cerebrospinal fluid pressure (300 mm water) was found. These findings strongly suggest that chronic vitamin A intoxication in adult man causes increase of cerebrospinal fluid pressure with diplopia, papilledema and headache. This is in contrast to the results of animal experiments

[19,20] but is in accord with the prompt bulging of fontanels observed in acute vitamin A intoxication in infants [21] as well as the observation of increased intracranial pressure and hydrocephalus in offspring of rats fed excessive doses of vitamin A [22].

Only few neurologic signs, other than increased intracranial pressure with associated diplopia, somnolence and headache, have been reported in man. Gerber and co-workers [6] described nystagmus, atrophy of selected muscles and sensory symptoms in the saddle area in their patient.

We would like to call attention to a neurologic symptom which, in one of our patients, led to the mistaken diagnosis of McArdle's disease. It consists of muscle stiffness which may or may not be present spontaneously but will occur or be markedly increased with activity and subside with rest. This sympton can become severe enough to make walking impossible, was observed in seven of the seventeen cases reported in the literature [6–8,11,15] and may lead to bizarre postures. It is not known whether this symptom is of myogenic or neurogenic origin.

Psychiatric manifestations have been prominent in several cases and may lead to social isolation of the patient; in mild cases they presented as depression or irritability.

Numerous central nervous system changes have been reported to occur in vitamin A intoxication of experimental animals, including exencephaly and anencephaly in offspring of vitamin A-intoxicated rats [22], neuronal changes in the neuroepithelial zone in offspring of mice [23], higher incidence of postvaccinal encephalomyelitis in rabbits [24] and widespread neuronal degeneration in guinea pigs [25].

The rather striking gingivitis present in one of our patients has been reported on only one other occasion [16].

Paronychia and infected ingrown toenails associated with abnormal granulation tissue in one of our patients subsided after vitamin A therapy was discontinued and were probably related to the hypervitaminosis.

We have no explanation for the craving for food with high vitamin A content which has been reported by others and was present in one of our patients. It occurs during the state of hypervitaminosis.

Laboratory tests in the reported cases showed variable results except for consistently increased serum vitamin A levels. Other abnormal findings were increased cerebrospinal fluid pressure and abnormal liver function tests. Anemia, leukopenia and proteinuria were present in a few cases. Electroencephalographic abnormalities were reported in two cases in which there was evidence of increased intracranial pressure. Demineralization of bones was detected roentgenologically in only two cases, in contrast to marked bone abnormalities with spontaneous fractures usually noted in acute animal experiments. In one of our cases there were no grossly detectable roentgenologic bone changes, but marked alterations in bone turnover were noted in the biopsy specimen [1].

It is of importance that, in chronic vitamin A intoxication, storage of vitamin A in the liver and serum levels of vitamin A are not proportionally related. During early stages of intoxication much of the vitamin A is stored in the liver, and the serum level remains low. Once the capacity for storage is exhausted, the serum level increases rapidly. For this reason, serum vitamin A levels may be high if a relatively small amount of vitamin A is given for a sufficiently long period. The serum vitamin A level may remain low if large amounts of vitamin A are given for short periods.

REFERENCES

1. Jowsey J, Riggs BL: Bone changes in a patient with hypervitaminosis A. J Clin Endocr 28: 1833, 1968.
2. Thompson SW: Selected Histochemical and Histopathological Methods, Springfield, Ill, Charles C Thomas, 1966, p 1249.
3. Sulzberger MB, Lazar MP: Hypervitaminosis A. Report of a case in an adult. JAMA 146: 788, 1951.
4. Shaw EW, Niccoli JZ: Hypervitaminosis A. Report of case in an adult male. Ann Intern Med 39: 131, 1953.
5. Bifulco E: Vitamin A intoxication. Report of a case in an adult. New Eng J Med 248: 690, 1953.
6. Gerber A, Raab AP, Sobel AE: Vitamin A poisoning in adults with description of a case. Amer J Med 16: 729, 1954.
7. Elliott RA Jr, Dryer RL: Hypervitaminosis A. Report of a case in an adult. JAMA 161: 1157, 1956.
8. Oliver TK Jr: Chronic vitamin A intoxication. Report of a case in an older child and review of the literature. Amer J Dis Child 95: 57, 1958.
9. Morrice G Jr, Havener WH, Kapetansky F: Vitamin A as a cause of pseudotumor cerebri. JAMA 173: 1802, 1960.
10. Stimson WH: Vitamin A intoxication in adults. Report of a case with a summary of literature. New Eng J Med 265: 369, 1961.
11. Soler-Bechara J, Soscia JL: Chronic hypervitaminosis A. Report of a case in an adult. Arch Intern Med (Chicago) 112: 462, 1963.
12. Bergen SS Jr, Roels OA: Hypervitaminosis A. Report of a case. Amer J Clin Nutr 16: 265, 1965.

13. Jennekens FGI, Van Veelen CWM: Hypervitaminosis A. Presse Med 74: 2925, 1966.
14. Wisse Smit J, Pott Hofstede D: Vitamine a-intoxicatie bij volwassenen. T Geneesk 110: 10, 1966.
15. Di Benedetto RS: Chronic hypervitaminosis A in an adult. JAMA 201: 700, 1967.
16. Smith JH: Hypervitaminosis A. Report of a case. Oral Surg 17 (supp 3): 305, 1964.
17. Nieman C, Klein Obbink HJ: The biochemistry and pathology of hypervitaminosis A. Vitamins Hormones (NY) 12: 69, 1954.
18. Misra UK: Fatty acids of brain in hypervitaminosis A in rats. Canad J Biochem 44: 1539, 1966.
19. Nelson EC, Dehority BA, Teague HS, Grifo AP Jr, Sanger VL: Effect of vitamin A and vitamin A acid on cerebrospinal fluid pressure and blood and liver vitamin A concentrations in the pig. J Nutr 82: 263, 1964.
20. Hurt HD, Eaton HD, Rousseau JE Jr, Hall RC Jr: Rates of formation and absorption of cerebrospinal fluid in chronic bovine hypervitaminosis A. J Dairy Sci 50: 1941, 1967.
21. Knudson AG Jr, Rothman PE: Hypervitaminosis A. A review with a discussion of vitamin A. Amer J Dis Child 85: 316, 1953.
22. Cohlan SA: Excessive intake of vitamin A as a cause of congenital anomalies in the rat. Science 117: 535, 1953.
23. Langman J, Welch GW: Excess vitamin A and development of the cerebral cortex. J Comp Neurol 131: 15, 1967.
24. Ehrengut W: Hypervitaminosis A and infection: Experimental studies on a model of vaccine infection. Vitamins Hormones (NY) 8: 501, 1961.
25. Brusa A, Testa F: Lesioni nel sistema nervoso centrale di cavie in ipervitaminosi A. Int Z Vitaminforsch 25: 55, 1953–1955.