

INFLUENCE OF IMPROVED NUTRITION ON THE
CHOLESTEROL VITAMIN A AND CAROTENE OF
THE BLOOD SERUM OF PATIENTS WITH FAR
ADVANCED ACTIVE TUBERCULOSIS

Thesis for the Degree of M. S.,
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INFLUENCE OF IMPROVED NUTRITION ON THE CHOLESTEROL
VITAMIN A AND CAROTENE OF THE BLOOD SERUM
OF PATIENTS WITH FAR ADVANCED
ACTIVE TUBERCULOSIS

By

Evadne Chitrangani Ameresekere

AN ABSTRACT

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Adrian C. Cedergren

Blood serum vitamin A, carotene, and cholesterol concentrations were determined for 17 patients with far advanced pulmonary tuberculosis, and were used to evaluate their state of nutrition, and to determine the adequacy of liver function during a period of protein repletion in these patients.

Subjects were those patients who did not respond to the hospital regimen of antibiotics, bedrest, vitamin and mineral supplements, and a diet high in calories and protein. Repletion therapy varied from eight months to two years and eight months, with the exception of one patient who left after four months of repletion therapy. Vitamin A supplements varied from 5,000 to 20,000 International Units, daily, for 16 patients; whereas the remaining patient received 20,000 to 50,000 International Units daily.

Patients were classified as poor, if they failed to improve, and good if they showed signs of consistent improvement. Two of the patients who were rated poor died soon after the study, and two of the patients rated good left the hospital before the study ended.

Weight gains of one kilogram or above per month were observed for some of the patients classified as good. Weight gains were negligible for patients who were classified as poor, while one patient in this group showed a slight loss in body weight.

Blood serum vitamin A and carotene concentrations were determined for eight patients before and during repletion therapy, and for nine additional patients during repletion therapy. Concentrations of blood serum vitamin A were higher for those patients classified as good than for those patients classified as poor. Increases in blood serum vitamin A were greater for those patients who were classified as good than for patients classified as poor, during the repletion program. Prior to therapy, blood serum carotene values ranged from 15 to 87 micrograms per 100 milliliters; the lowest values were for two patients who died soon after the termination of the study.

All the patients had total serum cholesterol values comparable to those of healthy adults, but the percentage of free in total cholesterol varied. Six out of 17 patients had free in total cholesterol values within the range of 24 to 34 percent, indicating satisfactory functioning of the liver with respect to serum lipids. Ratios of free in total cholesterol for the other patients exceeded this range either before and/or during repletion therapy. Serum cholesterol concentrations which were initially low, tended to approach the range for healthy adults.

Prior to repletion therapy, all but one patient had albumin-globulin ratios less than the 1.2 to 2.6 range associated with healthy adults. Three of the patients had values within this range at the close of the study, and eight patients showed increases approaching normal values during therapy.

Before therapy, four patients had serum albumin values similar to that of healthy adults, while serum globulin values exceeded the range for healthy adults for all the patients. During therapy, there was a tendency towards an increase in serum albumin, and a decrease in serum globulin.

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INTRODUCTION

Studies of the protein repletion of patients with far advanced, active tuberculosis have been in progress for several years at the Saginaw County Hospital under the direction of Dr. J. Mott Rawlings, a physician from Flint, Michigan. The Department of Foods and Nutrition at Michigan State University has cooperated in this research, particularly with that phase of research concerned with changes in biochemical constituents during nutritional repletion.

According to Rawlings and Hergt (1953), the degeneration of the protoplasmic mass of the body in far advanced tuberculosis indicates that a state of severe undernutrition may exist. Extensive loss of body weight often occurs in far advanced, active tuberculosis. If the nutritional state of the patient with far advanced tuberculosis can be improved, specific therapy for tuberculosis may be more effective than when the patient is in a depleted nutritional state.

Liver disease was found to be a significant factor in the nutrition of forty-six patients with far advanced, active pulmonary tuberculosis and of fourteen patients with moderately advanced, active pulmonary tuberculosis (Ban, 1955). According to Man et al. (1945), the normal pattern of serum lipid concentrations is dependent

on the orderly functioning of the liver cells. Ralli et al. (1941) indicated that the serum carotene and vitamin A values of patients were helpful in the diagnosis of liver dysfunction. Biochemical studies of the blood of tuberculous patients by Getz and co-workers (1944, 1950, 1955) demonstrated that patients with active pulmonary tuberculosis may have a deficiency of several essential nutrients, including vitamin A.

This study was planned to investigate the serum cholesterol, vitamin A, and carotene values of patients with far advanced, pulmonary tuberculosis as a basis for evaluation of the state of nutrition and the adequacy of liver function of the patients with respect to these nutrients.

REVIEW OF LITERATURE

Nutrition and Tuberculosis

Nutrition is an important factor in the resistance of an individual to disease. Gorden and Flanders (1931) found a high incidence of respiratory infection among adults and children having marked malnutrition. Tissue (1940) reported that lowered resistance to tuberculosis was often associated with a period of dietary deficiency in children from three to eleven years of age. Further, a study of repatriated military personnel after World War II revealed that about one-third of the personnel subjected to prolonged malnutrition had tuberculosis (Sneeden, 1946).

Protein metabolism. A study of the increased incidence of tuberculosis in Denmark following World War I revealed that protein was the nutrient most noticeably lacking in the diet of the population (Faber, 1938). Experiments by Dubos and Pierce (1948) showed that there was a noticeable decrease in survival period of mice on a low protein diet if the animals were inoculated with mammalian tubercle bacilli. Sako (1942) obtained similar results with animals on varied protein diets. Protein has been reported to

play an important part in building up resistance to many infections including tuberculosis (Cannon, 1945).

Cannon (1945) stated that in progressive undernutrition the total amount of protein that can be withdrawn from reserve stores is so depleted that nourishment of the mesenchymal cells is impaired, resulting in tissue atrophy. Under such conditions the susceptibility to infection apparently is increased, as evidenced by the tendency for poorly nourished individuals to acquire various types of disease, including tuberculosis.

Berry (1947) indicated that hepatic, renal, gastric, and intestinal disturbances are common occurrences in starvation. Tuberculous patients suffer from similar disturbances. Many cases of advanced pulmonary tuberculosis are characterized by ulcers or lesions in the intestinal tract that are tuberculous in nature; furthermore, many patients have active peristaltic action which interferes with the proper absorption of nutrients. This explains, in part, the evidence of malnutrition among patients with far advanced, active tuberculosis (Getz, 1954).

In cases of malnutrition, a reduction of serum albumin values is normally observed when there is protein depletion; an increase in serum albumin occurs with protein repletion. Serum globulin is often high in malnutrition, particularly if it is accompanied by an

infection such as tuberculosis. Marche and Gounelle (1950) reported a slight increase of serum gamma-globulin and a decrease of serum albumin in the early stages of tuberculosis as compared with values for healthy individuals. The alpha-globulin fraction of the serum was found to increase with the progress of the disease. Seibert et al. (1947) demonstrated that there was a decrease in the serum albumin-globulin ratio in minimal tuberculosis, and a rise in the gamma-globulin of the serum. With progress of the disease, all globulin fractions of the serum were increased, while the serum albumin was decreased.

Synthesis of tissue protein requires a supply of nutrients which are an integral part of the tissue structure (Cannon et al., 1952). Holman et al. (1934) demonstrated that the protein requirement of a fasting dog could be supplied by vein for weeks at a time in the form of plasma protein, and that tissue repair was promoted and tissue injury prevented when plasma proteins were administered. Plasma proteins given intraperitoneally to plasma-depleted dogs were completely utilized without any nitrogen loss or change in the albumin-globulin ratio (Whipple et al., 1947). Allen et al. (1948, 1950) treated surgical patients with hypoproteinemia by large transfusions of blood and plasma and observed that there were marked

nitrogen retentions, and an increase in the concentration of total circulating plasma proteins following the transfusions.

Studies of the nitrogen metabolism of tuberculosis patients have indicated that nitrogen equilibrium was attained at approximately the same dietary intake as for healthy individuals (McCann, 1922; Brewer, 1949). Dietary allowances of protein suggested for tuberculosis patients have been higher than recommended allowances of the Food and Nutrition Board of the National Research Council (1953) for protein for healthy individuals. Brewer et al. (1949) recommended an intake of 80 grams of protein per day for women with moderately advanced, active tuberculosis as an intake which would be acceptable to the patient and would allow also for some retention of nitrogen. Pottenger and Pottenger (1946) have reported that the diet of the Pottenger Sanatorium in California supplies 231 grams of protein daily for the tuberculous patients. Getz (1950, 1954) recommended that hospital diets should be planned to include approximately 120 grams of protein daily in order to provide for the consumption of at least 90 grams of protein per patient per day.

Vitamin A. Numerous investigations have been carried out on the relationship of vitamin A nutrition to tuberculosis. Breeze

et al. (1942) reported that the ability of patients with acute pulmonary tuberculosis to absorb vitamin A was low, particularly in cases where intestinal tuberculosis was also present. Shaw and co-workers (1950) investigated the nutritional status of 197 patients classified according to various stages of tuberculosis. Values of serum carotene and vitamin A were similar to those of healthy adults for all patients whose dietary intake of vitamin A was equivalent to the recommended dietary allowances, with the exception of the group of patients with advanced stages of tuberculosis.

A series of studies by Getz and co-workers (1941, 1943, 1955) has indicated that there is disturbed vitamin A metabolism in tuberculous patients and that the dietary requirement of vitamin A in tuberculosis is in excess of that of healthy adults. There is some evidence that tuberculosis appears to affect the ability of the body to convert carotene to vitamin A (Getz, 1950).

Investigation of the vitamin A content of the livers after autopsy of fifty patients who died from tuberculosis, indicated that 14 percent of the patients had depleted stores of Vitamin A in the liver (Crimm and Short, 1939).

Other nutrients. Hypovitaminosis C invariably is present in tuberculosis, and the degree of deficiency apparently parallels the

extent of tuberculous involvement (Kaplan and Zonnis, 1940; Farber and Miller, 1943). Tissue saturation tests on tuberculous patients have shown a correlation between severity of the disease, and the degree of vitamin C saturation of the tissues (Heise and Martin, 1936; Sweany et al., 1941). Getz et al. (1941, 1951) reported that 75 percent of the tuberculosis patients studied had less than 0.6 milligrams of ascorbic acid per 100 milliliters in the blood.

Getz and co-workers (1944) also found that blood values of calcium and phosphorous of the tuberculous patient were lower than those of healthy individuals. Johnston (1947) studied the nutritional requirements of adolescents and found that a relationship existed between the decreased ability of adolescents to retain calcium and nitrogen, and a lowered resistance to tuberculosis at adolescence. Brewer and co-workers (1954) reported that the dietary intake of calcium which was required by tuberculous women for calcium equilibrium was greater than that required by healthy women. Intakes of 1.22 grams of calcium and 1.38 grams of phosphorus were predicted for equilibrium for women with moderately advanced tuberculosis.

Brewer and co-workers (1949) have reported that the thiamine and riboflavin metabolism of tuberculous patients was similar to that of healthy college women. Relatively little study has been made of the metabolism of other factors of the vitamin B

complex in tuberculosis. However, it has been reported that the pyridoxine needs were increased by the use of isoniazid in the treatment of tuberculous patients (Biehl and Vilter, 1954).

Blood Constituents of Tuberculosis Patients and Healthy Adults

Plasma proteins. Concentrations of protein in the blood plasma or serum have been studied as one indication of the protein nutrition of individuals. Milam and Durham (1946) reported studies of a population with no apparent signs of malnutrition. The mean concentration of serum total protein was 7.19 grams per 100 milliliters for white persons and 7.14 grams per 100 milliliters for the Negro population. The mean concentration of serum albumin was 4.65 grams and 4.45 grams per 100 milliliters for white and Negro populations, respectively. The mean serum globulin was 3.04 grams for white people and 2.59 grams per 100 milliliters for Negro persons; this indicated that there was a racial difference in serum albumin-globulin ratios. The values were 1.46 for Negroes and 1.80 grams for white persons.

Ryland (1939) found that the serum albumin concentration of apparently normal subjects ranged from 3.6 to 5.4 grams per 100 milliliters. Serum globulin values ranged from 2.1 to 4.5 percent.

Keys et al. (1950) observed mean blood serum total protein concentration of 6.7 grams per 100 milliliters for thirty-two healthy adults. The average concentration of serum albumin was 4.28 grams per 100 milliliters. The average blood serum globulin value was 2.39 grams per 100 milliliters, while the mean albumin-globulin ratio was 1.89.

Serum protein values of apparently healthy individuals ranged from 6 to 8 grams per 100 milliliters of blood serum (Bruckman and Peters, 1930; Milam and Durham, 1946; Myers and Muntwyler, 1940; Kagan, 1943).

In early stages of protein deficiency there appears to be a reserve protein available for mobilization, which is used in an attempt to maintain the normal serum protein concentration in the body (Madden and Whipple, 1940). Bruckman and Peters (1930) observed that in twenty-eight patients with diabetes mellitus, without signs of undernutrition, the concentration of total serum protein was similar to that of healthy subjects; nine patients with evidence of malnutrition showed decreased blood serum plasma protein levels.

Reduction of serum protein in blood below the range of healthy individuals may occur in patients with far advanced, active tuberculosis according to Getz (1954); however, a change in concentration of total protein in the serum seldom occurs for patients

with minimal or moderately advanced, active tuberculosis. Mean ratios of albumin to globulin of 0.66 and 0.64 were reported by Baldwin and Iland (1953) for seven patients with advanced tuberculosis and seven patients with far advanced tuberculosis, respectively. These ratios were considerably lower than the average ratios of 1.23 and 1.13 found for five normal persons and for six patients with minimal advanced active tuberculosis, respectively.

Serum cholesterol. In 1933, Man and Peters reported that the concentration of cholesterol in the serum of ten healthy adults varied from 162 to 256 milligrams percent, with an average concentration of 208 milligrams percent. A wider range of values was observed by Sperry (1936) for ninety-one healthy adults, nineteen to forty-three years of age. Values of serum cholesterol ranged from 131 to 392 milligrams per 100 milliliters of blood serum, with an average of 210 milligrams per 100 milliliters of blood serum. The range of free in total cholesterol was 24 to 30 milligrams percent, with an average of 27 percent. Serum cholesterol values were relatively constant for an individual over a period of time.

This study supported a previous investigation by Boyd (1935) in which he concluded that the blood serum cholesterol values of

healthy individuals were uninfluenced by diet. Concentrations of ester, free and total cholesterol remained constant during the day for one individual, but differed from one individual to another. The serum total cholesterol varied from 177 to 183 milligrams per 100 cubic milliliters of blood serum; serum free cholesterol values ranged from 51 to 54 milligrams per 100 cubic milliliters, while the ester cholesterol was 118 to 129 milligrams per 100 cubic milliliters.

On the other hand, Gillum et al. (1955a) found that there was a positive correlation between serum cholesterol values of the blood and the cholesterol intake for 573 healthy individuals over fifty years of age. Keys and co-workers (1956), however, questioned whether cholesterol was the only variable in the diet of the California study. Keys et al. concluded from controlled dietary studies as well as population studies that the serum cholesterol level was essentially independent of the cholesterol intake.

Much attention has been focused in recent years on the possible relationship of blood serum cholesterol and atherosclerosis (Anfinsen, 1956; Stare, 1956). This research has resulted in the investigation of the influence of various factors on serum cholesterol. Although Keys and co-workers have found that the cholesterol content of the diet does not affect serum cholesterol

values, these workers have presented evidence to indicate that the amount of fat in the diet is related to the concentration of cholesterol in blood serum (Keys et al., 1956). Kornerup (1950) and Gillum et al. (1955a) found higher values for serum cholesterol among women than among men.

An increase in serum cholesterol with age to the sixth decade and a subsequent decrease in serum cholesterol with age has been reported by Keys (1952). Gillum et al. (1955a) also found that there was a significant decrease in serum cholesterol for both men and women between the ages of seventy-five and eighty years as compared with younger adults. Further evidence of the relationship of age to serum cholesterol has been reported by Butler et al. (1956) and Swanson et al. (1955).

In 1936, Sperry analyzed 179 samples of blood serum from 117 children and found that there was an increase of the free cholesterol in the serum of patients with liver disease. Case histories of the subjects indicated that all but eight had infection or liver disease, or both. Children without a history of liver disease had a concentration of 24 to 34.5 percent free cholesterol in the serum total cholesterol. The other children had an average of 43.5 percent free in total cholesterol in the serum.

Man and co-workers (1945) studied 70 patients with hepatic disease and found also that there was an increase in the ratio of serum free to total cholesterol among these patients as compared with healthy individuals. Van Eck et al. (1952) reported that a ratio of free to total cholesterol above 0.32 was indicative of disease. Stoesser (1935) studied twelve children, of whom six had extensive infection of the upper respiratory tract and six had pneumonia. Stoesser found that there was a fall of serum total cholesterol and of the cholesterol ester during the period of illness. During convalescence an increase in both fractions occurred. However, the serum free cholesterol was relatively constant throughout the study.

Studies of serum cholesterol of tuberculous patients have not been found in the available literature. Reports of hepatic disease among tuberculous patients, however, have been published by Steidl and Heise (1933), Hurst and co-workers (1947), and Ban (1955). Abnormal cephalin flocculation tests were found for forty-five out of a group of sixty patients with pulmonary tuberculosis in the study reported by Ban (1955).

Vitamin A and carotene. A wide range of vitamin A and carotene concentrations has been observed for healthy

individuals. According to Bessey et al. (1946), a range of 39 ± 5 to 74 ± 5 micrograms of vitamin A per 100 milliliters of blood serum is indicative of an adequate nutritional state with respect to vitamin A. Shaw and co-workers (1950) found that the range of blood serum vitamin A for healthy adults was 30 to 75 micrograms per 100 milliliters.

Values for blood serum carotene for healthy persons have varied from 50 to 370 micrograms per 100 milliliters (Kimble, 1939; Yudkin, 1941; Murril et al., 1941; Shaw et al., 1950).

Yiengst and Shock (1949) studied 126 healthy male subjects and reported that no changes in blood serum carotene and vitamin A could be observed with age. Gillum et al. (1955b) found, however, that concentrations of carotene and vitamin A in the blood serum declined slightly with age.

The influence of dietary intakes of vitamin A and carotene on the concentration of these constituents in blood serum was studied by Hoch (1943), who observed that a large intake of carotene raised the blood serum carotene levels of the subjects, without affecting the concentration of blood serum vitamin A. Gillum et al. (1955b) reported a positive correlation between the total vitamin A intake and serum vitamin A, and between the carotene intake and the serum carotene. However, there was no

significant relationship between the intake of carotene and the concentration of blood serum vitamin A or the total intake of vitamin A and blood serum carotene concentrations.

Shaw et al. (1950) reported serum vitamin A and carotene values for nontuberculous persons and for tuberculous patients. Of twelve patients with advanced tuberculosis, 35 percent had vitamin A values under 30 micrograms per 100 milliliters, 59 percent had values between 30 and 69 micrograms per 100 milliliters, and 8 percent had values greater than 70 micrograms per 100 milliliters. In comparison, only 6 percent of the nontuberculous persons and 9 percent of the patients with minimal tuberculosis had serum vitamin A values less than 50 micrograms per 100 milliliters. A higher percentage of patients with far advanced tuberculosis had serum carotene values less than 75 micrograms per 100 milliliters than did the nontuberculous persons.

Getz et al. (1944) selected 110 International Units of vitamin A per 100 milliliters of serum as the criterion of adequacy of vitamin A in the study of tuberculous and nontuberculous persons. Forty-one percent of 266 nontuberculous persons had serum vitamin A values of 110 International Units of vitamin A per 100 milliliters or greater. In contrast, only 25 percent of patients with minimal advanced, 24 percent of patients with moderately advanced, and 15

percent of patients with far advanced tuberculosis had serum vitamin A values of 110 International Units per 100 milliliters of serum or greater.

In a later study, Getz (1955) reported that thirty out of a group of seventy-eight patients with moderately advanced tuberculosis had plasma vitamin A concentrations less than 26 micrograms per 100 milliliters. Little increase in plasma vitamin A concentrations of the patients occurred on the basic hospital diet. However, vitamin supplementation raised the plasma concentration of vitamin A significantly. Cod liver oil was more effective than synthetic vitamin A in effecting an increase in vitamin A of the plasma.

EXPERIMENTAL PROCEDURE

Experimental Plan

The study was planned to investigate the concentrations of vitamin A, carotene, and cholesterol of the blood sera of seventeen patients with far advanced, active pulmonary tuberculosis during a period of protein repletion.

The patients were subjects of a research study conducted by Dr. J. Mott Rawlings at the Saginaw County Hospital. The research was an investigation of the nutritional and biochemical status of patients with far advanced, active tuberculosis and the possible influence of protein repletion therapy on the nutritional status of the patients. Various observations were made by the hospital staff including weight and height measurements, body composition studies, blood protein, blood volume studies, and liver function tests.

The present study was carried out as a part of this larger research program. Investigation of the concentrations of vitamin A, carotene, and total and free cholesterol of the blood sera of the patients were made as a basis of evaluation of the state of nutrition and the adequacy of liver function of the patients with respect to these nutrients.

The blood samples were taken by the hospital technicians at intervals established for other biochemical studies made at the sanatorium. Thus the time factor was not controlled for this particular study.

Subjects

The subjects were seventeen patients with far advanced, active pulmonary tuberculosis at the Saginaw County Sanatorium, Saginaw, Michigan. Sixteen of the patients were males, aged twenty-one to sixty-nine years; one was female, aged thirty-one years. Thirteen of the men and the female patient were white; three of the males were of Mexican descent.

Prior to the study, all of the patients were on the usual hospital regimen of antibiotics, bed-rest, and a high calorie-high protein diet. Only patients who did not respond satisfactorily to this regimen were selected for subjects of the study. Chest X rays at the time of admission indicated that each of the sixteen males had far advanced tuberculosis. The female patient had moderately advanced, active tuberculosis at admission, but was reclassified at the time of the study as a patient with far advanced, active tuberculosis. The disease was progressive for all of the patients; the prognosis, based on response to chemotherapeutic therapy, was

unfavorable. All of the patients had positive sputum reactions at the beginning of the study. Two patients died during the course of the study, and two left the hospital against medical advice.

Protein Repletion Therapy

The program of nutritional therapy consisted of infusions of plasma protein (whole blood, human plasma, or serum albumin), male hormones (usually testosterone propionate in quantities up to 25 milligrams or as tolerated), and supplementary nutrients consisting of minerals and vitamins. This therapy was given to the patients in addition to the usual hospital regimen.

Four of the patients were started on the protein repletion therapy as early as March, May, July, and August, 1953. Five of the patients were started on the protein repletion therapy in 1954; the remaining patients received protein repletion therapy only after December, 1955. The study was continued until January, 1956. Thus the periods of special nutritional therapy varied in length for individual subjects from eight months to two years and eight months, with the exception of one patient who left against medical advice, and received only four months of repletion therapy.

Biochemical Studies

Biochemical studies were not made prior to the protein repletion program for nine of the subjects. However, for eight

subjects, biochemical studies of blood constituents were determined before, as well as one or more times during the program of special therapy. The blood constituents reported here are serum cholesterol, vitamin A, and carotene.

Blood samples were taken by the hospital technicians from the antecubital vein. The sera were separated by centrifugation, frozen, and transported to the laboratory in the frozen state.

Vitamin A and carotene. Analyses of vitamin A and carotene were made in triplicate, using 200 millimeters of serum for each sample, according to a modification of the method of Bessey et al. (1946). The sample was saponified with alcoholic potassium hydroxide, and vitamin A and carotene were extracted with a mixture of kerosene and xylene.

A spectrophotometer¹ was used to measure the optical density of vitamin A at a wavelength of 328 millimicrons, and carotene at 460 millimicrons. The sample was then transferred to a soft glass tube and irradiated with an ultraviolet lamp² for 70 minutes to destroy the vitamin A.

¹Beckman spectrophotometer, model D.U., Central Scientific Co., Pasadena, California.

²B.H.4, General Electric Co.

The compounds that interfere with the absorption of vitamin A at 328 millimicrons wavelength were determined by measuring the absorption of the irradiated sample at this wavelength. The concentrations of vitamin A and carotene were expressed in micrograms per 100 milliliters of serum.

Cholesterol. Concentrations of total and free cholesterol were determined by a modification of the method of Schoenheimer and Sperry (1934).

Extraction of cholesterol was done by the addition of 200 cubic millimeters of the serum to a warm solution of alcohol-acetone in a 5 milliliter volumetric flask. The contents of the flask were cooled, made to volume, and filtered through fat-free filter paper. Triplicate samples of the filtrate were pipetted into 5-milliliter centrifuge tubes, and cholesterol was precipitated as cholesterol digitonide. The tubes were covered and allowed to stand for two days.

Total cholesterol was obtained by hydrolysis of the cholesterol ester of the sample with potassium hydroxide; after hydrolysis, the solution was titrated with acetic acid in alcohol (using phenolphthalein indicator) to prevent the interference of excess alkali in the

precipitation of the cholesterol digitonide. The cholesterol was precipitated as cholesterol digitonide in the same manner as for free cholesterol.

After the two-day period, the cholesterol digitonide was separated by centrifugation at 2,500 r.p.m. The precipitate was washed first with acetone-ether, then with two successive portions of ether. Finally the precipitate was heated in a water bath to remove traces of ether. Glacial acetic acid was added to the tube to dissolve the cholesterol digitonide, and then two milliliters of freshly prepared acetic anhydride-sulphuric acid were added to obtain the blue color, characteristic of the Liebermann-Burchard color reaction. The optical density of the sample was measured 27 to 30 minutes later, with a spectrophotometer at a wavelength of 620 millimicrons.

Concentrations of free and total cholesterol were expressed as milligrams per 100 milliliters.

Supplementary Information

Values for the concentration of serum albumin and serum globulin were obtained from Rawlings (1956). Records of body weight, sputum reaction, and the interpretations of roentgenograms were obtained from the medical histories of the patients.

Information about the vitamin, mineral, and hormone supplements and the medication, including antibiotics, given the patient was obtained from the clinical records.

The dietary intakes of the subjects studied here were investigated as a phase of another study (Smith, 1956).

RESULTS AND DISCUSSION

Table I presents the clinical evaluation of the progress of **seventeen** patients with far advanced, active pulmonary tuberculosis **and** changes in body weights of the patients during the period in **which** plasma protein and supplementary nutritional therapy were **administered**.

Patients with a clinical rating of poor showed progressive development of the disease process. Four of the patients (F.C., G.L., C.A., and O.M.) were classified as respiratory cripples, **indicating** that they had insufficient lung tissue for satisfactory **exchange** of oxygen. Patients C.P. and M.D. were not considered **respiratory** cripples, but X-ray findings indicated that no healing had **occurred** during the study; neither was there any improvement in **the** clinical condition of the patients. Sputum tests were positive at **all** times for patients with a clinical rating of poor. Patient M.D. was the one woman among the group.

Two of the patients, O.M. and R.M., died shortly after the **termination** of the study and the disease process was progressive until **death**. Patient O.M. was a respiratory cripple. Although there was indication that the disease process had increased, this

TABLE I

**PHYSICAL DESCRIPTION OF SEVENTEEN PATIENTS WITH
FAR ADVANCED ACTIVE PULMONARY TUBERCULOSIS**

Pa- tient	Clin- ical Rat- ing ¹	Height (cm.)	Age (yrs.)	Body Weight in Kilograms					Mos. of Protein Repletion Therapy
				Ini- tial Wt.	Fi- nal Wt.	Gain or Loss	Time in Mos. ²	Gain or Loss per Mo.	
F.C.	poor	165	42	67.4	67.8	+ 0.4	8	+0.05	8
C.A.	poor	175	42	78.2	83.4	+ 5.2	7	+0.7	12
G.L.	poor	175	51	69.0	70.0	+ 1.0	3	+0.3	8
J.V.	poor	-	51	41.8	40.4	- 1.4	11	-0.1	18
C.P.	poor	174	38	71.8	73.8	+ 2.0	19.5	+0.1	19
M.D.	poor	-	31	62.5	-	-	-	-	12
O.M.	poor	170	35	73.6	78.9	+ 5.3	10	+0.5	9
R.M.	poor	-	60	49.5	51.0	+ 1.5	8	+0.2	10
A.P.	good	175	43	87.5	89.0	+ 1.5	4	+0.4	4
C.M.	good	175	57	50.6	85.6	+35.0	16	+2.2	25
S.H.	good	172	29	64.4	65.7	+ 1.3	12	+0.1	13
A.R.	good	-	24	47.6	57.4	+ 9.8	20	+0.5	22
S.S.	good	-	36	47.7	73.0	+25.3	22.5	+1.1	27
P.E.	good	-	69	46.3	66.7	+20.4	26	+0.8	32
T.C.	good	168	45	50.3	73.5	+23.2	14	+1.6	18
V.R.	good	159	21	56.8	57.8	+ 1.0	20	+0.05	20
G.A.	good	165	31	56.8	59.5	+ 2.7	27	+0.1	27

¹At end of study.

²Final body weight was the weight most nearly at end of study. Some patients were weighed before and some after the end of the study.

patient gained weight at the rate of 0.5 kilograms per month; the total gain in weight during protein repletion therapy was 5.3 kilograms. Patient R.M. had advanced bilateral pulmonary tuberculosis, along with chronic ulcerative colitis. This patient had an average weight gain of 0.2 kilograms per month during repletion therapy, with a total gain of 1.5 kilograms by the time of his death.

Subject C.A. also had a gain in body weight during protein repletion therapy, although he was classified as a respiratory cripple. This patient gained 5.2 kilograms during a period of seven months. His prognosis, however, was poor. Changes in body weights of the other patients with a clinical rating of poor were negligible.

Nine patients had a clinical rating of good. These patients showed consistent progress toward control of the disease process during protein repletion therapy and the prognosis was good. Sputum tests changed from positive to negative for all of the patients in this group during protein repletion therapy and remained negative until the end of the study. There was an average gain in body weight of 13.4 kilograms. Three of the subjects, S.S., C.M., and T.C., gained weight at the rate of 1.1, 2.2, and 1.6 kilograms per month, respectively.

Patients A.R. and G.A. left the sanatorium against medical advice. The progress of these patients had been satisfactory until the time of their departure and they were included here with the group classified as good.

Case histories of the patients who were subjects in this study are given in the Appendix.

Serum Vitamin A and Carotene

Concentrations of vitamin A and carotene in the blood sera of seventeen patients with far advanced, active pulmonary tuberculosis are presented in Table II and the average serum vitamin A values are shown graphically in Figure I. Values for eight patients are given both preceding and during the period of administration of plasma protein and supplementary nutritional therapy. Blood samples were not obtained before the period of protein repletion therapy for the other nine patients.

Daily dietary intakes of vitamin A for the patients were estimated to range from 3,600 to 13,000 International Units (Smith, 1956). Daily dietary supplements of vitamin A ranged from 5,000 to 20,000 International Units for sixteen patients. One patient, M.D., was given dietary supplements of 20,000 to 50,000 International Units of vitamin A daily.

TABLE II

BLOOD SERUM VITAMIN A AND CAROTENE OF SEVENTEEN
PATIENTS WITH FAR ADVANCED ACTIVE
PULMONARY TUBERCULOSIS

Pa- tient	Before Reple- tion Ther- apy ¹	Serum Vitamin A (micrograms per 100 milliliters)						
		Months of Protein Repletion Therapy						
		1-3	4-6	7-8	9-10	11-12	13-24	25-30
F.C.	45(2)	44	35					
C.A.	55	67(2) ²	90	73				
G.L.	62(2)	28						
A.P.	76(2)	92						
O.M.	32(2)	66						
C.M.	80						56(2)	
R.M.	115	57		81				
S.H.	111	51(2)	73(2)	38				
J.V.		48			58			
C.P.						52(2)	45	
M.D.		26	53					
A.R.							92	54
S.S.							66(7)	
P.E.							27	114
T.C.		46	49(2)	77	61(2)		75	
V.R.				60	37		118(3)	
G.A.							114	

¹Sample taken within two months prior to therapy.

²Number in parentheses indicates number of observations included in average value. Only one observation per unit of time unless otherwise indicated.

TABLE II (Continued)

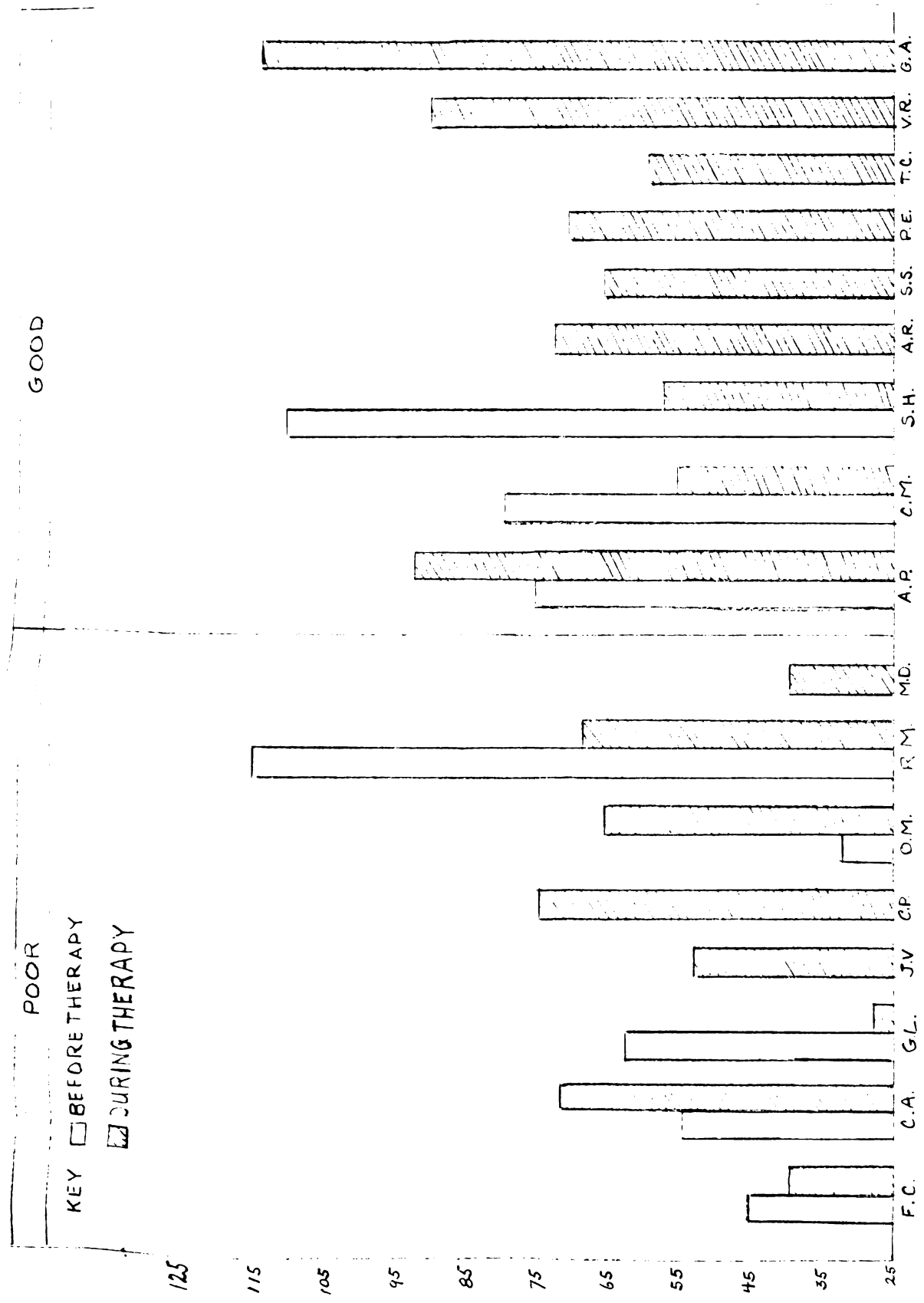
Serum Carotene (micrograms per 100 milliliters)								Clin- ical Rat- ing	Dietary Supple- ment of Vit. A (1,000 I.U./day)
Before Reple- tion Ther- apy	Months of Protein Repletion Therapy								
	1-3	4-6	7-8	9-10	11-12	13-24	25-30		
42	63	89						poor	10-20
84	124(2)	126	96					poor	5-10
38(2)	136							poor	10
87(2)	92							good	10
24(2)	33							poor	5
77						44(2)		good	10
15	23		19					poor	5
77	22(2)	78(2)	73					good	5-10
	22			9				poor	10
					30(2)	99		poor	10
	29	37						poor	20-50
						146	147	good	5-10
						53(7)		good	5-10
						25	97	good	5-10
	40	95(2)	77(2)	79		117		good	5-10
			135	26		45(3)		good	5-10
						74		good	5-10

FIGURE 1

VITAMIN A VALUES

IN THE BLOOD SERA OF SEVENTEEN PATIENTS

WITH FAR ADVANCED, ACTIVE PULMONARY TUBERCULOSIS



Vitamin A in Blood Serum - micrograms/100 mls.

A range of 30 to 75 micrograms of vitamin A per 100 milliliters of blood serum has been associated with satisfactory vitamin A nutrition for healthy individuals (Shaw et al., 1950; Bessey et al., 1946). Concentrations of serum carotene reported for healthy individuals have ranged from 50 to 370 micrograms per 100 milliliters of blood serum (Kimble, 1939; Yudkin, 1941; Murril et al., 1941; Shaw et al., 1950). Serum vitamin A concentrations ranged from 32 to 115 micrograms per 100 milliliters for the eight patients for whom blood samples were available for analysis before protein repletion therapy. Thus, serum vitamin A values for this group of patients were within or exceeded the range of values associated with satisfactory vitamin A nutrition for healthy adults. Serum carotene values ranged from 15 to 87 micrograms per 100 milliliters for the eight patients for whom blood samples were available for analysis before repletion therapy. The lowest values for serum carotene were found for the two patients who died soon after the study. Values were 15 and 24 micrograms of carotene per 100 milliliters of serum for patients R.M. and O.M., respectively. These low values may have been associated with failure of the patients to eat fruits and vegetables or with poor absorption of carotene from the gastrointestinal tract.

The serum vitamin A value for subject R.M. was 115 micrograms per 100 milliliters before protein repletion therapy. The concentration of serum vitamin A for this patient was decreased to 57 micrograms per 100 milliliters during the first four months of therapy with plasma protein and special nutritional supplements. After nutritional therapy had continued for seven to nine months, however, an increase in concentration of serum vitamin A to 81 micrograms per 100 milliliters was found. The concentration of serum carotene obtained at three intervals during the study were 15, 23, and 19 micrograms per 100 milliliters.

Three additional patients for whom blood samples were available for analysis both before and during the program of special nutritional therapy had a clinical rating of poor. These patients were subjects G.L., F.C., and C.A.

Only one sample of blood serum was obtained for patient G.L. after the protein repletion therapy program was instituted. This sample was taken within a period of one to four months of therapy. The concentration of vitamin A in the serum was only 28 micrograms per 100 milliliters, as compared with a value of 63 micrograms of vitamin A per 100 milliliters of serum before the program of nutritional therapy. An increase in the concentration of serum carotene occurred concomitantly with the decrease in serum

vitamin A. Serum carotene values before and after the protein repletion therapy were 38 and 136 micrograms of carotene per 100 milliliters, respectively.

The concentration of vitamin A in the serum of patient F.C. was essentially constant before and after protein repletion therapy. The serum vitamin A concentration before protein repletion therapy was 45 micrograms per 100 milliliters. Values were 44 and 35 micrograms per 100 milliliters for periods of one to three months and four to six months following therapy. Some increase in serum concentration of carotene for this patient occurred during the protein repletion therapy.

There was considerable fluctuation in both serum vitamin A and serum carotene values for patient C.A. during the period of administration of plasma protein and supplementary nutritional therapy. Concentrations of serum vitamin A and carotene increased during the first seven months of protein repletion therapy. A decrease in the concentrations of both serum vitamin A and carotene occurred during the next three months. However the final values for vitamin A and carotene were greater than the concentrations before therapy.

Values for serum vitamin A and carotene were obtained for only three of the patients with a clinical rating of good before the nutritional repletion therapy was instituted. These patients,

subjects A.P., C.M., and S.H., had values of 76, 80, and 111 micrograms of vitamin A per 100 milliliters, respectively. Thus all of these patients had initial values which were in the upper range of values for healthy adults.

Only one value for serum vitamin A and for serum carotene was obtained for patient A.P. during protein repletion therapy. The concentration of serum vitamin A was increased from 76 to 92 micrograms per 100 milliliters; the concentration of serum carotene, 92 micrograms per 100 milliliters, was essentially the same as before protein repletion therapy.

Serum vitamin A concentrations for patients S.H. and C.M. were lower during protein repletion therapy than before the administration of therapy. After seven to eight months of protein repletion therapy, the serum vitamin A for patient SH was only 38 micrograms per 100 milliliters, as compared with an initial concentration of 115 micrograms per 100 milliliters. The concentrations of serum vitamin A for patient C.M. was approximately 24 micrograms per 100 milliliters less after one year of protein repletion therapy than initially.

There were nine patients for whom blood samples were available for analysis only after the program of protein repletion therapy had been in progress. Three of the patients in this group

were classified as poor. These were J.V., C.P., and M.D. Concentrations of blood serum vitamin A were essentially constant for patients J.V. and C.P. during the protein repletion therapy. Patient M.D. had a rise in blood serum vitamin A from 26 micrograms per 100 milliliters of blood serum during the period of one to four months of therapy to 53 micrograms per 100 milliliters of serum during the period of four to six months of repletion therapy. Concentrations of blood serum carotene were relatively low for the three patients during the period of protein repletion, although there was an increase from 30 to 99 micrograms per 100 milliliters of serum for patient C.P.

There were four patients with a clinical rating of good for whom more than one sample of blood serum was available for analysis during protein repletion therapy. Only one, subject A.R., had a decrease in serum vitamin A values; this decrease was from 92 to 54 micrograms per 100 milliliters and occurred between the second and third years of repletion therapy. Serum vitamin A values for subjects T.C. and V.R. fluctuated during the period of therapy but the changes were in the direction of increase in the concentration of serum vitamin A. The concentration of vitamin A in the serum of patient P.E. was only 27 micrograms per 100 milliliters after one year of protein repletion therapy;

however, the concentration was 114 micrograms per 100 milliliters after two years of repletion therapy.

It would appear, therefore, that changes in the concentration of serum vitamin A of these patients were not related directly to the clinical status of the patients. The average concentration of vitamin A in the serum of patients with a clinical rating of poor was 55 micrograms per 100 milliliters based on the last sample analyzed for each of these patients. In comparison, the average concentration of vitamin A in the serum of patients with a clinical rating of good was 71 micrograms per 100 milliliters.

Only one patient, G.L., had a relatively high serum carotene value associated with a relatively low serum vitamin A value. This was the only case in which failure of conversion of carotene to vitamin A may have existed. It is difficult to interpret the significance of the low carotene values among five of the patients, all of whom had serum concentrations less than 50 micrograms per 100 milliliters. As suggested earlier, these low values may have been associated with failure of the patients to eat fruits and vegetables or with poor absorption of carotene from the gastrointestinal tract. Daily dietary supplements of vitamin A were, however, adequate to maintain normal or nearly normal vitamin A concentrations in the serum.

There were four patients for whom the final values for serum vitamin A exceeded the upper limit of the range for healthy adults; i.e., 75 micrograms per 100 milliliters. However, high values of vitamin A in the serum following the ingestion of large doses of vitamin A have been reported by Weeks and Sevigne (1950). Serum vitamin A values of subjects following a test dose of 134,000 micrograms of vitamin A ranged from 66 to 1,440 micrograms per 100 milliliters. Twenty-four hours after the test dose, serum vitamin A values varied from 45 to 249 micrograms per 100 milliliters. Thus the relatively high serum vitamin A values of the four patients of this study may have reflected the daily dietary supplement rather than abnormal vitamin A metabolism.

Serum Cholesterol

Values for the total and free cholesterol of the blood sera of seventeen patients with far advanced, active pulmonary tuberculosis are presented in Table III.

Analyses of the blood sera of eight patients were made for free and total cholesterol before the program of nutritional repletion therapy. Concentrations of free and total serum cholesterol were determined for six of the eight patients both before and during the nutritional repletion therapy. The blood sera of nine



TABLE III

FREE AND TOTAL CHOLESTEROL IN THE BLOOD SERA OF
SEVENTEEN PATIENTS WITH FAR ADVANCED
PULMONARY TUBERCULOSIS

Pa- tient	Age (yrs.)	Clin- ical Rat- ing	Serum Free Cholesterol (mg. per 100 ml.)							
			Before Reple- tion Ther- apy	Months of Protein Repletion Therapy						
				1-3	4-6	7-8	9-10	11-12	13-24	25-30
C.A.	36	poor	79	69(2)	78					
F.C.	42	poor	118	72	94					
G.L.	51	poor	70(2)	93						
O.M.	35	poor	70	53						
R.M.	60	poor	97			87				
A.P.	43	good	98(2)							
C.M.	57	good	80							
S.H.	29	good	71	56	63	58				
J.V.	51	poor		40			68			
C.P.	38	poor						70(2)	98	
M.D.	31	poor		37	58					
A.R.	24	good							65	81
S.S.	36	good							72(4)	
P.E.	69	good							88	
T.C.	45	good		40	61(2)		98	48	78	
V.R.	21	good				63			59(3)	
G.A.	31	good							43	

¹ Keys (1952) except for patient M.D.; Butler et al. (1956) for patient M.D.

² Averages: see vitamin A footnote.

TABLE III (Continued)

Serum Total Cholesterol (mg. per 100 ml.)								Range for Healthy Per- sons ¹
Before Reple- tion Ther- apy	Months of Protein Repletion Therapy							
	1-3	4-6	7-8	9-10	11-12	13-24	25-30	
273	219(2)	168						158-242
183	182	250						188-258
147(2)	245							202-292
170	180							154-242
306			225					202-298
264(2)								188-261
301								208-296
224	161	189	224					156-230
	98			266				202-292
					190(2)	188		168-244
	110	195						186-228
						195	276	144-211
						194(4)		159-241
						228		190-272
	100	173(2)		188	181	188		198-264
			219			181(3)		144-230
						150		158-238

patients was analyzed for cholesterol during but not previous to the protein repletion therapy.

Values for serum total cholesterol were compared with mean serum total cholesterol values at different ages for 1,492 healthy men, reported by Keys (1952). Of the eight subjects studied prior to protein repletion therapy, five were rated clinically as poor. Of these, one had a low serum total cholesterol; two had high serum total cholesterol values, and two were within the range of one standard deviation of the mean serum total cholesterol of healthy men of corresponding ages. Of the three subjects with a clinical rating of good, two had serum total cholesterol values within the range for healthy men; one patient had a high serum total cholesterol.

Two patients with a clinical rating of poor were among those for whom blood samples were available only after the beginning of the nutritional repletion therapy. The initial value for patient J.V. was 98 milligrams cholesterol per 100 milliliters of serum. This was low in relation to the mean for healthy men. Subject C.P. had an initial serum total cholesterol of 190 milligrams percent. This was within the range for healthy men of similar age.

Patient M.D. was the only woman in the group. Blood serum was not available prior to repletion therapy for this subject. The initial value which was determined during nutritional therapy was

110 milligrams per 100 milliliters of serum. This was lower than the mean serum total cholesterol reported by Butler et al. (1956) for women of a comparable age. This subject was rated clinically as poor.

There were six patients who were given a clinical rating of good for whom blood samples were available only after the beginning of the nutritional repletion therapy. Serum total cholesterol values for four of these patients were within the range for healthy men of corresponding ages. Subjects A.R. and V.R. had values for serum total cholesterol which were above the range for healthy men.

There was an increase in serum total cholesterol during protein repletion therapy for the three patients whose initial values were low in comparison with healthy adults. In each case, the increase was of sufficient magnitude that the values determined finally were within the range of healthy adults. One subject, A.R., also had an increase in serum total cholesterol during the protein repletion therapy. In this instance, the final value exceeded the range of values reported by Keys (1952) for healthy adults of a similar age.

Two subjects, C.A. and R.M., whose initial serum total cholesterol values were above the range for healthy adults, had some decrease in serum total cholesterol so that the values

determined finally were within the range of healthy adults. It is difficult to interpret the significance of this, however, since both patients had a clinical rating of poor, and one, R.M., died shortly after the study had been completed.

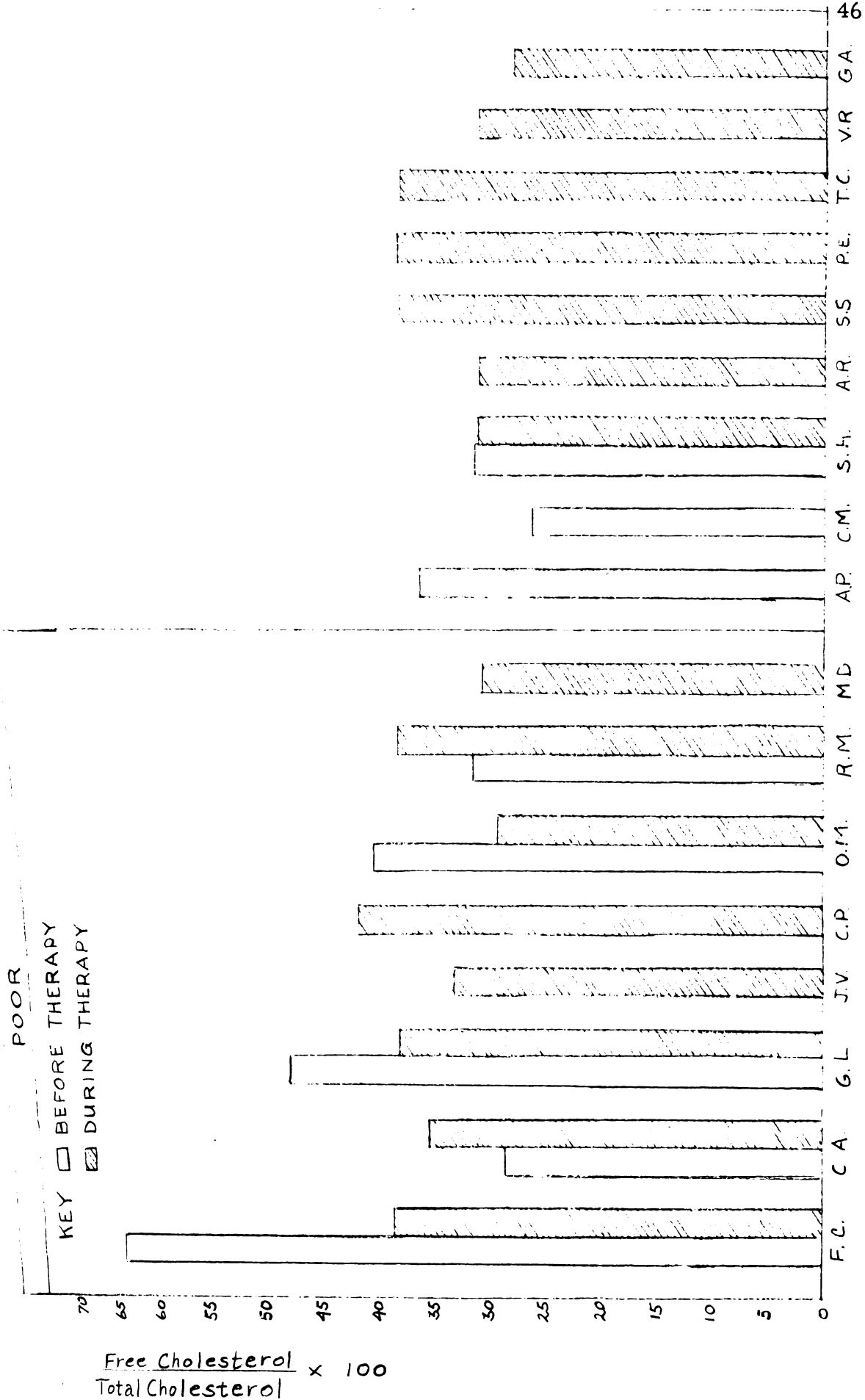
The ratios of free cholesterol to total cholesterol in the sera of the seventeen patients are shown in Figure 2. The graph presents values obtained before the protein repletion therapy and the average of observations made during protein repletion therapy. Ratios of free cholesterol to total cholesterol in the sera of healthy adults ranged from 24 to 32 percent, according to Sperry (1936) and Peters et al. (1943). Four of the eight patients for whom blood serum samples were available prior to protein repletion therapy had percentages of free in total cholesterol within this range. The percentage of free in total cholesterol exceeded this range for the other four patients.

Two of these patients, C.A. and R.M., had a clinical rating of poor at the end of the study. There was an increase in the ratio of free to total cholesterol in the serum of both patients during protein repletion therapy. However, ratios of free to total cholesterol were lower during repletion therapy than initially for patients F.C., O.M., and G.L., who also had a clinical rating of poor.

FIGURE 2

PERCENTAGE OF FREE TO TOTAL CHOLESTEROL
IN BLOOD SERA OF SEVENTEEN PATIENTS
WITH FAR ADVANCED, ACTIVE PULMONARY TUBERCULOSIS

GOOD



There was only one patient (S.H.) with a clinical rating of good for whom blood samples were available for analysis both before and during protein repletion therapy. The ratio of free to total cholesterol in the serum of this patient was constant; i.e., 32 percent before and 31 percent during protein repletion therapy. However, there was a decrease in both free cholesterol and total cholesterol of the serum with protein repletion therapy.

Of the total group of seventeen patients, six had ratios of free to total cholesterol in the serum within the range of 24 to 32 percent. Ratios of serum free to total cholesterol for the other patients exceeded this range either before or during protein repletion therapy, or both.

Blood Serum Albumin and Globulin

Seibert et al. (1947) observed a decrease in serum albumin-globulin ratio during various disease conditions, of which tuberculosis was one. In minimal tuberculosis, the decrease in the serum albumin-globulin ratio was accompanied by a rise in the gamma globulin of the serum; with increase of the condition of disease, all globulin fractions were observed to rise, and the albumin fraction was decreased.

Serum albumin and globulin values¹ for the sixteen patients with far advanced, active pulmonary tuberculosis are presented in Table IV as a further basis for evaluation of the nutritional state of these patients.

Before protein repletion therapy, ratios of albumin to globulin in the serum of all but one of the patients were less than the range of 1.2 to 2.6, reported by Myers and Muntwyler (1940) for healthy persons. Patient V.R. had a serum albumin-globulin ratio of 1.25, barely within this range. Myers and Muntwyler reported a range of 3.4 to 5.6 grams of albumin per 100 milliliters of serum and 1.35 to 3.55 grams of globulin per 100 milliliters of serum for healthy persons. Of fourteen subjects studied before protein repletion therapy, four had serum albumin values less than this range. Serum globulin values for all of the patients exceeded the range for healthy individuals.

After protein repletion therapy, three of sixteen patients had ratios of serum albumin to globulin within the range of 1.2 to 2.6. However, there were increases in the serum albumin-globulin ratios during protein repletion therapy for eight patients. These

¹Acknowledgment is made to Dr. J. Mott Rawlings and the medical staff of the Saginaw County Hospital for the use of these data.

TABLE IV

**BLOOD SERUM ALBUMIN AND GLOBULIN VALUES, AND
ALBUMIN-GLOBULIN RATIOS FOR SIXTEEN PATIENTS
WITH FAR ADVANCED PULMONARY TUBERCULOSIS**

Pa- tient	Before Protein Repletion Therapy			After Protein Repletion Therapy			Period During Ther- apy (mos.)	Clin- ical Rat- ing
	Albu- min (gms./ 100 mls.)	Glob- ulin (gms./ 100 mls.)	Albu- min/ Glob- ulin	Albu- min (gms./ 100 mls.)	Glob- ulin (gms./ 100 mls.)	Albu- min/ Glob- ulin		
F.C.	3.5	4.9	0.71	4.1	3.8	1.08	1-5	poor
J.V.	2.1	5.5	0.38	3.7	5.7	0.65		poor
O.M.	3.6	4.0	0.90	4.3	4.1	1.05		poor
R.M.	3.0	5.6	0.54	3.7	5.4	0.69		poor
A.P.	4.4	5.5	0.80	4.2	3.5	1.20		good
C.A.	3.8	5.2	0.73	5.7	4.1	1.40	6-8	poor
S.H.	4.3	5.2	0.83	4.2	4.7	0.89		good
M.D.	3.6	4.6	0.46	4.3	5.4	0.80		poor
C.P.	4.0	4.3	0.94	4.3	4.5	0.96	9-16	poor
G.L.	3.0	5.7	0.53	4.3	4.6	0.93		poor
V.R.	4.5	3.6	1.25	3.9	3.4	1.15		good
T.C.	1.7	6.5	0.26	4.8	3.4	1.41		good
C.M.	2.6	5.8	0.45	3.9	4.2	0.93		good
S.S.	3.5	6.4	0.55	4.9	5.2	0.94	17-24	good
P.E.	-	-	-	3.8	4.0	0.95		good
A.R.	-	-	0.45	4.3	4.1	1.04		good

¹No values for patient G.A.

²Data supplied by Dr. J. Mott Rawlings.

increases were due to higher albumin concentrations and lower globulin concentrations in the sera of five patients, three with a clinical rating of poor and two with a clinical rating of good. Four patients had an increase in serum albumin during protein repletion therapy without a corresponding change in serum globulin. All of these patients were rated clinically as poor. Two patients who were rated clinically as good had a reduction in serum globulin concentration during protein repletion therapy but not a corresponding increase in serum albumin.

Discussion

Multiple factors influence the clinical status of patients with tuberculosis and the progress toward arrest of the disease process. Such factors include emotion, secondary infections, stress, as well as diet, rest, and response to chemotherapy.

The data presented here appear to indicate that patients with far advanced, active tuberculosis can maintain serum vitamin A concentrations comparable to healthy persons when the diet is supplemented with vitamin A. This was true of patients with a clinical rating of poor as well as those with a rating of good.

Serum cholesterol values comparable to those of healthy persons also were observed for patients with a clinical rating of

poor, as well as those rated clinically as good. However, the only cases of low serum total cholesterol were among patients whose prognosis was poor. Even so, the serum total cholesterol values of these patients were increased during protein repletion therapy and the serum albumin-globulin ratio was increased for two of these patients.

It may be assumed that the six patients who had ratios of free to total cholesterol in the serum within the range of 24 to 32 percent had satisfactory liver functioning with respect to the maintenance of serum lipids. There is the possibility that some disturbance of liver function existed among the other patients. It is of interest, though, that all of the patients had serum total cholesterol values within or above the range of healthy persons.

Since vitamin A was supplied to the patients in the preformed state, the serum vitamin A values do not provide information about the ability of the patient to convert carotene to vitamin A. Only in one instance was there a relatively high serum carotene value along with a relatively low serum vitamin A value.

The patients were given a generous hospital diet before, as well as during, protein repletion therapy. Lack of appetite and failure to accept food, however, characterize many patients with far advanced, active tuberculosis. There were individual variations

in the biochemical response to protein repletion therapy among patients rated clinically as good, as well as those rated clinically as poor. In general, the changes in serum constituents for patients in both groups were in the direction of reduced serum globulin, increased serum albumin and increased serum vitamin A. Serum cholesterol concentrations which were low initially, tended to approach the range for healthy persons.

Summary and Conclusions

Concentrations of blood serum cholesterol, vitamin A, and carotene were determined for seventeen patients with far advanced, active pulmonary tuberculosis, during a protein repletion program, as a basis for the evaluation of the nutritional status of the patients, and the functioning of the liver with respect to these nutrients.

Periods of protein repletion varied for individual patients, as they were subjects of research by Doctor Rawlings of Flint, Michigan, and were on the special repletion therapy for varying lengths of time, before the present study was begun.

Patients were clinically classified as poor and good. It was observed that those patients classified as poor had negligible gain in body weight per month, while gain in body weight of one kilogram

or more per month, were observed for some of the patients classified as good.

Concentrations of blood serum vitamin A were higher for those patients classified as good than for those patients classified as poor. The increase in blood serum vitamin A was observed to be higher during the repletion program for those patients classified as good, than for those patients classified as poor, for the different periods of therapy. There is an indication that patients with far advanced tuberculosis on vitamin A supplement have serum vitamin A levels comparable to those of healthy adults.

Concentrations of total blood serum cholesterol were within the normal range suggested for healthy adults, but the percentage of free in total cholesterol varied for the patients. Only six of the patients had percentages of free in total blood serum cholesterol, that was within the range of 24 to 34 percent during the repletion therapy, indicating satisfactory liver functioning with respect to the maintenance of serum lipids.

The changes in serum constituents during repletion therapy were in the direction of reduced serum globulin, increased serum albumin, and increased serum vitamin A. Serum cholesterol concentrations which were initially low, tended to approach the range for healthy adults.

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APPENDIX

CASE HISTORIES

Patient F.C. was a forty-two-year-old white male. X-ray findings indicated active bilateral pulmonary tuberculosis at admission in December, 1950. He was reclassified in April, 1955, as having far advanced pulmonary tuberculosis, and probable silicosis. Sputum tests were positive from the time of admission, throughout the study. Chemotherapeutic treatment included para-amino salicylic acid, streptomycin, isoniazid, viomycin, and tibione. Daily supplements of various vitamins and minerals were given before and during the period of special therapy, which was begun in June, 1955. Weight gain was 0.4 kilograms from the start of the therapy, through a period of eight months. The prognosis was poor. Considerable cough, expectoration, and dyspnoea were present.

Patient C.A. was a thirty-six-year-old white male, who was admitted to the sanatorium in July, 1952, with far advanced active pulmonary tuberculosis. Sputum tests were positive at all times. Chemotherapeutic treatment included dehydro-streptomycin, isoniazid, and paskalium. Tubercle bacilli were found to be drug resistant, but patient was continued on paskalium and isoniazid. Protein repletion was begun in January, 1955, approximately two and one-half years after admission to the sanatorium. Gain in body

weight of 5.2 kilograms occurred within twelve months after the start of the special therapy. X-ray findings in January, 1956, showed no clinical improvement. The prognosis was poor.

Patient G.L. was a fifty-one-year-old white male with far advanced, active bilateral pulmonary tuberculosis, on admission to the sanatorium in February, 1950. Sputum tests were positive at all times. Chemotherapeutic treatment included para-amino salicylic acid, streptomycin, isoniazid, viomycin, and tibione. Nutritional repletion therapy was begun in May, 1955. Weight increase was 1.0 kilogram, up to August, 1955. X-ray findings indicated no improvement in the condition of the lungs. Prognosis poor.

Patient J.V. was a fifty-one-year-old white male, admitted to the sanatorium in May, 1954, with far advanced, active pulmonary tuberculosis. There was extensive involvement and cavitation in the right lung, and a little scattered disease on the left. The patient was acutely ill and febrile; too ill to be weighed. Chemotherapeutic treatment included para-amino salicylic acid, isoniazid, and streptomycin. Tubercle bacilli were drug resistant to all antibiotics, except viomycin. Nutritional therapy was begun in August, 1954. Sputum tests were positive at all times. Loss in body weight was 1.4 kilograms, eighteen months after the repletion

therapy was begun. X-ray taken in December, 1955, showed no improvement. Prognosis, poor.

Patient C.P. was a thirty-six-year-old white male, whose first admission was in June, 1945. Second admission in June, 1954, showed patient to be chronically ill to a moderate degree. Patient had far advanced, active, bilateral pulmonary tuberculosis, with pleurisy of the left lung. A partial thorocoplasty was done in April, 1953. Chemotherapeutic treatment included streptomycin, isoniazid, and viomycin. Nutritional repletion therapy was begun in October, 1954. Patient gained 2.0 kilograms in body weight, 19.5 months after the repletion therapy was begun. Sputum tests were positive at all times. X-ray showed no improvement in the condition of lungs. Prognosis, poor.

Patient M.D. was a white female, aged thirty-one years at the time of admission in January, 1953; classified as a moderately advanced case of pulmonary tuberculosis. After surgical resection of the left upper lobe of lung in February, 1954, patient was reclassified as having far advanced pulmonary tuberculosis. Chemotherapeutic treatment included isoniazid, streptomycin, and viomycin. Nutritional repletion therapy was begun in January, 1955. X-ray findings showed no improvement in condition of patient. Sputum tests were positive at all times. Prognosis, poor.

Patient O.M. was a thirty-six-year-old white male, admitted to the sanatorium in July, 1954, with far advanced, active, bilateral, pulmonary tuberculosis, with advanced tuberculous involvement of both lungs. Chemotherapeutic treatment included para-amino salicylic acid, streptomycin, isoniazid. Nutritional therapy was begun in April, 1955. X-ray in November, 1955, showed possibly a further increase of the disease. Sputum tests were positive at the time of death in March, 1956. Gain in body weight was 5.3 kilograms from the beginning of the repletion therapy, up to January, 1956.

Patient R.M. was a sixty-year-old white male, classified on admission, in October, 1951, as a far advanced, active, chronic pulmonary tuberculosis patient, fibrotic, with associated emphysema. Nutritional repletion was begun in March, 1955. Condition was complicated by chronic ulcerative colitis. Chemotherapeutic treatment included streptomycin, isoniazid, and viomycin. Sputum was positive at all times. Patient gained 1.5 kilograms during eight months of repletion therapy. Expired in February, 1956.

Patient A.P. was a forty-three-year-old white male, first admitted in October, 1949. Second admission was in November, 1954. At this time, diagnosis was far advanced, active, bilateral pulmonary tuberculosis. Chemotherapeutic treatment included

streptomycin, para-amino salicylic acid, isoniazid, viomycin, and tibione. Thorocoplasty on left lung was done in November, 1954. Nutritional repletion therapy was begun in May, 1955. Sputum tests were positive at all times, even after thorocoplasty, and became negative only after the special therapy was begun. Patient was discharged in October, 1955, against medical advice. Lung X ray at the time showed the disease to be arrested. Gain in body weight was 0.3 kilograms, four months after the start of the repletion therapy. Prognosis, good.

Patient A.R. was a twenty-four-year-old Mexican male, admitted in June, 1953, with very extensive exudative pulmonary tuberculosis and tuberculosis of the spine. Patient also had Potts disease. Nutritional repletion therapy was begun in July, 1953. Chemotherapeutic treatment included para-amino salicylic acid, streptomycin, and isoniazid. Sputum tests were negative soon after therapy was begun. X-ray findings in March, 1955, indicated definite improvement of the lungs, with clearing of exudative elements; tuberculosis of the spine had stabilized. Patient left sanatorium against medical advice in May, 1955. Gain in body weight was 9.8 kilograms, from the beginning of therapy to the time he was discharged. Prognosis, good.

Patient C.M. was a fifty-seven-year-old white male, admitted in December, 1953, with far advanced, active, bilateral, pulmonary tuberculosis, with most of the active disease in the right lung. Extensive pleural calcification was observed in the left lung. Chemotherapeutic treatment included streptomycin, para-amino salicylic acid, isoniazid, viomycin, and paskalium. Nutritional repletion was begun in January, 1954. Sputum tests were positive at the close of the study. Gain in body weight was 35.0 kilograms during the twenty-five months of protein repletion therapy. Prognosis, good.

Patient S.S. was a thirty-six-year-old white male, admitted in August, 1953, with very acute, febrile, far advanced, active, bilateral pulmonary tuberculosis. Nutritional repletion therapy was begun in October, 1953. Chemotherapeutic treatment included para-amino salicylic acid, streptomycin, isoniazid, and viomycin. Sputum tests changed from positive to negative in January, 1954. X ray, before the close of the study, showed excellent clearing of the lungs, with only small residual cavities. Weight gain, after the special therapy was begun, and to November, 1955, was 25.3 kilograms. Prognosis, good.

Patient P.E. was a sixty-nine-year-old white male, admitted in February, 1953, with very far advanced, active, bilateral, pulmonary tuberculosis, with the left lung nearly excavated.

Chemotherapeutic treatment included streptomycin, isoniazid, and para-amino salicylic acid. Nutritional repletion was begun in May, 1953. Lungs appeared stabilized by September, 1953, and a self-thorocoplasty was observed. Sputum tests changed from positive to negative, in August, 1953. A gain in body weight of 20.4 kilograms occurred during the protein repletion period of two years eight months. Prognosis, good.

Patient T.C. was a forty-five-year-old white male, admitted in June, 1954, with far advanced, active, pulmonary tuberculosis. He was also an alcoholic. Chemotherapeutic treatment included para-amino salicylic acid, streptomycin, and isoniazid. Nutritional therapy was begun in August, 1954. Sputum reaction changed from positive to negative, by November, 1954. X ray in December, 1955, showed remarkable improvement of lungs, although cavities persisted apically and bilaterally. Patient gained 23.2 kilograms in fourteen months, after the special therapy was begun. Prognosis, good.

Patient V.R. was a twenty-one-year-old Mexican male admitted in January, 1951, with far advanced, active, bilateral, pulmonary tuberculosis. Chemotherapeutic treatment included para-amino salicylic acid, viomycin, and tibione. Nutritional therapy was begun in May, 1954. Sputum tests were positive at the time

of admission, and were alternately negative and positive, throughout the study. Sputum tests were negative in January, 1956. Weight gain during the twenty months of nutritional therapy was 1 kilogram.

Patient S.H. was a twenty-nine-year-old Mexican male, admitted in May, 1953, with very far advanced, active, pulmonary tuberculosis. Chemotherapeutic treatment included viomycin, streptomycin, and para-amino salicylic acid. Nutritional repletion therapy was begun in January, 1955. A successful resection of the right upper lobe was performed in October, 1955. Sputum tests were negative, beginning December, 1955. Patient gained 1.3 kilograms for a period of twelve months during therapy.

Patient G.A. was a thirty-one-year-old Mexican male, admitted in February, 1953, with very extensive, reactivated, acute, bilateral pulmonary tuberculosis, and tuberculosis of the larynx. This was the third admission. Chemotherapeutic treatment included, isoniazid, streptomycin, and para-amino salicylic acid. Nutritional repletion was begun the same month of admission. Sputum tests changed to negative two months after the start of the therapy. Patient left sanatorium in May, 1955. Gain in body weight was 2.7 kilograms, approximately two years and three months after the start of therapy. Prognosis, good.

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