THE RELATION OF PROTEIN SCARCITY AND MODIFICATION OF BLOOD PROTEIN TO TUBERCULOSIS AMONG UNDERNOURISHED SUBJECTS

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RECENT studies, particularly those of Cannon, have demonstrated that the proteins, and more especially the globulins, play a major role in the defense and immunization processes of the body. It is believed that a diet deficient in protein and the resulting decline in the total plasma globulin are factors in the lowered resistance to infections. The observations on tuberculosis which we were able to make in France during the occupation, from 1940 to 1945, indicate such a relationship and it is of interest to report them briefly.

Tuberculosis and War. Numerous statistics show that there is always a serious increase in tuberculosis during periods of war. The experience of France particularly demonstrates this point.

During the War of 1870–1871, mortality from tuberculosis rose in Paris from 528 per 100,000 persons in 1868–1869 to 664 in 1870, and to 737 in 1871; then it fell to 468 in 1872. In the days after the Siege of Paris it may be stated that famine and tuberculosis, following each other, caused more deaths than the war and the riots of the revolution.

The same change took place during the First World War, when the total deaths from tuberculosis per 100,000 population rose from 213 in 1913 to 273 in 1918 (a rise of 28 per cent) and declined to 220 in 1920. The change was particularly evident in the occupied territory of northern France, where the lack of food was great. For example, at Lille, tuberculosis mortality rose from 315 per 100,000 in 1914 to 573 in 1918. Mouriquand, Breton and Ducamp (1), reporting on this subject at the 5th International Tuberculosis Congress in Strasbourg in 1923, stressed the essential role of undernourishment in the occur-

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rence of tuberculosis during the war. This was observed also in other countries, both belligerents and neutrals.

Table 1 shows the death rates from tuberculosis registered in various European countries from 1913 through 1922. The increase in tuberculous infection during the war years is evident, and as K. Faber (2) has emphasized rightly, there is a definite relation between these fluctuations and the changing food situation in each of these countries.

During the Second World War the same situation developed. Tuberculosis was rampant in France as soon as food rationing began. It was first manifested by a notable increase in cases of exceptional severity among members of groups in institutions, lunatic asylums, and prisons who were subject to strict rationing measures. It then appeared among the general population but more especially among those living in cities. We shall not mention all of the studies devoted to the subject, but we shall present a few of the more significant findings.

Paris. In studying the rates for newly-diagnosed cases of tuberculosis which were bacteriologically tested and diagnosed in seventeen dispensaries of the Social Hygiene Department of the Seine Division, an official organization for the diagnosis and treatment of tuberculosis, Troisier (3) noted that the total rate rose from 141 in 1938 to 176 per 100,000 population in 1942, an increase of 24.8 per cent.

At the National Committee for the Fight Against Tuberculosis and in a speech given during the same period at the Academy of Medicine in Paris, Moine and Boulenger (4, 5) stressed

Table 1. Mortality from tuberculosis (all categories) per 100,000 population, 1913–1922.

Country	1913	1914	1915	1916	1917	1918	1919	1920	1921	1922
Germany	142	143	148	162	206	230	211	154	137	142
Italy	156	145	157	166	175	209	172	160	142	143
Holland	141	140	144	168	181	203	173	147	127	115
Great Britain	134	136	147	146	151	157	126	113	113	112
Denmark	135	138	132	155	176	138	119	117	107	101
Sweden	232	238	245	235	227	208	200	186	168	165

the fact that tuberculosis was a menace to the French people. They reported that the number of cases of tuberculosis[2] per 100,000 persons in Paris rose from 315 in 1939 to 455 in 1941, and that the death rate in the Paris District rose from 155 in 1939 to 214 in 1941. These figures, which were reported by a highly-qualified statistician from information obtained from important Health Services about a great many cases exposed to maximum privation, are of greater value and interest than the national statistics. The latter also show a definite increase in the tuberculosis mortality rates in 1941 and 1942, but the errors in them in both directions were so great that little faith can be accorded them.

In our rural areas, statistics for cases of tuberculosis and causes of death generally were always difficult to establish precisely. During the occupation the clandestine way of life (underground, etc.) of a large number of young people and the stratagems utilized to avoid deportation of many of them further contributed to inaccuracies in these statistics. Moreover, the food situation in rural areas was not modified by the war, with the exception of the rural part of southeast France.

On the whole, statistics, especially those for towns, agreed with reports by clinical observers at the end of the first year of occupation and undernourishment that *cases of tuberculosis were abnormally numerous and particularly grave at that time and frequently resulted in death within a few months.*

The Role of Nutrition. Divers factors have been mentioned to explain the spread of tuberculous infection observed during periods of social upheaval, particularly during periods of war: migration of peoples, moral sufferings, and *especially undernourishment.* We agree with M. Bariety (7) that the exodus of peoples brings about undesirable promiscuity and a rapid dissemination of infectious diseases; we also agree that psychological factors produce somatic effects that are beyond dispute, and that overtiring is still more harmful to un-

[2] The figures were taken from diagnoses made in the dispensaries of the Social Hygiene Department.

dernourished persons. However, we believe, as do the majority of French and foreign authors, *that nutritional deficiency is the prime factor.*

We shall not dwell at length upon the problem at this time. We shall indicate, however, those points that support the factor of undernourishment. They may be envisaged from various aspects.

(a) *Individually.* Whatever the cause, tuberculosis is remarkably frequent among persons who are undernourished. Various authors, M. Labbé in particular, have emphasized the frequency of tuberculosis among the obese who have been submitted to reducing cures.

(b) *Collectively.* In lunatic asylums, where tuberculosis caused a considerable number of deaths, the psychological factor could not be taken into consideration, and general living conditions, other than dietary, had not become modified. This was true in the institution where we conducted part of our research. P. Bourgeois (6) reported that tuberculosis cases rose 50 per cent from 1938 to 1943 in the sanatorium of a psychiatric institution where all conditions, including heating, other than dietary remained unchanged. Therefore, it appeared to him that undernourishment was the only responsible factor. On the other hand, M. Bariety (7) was able to observe illness and death from tuberculosis among personnel of the Paris fire brigade. These men, who were submitted to regular and intense physical activity and to frequent overtiring because of bombardments, were entitled always to an exceptionally large and well-balanced ration. Among that group sickness and death from tuberculosis remained the same as that registered before the war.

(c) *Regionally.* In France during the occupation, as in Denmark in 1916 and 1917 and in Germany in 1917 and 1918, tuberculosis increased in towns, especially large towns, but it did not spread in rural areas. What is more, in certain regions rich in food production, as in Brittany, it was noted that tuberculosis diminished.

(d) *Nationally.* During the First World War, deaths from tuberculosis increased greatly in *neutral* countries such as Denmark or Holland when food became scarce. In England, the mortality rate from tuberculosis increased only at a much later time and to a slight degree. Even though this was a *belligerent* country *food was available in sufficient quantities for nearly the whole duration of hostilities.*

Comparing tuberculosis mortality among the French populations in the various categories for rationing, L. Bourgeois, M. Fourestier, and Mlle. della Torre (6) made the following interesting observations in 1944: Among young children (Category E) whose official energy ration was 38 per cent above the vital minimum, tuberculosis mortality showed a decrease of 10 per cent in 1941 over 1938; however, among children of school age (Categories J-1 and J-2) whose ration was 23 per cent below the vital minimum, tuberculosis mortality showed an increase of 100 per cent.

Personal Research. Following a great deal of research on food, health, and biology among various groups (8, 9) we tried in 1944 to estimate the time when tuberculosis spread menacingly among the groups under observation, and to determine which were the principal food and biological conditions causing this spread. We present the facts we observed and the conclusions we reached (10).

Table 2. Average nutrient content of diets of various groups.

Groups	Nutrients Furnished			
	Calories	Protein—Gm.		
		Total	Animal	Vegetable
Minimum Physiological	2,400	70.0	30.0	40.0
X Prison, April, 1941	1,437	46.3	0.6	45.7
S.M. Lunatic Asylum, April, 1941	1,436	54.0	18.0	36.0
Adults, Paris, 1941	1,804	63.8	21.5	42.3
65 Families, Paris, 1941	1,764	67.3	24.2	43.1

[a] Only the total amount was noted.

1. *Beginning of the Increase in Tuberculosis.* This took place in the spring of 1941 after a particularly hard winter during which it became more and more difficult to obtain food. In the preceding autumn family reserves were exhausted and clandestine shipments of food had not yet become organized. That was the "rutabaga" winter during which our compatriots had to live within the official ration of 1,200 calories and thus lost from 10 to 15 kilos. All statistics show that the general death rate, as well as that from tuberculosis, rose suddenly and considerably during May and June, 1941.

We had occasion to observe these facts in a very precise way (8, 9). Research work was carried on in April, 1941, in a prison in the provinces and in a big lunatic asylum of the Paris region. This research was done because of the considerable loss of weight of the inmates. A few weeks later there appeared among these groups, almost simultaneously and very extensively, edema, hypoglycemia, pellagra, and then *acute tuberculosis* or, in other words, the main signs of famine pathology. The diet and biological research carried on during the previous month made it possible for us to know precisely what conditions brought about the development of these disorders, particularly the many cases of tuberculosis.

2. *Dietary Conditions.* The average amounts of calories and of various nutrients supplied by the diets of four different

BY THE DIETS OF SPECIFIED GROUPS

Fat—Gm.			CHO Gm.	Calcium Mg.	Vitamin A I.U.	Ascorbic Acid Mg.
Total	Animal	Vegetable				
40.0	25.0	15.0	420	840	6,000	70
10.7	0.0	10.7	289	345	129	69
22.0	[a]	[a]	256	395	6,710[b]	191
42.1	27.9	14.2	292	464	—	—
42.1	35.0	7.1	277	546	4,215	65

[b] Includes carotene.

groups are shown in Table 2, as well as the amounts of these nutrients supplied by the minimum physiological diet.

The chief characteristic of the Parisians, taken as a group in apparently good health, was a double deficiency in carbohydrates and calories, the second being mainly the consequence of the first. But since the fat and protein content was low, the diet appeared almost balanced in spite of its insufficiency (Gounelle and Mande) (15).

The carbohydrate deficit in the diets of inmates of prisons and asylums (tuberculosis candidates) was similar to that of Parisian families but the fat and protein contents were much lower, resulting in a reduction of the energy value to a total (1,435 calories) equivalent to famine. In addition these diets were completely unbalanced since the lipids and proteins of vegetable origin were greater than those of animal extraction.

The ration for the Parisians, as for the incarcerated, contained a theoretically sufficient quantity of vitamin B and ascorbic acid but it was deficient in A, D, and niacin. What actually characterized the ration of these persons was an important deficit in lipids and proteins of animal origin.

3. *Biological Conditions.* Research conducted in 1941 among various classes of the French population revealed vitamin deficiencies which were clinically invisible but biologically evident. The determination of vitamin A, niacin, and ascorbic acid in the blood of a large number of persons showed generally lower values than those which can be considered normal. The lowest values were noted usually among the incarcerated, but identical results were found often among persons supposed to be in good health and who came through the whole of the occupation period without notable pathological incidents (11). The total lipids and cholesterol in the blood were found normal or a little lowered among all of the subjects examined.

Among the determinations for blood constituents, only the modification of blood proteins appears to characterize the state of malnutrition favoring the development of the usual manifestations of famine pathology and especially of tuberculosis. This

question has been discussed in detail by Gounelle. Therefore, only the points which appear essential will be presented here.

(a) As Gounelle, *et al.* (9) pointed out when they conducted research among the inmates of prisons and asylums in 1941, the first modification of the blood protein balance is a decline in the total globulin. The value is generally less than 2.0 gms. per cent and frequently less than 1.5 gm. On the other hand, the serum albumin total is nearly always normal at this stage. The result is a slightly lower amount of total protein and an abnormally high albumin-globulin ratio. As we have indicated many times since that period, the drop in plasma globulin appears to be the earliest symptom of protein deficiency, preceding the appearance of edemas characteristic of the state in which famine tuberculosis develops. One may even wonder if this globulin deficiency is not the state of least resistance to infections which is always evident in cases of malnutrition. Recent work related to the physiology of the globulins and the studies of Cannon (12) argue in that direction.

(b) At a more advanced stage of famine, the decline in serum albumin may be considered characteristic. The total globulin is normal or slightly higher at this time, resulting in a low total protein and a decline in the albumin-globulin ratio. It is the usual characteristic of a state of malnutrition with edema.

Certain biological and clinical characteristics of famine tuberculosis were demonstrated by M. Bachet and J. Marche (13) in 1943 and have been noted by various observers since. In conditions of undernourishment complicated by tuberculosis, the protein content of the blood is very specific; the total serum albumin is subnormal or very low, while the total serum globulin is abnormally high, as in the case of infections of all types. As a result, the total protein often appears normal but there is a considerable lowering or an extreme inversion in the albumin-globulin ratio. This modification is so characteristic that we automatically looked for tuberculosis when, upon examining an

undernourished subject, we found a high total globulin or a progressive rise after several determinations.

Clinically, famine tuberculosis is characterized both by its gravity (frequency of miliary and bronchopneumonic forms) and by its torpidity (minimum of general signs) and also by its exudative tendency. As Bachet and Marche (13) have shown, there is frequently a pleuro-pulmonary tuberculosis with pleuritic fluid in the foreground and with a chronic evolution independent from that of edemas. Bariety and Barrabé (7) also have emphasized the frequency of interminable inflammations of serosa which occurred among repatriated persons during the same period. After the liberation of persons interned in Germany several observers noted similar findings. It is probably a fact that the modifications in the protein balance and a disturbance of the metabolism of water coupled with undernourishment play a part in the appearance of these forms of tuberculosis.

On the whole, the real characteristic was the decline in the total globulin in the blood of undernourished persons who were tuberculosis candidates. Following that, a decline in serum albumin indicated a serious malnutrition, while a rise in globulin usually accompanied the development of tuberculosis. These tests, which were carried out solely on the basis of loss of weight, demonstrated that a deficiency in fats and proteins and a drop in plasma globulin were the two most outstanding conditions among the persons threatened with famine tuberculosis.

It appears useful to point out which of the two, fat or protein, is the more dangerous deficiency. Certain facts tend to prove that the protein ration plays the more important role.

The Brittany Experiment. Until 1939 the Brittany departments were taxed heavily by tuberculosis. The morbidity and mortality rates from tuberculosis there were the highest in France and even in Europe. Alcoholism was considered to be the principal cause of this situation. However, during the war tuberculosis declined perceptibly in this region of France while it increased everywhere else. This fact, which was observed by

local doctors, was confirmed completely by statistics. For example, in the Cotes-du-Nord department where we personally did research on the subject, tuberculosis caused 257 deaths per 100,000 population in 1938. Although there were no notable shifts in the population, mortality dropped to 189 in 1941 and to 156 in 1942. The same favorable change took place in various departments whose population is essentially rural. Our research in this region in 1943 revealed the following facts: Alcoholism had not diminished there; the Breton peasants drank as much cider and "eau-de-vie" (cognac) as they did in 1938 since they produced both. However, food habits had become radically changed. Because of the clandestine slaughtering of cattle, the intake of red and fresh meat had become customary and had been substituted for pork and especially for lard, which until that time had been the principal meat products in the diet. In addition to this, we must emphasize the fact that the intake of cereals, of green vegetables, and of milk products remained as abundant during the war as previously.

The observations in Brittany should be compared with those found in a village of the Morvan in France by Ch. and F. Flandin (14). Tuberculosis cases were numerous there from 1890 to 1914. The exodus to towns by the young people and the infectious contacts resulting from this appeared to be responsible. At that time peasant life was rather poor and the diet was composed principally of lard and vegetables, butchered meat being eaten not more than once a week. But during the period from 1919 to 1939, although the exodus to towns continued and the contaminating contacts were multiplied, tuberculosis practically disappeared in this village where no anti-tuberculosis measures were taken. By carrying on research in this part of France where they were born, Ch. and F. Flandin tried to explain these circumstances. The only explanation that they found was the change in the eating habits of the peasants. After their return from the First World War the men regularly ate fresh meat which since that time has been a part of the regular diet of the population.

The Danish Experiment (2). In 1914, Denmark, a cattle-raising country, was supported by exports to Germany and England of its meat, milk, butter, cheese, and eggs. At the request of its buyers and in order to obtain basic necessities, Denmark considerably increased its exports in 1915. Fresh meat remained an important part of the diet, averaging 40.9 kg. per person per year; but in cities butter disappeared, the average intake falling from 8.1 kg. to 3.3 kg., and an epidemic of keratomalacia from avitaminosis A occurred. Because of a great increase in exports in 1916, products of animal origin became scarcer than ever and very expensive in the towns. The intake of butter remained low and that of fresh meat literally crumbled, being 3.2 kg. and 26.2 kg., respectively, per person per year. The cases of avitaminosis A remained numerous and a new factor was added. Cases of tuberculous edema showed a tremendous increase especially in the towns. Deaths from tuberculosis per 100,000 persons were 155 in 1916 and 176 in 1917 compared with 135, 138, and 132 in 1913, 1914, and 1915.

After the blockade had stopped exports in 1917 and feed for cattle had become scarce, the intake of butter and fresh meat became normal again, averaging 9.9 kg. and 44.7 kg. The effect was felt rapidly. In 1918 keratomalacia entirely disappeared and tuberculosis mortality declined to 138. On the other hand, this was the year of greatest scarcity in the rest of Europe.

These interesting statistics, established with a great deal of precision for a small country relatively isolated from the rest of Europe, demonstrated *a priori* that the lipid and protein deficiencies were the chief factors in the increase in tuberculosis observed in 1916 and 1917. Since there was no scarcity of carbohydrates before 1917, the energy ration remaining unchanged throughout the war period, it is evident that an insufficient caloric content of the diet could not be blamed, nor could the scarcity of vitamin C. Furthermore, when a new "butter crisis" was brought about by large exports in 1920, the intake of butter in the country again dropped to 3.3 kg., as in 1915. Cases of avitaminosis A became more numerous but an increase in tu-

berculosis did not appear, the death rate remaining very low (117 per 100,000 persons).

K. Faber who analyzed this situation with the greatest of care and reported these data, did not hesitate to conclude that the rise in tuberculosis in Denmark in 1916 and 1917 was only transitory, corresponding with the period of scarcity in fresh meat, and that the scarcity in protein of animal origin was the cause of this incident. The facts which we have observed are in agreement with these conclusions.

General Conclusions. Tuberculosis is one of the manifestations of famine pathology. A deficiency in animal proteins appears to be an essential determining factor in this situation. Our research indicates this and is in accord with the study of tuberculosis in Denmark during the First World War.

A decrease in the total plasma protein, especially globulin, is usually found for persons whose diets are deficient in animal protein. This condition is possibly a factor in the state of lowered resistance which brings about the development and the severity of the tuberculous infection.

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