A CLINICAL STUDY OF MALNUTRITION IN JAPANESE PRISONERS OF WAR*

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DURING World War I the famine and starvation that occurred in certain parts of central Europe prompted some studies,[1, 2, 3] particularly concerning the associated edema. The events of World War II, especially the lengthy periods of starvation that occurred in various prison camps, further stimulated numerous researches on the effects of starvation in the human subject.[4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23] The majority of these studies centered their attention on the edema, but a few included such phases as the burning feet syndrome, the neuropathy, the amblyopia and the hematologic changes. Despite some puzzling facts concerning the edema of war famine,[24, 25, 26] at the beginning of World War II it was still generally held that an inadequate diet led to protein deficiency, which in turn decreased the colloid osmotic pressure of the blood, with resulting edema. Also considered to be of great importance in the picture, particularly with reference to pains in the legs, was vitamin B_1 (thiamin chloride) deficiency. Several careful metabolic studies [27, 28, 29, 30] have thrown much light on the mechanisms involved in famine edema, but there still are important questions left unanswered, as emphasized by Beattie and his associates.[29, 30] It is the purpose of this report to place on record rather extensive clinical data that were accumulated in a special study in a Japanese prison camp in the Philippine Islands in the fall of 1945.

With the defeat of the Japanese in the Philippine Islands during the spring of 1945, their armies began to retreat into the hills of Luzon. There they had to separate into small groups for food, pilfering as they went. Hence, April, May and June of 1945 brought increasing starvation to the Japanese, who had to live chiefly on such substances as grasses, leaves, and potato tops. The usual rice, sugar cane, carabao meat and vegetables were kept from them by the Filipinos. Thousands of Japanese developed malaria, dysentery and edema during this period, and many died.

After V–J day, September 2, 1945, Japanese troops began to surrender by the thousands, so that by early October approximately 80,000 had been confined in New Bilibid Prison. With this the 174th Station Hospital, a 250-bed installation at New Bilibid Prison, was suddenly overwhelmed with the care of 5,700 of these prisoners, many of whom were too ill to move from their cots. An organization was quickly set up utilizing captured

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Japanese doctors, nurses and ward men to care for these patients under the supervision of American medical officers.

This circumstance brought about a most unusual spectacle of severe starvation in the human subject in its various stages and manifestations. The pitiful physical state of these individuals immediately stimulated interest to make certain observations and to carry out treatment.*

Nature of the Material

From a scientific standpoint it would have been highly desirable to carry out detailed balance studies, including vitamin assays, and to institute experimental treatments and study their results. The observations had to remain clinical, however, for four reasons. First, it was the Government's plan to evacuate all these patients to Japan by January 1, 1946. The group was permitted only six weeks in which to make its observations. Second was the difficulty in selecting enough well qualified medical officers who could be spared from Military Hospital duty. No one was found who was qualified to do vitamin assays. Third, there was a shortage of special medicaments such as amino acids, injectable vitamin preparations, and other items needed for clinical therapeutic research. Fourth, we were instructed that the rules of the Geneva Conference provided that no experimentation could be carried out on any prisoners. We could treat them, make observations and record our results. At the same time, we were not allowed to show any partiality to the group of cases selected. We had to give the same diet and medicaments to a final total of 8,000 patients that we gave to the special group under study, thereby limiting the amount of vitamins and medicines available for the special group.

However, subject to these restrictions, it was agreed to select for special study a small group of the most severely starved patients. Twenty-four cases were selected, 12 with massive edema (so-called "wet" beriberi) and 12 with no edema (so-called "dry" beriberi). Care was taken not to include any victims of tuberculosis or other chronic debilitating diseases that might simulate or aggravate the effects of starvation. These 24 patients were placed in a special ward staffed by Japanese personnel and given ordinary good medical care, including a diet of 3,400 calories, which contained 12 ounces of meat per day and citrus fruit juices, and which was supplemented by 24 yeast tablets, 10 mg. of thiamin chloride and 15 gr. of ferrous sulfate by mouth daily.

The study included a history with special emphasis on diet, complete physical examination, routine laboratory studies before, during and after treatment, and certain special procedures of interest in malnutrition. Any

* Through the efforts of Brig. Gen. Jos. I. Martin, Chief Surgeon, AFWESPAC, Brig. Gen. Hugh J. Morgan, Chief Medical Consultant, and Col. Francis R. Dieuaide, Consultant in Tropical Diseases, Surgeon General's Office, Washington, and Col. Roy H. Turner, Medical Consultant, AFPAC, a ward for special studies was set aside and an outline of investigation and care for these patients was formulated.

patients in this group who died were to have complete postmortem examination performed. Since a representative picture of malnutrition was desired, it was planned that if very few in this group died, autopsies were to be performed on several other fatal cases of starvation not especially studied.

For controls, 24 apparently healthy Japanese ward boys were selected for physical examination and certain laboratory studies to compare with the group under investigation.

Clinical Findings

All the patients were males ranging in age from 21 to 49 years. Patients number 1 through 12 were labeled "wet," and patients number 13 through 24 were labeled "dry." Any replacements for those who died received the same numerals, followed by an "A." There were four deaths with three replacements, two in the wet group and one in the dry. The fourth patient, a dry case, died so near the end of the study that a replacement was not made.

History

All histories were obtained through two Nisei interpreters, under instruction of Captain Arthur L. Ruby and one of us (P. M.). Although the patients had so recently been enemies, their full coöperation was quickly obtained.

As has been stated, the period of their starvation began in March, 1945, and continued through September, a period of five to six months. Their diet, from rough estimation, had averaged 800 to 1,000 calories, often less. We were unable to make any reasonable estimate of the amount of protein, vitamins or salt intake prior to capture.

The onset of symptoms was gradual and insidious except in nine patients (three wet and six dry), in whom it was abrupt following an attack of malaria. Approximately three-fourths of the patients gave a history of malaria and about two-thirds a history of diarrhea prior to capture, about equal in the wet and dry groups. Marked weakness was a universal complaint, and it was, as a rule, the initial one. Twelve patients (four wet and eight dry) were so weak that they were bed-fast on admission. Loss of appetite was a common early symptom. It was present in eight of the wet cases and 11 of the dry.

Marked loss of weight was a uniform finding, in the wet cases as well as in the dry. The patient's statement of his former measured body weight was accepted, but estimates were not. The average weight of these patients in health was about 110 to 120 pounds. The average weight of the dry group upon admission, and of the wet group after loss of edema, was about 75 pounds. Thus the loss of weight was about 40 to 50 pounds per person, or approximately 40 per cent of body weight.

Edema occurred not only in all of the wet cases but also at some time in 10 of the dry cases. Of the final number of 13 cases in the dry group,

nine had had edema before capture and one developed edema by the end of the study. Only three of the 13 dry cases showed no edema at any time. Edema, when marked, was usually associated with palpitation, dyspnea on exertion and postprandial epigastric fullness. It became very apparent in the history that oliguria was the rule as the edema accumulated and that polyuria occurred as it receded.

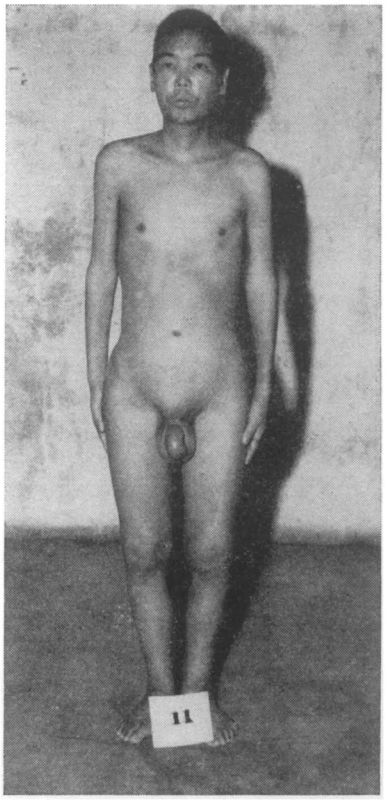

FIG. 1. A typical "wet" case. The edema is generalized, including the genitals.

Only two in each group complained of mild disturbances of vision. None had night blindness. One of the dry cases and eight of the wet cases complained of some diminution of hearing. Five in the dry group and one in the wet group gave a history of sore tongue. Two, one in each group, had cheilitis.

All of the patients in the wet group gave a history of dyspnea and palpitation as a major complaint. In contrast, one-third of the dry group had such symptoms, and only on exertion. None gave a history of anginal pain or cough.

Most of the patients complained of anorexia, aggravated by malaria or diarrhea; in the wet group, particularly those with ascites, many complained

of a full feeling following the ingestion of only a mouthful of food. None gave a history of nausea or vomiting. Five of the dry group had had periodic episodes of lower abdominal cramps. Diarrhea was complained of in seven of the wet cases and in 11 of the dry cases.

None complained of any significant urinary symptoms. Two or three gave a history of transient hematuria, and one patient had possibly had an attack of renal colic.

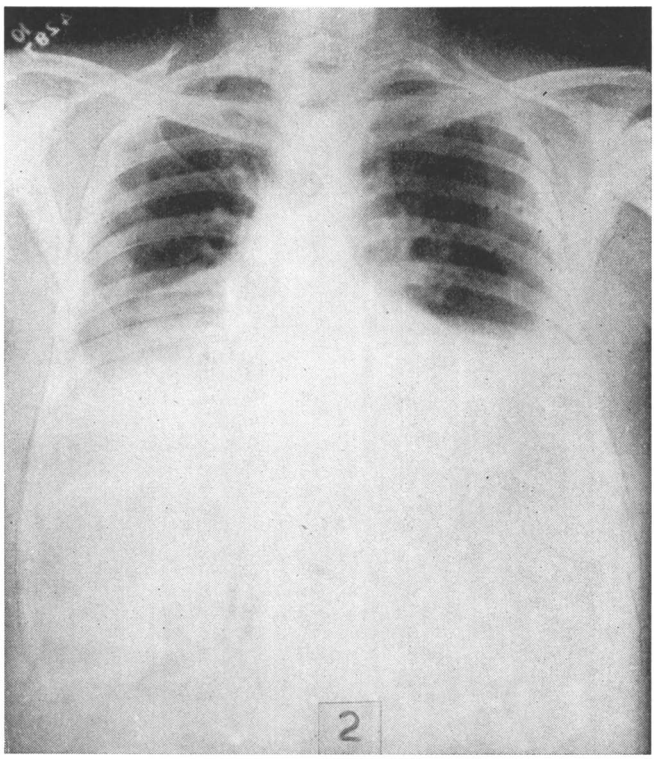

FIG. 2. A roentgenogram of the chest from a "wet" case.

It seemed to us remarkable that only a few (five of the wet and eight of the dry cases) gave a history of subjective neurologic symptoms, numbness, tingling and weakness of the lower extremities. Nearly all of the patients, however, did complain of heaviness of the legs when edema was present. No instance was encountered of the "burning feet syndrome" described often in the recent literature on malnutrition.[4, 12, 18, 19, 20]

From the standpoint of a detailed history, it was rather striking how few gave any clear-cut history of vitamin deficiency, such as visual disturbances, sore mouth or tongue, or neurologic manifestations. Rather, their chief symptoms were of illnesses such as diarrhea and malaria, and weakness, dyspnea, anorexia, and heaviness of the legs with edema.

Physical Findings

All the patients were in such poor physical state that they were at first confined to bed. Three in the wet group and six in the dry group were unable to sit up unaided.

Edema. The 12 patients in the wet group had "moderate" to "very marked" edema. It was most pronounced in the abdomen and lower extremities. In all cases it was of the soft, pitting type. Two of these required abdominal paracentesis. Many had myoedema with pitting of the

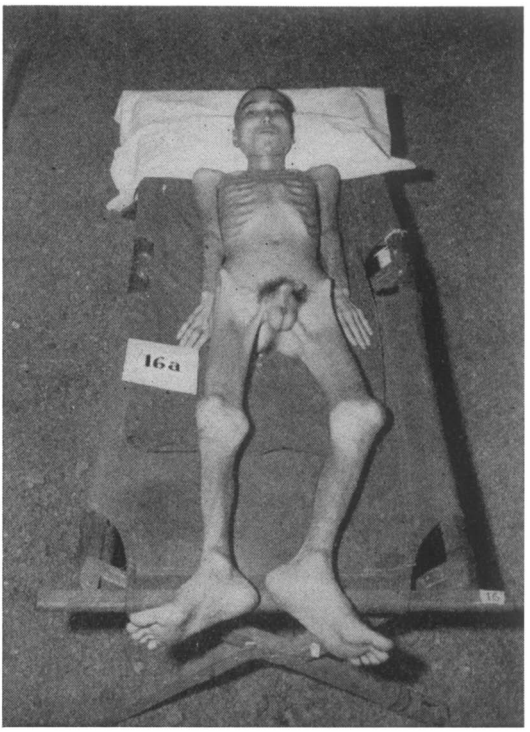

Fig. 3. A typical "dry" case, showing the severe degree of malnutrition.

skin surface. A third of this group had edema of the genitalia. Several had edema of the face and hands. Only three in this group did not have pleural effusion, but they all had pulmonary congestion. A typical example of a wet case is shown in figure 1. Figure 2 illustrates the usual roentgenogram of the chest in one of this group.

In contrast, the patients in the dry group looked like "skin and bones." As has been mentioned, practically all of the patients in this group had given a history of variable edema before hospitalization. At the time of selection, however, and on initial examination, only three had 1 plus edema that was limited to the feet. Figure 3 shows a typical example of a dry case. Only

one of this group had slight pleural effusion. The remainder had a roentgenogram of the chest such as is shown in figure 4.

Skin. Examination of the skin usually disclosed a dry, loose and atrophic integument except when tense over edematous areas. Five in the dry group and one in the wet group had scabies. In both groups, about half of the patients showed a hyperkeratotic "goose flesh" skin, particularly over the abdomen and anterior aspects of the thighs. This suggested vitamin A deficiency, but it was remarkable how well the skin cleared up in a few

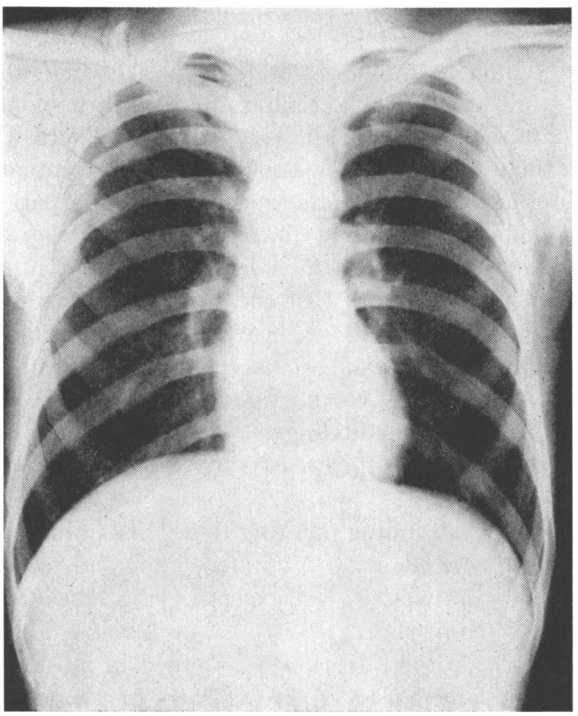

FIG. 4. A roentgenogram of the chest from a "dry" case.

days with soap and water. No distinct pellagrous lesions were seen. Over edematous regions there appeared numerous areas of brown mottling with scaling, more noticeable as the fluid disappeared. There were a few instances of trichophytosis. Three of the wet and two of the dry cases had decubitus ulcers. Others (all in the wet group) had ulcerative lesions of the extremities. Patient 18 had an eczematous, weeping, generalized eruption. A most unusual finding occurred in three patients in the dry group; a peculiar uniform orange (nicotine stain color) discoloration of the nails of both hands and feet. Its significance was not at all clear. As the nails grew out a normal appearing structure appeared, the nicotine discoloration advancing distally. In general, the condition of the nails was good.

The *eyes,* including ophthalmoscopic examination, were negative except for pallor of the conjunctivae, and in two cases (one in each group), conjunctivitis.

One wet and two dry cases had discharging *ears,* all three with old perforations of the drum.

Most of the patients showed some degree of marginal papillary atrophy of the *tongue.* One case in the wet and three cases in the dry group had severe atrophy and marked reddening, with a magenta color in one.

In general the *teeth* were in bad condition but were adequate for mastication. Only one (case 8) had bleeding gums, but no sponginess to suggest scurvy.

The Heart. Upon examination, none of the patients showed significant enlargement of the heart. On auscultation the heart sounds were rather impure and distant, equally so in the two groups. There was some accentuation of P_2 in the wet group, a few others with A_2 accentuated, and several with distinct diminution of S_1 at the apex. Only one patient (in the wet group) had a soft, blowing systolic murmur at the apex, grade II, that was considered to be functional. It was a little surprising, in the presence of the anemia found later, that most of the cases had no murmur whatever. No pericardial friction rub was ever heard in either group. No diagnosis of valvular heart disease was made. Except for the increased P_2 in the wet group mentioned above, there was no significant difference between the wet and dry groups in their cardiac findings. The pulse usually was quite labile. It was noted to be considerably increased by even slight exertion, and with fever.

There was no physical finding pointing to cardiac failure, as with beriberi heart, as the cause of the edema. As stated, none showed cardiac enlargement, and no tachycardia was present except during febrile episodes or with attempted exertion. None showed distended neck veins. No gallop rhythm was heard. Dyspnea on mild exertion was noted in most of the wet cases, but this could be explained usually on the basis of marked ascites and the collection of fluid in the pleural cavities. None was orthopneic, all could lie flat. No instance of bradycardia was found.

The *blood pressure* was normal to low in most instances, a little higher on the average in the wet group. To state it in another way, according to our American standards the patients in the wet group had normal blood pressures, 100 to 130 mm. mercury systolic, 60 to 90 mm. mercury diastolic. In contrast, the patients in the dry group had lower blood pressure readings, average 80 to 105 mm. mercury systolic and 50 to 85 mm. mercury diastolic. Parenthetically it should be remarked that the 24 control subjects had, for the most part, low blood pressures, with systolic readings of 80 to 100 mm. mercury and diastolic levels of 45 to 80 mm. mercury. Thus, compared with the controls, the blood pressure was normal in the dry and high in the wet group.

The *lungs* revealed no abnormality except the pleural effusion or congestion in the wet group.

In the *abdomen,* ascites was present in all of the wet group in sufficient amount to preclude palpation of abdominal masses. As the ascites subsided, an enlarged, nontender liver was found in two of the wet cases, but the spleen was not felt in any patient in either group. One patient (case 16) developed abdominal pain and tenderness during the first few days of the study and died from peritonitis due to rupture of an amebic ulcer of the bowel.

The *genitalia* were negative except for edema in the wet cases.

There was no significant lymphadenopathy in the series except in case 16A, in whom there was mild generalized glandular enlargement, particularly in the groins. Roentgenograms showed mediastinal enlargement, presumed to be due to glands, in case 21, but there was no associated regional adenopathy. The cause of these enlargements was not determined.

Neurologic Findings. In the course of accumulating the data there occurred many variations in the neurologic findings as recorded by different observers on different occasions. Such disturbances of sensory and motor function as were found occurred chiefly in the lower extremities. Four of the patients, one in the wet and three in the dry group, showed diminution of pain sensation in the feet. Two of these in the dry group also had some loss of tactile sensation in the thighs. Eight other patients (five in the wet and three in the dry group) were recorded as having some loss of tactile sensation with loss of pain sense in the lower legs. One of these (case 17 in the dry group) showed a stocking area of hypesthesia reaching to the midthigh bilaterally. In no case was vibratory sensation lost, although several in both groups showed a transient diminution to the tuning fork test. Position sense was normal in all.

Although all patients showed generalized muscular wasting, no frank paralysis was encountered. One patient in the wet group had distinct weakness of the calf muscles. Five patients in the dry group were recorded as showing weakness in the quadriceps groups of muscles. No distinct peroneal involvement was found. A few in the dry group presented what appeared to be disproportionate atrophy of the interossei and the thenar and hypothenar eminences of the hands. Muscular fibrillary twitchings were not observed in any patient. In the deep tendon reflexes also there was much variation. In nine of the cases (six wet and three dry), the reflexes were always active and brisk. In the remainder the findings were quite variable, sometimes active, at other times sluggish, with a slight tendency toward improvement during the period of observation. In no case were deep tendon reflexes persistently absent. All had active abdominal and cremasteric reflexes. None showed a positive Romberg or Babinski sign.

Laboratory Findings

At the beginning of the study all laboratory procedures were done as expeditiously as possible for comparison with later data. Certain of the more important observations were repeated at weekly intervals, others were done only at the beginning and at the end of the six weeks' study. To avoid lengthy tables and to conserve space table 1 has been drawn up giving the initial figures (average) at the beginning of the study, with the variations in parentheses, and the final figures for comparison.

Table I

Laboratory Data

(Average values. The range is given in parentheses)

	Initial Values		Final Values		Controls
	Wet	Dry	Wet	Dry	
Hemoglobin	9.3 gm. (6.8–13.2)	8.6 gm. (6.5–12.6)	10.6 gm. (8.2–14.2)	9.4 gm. (7.0–11.4)	14.7 gm. (13.2–16.8)
Red blood cells	3.42M (2.11–4.36)	2.80M (1.76–3.80)	3.64M (2.9–4.0)	3.27M (2.7–3.8)	4.66M (4.3–5.2)
White blood cells	7,810 (3.5–22.3)	7,425 (2.6–15.9)	11,050 (9.0–12.7)	10,740 (8.0–14.2)	8,200 (6.1–14.4)
Hematocrit	32% (21–44)	27% (16–41)	34% (27–44)	31% (25–36)	43% (33–49)
Mean corp. vol.	93 (59–115)	99 (84–124)	92 (83–103)	101 (79–116)	85 (79–92)
Mean. corp. hem.	29 (21–38)	31 (26–37)	30 (23–36)	30 (25–37)	32 (31–33)
Mean. corp. hem. conc.	30 (21–37)	31 (30–35)	32 (28–35)	31 (28–34)	34 (32–36)
Blood sp. gr.	1.0412 (1.036–1.051)	1.0397 (1.034–1.046)	1.0461 (1.039–1.054)	1.0430 (1.037–1.048)	1.0572 (1.054–1.061)
Sed. rate	34 (7–64)	37 (11–76)	39 (15–56)	54 (38–65)	24 (4–50)
Cholesterol	122 mg. (75–256)	79 mg. (62–107)	143 mg. (108–197)	125 mg. (81–181)	126 mg. (80–183)
Whole blood chloride	464 mg. (437–487)	463 mg. (439–485)			not done
Urinary creatine	0.530 gm. (0.223–0.850)	0.420 gm. (0.103–0.648)			not done
B.M.R.	−10 per cent (+8.5 to −23.5)	−7 per cent (+7 to −15.5)			not done
Circ. time	13.5 sec. (12.0–18.5)	13.5 sec. (10.0–17.5)			not done
Venous pressure	110 mm. (44–190)	93 mm. (40–138)			not done
Thymol turbidity	12.3 units (5.0–19.0)	10.3 units (5.0–19.0)	14.0 units (8.0–19.0)	14.8 units (8.0–21.0)	10.0 units (4.0–16.0)
B.S.P.	4.0 per cent (1.0–8.0)	1.9 per cent (0.0–7.5)	3.1 per cent (0.0–7.5)	1.3 per cent (0.0–3.5)	not done
P.S.P.	36 per cent (20–50)	47.5 per cent (15–70)	57 per cent (40–97)	48 per cent (42.5–62.5)	not done

Hematology. The following studies were performed at weekly intervals, using methods standard in the Army during World War II (T.M. 8–227): hemoglobin by the specific gravity method using copper sulfate; red blood cell, white blood cell and differential counts using finger blood in the usual manner; blood sedimentation rate by the method of Wintrobe. No correction was made for anemia. Blood hematocrit by centrifuging a Wintrobe tube one-half hour at 3,000 r.p.m.; blood specific gravity was done by the drop method using copper sulfate solution. Bone marrow studies were not performed.

All of the patients, when contrasted with the Japanese control subjects, had a moderate to severe degree of anemia. The type and degree of anemia had to be evaluated from the red blood cell counts, hematocrit, mean corpuscular volume and the smears, for the other studies, showing lowered total plasma proteins, invalidated the drop method in copper sulfate for hemoglobin estimations. In the same way, the data regarding the mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration are inaccurate, but the figures for mean corpuscular volume appear to be adequate.

The types of anemia and their relative lack of response to treatment during the six weeks of observation are shown in table 2. The figures are based on mean corpuscular volume determination.

TABLE II

Types of Anemia

	Initial Values			Final Values		
	Wet	Dry	Total	Wet	Dry	Total
Macrocytic	7	8	15	4	5	9
Normocytic	4	4	8	5	2	7
Microcytic (hypochromic)	1	0	1	1	3	4

In addition to inadequate intake of food and iron, malaria and the presence of intestinal parasites certainly contributed to the production and persistence of the anemia. During the course of therapy with ferrous sulfate, 5 gr. three times a day, 14 cases (eight wet and six dry) showed some improvement; six cases (two wet and four dry) showed a drop in all values, and in the remaining four the results could not be ascertained because of death. One patient in the wet group changed from a slight macrocytic anemia, with repeated debilitating attacks of falciparum malaria, to a marked microcytic anemia. Two cases, one wet and one dry, changed from a picture of macrocytosis to a normocytosis without significant change in the red blood cell count. No liver or folic acid or whole blood transfusion was given; no reticulocyte count was done during the iron therapy.

A study of the blood *leukocytes* showed essentially normal total counts at the beginning of the study, with slight elevation at the end of the period of observation. A phenomenon curious to us occurred in many instances during an attack of malaria. Whereas in our American soldiers a leukopenia usually occurred with malaria, in these Japanese prisoners a leukocytosis as high as 12,000 to 14,000 cells per cu. mm. frequently developed. During the course of the study the polymorphonuclear leukocytes averaged about 70 per cent and the lymphocytes approximately 21 per cent. Several showed a monocytosis of 4 to 7 per cent.

Despite the almost universal incidence of intestinal parasites in these patients, only seven (five in the wet and two in the dry group) showed an eosinophilia over

5 per cent. These cases (two wet and one dry) showed values of 19, 10 and 19 per cent, respectively. The eosinophilia had disappeared in all cases (only one showed 2 per cent and two showed 1 per cent) by the end of the study, even though no antiparasitic treatment had been carried out and the intestinal worms or ova were still found in nearly all stools.

At the beginning of the study the values for blood specific gravity were lowered below the normal of 1.052 to 1.055 in all the cases, equally so in both wet and dry groups. By the end of the study there was but very slight improvement, the average reading being about 1.040. The values in the control subjects averaged 1.057.

Blood Proteins. The blood serum total proteins, albumin, globulin and albumin-globulin ratios were determined on each patient at weekly intervals. The procedure employed was the method of Kingsley,[31] with normal total protein values 6.5 to 8.0 gm., albumin 4.5 to 6.5 gm., globulin 1.5 to 2.5 gm. per 100 c.c., and an A–G ratio of 2.0 to 2.3.

TABLE III

Blood Protein Studies

(Average values; the range is given in parentheses)

	Initial Values		Final Values		Controls
	Wet	Dry	Wet	Dry	
Total protein	4.48 gm. (3.4–5.3)	4.75 gm. (4.0–6.1)	4.92 gm. (3.7–6.6)	4.88 gm. (3.9–6.1)	6.98 gm. (6.4–7.6)
Albumin	1.96 gm. (1.5–2.5)	1.87 gm. (1.4–2.4)	2.07 gm. (1.1–3.4)	1.92 gm. (1.3–3.1)	4.47 gm. (4.0–4.8)
Globulin	2.51 gm. (1.8–3.3)	2.77 gm. (2.4–3.8)	2.85 gm. (2.1–4.1)	2.94 gm. (2.4–3.5)	2.58 gm. (2.0–3.8)
A/G ratio	0.810 (0.54–1.08)	0.675 (0.44–0.96)	0.716 (0.35–1.36)	0.662 (0.38–1.35)	1.81 (1.2–2.4)

Since the blood proteins constituted a most important element of the study, the results are tabulated separately in table 3. In the initial studies all values were lowered. Repeated determinations to the end of the study showed a slight but definite rise in nearly all elements in both groups. However, there was no remarkable improvement during the period of observation. In fact, in no case in either the wet or the dry groups did the blood proteins return to normal levels after six weeks of adequate protein feeding.

In a careful examination of all the blood protein studies no significant difference was detected between the wet and the dry groups. Even the three cases in the dry group who never showed edema (16A, 22 and 23) were equally hypoproteinemic.

Studies of the 24 Japanese controls showed values resembling normal American standards for blood proteins, with an average total protein of 6.98 gm. per 100 c.c., albumin 4.47 and globulin 2.58 gm. per 100 c.c.

Blood Cholesterol. These studies were performed using a modified method of Sperry [32] in which the normal values for Occidentals range between 140 and 190 mg. per 100 c.c. However, it has been noted by Snapper [33] that blood cholesterol levels are somewhat lower in Orientals. We found low values also in our control series, average 126 mg. per 100 c.c.

In comparing the two groups under study, the average value in the wet group was similar to that in the controls, but the range was wider, reaching as high as 256

mg. per 100 c.c. The average pretreatment value for cholesterol in the dry group was much lower than in the controls. Early in the course of treatment the cholesterol level fell in some cases, and in case 19 it reached a nadir of 46 mg. per 100 c.c. By the end of treatment the cholesterol level in the dry cases was similar to that in the control group.

Blood Chlorides. The profound weakness seen in these patients made determination of the plasma sodium and chloride advisable to investigate the possibility of Addison's disease and of hyponatremia and hypochloremia due to other causes. Facilities were not available for doing sodium studies, but whole blood chlorides were determined in all cases using the standard silver nitrate method. Normal values range from 450 to 500 mg. per 100 c.c. Such procedures as the Kepler-Power water test to detect early Addison's disease were not carried out.

TABLE IV

Glucose Tolerance Tests

Patient No.	Fasting	30 min.	1 hour	2 hour	3 hour
(wet) 1	66 mg.	50 mg.	180 mg.	180 mg.	197 mg.
2	77	113	117	115	97
3	89	126	186	121	80
4	74	101	131	97	80
5	73	97	98	136	124
6	79	130	136	150	84
7	71	107	110	72	71
8	83	91	98	97	79
9	86	89	93	90	84
10A	71	116	138	156	143
11	84	106	133	147	130
(dry) 13	79	169	176	229	208
14	93	115	117	126	132
15	87	116	143	190	186
16A	63	115	143	156	88
17	66	107	108	97	94
18	73	88	91	111	83
19	73	112	125	167	150
21	63	90	107	124	130
22	67	122	143	122	125
23	85	153	170	134	115
24	73	88	111	96	122

In nearly all cases in both groups the whole blood chloride values were well within normal limits. Three in the wet group and two in the dry had values between 437 and 449 mg. per 100 c.c., but these were not considered of any significance. Because of these normal findings, determinations of blood chlorides were not carried out in the control subjects.

Blood Sugar. Oral glucose tolerance tests were done on all patients except two. Patient 12A in the wet group could not tolerate the sweet drink, and patient 20 in the dry group died the day before the tests were scheduled to be done. The standard method of Folin and Wu was used, giving 100 gm. of glucose by mouth after taking a fasting sample of venous blood and collecting further blood specimens at 30, 60, 120 and 180 minutes. The normal fasting values by this procedure are 80 to 120 mg. per 100 c.c. of blood. Tests using the intravenous administration of sugar were not carried out.

Since composite curves do not show the marked variations that occurred in both groups of cases, table 4 is given to show all of the blood sugar values in all cases tested.

Three cases in the wet group and three in the dry presented curves that usually are considered to be of a normal type. Four in the wet group and three in the dry had "flat" curves, that is, the peak value never rose above 120 mg. per 100 c.c. of blood. Four cases in the wet group and five in the dry had a delayed rise in the peak level, that is, to the second or third hour, with a value as high as 208 mg. per 100 c.c. at the third hour in case 13. None of the latter cases experienced nausea to suggest delayed emptying from the stomach. The fasting blood sugar was below 95 mg. per 100 c.c. in all cases and usually ranged between 60 and 80 mg. per 100 c.c. No instance of diabetes mellitus was found in the series. The type of curve presented by case 13 suggested diabetes, but at no time did this patient show glycosuria. Circumstances did not permit repetition of the glucose tolerance tests at the end of the study.

Blood Serology. The routine serologic test for syphilis that was used (Kahn) was negative in all cases except patients 8, 10A and 11 in the wet group. No quantitative tests were done.

Urine. Three routine urinalyses were carried out on each patient; additional examinations were done as indicated. The values for specific gravity were within normal limits but varied considerably with urinary output. The values were particularly high in the wet group: with edema present with oliguria, 1.028 to 1.032; with diuresis and loss of edema, 1.002 to 1.006. In the dry group the specific gravity ranged usually between 1.012 and 1.024. Albuminuria was unusual, never greater than 1 plus, and then transient, in the wet and dry groups equally. There were occasional instances also of 1 plus glycosuria, again transient, in both groups. As already stated, no instance of diabetes mellitus was encountered. A few cases in both groups showed 2 to 4 red blood cells per high power field of centrifuged urine, to be negative later on subsequent examination. Occasional patients also showed many white blood cells in the urine that disappeared later. After careful consideration, no diagnosis of nephritis was made in either group.

Creatine in the Urine. In males an increase in the excretion of creatine in the urine usually is associated with muscular wasting. Because of the severe muscular wasting found in this group of individuals, determinations of 24 hour urinary excretion of creatine were done, using the method of Hawk and Bergeim.[34] By this procedure the normal urinary creatine excretion is 0 to 0.100 gm. per 24 hours.

Two patients (12A in the wet group and 16A in the dry) showed very slight elevations. Eleven cases in the wet group and nine in the dry had values well over 0.200 gm., and some as high as 0.85 gm. per 24 hours. The average creatine excretion in the wet group was 0.53 gm., and in the dry group 0.420 gm. per 24 hours. Rather marked creatinuria was present equally in the wet and dry groups. These tests were performed at about the middle of the study and were not repeated.

Stools. At least four freshly passed stools from each patient were examined on a warm stage for *E. histolytica* or ova and other parasites. In addition, each patient had a proctoscopic examination, at which time mucosal smears were taken from suspicious areas, if present, and were examined immediately at the bedside for amebae on a warm stage microscope by several observers. It is of interest that no specimen was found to contain amebae at any time. However, case 16 in the dry group died early in the study of amebic peritonitis. Stool studies had been negative for amebae but a proctoscopic examination had not been made.

Seven-eighths of the patients, equally distributed in both groups, had ova of intestinal worms present. Thirteen patients showed the ova of *Ascaris lumbricoides,* 11 had *Necator americanus,* eight had *Trichuris trichiura,* and three had *Strongyloides.* One patient in each group had *Giardia lamblia.* Of the 22 patients who had intestinal parasites, 12 had a single infestation, six had two, two had three, and two had four different parasites present.

Three bacteriologic cultures taken from rectal swab smears were done on each patient. All cultures were negative for the typhoid, paratyphoid and dysentery groups of organisms, with the exception of three cases which had, respectively, *Shigella paradysenteriae*, Boyd P 274 (case 5); *Salmonella enteriditis* (case 21), and *Shigella paradysenteriae*, Boyd P 275 (case 24). In cases 5 and 24 the cultures were positive only once; in case 21 they were positive twice.

From an examination of the stools a diagnosis of sprue could not be made in any case. Unfortunately, facilities did not permit barium meal motor studies of the small intestines to be carried out.

Special Studies

In a study of this kind, a few special examinations were desirable in an attempt to throw further light on the problem.

Basal Metabolic Rate. Numerous studies during starvation in the past have shown a marked lowering of the basal metabolic rate. In this study the determinations were performed at the bedside, in the fasting state, with a Sanborn waterless apparatus. The weights recorded at the time of the tests were with or without edema, as the case happened to be; no correction was made for the edema.

Nearly all cases gave readings in the minus zone. In the wet group the readings averaged about minus 10 per cent, with only two cases showing plus readings, case 3 a plus 8.5 per cent and case 11 a plus 5 per cent. In the dry groups the readings were not quite so low, probably due to difference in surface area, with an average of minus 7 per cent. Again, only two cases showed plus readings, case 13 a plus 7 per cent and case 18 a plus 2.5 per cent. No determination of basal metabolic rate was done on the control subjects.

Heart and Circulation. A study of the heart size by 6 foot roentgenograms revealed no instance of gross cardiac enlargement. Early in the study it was impossible to measure the cardiac borders in the wet group because of the presence of pleural effusion. Later, when they could be measured, the hearts in the wet group were all normal in size. In a comparative study, the hearts in the wet cases were slightly larger than those in the dry group but, interestingly in both groups, they were smaller by measurement than in the controls. Abnormalities of cardiac contour were not encountered. Parenthetically, there was no instance of pulmonary parenchymal disease seen by roentgenogram in either group.

Circulation Time. The circulation time, arm-to-tongue, was performed by the intravenous injection of 10.0 c.c. of 10 per cent calcium gluconate, once repeated, determining the end-point with a stop watch. The results were all normal, that is, 12 to 18 seconds, except in one patient in the dry group, who had a circulation time of 10 seconds. There were some wide variations in single tests but at some time all showed normal values.

Venous Pressure. Measurements of venous pressure by the direct method, using a spinal manometer, showed rather marked variations. The readings varied for the most part between 50 and 150 mm. of water. In the wet group six patients had readings over 100 mm. of water, five showing such readings in the dry group. There was a tendency to slightly higher readings in the wet group than in the dry.

Electrocardiograms. The standard limb leads and precordial leads CF_1 to CF_6, inclusive, were taken on each patient with a Sanborn cardiette. For the most part the electrocardiograms were well within normal limits, a few showing low voltage and minor T wave changes. There was no difference between the two groups. Low voltage, particularly in the limb leads, was observed in five cases in the wet group and two in the dry group. Of these, two in each group also showed relatively low voltage in all of the precordial leads. There was no increase or abnormal shortening of P–R or QRS conduction. Bizarre forms were not observed. The T-wave changes

consisted of flattening, with only occasional slight inversion, seven in each group showing such changes.

Upon the usual inspection of the tracings it appeared in a few that there might be slight prolongation of the Q–T interval. Careful measurements, however, revealed the majority to be well within normal limits. The Q–T ratios determined by the nomographic method of Goldberger [35] revealed values that ranged between 0.82 and 0.16 in the wet group and between 0.80 and 1.15 in the dry group. Six cases, three

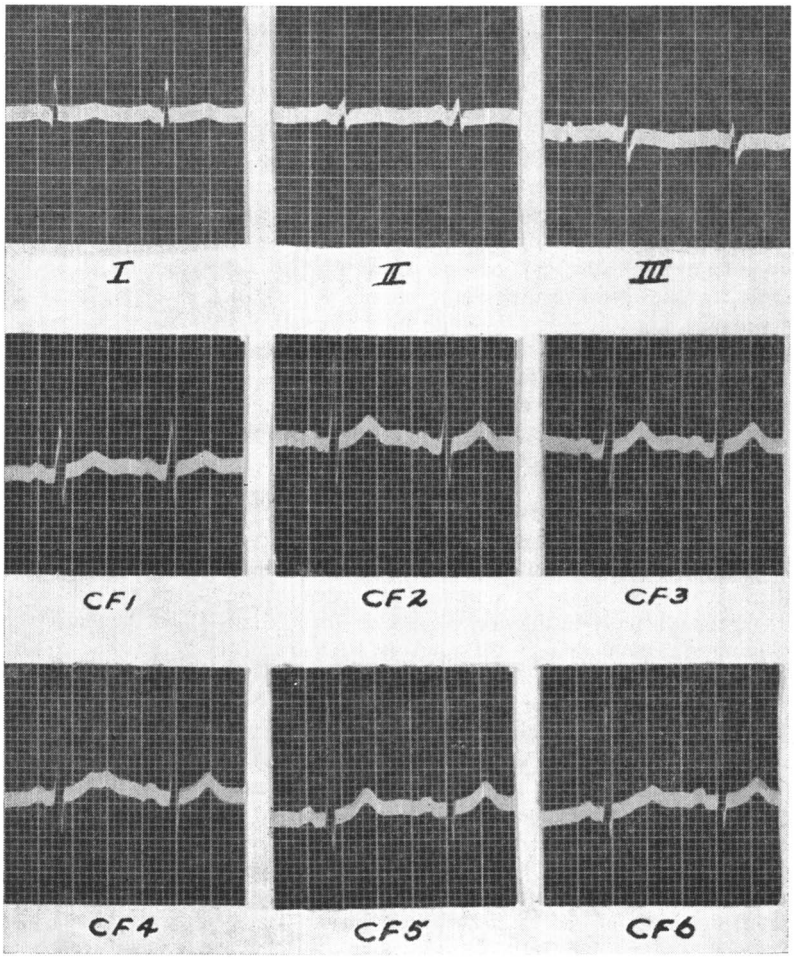

FIG. 5. A representative electrocardiogram taken from one of the "wet" cases.

in each group, showed values higher than 1.09, the upper limit of normal for men,[35] the three wet cases presenting ratios of 1.15, 1.16, and 1.10, and the three dry cases 1.11, 1.15 and 1.10, respectively.

The electrocardiographic tracings in the control subjects were all normal. Not shown in the wet and dry groups were several instances of slight elevation and abrupt take-off of T waves, with tall, pointed T. The ratios for the Q–T intervals were also slightly less in the control subjects, ranging between 0.96 and 1.10.

A typical electrocardiogram from one of the wet cases is shown in figure 5.

The Liver. Clinically there was no evident jaundice in any patient. Determinations of serum bilirubin were carried out according to the method of Malloy and Evelyn,[36] all patients showing less than 1.0 mg. per 100 c.c. of blood at intervals throughout the study. There was no essential difference between the wet and the dry groups.

Tests of thymol turbidity on blood serum by the method of Maclagan[37] were done at weekly intervals. Throughout the study all patients, as well as controls, showed readings higher than four units, the amount regarded as the upper limit of normal for Americans. At the beginning of the study the patients in the wet group ranged in values from five to 19 units, average 12.3, and in the dry group from five to 19 units, average 10.3. By the end of the study the values in both groups were still elevated, in the wet cases ranging from eight to 19 units, average 14.0, and in the dry group ranging from eight to 21 units, average 14.8. These high levels cannot be regarded as due to malnutrition, since the 24 normal Japanese controls showed values ranging from four to 16 units, average 10.

Bromsulfalein Liver Function Test. This test was performed three times on each patient, using 5.0 mg. of the dye per kilogram of body weight. Zero to 1.0 per cent of the dye retained in 45 minutes was considered to be normal. Sixteen of the patients, 10 in the wet and six in the dry group, showed more than 1.0 per cent of the dye retained. There was a tendency toward greater retention (higher readings) in the wet group, four cases showing readings as high as 6 and 8 per cent. In the dry group the range was from 2 to 4 per cent, with one patient showing a reading of 7.5 per cent. As the observations continued, only two in the wet group and one in the dry group showed significant improvement in this test.

Urine Bilirubin Excretion. Partly as a check against serum bilirubin studies, and partly from a desire for more experience with the Watson-Turner modification of the Harrison test for bilirubin excretion in the urine,[38] two series of tests were performed on each patient. Morning urine specimens for six successive days were examined on each patient during two different weeks. Six patients in the wet group gave positive reactions consistently, five of mild degree, one with readings of 2 and 3 plus. In the dry group, four patients gave sporadic readings of trace to 1 plus. Patient 9 in the wet group, who died with cirrhosis of the liver, had a persistently positive reaction of trace to 1 plus, with readings of 2 plus on two occasions.

TABLE V

Free HCl in Relation to Type of Anemia

	Free HCl		No Free HCl (After Histamine)	
	Wet	Dry	Wet	Dry
Macrocytic	4	5	4	3
Normocytic	1	1	3	3
Microcytic	0	0	0	0

Stomach and Intestines. Because of the presence of a macrocytic anemia in a significant number of cases in both groups, gastric analyses were done on all patients. If the fasting specimens did not contain free hydrochloric acid, 0.5 c.c. histamine was given subcutaneously. As shown in table 5, over half the cases with a macrocytic type of anemia had free HCl present in the gastric juice; the remainder did not. Most of the cases with a normocytic anemia had no free hydrochloric acid present even after the histamine stimulation. Tests were repeated in all cases showing no

free HCl with histamine, and only one, a dry case, showed seven units in the second test.

Three patients in the dry group presented enough symptoms of gastrointestinal disturbance to allow roentgenologic studies to be carried out. It was unfortunate that all could not have had such examinations made. During observation, patient 18 developed anorexia, epigastric burning and cramps with distention, chiefly at night, with tarry stools that were guaiac positive after iron had been stopped. Roentgenograms showed a normal stomach and duodenum. Patient 19 developed persistent sharp pain in the epigastrium and right upper quadrant, but both stomach and duodenum were normal fluoroscopically. A week later he developed a purulent right empyema, sterile on smear and culture, that probably was the cause.

The majority of the patients had diarrhea just prior to or at the time of hospitalization that subsided promptly without special treatment. In patient 21, however, a mucous diarrhea with occasional blood persisted. Proctoscopic examination showed only mucus with some reddening of the mucosa, without amebae, and stools were negative for pathogens on culture.

Kidneys. Two kidney function tests, using phenolsulfonphthalein, 1.0 mg. intravenously, were done on each patient, with collection of urine samples at the end of one and two hours. On the first test only three of the wet cases showed as much as 40 per cent excretion in an hour. In the second hour both groups were similar, 15 to 20 per cent excretion. One week later all patients in both groups showed values within normal limits, the wet cases showing nearly 50 per cent excretion of dye in one hour and a total of nearly 50 per cent in two hours. Only one patient in each group excreted over 70 per cent of the dye in two hours.

The Dyes. A Japanese ophthalmologist performed this test with Snellen charts. Four patients, two in each group, with vision less than normal had worn glasses for correction for from four to 18 years. Patient 14 had defective vision of the right eye following an injury. All other patients had essentially normal vision.

Autopsy Findings *

The five patients in the study group who died (9, 10, 12, 16 and 20) were examined at autopsy. Unfortunately the autopsy protocol was lost for patient 10, who died of disseminated tuberculosis, and this case is not included in the discussion. The remaining patients included two "wet" and two "dry" cases. In order to augment the pathologic data, an autopsy was done on six additional patients who died among the general hospital population. The ostensible cause of death of these patients was starvation, and the patients included five wet cases and one dry case. Three aspects of the pathologic data have been selected for discussion.

The first consideration of the pathologic data is the presence of a disease state that is of importance as a cause of death. One of the wet patients in the study group (case 9) had atrophic cirrhosis of the liver, the diagnosis of which had been considered but had not been established prior to death. The liver weighed 660 gm., its surface was nodular, it was firm in consistency, and it had a dull grayish brown color. The liver offered increased resistance on sectioning, the cut surface was nodular and dull brown in color, and its normal architecture was destroyed. The microscopic sections

* All autopsies were performed by Capt. Sam. D. Cummins, M. C., on the unembalmed cadavers, in most instances within one hour of death.

showed perilobular infiltration with macrophages and lymphocytes, marked fibroblastic proliferation and regeneration of bile ducts. A dry patient in the study group (case 16) had an extensive *Endamoeba histolytica* ulcerative colitis and acute fibrinous peritonitis. The patient had had severe abdominal pain and a bloody diarrhea and was prostrated, but the diagnosis had not been established because stool examinations for amebae had been negative and a proctoscopic examination had not been done. At autopsy the entire colon and rectum (but not the appendix) showed numerous ulcers with ragged, undermined borders, that penetrated to the serosa. The ulcers varied in size, the largest measuring 8 by 2 cm. The microscopic sections showed numerous trophozoites of *E. histolytica* in the submucosa and a few in the serosa. Although a grossly visible perforation of the colon was not demonstrated, the peritonitis was considered to be secondary to the amebic colitis. Among the six patients who died in the general hospital population and who were selected for postmortem examination, only two had a specific disease that was of importance as a cause of death. In both cases there were numerous deep ulcers involving the entire colon which measured up to 3 by 2 cm. The gross and microscopic appearance of the ulcer was typical of that caused by *Shigella*. There was, however, no bacteriologic confirmation in either case.

The second aspect of the pathologic data selected for consideration is the tissue changes due to starvation. The findings in the wet patients and the dry patients were similar. The *subcutaneous fat* in every case was described as being scant or absent. The *skeletal muscles* grossly were atrophic, flabby and pale brown in color, and the microscopic sections showed the fibers to be small and separated from the sarcolemma, with degeneration of the fibers in some instances. They stained poorly, and the striations were indistinct or absent. The nuclei were closely approximated. The *heart* in every case was atrophied, with an average weight of 164.5 gm. and a range of 140 to 200 gm. The muscle was easily compressible and pale brown in color. The valves were competent and normal and the coronary arteries patent and normal in every case except one, which showed an occasional, small (3 by 4 mm.) atheromatous plaque. The microscopic sections showed fragmentation of the myofibrils, with loss of striations and small nuclei in close approximation. Occasionally small focal infiltrations of round cells were present in the subepicardium and myocardium. The *liver* was atrophic and was similar in all the cases except the one (case 9) of atrophic cirrhosis described above. In the microscopic sections the hepatic cells were small and the cytoplasm stained poorly. The nuclei were in close approximation. In many cases there were small collections of round cells in the portal spaces. In one case, central necrosis of the lobules, with infiltration of round cells and polymorphonuclear neutrophils and regeneration of the liver cells, suggested a mild infectious hepatitis. The gall-bladder and common duct were normal in every case. The *pancreas* was atrophied in every instance and the lobules were small. In the microscopic sections

the acinous cells were shrunken and the cytoplasm was granular and stained poorly. The nuclei were small and in close approximation. Many of the acinous cells were vacuolated. The islets of Langerhans were small and stained poorly in many cases. Small collections of round cells were present in the connective tissue in many sections. The *kidneys* did not show striking changes due to starvation and were normal except in one case. This patient, a wet case, had evidence of nephrosclerosis and pyelonephritis, with thickened arteriolar walls and narrowed lumina with glomeruli in various stages of fibrosis. Collections of round cells around the glomeruli and infiltrations of round cells and polymorphonuclear neutrophils in the interstitial tissues and around the collecting tubules were present in this case. In the remaining cases the arterioles were normal while the glomeruli were smaller than normal in size. The collecting tubules frequently stained poorly, and occasionally the epithelial cells were vacuolated. There was very little round cell infiltration in the kidney sections. The *testes* did not show a uniform effect from starvation. Two cases showed no evidence of spermatogenesis, and another two cases showed but little spermatogenesis. There was some atrophy of the tubules but only a rare collection of round cells in the interstitial tissues. The *thyroid* gland was uniformly affected. The follicles were small, the epithelium was flattened, and colloid material was decreased or absent. In a few sections the connective tissue was increased and there were collections of round cells. The cortex of the *adrenal* glands was poorly stained, with a foamy or vacuolated appearance in every case. Similar changes were noted in the medulla in three cases. In the *pons* the ganglion cells uniformly were poorly stained, with granular cytoplasm and eccentric nuclei. The microscopic sections of the *myelinated nerves* showed varying degrees of degeneration and vacuolation of the myelin sheath and, in several cases, round cell infiltration of the epineurium. Microscopic sections of the *bone marrow* were reported in six cases, and were normal in four of them. Eosinophilia was present in two cases. One of the cases had ancylostomiasis and the other case had no intestinal parasites. Thus the bone marrow did not appear to be affected by starvation in this series of cases.

The third aspect of the pathologic data selected for discussion is some incidental findings. Edema was a striking clinical feature in the wet patients. It was present in the dependent subcutaneous tissues and in the loose areolar tissues of the omentum, mesentery, mediastinum and subepicardium, also occurring as free fluid in the peritoneal and pleural cavities. In the dry cases these tissues were dry. Edema was not present in the various organs of the wet or dry groups. Thus the weight of the brain in the seven wet cases ranged between 1,150 and 1,300 gm. with an average weight of 1,256 gm., as compared to a range in the three dry cases of 1,250 to 1,450 gm., with an average of 1,325 gm. The weight of the liver in the wet cases ranged between 525 and 1,000 gm., with an average weight of 765 gm., and in the dry cases the range was 750 to 1,050 gm., with an

average of 853 gm. The incidence of intestinal infestation was high. Seven of the 10 patients had a parasite at autopsy, five being infested with *Ascaris lumbricoides,* one with *Ascaris* and *Ancylostoma,* and one with *Ancylostoma.* Finally, the incidence of extensive dental caries was high, occurring in seven of the 10 patients.

Response to Treatment

The response to the treatment used was slow. During the first few days many patients ate only a small portion of the nutritious, but to them unpalatable, Army fare. This was improved considerably in the second week by having Japanese cooks prepare the food in their own way and by allowing the addition of some soy bean sauce. The latter, with its salt content, frequently caused edema to appear, if it was not present, or to reappear. Improvement was delayed further in 17 of the cases by attacks of malaria or episodes of diarrhea. Poor absorption of foodstuffs, likewise, is thought to have played an important rôle in delaying recovery, particularly in some of the more severe cases, as large masses of undigested food were found frequently in the feces on gross inspection.

In the wet group, six cases showed a moderate increase in strength, three a slight increase; in the remainder a definite progression of weakness culminated in death in two instances. Three cases lost none of their edema and six lost all of their edema, three of the latter with the help of mercurial diuretics. It was impossible to measure weight changes accurately in this group, but in general there was no apparent gain in weight.

In the dry group, four cases showed transient edema during the course of the study, usually in relation to a febrile episode due to malaria. As the malaria was brought under control, the edema subsided spontaneously and rather promptly. Two of the cases showed moderate increase in strength, eight showed none whatsoever, and two declined in vigor and eventually died. The weight could be measured more accurately in this group and only five showed a gain, which ranged from two to 11 pounds. Three showed no change at all, and four actually lost weight during the period of observation.

Improvement in the level of blood protein was almost negligible. There was a slight rise in albumin, globulin and total protein, yet the albumin fractions were still well below the so-called critical levels of 2.50 gm. per 100 c.c. for edema formation at the end of the study, when most of the patients were clinically edema-free.

Despite an adequate diet and daily administration of iron, there was very little rise in hemoglobin and red blood cell levels, at most about 1.0 gm. hemoglobin and 500,000 red blood cells in six weeks' time. If an erythrocyte sedimentation rate were to be used as any index of the patient's general condition, the progressive increase in this test during the study might suggest that at the end the patients were sicker than in the beginning. Such was not the case, however.

The most apparent improvement in the laboratory data occurred in the rise in blood cholesterol values in the dry group, which increased from an average low value of 79 mg. per 100 c.c. to a normal value for these Orientals of 125 mg. per 100 c.c.

The evidence from the serum thymol turbidity tests also would suggest that these patients were worse at the end of the study than at the beginning, but according to the bromsulfalein tests there was improvement.

At the end of six weeks the patients who survived were distinctly better. All were able to be up and about and were eating fairly well, and only a few showed significant edema on routine examination. Bladder and bowel function were becoming normal and bouts of diarrhea less frequent. The patients seemed to be gaining strength slowly.

Discussion

The special group of cases selected presented young and middle-aged males who had subsisted on a starvation diet of mostly vegetables and grasses for five to six months. During this period most of them had had bouts of malaria and diarrhea, had developed edema and had lost much weight. All were very weak. In their poor physical state the question that aroused our chief interest was the cause of the edema. Why should some of the cases have such massive accumulations of edema, and others none, with the majority of the other physical and laboratory findings so comparable in the two groups?

The first assumption was that we were dealing with beriberi, wet and dry. Our knowledge of beriberi consisted chiefly of the descriptions we had had from the studies of Keefer,[39] Weiss and Wilkins [40] and Blankenhorn.[41] Our patients did present edema and neurologic findings, but here the similarity stopped. Keefer mentioned serous effusions in beriberi to which our cases would conform. Weiss and Wilkins mentioned moderate lowering of serum proteins and moderate elevation of fasting blood sugar. In contrast, our cases had rather marked lowering of serum proteins, and normal to low fasting blood sugar levels. On neurologic examination the patients in this series showed rather minor sensory and few motor changes. These were not striking. In comparing these findings with those recorded during the war by Spillane,[42] we felt that our cases were not beriberi. They did not respond at all well to treatment, or develop chronic and severe neurologic manifestations, as Spillane points out for subacute and chronic beriberi. Furthermore, during the course of the study the Japanese doctors maintained that these were not cases of beriberi, but could not explain their reasons to our satisfaction. Finally, pathologic study failed to reveal the "hydropic degeneration" described by Keefer [39] and Weiss and Wilkins [40] for beriberi heart.

The presence of dyspnea, palpitation and pleural effusion, as well as peripheral edema, particularly in the wet group, next centered our attention

on the heart. The findings of a heart of normal size in all, normal or low blood pressure, no murmur or gallop rhythm, a normal venous pressure, whether in the wet or dry group, and no significant electrocardiographic change were to us good evidences against heart disease and heart failure as the cause of the edema. Digitalis was not administered to any patient, and yet many of them lost their edema while under observation. Pathologic study of the hearts did reveal some brown atrophy, fragmentation of myofibrils and loss of muscle striation.

Careful observations were carried out to detect a renal component in the picture. There was transient albuminuria and glycosuria, but in our further studies we were unable to establish clinically the presence of nephritis as the cause of the edema. Furthermore, microscopic examination of the kidneys showed no evidence of nephritis, except in one wet case (taken from outside the series) with pyelonephritis.

There was no evidence of venous or lymphatic obstruction as the cause of the edema.

We had no way of estimating the probable sodium intake of these prisoners prior to capture. There may also have been differences in sodium clearance in the two groups. The effect of sodium on edema formation became strikingly apparent in some of the cases upon the addition of salty soy bean sauce to the diet to encourage food intake. Even so, all patients did not develop edema on soy sauce and, in some, edema receded with its continued use. Studies of sodium clearance might yield valuable information in future investigations of this sort.

An association between edema formation and the presence of an attack of malaria [40] or diarrhea became very obvious, but an increase in edema after the institution of a normal diet, as mentioned by Stapleton,[21] was not apparent in these Japanese prisoners. The edema responded quite well to mercurial diuretics in the few instances in which they were used.

What then might explain the clinical picture which we encountered? The wet cases in our series appeared to fall into group 2 of famine edema, described by Beattie, Herbert and Bell [30] under the term "hypoproteinemic famine edema." (Group 1 is "isohydric famine edema," in which total plasma proteins and the albumin fraction are normal.) Presumably such cases may have an increased capillary permeability with the escape of protein into the extracellular fluid compartment. This still does not explain the lack of edema with the same total protein and albumin levels in the dry group. Interestingly, Beattie et al. found hydrothorax and hydroperitoneum for a brief period in only one of 11 patients with hypoproteinemic edema, whereas all of our wet cases except two had hydrothorax of mild to marked degree, with ascites present in 11. We likewise observed a delayed diuresis, slow disappearance of edema and, frequently, weight loss under treatment, as did Beattie, Herbert and Bell.

Our cases also are comparable in some respects to the volunteers studied by Keys [27] and Henschel [28] and their associates, with four major differences.

None of our cases showed (1) profound bradycardia, (2) a notable fall in plasma protein concentration, (3) a venous pressure of 50 per cent below normal; and (4) pleural and peritoneal effusion was present (in the wet group). In none of Henschel's 32 cases was there ever ascites or hydrothorax. In fact, this author states that "this again is similar to natural famine edema where accumulations of fluid in the body cavities is not common except in the presence of other complications." In our series of Japanese prisoners we found no "complications" to explain the serous effusions in the wet group.

From their studies, Keys and Henschel concluded that the edema of simple caloric starvation is a manifestation of a state of dynamic non-equilibrium of the capillary wall, reflecting largely a reduction in cellular mass without a large change in the absolute amount of extracellular fluid. Youmans [22] would place such simple caloric starvation almost entirely on a protein deficiency basis.

The evidence in our series of cases seems to suggest five factors in the causation of the clinical picture: (1) inadequate food intake, probably largely in protein; (2) changes in the bowel, along with infection and worms, causing diarrhea (? sprue) with resulting lack of proper absorption and assimilation of food; (3) consequent lowering of plasma total proteins and its effect on colloid osmotic pressure; (4) anemia, frequently macrocytic, and (5) some element of vitamin deficiency, probably B and possibly C, to account for the neurologic changes and the altered capillary permeability mentioned by Keys and Henschel.

The lack of adequate food intake was evident. But the majority of the facts seemed to point to disturbances in the gastrointestinal tract as second in importance to lack of food intake as the cause of the clinical picture.

The relatively large number of cases with achlorhydria was of interest. That all of them had intestinal parasites may have added to the picture. The lack of proper absorption of foodstuffs was manifest in many ways. Even to the end of the study, some patients were still passing rather large quantities of undigested food particles by rectum. The flat glucose tolerance tests, the macrocytic anemia (? deficient absorption of extrinsic factor), the failure to improve the hematologic picture significantly with diet and iron (? lack of protein or iron absorption, or both), the very slow rise of plasma protein values, the ineffectiveness of oral atabrine to counteract malaria in some cases, and, finally, the failure of the majority to gain weight were to us evidences of faulty absorption in the intestinal tract. Yet that was not true apparently for all substances, for the subsequent return to normal of low cholesterol values in the dry group can be explained best on the basis of lack of intake, followed by adequate absorption after an adequate diet was supplied. As these evidences became apparent, it was most unfortunate that roentgenographic studies of the small bowel could not be carried out, since they might have been enlightening.

Of additional interest were the disturbances of liver function by several tests, the normal or even elevated basal metabolic rates despite malnutrition, and the rather marked creatinuria associated with the muscle wasting.

Our cases appear to fit best into a category of *chronic malnutrition with diarrhea,* with or without nutritional neuropathy, as described by Spillane.[42] He cites the effectiveness of nicotinic acid in controlling such diarrhea. We had no nicotinic acid to administer, but the diarrhea often subsided spontaneously within a few days. Although our study lacked roentgen surveys of the small bowel, in Spillane's series of such cases in German and British patients radiologic examinations by the method of Golden [43] showed no sigficant abnormality.

A number of the findings hinted at sprue. Although all of the patients did not have all of the features, the presence of glossitis, macrocytic anemia and diarrhea with undigested food particles was suggestive. There was no excess of fat in the stools. Liver extract or folic acid was not available for therapeutic trial.

The clinical picture in this group of Japanese prisoners appears to have been one of nutritional hypoproteinemia with a spruelike syndrome. We have no adequate explanation for the fact that some presented massive edema and others did not.

Summary and Conclusions

From among thousands of Japanese prisoners of war at the 174th Station Hospital, New Bilibid Prison, Muntinlupa, Luzon, Philippine Islands, 24 of the most starved patients were selected for special study. They were divided into two groups, 12 with massive edema and 12 with no edema. Detailed clinical and laboratory studies were carried out over a period of six weeks for comparison of the two groups. Twenty-four apparently healthy Japanese ward helpers were used as controls.

All of the cases showed loss of weight, wasting, diarrhea, dyspnea and palpitation on exertion, and a few showed limited neurologic symptoms. All had anemia, intestinal parasites, hypoproteinemia, abnormal liver function tests and evidences of improper intestinal absorption. All of the "wet" cases had hydrothorax and ascites, whereas their absence was striking in the "dry" group.

Many other studies, including blood hematocrit, specific gravity, sedimentation rate, urinalyses, stool examinations, blood chloride levels, glucose tolerance tests, basal metabolic rates, urinary creatine, studies of the heart and circulation, viz., circulation time, venous pressure, electrocardiograms, liver studies, such as thymol turbidity and bromsulfalein tests, bilirubin excretion, and renal function tests, failed to elucidate significant differences between the "wet" and "dry" cases. The only essential difference in the two groups, and one which we are unable to explain, was a consistently lowered blood cholesterol in the dry group, which returned rather promptly to normal under dietary treatment.

Despite good medical care and a high calorie, high vitamin diet, including yeast and vitamin supplements, the response of these patients to treatment was slow.

During the course of the study five of the group of 24 cases died and were autopsied. Six additional cases from outside this special group who died from malnutrition alone also were autopsied, to augment the necropsy material for study. The atrophic changes in tissue, cellular infiltrations, etc. were the same in the two groups, the only difference being the presence or absence of edema.

From this study we have drawn the following conclusions:

1. An analysis of the findings does not support our early assumption that these were cases of wet and dry beriberi.

2. There was no evidence clinically or pathologically of beriberi heart disease or other organic heart disease, nephritis, or venous or lymphatic obstruction to account for the edema.

3. A number of the patients, both wet and dry, exhibited increasing edema with an intercurrent attack of malaria. On the other hand, control of the malarial attack was frequently associated with diuresis and loss of edema fluid. The reasons for this were not apparent.

4. The clinical picture was one of nutritional hypoproteinemia, with a spruelike syndrome manifested by marked alterations of serum proteins, with or without edema, with glossitis, diarrhea and marked wasting. These changes were attributed to inadequate food intake, probably with secondary alterations in the gastrointestinal tract which prevented the proper absorption and assimilation of foodstuffs.

5. With nearly all of the abnormal findings so similar in the two groups, we are unable to explain why some should have had such massive edema and the others none. Possibly differences in sodium intake prior to capture, or in sodium clearance, may suggest an answer.

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