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EPIDEMIC HAEMORRHAGIC FEVER

40 CASES FROM KOREA

BY

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This paper is written from experience gained at the British Commonwealth General Hospital (Japan) in treating 40 cases of this disease during the eight-months period June, 1951, to January, 1952. A far greater number of cases occurring in members of the United Nations Forces have been treated by American hospitals in Korea and Japan, and therefore their figures, when published, will be of greater statistical significance than my own.

Historical

Available literature indicates that the disease was known to the Japanese during their occupation of Manchuria after 1939, and was called variously after the place names where it was endemic—Ehr-Tao-Kang disease, Sun-wu disease, and Songo fever—until the identity of the condition was realized, when the descriptive title "epidemic haemorrhagic fever" was coined.

By 1942 investigations into its aetiology resulted in the belief that the responsible agent was a virus transmitted by the bite of an infected mite (*Laelaps jettmari litzhum*). Such mites were harboured by the field rodent *Apodemus agrarius*, which was as common in Manchuria as in Korea. The Japanese succeeded in producing fever in one monkey 19 days after a subcutaneous injection of 1 ml. of an emulsion of 203 mites collected from 40 *A. agrarius* rodents, and in producing fever, albuminuria, and the characteristic kidney lesion in a second monkey 12 days after its inoculation with the blood from the first.

The incidence of the disease was greatest in the months of May, June, October, and November, and was most prevalent among troops stationed on damp ground and near river banks. Those men who were often in close contact with pack animals also seemed to be prone to the infection. Epidemics varied in their severity and carried case mortalities of from 15 to 50%. The incubation period was estimated at two to three weeks, and ranged from one week to one month.

Incidence in Commonwealth Troops

The cases were scattered among 15 regiments and corps, the maximum number occurring in any one of these not exceeding four during any month from June, 1951, to January, 1952. Cross-infection was therefore improbable. There was, however, an apparent increase in morbidity during the autumn months, and fully half the cases arose during November, 1951.

All cases of the disease in these troops arose during service in Korea or not later than eight days after leaving that country. The endemic areas, chiefly bordering on the River Imjin, had previously been occupied by Chinese and North Korean troops with their pack animals; the vegetation along the river banks is believed to be most favourable for the *A. agrarius* rodent, though these are common throughout Korea. Our patients remembered the friendly habits of these "field mice," which were to be found in the straw insulating shields covering their trenches, and frequently venturing within. Some were tame enough to take food from the men's hands. One patient found one in his bedding a month before his disease began; he developed severe haemorrhages during the course of his illness and died.

Early Symptoms

Initial symptoms were commonly of sudden onset and were attributed by the sufferer to a "flu-like" cold. Chills, headache, anorexia, and nausea were noted by most patients on the first day; sore throat, vertigo, abdominal pain, and vomiting were initial symptoms noted by a few. The chronological order and severity of these symptoms were very variable: chills, 85%; headache, 74%; anorexia, 65%; abdominal pain, 44%; prostration, 30%; vomiting, 24%; sore throat, 17%; vertigo, 15%.

The chills recurred frequently and were accompanied by tremors, which were often remarked upon by the patient's friends before they were noted by him. Headache was absent in no less than 26%, and was often mild and limited to the retro-orbital regions; later it became severe in a few, and was then usually frontal. Vertigo and sufficient subjective loss of postural sensation to cause periodic stagger were present in a minority of cases on the first and second days; dizziness was more commonly described. Abdominal symptoms were early in less than half the cases if slight anorexia and nausea alone are not included. However, within three days pain in the right upper quadrant, with vomiting, frequently became severe, and an initial diagnosis of intestinal obstruction or infective hepatitis was often made. Sore throats and cough were seldom troublesome, and myalgia of back and limbs, though present in most, was rarely severe.

The majority of our cases did not report sick until the third day of illness, when their average temperature was 102.6° F. (39.2° C.).

The Febrile Period

Duration.—The period of fever noted in 34 cases averaged 5.5 days; two cases had a three-day fever, five a four-day fever, seven a five-day fever, eleven a six-day fever, and nine remained febrile on or after the seventh day of the disease. As this duration was estimated from the first day of illness and these patients did not report sick and have their temperature noted until the second or third day, it is possible that the actual duration of fever was shorter in some owing to a brief afebrile prodromal period being included. It appears likely, however, that the discrepancy is slight, as 85% of our cases described chills on their first day's illness, and these presumably coincided with the onset of the febrile period.

Temperature Trends.—An accurate appreciation of the initial two days' fever could not be made owing to lack of temperature recordings over this period in most cases, indeed, only 13 cases reported sick on the second day. The latter showed a temperature of 100–105° F. (37.8–40.6° C.). If the temperature was below 103° F. (39.4° C.) its trend was to rise gradually to a peak of 104–105° F. (40–40.6° C.) on the third or fourth day and then to decline steadily, suddenly, or occasionally intermittently to normal over the next 48 hours. If the temperature on the second day was recorded as 104–105° F. (40–40.6° C.) this appears to have been the fastigium, and it then fell by crisis or by lysis over a similar period. Once the temperature returned to normal it seldom attained 99° F. (37.2° C.) thereafter, and no true relapses occurred.

The more severe haemorrhagic manifestations occurred as sequelae to a sustained fever or to one with a temperature of 104–105° F. (40–40.6° C.) at some time. During the febrile stage a relative bradycardia was commonest.

Symptoms and Signs

Gastro-intestinal

Discomfort and tenderness in the central abdomen, epigastrium, or right hypochondrium generally preceded the vomiting phase and continued after this had ceased. Described as colicky with a lingering dull ache, it was often so mild as to cause no complaint, or it was so severe as to require antispasmodics and opiates for its relief. There was a tendency for gaseous distension and constipation to accompany the complete anorexia, the distension being aggravated by hiccup.

Vomiting began 48–72 hours before the fever abated but at any time between the first and seventh days of illness; it continued for an average period of 4.8 days, with extremes of 1 and 14 days, and was perhaps the most distressing and important sign that occurred during the febrile period. The vomiting appeared to cause greater exhaustion than shown by a case of diarrhoea with equivalent fluid losses. Severe diarrhoea was not an added feature, fortunately. Several of our patients vomited and retched every hour of the day and night for 48 hours or more: there appeared to be little change whether the stomach was given small amounts of semi-solid food or kept empty by continuous aspiration; vomiting of small-gut contents containing bile and pancreatic juices still occurred, and we felt that in most cases 4–6 oz. (114–170 ml.) of fluid hourly by mouth gave the patient most comfort.

Urinary

Albuminuria began on the fourth to the sixth day of illness. It preceded the onset of vomiting in two cases, but in the remainder no albuminuria was found until vomiting had proceeded for two or more days. The two symptoms bore no relationship to each other in respect of severity: albuminuria always continued the longer, and was attri-

buted to an acute nephritis owing to the presence of red cells and casts in the urine in all cases. Glomerular damage usually occurred first, as the specific gravity of the urine was high and microscopy showed many red cells; granular and hyaline casts appeared later, with a steady lowering of specific gravity. The urine boiled solid in three cases. Oliguria lasted 2 to 14 days; suppression to the degree of clinical anuria occurred in seven cases and lasted 1 to 10 days.

Chloride loss by vomiting was not compensated by the kidneys, and urinary chloride levels gave no indication of the resulting hypochloraemia, which was often severe and tended to enhance the nephritis and nitrogen retention.

Oedema was seldom notable, and was confined to the face, making this look bloated until diuresis occurred. Exceptionally, the conjunctivae appeared chemotic; abdominal distension and loin pain were partially attributable to oedema of the abdominal viscera, particularly the perirenal tissues; lethargy, apathy, sluggish tendon reflexes, and cerebral irritation accompanied by fits may have been due to oedema of the central nervous system combined with a relative chloride depletion.

Vascular

Vascular dilatation was chiefly noted in the face, which appeared sunburnt throughout the acute illness, and by inference from blood-pressure recordings. By the time the patient was admitted to hospital the blood pressure was generally normal or high and albuminuria had already begun, but readings taken before admission indicated that there had been a phase of hypotension preceding the onset of nephritis in nearly every case upon which a record had been kept. It was common for us to find that a patient admitted on the ninth or tenth day with a blood pressure of 150/120 had had a recorded pressure of 90/60 on the fifth or sixth day, and that for one or two days this hypotension accompanied the onset of albuminuria and deferescence. Thereafter a plateau rise of blood pressure usually occurred; the hypertension continued throughout the nephritic stage and for several days into the convalescent period.

The most noteworthy vascular changes were those of capillary endothelial damage occurring throughout the body, manifested in all cases by petechial haemorrhages into the skin and visible mucous membranes, and in the most severe cases by overt haemorrhages from the respiratory, gastro-intestinal, and urinary tracts. As a rule these did not begin until the third to sixth day of illness, and continued until the tenth day. Injection of the conjunctivae and the appearance of a few petechiae in the sublingual mucosa were the only manifestations in mild cases; in those more severely afflicted subconjunctival haemorrhages occurred, often visible over the peripheral sclera only after eversion of the eyelids. Thirteen of our cases showed such haemorrhages in one or both eyes, but in none did they assume the grosser form described, in which the whole sclera of both eyes appeared cherry red. Petechiae in the skin occurred in approximately half the cases, generally confined to the neck and axillary folds, more rarely over thorax, abdomen, and limbs.

Epistaxis was noted in 12 cases, in 2 of which it was severe. Haemoptysis is said to be a sign, but was absent in our cases. Haematuria sufficient to colour the urine was present in six cases and continued for several days; in the majority, microscopic haematuria was noted on the day albuminuria was discovered. Haematemeses was noted in six cases but melaena in only one case.

The Blood

An initial leucopenia is said to be characteristic of the disease, but was noted in one case only, which showed a white-cell count of 3,000 per c.mm. on the third day; however, no case had a white-cell count recorded before the third day. Leucocytosis was noted on or after the third

day in all other cases; however, there were as many cases showing a total count below 10,000 as above this figure on the third day. The peak leucocytosis of 10,000 to 64,000 was generally found on the sixth day, and on that day as many cases showed a count of 10,000 to 20,000 as showed a count of 20,000 to 64,000. The increase was greatest in the polymorph neutrophils, which showed a shift to the left; primitive cells of the myeloid series appeared in the peripheral blood in 14 cases. Red-cell counts were not performed routinely; haemoglobin estimations yielded high figures in the early part of the febrile period secondary to haemoconcentration, and they seldom became low except in the presence of frank haemorrhages. Thrombocytopenia, which is said to occur in the fastigium, was not noted, but insufficient counts were made to assess any change.

Those cases in which prothrombin times were estimated showed no appreciable increase. Clotting-times were normal and bleeding-times not increased in our earlier cases; routine examinations were not carried out in later cases, and little appreciable change has been reported by other workers. Clot-retraction time has been found to be prolonged during the fastigium.

Blood chlorides showed a decrease as early as the fifth day, and unless measures were taken to restore the deficiency they continued to decrease until convalescence was reached. In most cases in which vomiting ceased within three to four days, chloride by mouth could be given and retained, but in others it was given parenterally; chloride by either route was found to be rapidly excreted by the kidneys, and the deficiency could never be fully overcome.

Blood urea levels of 150–450 mg. per 100 ml. were recorded; the rise tended to continue for several days after vomiting had ceased and diuresis had begun.

Central Nervous System

Mental apathy and lethargy were common, and from the earliest days of the illness some patients felt muzzy-headed, failed to recognize friends, and lost memory for recent events; later, in those severely ill there was delirium, with a tendency to wander at night, to spit, shout, or swear in garbled fashion, and to be averse to any interference.

Blurred vision was noted by 15 patients, beginning in the first two-weeks period, and continuing for one to seven days; it was commonest during the period of oliguria, and usually disappeared after the onset of diuresis. Transient diplopia on the second and third days was noted by one patient. Mydriasis, apparently characteristic of the disease, was infrequently found, and the blurred vision could not be attributed to it; in one case, however, the pupils were at maximum diameter, and an associated sleeplessness and autonomic disturbance suggested a hypothalamic lesion.

Tendon reflexes were normal in 17 cases, brisk in 5, and sluggish in 2; in one case they could not be elicited on the third day but were remarkably brisk on the fifth.

Photophobia was noted by one patient only; he had Jacksonian fits on the tenth day and meningismus on the twelfth, when his C.S.F. was normal. Another patient had fits on the eighth day, when examination showed: blood pressure, 180/120; blood urea, 184 mg. per 100 ml.; blood chloride (as NaCl), 397 mg. per 100 ml. Fits recurred on the thirteenth and fourteenth days, to be apparently terminated by relief of a high C.S.F. pressure (230 mm. C.S.F.; cells 3 per c.mm.; protein 55 mg. per 100 ml., globulin not increased, sugar 50 mg. per 100 ml., chlorides 770 mg. per 100 ml.). A third patient had fits of epileptiform character on the twelfth and thirteenth days, starting after the onset of diuresis following anuria on the second day and macroscopic haematuria from the ninth day; these fits were probably occasioned by electrolyte imbalance and a high blood urea or by haemorrhages in the brain. In no case were any permanent changes recognized, and none of these patients admitted to a past epileptic history.

Convalescent Phase

It has been noted above that after defervescence, vomiting commonly continued for three to four days, haemorrhagic manifestations for four to five days, and albuminuria with cylinduria for a week or longer. The full effects of the infection thus seemed to arise paradoxically after the fever, and to be due to a combination of toxic effects from the infection itself upon certain capillaries, the kidneys, and stomach, and of resultant secondary biochemical changes, which often progressed towards exacerbation of the primary cause. Thus vomiting would be exacerbated by the uraemia following renal failure; and chloride loss from vomiting, with haemoconcentration from capillary transudation, would exacerbate renal failure.

The most permanent effects noted were those upon the kidney. Casts disappeared often by the end of the first week, and always by the end of the third week; such evidence of tubular damage was always followed by a failure of the kidney to concentrate urine for a considerably longer period, up to three months. This was not shown as a fixed urinary specific gravity: dilution of the urine below an S.G. of 1010 was always possible. The diuresis, which began generally between the eighth and eleventh days and continued for a week or more, was also usually followed by an apparent lack of the normal nocturnal inhibition of urinary secretion, and night and day urines became approximated in volume. These effects, it was suggested, might well have arisen from pituitary or hypothalamic disturbance, but experimentally they were not overcome in three cases which were given 1-ml. injections of posterior lobe extract after 18 hours' abstention from fluids; there was some lessening of nocturia but no increase in concentrating power of the renal tubules following this trial.

Continued low lumbar ache was persistent and a cause of complaint in about half our cases after all other symptoms had disappeared; it seemed to be spinal or ligamentous in origin, and was exacerbated by walking relatively short distances, so that a patient returning from the convalescent home at the sixth or seventh week after the onset of his disease would state that he could not keep up a walk for more than 10–15 minutes, as his backache then became severe.

Treatment

The earliest case of infection, diagnosed in retrospect, occurred in June, 1951, and was treated by Lieutenant Poole under the direction of Lieutenant-Colonel Mackay Dick. This patient had been ill for seven days and anuric for four days before admission to this hospital. Treatment along modern lines by intragastric drip of a Hammersmith cocktail mixture (400 g. glucose, 100 g. peanut oil, acacia q.s. to emulsify, water to 1 litre) was immediately started, the vomitus being filtered and returned to the stomach to prevent loss of electrolytes. Four days later, after an intake of 1 litre of this mixture daily, the patient excreted 7 oz. (200 ml.) urine; after seven days of this treatment there was natural micturition of 32 oz. (900 ml.) in 24 hours; after 12 days the treatment was stopped. Intravenously, one-fifth normal saline with 4% glucose was given after the kidneys had resumed some function, and this was later increased to one-half strength normal saline because blood and urinary chlorides were low. This case had been given aureomycin and penicillin at the advanced dressing station, where acute bronchitis had been noted; and procaine penicillin, 60,000 units twice daily, was given in hospital for nine days, the course being terminated on the appearance of a penicillin rash.

For later cases presenting anuria the same principles of treatment were followed—namely, limitation of fluid intake; conservation of electrolytes; and the supply of minimum daily energy requirements by a high-carbohydrate and high-fat diet in fluid form.

Chemotherapy was not given in uncomplicated cases, as no benefit was derived from the use of chloramphenicol, streptomycin, aureomycin, or penicillin in this disease.

Convalescent serum is stated to be of value if given intravenously during the early phase of infection. Three of our cases were treated with this rather later, and no appreciable benefit could then be attributed to it.

Sedation was often required for restlessness or delirium: paraldehyde by intramuscular injection sometimes exacerbated these conditions; parenteral barbiturates were found more effective, but were limited owing to their possible cumulative effects.

Hiccups often appeared intractable to any form of treatment, including the administration of oxygen and 5% CO₂, intramuscular magnesium sulphate 8% solution or ether, and sedatives.

Case 37

A lieutenant aged 28 was admitted on September 16, 1951. On September 9–10 he had led an artillery section on the south bank of the River Imjin, and ate little food and had no sleep. On the 11th he felt ill and shivered, retired to rest, and three hours later could not rise to micturate but filled a 2-pint (1-litre) pot with urine which looked red. Severe headache and vomiting started while he was on his way to the field ambulance, where a temperature of 105.6° F. (40.9° C.), pulse 84–104, and signs of bronchopneumonia were found. Penicillin and sulphadimidine courses were begun.

2nd day.—T. 103.4° F. (39.7° C.), signs of pneumonia extending.

3rd day.—T. 101–99° F. (38.3–37.2° C.), great mental depression, persistent hiccup.

4th day.—T. normal, bronchial breathing entire chest, few rales only at left lower lobe.

5th day.—Claimed not to have voided for several days. Catheterized, 3 oz. (85 ml.) dark urine, S.G. 1017, albumin 4 plus, frequent white and red blood cells.

6th day.—Circulatory failure on arrival at airport during evacuation to Japan, O₂ and intravenous glucose given. On admission to this hospital he complained of backache, headache, intense thirst, hiccups, suppression of urine, and vomiting of blood-stained mucus of three days' duration. T. 97° F. (36.1° C.), P. 105, R. 25, B.P. 115/70. Appeared very ill; conjunctival injection, dry tongue, mydriasis. No adenopathy. Heart and lungs normal. Slight abdominal distension and renal tenderness, no organ enlargement. Catheterized, 4 oz. (114 ml.) dark-yellow urine—acid, albumin 3 plus, no sugar; microscopic examination: W.B.C. and R.B.C. filled the field, no casts or crystals seen, numerous epithelial cells, cellulose test for sulphonamides positive, culture sterile. C.N.S. normal but for mental retardation. Blood urea 240 mg. per 100 ml., W.B.C. 21,000 (P. 74%, L. 14%, M. 12%). The diagnosis made was ? Weil's disease. Treatment: intragastric drip of Hammersmith cocktail, 3,000,000 units penicillin daily, chloramphenicol 3 g. followed by 0.5 g. six hourly.

8th day.—Very drowsy, but by this time had voided 68 oz. (1.9 litres) urine. Abdomen greatly distended, bowel sounds absent, intestinal obstruction considered present, and Miller-Abbott tube inserted following enema. B.P. 110/70, P. 110. Reflexes hypoactive in upper limbs and absent in lower limbs. Intravenous saline given slowly.

9th day.—Unable to tolerate tube, but abdomen less distended, green foul-smelling stools passed, no further vomiting. His respirations slowed to 10 a minute and oxygen and nikethamide given. B.P. 170/95. Urinary output 97 oz. (2.8 litres), containing scanty R.B.C., few W.B.C., no casts.

10th day.—Still drowsy. B.P. 150/75. Rales appeared at both lung bases and a mitral systolic murmur was evident. Blood urea, 265 mg. per 100 ml. Plasma proteins, 6.2 g. %; W.B.C. 14,600 (P. 83%, L. 14%, M. 2%, E. 1%); R.B.C., 2,100,000; Hb, 8 g. %. Blood transfusion of 2 pints (1.1 litres) fresh blood.

12th day.—Less drowsy, fewer hiccups. Serum chlorides, 590 mg. per 100 ml.; Hb 9 g. %; R.B.C. 2,500,000.

Albuminuria continued in diminishing quantities; he was now able to take a low protein diet and an adequate quantity of fluid orally. Casts were not found in the urine until September 28 (18th day).

19th day.—A second blood transfusion of 1 pint (570 ml.) whole blood was given with improvement of his anaemia. Thereafter he made slow recovery; urinary specific gravity remained low and did not reach 1025 in the concentration test for three months, after which he was discharged from hospital. Weil-Felix, leptospiral agglutinins negative.

Case 2

A private aged 23 was admitted on October 24, 1951. History: back from Korea one week. Nausea, headache, abdominal discomfort, non-productive cough. T. 103.6° F., P. 100; clinical examination negative. Blood smears: no malaria parasites, blood culture sterile, W.B.C. 8,000 (P. 74%, L. 24%, M. 2%). Urine N.A.D.

3rd day.—T. 102° F. (38.9° C.) to normal. Felt dopy, but wanted to get up. Bowels loose, no vomiting. B.P. 105/85.

4th day.—Uncontrollable during the night but now afebrile. Petechiae in buccal and sublingual mucosa and in both axillae. B.P. 102/80, heart normal, chest x-ray film normal. Tender renal angles with backache. Urine: albumin 2 plus, granular and hyaline casts and red cells, sterile on culture. Diagnosed epidemic haemorrhagic fever.

5th day.—Severe backache, oliguria. B.P. rising, 120/90. Intermittent hiccup with abdominal distension. Epistaxis.

6th day.—Appeared bloated; hiccup severe, urine frankly blood-stained and more petechial haemorrhages in axillae and over limbs. B.P. 170/110. W.B.C. 34,000; differential count showed metamyelocytes 6% and myelocytes 3%; normoblasts early 0.5%, intermediate 5%, and late 3%. Blood urea 130 mg. per 100 ml.; Hb 77%; R.B.C. 4,300,000. Profuse epistaxis requiring morphine.

7th day.—Petechiae disappearing from mouth, extending over chest and abdomen and dorsum of feet; needle punctures ecchymotic. Hiccups less, brighter mentally. Recurrent epistaxes. Bleeding-time 3 minutes.

8th day.—W.B.C. 15,400; Hb 64%; blood urea 128 mg. per 100 ml. Urine less blood-stained.

10th day.—One pint (570 ml.) whole blood transfused. Blood urea 164 mg. per 100 ml.; W.B.C. 7,000; Hb 68%. No backache or abdominal pain. Felt well; B.P. 170/90. Urine blood-stained.

12th day.—B.P. 160/100. Urine showed heavy cloud of albumin, 10–20 R.B.C. and 3–4 W.B.C. per field; no casts seen. Diuresis began.

17th day.—Haematuria persisting, this continued until the 19th day.

21st day.—Blood urea, 37 mg. per 100 ml. Nocturia and diurnal frequency disappearing.

28th day.—B.P. 160/100. Developed a carbuncle on the neck, which cleared up with local treatment. He was evacuated to Australia five days later, feeling fit but unable to concentrate his urine.

Case 8

A gunner aged 26 was admitted on November 24, 1951. Onset of disease on November 15 with headache and fever.

3rd day.—Reported sick with cough, anorexia, and backache; T. 104° F. (40° C.), signs of bronchopneumonia. Treated with penicillin.

6th day.—Vomiting and abdominal pain; T. 102.6° F. (39.2° C.). B.P. 90/60, W.B.C. 26,000, white-cell precursors present.

7th day.—Afebrile. Anuric for 36 hours. B.P. 110/78. Conjunctival haemorrhage, epigastric tenderness, albuminuria, and haematuria noted. Patient became irrational.

8th day.—Voided urine, vomiting ceased. Restraint necessary to prevent patient escaping.

9th day.—Drowsy, but ate breakfast. Complained of blurred vision. B.P. 120/80. N.P.N., 51 mg. per 100 ml.; W.B.C., 27,000 (P. 64%, L. 32%, M. 5%, E. 2%).

10th day.—Admitted this hospital. Both eyes showed conjunctival haemorrhages, petechiae noted in mouth and over chest and abdomen scantily. Breath uraemic. Pupils small. Sores around lips; sore throat, and submandibular adenitis. B.P. 150/100. Abdomen slightly distended, spleen and liver impalpable. Hyperreflexia but no meningism present. Urine albumin 1 plus. Fluids forced.

11th day.—Less drowsy. B.P. 130/80. Voiding urine normally.

12th day.—Blood urea, 230 mg. per 100 ml.; blood chloride, 363 mg. per 100 ml. Prothombin time 12 seconds (control 12.5 seconds). Urine: albumin 1 plus, 20–30 R.B.C., 3–4 W.B.C. per field and occasional hyaline casts seen. Urine chloride 1 g. per litre. Additional salt given orally.

13th day.—Blood urea 88 mg. per 100 ml. Albuminuria diminishing.

15th day.—Albuminuria ceased.

16th day.—Diuresis with nocturia, voiding four times during day and six times during night.

21st day.—Backache persisted, with some headache. B.P. 128/90. Nocturia now twice each night.

23rd day.—Blood urea 37 mg. per 100 ml.

28th day.—Evacuated home; unable to concentrate urine, but ambulant.

Case 9

A gunner was admitted on November 20, 1951, the sixth day of disease. While stationed near the River Imjin had onset of chills and frontal headache on November 12. Reported sick next day, as chills recurred in evening.

3rd day.—Passed no urine.

4th day.—Drenching sweats, backache, and delirium.

5th day.—T. 102° F. (38.9° C.). W.B.C., 6,000. Cough began.

6th day.—T. 102° F. (38.9° C.), P. 100, R. 30, cyanotic. Rhonchi heard in all lobes. B.P. 90/70. Urine contained albumin, granular casts, and few R.B.C.s. W.B.C. 8,000.

7th day.—Vomited for first time. Petechiae on palate. B.P. 120/84. W.B.C., 8,150; T. 99° F. (37.2° C.).

8th day.—Frequent vomiting, epistaxis, suppression of urine. Afebrile.

9th day.—Remained afebrile. Urine boiled solid, contained 5 g. chloride per litre. Blood chloride 370 mg. per 100 ml. B.P. 150/120, P. 56. Petechiae noted in mouth and axillae. Appeared dehydrated; intravenous saline given.

10th day.—Stopped vomiting. Urine output increasing, blood-stained. Blood chloride, 495 mg. per 100 ml.; blood urea, 248 mg. per 100 ml.; W.B.C., 7,500.

11th day.—Diuresis began, urine still blood-stained.

12th day.—Vomiting small quantities of bile-stained fluid. B.P. 140/90. Typical epileptiform convulsions repeated six times; treated by venesection followed by 2.7% NaCl and 5% glucose—250 ml. intravenous drip containing sodium lactate and bicarbonate to combat acidosis. Serum chloride, 550 mg. per 100 ml.; blood urea, 197 mg. per 100 ml.

13th day.—Settled, but drowsy and complaining of blurred vision. B.P. 155/115. W.B.C. 6,500, metamyelocytes present.

14th day.—Rational. No further vomiting. B.P. 150/110.

15th day.—Blood chloride 390 mg. per 100 ml. Urine: albumin 1 plus, 10–15 R.B.C. and 2–3 W.B.C. per field; occasional hyaline casts.

25th day.—Nocturia and backache the only symptoms. Albuminuria much diminished. No casts in urine, which contained 1–2 R.B.C. and 4–5 W.B.C. per field.

Pathology

One of our patients died. The following account, with post-mortem report, is provided by Captain Knudsen.

Patient left Korea on November 8, 1951. History of close contact with field mice. Onset of symptoms November 18, with headache, fever, and anorexia. Vomiting began on November 21, with developing oliguria. November 23; W.B.C. 64,000, numerous juvenile forms; blood urea, 112 mg. per 100 ml. Treated symptomatically and by intravenous fluids. November 25: severe epistaxis. November 26: melaena; Hb. 44%. Further epistaxis, increasing mental confusion, signs of circulatory failure. Death occurred on November 27 following vomit of about 1 pint (570 ml.) of altered blood, which was partly inhaled.

External appearances: the body was that of a well-nourished young man. Scattered petechiae were present. A sternal puncture mark was present over the first segment of the sternum. The conjunctivae were normal.

Internal appearances.—Pleural: parietal and visceral pleurae showed petechiae. No fluid present. Pericardium: both visceral and parietal showed numerous petechiae; fluid normal volume but deeply blood-stained. Heart: scattered subendocardial haemorrhages and haemorrhage into the cusps of the aortic and mitral valves; the myocardium was normal and the chambers were of normal size. Lungs: both lungs showed gross haemorrhage into their substance, mainly affecting the lower lobes; a moderate degree of oedema was present. Trachea and bronchi: the trachea and main bronchi contained bloody fluid similar to that present in the stomach, but were otherwise normal. Oesophagus: normal. Aorta: early atheroma and an area of subintimal haemorrhage 2 by 1 in. (5 by 2.5 cm.) in the arch. Thyroid: normal.

Abdomen: the peritoneum showed scattered petechiae; no free fluid; the stomach showed extensive submucous haemorrhages and contained several ounces of bloody fluid; the duodenum and small gut showed extensive petechial mucosal haemorrhages and contained bloody contents; the colon showed petechial haemorrhages but was less affected; pancreas normal; spleen normal size, with a few serosal petechiae and small haemorrhages into its substance. Suprarenals: both suprarenals were disorganized by gross haemorrhage; only a shell of gland tissue 1 mm. thick remained. Kidneys: normal size, capsule stripped easily, revealing numerous surface petechiae; on section there were scattered small haemorrhages into the cortex; the medulla was deep red (? haemorrhage ? congestion); the renal pattern was preserved and the vessels appeared normal; both ureters were normal; the renal pelves both showed small subepithelial haemorrhages. Liver: normal size, few surface petechiae. Gall-bladder: normal. Bladder and testes: normal.

Brain: skull and membranes normal; gross haemorrhage into the infundibular stalk and the pituitary gland; on section the haemorrhage was seen to involve the entire stalk and the periphery of the gland. The remainder of the brain was normal.

Cause of death: epidemic haemorrhagic fever with widespread haemorrhages and terminal inhalation of vomit.

Previous Reports

Death has usually occurred about the tenth day of illness. Haemorrhage into the kidney has been outstanding, haemorrhages into the suprarenal and pituitary glands are often found, and parenchymatous degeneration with diffuse capillary damage in many organs has been reported.

Discussion

The aetiology of this disease is not yet known. American workers in the field seem to be confident of a virus aetiology, but had been unable to corroborate the earlier Japanese findings at the time this report was written.

The disease resembles a non-icteric form of Weil's disease and may prove to be caused by a leptospire. Its prevalence along river banks and estuaries in North Korea during autumn months, the presence of a suitable rodent carrier in vast numbers, and its general clinical course, with special emphasis upon renal involvement, are all suggestive of such an infection despite the absence of positive proof by laboratory demonstration. Weil's disease has a case mortality of 3% for the age group 16-30 (Broom, 1951), our mortality was 1 in 40 (2.5%), but diagnosis was possibly made more often in milder cases owing to its epidemic quality. All agglutination tests for leptospirosis were negative. As renal failure in this disease follows a period of hypotension it may be due to anoxia, which Darmady and his colleagues (1944) suggest is the causative mechanism in Weil's disease; the pathological picture of the kidney is one of cortical pallor and medullary hyperaemia, suggesting an alteration in the distribution of blood flow in the kidney which may short-circuit the glomeruli, as has been shown in rabbits by Trueta *et al.* (1947). Paralysis of the sympathetic nerves by high spinal anaesthesia was not attempted in our cases.

The hypothalamic and pituitary lesions possibly have far-reaching effects upon the hormonal control of urinary secretion and upon the autonomic control of the vascular system, and may be responsible in part for the tendency to inversion of sleep rhythm noted in some of our cases. Adrenal cortical damage may be responsible for the prostration and electrolyte imbalance seen early in the disease and for the delayed water excretion and apparent lack of concentrating power of the kidneys in the later phases.

Summary

An epidemic disease broke out among our troops stationed in Korea during the autumn months of 1951; a summary of its characteristic features as seen in 40 cases treated at the British Commonwealth General Hospital, Kure, Japan, has been presented, together with some of its complications. Its aetiology remains obscure; its similarity to anicteric forms of Weil's disease is noted. Chemotherapeutic and antibiotic agents have been proved of doubtful value in treatment.

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The first standard nomenclature in malariology (*Report on Terminology in Malaria*) was published by the Malaria Commission of the League of Nations in 1940. It has now been revised by a drafting committee (Professor N. H. Swellengrebel, Sir Gordon Covell, and Dr. P. F. Russell) appointed by the World Health Organization, and is issued as No. 13 in the W.H.O. Monograph series. Part 1 of *Malaria Terminology* is a commentary on the terms used by malariologists and falls into three sections, covering the parasites and the infections to which they give rise, the measurement of malaria in the community, and the vector itself. Part 2 is a comprehensive glossary. The price of this publication is 5s.

PARALYSIS FOLLOWING POISONING BY A NEW ORGANIC PHOSPHORUS INSECTICIDE (MIPAFOX)

REPORT ON TWO CASES

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The purpose of this paper is to report two cases of paralysis which developed in the third week after the onset of symptoms of acute organic phosphorus poisoning due to a new compound, *bis*-(mono-isopropylamino)-fluorophosphine oxide. The common name recommended for this substance by the British Standards Institution is mipafox. Like other organic phosphorus compounds used as insecticides, mipafox is an inhibitor of cholinesterase *in vitro* and *in vivo*. Preliminary tests had indicated that the new compound was effective as an insecticide, and that the oral toxicity to rabbits and guinea-pigs was only a twenty-sixth of that of "parathion" (*Nature*, 1951).

In August, 1951, three people employed in the manufacture of a small quantity of this substance by a pilot process developed the symptoms and signs characteristic of acute organic phosphorus poisoning, and two were admitted to hospital.

Case 1

The patient, a female research chemist aged 28, had been employed on the development of organic phosphorus compounds for 21 months before admission to hospital on August 15, 1951. During this time she had handled a number of substances in this group, and, although her exposure to them was mainly in the laboratory, she was concerned occasionally in the manufacture of small amounts of new compounds in pilot plants. She had experienced symptoms of mild organic phosphorus poisoning on at least three occasions during this time, and was away from contact with organic phosphorus compounds for two or three weeks in June, 1951, following one of these attacks.

At about 8 p.m. on August 15, when she had been working long hours on the pilot-scale production of mipafox for three days, she began to feel sick and tired. She attributed these symptoms to fatigue, and continued at work although the symptoms became gradually worse. She left the factory at 12 midnight and returned to lodgings, where she was quite alone. At about 2 a.m. on August 16 she began to suffer from vomiting and involuntary defaecation, and this continued at intervals of a few minutes until 3.30 p.m., when she was given 1/50 gr. (1.3 mg.) atropine by intramuscular injection and admitted to Addenbrooke's Hospital under the care of Dr. A. P. Dick. The vomiting and involuntary defaecation were accompanied by cramps in the muscles of the legs, and by 5 a.m. generalized muscular weakness was so great that she was unable to get out of bed to seek assistance.

The administration of atropine relieved the vomiting and diarrhoea within half an hour, but nausea and muscular twitchings persisted. On admission to hospital significant findings were suffusion of the conjunctivae, pin-point pupils, twitching of the facial and sterno-mastoid muscles, and