is read from the scale on the test-tube. If this method is employed care should be taken to ensure that the tubes used are properly calibrated and of the same diameter.

Summary and Conclusions

The haem-pigments circulating in the blood may be divided into an active fraction, reduced and oxyhaemoglobin, and an inactive fraction chiefly carboxyhaemoglobin and methaemoglobin. A satisfactory method for estimating haemoglobin should measure both fractions.

The Haldane and acid haematin methods may not measure total pigment with the degree of accuracy desirable. Commercial standards are often unreliable and may fade. The pyridine haemochromagen method is rejected because of the objectionable nature of the reagents employed.

Criteria of a satisfactory method are described. These include the measurement of total pigment, reasonable accuracy, simplicity, the use of non-toxic reagents, and some permanent easily reproducible standard.

The alkaline haematin method of Wu eliminates errors which arise in the acid haematin procedure due to lipids, the colloidal nature of acid haematin, and the presence of inactive haemoglobin. Alkaline haematin has the advantage of being a true solution and is easily prepared both from haemoglobin and from crystalline haemin. Haemin is easy to prepare in a pure state from haemoglobin, and its iron content may be estimated with accuracy. Thus it appeared to satisfy our criteria for a suitable standard, and was investigated for this purpose.

Sixteen samples of crystalline haemin were prepared from ox and human bloods and the iron content of each determined. Solutions of alkaline haematin were prepared from each sample. The specific extinction coefficients were found to agree closely. The intensity of colour was proportional to the concentration of haemin iron, and impurities failed to influence the colour.

Several forms of haemoglobin occur in normal blood, some of which are resistant to alkali denaturation. Whatever the proportion of alkali-resistant haemoglobin in a blood sample, if a 1 in 100 dilution in decinormal soda is prepared and placed in a boiling-water bath for five minutes all the haemoglobin is converted into alkaline haematin.

Similar treatment converts all inactive forms of haemoglobin into alkaline haematin. The colour developed is not significantly influenced by the amount of lipid or plasma in the sample.

Determinations of haemoglobin in blood samples based on the assumption that 1 mg. haemin iron in the standard was equivalent to 1 mg. haemoglobin iron in the test yielded results uniformly about 30% higher than determinations based on the oxygen-carrying power of the same sample. It was then found that solutions prepared from haemin and blood gave colours whose absorption curves differed slightly in the red portion of the spectrum.

Samples of human and ox haemoglobin were prepared and their iron content determined. Solutions of alkaline haematin were prepared from each sample and their specific extinction coefficients and absorption curves determined. The curves derived from the haemoglobin solutions were identical with that from blood, and the colour produced was 30% higher than would be anticipated from the iron content, when compared with haemin standards.

Thus haemin is not a theoretical standard in the sense that four molecules of haemin should give the same colour as one molecule of haemoglobin; but it can be employed satisfactorily as an artificial standard. The colours of the solutions are almost identical in the concentrations used for the test, and are matched with ease and accuracy. The standard appears to be unchanged during several months.

Details of methods for the estimation of total haemoglobin using haemin as a standard are given, together with instructions for the preparation of standard solutions equivalent to 100% of the Haldane, Sahli, and Haden scales.

We have employed this method for many months and have found it to give excellent results. Where many determinations are made daily it is quicker and more reliable than other methods we have used.

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LOUSE-BORNE TYPHUS FEVER

BY

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(From a Prison Camp in Germany)

The articles on this subject that appeared in the *British Medical Journal* of Dec. 6 and 20, 1941, have induced us to record our observations on a series of 21 cases occurring in a prison camp in Germany, of which 3 (14.28%) were fatal; 16 (76.18%) arose in men employed in handling clothing at the camp disinfectory. In only 2 cases was it possible to determine the incubation period, and this was in accordance with the usual period of 12 to 14 days.

Onset

The illness was in some cases ushered in by severe frontal headaches, shivering, occasionally epistaxis, soreness of the throat, and thirst, followed by a general feverish feeling, like influenza. In milder cases, on the other hand, the patients felt quite well during the first 3 or 4 days in spite of their temperature being in the region of 102° F.

One patient gave a history of an attack of influenza for one day. He felt better the next day, but was cold and shivery; on the fourth day he suddenly developed acute abdominal pain, vomited twice, and was admitted to hospital as a case of acute appendicitis. His temperature was 102.2°, and his pulse 100; his urine contained nothing abnormal. A laparotomy was performed and the next morning his temperature and pulse fell to normal, but the same evening they rose to 102.9° and 112 per minute respectively, and remained about this level. On the third day after his operation the rash appeared—i.e., 6 days after his initial attack of influenza.

General Appearance immediately before Occurrence of Rash.—The conjunctival vessels were injected and the eyes assumed a heavy appearance reminiscent of measles without photophobia and lacrimation. The face was flushed and a dusky tinge or distinct cyanosis was present in the skin. The tongue was dry and thickly coated with white or brownish-white fur. Sordes of the mouth was very marked until frequent cleansing was adopted. The facial expression was worried, with a continual frown which was aggravated by questioning or outside interference. Speech was sluggish, and the patients appeared to have difficulty in expressing themselves. In some cases there was delirium immediately before the appearance of the rash, and all became increasingly drowsy. Acute dyspnoea usually occurred towards the end of this phase, and was suggestive of bronchopneumonia with only a few crepitations in the lungs.

The Rash : Character and Distribution

The rash appeared on the average on the sixth day; the shortest period was 5 days and the longest 10. It consisted of pink papulo-macules which later became bluish-red and slaty-blue in colour. It first appeared on the shoulder areas, back and front, especially in the neighbourhood of the axillary folds, on the upper abdomen, and on the flanks, and later it showed on the rest of the trunk and the limbs. It was especially prominent on the forearms, the backs of the hands, and the dorsal surfaces of the feet, and was to be clearly seen on the thenar eminences of the hands and on the medial aspects of the soles of the feet. In 4 (19%) cases the rash appeared on the frontal and temporal aspects of the face. As the macules started to fade subcuticular mottling made its appearance and persisted for about 4 weeks. In 9 (42.8%) cases the rash became petechial 2 or 3 days after the appearance of the macules, and involved the same areas. In one case the petechiae were extremely profuse and generalized; the mucous membrane of the mouth was involved and there was a large subconjunctival haemorrhage. In some cases the petechiae became confluent, over the pressure areas of the shoulders, heels, and sacrum, to form areas of ecchymosis. Later, in spite of precautions, some of these areas formed deep-seated, gangrenous bed-sores which healed very slowly (one remained incompletely healed after 6 months). In cases in which the petechial rash appeared it was noticed that the illness was much more severe but not appreciably altered in duration.

Fine branny desquamation started towards the end of the third week from all areas in which the rash appeared, and included the face only in cases with a facial rash. Coarse desquamation occurred from the soles of the feet at this time. The desquamation lasted for about 2 weeks. In 5 (23.8%) cases there was no rash, and in those cases the illness was much milder.

The Fever

The fever proper lasted on an average 17 days. It was of a continuous type, between 100.4° and 103.2° F. (axillary). The maximum temperature recorded was 104.7°. The pulse rate was proportionate to the temperature on the whole, but at times it was disproportionately high. The pulse was easily compressible throughout. The respiration rate was markedly increased, and generally fell a day or two before lysis occurred. The fever tended to end by lysis over 3 to 4 days.

In 4 cases a sudden crisis followed by a rise of temperature in 24 hours, which was sustained over 3 to 4 days, did not prove fatal.

Observation of Patients during Febrile Stage.—During the first week of the fever the drowsy-stuporous condition increased daily. It became more difficult to rouse the patients; they were very restless, slept little, and their resentment of interference of any kind became more marked. Speech became more hesitant and incoherent; low muttering delirious bouts were frequent, and towards the end of the week the patients were semi-comatose. The dusky and cyanosis of the skin increased in intensity and the respiration became more laboured. The tongue remained dry and furred, and it was difficult to get patients to drink although they complained of thirst. In the second week they passed into a state of coma vigil, in which they lay with open eyes, taking no notice of their surroundings although they still resented interference. At this phase the lips and the tongue were very tremulous, and the latter was difficult to protrude, this being done in a very slow jerky manner. In some cases the tongue appeared to be diminished in size and in 2 cases it was definitely shrivelled and almost black. The patients were becoming progressively more prostrate and their mental state was seldom lucid. Towards the end of the second week they seemed brighter, the tongue became moist, began to clean from the tip and edges, and was protruded more easily and less jerkily. The cyanotic tinge started to disappear and the respiration rate began to fall. The patients then had short periods of mental clarity during which they would ask to micturate, whereas they had previously been incontinent. During the first half of the third week the temperature and pulse rate fell by lysis and there was a marked day-to-day improvement in their condition. There was no abrupt passage from the stage of nervous excitement to that

of defervescence. After the defervescence the patients were very emotional; they continued to have bouts of delirium and transient delusions, and were disinterested in and unnoticing of their surroundings and fellow patients until convalescence was well established.

Systemic Manifestations

Alimentary System.—Only in one case was the rash seen on the buccal mucous membrane, and there were no cases of parotitis. The fauces were slightly injected at the onset of the illness. Nausea was frequently complained of early, and vomiting was met with occasionally. Constipation was the general rule, but in 3 cases diarrhoea occurred at the end of the first week. Faecal incontinence was not uncommon during the second week. Abdominal pain occurred, and was so severe in one case that a laparotomy was performed (see above).

In 4 other cases suprapubic pain was associated with difficulty and pain on passing urine.

Respiratory System.—Marked dyspnoea with stertorous breathing and employment of the alae nasi occurred in all cases, and there was a short period of Cheyne-Stokes respiration just before the defervescence. There were 2 cases very suggestive of bronchopneumonia, but the only signs elicited in the others were a few isolated crepitations.

Cardiovascular System.—The pulse was easily compressible throughout the febrile stage, and one case exhibited pulsus paradoxus. The heart sounds became weaker as prostration became more marked, but there was no cardiac enlargement, no murmurs were detected, and no oedema occurred. The blood pressure was not influenced except in one patient, who developed a hypertension of between 180/90 and 190/110 during early convalescence; this still persisted after 6 months with clear urine, but is now resolving.

Eyes.—All cases showed the marked injection of the conjunctival vessels and the heavy appearance already described. Subconjunctival haemorrhages were seen in 2 cases, and one of them showed a small superficial retinal haemorrhage. During convalescence one patient complained of "spots in front of his eyes," and examination revealed recent translucent opacities of the vitreous. These were still present after 6 months. One patient complained of blurring of vision, and definite swelling of the disk was found on both sides. He subsequently made a complete recovery. Prior to defervescence in some cases, the pupils became constricted, but not to pin-point proportions, and showed sluggish reaction to light and accommodation. Several of the patients complained of diplopia, and transient squinting was noticed.

Ears.—Transient deafness was often experienced. In one case severe tinnitus and deafness persisted until 2 weeks after defervescence and then gradually cleared up. In another case severe vertigo, with the patient falling to the left, occurred, and still persists after 6 months.

Central Nervous System.—The mental condition has already been described, but again it must be stressed that the improvement with defervescence was not so dramatic as one would expect from the textbook descriptions. Cerebral irritation was indicated by muscular twitching of varying degree in 16 cases (76%). This variation extended from fine fibrillary tremor of the facial muscles to gross twitching of phalanges, wrist, and ankle-joints, and groups of muscles were observed to contract. It was noticed that the more extensive the petechial change the more marked was the state of nervous excitement.

One patient on the sixth day of illness began to twitch in the muscles of the face and hands and to complain of double vision; by the tenth day he had a mask-like facies, and movement of all muscles was slow, death occurring on the fifteenth day. Another patient developed facial tremor during the second week of the fever; and 3 days before defervescence, which occurred on the twenty-first day, he developed the torpid facies and gross twitching of phalanges, wrist, and ankles; this was almost choreic in type, and was not a peripheral tetany. Prowazek's and Chvostek's tests were negative, and venous congestion had no effect. There was a pseudo-spasticity of the limbs, the deep reflexes were never more than brisk, the plantars were flexor, and there was no Kernig's sign. The nervous manifestations reached their maximum just before defervescence and passed off during early convalescence, when the patient complained of blurring of vision and was found to have bilateral disk swelling. In his case ulnar neuritis occurred

early in the febrile stage. He complained of severe pain in the little and ring fingers of the right hand, and this settled down to a dull ache and numb feeling; there was no muscle-wasting, and only the loss of the sense of light touch over the little finger, the ulnar half of the ring finger, and the adjacent part of the palm. This still persists after 6 months.

Fine tremor of the fingers was present in all cases during the febrile stage and passed off during early convalescence, when severe neuralgic pains in the feet and legs were complained of.

C.S.F.—Lumbar puncture was not done as a routine but only in those cases with marked cerebral irritation: in all except one case the findings were normal. In the case already described with torpor, Parkinsonism, and disk swelling, the day before defervescence the fluid was clear, and under pressure of 100 c.mm. There were 261 cells per c.mm.—lymphocytes 74%, polymorphs 25%, endothelial cells 1%—and an abnormal increase in globulin.

Genito-urinary System.—All cases had an initial oliguria followed by incontinence. Four patients at the end of the first week, and the others after the defervescence, complained of pain on micturition, having to strain, and a constant desire to micturate without being able to do so. All cases showed albuminuria, red blood cells, epithelial cells, and cellular casts in the urine, which cleared during convalescence; and during the periods of dysuria Gram-negative motile bacilli were found in non-catheter specimens.

Blood Examination.—There was an initial polycythaemia, which may be attributed to the early low fluid intake, to the fluid lost through forceful respiration, and to that lost secondarily by sweating. The haemoglobin percentage and red blood cells fell by from 20 to 30% and from $1\frac{1}{2}$ to 2 millions respectively after the appearance of the petechial rash. In cases with no petechial rash there was not this proportionate fall. The Hb and red cells were quickly made up during convalescence. The white cells varied considerably; the maximum count was 30,200, two were in the region of 18,000, and of the others the highest was 13,000 and the lowest 4,400. Neutrophils constituted 60 to 83% of the count. The granules in the polymorphs appeared to be coarser and more highly stained than the normal. In the 2 fatal cases the counts were R.B.C. 4,600,000, Hb 72%, W.B.C. 4,400; and R.B.C. 4,860,000, Hb 78%, W.B.C. 6,400—taken on the fifth and seventh days respectively. Small extracellular coccal and cocco-bacillary bodies, occurring in pairs and in clusters, violet in Giemsa-stained specimens, were found in a number of the films. These were presumed to be Rickettsia bodies, and were found in one case 6 months after the onset of the illness.

Blood Sedimentation Rate (200-mm. tube Westergren, one hour).—In one case the B.S.R. readings were: 35 two days before rash, 129 three days before defervescence, 83 twelve days after defervescence, 51 nineteen days after defervescence, and 7 three weeks later. In a case with persistent tachycardia the figures were: $2\frac{1}{2}$ months 91, 3 months 94, $3\frac{1}{2}$ months 20, 4 months 38, and $4\frac{1}{2}$ months 22. In the other cases the B.S.R. was not done frequently, but was in single figures in the second week of convalescence.

Laboratory Findings.—The Weil-Felix reaction was positive in all cases tested after the seventh day of fever; in those done on or before the fifth day a negative return was obtained. It was noticed that in the cases in which no rash appeared the titre was lower (1:80 to 1:800) than in petechial cases (1:200 to 1:6400). Successive titre readings could not be made a basis for estimating the severity of the illness, but a rising titre in one case indicated more severe prostration. The Wassermann reaction was frequently positive, but not invariably so, and this test could not be done often enough to be of value. It always became negative after the defervescence. Blood, stool, and urine culture results were negative, but as the specimens were dispatched a considerable distance they were of no value for culturing.

Post-mortem Findings.—In one case ending fatally on the fifteenth day necropsy revealed the cause of death as haemorrhagic bronchopneumonia. The only other significant findings were a marked diminution in body and mesenteric fat, the occurrence of numerous subpleural haemorrhages, and a vivid scarlet coloration in the left lung. The pons and medulla were sent for section, and the translated German report read:

Pieces of Brain Stem.—There are numerous perivascular nodules of polymorphous glial cells in all parts of the brain stem and in the cerebellar cortex. There are changes in the ganglion cells (chromatolysis) and exuberant growth of red cells. Isolated annular perivascular infiltration of lymphocytes and very small haemorrhages. The meninges are infiltrated with lymphocytes, plasma cells, and macrophages. Signs of brain oedema. **Diagnosis:** Typhus meningo-encephalitis.

The histological report suggests a close association with encephalitis.

Treatment Given

Sulphonamides, sulphapyridine, and the ordinary antipyretics were useless. Neither atebirin nor hexamine had any effect on the course of the disease.

The main part of the treatment consisted in giving fluids with glucose *ad lib.*, and when the patient would not, or could not, take them by mouth they were supplemented by the rectal or intravenous route. By this method up to 5 or 6 litres could be given in 24 hours. When prostration was most severe a glucose-saline with 0.00025 g. of strophanthin intravenously resulted in marked improvement. When there was severe cerebral irritation lumbar puncture resulted in an amelioration of symptoms. In one case 50 c.cm. of serum from a convalescent case was injected intramuscularly. The patient improved considerably, but as he had had an intravenous saline and also a lumbar puncture the same day the improvement could not be attributed to any one factor. Cardiac stimulants were given by mouth during the febrile and early convalescent stages. Luminal and scopolamine-eucodal-ephedrine (omnophon-scopolamine) were effective in controlling the acute delirium and insomnia. Tepid sponging was most effective in relieving mental and physical distress. Oral hygiene and care of the skin were insisted on.

As can be seen, the essential part of the treatment consisted of good nursing.

The complications arising consisted of bed-sores, disk swelling (transient), lung abscess (fatal), partial atelectasis, persistent vertigo, persistent ulnar neuritis, and persistent hypertension.

Diagnosis

The problem of diagnosis is an urgent one during the initial phase and in the milder type of case in which there may be no rash. The differential diagnosis has to be made from, for example, influenza, bronchopneumonia, tonsillitis, acute nephritis, enteric fever, meningitis, acute abdomen, acute encephalitis.

Aids to diagnosis are: (1) Occupation. (2) Presence of lice. (3) Severe frontal headache and fever, with failure to respond to ordinary antipyretics. (4) Typical facies with heavy injected eyes. (5) Acute dyspnoea with disproportionate signs. (6) Absence of neck rigidity. (7) Blood picture: polycythaemia with leucocytosis in which the granules are coarser than normal (in enteric there is usually a relative lymphocytosis). (8) The rash, when and if it does appear, is more profuse than in enteric fever. (9) The Weil-Felix test is the deciding factor, and is seldom positive before the appearance of the rash.

Summary

The principal points of interest in this series of 21 cases are:

The occupational association of the "epidemic."

The occurrence of the rash on the face in 19% of cases.

The blood picture: the main features being: (a) the initial polycythaemia,* (b) the fall in haemoglobin and red cells after the appearance of the petechial rash, (c) the occurrence of ? Rickettsia bodies, (d) the coarseness of the granules in the polymorphs.

The close similarity between typhus fever and epidemic encephalitis both clinically and pathologically.

The urinary symptoms and findings.

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* Harries, E. H. R., and Mitman, M. (1940). *Clinical Practice in Infectious Diseases*, Livingstone, Edinburgh.