nutrition; of 14 cases admitted to hospital, all died.¹ Figures on the incidence and mortality of infective hepatitis in India Command during 1944 were collected by Lieut.-Col. Stuart McDonald.¹ These figures showed the usual difference between officers and other ranks. In addition they showed that the incidence of jaundice was five times as high in British troops as in Indian troops, but, on the other hand, the mortality was five times as great in the Indians as in the British. In the final issue British troops and Indian troops had an equal chance of dying of jaundice. There is some evidence that while malnutrition favours bacterial infection it antagonizes infection by viruses (Foster *et al.*, 1944). There was a good deal of anaemia and malnutrition among Indian troops.^{2,3} One cannot say whether the low incidence in Indians was due to nutritional factors or to previous exposure, but there is a strong suggestion that the relatively high death rate was due to malnutrition.

Discussion

A survey of the animal experiments leaves us in little doubt as to the importance of the lipotropic factors and the thio-amino-acids to the health of the liver. An excessive intake of fat will be harmful to the liver unless it is balanced by a corresponding increase in lipotropic factors, while a high-carbohydrate regimen helps by sparing the reserve stores of protein in the liver and providing easily available energy. Proteins supply the essential methyl and sulphydryl groups, but they may also contain harmful residues which are badly tolerated in acute and chronic liver disease. Milk proteins appear to be innocuous in this regard, whereas meat and meat extracts are harmful. Choline and lecithin are present in most animal and plant tissues, and the thio-amino-acids are particularly well represented in the proteins of milk.

The most important lipotropic factors are those which provide the labile methyl groups for the manufacture of phospholipins, without which fat transport comes to a standstill. Excess of fat in the liver leads to a gradual pressure atrophy of the cells and portal fibrosis, and it also accentuates the effect of the many toxic substances which are more soluble in fat than in water. Tropical cirrhosis and alcoholic cirrhosis of the liver in man appear to be due mainly to a deficient intake of lipotropic factors, but in both disorders a toxic factor is still suspected by many people.

The effects of a deficiency of protein sulphur are more subtle and profound. The sulphydryl groups are attached to the vital enzyme systems in the liver. Protein starvation depletes the liver of these sulphur-rich components, and if the process goes far enough the cell must die. Methionine and cystine are rapidly incorporated in the depleted liver to make good the deficiency. Chloroform and arsenicals disturb the enzyme systems, presumably by combining with or neutralizing the sulphydryl groups. The disturbance is reversible within the first three or four hours of administration of the poison, but after that methionine is no longer effective, and it is clear that viable liver cells are essential for the rapid uptake of methionine. Chloroform combines with the sulphydryl groups to form the non-toxic mercapturic acids. The action of arsenicals has been reviewed by Peters, Stocken, and Thompson (1945), who showed that they have a selective action upon the pyruvate enzyme system and that an essential sulphydryl component of the protein constituent of the system is attacked. As a result of their studies they introduced the dithiol compound

BAL, which prevents the toxic action of arsenic and some of the heavy metals if given before the administration of the poison and neutralizes it if the toxicity is not too long established.

Himsworth and Glynn (1944b) in their paper on toxipathic and trophopathic hepatitis have tried to integrate these data, and have suggested that in the final issue hepatic necrosis is always nutritional in origin, always due to a deficiency of essential factors. This deficiency may be primary, or it may be secondary to the increased metabolism, the swelling of the liver, and the disturbance of the circulation which result from infection or poisoning of the liver. The argument is an ingenious one, but it does not get us very far. The liver can be protected against poisons such as chloroform and arsenic by simple chemicals such as sodium thioglycollate and BAL, which act as rather specific antidotes, and it is unlikely that the results obtained with chemical poisons can be transferred without change to the action of biological toxins and viruses. In the latter conditions thio-amino-acids may act, if they act at all, by providing sulphydryl groups attached to the appropriate amino-acid residue for re-synthesis of essential sulphur proteins which have been inactivated, rather than by neutralizing the noxious agent.

[The second lecture, with a list of references, will appear in our next issue.]

OBSERVATIONS ON PLAGUE MENINGITIS

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Meningeal involvement in plague has occasionally been recorded, the earliest reports apparently being by the German Indian Plague Commission of 1897 and the Austrian Commission of the same year. These are cited by Meyer, Connor, Smyth, and Eddie (1937) in their review of most of the recorded cases of plague meningitis up to that year, while they discuss in detail their own case of "chronic relapsing latent meningeal plague" in California occurring in a patient whose illness began with an axillary bubo. Since then further cases have been reported, including one from Uganda by Burton and Hennessy (1940) of "subacute or chronic plague terminating in haematogenous meningeal infection," and four cases of plague meningitis complicating bubonic plague from South America by de Villafañe Lastra and Rodeiro (1942).

A particularly rare clinical form—primary plague meningitis—was reported from Dakar by Lafont, Lecomte, and Heckenroth (1915). Williams (1934) had a similar case in East Africa; and Lewillon, Devignat, and Schoetter (1940) reported still another from the Belgian Congo. These cases, like the one described in this paper (Case VIII), presented the common clinical features of meningitis with no bubo formation. In China Pollitzer (1946) has observed meningeal involvement in most recent outbreaks. In this connexion, therefore, it seems worth while to record eight cases of meningitis in a series of 203 cases of plague admitted to the General Hospital, Chuanchow, South China, during the years 1943–5.

Symptomatology

In all except one of our cases (No. VIII) meningeal involvement was a complication of pre-existing bubonic plague, symptoms appearing at the earliest on the ninth and at the latest on the seventeenth day of the disease. The clinical features closely resembled those of cerebrospinal fever or other acute meningitis. Headache, painful stiffness of the neck, and Kernig's sign appeared early and prominently. Special symptoms included convulsions (Cases III, VIII), cranial-nerve affections

¹ Unpublished reports to M.R.C. Jaundice Committee.

² Report on Investigations on Anaemia in the Indian Soldier from the Anaemia Investigation Team, G.H.Q., India, 1943–5; New Delhi, 1945.

³ Proceedings of the Central Command Conference on Anaemia, held at Agra on Nov. 20 and 21, 1944; Benares, 1945.

(IV, V), vestibulo-cerebellar symptoms (VII), deep coma (II), and vasomotor crisis (III). Case VIII, differing from the rest, presented as a pyrexial illness with signs of meningeal irritation, no buboes or other signs being found. There was a coincidental malarial infection. The clinical picture was that of primary plague meningitis.

On lumbar puncture the pressure of the cerebrospinal fluid was as a rule raised; the fluid was cloudy, and in some cases of a canary-yellow colour. Other changes resembled those of an acute suppurative meningitis: polymorphonuclear leucocytosis, increased protein, and disappearance of sugar. *Pasteurella pestis* was found in the cerebrospinal fluid in five cases by smear and/or culture. Examination of the blood revealed a marked polymorphonuclear leucocytosis with absence of eosinophil granulocytes. All the cases were fatal, development of internal hydrocephalus being the probable cause of death. The longest period of survival was 29 days from the onset of the disease.

Pathology

Post-mortem examination in one case (No. VIII) revealed the following:

Body wasted; no petechial or skin lesions.

Brain: Marked congestion; convolutions and sulci flattened; softening of all brain tissue. Thick canary-yellow fibrino-purulent exudate covering most of the external surface, especially the parietal and frontal lobes, temporal pole, Sylvian fissure (spreading along middle meningeal artery), base of brain (especially cisterna basalis) involving all the cranial nerves, roof of fourth ventricle (cisterna magna), and the inferior, posterior, and superior surfaces of the cerebellum in the midline. Ventricles, especially the lateral ventricles, greatly dilated, with thinning of overlying brain tissue, containing a considerable quantity of yellow slightly turbid fluid—i.e., marked degree of internal hydrocephalus. Spinal Cord: Marked congestion; fibrino-purulent exudate less pronounced, but very thick in cauda equina region, matting together cord and nerve roots into a jelly-like mass (cf. "dry" lumbar puncture).

Glands: Cervical, axillary, inguinal—reddish-brown on section, congested, not enlarged. Spleen: Enlarged soft "septic" spleen; diffuent dark-red jam-like cut surface. Liver: Soft, slightly congested; noticeable cloudy swelling. Heart: Patchy congestion of epicardium; cloudy swelling of myocardium; fibrinous exudate adherent to contact margins of cusps of mitral valve (fibrinous endocarditis). Lungs: Pink, float in water; pleural surfaces smooth, shiny, patchy congestion; section revealed general congestion; no consolidation or other pneumonic signs. Kidneys: Pale; cloudy swelling of cortex; congestion of medulla. Suprarenal Glands: Pale cortex; moderately distinct pigment zone; congested medulla. Testis, Epididymis (both sides): Marked congestion; large clear hydrocele on right, small hydrocele on left. Alimentary Canal: Outwardly normal; not specifically examined. Pancreas, Thymus: Pale, apparently normal.

The presence of pericardial, pleural, and peritoneal fluids was unfortunately not looked for. In smears from the spleen numerous *Past. pestis* were found. Only a few organisms were discovered in the meningeal exudate, while smears from the liver, blood, and fibrinous exudate on the cardiac valve were negative for *Past. pestis*.

Diagnosis

The clinical diagnosis of meningitis occurring as a complication of bubonic plague ("secondary plague meningitis") presented little difficulty. Cases in which *Past. pestis* was not found in the cerebrospinal fluid (V, VI, VII) were confusing, with the possibility in our minds of the meningeal process being allergic in nature, from initial serum administration. In contrast, the other findings in the cerebrospinal fluid, especially the absence of sugar, pointed almost certainly to acute infection with pathogenic organisms, these presumably being *Past. pestis*. But the whole morbid process in these cases so closely resembled that found generally in the series that there was little reason to doubt their plague nature. Case VIII was not suspected of being plague until culture of the cerebrospinal fluid proved the presence of *Past. pestis*.

Treatment

Bubonic Plague.—The mainstay in many cases in 1944 and most cases in 1945 was oral sulphathiazole. The total amount given to each patient was usually over 50 g. Anti-plague serum was given in most cases in 1945—40 ml. intravenously on each

of the first five successive days. Other treatment was mainly symptomatic.

Plague Meningitis.—With the onset of meningitis sulphathiazole was restarted if it had already been stopped. Anti-plague serum was injected intrathecally in most cases, but it was suspended or withheld in some others (III, IV, VI) where doubt existed at the time as to the nature of the morbid process. Daily lumbar puncture for drainage of the sub-arachnoid space was the rule, while cisternal puncture was performed in some instances if the former was unsatisfactory.

Discussion, with Special Reference to Pathogenesis

The thick fibrino-purulent exudate found over the brain and spinal cord during the necropsy on Case VIII may be presumed to be present in the other cases as well. A similar exudate and distribution were found by Meyer *et al.* (1937) in their case, but the lateral ventricles were involved while the spinal cord was free. Other similarities included the presence of internal hydrocephalus, the enlargement of the spleen, and the negative findings in the lymph nodes. It is possible that such an exudate would tend to hold back the organisms in its meshes, making difficult their recovery on examination of the cerebrospinal fluid. Negative findings in smear and culture were noted on initial lumbar puncture by Meyer *et al.*, and also in another case reported by Rivoalen and Montagne (cited by Meyer *et al.*). It is regrettable that no cultures could be made in two of our cases (V, VII) where the smear was negative or doubtful. In Case VII, while no typical plague bacilli were found in the smear, organisms having the appearance of Gram-negative diplococci were present. The possibility of mixed infection with meningococcus or of a secondary invasion of the meninges by this or other member of the *Neisseria* has to be taken into consideration, but such assumptions are not very likely. It is more probable that the organisms seen in this instance were atypical plague bacilli appearing in the "coccoid" form.

The pathogenesis of our own and other cases of primary plague meningitis is difficult to explain. That infection may be due not to invasion through the blood stream but to drop-let infection as in cerebrospinal fever is altogether unlikely. Our patient had not been in contact with pneumonic plague. Conversely, supposing the disease to be a variety of primary septicaemic plague, this latter disease, in China at least, is a rapidly fatal one, so that there would be no time for localization in the meninges to take place even if that tendency were present.

Under such circumstances one is led to wonder whether these patients, supposed to be suffering from primary plague meningitis, have not in fact, at some stage of the disease, a bubo. According to Pollitzer (1945) there are really four varieties of bubonic plague: (1) *pestis minor*; (2) well-marked bubonic infection not leading to secondary septicaemia; (3) bubonic affection followed by secondary septicaemia; and (4) a form characterized by most serious general (septicaemia) symptoms combined with but slight affection of the lymph glands, which obviously have early failed in their attempt to hold back the invading organisms. One can conceive of the gland process being overlooked in this last variety (which incidentally represents a transition stage to primary septicaemic plague), especially if, as happened in our case, the patients are not under close observation throughout the course of the illness; in which circumstances, should meningitis develop, the clinical presentation of primary meningitis is obtained.

Factors which may have influenced the development of meningitis in our cases may thus be tabulated:

Case No.	Age (years)	Sex	Localization of Buboes	Time of Appearance of Meningeal Process	Time of Death
I	4	M	Cervical	12th day of illness	12th day of illness
II	26	M	Axillary	9th " "	22nd " "
III	40	F	"	10th " "	22nd " "
IV	37	M	"	16th " "	19th " "
V	28	M	Inguinal	12th " "	14th " "
VI	16	M	"	17th " "	29th " "
VII	39	F	Epitrochlear and axillary	15th " "	17th " "
VIII	1/12	M	—	?	17th " "

So far as these figures go, males seem to be more susceptible; age appears to play no part. It should be noted in this connexion that bubonic plague in China is usually most frequent among young adults. Only two of seven patients with manifest bubonic plague had groin buboes, whereas this localization is present in at least 60% of plague sufferers in general. This is in keeping with the generally accepted view that inguinal bubonic plague is less dangerous than axillary or cervical forms.

The course of illness in all these patients was longer than is usual in plague, and symptoms of meningitis invariably appeared late in the disease. Bearing in mind that (1) the incidence of meningeal complications was much higher among our patients compared with that in other recent outbreaks in China, and (2) we were able to treat many of our patients more energetically than was possible elsewhere, we wonder whether our therapeutic measures did not facilitate meningeal involvement by prolonging the course of illness in those patients who would otherwise have died earlier. The accompanying table, showing the amount of "specific" drugs used in the treatment of plague during the years under review, supports this assumption.

Year:	1943	1944	1945
Total No. of plague cases	88	46	69
No. of cases of secondary plague meningitis:	1	2	4
Anti-plague serum used (ml.):			
Total (approx.)	920	1,530	6,330
Per patient	10	33	92
Sulphathiazole used (g.):			
Total (approx.)	—	390	2,250
Per patient	—	8	33
Sulphapyridine (I.M. suspension) used (g.):			
Total (approx.)	327	2	—
Per patient	4	—	—

NOTE.—Patients dying soon after admission received little or no specific treatment; this considerably lowers the figures for the average amount given per patient.

For the treatment of plague in general, including the prevention of meningeal complications, more effective means are called for. Wagle (1944) found sulphadiazine to be superior to sulphathiazole; our own recent experience agrees with this. Sodium sulphadiazine given parenterally should be still more effective during the initial stages of particularly severe infection. According to Pollitzer (1946), streptomycin is also a most promising new therapeutic agent. Whether and how far it will be advisable to combine these new methods of treatment with serum administration remains to be seen.

Finally, it should be stated that in Chuanchow the shortage of drugs was severe in 1943 and 1944, while the exigencies of wartime China made the clinical and pathological study of these cases obviously incomplete.

Case Reports

[The following is a key to the abbreviations used in the case notes below:—Aspn.: Aspiration of bubo, with examination of smear. C.: Culture. I.M., I.V., I.Th.: Intramuscular, intravenous, intrathecal routes. L.P.: Lumbar puncture, thecal drainage (cells: cells in C.S.F. per c.mm.; G.: globulin; S.: sugar). Serum: Anti-plague serum. Sulphath.: Sulphathiazole. Sulphap.: Sulphapyridine. Sulphanil.: Sulphanilamide. (These three drugs were given orally unless otherwise stated.) W.B.C.: White blood cells per c.mm. (N.: neutrophil granulocytes; E.: eosinophil granulocytes; B.: basophil granulocytes; L.: lymphocytes; M.: monocytes.)]

Case I: Primary Skin Plague; Cervical Bubonic Plague; Secondary Plague Meningitis

Male aged 4; seen 3/7/43, giving a history of one day's high fever, diarrhoea, tender swelling rt. side of neck. T. 103° F. (39.4° C.); vesicle with raised dusky areola in rt. parietal region; tender enlarged gland in rt. posterior triangle. Aspn., *Past. pestis* found ++. Parents refused treatment.

Patient admitted 13/7/43. T. 105.2° F. (40.7° C.), P. 140, R. 40. Toxic, restless; large fluctuant swelling with surrounding brawny oedema whole rt. side of neck. Blood: W.B.C. 25,500 (N. 83%, L. 14%, M. 1%). The bubo was incised and drained.

Course.—14/7/43: T. 105–106° F. (40.6–41.1° C.); neck rigidity ++; Kernig's sign ++; L.P. Smear of C.S.F.: *Past. pestis* found. Patient died shortly after.

Treatment.—150 ml. serum (? route), 4 g. sulphanil., 5–6 g. sulphap., all before admission. After admission 30 ml. serum I.M., 10 ml. I.Th.; sulphap., 0.5 g. I.M.

Case II: Axillary Bubonic Plague; Secondary Plague Meningitis

Male aged 26; admitted 12/6/45, with history of one day's high fever, delirium, painful swelling rt. axilla. T. 104.2° F. (40.1° C.), P. 118, R. 24; tender swollen gland rt. axilla. Aspn.: *Past. pestis* not found. Clinically, typical bubonic plague.

Course.—Bubo steadily enlarged, while general symptoms improved. 20/6/45: T. 104° F. (40° C.), P. 90, R. 24; severe headache; neck rigidity ++; Kernig's sign ++. L.P.: turbid yellow fluid; cells 530, G. +, S. —. Smear: Gram-negative bacillus (? *Past. pestis*) found (few). C. of C.S.F.: *Past. pestis* isolated. 21/6/45: W.B.C. 11,000 (N. 83%, L. 16%, M. 1%). 22/6/45: T. 100° F. (37.8° C.), P. 80: patient much improved; bubo subsided.

25/6/45: T. 103° F. (39.4° C.), P. 90; return of pyrexia. 27/6/45: T. 102.6° F. (39.2° C.), P. 90; severe headache; neck rigidity ++; Kernig's sign ++. 29/6/45: L.P. C.S.F.: G. +, S. —. Smear: organisms not found. Patient becoming comatose. 1/7/45: T. 97° F. (36.1° C.), P. 70, R. 20; deep coma; pupils dilated; corneal reflexes absent; pulse, good volume. Cisternal puncture: 50 ml. cloudy yellowish fluid; cells 280, G. +, S. —. Smear: N. predominate; organisms not found. Cisternal drainage repeated same day. 3/7/45: T. 99.8° F. (37.7° C.), P. 130, R. 30; patient died (pre-mortem T. 102° F.—38.9° C.).

Treatment.—Serum 200 ml. (180 ml. I.V., 20 ml. I.M.) first 5 days; onset of meningitis to death, 220 ml. (180 ml. I.Th., 40 ml. I.V.) Sulphath. 141 g.; sodium sulphath. I.M. 2 g.

Case III: Axillary Bubonic Plague; Secondary Plague Meningitis

Female aged 40; admitted 23/6/45, with history of 3 days' fever, pain in lt. axilla. T. 102° F. (38.9° C.), P. 108, R. 24; tender swollen gland lt. axilla. Aspn. not performed. Clinically, typical bubonic plague.

Course.—24/6/45: Another bubo rt. groin. 27/6/45: T. 100° F. (37.8° C.), P. 84, R. 20; general condition improved; buboes larger 30/6/45: T. 104° F. (40° C.), P. 100, R. 24; headache, clouded mentality; neck rigidity ++; Kernig's sign ++; buboes much regressed, non-tender. L.P.: cloudy fluid; cells 800, G. +, S. —. Smear: N. predominate, organisms not found. 2/7/45: T. 102° F. (38.9° C.), P. 96, R. 24. L.P. C.S.F.: S. —; C., no growth Blood: W.B.C. 16,300 (N. 91%, B. 1%, L. 8%).

10/7/45: Sudden attack of profuse sweating, flushing of face (T. 95° F. (35° C.), P. 80, R. 24). Blood: W.B.C. 6,000 (N. 80%, L. 20%). 11/7/45: Sudden onset of coma; epileptiform convulsions, prolonged and generalized, controlled with general anaesthetic, morphine, hyoscine. L.P.: canary-yellow fluid under pressure 12/7/45: T. 100° F. (37.8° C.), P. 124, R. 30; pulse weakening, marked conjunctival congestion. Patient died. Post-mortem cisternal puncture: C. of C.S.F., *Past. pestis* isolated.

Treatment.—Serum 320 ml. (40 ml. I.Th., 280 ml. I.V.) in first 10 days. Sulphath. 35 g. in first 5 days; 54 g. from 9th to 17th day Sulphath. suspension 8 g. I.M. between 6th and 7th days.

Case IV: Malaria; Axillary Bubonic Plague; Secondary Plague Meningitis

Male aged 37; admitted 25/6/45, with history of 3 days' chill, high fever; one day painful swelling lt. axilla. T. 104.2° F. (40.1° C.), P. 140; acute lt. axillary adenitis. Aspn.: *Past. pestis* found ++. Blood film: *Plasmodium vivax* found (few). Spleen enlarged.

Course.—2/7/45: T. 100° F. (37.8° C.), P. 84; general condition much improved; bubo very large; marked periaenitis. 5/7/45: Bubo softening. 8/7/45: T. 103° F. (39.4° C.), P. 96; bubo incised, drained. Blood: W.B.C. 26,400 (N. 93%, L. 7%). 10/7/45: T. 103° F., P. 100; patient wasted, drowsy, vomiting; facial palsy (no record which side). L.P.: opalescent fluid; cells 350, G. trace, S. —. Smear: N. predominate, organisms not found. C., *Past. pestis* isolated. 12/7/45: T. 103° F., P. 100; facial palsy disappeared, neck rigidity ++. 13/7/45: T. 100° F. (37.8° C.), P. 100; comatose, subsultus tendinum; incontinence of urine; neck rigidity ++; Kernig's sign ++. L.P.: cloudy yellow fluid. Smear: *Past. pestis* found ++. C., *Past. pestis* isolated. Blood: W.B.C. 17,000 (N. 91%, L. 9%). Patient died, with pre-mortem rise in T. and P.

Treatment.—Serum 200 ml.; sulphath. 127 g.; quinine bisulphate 153 gr. (10 g.).

Case V: Inguinal Bubonic Plague; Secondary Plague Meningitis

Male aged 28; admitted 10/7/44, with history of 4 days' high fever, painful swelling lt. groin. T. 105° F. (40.6° C.), P. 110, R. 40; small atypical vesicle lt. ankle; tender swollen gland in lt. groin. Aspn.: *Past. pestis* found (few).

Course.—16/7/44: T. 100° F. (37.8° C.), P. 80, R. 25; generally much improved; bubo dull red, indurated, non-tender. 20/7/44: T. 104° F. (40° C.), P. 100, R. 28; severe headache for 2 days;

frequent vomiting; sleepiness, dull mentality; neck rigidity +; Kernig's sign +; lt. external rectus palsy. Blood: W.B.C. 18,400 (N. 97%, L. 3%). L.P.: canary-yellow cloudy fluid released under high pressure; cells 5,060, G. +, S. —. Smear: N. predominate, no organisms found. Patient passed into coma, with weakening pulse, sluggish pupils, general flaccidity, and died.

Treatment.—Serum 200 ml. (195 ml. I.V., 5 ml. I.M.) first 6 days; after onset of meningitis, 10 ml. I.Th., 20 ml. I.V. Sulphath. 29 g. first 4 days; later 5 g.

Case VI: Inguinal Bubonic Plague; Secondary Plague Meningitis

Male aged 16; admitted 15/6/45, with history of 2 days' chill, fever, painful swelling rt. groin. T. 103° F. (39.4° C.), P. 120, R. 25; tender swollen rt. inguinal gland. Aspn.: *Past. pestis* found (few).

Course.—General condition gradually improved; bubo steadily enlarged. 24/6/45: T. 103° F., P. 90, R. 24; commencing suppuration in bubo. 27/6/45: T. 103° F., P. 90, R. 24; bubo incised, drained. 30/6/45: T. 102° F. (38.9° C.), P. 90, R. 24; headache, clouded mentality; neck rigidity +; Kernig's sign +. L.P.: cloudy fluid; cells 1,000, G. +, S. —. Smear: N. predominate, organisms not found. 1/7/45: Neck more rigid, with head retraction, opisthotonos; deafness.

2/7/45: Symptoms improved. L.P.: C.S.F. cloudy, yellow; S. —; C., no growth. Blood: W.B.C. 9,000 (N. 88%, L. 12%). 3/7/45: T. 98° F. (36.7° C.), P. 90, R. 24; further improvement. 5/7/45: T. 100° F. (37.8° C.), P. 100, R. 24. Patient insisted on leaving hospital, and died about a week later.

Treatment.—Serum 200 ml. I.V. in first 5 days; onset of meningitis onwards, 60 ml. I.Th., 20 ml. I.V. Sulphath. 52 g. in first 8 days; onset of meningitis onwards, 20 g.

Case VII: Epitrochlear and Axillary Bubonic Plague; Secondary Plague Meningitis

Female aged 39; admitted 28/7/44, with history of 2 days' high fever, painful swelling at lt. elbow and lt. axilla. T. 102.4° F. (39.1° C.), P. 104, R. 26; acute lt. epitrochlear and axillary adenitis with peradenitis. Epitrochlear gland aspn.: *Past. pestis* found +. Blood: W.B.C. 10,400 (N. 84%, L. 15%, M. 1%). Urine: moderate albuminuria, few pus cells.

Course.—Pyrexia maintained; buboes increased in size; oedema of whole limb down to fingers. 9/8/44: W.B.C. 16,900. 10/8/44: T. 103° F. (39.4° C.), P. 100, R. 30; buboes and oedema subsiding. Onset of painful stiff neck, headache, marked vertigo, relieved by keeping eyes shut, vomiting. Neck rigidity +; Kernig's sign +. Eyes: fine rotatory nystagmus on looking to lt., coarse jerking nystagmus on looking to rt. L.P.: clear fluid; cells 210, G. +, S. —. Smear: N. predominate; "Gram-negative diplococcus" (?) found. Urine: slight albuminuria. 12/8/44: Clouded mentality; irritability, nausea, severe vertigo, tinnitus; nystagmus pronounced, jerking, especially on lateral deviation; limbs flaccid; incoordination in finger-nose test on lt. L.P.: clear fluid; cells 500, G. +, S. —. Smear: N. predominate, no organisms found. Patient passed into coma and died.

Treatment.—Serum 200 ml. I.V. first 4 days. Sulphath. 37 g. 7 days beginning 31/7/44. Onset of meningitis: sulphath. 4 g., sulphap. 9 g., anti-meningococcal serum 20 ml. I.M.

Case VIII: Malaria; Primary Plague Meningitis

Male one month old; admitted 9/7/45, with history of 4 days' fever and slight convulsive movements. T. 104.4° F. (40.2° C.); irritable; fontanelle tense; slight neck rigidity; Kernig's sign equivocal. Blood: W.B.C. 17,000; film: *Plasmodium vivax* gametocytes found (few).

Course.—L.P. attempted many times without success. 12/7/45: T. 103° F. (39.4° C.); slight jaundice; neck rigidity +; Kernig's sign —. L.P.: few ml. turbid yellow fluid; cells 400, G. +, S. —. Smear: Gram-negative bacillus found (? *Past. pestis*). C.: *Past. pestis* isolated. 15/7/45: T. 99° F. (37.2° C.); head retraction; Kernig's sign +. 19/7/45: T. 100° F. (37.8° C.); pale, wasted; epileptiform convulsions, especially rt. face. 21/7/45: T. 101° F. (38.3° C.). L.P.: bead of pus at end of needle. Smear: Gram-negative bacillus found (? *Past. pestis*). (L.P. performed repeatedly from 12/7/45 onwards had only "dry" result.) Convulsions generalized, frequent; patient died 22/7/45.

Treatment.—Sulphap. 1.5 g. first 3 days, repeated last 2 days. Sulphath. 8.125 g., commencing 4th day, for 7 days. Serum 50 ml.

Summary

Eight cases of plague meningitis are described, occurring in a series of 203 cases of plague treated in South China during the years 1943–5.

The occurrence of a rare clinical form—primary plague meningitis—is recognized; one case is described and its pathogenesis discussed.

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"SULPHA-COMBINATION"—A NEW CHEMOTHERAPEUTIC PRINCIPLE

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The commonly used sulphonamides—sulphathiazole, sulphadiazine, and sulphamerazine—have on the whole the same effect when employed clinically. The two pyrimidine compounds, however, are less toxic than sulphathiazole, and are therefore better tolerated. From the therapeutic point of view sulphonamide treatment might be regarded as more or less perfect if it were not attended by the risk of damage to the blood and kidneys. Toxic effects on the blood are, however, extremely rare with the above-mentioned drugs. Renal complications are more common: they may have a toxic or allergic origin, but in most cases are due to a deposition of the sulphonamide compounds, or their acetyl derivatives, in the tubules from supersaturated solutions. This risk can be reduced by the introduction of acid-binding media and the maintenance of a high diuresis. With these precautions renal complications are rare, but the risk remains, and for this reason inadequate and ineffective doses are often given. Thus the importance of reducing concrement formation is evident.

Provided that the sulphonamides do not affect each other's solubility but dissolve independently, which is to be expected from the chemical point of view, the risk of concrement formation might be reduced if, for the attainment of a certain blood concentration or effect, not merely one compound but a mixture of several equivalent sulphonamides was employed. From the clinical standpoint it cannot make any difference if several compounds are used instead of one when all the drugs are equally effective. The risk of concrement formation will, however, be reduced in this case, since each drug in the mixture is present in a considerably lower degree of saturation than when a single compound is employed. This new therapeutic principle we have named the "sulpha-combination principle."

In cases where it is desired to increase the dose beyond the normal limits, resulting in higher blood concentration and better therapeutic outcome, the same principle can be applied. If in such cases a single compound is used the risk will be increased. On the other hand, when a mixture of several drugs is employed the risk will be reduced. The method has been used in a preliminary form (a mixture of equal parts of sulphathiazole and sulphadiazine) in Sweden for more than three years in the treatment of gonorrhoea (Hagerman, 1944; Herlitz, 1944; Werkö, 1945). In spite of the very high dosage (12 g. a day for four days) remarkably few renal complications occurred (Nilzén, 1946a).