of tuberculosis. It seems highly probable that occupational factors are also concerned to an important extent in the aetiology of bronchitis.

One of the general practitioners taking part in the present survey wrote: "I feel that the specialized fields of the profession have little conception of the actual work that is done by the general practitioners, and too much attention is paid to fields of medicine which the future general practitioner is rarely if ever called upon to practise."

The present survey does indeed suggest that the student who intends to become a general practitioner may spend a disproportionate amount of time in examining and studying relatively rare diseases. He would benefit from seeing more cases of minor illness than he can hope to find in a teaching hospital and from more opportunities of seeing

The following general practitioners, by their careful collection of data, made this survey possible: Drs. B. Droller, H. Droller, C. H. Foggitt, M. Jacob, R. B. Knowles, G. E. Tilsley, W. Toms, and E. Zadik. I wish to thank all of them for allowing me to use their records and for their suggestions with regard to the interpretation of the figures. The severe frosts and heavy snowfalls made the work particularly difficult during the winter week. I am indebted to Professor C. H. Stuart-Harris for helpful advice and criticism, and to Miss B. I. Richardson for valuable assistance in the analysis of the data.

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AFEBRILE CASES OF MELIOIDOSIS

BY

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Recovery from infection with *Pfeifferella whitmori* is rare, the death rate being about 95%, and cases of melioidosis with freedom from marked constitutional symptoms are rarer still. The case history of an afebrile patient observed in Malaya in September, 1941, is given below. He had a localized infection with *Pf. whitmori* in a cervical gland, but remained free from general symptoms. He was treated by aspiration of the gland abscess, and when this refilled he was apparently cured by treatment with sulphapyridine. His response to the drug was in keeping with the findings of investigators from 1943 onwards—of which a brief review is given. Reference is made to five other afebrile cases of melioidosis observed in South-East Asia. The *in vitro* effects on *Pf. whitmori* of newer antibiotics such as streptomycin, "polymyxin," and "chloromycetin" are also described and compared with penicillin.

Case History

A male Indian artisan aged 30 was admitted to hospital in, Kuala Lumpur during September, 1941, for treatment of quartan malaria. While in hospital a swelling of one of the cervical glands was noted. This was painful and tender, but was relieved somewhat by glycerin and ichthyol dressings. After receiving quinine treatment for his malaria he had no fever on the fifth, sixth, and seventh days and was discharged, at his own request. He returned to work, but one month later was readmitted to hospital because of further pain and swelling in the cervical gland, which by this time was fluctuating in the centre. He had no fever on readmission or during his six-weeks stay in hospital. The swelling was aspirated on the second day after readmission and thick mucoid pus was withdrawn. On culture the pus yielded a pure growth of *Pf. whitmori*.

A guinea-pig which was injected with 0.03 ml. of a peptone-water culture of the patient's organism died within sixty hours, the animal's skin showing intense oedema, with commencing haemorrhagic necrosis at the site of inoculation. When recovered from the pericardial fluid of the dead guinea-pig and cultured on glycerin agar the organism showed some intensification of its original rugose growth. This type of growth has been shown by Nicholls (1934) to be associated with the more virulent variant of *Pf. whitmori*—in distinction to the mucoid type.

Distribution of cases of bronchitis by sex and age group, compared with the notifications of pulmonary tuberculosis in Sheffield in 1947.

disease in its early stages. Some experience in the treatment of the chronic sick and of infirm old people in the home would also be of value to him. Suitably staffed health centres and home visiting from these centres might in the future be used with advantage for the demonstration of such cases to the medical student. In the health centres he could also learn to appreciate the opportunities for practising preventive medicine which occur in general practice.

Summary

The 4,656 consultations undertaken by eight general practitioners in one winter and one summer week are analysed by sex, age, and diagnosis.

Bronchitis was found to be the commonest condition in summer and in winter for which medical advice was sought, accounting for 11% of all cases.

The relation between the work done in general practice and the training of medical students is briefly considered.

Other cultural characteristics of the patient's bacillus agreed entirely with those described by Stanton and Fletcher (1932). The patient's serum agglutinated his own strain of *Pf. whitmori* to a titre of 1 in 680. A known *Pf. whitmori* serum agglutinated the patient's strain of *Pf. whitmori* to a titre of 1 in 880. He continued to remain constitutionally well and had no fever. The leucocyte picture also remained within normal limits. His cervical gland was reaspirated eleven days after admission and *Pf. whitmori* was again isolated. This re-isolated organism was fully investigated and guinea-pigs were again inoculated; all the bacteriological findings coincided with the first aspiration. These findings, together with the rapid death of the guinea-pigs—the males showing the "Straus reaction"—left little doubt concerning the virulence of the strain of *Pf. whitmori* which was infecting the patient.

The abscess in the cervical gland remained with the skin unbroken, but it tended to refill after aspiration and to show central softening. About four weeks after readmission the abscess seemed about to burst through the skin. A third aspiration was considered, but it was decided to try a course of sulphapyridine instead. Over a period of six days the number of 0.5-g. tablets given daily by mouth was 6, 4, 0, 4, 4, and 6, treatment being interrupted on the third day because the patient, who was feeling quite well, absented himself to attend to some private affairs.

Two days after the course of sulphapyridine treatment had been completed the swelling in the gland subsided. Attempts to reaspirate resulted in the withdrawal of a little blood-stained fluid which on culture did not show the presence of *Pf. whitmori*. A few days later the patient left the hospital.

He was lost sight of during the years following the Japanese occupation of Malaya, but in May, 1948, he was traced and interviewed. He stated that he had remained constitutionally well, and on examination no evidence of ill-health was found. The former swelling in the cervical gland had disappeared completely and there were no external signs. The only remnant of the former *Pf. whitmori* infection was some slight palpable thickening in the periglandular tissues, probably due to adhesions.

Notes on Similar Cases

The absence of constitutional symptoms in the above case was a remarkable feature. Stanton and Fletcher (1932) cite 83 recorded cases of human infection with *Pf. whitmori* and state that "melioidosis is a very deadly disease and, of known cases, only two have recovered." Full details of these two recovered cases are then given. One is described as being "desperately ill with fever, cough, and chest pains," and the second case is recorded as having "high swinging temperature and bronchopneumonia. . . . For several weeks he lay in a drowsy typhoid condition." In their first case the fever lasted for three months and in the second case for four months.

Cases of melioidosis without marked constitutional symptoms have been recorded. Peck and Zwanenburg (1947) reported the case of an Indian havildar who developed a midline abscess of the neck above the suprasternal notch from which *Pf. whitmori* was obtained in pure culture. The patient had no constitutional symptoms, fever, or glandular enlargement. His serum agglutinated the organism to a titre of 1 in 80. The leucocyte count, both total and differential, showed no unusual features. Hasle and Nguyen-Duc-Khoi (1937) described the case of a Chinese with a suppurative adenitis of the neck from which *Pf. whitmori* was cultured. The patient had no general symptoms or fever. Recovery followed the formation of a fistula.

Other cases of melioidosis remarkable for the absence of constitutional symptoms have occurred in Java, but the infection has been confined to superficial skin lesions. De Moor, Soekarnen, and van der Walle (1932) investigated the chronic skin lesion of the buttock and thigh of an elderly Javanese. This had been present for about

eighteen months and was painless. The skin was thickened and was beset with nodules containing pus from which *Pf. whitmori* was repeatedly isolated. Their illustrations show the absence of ulceration. The blood picture was normal and there was no fever. The patient's serum agglutinated his strain of *Pf. whitmori* to a titre of 1 in 600.

Again, Sudibyo (1938) described superficial serpiginous ulcers occurring in two elderly Javanese. His illustrations show healed scarred centres of the ulcers bordered by raised nodular spreading edges. Sudibyo was able to isolate *Pf. whitmori* in practically pure culture from all over the lesions, and found that serum agglutination tests against the patients' organisms were positive at titres of 1 in 400 and 1 in 800. His two patients had no loss of appetite, no emaciation, and no fever.

Treatment of Melioidosis with Sulphonamides

The majority of the cases of melioidosis occurring in South-East Asia have been investigated during the two decades preceding the Japanese occupation from 1941 to 1945, but sulphonamide compounds were available only towards the end of the second decade. Again, melioidosis is seldom diagnosed at the bedside; more often diagnosis is made in the laboratory or post-mortem room, although Stanton and Fletcher (1932) estimate that 200 cases occur each year in Malaya. Thus the factors cited above would account for the scarcity of literature on cases and their treatment with sulphonamides.

Records of treatment of melioidosis with sulphonamides begin with those of Grant and Barwell (1943) and of Mayer and Finlayson (1944), and sulphadiazine treatment is suggested by *in vitro* tests carried out by Mirick and colleagues (1946); but the clinical response to sulphonamides is more extensively investigated in an admirable paper by Harries and co-workers (1948), who conclude that the most effective treatment for the disease is 2 g. of sulphamezathine four-hourly together with local penicillin treatment, where this is possible, combined with autogenous vaccine therapy.

These findings and our case of the Indian artisan described above, who responded in 1941 to sulphapyridine treatment by reduction of his abscess and disappearance of *Pf. whitmori* from the pus, prompted us to investigate further the *in vitro* effects of the sulphonamide compounds on strains of *Pf. whitmori*, but unfortunately all our Malayan strains were lost during the Japanese occupation. Also, this investigation had to be postponed until recently, and the only strain of *Pf. whitmori* available was one isolated by Major Harries in Burma and received by courtesy of the Bland-Sutton Institute for Pathology through Dr. F. R. Selbie and Dr. R. Lewthwaite. The response of this strain to *in vitro* tests against various sulphonamide compounds is shown in the accompanying table. Fleming's "gutter technique" as described by Mackie and McCartney (1946) was used.

Drug 1 in 5,000	Inhibition Zone in mm. Occurring with Dilutions of the Bacterial Inoculum		
	1 in 10	1 in 100	1 in 500
Sulphanilamide ..	Nil	Nil	Nil
Sulphapyridine ..	"	"	2
Sulphathiazole ..	"	11	18
Soluthiazole ..	"	Nil	12
Sulphamezathine ..	"	"	Nil
Sulphadiazine ..	10	12	17

Allowing for possible differences in the diffusibility of the drugs within the agar medium, these *in vitro* results suggest the further clinical use of sulphathiazole or the somewhat less toxic sulphadiazine in cases of melioidosis. (Mirick *et al.* (1946), when using 15 µg. per ml. of sulphadiazine,

observed complete inhibition of growth in *Pf. whitmori* broth cultures.)

Effect of Antibiotics on *Pf. Whitmori*

Harries *et al.* (1948), in addition to using suphamezathine for melioidosis, treated a lung cavity locally by direct injection of 6 ml. of saline containing 300,000 units of penicillin (i.e., 50,000 units per ml.), having found previously by *in vitro* experiments that at least 650 units of penicillin per ml. were necessary to inhibit the growth of *Pf. whitmori*. Miller and co-workers (1948) state that penicillin at concentrations of 1,000 units per ml. has no immediate effect on *Pf. whitmori*, and they use penicillin in such concentrations for three hours at 37° C. to get rid of unwanted organisms when culturing material for isolation of *Pf. whitmori*.

The use of penicillin in melioidosis is thus confined to local treatment, using concentrations many times higher than could be obtained in the blood stream. Some newer antibiotics such as chloromycetin, streptomycin, and polymyxin, however, have a wide range of activity on Gram-negative organisms, and two are known to be capable of attaining a fairly high concentration in the blood stream; for example, chloromycetin can be initiated at 40 to 80 µg. per ml. and maintained at 20 µg. per ml. when given by mouth (Woodward *et al.*, 1948), and streptomycin, by injection, between 10 and 20 µg. per ml. (Merck, 1947). We therefore considered it of some importance to undertake *in vitro* tests with these newer antibiotics against *Pf. whitmori*.

There is considerable literature on streptomycin and its properties, but less information about chloromycetin and polymyxin. We therefore give a few notes.

Chloromycetin, together with its production, purification, and antibacterial effects, both *in vitro* and in experimental animals, is fully described by Smith and co-workers (1948); the first general announcement on this antibiotic was made by Ehrlich and his colleagues (1947). This latter paper was summarized in a leading article in the *British Medical Journal* of Aug. 28, 1948 (p. 428). Chloromycetin is an antibiotic substance obtained during the growth in culture of a variety of *Streptomyces* isolated from soil in Venezuela. An identical substance has been obtained from a variety isolated from compost in Illinois (Carter *et al.*, 1948).

As an antibiotic, chloromycetin is unique in so far as it contains both nitrogen and non-ionic chlorine and in being well absorbed when taken by mouth. It is a crystalline substance and is comparatively stable under conditions of widely varying temperature and pH. (We have found no loss of potency in chloromycetin-saline solutions kept in the refrigerator for three months.) It also has a low degree of toxicity in experimental animals.

Chloromycetin inhibits the growth of rickettsiae and of various Gram-negative organisms, including *Brucella*, *Bacterium coli*, *Shigella paradysenteriae*, and Friedländer's bacillus, the last two being conveniently used as test organisms. We have found it markedly inhibitive *in vitro* to 15 Malayan strains of *Salmonella typhi*, to the "Inaba" and "Ogawa" strains of *Vibrio cholerae*, and to *Haemophilus influenzae* (a Malayan penicillin-insensitive strain), using concentrations of chloromycetin obtainable in the blood when given by mouth—that is, 40 to 60 µg. per ml. (Supplies of chloromycetin for such tests were received by courtesy of Dr. J. E. Smadel, who also provided samples of polymyxin, these two antibiotics being at present produced in experimental quantities by Parke, Davis and Co. and Lederle Laboratories respectively.)

Polymyxin is an antibiotic elaborated during the fermentation of various media by certain strains of *Bacillus*

polymyxa (Benedict and Langlykke, 1947; Stansly and colleagues, 1947). It is said to inhibit a wide variety of Gram-negative and Gram-positive bacteria. *Brucella* and *Bact. coli* are used as test organisms in assaying the amounts of polymyxin in solutions. This antibiotic appears to be a basic polypeptide (Florey, 1948—personal communication), and we have found that it inhibits Malayan strains of *Salm. typhi* but is less active against *Salm. paratyphi A* and *Salm. paratyphi B* when used in the same relatively small concentrations (1 to 5 µg. per ml.).

The technique of testing was the ring-cup method, varying concentrations of the four antibiotics being placed in glass cylinders 15 mm. in diameter sealed on to the surface of culture plates seeded with *Pf. whitmori*. The results of repeated tests were as follows: streptomycin and polymyxin in concentrations up to 1,400 µg. per ml. failed to inhibit the growth of *Pf. whitmori*; penicillin up to 700 units (525 µg.) per ml. showed a maximum inhibition zone of 28 mm.* Chloromycetin, however, in concentrations clinically obtainable in the blood (60 µg. per ml.) gave an inhibition ring of 24 mm. Similar amounts of chloromycetin tested against 15 Malayan strains of *Salm. typhi* gave inhibition zones of 29 to 31 mm.

It is concluded that in cases of melioidosis chloromycetin should be of some benefit when used alone or combined with one of the sulphonamide compounds—sulphamezathine, sulphathiazole, or sulphadiazine.

Comment

It was of particular interest to note the inhibitory effect on *Pf. whitmori* of chloromycetin, which is produced by one species of streptomycetes, as against the complete lack of effect from streptomycin, which is elaborated by another—i.e., *Streptomyces griseus*. But the streptomycetes, which are likely to receive further attention as a source of antibiotics, present puzzling features; and Carter *et al.* (1948) have pointed out that the two varieties of streptomycetes of widely differing origin (Venezuela and Illinois) which produce the lowly toxic chloromycetin are very closely related to *Streptomyces lavendulae*, from which the more toxic streptothricin is obtained.

The complexity of this subject, however, has been stressed by Waksman (1947), who mentions the widely differing chemical nature of antibiotic substances—for example, lipid-like bodies (pyocyanase), pigments (pyocyanin), polypeptides (gramicidin), sulphur-bearing compounds (penicillin), and quinones and organic bases (streptomycin)—that is, they have no resemblance except for their general origin.

Summary

The case history of a patient with melioidosis is given. He remained afebrile throughout weeks of observation. His gland abscess resolved rapidly under treatment with sulphapyridine, and during the subsequent six years he had no recurrence.

Sulphamezathine, sulphathiazole, and sulphadiazine have also been used for treating melioidosis (abscesses in bone, skin, and lung). Sulphadiazine is one of the less toxic compounds, and it showed relatively a more marked inhibition of *Pf. whitmori* in a series of *in vitro* tests.

The antibiotics streptomycin and polymyxin were found to have no inhibitory effect on *Pf. whitmori*. Penicillin, except in very high concentrations unobtainable in the blood stream, also had no effect.

Chloromycetin, a new antibiotic obtained from a streptomycetes, inhibited the growth of *Pf. whitmori* at concentrations obtainable in the blood when the antibiotic is given by mouth, and its clinical use, either alone or in combination with sulphonamides, is therefore suggested.

*But only 2.5 units of penicillin per ml. are obtainable in the blood after an intramuscular injection of 250,000 units (Dyke, 1947).

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elbow, but some weak flexion was possible at the left elbow. Dorsi-flexion of both wrists was very weak. There was marked wasting of both deltoid and biceps muscles and of the intrinsic muscles of both hands. In contrast to this weakness of flexion, extension at the elbows was quite strong. In the lower limbs the power was good in all muscle groups, but there was some sensory ataxia, as shown by the heel-to-knee test, especially on the left. The triceps jerk was active on both sides, but the biceps and supinator jerks were absent. The abdominal reflexes were very active. The knee jerks were present on both sides, but the ankle jerks were absent. Plantar response was indeterminate. There was no loss of appreciation of pin-prick or light touch, and some hyperaesthesia was present in the lower limbs. The sense of position was normal and Romberg's sign was positive. Sensibility to deep pain was much diminished, but the vibration sense was normal. There was no astereognosis. At first some difficulty was experienced in micturition, but this soon disappeared.

Investigations.—The cerebrospinal fluid was normal in appearance, with no increased tension; cell count, 2 per c.mm.; albumin, 70 mg. per 100 ml.; globulin, 10 mg. per 100 ml.; colloidal benzoin reaction, 0000022200000000; Kahn test and Wassermann reactions, negative.

Radiograph showing bony changes

Medical Memoranda

A Case of Charcot's Disease of the Cervical Spine

The following case of Charcot's joint disease of the cervical spine was recently under treatment at the C.M.S. Hospital, Old Cairo.

CASE HISTORY

The patient, an Egyptian, first came to the hospital in 1944 complaining of difficulty in walking. A Kahn test of cerebrospinal fluid and blood was negative, but the C.S.F. contained 70 mg. of albumin per 100 ml. and 76 cells per c.mm., and clinically the case appeared to be one of tabes dorsalis, a rare disease in Egypt. This diagnosis was confirmed by Colonel Spillane, neurological specialist, who kindly examined him.

During the next year the patient had almost continuous treatment with N.A.B. and bismuth and improved considerably until he became able to walk two to three miles without undue fatigue. He remained well until April, 1947, when he began to feel "pins and needles" in the right arm and noticed some wasting of the muscles of his right hand; there was also clicking in the neck on forward and backward movement of the head. He did not suffer any serious disability, however, and continued his work as a clerk until October, 1947, when he quite suddenly had an attack of retention of urine, which had to be relieved by catheter. From this time onwards he had difficulty in micturition on and off, and gradual loss of power in the right arm and hand until Feb. 6, 1948, when he suddenly became unable to raise the arms at the shoulders or to flex them at the elbows, and there was a burning pain in the region of the right shoulder, made worse by bending the head backwards. He had also noticed girdle pains.

On Feb. 13 he was admitted to hospital. On examination he was seen to be a thin, ill-looking man, aged 55. He was alert mentally, he answered questions intelligently, and his speech was normal. He gave a history of having had syphilis at the age of 18, and stated that a Kahn test on the blood serum, done a few weeks previously, had proved mildly positive. He held his head somewhat flexed. Flexion and extension of the neck were fairly free, but there was marked clicking on bending the head backwards, and this movement caused a severe pain to radiate down the right arm. Examination revealed the following signs:

A left internal squint, stated by the patient to have been present since he was 18 years of age. Very small regular pupils, inactive to light and reacting sluggishly to accommodation. The cranial nerves, apart from the 6th, were normal. There was complete loss of power of abduction of the arms at the shoulders and of flexion at the right

The Kahn blood reaction was also negative. Radiographs showed marked bony changes (see fig.). I am indebted to Dr. Nessem Abu Saif, professor of radiology at Kasr-el-Aini Hospital, for the following report: "There is deformity, partial collapse, and backward subluxation of C3, 4, and 5, with bony condensation of an ivory appearance and irregular new bone formation, especially on the anterior aspects of these vertebrae. The intervertebral disks are preserved. This bizarre deformity is typical of Charcot's joint disease."

Treatment.—The patient was put on antisyphilitic treatment and received 500,000 units of penicillin daily for 10 days; 10 injections of N.A.B., given twice weekly, the dose rising from 0.15 g. to 0.6 g., then 0.6 g. weekly for 10 weeks; and "bismostab" 1 ml. weekly for the last five weeks. During the whole period he was taking by mouth liq. hyd. perchlor. $\frac{1}{4}$ dr. (1.75 ml.) and pot. iod. 10 gr. (0.65 g.) three times a day.

Under this treatment there has been definite clinical improvement. Micturition is normal. He can walk better and there has been a return of power to a limited extent of flexion at the elbow. He can now bring his hand to his mouth. The shoulder muscles, however, are still very weak, and the small muscles of the hand on both sides are very wasted. The sensation of pain in the right shoulder, of which he complained, is much less, but is felt occasionally. It is considered unlikely that any more improvement can be expected.

The interest of the case lies in the fact, first, that while the clinical picture is atypical, and there are only very mild changes in the C.S.F. to indicate an old syphilitic infection, the changes in the cervical spine are typical of Charcot's disease of the spine; secondly, that the cervical spine is very rarely affected by tabetic arthropathy, the lumbar region being the commonest site.

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The Ministry of Health has issued a new list of treatment centres for venereal diseases. It covers the United Kingdom and Eire, and gives the names of the centres, the towns where they are situated, and the times when patients are seen.