

SUMMARY

(1) Hitherto tsutsugamushi and the rural form of tropical typhus (scrub typhus) have been thought to be separate diseases in virtue of the presence of a primary dermal lesion and attendant bubo in tsutsugamushi and their supposed absence in rural typhus.

(2) Their clinical picture, pathology, ætiology, and epidemiology are described, and the results of experiments are recorded. From consideration of these, especially of cross-immunity tests between strains of the two clinical types, the conclusion is drawn that one and the same virus may cause various gradations of dermal lesion, and that tsutsugamushi and rural typhus are identical. Rural typhus not being a disease sui generis, this term should be discarded and the older term "tsutsugamushi" retained.

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Sir Stanley Woodwark has been appointed senior physician to the Westminster Hospital in succession to Dr. Hildred Carlill. Dr. Carlill has been a member of the honorary staff of the hospital for 22 years.

ARRANGEMENTS have been made to provide Scotland with a bacteriological service for the duration of the war based on the central laboratories established at the four Scottish universities and under the general supervision of the professors of bacteriology. In addition, subsidiary laboratories have been set up at various centres. Most of these are existing institutions, but three are, in effect, new. Provision has also been made for setting up emergency laboratories in remote districts in the event of serious local outbreaks of infectious disease.

TREATMENT OF PNEUMONIA WITH M. & B. 693

WITH AND WITHOUT SPECIFIC SERUM

BY

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JUST over a year ago, when favourable results of the treatment of pneumonia with M. & B. 693 had been published, it was decided to conduct a fully controlled investigation of cases of lobar pneumonia admitted to Crumpsall Hospital, Manchester, making full use of X-ray and laboratory facilities. All pneumonia cases have been included in the scheme irrespective of the condition on admission or the stage of the disease. A strict rota of the cases was kept, and these were selected as follows. The first case was treated as a control, and every subsequent third case was also treated as a control. Of the remaining cases every alternate type-I case was treated with M. & B. 693 alone and every other type-I case (other than controls) with the drug plus specific serum. Similarly, apart from controls, every alternate type-II case was treated with M. & B. 693 alone and every other type-II case with the drug plus specific serum. All other types, except controls, were treated with M. & B. 693 alone. The patients were nursed in special wards, and all received the same nursing attention and the ordinary pneumonia routine: Antiphlogistine, expectorant mixtures, sedatives, and stimulants.

INVESTIGATION

The following laboratory investigations were undertaken on admission and before treatment was begun:

(1) *Blood-cultures* were taken immediately on admission to hospital, before any treatment was given, and thereafter daily as long as the pyrexia persisted. During laboratory hours blood-cultures were taken into Liquoid broth, saponin-citrate broth, and Wright's broth. Outside laboratory hours 5 c.cm. of blood was introduced into 50 c.cm. of Wright's broth and immediately incubated.

(2) *Typing of pneumococci* from sputum, with the direct slide Neufeld reaction with Lederle's sera. Sputa which did not give an immediate typing were cultured on blood-agar and in Wright's broth, but mouse inoculation was not used.

(3) *Wassermann reaction*.

(4) *Leucocyte counts* on admission and thereafter daily as far as possible while the temperature persisted.

(5) *Quantitative estimation of serum bilirubin* was done in view of the recognised unfavourable association of jaundice and pneumonia, but later it was discontinued, having been estimated in 66 per cent. of the cases.

TREATMENT

The dosage of M. & B. 693 was that recommended by Evans and Gaisford (1938)—namely, 2 g. immediately by mouth, followed by 1 g. four-hourly. This was continued for twenty-four hours after the temperature had fallen to normal and was restarted

if the temperature subsequently rose. If a patient was admitted during the night, the typing of the sputum was postponed until the next morning. Thus, some patients requiring serum plus M. & B. 693 had to wait for some hours before receiving the specific serum, although the drug had been given on admission. The dosage of serum was as follows: patients under forty years old admitted within ninety-six hours of the onset received 50,000 units intravenously, and all other patients 100,000 units. No additional doses of serum were given. No sensitivity tests were performed. The serum was warmed and given slowly. Adrenaline was given whenever necessary to counteract untoward symptoms, such as rigor and dyspnoea. The chest was radiographed as soon as was convenient.

COMPARISON OF CASES TREATED WITH M. & B. 693 AND CONTROLS

In pneumonia the case-mortality is unfavourably influenced by increasing age. On comparing the ages of the patients treated with M. & B. 693 with those of the controls it was a little disappointing to find that, in the males, age favoured the patients treated with M. & B. 693, for 59 per cent. were under forty, whereas only 47 per cent. of the controls were under that age. In the females the age-distribution of the controls was similar to that of those treated with M. & B. 693, and the results are therefore more strictly comparable. In the males we had 55 controls with 15 deaths and 84 cases treated with M. & B. 693 with 8 deaths. Age is not the real determining factor in this low case-mortality, for there were 12 deaths in the 29 controls aged forty or over, whereas in the patients treated with M. & B. 693 there were 36 aged forty or over with only 6 deaths. It is clear that not only has the case-mortality of the whole group treated with M. & B. 693 been reduced, but also the reduction is maintained in the patients aged forty or over. In the females there were 23 controls with 6 deaths, whereas there were 35 cases treated with M. & B. 693 with no deaths. This is far more striking than in the males, and it is to be remembered that the ages are comparable. On combining the figures for males and for females (table I) one finds that there were 78 controls with 21 deaths. On looking up a series of 870 cases of lobar pneumonia treated in this hospital in 1935-37, before the introduction of M. & B. 693, we found that the case-mortality among 624 males was 33.8 per cent. and among 246 females 21 per cent., that for the 870 cases being 30 per cent. Our figures were 119 cases treated with M. & B. 693 with 8 deaths, a case-mortality of 6.7 per cent. This compares closely with the rates given in other papers.

It is interesting to compare the case-mortality in the patients aged fifty-five or over. There were 21 controls with 9 deaths and 24 cases treated with M. & B. 693 with 4 deaths, which is a higher case-mortality than for those under fifty-five; but it is an improvement. It is well known that type-III pneumonias tend to affect elderly persons, and this age factor, together with the nature of the infecting organism, leads to a high case-mortality, given by various authors as 50-60 per cent. In our control series there were 14 type-III cases with 6 deaths, whereas among the patients treated with M. & B. 693 there were 13 cases with 2 deaths. We were particularly impressed by the favourable prognosis with treatment with M. & B. 693 in type-I pneumonias, of which there were 34 cases with no deaths.

All writers on this subject have been struck by the rapid movement which follows treatment with M. & B. 693. We, the visiting medical staff, saw these patients generally on the day after their admission, when

they had already been treated with M. & B. 693 for about twelve to twenty-four hours, and we were so struck by the difference in appearance between the treated and the control cases that at first we thought that chance was favouring the treated. We realised later that we were already observing the results of the treatment. In most of the cases treated with M. & B. 693 the temperature fell rapidly to normal in twenty-four to thirty-six hours, and it was unusual to find any patient without a decided fall in temperature twenty-four hours after treatment had been started. On some occasions a secondary rise followed cessation of treatment with the drug, but a second course usually brought the temperature back to normal, except where a complication was developing.

We agree with other writers, notably Evans and Gaisford (1938) and Anderson et al. (1939), that resolution of the lung was not in any degree hastened by this treatment; in fact, we feel that in some cases it may have been delayed. Anderson et al. (1939) also commented on the fact that their patients were not so bright after treatment with M. & B. 693 as with a natural crisis, and this has been our experience with some patients, although many others were, we thought, as well after their "forced crisis" as after a natural crisis. A general improvement always accompanies the fall in temperature and pulse-rate. Rusty sputum often continued for a couple of days after the temperature had fallen to normal.

TOXIC EFFECTS AND COMPLICATIONS

The commonly recognised disadvantages of treatment with M. & B. 693 are nausea, vomiting, cyanosis, and rarely agranulocytosis. In this series nausea was rather more common among the females than among the males. Vomiting caused the treatment to be stopped in 3 cases, but all other patients with nausea were coaxed by the ward sister to continue this treatment. In no case was cyanosis sufficiently pronounced to lead to cessation of treatment, although 1 case of moderate sulphæmoglobinæmia and 1 of methæmoglobinæmia were observed. Both rapidly improved when the drug was temporarily suspended. Barnett et al. (1939) observed methæmoglobinæmia in most of their intensely treated cases; so we appear to have been fortunate. Although agranulocytosis has been recorded often with the

TABLE I—COMPARISON OF RESULTS IN PNEUMONIA TREATED WITH M. & B. 693 AND IN CONTROLS

Pneumo-coccus type	Age	Males and females			
		Controls		Treated with M. & B. 693	
		Cases	Deaths	Cases	Deaths
I	Under 40	12	2	25	—
	Over 40	15	5	9	—
II	Under 40	8	2	10	1
	Over 40	5	2	5	—
III	Under 40	5	1	1	—
	Over 40	9	5	12	2
Other types	Under 40	14	1	34	1
	Over 40	10	3	23	4
Total	All ages	78	21	119	8

use of M. & B. 693, in our cases there did not appear to be any significant change in the behaviour of the leucocytes as between the cases treated with M. & B. 693 and the controls. There was no suggestion of agranulocytosis.

A short period of delirium seemed a little more common in the patients treated with M. & B. 693 than in the controls. We were probably fortunate also in that in only 1 case was a rash noticed, but Thompson (1939) mentions that the rash starts about the eighth to twelfth day of treatment, and it is possible that we may have missed a few slight rashes. In the 78 controls there were 4 empyemata, 4 sterile effusions, and 1 case of infective endocarditis and meningitis. In the 119 cases treated with M. & B. 693 there were 2 empyemata, 1 sterile effusion, 1 abscess of lung, and 1 case of gangrenous lung. Gaisford (1939) noted an increase in the number of sterile effusions and thought that such patients would have developed empyemata had they not received M. & B. 693.

RESULTS WITH M. & B. 693 ALONE AND COMBINED WITH SERUM IN INFECTIONS OF TYPES I AND II

Experimental evidence (Fleming 1938) suggests that the action of M. & B. 693 in pneumonia would be enhanced if the immunity of the patient to the infecting pneumococcus were increased simultaneously. We felt that it was necessary to investigate the combined action of the drug and of type-specific serum. We treated with M. & B. 693 plus serum 37 patients with pneumonia of either type I or type II. Of 25 with type I 2 died, compared with 7 deaths out of 27 con-

TABLE II—COMPARISON OF RESULTS IN TYPE-I AND TYPE-II PNEUMONIAS TREATED WITH M. & B. 693 ALONE AND WITH THE DRUG PLUS SERUM AND IN CONTROLS

Pneumo-coccus type	Age	Males and females					
		Controls		Treated with—			
				M. & B. 693		M. & B. 693 plus serum	
		Cases	Deaths	Cases	Deaths	Cases	Deaths
I	Under 40	12	2	25	—	11	1
	Over 40	15	5	9	—	14	1
II	Under 40	8	2	10	1	5	—
	Over 40	5	2	5	—	7	1
Total	All ages	40	11	49	1	37	3

trols and no deaths out of 34 cases treated with M. & B. 693 alone. Of 12 with type II treated with drug and serum 1 died, compared with 4 deaths out of 13 controls and 1 death out of 15 cases treated with the drug alone. The combined case-mortality for types I and II was as follows: controls, 11 deaths in 40 cases; drug alone, 1 death in 49 cases; and drug plus serum, 3 deaths in 37 cases (table II). The ages of the patients treated with drug plus serum correspond closely with those of our controls. The combination of drug and type-specific serum gives the same immediate improvement as the drug alone. It has, however, the disadvantage of serum reactions, which developed in a quarter of the cases, usually taking the form of a rigor. The reaction generally develops within an hour of receiving serum.

Of 49 patients with either type-I or type-II pneumonia treated with M. & B. 693 alone, in 14, after a fall to normal, there was a secondary rise of temperature to over 100° F., which was apparently due to the following complications: recurrence in another lobe (2); delayed resolution (3); lung abscess (1); gangrene of lung (1); tonsillitis during convalescence (1); and drug fever (1). In 5 there was no obvious cause. A similar secondary pyrexia developed in 6 of the 37 cases treated with M. & B. 693 plus serum, and in all of these the secondary rise of temperature began while

the patients were still receiving the drug. In 4 of the 6 cases the pyrexia was due to obvious causes: empyema (2), abscess of lung (1), and spread of infection to another lobe (1).

TABLE III—DEATHS IN PNEUMONIA WITH POSITIVE BLOOD-CULTURE

Pneumo-coccus type	Controls		Treated with—			
			M. & B. 693		M. & B. 693 plus serum	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
I	7	4	7	—	9	—
II	4	2	3	1	1	—
III	3	3	1	1	—	—
Other types	1	—	5	2	—	—
All types	15	9	16	4	10	—

It is generally considered that a positive blood-culture tends to indicate a severe form of the disease; therefore the blood-culture results (table III) deserve special notice. In the series as a whole there were 15 positive blood-cultures in the controls, with 9 deaths, whereas with M. & B. 693 there were 16 positive blood-cultures with 4 deaths. In the type-I and type-II pneumonias treated with the drug alone there was 1 death in 10 cases with a positive blood-culture, and no deaths in 10 cases with a positive blood-culture treated with the drug plus serum.

It is recognised that great caution is needed in drawing conclusions from these small figures, but the lowered case-mortality in the "treated" cases with positive blood-cultures is worthy of note. It was found in this series, as elsewhere, that repeated positive blood-cultures indicated a bad prognosis. In all our cases treated with M. & B. 693 alone or with the drug plus serum the blood-culture became negative in twenty-four hours except in patients who died or developed a complication.

LABORATORY AND POST-MORTEM FINDINGS

Typing of pneumococci.—The pneumococcus was isolated and typed from the sputum or the blood in 200 out of 234 cases (86 per cent.). In 1 case a pneumococcus was isolated but could not be typed with any of the thirty-one sera available. The failure to isolate the pneumococcus in 14 per cent. of the series, chiefly in the females, was due to the fact that in almost all of these the sputa were poor and watery. Two sputa yielded an almost pure culture of *Hæmophilus influenzae*, and these cases were considered to be influenzal pneumonias and excluded from the series. The percentage of successful typings compares favourably with those obtained in other published series. The distribution of types (table IV) does not call for special comment. Two cases, both controls, are of interest from an immunological point of view. In one of them type VII was isolated from the sputum, and fourteen days later, when another lobe was affected, type I was found. In the other case the sputum yielded a type V on first examination, and twelve days later, when the disease had spread to the other lung, a type IX was present.

Blood-cultures.—Wright's broth, a predigested veal broth, has been found to be a successful medium for the growth of pneumococci. Growth when present always appeared within eighteen hours and was usually luxuriant.

Post-mortem findings.—Necropsies were performed in 20 cases. In each the diagnosis of lobar pneumonia

was confirmed; in 2 cases there was purulent pericarditis, in 1 there were endocarditis and meningitis, and in 2 there were small hæmorrhages into the suprarenal cortex.

TABLE IV—INCIDENCE OF THE PNEUMOCOCCUS TYPES FOUND

Type of pneumococcus	Males under and over 40		Females under and over 40		Total	Type of pneumococcus	Males under and over 40		Females under and over 40		Total
	Under	Over	Under	Over			Under	Over	Under	Over	
I	38	31	10	7	86	XV	1	1	—	—	2
II	17	13	6	4	40	XVI	—	—	—	1	1
III	3	12	3	9	27	XVII	—	—	1	—	1
IV	2	—	—	1	3	XVIII	—	2	3	—	5
V	2	3	2	1	8	XIX	—	1	—	—	1
VII	1	2	2	—	5	XX	1	—	—	—	1
VIII	3	4	2	1	10	XXIII	1	—	1	—	2
IX	1	—	1	—	2	XXV	1	—	—	—	1
X	—	2	—	—	2	XXVII	—	1	—	—	1
XIII	—	1	—	—	1	No types	14	7	9	4	34
XIV	—	1	—	—	1	Total	85	81	40	28	234

SUMMARY

We have described a series of 234 cases of lobar pneumonia, of which 78 were controls with 21 deaths; 119 were treated with M. & B. 693 alone, giving a case-mortality of 6.7 per cent.; and 37 cases of either type I or type II treated with M. & B. 693 plus specific serum, with 3 deaths.

The case-mortality in patients aged fifty-five or over was more than halved by treatment with M. & B. 693, and a similar reduction was noted in the smaller number of type-III cases. We were impressed by the favourable outlook in type-I and type-II pneumonias treated with M. & B. 693 alone, 1 death taking place in 49 cases. The case-mortality in type-I and type-II infections was slightly better in the cases treated with M. & B. 693 alone than in those treated with the drug plus serum, but in view of the comparatively small numbers it is inadvisable to draw conclusions from this.

Of 15 control patients with positive blood-cultures (any type of pneumococcus) 9 died, whereas of 16 patients who had positive blood-cultures and were treated with M. & B. 693 only 4 died. A striking feature was the considerably reduced case-mortality in type-I and type-II infections with positive blood-cultures, as compared with similar control cases, in patients treated with "693" alone and with "693" plus serum (see table III).

Complications were fewer in the cases treated with M. & B. 693 and in those given the drug plus serum than in the controls.

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THE HYPERVENTILATION SYNDROME

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IN those illnesses in which psychological and somatic factors are interrelated each may aggravate the other until cause and effect become obscure. A condition of this type became very prevalent in the services during the last war and is likely to increase again in this. At that time many persons under varying war stresses complained of palpitation and breathlessness which were not related to any demonstrable organic lesion of the heart. This condition was often complicated by obvious psychological abnormalities or by disabling symptoms, such as fainting, dizziness and headaches. At the time the syndrome was known as "disordered action of the heart" (D.A.H.), but this term so obviously reflected only one aspect that it later fell into disrepute. Similar cases seen in peace-time have been reclassified in different terms. When anxiety precipitates the condition, or when during the attack the patient shows obvious psychological abnormalities, the case is regarded as one of "anxiety neurosis" or of "hysteria." If, on the other hand, a severe autonomic disturbance dominates the picture, the diagnoses of "neurocirculatory asthenia" and of "effort syndrome," whenever exertion aggravates the condition, have been used.

Unfortunately perhaps, differing labels have now been attached to cases which, having many features in common, should have been kept together. There are, for instance, the constantly recurring complaints by many of these patients of such symptoms as headache, dizziness, fainting attacks, and feelings of general bodily weakness which are said to follow the attacks of palpitation. Hitherto, for lack of an adequate explanation of their occurrence, except in terms of a psychological aetiology, and because of the frequent presence of hysterical behaviour during the attack, they have been dismissed as "functional." But there is now reason to believe that disorders of breathing may sometimes play a part in their production. Many patients complain of a sense of constriction in the chest or of difficulty in getting their breath when the palpitation comes on. To relieve these feelings they sigh excessively or breathe rapidly. As a result they consciously or unconsciously hyperventilate; in the severer cases this produces a definite gaseous alkalosis.

Various workers have recently emphasised that hyperventilation produces, apart from tetany, a wide variety of symptoms which are identical with those complained of by these patients. Early symptoms, such as frontal or occipital headache, dizziness, fainting attacks, and light feeling in the head, are common. A far-away feeling without loss of consciousness, general weakness, or extreme fatigue also occurs. Tetany is a well-known complication of hyperventilation, but the release of hysterical behaviour in an hysterical subject and the production of mental confusion as sequelæ to over-breathing are less generally recognised (Sargant and Fraser 1938a). Although there may be other causes for these symptoms, in those cases in which spontaneous hyperventilation is responsible they can be generally reproduced by voluntary hyperventilation and