SULPHAPYRIDINE (M & B 693) AND PNEUMOCOCCAL INFECTIONS*

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The purpose of this paper is to review briefly the main facts relating to sulphapyridine, and particularly to deal with its use in combating pneumococcal infections. Although only eighteen months have elapsed since Lionel Whitby¹ first published his discovery of the value of sulphapyridine, yet in this short time a large number of papers concerning it have been published in many countries. It is now established that sulphapyridine is a most effective agent against infections by pneumococci of all types.¹⁻⁶ In its action against the pneumococcus it represents an outstanding medical advance, for it is superior to specific antiserum and unapproached at present by any other sulphonamide compound. The chief evidence for these statements has been provided by the case series⁷⁻²⁶ summarized in Table I, reporting

TABLE I.—Mortality of Cases of Lobar Pneumonia Treated with Sulphapyridine

	Total of Treated Cases	Deaths
<i>Africa:</i>		
Agranat <i>et al.</i> ⁷	98	8
Anderson and Dowdeswell ⁸	50	1
<i>Canada:</i>		
Graham <i>et al.</i> ⁹	50	3
Meakins and Hanson ¹⁰	30	1
<i>Denmark:</i>		
Alsted ¹¹	28	1
Eldahl ¹²	54	4
Hjorth ¹³	28	0
Lundsteen and Mogensen ¹⁴	39	2
<i>Finland:</i>		
Saltzman ¹⁵	100	6
<i>Great Britain:</i>		
Anderson <i>et al.</i> ¹⁶	70	6
Banks ¹⁷	30	0
Dyke and Reid ¹⁸	8	0
Evans and Gaisford ¹⁹⁻²¹	627	34
Marriott ²²	25	0
<i>Norway:</i>		
Römcke and Vogt ²³	254	11
<i>U.S.A.:</i>		
Janney-Smith and Needles ²⁴	50	4
Pepper <i>et al.</i> ^{25, 90, 91}	400	28
Williams and Morgan ²⁶	50	1
Totals	1,991	110
Average mortality, 5.5 per cent.		

These series contain patients of all ages, but no series entirely composed of children is included. In the series of Agranat *et al.* I have excluded their native miner groups as being not comparable with the other series. In these miners so excluded there were only two deaths in 172 cases.

results in lobar pneumonia from various parts of the world. It has uniformly been found that the average gross mortality of cases treated with sulphapyridine is about 5 to 8 per cent., as compared with 20 to 30 per cent. in the former experience of the hospitals concerned or in control series.

In regard to infections by organisms other than the pneumococcus, the value of sulphapyridine relative to other sulphonamide compounds awaits final definition. Present opinion^{1-6, 27} suggests that: (1) it is about equal, or slightly superior, to sulphanilamide against haemolytic streptococci, meningococci,²⁸⁻³³ Friedländer's bacillus, *Clostridium welchii*, and *B. coli*³⁴; (2) it is the most effective of the sulphonamides against the gonococcus³⁵⁻⁴⁴; (3) it is the least ineffective against *Staphylococcus aureus*^{22, 45-47} and *Streptococcus viridans*^{4, 22, 48}; (4) it may be of value against *B. typhosus*,⁴⁹ *B. pestis*,⁵⁰ and

B. influenzae.⁵¹ At the present time sulphapyridine is undoubtedly the drug of choice for empirical use in any fever of uncertain causation probably due to bacterial infection.²⁷

Pharmacology of Sulphapyridine

Sulphapyridine is chemically 2-sulphanilyl-aminopyridine. It is a white powder, almost insoluble in water. It is, however, fairly rapidly absorbed⁵²⁻⁵⁴; the maximum blood concentration from a single dose is usually reached in about four hours. Thereafter the concentration slowly falls to zero in approximately forty-eight hours. In the blood the free form of the drug is slowly converted to the conjugated or acetylated form; the former is said to be therapeutically active, and the latter, which is even more insoluble, is said to be inactive. In twelve hours about half the sulphapyridine from a single dose is acetylated. The rate of acetylation appears to vary in different persons; it has been suggested that it may bear relation to the metabolic rate.⁵⁵ The kidneys are almost the sole channels of sulphapyridine excretion, and the free and acetylated forms are found in the urine in various amounts.⁵⁶ In the body fluids, such as cerebrospinal fluid, pleural fluid, or pus, the concentration of sulphapyridine is usually between 50 per cent. and 100 per cent. that of the blood at the same moment.^{5, 9, 30, 54, 56} The ready distribution of sulphapyridine between the blood and the body fluids renders intrathecal or intrapleural administration unnecessary.

How sulphapyridine produces its remarkable effects is still unknown.^{57, 58} Both *in vitro* and *in vivo* there is a lag period of six hours during which organisms multiply in spite of contact with the drug. Then the organisms increasingly die off^{1, 2, 57} from what appears to be direct action of the drug upon them.^{1, 2, 59, 60} It may be that the effect of the drug is the production of bacteriostasis, from starvation of the organisms due to inhibition of their enzymes,^{57, 67} and that the body does the actual killing of the invaders.⁶¹⁻⁶⁵ However, there does not seem as a rule to be any evidence of exceptional stimulation of the body's defence mechanisms,⁵⁷ nor indeed of interference with them.⁶⁶

Pneumococcal Infections of the Respiratory System

As before stated, the outstanding value of sulphapyridine against the pneumococcus was first convincingly demonstrated clinically in relation to lobar pneumonia. This demonstration was achieved by Evans and Gaisford¹⁹ following upon Whitby's discovery of the potency of sulphapyridine in the treatment of pneumococcal infections in mice.¹ The well-defined clinical course of lobar pneumonia renders recognition of the beneficial effect of the drug easy. Many confirmatory series⁷⁻²⁶ and striking individual cases^{59, 69-74} have been published. The principal points now established concerning the sulphapyridine treatment of lobar pneumonia are:

1. The average reduction in gross mortality is such that three patients out of four who would formerly have died may now live.

2. Sulphapyridine is particularly valuable in severe cases with bacteraemia.

3. The drug is as effective in the elderly as in the young. In persons of 50 and upwards gross mortality in the past^{20, 23, 75, 76} has usually been accepted as approaching in percentage figures the figures of the subjects' ages. In Table II are extracted from the main case series,⁷⁻²⁶ which give the requisite data, the mortality of all patients aged 50 or more treated with sulphapyridine. The average mortality is seen to be 16.6 per cent.

* Partly based on a paper prepared for the Annual Meeting of the Danish Medical Society to have been held on September 24, 1939, at Aarhus.

TABLE II.—*Mortality of Cases of Lobar Pneumonia, aged 50 or More, Treated with Sulphapyridine*

	Total of Treated Cases	Deaths
Agranat <i>et al.</i> ⁷	15	1
Graham <i>et al.</i> ⁹	15	3
Meakins and Hanson ¹⁰	6	1
Alsted ¹¹	5	0
Eldahl ¹²	14	3
Hjorth ¹³	8	0
Lundsteen and Mogensen ¹⁴	14	2
Anderson <i>et al.</i> ¹⁶	9	3
Dyke and Reid ¹⁸	2	0
Evans and Gaisford ¹⁹⁻²¹	86	21
Marriott ²²	9	0
Röncke and Vogt ²³	61	8
Pepper <i>et al.</i> ²⁵	124	19
Totals	368	61

Average mortality, 16.6 per cent.

4. Sulphapyridine appears to be very effective against pneumococci of all types.

5. Within twenty-four to thirty-six hours of sulphapyridine being begun, irrespective of the day of the disease, the temperature falls by rapid lysis and there is usually remarkable improvement in the patient's general condition. Uneventful recovery in most cases ensues, but the local condition in the lung does not seem to undergo resolution any faster.

6. The incidence of empyema appears lessened, but clear pleural effusions are commoner. Evans and Gaisford²⁰ regard the latter as empyemata aborted by sulphapyridine, since in their experience the total of empyemata plus clear effusions is the same as used to obtain for empyema alone.

7. In cases of lobar pneumonia treated with sulphapyridine specific agglutinins against pneumococci develop between the fifth and twelfth days of the disease as they do in untreated cases⁶⁶; their appearance is unaffected by the drop in temperature caused by the drug. This development of agglutinins by the body does not occur in cases effectively treated with specific anti-pneumococcus serum.⁶⁶

The excellent results in lobar pneumonia are paralleled in the less clearly defined pneumococcal chest infections. Results in bronchitis, bronchopneumonia,^{11 19 23 56} and post-operative pneumonia⁶⁸ are good.

Pneumococcal Meningitis and Peritonitis

Pneumococcal meningitis has in the past been generally considered to be invariably fatal. Sulphapyridine permits revision of the hopeless prognosis, though the condition is still to be regarded as very serious. A number of cures⁷⁷⁻⁸⁴ and a number of failures^{81 85-87} have been reported. In meningococcal meningitis sulphapyridine, like sulphanilamide, is extraordinarily successful. Not infrequently in practice the exact bacteriological diagnosis in a case of meningitis is not immediately obtainable. In all such cases, where the infecting organism is in doubt, sulphapyridine should be given⁸¹ because not only is it the best agent against the pneumococcus, but it is as good as or better than sulphanilamide against meningococcal, streptococcal, and staphylococcal infections.

The prognosis in pneumococcal peritonitis is also likely to be very much changed for the better by sulphapyridine. Barnett and his associates⁵⁶ record three cases of pneumococcal peritonitis in children treated with sulphapyridine (one received serum too), and MacColl⁸⁸ has also published a similar case. All four recovered. Chemotherapy,¹²⁰ combined with the other recently introduced measures of gastro-duodenal suction drainage and continuous parenteral fluid administration, will enormously reduce the mortality in all forms of peritonitis.

Toxic Effects of Sulphapyridine

Dangerous toxic effects from sulphapyridine in therapeutic doses are rare.⁷⁻²⁶ Gaisford, Evans, and White-

law,⁸⁹ in more than 1,000 cases, have not met with any serious complications due to the drug. Pepper and his associates^{25 90 91} have administered sulphapyridine to 500 patients without a death attributable to it.

Nausea or vomiting occurs in about half of all patients receiving sulphapyridine; the incidence is said to be less in children. In addition many patients feel depressed and languid and may have headache. These effects are unpleasant but not of serious significance. The vomiting appears most likely to be due to a central effect rather than to local gastro-irritation as was at first supposed. Cyanosis is less often seen with sulphanilamide. According to Campbell and Morgan⁹² the cyanosis due to sulphapyridine is from methaemoglobinaemia and not from sulphaemoglobinaemia as with sulphanilamide. Methaemoglobinaemia does not persist as long as sulphaemoglobinaemia. If considered to be dangerous, because affecting already anoxic patients, it may be quickly abolished by the administration of methylene-blue.^{9 86 93} This should very seldom be necessary.

Not strictly a toxic effect, but an effect consequent upon its insolubility, is the formation in the urine of jagged crystals or small calculi of acetylated sulphapyridine. The subject has been studied in laboratory animals.^{93 94} In patients receiving sulphapyridine red cells are found in the urine in a small proportion of cases. Rarely, gross haematuria, ureteric or bladder pain, and anuria may occur.^{9 12 24 25 95 98} Such effects have, however, been inconspicuous in the experience of observers of large series.⁷⁻²⁶ There is evidence that they are commoner in children, perhaps because of relatively larger dosage.

When sulphapyridine administration is continued beyond five days, which should not as a rule be necessary, drug fever and rashes^{99 100} become unpleasant and not infrequent features. The rarer but very dangerous manifestation of granulocytopenia may also occur.¹⁰¹⁻¹¹⁰ With drug fever the temperature may rise as high as 104° F. The rashes^{99 100} usually resemble the rashes of measles or German measles; occasionally they are urticarial or scarlatiniform. Differential diagnosis from the mentioned specific fevers may be difficult.

Dosage and Practical Points in Administration

It is necessary in treating pneumonia to aim at securing and maintaining a blood concentration of sulphapyridine of not less than 4 mg. per 100 c.cm. In adults this level is usually achieved by a dosage of 2 grammes, followed in four hours by 2 grammes, followed by 1 gramme four-hourly.² What sulphapyridine does it does quickly, but at the same time too early discontinuance may lead to relapse from spread of infection. Hence, after the patient has received a total of 18 grammes on the above scheme of dosage (that is, after two and a half days) the dose should be reduced to 0.5 gramme four-hourly for twenty-four hours and then to 0.5 gramme eight-hourly for thirty-two hours—a total of 23 grammes administered on a decreasing scale during five days.

For children the dosage should be in proportion to the body weight,¹⁹ but it is desirable to increase the dose relative to that of adults by 50 per cent. to secure adequate blood concentrations of sulphapyridine. Wilson and his collaborators¹¹¹ advise doses equivalent to twice those usually given to adults.

The estimation of sulphapyridine in the blood and body fluids is possible by relatively simple methods,^{6 54 112-114} and checking of the blood level is important if there is any doubt in regard to the attainment of an adequate

concentration. This may be of particular importance if there is much vomiting. The same dosage should be used whether the infection is mild or severe.³ The tablets should be administered crushed and suspended in water, milk, or fruit juices. In general the course of treatment should be neither less nor more than five days. Less may result in incomplete cure. More brings the risk of complications,² and particularly the grave danger of granulocytopenia; if continuance is deemed desirable, then close watch should be kept on the skin and temperature, and blood counts should be made on alternate days.

In all cases the ordinary general measures of medical and surgical treatment should be carried out. An adequate intake of fluid is of the greatest importance to avoid urinary crystallization.⁹⁷ Five pints (2,850 c.cm.) per twenty-four hours should be taken by an adult. The urine must be measured, and an output of less than 50 oz. (1,400 c.cm.) per twenty-four hours regarded as unsatisfactory. The urine should be examined daily for blood. Liberal administration of glucose is desirable not only because of its nutritional value but because it helps to prevent nausea and vomiting. In anoxic cases oxygen administration should not be delayed; Whitehead and Carter⁷¹ suggest that it may abolish nausea and vomiting.

Sulphapyridine is not a substitute for surgery. Collections of pus must be drained in accordance with established general principles. Vomiting is not an indication for stopping or reducing sulphapyridine. If administration is persisted with it is often found that the vomiting decreases or ceases.^{2,9} If an adequate blood concentration of sulphapyridine is not being sustained, then it may be necessary to pursue administration by the rectal introduction⁵⁶ or intramuscular^{84, 89, 117} or intravenous¹¹⁸ injection of the soluble sodium salt.^{3, 115, 116} This salt is now put up in ampoules containing 1 gramme in 3 c.cm. This amount may be given intramuscularly four-hourly. It should not be given subcutaneously because its high alkalinity causes severe pain and may induce sloughing. The technique of intravenous administration is not fully worked out; there would seem to be considerable possibilities in continuous-drip administration of dilute solutions. It might be possible to achieve rapidly and regulate accurately optimum blood levels.

When sulphapyridine is being administered it may induce photosensitivity in the patient. Hence exposure to strong natural or artificial sunlight must be avoided; such exposure may result in severe dermatitis.¹⁰¹ During the time the drug is being given it is very important that other drugs with a tendency to produce granulocytopenia, such as amidopyrine, should be avoided. In conditions such as gonorrhoea sulphapyridine may sometimes unavoidably be administered to ambulant patients. Like the other sulphonamide drugs, it may produce impairment of judgment of speed and distance.¹¹⁹ Patients taking it should be prohibited from driving cars or flying until two days after the last dose.

There is no antagonism between sulphapyridine and any form of associated treatment.³ In particular there is no reason why it should not be used in conjunction with serum^{121, 122} or vaccines⁶¹⁻⁶⁴ in pneumonia or other conditions.

Summary

The main facts relating to sulphapyridine are reviewed and special attention is paid to its use in pneumococcal infections.

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REFERENCES

- ¹ Whitby, L. E. H. (1938). *Lancet*, 1, 1210.
- ² — (1938). *Ibid.*, 2, 1095.
- ³ — (1939). *Proc. roy. Soc. Med.*, 32, 1063.
- ⁴ Macgrath, B. G., and Vollum, R. L. (1938). *British Medical Journal*, 2, 985.
- ⁵ Long, P. H. (1939). *J. Amer. med. Ass.*, 112, 538.
- ⁶ Report of Council on Pharmacy and Chemistry (1939). *Ibid.*, 112, 1830.
- ⁷ Agranat, A. L., Dreosti, A. O., and Ordman, D. (1939). *Lancet*, 1, 309.
- ⁸ Anderson, T. F., and Dowdeswell, R. M. (1939). *Ibid.*, 1, 252.
- ⁹ Graham, D., Warner, W. P., Dauphinee, J. A., and Dickson, R. C. (1939). *Canad. med. Ass. J.*, 40, 325.
- ¹⁰ Meakins, J. C., and Hanson, F. R. (1939). *Ibid.*, 40, 333.
- ¹¹ Alsted, G. (1939). *Ugeskr. Laeg.*, 101, 474, 480.
- ¹² Eldahl, A. (1939). *Nordisk Med.*, 2, 1807.
- ¹³ Hjorth, P. (1939). *Ugeskr. Laeg.*, 101, 477.
- ¹⁴ Lundsteen, E., and Mogensen, E. (1939). *Nordisk Med.*, 2, 1303.
- ¹⁵ Saltzman, F. (1939). *Ibid.*, 2, 1894.
- ¹⁶ Anderson, T., Cooper, E. D., Cairns, J. G., and Brown, D. R. (1939). *Lancet*, 2, 776.
- ¹⁷ Banks, H. S. (1939). *Proc. roy. Soc. Med.*, 32, 1076.
- ¹⁸ Dyke, S. C., and Reid, G. C. K. (1938). *Lancet*, 2, 1157.
- ¹⁹ Evans, G. M., and Gaisford, W. F. (1938). *Ibid.*, 2, 14.
- ²⁰ Gaisford, W. F. (1939). *Proc. roy. Soc. Med.*, 32, 1070.
- ²¹ — (1939). *Lancet*, 2, 372.
- ²² Marriott, H. L. Unpublished cases.
- ²³ Römcke, O., and Vogt, E. (1939). *Nordisk Med.*, 2, 1898.
- ²⁴ Janney-Smith, F., and Needles, R. J. (1939). *Amer. J. med. Sci.*, 198, 19.
- ²⁵ Pepper, D. S., Flippin, H. F., Schwartz, L., and Lockwood, J. S. (1939). *Ibid.*, 198, 22.
- ²⁶ Williams, R. H., and Morgan, H. J. (1939). *Southern med. J.*, 32, 601.
- ²⁷ Buttle, G. A. H. (1939). *British Medical Journal*, 2, 269.
- ²⁸ Dimson, S. B. (1938). *Lancet*, 2, 424.
- ²⁹ Hobson, F. G., and MacQuaide, D. H. G. (1938). *Ibid.*, 2, 1213.
- ³⁰ Banks, H. S. (1939). *Ibid.*, 2, 372.
- ³¹ Usher Somers, R. B. (1939). *Ibid.*, 1, 921.
- ³² Bryant, J., and Fairman, H. D. (1939). *Ibid.*, 1, 923.
- ³³ Osborn, W. H. (1939). *British Medical Journal*, 1, 1281.
- ³⁴ Melton, G., and Beck, A. (1939). *Lancet*, 1, 867.
- ³⁵ Lloyd, V. E., Erskine, D., and Johnson, A. G. (1938). *Ibid.*, 2, 1160.
- ³⁶ Prebble, E. E. (1938). *Ibid.*, 2, 1163.
- ³⁷ McGregor-Robertson, J. G. (1938). *Ibid.*, 2, 1463.
- ³⁸ Bowie, F. J. T. (1939). *Ibid.*, 2, 372.
- ³⁹ Marinkovitch, R. (1939). *British Medical Journal*, 1, 317.
- ⁴⁰ Brown, D. K. (1939). *Ibid.*, 1, 320.
- ⁴¹ Bowie, F. J. T., Anderson, T. E., Dawson, A., and Mackay, J. F. (1939). *Ibid.*, 1, 711.
- ⁴² Palazzoli, M. (1939). *Presse méd.*, 47, 766.
- ⁴³ Sommerville, J. (1939). *British Medical Journal*, 1, 1228.
- ⁴⁴ Reyn, A. (1939). *Ugeskr. Laeg.*, 101, 466.
- ⁴⁵ O'Brien, E. J., and McCarthy, C. J. (1938). *Lancet*, 2, 1232.
- ⁴⁶ Maxwell, J. (1938). *Ibid.*, 2, 1233.
- ⁴⁷ Wade, H. J. (1939). *Ibid.*, 1, 756.
- ⁴⁸ Ellis, G. R. (1938). *Ibid.*, 2, 1521.
- ⁴⁹ Harries, E. H. R., Swyer, R., and Thompson, N. (1939). *Ibid.*, 1, 1321.
- ⁵⁰ Schütze, H. (1939). *Ibid.*, 1, 266.
- ⁵¹ Roche, E. H., and Caughey, J. E. (1939). *Ibid.*, 2, 635.
- ⁵² Baines, E. J., and Wien, R. (1939). *Quart. J. Pharm. and Pharmacol.*, 12, 4.
- ⁵³ Schmidt, L. H., and Hughes, H. (1939). *Proc. Soc. exp. Biol., N.Y.*, 40, 409.
- ⁵⁴ Durel, P., Halpern, B. N., Dubost, P., and Allinne, M. (1939). *Presse méd.*, 47, 920.
- ⁵⁵ Bryce, D. A., and Climenko, D. R. (1939). *J. Amer. med. Ass.*, 112, 1182.
- ⁵⁶ Barnett, H. L., Hartmann, A. F., Perley, A. M., and Ruhoff, M. B. (1939). *Ibid.*, 112, 518.
- ⁵⁷ McIntosh, J., and Whitby, L. E. H. (1939). *Lancet*, 1, 431.
- ⁵⁸ Browning, C. H. (1939). *British Medical Journal*, 2, 265.
- ⁵⁹ Telling, M., and Oliver, W. A. (1938). *Lancet*, 1, 1391.
- ⁶⁰ Hilles, C., and Schmidt, L. H. (1939). *Proc. Soc. exp. Biol., N.Y.*, 40, 73.
- ⁶¹ Fleming, A. (1938). *Lancet*, 2, 74.
- ⁶² — (1938). *Proc. roy. Soc. Med.*, 32, 357.
- ⁶³ — (1939). *Ibid.*, 32, 1075.
- ⁶⁴ — Maclean, I. H., and Rogers, K. B. (1939). *Lancet*, 1, 562.
- ⁶⁵ Ross, R. W. (1939). *Ibid.*, 1, 1207.
- ⁶⁶ Löfström, G. (1939). *Nordisk Med.*, 2, 1927.
- ⁶⁷ Locke, A. (1939). *British Medical Journal*, 2, 249.
- ⁶⁸ Hinshaw, H. C., and Moersch, H. J. (1939). *Arch. Surg., Chicago*, 39, 275.
- ⁶⁹ Christie, J. M. (1938). *Lancet*, 2, 281.
- ⁷⁰ Dyke, S. C. (1938). *Ibid.*, 2, 621.
- ⁷¹ Langdale-Smith, H. G. (1939). *British Medical Journal*, 1, 506.
- ⁷² Blyth, W. (1939). *Ibid.*, 1, 873.
- ⁷³ Crawford, J. H. (1939). *Ibid.*, 1, 608.
- ⁷⁴ Whitehead, W. M., and Carter, C. C. (1939). *J. Amer. med. Ass.*, 112, 2594.
- ⁷⁵ Joules, H. (1933). *British Medical Journal*, 1, 455.
- ⁷⁶ Davies, D. T., Graham-Hodgson, H. K., and Whitby, L. E. H. (1935). *Lancet*, 1, 791.

- ⁷⁷ Reid, G. C. K., and Dyke, S. C. (1938). *Lancet*, 2, 619.
⁷⁸ Cunningham, A. A. (1938). *Ibid.*, 2, 1114.
⁷⁹ McAlpine, D., and Thomas, G. C. (1939). *Ibid.*, 1, 754.
⁸⁰ Yule, A. P. (1939). *British Medical Journal*, 1, 872.
⁸¹ MacKeith, R. C., and Oppenheimer, G. (1939). *Lancet*, 1, 1099.
⁸² Raman, P. S. (1939). *Ibid.*, 1, 1101.
⁸³ Dunlop, H., and Laurie, J. (1939). *Ibid.*, 1, 1437.
⁸⁴ Cable, J. V. (1939). *Ibid.*, 2, 73.
⁸⁵ May, K. (1939). *Ibid.*, 1, 1100.
⁸⁶ Aitchison, J. D. (1939). *Ibid.*, 1, 1436.
⁸⁷ Dowds, J. H. (1939). *Ibid.*, 1, 1436.
⁸⁸ MacColl, W. A. (1939). *J. Pediatr.*, 14, 277.
⁸⁹ Gaisford, W. F., Evans, G. M., and Whitelaw, W. (1939). *Lancet*, 2, 69.
⁹⁰ Pepper, D. S., and Flippin, H. F. (1938). *Amer. J. med. Sci.*, 196, 509.
⁹¹ ———, Schwartz, L., and Lockwood, J. S. (1939). *J. Amer. med. Ass.*, 112, 529.
⁹² Campbell, D., and Morgan, T. N. (1939). *Lancet*, 2, 123.
⁹³ Antopol, W., and Robinson, H. (1939). *Proc. Soc. exp. Biol.*, N.Y., 40, 428.
⁹⁴ Gross, P., Cooper, F. B., and Lewis, M. (1939). *Urol. cutan. Rev.*, 43, 299.
⁹⁵ Southworth, H., and Cooke, C. (1939). *J. Amer. med. Ass.*, 112, 1820.
⁹⁶ Nissen, N. I., and Roesgaard, C. R. (1939). *Nordisk Med.*, 2, 2461.
⁹⁷ Backhouse, T. C. (1939). *Lancet*, 2, 736.
⁹⁸ Tsao, Y. F., McCracken, M. E., Chen, J., Kuo, P. T., and Dale, C. L. (1939). *J. Amer. med. Ass.*, 113, 1316.
⁹⁹ Thompson, A. R. (1939). *British Medical Journal*, 2, 13.
¹⁰⁰ Erskine, D. (1939). *Ibid.*, 2, 104.
¹⁰¹ Hallam, R. (1939). *Ibid.*, 1, 559.
¹⁰² Johnston, F. D. (1938). *Lancet*, 2, 1044.
¹⁰³ Coxon, R. V., and Forbes, J. R. (1938). *Ibid.*, 2, 1412.
¹⁰⁴ Melton, G., and Beck, A. (1939). *Ibid.*, 1, 867.
¹⁰⁵ Sutherland, M. E. (1939). *Ibid.*, 1, 1208.
¹⁰⁶ Colebrook, L. (1939). *Ibid.*, 2, 158.
¹⁰⁷ Rosenthal, N., and Vogel, P. (1939). *J. Amer. med. Ass.*, 113, 584.
¹⁰⁸ Nicol, H., and Freedman, B. (1939). *Lancet*, 2, 647.
¹⁰⁹ Briggs, G. O. A. (1939). *Ibid.*, 2, 739.
¹¹⁰ Dolgopel, V. B., and Hobart, H. M. (1939). *J. Amer. med. Ass.*, 113, 1012.
¹¹¹ Wilson, A. T., Spreen, A. H., Cooper, M. L., Stevenson, F. E., Cullen, G. E., and Mitchell, A. G. (1939). *Ibid.*, 112, 1435.
¹¹² Proom, H. (1938). *Lancet*, 1, 260.
¹¹³ Werner, A. E. A. (1939). *Ibid.*, 1, 18.
¹¹⁴ van der Zoo de Jong, H. H. (1939). *Ibid.*, 2, 833.
¹¹⁵ Marshall, E. K., Bratton, A. C., and Litchfield, J. T. (1938). *Science*, 88, 597.
¹¹⁶ Long, P. H., and Feinstone, W. H. (1938). *Proc. Soc. exp. Biol.*, N.Y., 39, 486.
¹¹⁷ Coope, R., and Leather, E. (1939). *Lancet*, 2, 72.
¹¹⁸ Marshall, E. K., and Long, P. H. (1939). *J. Amer. med. Ass.*, 112, 1671.
¹¹⁹ Rook, A. F. (1939). *British Medical Journal*, 2, 306.
¹²⁰ Corry, D. C., Brewer, A. C., and Nicol, C. (1939). *Ibid.*, 2, 561.
¹²¹ Bullowa, J. G. M. (1939). *J. Amer. med. Ass.*, 113, 1402.
¹²² MacLeod, C. M. (1939). *Ibid.*, 113, 1405.

In maintaining the flow of arms and munitions the health and well-being of the industrial worker is clearly of the utmost importance, and no single factor has greater influence than the provision for nourishing and attractive meals during the hours of work. Industrial canteens have long been established, but the conditions of war production are likely to increase their usefulness greatly and to add to the number of firms who find it necessary to make arrangements for meals during working hours. The extension of the hours of work, the increase of night shifts, difficulties in transport, "black-out" conditions, all contribute to the strain of war-time production; the evacuation of the family often includes the wife of the industrial worker, and the industrial canteen to-day not only meets the needs of the workers during work hours, but in many factories canteens are already providing facilities for breakfasts and suppers for those workers who are left without anyone in their homes to prepare these meals. How best to organize canteen facilities is the practical question which the Industrial Welfare Society has attempted to answer in a booklet, *Canteens in Industry*, issued at 1s. from 14, Hobart Place, S.W.1. Though primarily concerned with the organization of canteens in industrial concerns, most of the booklet should be no less useful to those responsible for the provision of meals in schools, hospitals, or other institutions, or to those now arranging meals for evacuated school children and mothers and for A.R.P. workers.

PRODUCTION OF ANTIGONADOTROPHIC ACTIVITY IN MAN BY INJECTION OF EXTRACT OF PREGNANT MARES' SERUM

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The presence of a gonadotrophic substance in the serum of mares during the second and third months of pregnancy was discovered by Cole and Hart (1930). Highly purified extracts are now prepared from this source and are used clinically for various manifestations of hypogonadotrophism. In common with gonadotrophic extracts of the anterior pituitary gland and of human urine of pregnancy, the prolonged injection of extract of pregnant mares' serum to animals of a different species from that from which the preparation originated does not cause prolonged stimulation of the reproductive organs (Meyer and Gustus, 1935). This refractoriness is caused by the appearance in the blood of inhibitory substances, which can be demonstrated by the fact that the serum of desensitized animals has the power to inhibit, in other test animals, the activity of the extract in question.

The formation of these substances in the blood as the result of prolonged treatment with gonadotrophic extracts is likely to set a limit to their use as therapeutic agents. It was observed previously, however, by Spence, Scowen, and Rowlands (1938) that the prolonged administration to human patients of extracts prepared from the urine of pregnant women did not evoke the formation of these inhibitory substances, so that treatment could be carried on indefinitely. The presence of such inhibitory substances in the blood of man treated with extract of the serum of pregnant mares does not seem to have been demonstrated, but, as will be seen below, they are undoubtedly produced. It is obvious, therefore, that to continue treatment after such substances have formed would be futile, as most, if not all, of the extract would be neutralized in the circulation. Until a level of dosage and a method of spacing the injections have been found which will not induce the formation of these inhibitory substances care must be exercised in the clinical use of extracts of pregnant mares' serum.

Methods

PRODUCTION OF ANTISERUM

Nine patients with undescended testes were injected intramuscularly with a gonadotrophic extract prepared from the serum of pregnant mares by N.V. Organon (Oss, Holland). The extract was assayed in "rat units" by the manufacturers, there being at that time no international unit. An international standard and a unit defined in terms thereof are now being established,* however, and enough information is available to allow of an approximate estimate of the activity, in international units, of the serum preparation used. The manufacturers stated that 150 µg. was equivalent to 1 "rat unit," but the dosage

* See *Bulletin of the Health Organization of the League of Nations*, 1938, 7, 894.