TABLE III—COMPARATIVE TABLE OF TOTAL POSTOPERATIVE MORBIDITY AND MORTALITY

ABDOMINAL CASES			ALL TYPES OF CASE		
Complication	Gas-chloroform-ether series*	Modern anæsthesia series	Complication	Gas-chloroform-ether series*	Modern anæsthesia series
	%	%		%	%
Slight bronchitis	5·6	0·88	Slight bronchitis	5·9	0·3
Severe bronchitis	3·0	Nil	Severe bronchitis	2·5	Nil
Pneumonia	1·1	0·88	Pneumonia	0·99	0·3
Atelectasis	2·3	0·44	Atelectasis	1·39	0·2
Total pul. morbidity	12·0	2·20	Total pul. morbidity	11·9	0·8
Total pul. mortality	1·1	Nil	Total pul. mortality	0·7	Nil

* From tables published by Dawkins.[29]

There were two deaths within three days, both in moribund patients.

Male, aged 68. Fractured skull, ribs, clavicle, compound tibia; severe shock. Died, 24 hr. Cerebral compression, fractured base of skull at PM.

Male, aged 27. Right buttock, hip, thigh, leg, arm, completely pulped. Lacerated face. Profound shock. Died, 24 hr. Irreversible shock.

vomiting at all; of these 6% vomited once, 5% twice, 4% thrice and 5% more than thrice; 3·5% patients after spinals had moderate headache relieved by 'Veganin'; no true spinal headaches occurred. Of the 18 patients anæsthetised with the Oxford Vaporiser, 9 vomited, 3 once, 1 twice, 2 thrice and 3 more than thrice.

The immediate postoperative condition of the 1000 patients is summarised in table I. In the small Oxford Vaporiser series, where none of the patients was shocked or seriously ill before operation, the shortest time to recover consciousness was 15 min.; 6 of the 18 cases recovered within an hour; the longest time was 5 hr. and the average 2 hr. 7 min. One of these patients could take fluids by mouth after 30 min.; 3 within an hour; the longest time was 7½ hr. and the average 3 hr. 40 min.

The postoperative pulmonary complications are set out in table II, and the incidence is compared in table III with figures published by Dawkins from the Middlesex Hospital. In the 18 Oxford Vaporiser cases, though all had normal respiratory systems before operation, there was 1 case of slight bronchitis, 1 of interlobar empyema and 1 of bronchopneumonia.

SUMMARY

The patient's comfort and rapid convalescence, which should be the anæsthetist's major care after safety, have been largely neglected until lately. Many anæsthetists have thought that the only way to safety lies in adhering to the old and uncomfortable ways.

Chloroform and ether are the chief offenders against the patient's comfort, and it is unsound to judge their safety without following the patient's progress after leaving the theatre.

Chloroform has already been widely discarded because of its toxicity, and evidence is quoted to show that ether is so toxic and so liable to produce postoperative pulmonary complications that it should also be given up.

Nitrous oxide, pentothal and cyclopropane, combined with spinal or field blocks where deep relaxation is needed, can cover the whole field of surgery, including air-raid and front-line work.

Inexperienced anæsthetists can acquire sufficient skill to be much safer with these modern methods than if they use chloroform or ether.

In 1000 cases anæsthetised by modern non-volatile drugs the incidence of postoperative vomiting was only 20%, and the total postoperative pulmonary morbidity was 0·8%, compared with 11·9% in a comparable gas-chloroform-ether series.

I would like to thank my colleagues at the former American Hospital in Britain for their part in suggesting this study and their help in carrying it out; especially Dr. Charles Bradford of Boston, who mainly designed the follow-up card used.

(*References at foot of opposite column*)

LOBAR PNEUMONIA
TREATED WITH SULPHAMEZATHINE AND SULPHADIAZINE

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BECAUSE of the distressing toxic symptoms often seen in patients receiving sulphapyridine, other compounds of sulphanilamide, possessing the therapeutic activity of sulphapyridine but less liable to induce toxic side-effects, have been introduced. Both sulphathiazole and sulphadiazine have been found to be effective chemotherapeutic agents, and compare favourably with sulphapyridine as regards toxicity. Sulphathiazole, however, is not always free from emetic action, and sulphadiazine shares the tendency of other sulphanilamide derivatives to produce renal damage from precipitation in the renal tract (Thompson et al. 1941). This is due to the fact that, at physiological ranges of urinary pH, sulphadiazine is the least soluble of the sulphonamide compounds, although its acetyl derivative is much more so than the parent substance in an alkaline medium (Gilligan et al. 1943; Rose et al. 1943). To overcome this disadvantage, Rose and his colleagues, by introducing two methyl groups into the pyrimidine ring, prepared sulphamezathine (the 4:6-dimethylpyrimidine compound of sulphanilamide), and have reported on its chemistry and pharmacology. This substance and its acetyl derivative are approximately four times as soluble as the corresponding compounds of sulphadiazine. Sulphamezathine is rapidly absorbed from the intestinal tract, so that with regular dosage the concentration in the blood can be well maintained at 5–10 mg. per 100 c.cm. Preliminary clinical trials by Macartney and others (1942) suggested that it was of high therapeutic efficiency and low toxicity. Jennings and Patterson (1942) and Peters and Easby (1943) have also reported favourably on it.

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TABLE I—CASE-MORTALITY IN RELATION TO AGE

Age (yr.)	Sulphapyridine		Sulphadiazine		Sulphamezathine
	Cases	Deaths	Cases	Deaths	Cases (no deaths)
0– 9	2	.. ..	..	..	..
10–19	61	.. ..	16	..	12
20–29	78	5 (6·4%)	13	..	10
30–39	65	3 (4·6%)	9	..	15
40–49	55	10 (18%)	14	..	17
50–59	39	9 (23%)	7	..	7
60–69	37	9 (24·5%)	6	..	6
70–79	16	7 (43%)	3	1	1
80–89	1	1 (100%)	1	1	..

PRESENT INVESTIGATION

In this investigation an attempt was made to compare the efficacy and toxicity of sulphamezathine and sulphadiazine by treating in order of admission alternate cases of a series of 137 patients suffering from lobar pneumonia with either of the drugs, and to contrast the results obtained with 354 cases treated with sulphapyridine.

The diagnosis of lobar pneumonia was based on the history of the illness and physical examination, and on radiological examination carried out within twelve hours of admission and at weekly intervals thereafter. Before the beginning of treatment blood was obtained for culture and hæmatological examination, sputum was examined bacteriologically to confirm the predominance of pneumococci, and where possible the organism was typed. Only cases of true lobar pneumonia are included in this series. All cases of bronchopneumonia and atypical pneumonia, and cases showing a mixed flora on sputum examination, have been excluded.

The routine treatment in the case of all three drugs was essentially the same—administration of 4 g. of the drug, followed by 1 g. four-hourly. In the case of sulphamezathine and sulphadiazine the maximum total dose was 20–25 g. In the sulphapyridine cases a similar dosage was given, but a few cases received as much as 35 g. In addition to the usual symptomatic and nursing treatment, care was taken to ensure a large fluid intake.

In all cases radiological examination was carried out weekly, in an attempt to determine the time required for

TABLE II—INCIDENCE OF TOXIC MANIFESTATIONS

Sp = Sulphapyridine; Sd = Sulphadiazine; Sm = Sulphamezathine

Drug	No. of cases	Agranulocytosis	Jaundice	Oliguria	Cyanosis	Vomiting	Headache or confusion	Rash	Fever
		No. & %	No. & %	No. & %	No. & %	No. & %	No. & %	No. & %	No. & %
Sp	354	1 (0·2)	3 (0·8)	5 (1·4)	14 (3·9)	129 (36)	23 (6·5)	9 (2·5)	2 (0·5)
Sd	69	..	..	1 (1·4)	1 (1·4)	1 (1·4)	..	1 (1·4)	1 (1·4)
Sm	68	..	..	..	1 (1·4)	..	1 (1·4)	1 (1·4)	1 (1·4)

resolution of the pneumonic process, as judged by the disappearance of opacity in the lung. It was found that clinical recovery was seldom associated with a parallel disappearance of radiological signs, for the X-ray picture may be grossly abnormal two or more weeks after apparent recovery. In most cases however opacity in the lung fields had largely disappeared by 21 days, and persistence of lung shadows for a significantly longer period has therefore been regarded as evidence of delayed resolution. No account was taken of enlargement of hilar glands, which may persist for some time after the lungs have regained their translucency.

RESULTS

The relation of age to case-mortality is set out in table I, the incidence of toxic effects in table II and the incidence of complications and sequelæ in table III.

Sulphadiazine.—Of 69 cases treated with this drug, 12 were suffering from some pre-existing general disease which might have been expected to affect adversely the outcome of the pneumonia. There were 2 deaths; 3 cases showed bacteræmia on blood-culture. The average time required for the temperature to become normal in the 67 cases which recovered was 35 hours; 2 cases failed to respond to treatment.

Sulphamezathine.—Of 68 cases treated with this substance, 5 were suffering from a pre-existing disease. There were no deaths in this series and no bacteræmic cases. The average time required for the temperature to reach normal was 43 hours; 1 case failed to respond to treatment. In 2 cases the pneumonic process recurred after initial recovery, and in both the condition responded rapidly to further treatment with sulphamezathine. Four cases showed toxic effects; there was no case of oliguria or hæmaturia, and no vomiting or nausea. One patient developed transient but well-marked cyanosis due to methæmoglobinæmia.

TABLE III—INCIDENCE OF COMPLICATIONS AND SEQUELÆ

—	Sulphapyridine (354 cases)	Sulphadiazine (69 cases)	Sulphamezathine (68 cases)
	No. & %	No. & %	No. & %
Failed to respond to treatment	13 (3·6)	2 (2·8)	1 (1·4)
Empyema	9 (2·5)	2 (2·8)	2 (2·9)
Recurrence of pneumonia	2 (0·5)	.. ..	2 (2·9)
Pleural effusion*	23 (6·4)	15 (21·5)	10 (14·8)
Delayed resolution	27 (7·6)	5 (7·2)	6 (8·7)

* Sufficient to produce well-marked clinical and radiological signs and to require aspiration.

Sulphapyridine.—The results obtained with sulphapyridine, in spite of the difference in total numbers, present some interesting comparisons with those obtained with the newer compounds. Of 354 cases, 310 recovered, giving a case-mortality of 12·4%. Twenty-five cases were suffering from pre-existing disease. Of the 44 fatal cases, 16 died either before treatment could be adequately instituted or from some pre-existing condition unrelated to the pneumonic process during convalescence, so that the corrected case-mortality is 7·9%. Twenty-one cases gave positive blood-cultures on admission, and one of these died. The average time required for the fever to subside was 29 hours.

DISCUSSION

As will be seen from the tables, there can be little doubt about the effectiveness of sulphamezathine in the treatment of lobar pneumonia. In the present series the death-rate was lower with sulphamezathine and sulphadiazine than with sulphapyridine. The difference in total numbers in the two series must be taken into account. It seems clear, however, that sulphamezathine is at least as effective as sulphadiazine and sulphapyridine. There was no very marked difference in the incidence of sequelæ, such as empyema and delayed resolution, between the cases treated with the three drugs, except that the incidence of pleural effusion is higher in cases receiving sulphamezathine and sulphadiazine.

Toxic effects from sulphapyridine are of course common, but they are rare with sulphamezathine and sulphadiazine. Of particular interest is the absence of gastro-intestinal symptoms and oliguria where sulphamezathine is used.

One of the cases treated with sulphamezathine showed well-marked cyanosis, due to methæmoglobinæmia. This is not surprising, because with careful spectroscopic examination of the blood it was found that methæmoglobin could be detected in many of the cases treated

with sulphamezathine or sulphadiazine, although the degree of the methæmoglobinæmia was not sufficient to produce clinically remarkable cyanosis. Further, if either of these substances is administered along with confection of sulphur, sulphæmoglobin will be formed; so that, while the tendency of sulphamezathine and sulphadiazine to alter hæmoglobin is less than that of sulphapyridine, it is not entirely absent.

Two additional points of general clinical interest emerged. It was noted that in cases which recovered from pneumonia to develop empyema later, defervescence was slow; the average time for the fever to subside in such cases was 60 hours. As already stated, the radiographic signs of the lung lesion outlast the other clinical signs of pneumonia by some 1 or 2 weeks, and, in seeking for factors which might be correlated with the time of resolution, it was found that this had no relation to the duration of illness before treatment, the extent of the lung lesion, the apparent severity of the illness, or the total dose of chemotherapeutic agent employed. The incidence of this complication does however bear some relation to the age of the patient. Of 38 patients in which the pneumonia resolved slowly, 27 were over the age of 40.

SUMMARY

The results obtained by treating alternate members of a series of 137 cases of lobar pneumonia with sulphamezathine and sulphadiazine are compared with those in 354 cases treated seriatim with sulphapyridine.

The curative effect of sulphamezathine, as judged by case-mortality, is at least equal to that of sulphadiazine, and both drugs compare favourably with sulphapyridine.

In cases treated with sulphamezathine and sulphadiazine, the time required for the temperature to return to normal after the beginning of treatment is about the same, but is longer than in cases treated with sulphapyridine.

The incidence of toxic effects in cases treated with sulphamezathine and sulphadiazine was low—6% with sulphamezathine and 7% with sulphadiazine, as against 52% with sulphapyridine. Oliguria and gastro-intestinal disturbance were not seen in the cases treated with sulphamezathine.

In the incidence of sequelæ, there is little difference between these three drugs, except that with sulphadiazine and sulphamezathine pleural effusion during convalescence has been more frequent.

Delayed resolution is commonest in patients over 40, and a long period of defervescence is often followed by empyema.

We wish to thank Dr. H. J. Rae, medical officer of health for Aberdeen and Aberdeenshire, for permission to publish these cases.

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Medical Societies

SOCIETY OF MEDICAL OFFICERS OF HEALTH

AT a meeting of the Fever Group on Nov. 19, with Dr. ANDREW TOPPING in the chair, a discussion on

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was opened by Dr. G. W. GOODHART (LCC Pathological Service), who said that one of the difficulties in employing blood-counts in differential diagnosis is that the picture varies with the stage of the disease and this is often difficult to determine exactly. The prodromal stage of most fevers is characterised by a polymorph leucocytosis which persists into the eruptive stage in coccal diseases, whereas bacillary and viral infections tend at that stage to produce a leucopenia or a lymphocytic response. In scarlet fever a polymorph leucocytosis persists usually until the end of the second week and its absence in severe toxic cases is a bad prognostic sign. Eosinophilia, sometimes up to 10%, is characteristic. He would be chary of excluding scarlet fever even if there is no clear polymorph response. Prominent among the diseases marked by leucopenia with a relative lymphocytosis is enteric fever. These changes occur quite early but their importance in diagnosis is overshadowed by the development of modern bacteriological methods. Nevertheless, leucopenia is a valuable adjunct to diagnosis particularly in clinically atypical cases, while a blood-count can sometimes negative a diagnosis of typhoid which seems clinically probable but lacks bacteriological proof. Insufficient attention is paid nowadays to the characteristic absence of eosinophil cells in the leucopenia of typhoid fever. Leucopenia is not so constant in paratyphoid fever, and Dr. Goodhart has seen several mild cases in which there was a persistent polymorph leucocytosis. The blood-pictures in measles and rubella are roughly the same. With the appearance of the rash there is leucopenia with a relative lymphocytosis which often becomes an absolute lymphocytosis with a rising lymphocyte count. In rubella, plasma or Türck cells often appear in exceptional numbers They will be more helpful in differentiating rubella from scarlet fever than from measles since they are sometimes increased in measles also. Leucopenia with relative increase in lymphocytes occurs in mumps and could be used in differential diagnosis from septic adenitis where there is a polymorph response. It also helps to prevent confusion with glandular fever, though the rarer forms of this disease do show a leucopenia, distinguishable from mumps by the presence of atypical monocytes in stained films. Whooping-cough differs from other infectious diseases in raising the total white-cell count by increasing the lymphocytes. This change is found in the catarrhal stage before the whoop develops and may help the doctor to isolate contacts early. Lymphocytosis reaches its peak in the paroxysmal stage. Care is necessary in interpreting counts, particularly in the lower ranges, since the lymphatic apparatus in childhood can readily be stimulated by various pathological processes. Dr. Goodhart would put no great stress on figures below 20,000 per c.mm. except perhaps in adults and older children; even then he demands a high lymphocyte percentage unless the clinical picture is very suggestive. Exceptionally high total counts with comparatively few lymphocytes are not uncommon when complications arise. In a recent case of whooping-cough pneumonia there were 165,000 leucocytes per c.mm. of which 46·5% were polymorphs and only 42% lymphocytes. He felt it was unwise to talk too glibly of characteristic blood-counts in various fevers since many cases run a complete course without a greater change in the blood-picture than can be paralleled in healthy people. In convalescence anæmia should be estimated by blood-counts rather than on clinical appearances, which may often mislead in children. The blood-picture in the common infectious diseases needs further investigation, but the knowledge to be gained from a count should be weighed against possible emotional trauma in small children. Facilities for these and other investigations are deficient in most fever hospitals at present but there will doubtless be improvement in the future. It is a delusion to assume that anyone can do a blood-count: accurate results demand a technique only acquired by careful training, attention to detail and constant practice.

Dr. IAN TAYLOR (LCC) pointed out the difficulty of interpreting minor changes in the blood-count in children in the absence of exact standards of normality for the various age-group.—Dr. R. F. L. HEWLETT (LCC) had noted that in enteric fever with a respiratory onset there is sometimes a polymorph leucocytosis rather than a leucopenia, and other speakers agreed with Dr. Goodhart that leucocytosis is more likely to be met in paratyphoid than in typhoid.—Dr. A. L. K. RANKIN (Twickenham) felt that routine blood investigation in atypical throat infections would often uncover conditions such as the anginose type of glandular fever.—Dr. ROBERT CRUICKSHANK (LCC) supported this but pointed out that, since many of these cases have received antitoxin, a positive Paul-Bunnell reaction could not be accepted without further investigation. He wondered what is the signific-