SUMMARY

A method of studying death-certification habits in different countries is described. The results obtained in a pilot inquiry among hospital physicians in Norway, the United Kingdom, and the United States are discussed in relation to differences between these countries in the reported death rates from bronchitis and arteriosclerotic heart disease.

APPENDIX: CASE SUMMARIES

Case 1.—Aged 50. Cough for 10 years, worse recently and associated with increasing dyspnoea. Physical signs: stupor; cyanosis; jugular venous congestion, oedema; poor chest expansion, diffuse rhonchi, basal fine rales, and bronchial breathing. E.C.G.: pointed P in II. Hb 102%. Died 24 hours later. P.M.: right ventricular hypertrophy, moderate coronary atheroma; pulmonary congestion, oedema, and emphysema; stomach full of altered blood, acute duodenal ulcers.

Case 2.—Aged 64. Incipient gangrene of leg, with absent pulses. E.C.G.: Q and inverted T in II, III. No benefit from iliac thrombarterectomy. Leg amputation followed by gangrene spreading up from stump. No P.M.

Case 3.—Aged 47. Sudden onset of severe central chest pain. History of paroxysmal dyspnoea at age 44, when hypertension and proteinuria were noted. Physical signs: B.P. 150/105; cardiac enlargement. Heavy proteinuria. Blood urea 71 mg./100 ml. E.C.G.: recent infarction. Died 2 weeks later after further attack of pain. P.M.: old and recent infarction, and considerable hypertrophy, of left ventricle; right kidney small, with large area of cortical thinning; left kidney granular.

Case 4.—Aged 64. Productive cough and dyspnoea for years. Attacks in past 4 days of sudden faintness, sweating, and dyspnoea. Physical signs: cyanosis, dyspnoea, clubbing; barrel-shaped chest with many rhonchi. Serum potassium 7.6 mEq/l. Died 2 days later. No P.M.

Case 5.—Aged 42. Sore throat followed 1 month later by oedema; also by hypertension and proteinuria, which persisted. Readmitted 2 years later with heart failure. Hb 41%. Blood urea 216 mg./100 ml. P.M.: bullous emphysema; left ventricular hypertrophy; granular kidneys with thin cortices.

Case 6.—Aged 40. Collapsed at work. Hypertension first noted 3 years previously, when tuberculous kidney was removed. Physical signs: stupor, hemiparesis; B.P. 250/150; papilloedema and retinal exudates. Died in coma. No P.M.

Case 7.—Aged 45. Three-months history of lassitude and dyspnoea. Physical signs: prominent eyes, sweating; auricular

fibrillation, cardiac enlargement, jugular venous congestion; basal rales. E.C.G.: fibrillation, T waves all flat. B.M.R.: +55%, +27%, +13%. ¹³¹I uptake normal. Given carbimazole; improved for 6 months, then heart failure relapsed. Died suddenly. P.M.: pulmonary embolism and infarction; heart weight 735 g.; some pericardial adhesions.

Case 8.—Aged 51. Recurrent cough and dyspnoea since pneumonia 18 years earlier. Recent pleural pain. Physical signs: fever, cyanosis, dyspnoea; jugular venous congestion and oedema; fixed chest, scattered rhonchi, fine rales over right lower lobe. E.C.G.: tall pointed P in II. Proteinuria ++. Improved for 1 month, then died after sudden collapse with tachycardia and unrecordable blood-pressure. No P.M.

Case 9.—Aged 50. Ten-days history of headache, vertigo, vomiting. Cardiac infarction 5 years previously. Physical signs: stupor, aphasia, left facial weakness and hemianaesthesia; B.P. 165/115. Died in coma. P.M.: old and recent cardiac infarction; recent pontine infarction.

Case 10.—Aged 57. Sudden onset of headache and loss of speech. Proteinuria and hypertension discovered at age 51. Nephrectomy for renal carcinoma at age 56. Hemiplegia at age 56. Physical signs: dysphasia, confusion, hemiparesis; B.P. 200/140; left ventricular enlargement. Urine: protein ++. Died in coma. No P.M.

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Antimalarial Effect of Sulphorthodimethoxine (Fanasil)

Brit. med. J., 1964, **2**, 1439–1440

The new long-acting sulphonamide sulphorthodimethoxine¹ (Fanasil) was used in a preliminary trial to test the potentiating effect of sulphonamide with pyrimethamine (Hurly, 1959; McGregor, Williams, and Goodwin, 1963) against pyrimethamine-resistant malaria. The drug is closely related to sulphadimethoxine² (Madribon), of which it is an isomer, but the rearrangement of the molecule gives it different properties. These include a more prolonged antibacterial action, a dose of 1 g. weekly being therapeutically equivalent to 1 g. daily of sulphadimethoxine or other long-acting sulphonamides such as sulphamethoxypyridazine³ (Lederkyn, Midicel) or sulphaphenazole⁴ (Orisul). Sulphorthodimethoxine was chosen because of this sustained concentration in the plasma, so

matching better than other sulphonamides the persistent plasma concentration of pyrimethamine.

The work was done among schoolchildren in the Muheza district of Tanga, north-east Tanganyika, where malaria is holo-endemic and the children have a high degree of acquired immunity (asexual parasite rates of 60–80% are the rule). Pyrimethamine-resistant falciparum malaria was found in this and adjacent areas by Clyde and Shute (1957), and recent surveys have shown that it is still present.

Prior to giving sulphorthodimethoxine, all children were given 25 mg. of pyrimethamine (the recommended adult dose) weekly for two months to eliminate drug-sensitive parasites. A survey done at the end of this period showed an asexual parasite rate of 27% (all *Plasmodium falciparum*). Sulphorthodimethoxine in 500-mg. doses was then given weekly, together with pyrimethamine at the same dosage as before, to one group of 191 children; another similar group (208 children) was given 500-mg. doses of the sulphonamide alone, while a third group (192 children) continued with pyrimethamine as before. A blood survey after six weeks showed that asexual parasitaemia

had disappeared not only in the group treated with the sulphonamide-pyrimethamine combination but also in the group given sulphonamide alone; in the third group the asexual parasite rate was 26%, with densities approximately those in "untreated" infections.

These results indicate that in combating pyrimethamine-resistant malaria, not only is sulphathodimethoxine apparently successful in combination with pyrimethamine but it is equally effective when used alone. Details of this and subsequent drug trials will be published in due course.

COMMENT

This example of the schizonticidal action of a long-acting sulphonamide against pyrimethamine-resistant forms of *P. falciparum* should encourage further investigations into the antimalarial action of sulphonamides, at least in the suppressive field. For treatment of the acute attack of malaria preliminary tests suggest that the action of sulphathodimethoxine is too slow.

SUMMARY

A preliminary field trial to test the potentiative effect of giving sulphonamide with pyrimethamine against pyrimethamine-resistant falciparum malaria was carried out among African schoolchildren in north-east Tanganyika, where drug-resistance was known to be present.

A surprising finding was that the sulphonamide used, the long-acting sulphathodimethoxine (Fanasil), was equally effective as a schizonticide in weekly doses of 500 mg. *per se* as when given with weekly 25-mg. doses of pyrimethamine.

I should like to thank Dr. J. Garrod, of Roche Products Ltd., for information and advice on sulphathodimethoxine, and to the firm for supplies of the drug.

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FOOTNOTES

1. 4-sulphanilamido-5,6-dimethoxypyrimidine

(Fanasil)

2. 4-sulphanilamido-2,6-dimethoxypyrimidine

(Madribon)

3. 3-sulphanilamido-6-methoxypyridazine

(Lederkyn, Midicel)

4. 1-phenyl-5-sulphanilamido-pyrazole

(Orisul)

Medical Memoranda

Carcinoid Syndrome Due to Carcinoid
Tumour of the Ovary

Brit. med. J., 1964, **2**, 1440-1441

Carcinoid tissue in an ovarian teratoma was first described in 1939 (Stewart *et al.*). The association of the carcinoid syndrome with ovarian teratomas, though well recognized, must be rare. Since the first case, described by Sauer *et al.* (1958), only three reports have appeared in the literature (Thorson *et al.*, 1958; Torvik, 1960; Kephart *et al.*, 1960).

The importance of recognizing this association lies in the fact that surgical removal of the ovarian teratoma has, in these cases, resulted in complete arrest of the syndrome.

Before this association was recognized extensive hepatic secondaries had been considered necessary for the development of the carcinoid syndrome. The 5-hydroxytryptamine (5-HT) secreted by the primary intestinal tumour is thought to be inactivated by monoamine oxidase in the liver. In the same way other substances produced by the tumour, which may be more important for the development of the syndrome, may also be inactivated by the liver. Hepatic metastases, apart from providing an increase in the mass of secreting tumour, are drained more directly into the caval system, and therefore

avoid this "trap" (Thorson, 1958). Similarly, the venous drainage of the ovary is into the inferior vena cava, which accounts for the development of the syndrome in the absence of hepatic metastases in the above cases.

The following case is a further example of an ovarian tumour associated with the carcinoid syndrome. Of additional interest was the finding of terminal uraemia.

CASE REPORT

A woman of 73 was admitted to hospital in January 1963 with a history of severe diarrhoea and abdominal pain for three years, and oedema, ascites, and blood loss per rectum for the past three months. She died 24 hours after admission.

For the previous nine months she had experienced flushing attacks after meals. Her face and neck would become purple, the colour fading after about 15 minutes. Frequent attacks of colicky abdominal pain often coincided with the flushes.

On examination she was in a stupor and grossly anaemic. She was in severe congestive cardiac failure with atrial fibrillation and generalized oedema; her blood-pressure was 90/70 mm. Hg. A loud systolic murmur was heard, maximal at the left sternal edge. The chest was clear; the abdomen was distended with ascites. On rectal examination there was watery, dark red stool; on vaginal examination a fixed mass was felt in the pouch of Douglas.

The results of investigations carried out before death were as follows: haemoglobin 7.2 g./100 ml., with an M.C.H.C. of 30%.