A paper by W. D. Rees and S. G. Lutkins printed at page 13 of this week's *B.M.J.* describes the effect of a death in the family on the death-rate of the surviving members. Their most striking finding in the semi-rural Welsh community which they studied is a mortality rate among newly bereaved family members six times greater than the mortality rate among non-bereaved control families. They confirm the findings of several other studies that there is an increase in mortality rates among widows and widowers and that this increase is most marked during the first year of bereavement.

Granted that there is an association between bereavement and mortality, how can this be explained? The evidence so far reported does not allow us to do more than guess. Does bereavement influence the incidence of disease or simply increase the mortality rate among those already affected? Is it the psychological state of grief which alters physiological processes in a pathological manner? Or does grief have secondary effects on diet, smoking habits, and alcohol intake, which are themselves pathological in their effects? Further research must answer these questions, but in the meantime doctors should ask themselves whether there is anything which they should be doing to mitigate the effects of bereavement.

In public health terms the relatives of dying patients are a high-risk group akin to the relatives of patients with tuberculosis. Rees and Lutkins's figures suggest that young and middle-aged men who lose wives from an illness which causes them to die away from home are particularly at risk. Recent work in Britain and the United States seems to indicate that major bereavements influence physical and mental health in many ways and that bereaved people commonly seek help from their medical practitioners. The clergyman, whose traditional role includes the succouring of the bereaved, has now in Britain been largely replaced by the general practitioner, the professional man to whom the bereaved will turn most readily. It is unfortunate that medical education does little to prepare doctors for this role.

Much is known about the form and nature of grief. Grief is the psychological process which cushions the impact of disaster and enables a bereaved person gradually to work towards an acceptance of what has happened. It is a mixture of pining and resignation, searching and apathy, denial and acceptance; small wonder that some are unable to cope effectively with this conflict. Pathological forms of grief have been recognized since E. Lindemann's classic account⁴ of grief among the relatives of those who died in the Coconut Grove fire. More recently papers by C. Anderson⁵ and Parkes⁶ have enabled the classification of bereavement reactions to be carried out. A common form is the "chronic grief" syndrome epitomized by Queen Victoria. Here, intense grief, instead of resolving, becomes habitual, and mourning persists. Another form may occur among persons who defend themselves so vigorously against the pain of grief that they "feel nothing" for months after bereavement. Thereafter they tend to break down with a particularly severe reaction. Identification symptoms (hypochondriacal symptoms resembling those suffered by the dead person during his terminal illness), panic attacks, insomnia, and headaches are

all likely to bring the bereaved person into the care of a physician.

At present too little is known about the factors which decide who will break down and who will emerge from the stress of grief stronger and wiser. Personality factors, social isolation, age (old people withstand bereavement better than young), and the nature and magnitude of the loss itself all seem to be important factors. When the bereaved person is supported by a united and affectionate family, when there is something left to live for, when the person has been adequately prepared for the loss, and when it can be fitted into a secure religious or philosophical attitude to life and death there will seldom be much need for professional help. When, however, the bereaved person is left alone in a world which is seen as hostile and insecure, when the future is black and the loss has not been prepared for, help may be needed.

What can doctors offer? A willing ear, tolerant of confusion and anger, and a knowledge of community resources are probably more important than tonics and sedatives. In addition, the Cruse Clubs Counselling Service for Widows,⁷ the citizens' advice bureaux, the local church, mental welfare officers, social workers, and voluntary organizations of all kinds are available in many areas. There is little doubt that time spent in helping patients to prepare for and cope with the disasters in their lives will improve community mental health and may even reduce the post-bereavement mortality rate.

Prevention of Rhesus Haemolytic Disease

Rhesus haemolytic disease of infants takes several forms. In the mildest cases the infant is merely jaundiced and this soon disappears; in severer cases there is actual haemolytic anaemia, and this, if untreated, can be fatal; the disease can so affect the foetus that it will die in utero and be stillborn; and the hyperbilirubinaemia can affect the brain, producing the condition of kernicterus, which causes mental abnormality. The anaemia has been successfully treated by the method of exchange transfusion, and recently this procedure has been carried out before birth by the technique of intrauterine transfusion.¹ Early induction of labour has reduced the number of stillbirths, especially since the introduction of a method of using samples of amniotic fluid to give warning of dangerous concentrations of bilirubin.^{2 3} Nevertheless, it would be far more satisfactory to prevent this disease occurring at all. For the past nine years a group of doctors at Liverpool have been working on this problem, and they have now reached the point where the possibility of successful protection against rhesus haemolytic disease has been demonstrated and practical methods for making this protection available can be discussed. In his Lumleian lecture to the Royal College of Physicians printed on page 7 of this issue, Professor C. A. Clarke reviews the inception and development of this work in Liverpool and the information now available from other centres. It is an impressive story.

We now know that the cause of the disease is the development in the mother's blood of anti-Rh antibodies which pass the placenta and destroy the infant's red cells. The development of these antibodies in the mother's plasma is

¹ Heberden, W., (attrib.) 1759, Bill of Causes of Death, quoted from *Report of the County Medical Officer of Health, the London County Council, 1957*, p. 165, 1958.

² Rush, B., *Medical Inquiries and Observations upon the Diseases of the Mind*, 5th edition, 1835. Philadelphia.

³ *Brit. med. J.*, 1967, 3, 232.

⁴ Lindemann, E., *Amer. J. Psychiat.*, 1944, 101, 141.

⁵ Anderson, C., *Int. J. Psycho-Anal.*, 1949, 30, 48.

⁶ Parkes, C. M., *Brit. J. med. Psychol.*, 1965, 38, 1.

⁷ Cruse Clubs Counselling Service for Widows, 6 Lion Gate Gardens, Richmond, Surrey.

¹ Liley, A. W., *Brit. med. J.*, 1963, 2, 1107.

² Bevis, D. C. A., *Lancet*, 1950, 2, 443.

³ Bower, D., and Swale, J., *ibid.*, 1966, 1, 1009.

stimulated by the passage of Rh-positive red cells from the infant to the mother across the placenta during labour. Another possible cause is the previous transfusion of the mother before her pregnancy with Rh-positive blood, but such an event is rare today. It follows that it is the second and subsequent children that are at risk, and since the stimulation may produce increasing levels of Rh-antibody production the risk is greater for each succeeding child. But in practice only a small proportion of the children at risk actually develop signs of rhesus haemolytic disease. There are at least two reasons for this. Different individuals react differently to similar antigenic stimuli, so in some families the second child is affected, whereas in others of three or sometimes more children no cases have occurred. Secondly, we know that if mother and child have different ABO blood groups, Rh immunization rarely occurs, presumably because the incompatible red blood cells from the child are destroyed in the mother's blood before they can do any damage.

It was this protection afforded by ABO group incompatibility that suggested a possible line of approach to Professor Clarke and his colleagues. If a potent anti-Rh serum was available, would it protect mothers against Rh immunization and their children against risk of rhesus haemolytic disease? When Rh-positive red blood cells were given to Rh-negative male volunteers they produced Rh antibody in their plasma. It was found that antibody formation could be prevented by giving a potent anti-Rh (anti-D) plasma, provided the "incomplete" (albumin) antibody was used. The next step was to give to women at risk, within 48 hours of delivery, 5 ml. of gammaglobulin containing incomplete anti-D of suitable activity. The trial was limited to primiparous women who were found to have foetal red cells present in their own blood after delivery—a group known to be at risk. Alternate patients were given the serum. After six months none of the 78 treated women had developed immune antibody, whereas 19 of the 78 controls had done so. Results up to date from various centres collected by Clarke show that out of 559 control cases 75 (13%) had become immunized six months after labour, whereas out of 628 protected by anti-D gammaglobulin none was immunized—a result which Clarke calls "almost alarmingly successful." Further results have shown that the protective effect will persist through a further pregnancy when the foetus is Rh-positive and ABO compatible; combined results show that out of 66 women immunized during and after pregnancy none produced antibodies in the subsequent pregnancy, whereas out of 63 control cases 15 (24%) produced antibodies.

There is thus clear evidence that women at risk can be protected against Rh-immunization and their children against rhesus haemolytic disease. Professor Clarke deals then with two further questions that arise. What are the risks of the procedures? Can enough anti-D gammaglobulin be obtained? The risk to the mother is trivial; only minor local reactions have occurred and the risk of serum jaundice can be eliminated by appropriate methods of preparing the gammaglobulin. The male volunteer who is injected with Rh-positive blood risks being infected by the virus of homologous serum-jaundice. The risk can be minimized but not eliminated by following W.H.O. recommendations. A better way, proposed by Clarke, is to use a small number of donors made hyper-immune by small repeated injections of sensitizing antigen and to obtain plasma by plasmapheresis—that is, to take off plasma and return the red cells to the donor. Put against the possibility of eliminating unnecessary stillbirths, some

cases of mental deficiency, and the whole apparatus of exchange transfusion, Clarke considers that these risks are acceptable, though others may not agree.

To get enough protective anti-D gammaglobulin, Clarke calculates that for every million of the population 15 hyper-immunized donors, willing to give 500 ml. of plasma once a month, would be needed. The organization of the immunization of donors, the collection of plasma, and the preparation of protective antibody will therefore require quite a large staff with necessary equipment, but it could also be found by proper expansion of the present national blood transfusion centres.

Metronidazole and Syphilis

Metronidazole (Flagyl) was introduced to therapeutics in 1959 after C. Cosar and L. Julou¹ had shown it to be active against *Trichomonas vaginalis* in vitro and in mice, and P. Durel and colleagues² reported on its efficacy in curing trichomoniasis in patients of both sexes. They gave combined oral and local treatment to their women patients, but in 1960 excellent results in women with oral treatment alone were reported from several centres.³⁻⁶ Metronidazole by mouth is now generally accepted as the drug of choice for the treatment of trichomoniasis.

The therapeutic range of the drug was increased in 1962, when D. L. S. Shinn⁷ found it to be highly effective in treating Vincent's gingivitis. This led to an investigation into any possible effect of the drug on *Treponema pallidum*. Many patients attending venereal disease clinics are treated for trichomoniasis, which is usually sexually transmitted. Some of these patients may be incubating syphilis, and it is obviously important to know if metronidazole in the dosage usually given can destroy *T. pallidum*.

M. Scott-Gray and M. Murrell⁸ had previously shown that metronidazole 1.8 g. in 48 hours had no effect on a patient with primary syphilis. In 1966 A. R. Yobs and colleagues⁹ found that relatively large doses had no effect on the course of syphilis in rabbits. Two recent papers cast further light on this important problem. A. H. Davies¹⁰ treated six patients with secondary syphilis with doses of metronidazole ranging from 13.5 g. in five days to 34 g. in nine days. The local lesions healed and material from these patients showed disappearance of *T. pallidum* on dark-field examination. A. E. Wilkinson and his colleagues¹¹ showed that sera from patients under treatment for trichomoniasis may immobilize *T. pallidum* (Nichols strain) in vitro, but treatment of a patient with primary syphilis (positive on dark-field examination) with 200 mg. metronidazole three times daily for seven days did not heal the lesions, and *T. pallidum* was still detected at the end of the course.

It seems that the ability of metronidazole to eliminate *T. pallidum* depends on the daily dosage level: the organism

¹ Cosar, C., and Julou, L., *Ann. Inst. Pasteur*, 1959, **96**, 238.

² Durel, P., Roiron, V., Siboulet, A., and Borel, L. J., *C. R. Soc. franç. Gynéc.*, 1959, **29**, 36.

³ Watt, L., and Jennison, R. F., *Brit. med. J.*, 1960, **2**, 902.

⁴ Rees, E., *ibid.*, 1960, **2**, 906.

⁵ Moffett, M., and McGill, M. I., *ibid.*, 1960, **2**, 910.

⁶ Rodin, P., King, A. J., Nicol, C. S., and Barrow, J., *Brit. J. vener. Dis.*, 1960, **36**, 147.

⁷ Shinn, D. L. S., *Lancet*, 1962, **1**, 1191.

⁸ Scott-Gray, M., and Murrell, M., *Practitioner*, 1961, **186**, 218.

⁹ Yobs, A. R., Clark, J. W., and Schroeter, A. L., *Brit. J. vener. Dis.*, 1966, **42**, 122.

¹⁰ Davies, A. H., *ibid.*, 1967, **43**, 197.

¹¹ Wilkinson, A. E., Rodin, P., McFadzean, J. A., and Squires, S., *ibid.*, 1967, **43**, 201.