complications. In a world where the incidence of iatrogenic disease is rising steeply we are becoming increasingly conscious of the need to balance the ills we cure against the ills we cause. In this instance the argument is complicated by the difficulty of defining what ills would result if oral contraceptives were not used at all. According to the report from the Food and Drug Administration,[1] the mortality from venous thrombosis was 12.1 per million in women taking Enovid (norethynodrel together with mestranol)—the most widely used oral contraceptive—and 8.4 per million in the general population. Considered at face value this preparation might be supposed to have added 3.7 deaths per million. Therefore of the 800,000 women taking oral contraceptives in Britain 2.96 would die every year as a result of their medication. Taking the gloomiest view the M.R.C. report estimates that the most deaths attributable to oral contraceptives in 1966 were 19, a much larger figure. What should one set against these deaths of healthy young women? One possibility is to consider what might have happened to the 800,000 women if they had not used oral progestogens but a variety of other contraceptive techniques. It is generally accepted that the overall failure rate of other methods of contraception is about 10% per woman year, and it might be estimated therefore that about 80,000 of these women would have become pregnant. From current maternity mortality figures it can be expected that 10 to 13 of these women would die as a result of the pregnancy. At most, therefore, at present nine extra women die each year because of oral contraceptives and very likely the figure is less. Indeed, in Table II of the M.R.C. report it can be seen that since 1961 there has been no increase in the incidence of thromboembolic disease, while at the same time there has been a great increase in the number of women in the population at risk who use oral contraceptives.

For the individual doctor the attempt to assess the consequences of prescribing oral contraceptives is bound to be difficult. How does one measure the misery of unwanted pregnancy? Or for that matter the joy that often results from an unplanned pregnancy? Arguments derived from comparisons of average figures can conceal important variations between individuals. For instance, the failure rate of mechanical types of contraception varies from one person to another in relation to factors that may sometimes be identifiable in the individual case. Some people are habitually more careful than others. Likewise, the risk of thrombosis may in future be shown to vary in accordance with biochemical factors ascertainable in each woman. It is thus as important to bear in mind in this context, as in others, that statements of average risk need to be interpreted for each individual.

The reports of the M.R.C. and the Royal College of General Practitioners apply only to vascular complications, and one can fairly consider in this context only thromboembolic disease in pregnancy. Morbidity statistics modify somewhat the conclusions which might be drawn from maternal mortality alone. The M.R.C. report suggests that oral contraceptives increase the risk of venous thrombosis three times, while pregnancy increases it six times. Pregnancy and oral contraceptives may be regarded as alternatives only in a limited sense, but in so far as such a comparison can be made it redresses the balance in favour of oral contraceptives.

The M.R.C. report deals with one aspect of oral contraceptives only—that of thromboembolic phenomena. It may well be that other factors such as cancer or endocrine injury will in the end be found to bear more heavily. It is unreasonable to seek an evaluation of other factors in this report, but it is a pity that within the context of this single aspect oral contraceptives should be treated as though they were a physiological entity. They are chemically diverse and physiologically composed of at least three clearly separate elements—oestrogens, nortestosterone derivatives, and 17α-hydroxyprogesterone derivatives. We do not know whether the tendency to thrombosis derives from the oestrogen or the gestagen. As for the gestagens themselves, it is at least as likely that 21-carbon compounds differ from the 18-carbon nortestosterones as it is that they have equal potentialities for causing thrombosis.

There is evidence that the incidence of death from thromboembolic disease is increasing,[4,5] but not that oral contraceptives are a major component in this increase. Oral contraceptives cause a small amount of morbidity and mortality. Compared with the large amount of thromboembolic disease contributed by other causes the fraction contributed by oral contraceptives is so small that it can be detected only by careful statistical techniques. Nevertheless, many doctors will regard the prescribing of the present oral contraceptives as an interim measure until safer means are available.

[1] *Final Report on Enovid by the Ad Hoc Committee for the Evaluation of a Possible Etiologic Relation with Thrombo-embolic Conditions*, 1965. Food and Drug Administration, Department of Health, Education and Welfare, U.S.A.; Washington.
[2] *Clinical Aspects of Oral Gestogens*, 1965. Technical Report Series No. 326 World Health Organization, Geneva.
[3] Collective Investigation, Royal College of General Practitioners, *J. Coll. gen. Practit.*, 1967, **13**, 267.
[4] Morrell, M. T., Truelove, S. C., and Barr, A., *Brit. med. J.*, 1963, **2**, 830.
[5] Loehry, C. A., ibid., 1966, **1**, 1327.

Outlook in Hodgkin's Disease

Hodgkin's disease may occur at any age. It is slightly more frequent in males than females. And though it is not a common disease, with an annual death rate in England and Wales of about 18 per million,[1] several new cases may be seen in a large hospital every year.

It is primarily a disease of lymphoid tissue, and it may present with enlargement of any group of lymph nodes. The patient is usually free of symptoms at this stage, and, if untreated, further enlargement of the original group of glands together with the appearance of enlarged nodes elsewhere is the rule. General symptoms may now appear, notably fever, lassitude, anorexia, loss of weight, pruritus, pain in the chest and abdomen, dyspnoea, and non-productive cough. At this stage the patient may be found to have a cachectic, pigmented appearance with anaemia, painless enlargement of lymph nodes, and an enlarged spleen and liver. If the disease is not halted, jaundice, bleeding, neurological complications, and severe infection by opportunist micro-organisms will terminate life.

[1] *The Registrar General's Statistical Review of England and Wales for the Year 1965*, Part 1, Tables, Medical, 1967. H.M.S.O.
[2] Jackson, H., jun., and Parker, F., jun., *New Engl. J. Med.*, 1944, **230**, 1.
[3] Brewin, T. B., *Brit. med. J.*, 1966, **2**, 437.
[4] Ibid., 1965, **1**, 943.
[5] Ultmann, J. E., *Cancer (Philad.)*, 1966, **19**, 297.
[6] Peters, M. V., and Middlemiss, K. C. H., *Amer. J. Roentgenol.*, 1958, **79**, 114.
[7] Easson, E. C., *Cancer Res.*, 1966, **26**, 1244.
[8] Kaplan, H. S., ibid., 1966, **26**, 1250.
[9] —— and Smithers, D. W., *Lancet*, 1959, **2**, 1.
[10] Aisenberg, A. C., *Cancer Res.*, 1966, **26**, 1152.

The classical picture is subject to infinite variation owing to the widespread distribution of the lymphatic system. No account of the initial presentation of Hodgkin's disease can hope to be complete. The commonest presenting feature is cervical lymphadenopathy, axillary and inguinal nodes being affected initially in only 10% of cases.[2] Though any group of cervical nodes may be attacked, those in the posterior triangle are affected most frequently. Glandular enlargement may first be noted after an upper respiratory tract infection. The nodes may fluctuate in size at first and almost disappear only to return, and this should not exclude the diagnosis. They may thus fluctuate for some years. Though usually the glands are neither tender nor hard and are mobile, they may become painful and swollen in some patients when they take alcohol.[3]

A lymphadenopathy may persist for more than a few months and have the features of Hodgkin's disease yet be due to tuberculosis or sarcoidosis. Occasionally the lymphadenopathy of glandular fever may persist; less common infections are those due to *Toxoplasma gondii, Toxocara canis,* and "cat scratch" disease. Some patients on antiepileptic drugs such as the hydantoinates develop lymphadenopathy. Biopsy of any persistent node for which a cause cannot be found is essential. The finding of Sternberg–Reed cells on histological examination is diagnostic of Hodgkin's disease.

Lymph nodes at certain sites will give rise to mechanical effects—particularly in the mediastinum, when cough, dyspnoea, and dysphagia may be presenting features. Radiographic confirmation of enlarged nodes in the anterior mediastinum is very suggestive that the symptoms are due to Hodgkin's disease. Jaundice may be due to disease of the glands in the porta hepatis. Oedema of the legs or abdominal pain may result from enlargement of para-aortic or pelvic nodes.

Though lymph tissue does not occur in the central nervous system, encroachment on it by swollen extradural lymph tissue may result in cranial nerve palsies, particularly of the oculomotor and facial nerves, or in a rapidly developing paraplegia. Polyneuropathy, brachial neuritis, laryngeal palsy, and myopathies have also been reported.[4] Local intermittent sensory impairment and vocal cord paralysis may occur in patients taking alcohol.

Patients present with symptoms referred to the skin about as often as with neurological symptoms. A general pruritus occurs in some 15% as an initial finding.[5] Nodules of Hodgkin's tissue or ulcerating lesions in the skin may also be seen. Herpes zoster may precede or accompany the onset. Infiltration of the bone with Hodgkin's tissue may sometimes give rise to pain, particularly in the spine.

There is no doubt that diagnosis at an early stage and treatment with radiotherapy can result in a cure[6–8] There is need to dispel the pessimistic attitude sometimes taken to this disease. Thus when local disease in a young patient is treated by radiotherapy more than half the males and more than three-quarters of the females can be expected to survive for five years. After five years the mortality in this group is similar to that in a normal control population.[7] If all age groups are taken together, then 40% of patients with Hodgkin's disease will be alive after 15 years. In contrast, patients with generalized disease and symptoms such as pyrexia or pruritus do not do so well, the 15-year survival rate being 10%. The better outlook in this condition could be lost if either pessimism or the ready availability of chemotherapeutic drugs resulted in their use during the early stages. Chemotherapy is of great benefit but should be employed only in the generalized form of the disease. Though it is sometimes given early as a planned adjunct to radiotherapy in mediastinal obstruction, it should be withheld in the early stages.

The cause of Hodgkin's disease has always been an enigma, and theories relating to it have tended to mirror currently accepted ideas on the causation of disease. The immunological abnormalities that are such a feature of the condition are discussed by Professor D. W. Smithers in his Bradshaw lecture published in this and last weeks' issues of the *B.M.J.* H. S. Kaplan and Professor Smithers[9] first pointed out that certain similarities existed between the course of Hodgkin's disease and animals suffering from graft-versus-host reaction. Wasting, anaemia, and lymphoid depletion seen in these immunological experiments have been termed "homologous disease." But A. C. Aisenberg[10] has pointed out certain objections to Hodgkin's disease being thought of as a human form of homologous disease. Sternberg–Reed cells are very characteristic of Hodgkin's disease but are not seen in homologous disease; lymphoid depletion, which occurs early in homologous disease, is not seen until a late stage of Hodgkin's disease; and finally in homologous disease both delayed hypersensitivity and humoral antibody defects occur, whereas in Hodgkin's disease the latter are uncommon and usually late in its course. Nevertheless, debate on these important questions and the wealth of information presented by Professor Smithers in this year's Bradshaw lecture can serve only to heighten the interest in a condition which remains as enigmatic as it was when Thomas Hodgkin first described it 135 years ago.

Ophthalmic Graves's Disease

In most patients with Graves's disease eye symptoms are associated with goitre and hyperthyroidism and there is little difficulty in diagnosis. When the eye symptoms occur in the absence of goitre and hyperthyroidism the condition is best referred to as the "ophthalmic form of Graves's disease."[1] If the eye symptoms are unilateral the true nature of their origin is easily overlooked. The patient who is referred to an ophthalmologist may be considered to have an orbital tumour and the orbit may be explored. Referral to an otolaryngologist may result in operation on the paranasal sinuses. A physician may mistake a concomitant anxiety state for hyperthyroidism and then treatment results in hypothyroidism. A neurologist will occasionally recommend carotid angiography or other unpleasant investigation.

The ophthalmic form of Graves's disease can be recognized by careful consideration of the clinical features aided by special laboratory investigations. The eye symptoms consist of exophthalmos and bulging of the eyelids, lid retraction, and ophthalmoplegia. These may occur singly or in any combination. Exophthalmos and bulging of the eyelids result from increase in bulk of the orbital contents, especially of the fibro-fatty tissue and the extrinsic ocular muscles. This is a non-specific symptom and is found when any lesion increases pressure in the orbit. In classical Graves's disease with hyperthyroidism the exophthalmos is usually symmetrical, but in the ophthalmic form asymmetry is more frequent, though rarely as noticeably as in cases of orbital tumours.[1]