whether it continues or not, is not without risks and disadvantages for them. And it would do nothing but good for parents of adolescents to be reminded at intervals of the responsibility they have for the upbringing and welfare of their children. This may seem a formidable task, though not an impossible one if sufficient people care about adolescents, and especially about the nearly 5000 young schoolgirls each year in Britain who find themselves pregnant before they have much idea of what life has to offer.

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Elective surgery and the pill

The large scale of the prescription of oestrogens as oral contraceptives and more recently as hormone replacement treatment for menopausal symptoms has brought new clinical problems. One of these concerns the policy to be adopted when surgical procedures need to be performed on women taking oestrogens in view of the association between their use and an increased risk of thromboembolism.[1-3]

Oestrogens accelerate blood clotting and platelet aggregation as well as causing changes in the blood vessel wall,[4] all of which may be factors in intravascular clotting. The first two are more easily studied. Oestrogen-progestogen combinations used as oral contraceptives accelerate the broad-spectrum clotting tests, the prothrombin time, and partial thromboplastin time, and cause rises in specific clotting factors, namely, factors I (fibrinogen), II (prothrombin), VII, VIII, IX, and X.[5-9] In addition, reduction of antithrombin III[10 11] and increases of antiplasmins[12] and of antiactivators of fibrinolysis have been held to be concomitant factors in the production of a hypercoagulable state. Increased platelet aggregation with collagen and thrombin has also been observed after administration of oestrogen.[15-16] Changes in the coagulation system have been reported too when oestrogen alone has been given as hormone replacement therapy.[17] In contrast progestogens given alone do not produce appreciable changes in clotting factors.[18]

While the epidemiological and coagulation studies have been widely accepted as clear evidence of the increased risk of thromboembolic disease during oestrogen therapy, controlled clinical evidence has been scanty.[19] Nevertheless, a recent prospective trial by Sagar and co-workers[20] using the radioiodine fibrinogen uptake test has clearly shown that patients who have taken oral contraceptives during the months before surgery have an increased incidence of postoperative deep vein thrombosis.

Clinicians should therefore consider what action is justified to take account of this risk. Withdrawal of oral contraceptives for four or six weeks before surgery is of doubtful rationale. Some of the changes in clotting factor persist for weeks or months after the discontinuation of oestrogens.[21 22] Furthermore, there is a risk of unwanted pregnancy while the woman is waiting for her operation, for substitute contraceptives are likely to be less reliable. Each case warrants individual assessment. The additional thrombotic risk could be minimised by prophylaxis with low-dose heparin or possibly, where facilities are available, mechanical stimulation of the venous return (without stopping oral contraception), and such treatment may indeed be justified for all but minor surgical procedures.[23]

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HLA and disease: a conundrum

What do dermatologists, neurologists, mouse geneticists, human geneticists, Nobel prizewinners, gastroenterologists, surgeons, tissue typers, paediatricians, and rheumatologists have in common? One answer is an interest in the major histocompatibility complex (MHC), and in Paris from 23 to 25 June it brought these individualists together. The MHC is a system of closely linked multiple genes known in man as the HLA region.[1-3] These genes are located on chromosome 6 and include the A, B, and C loci controlling cell surface glycoproteins detectable serologically, the D locus controlling cell

surface antigens detectable in mixed lymphocyte reactions, and other loci controlling various components of complement and transplantation antigens. Some 20 allelic variants of the A and B antigens are now recognised, and polymorphism of the C and D locus antigens is also established.

The First International Symposium on HLA and Disease[4] was a unique blend of clinicians and experimental scientists, each group with something to learn and to impart in return. Histocompatibility antigens, which until recently were regarded as interesting only to mouse geneticists and some transplantation surgeons, have suddenly become the common property of many biological sciences. We are still exploring the implications of the discovery in mouse and man of specialised genetic mechanisms associated with immune responses and disease.

To the practising clinician the relevance of this collaborative venture is the question, "Will HLA help me to diagnose or treat my patients more effectively?" If experiments on mice are any guide, the answers will not be simple. Early studies showed that in mice susceptibility or resistance to disease (in particular some virus infections) was strongly influenced by genes within the MHC.[5] Later it became clear that not all immune responses were the result of genes within this complex. In some infections or responses additional genes on several other chromosomes were implicated.[6] Recently, it has become evident that some tissue cells, in particular B lymphocytes and monocytes, carry immune associated antigens comparable with those already described in mice and that these, too, are either closely related or identical to the HLA D antigens.[7]

Many of the HLA associations fall into two broad groups. Firstly, there is a category showing strong association with the B locus antigens. These tend to be diseases with a male predominance, and sometimes there is indirect evidence of bacterial infection. The association of the B27 antigen with ankylosing spondylitis, Reiter's disease, and uveitis are well-established examples. Secondly, some diseases originally found to be associated relatively weakly with B locus antigens have now been shown to have a closer association with the D locus. Often there is a female predominance in these diseases, and in some a latent virus infection is suspected. Examples include multiple sclerosis, which is associated with the DW2 antigen (W indicates a "workshop" nomenclature), gluten sensitive enteropathy and dermatitis herpetiformis (DW3), and very recently rheumatoid arthritis, where an association with the DW4 antigen was reported by four independent groups at the meeting. Among the puzzling features is the preponderance of diseases with a strong hereditary component but an unknown aetiology, such as juvenile diabetes. Furthermore, in mice the strongest associations have been between MHC antigens and the growth of tumours induced by oncogenic RNA viruses, whereas in man HLA associations with malignant disease have been among the weakest described.

Four main hypotheses have been proposed to account for these observations. Firstly the simplest, molecular mimicry hypothesis, suggests that the HLA antigen is cross-reactive with the causative agent.[5] Secondly, HLA antigens, being cell-surface structures, might act as convenient receptors for viruses or bacterial products which might then trigger disease. One finding consistent with this theory is the association of BW35 and non-streptococcal (probably viral) glomerulonephritis, reported independently by three groups in Paris.[4] A third mechanism proposed at the meeting by Svejgaard contained elements of both the molecular mimicry and the receptor hypotheses, since it invoked a structural similarity between certain HLA antigens and, say, hormone receptors. The resultant competitive binding could cause the hormone to be rapidly absorbed on to the wrong receptors.

The fourth proposed mechanism, popular with immunologists, is the immune response gene. This hypothesis envisages a class of molecules distinct from immunoglobulins but capable of interacting specifically with antigen and composed partially or totally of gene products of the MHC.

Immune response genes are known to occur in the mouse MHC, and if they exist in man they may share some of the unusual genetic features of HLA genes. Some A and B antigens of the HLA system occur together more often than would be expected if the genes underwent normal random segregation.[8] For example, the haplotype A1, B8 occurs more frequently in European populations than would be predicted by the product of the separate gene frequencies for A1 and B8. This phenomenon is known as linkage disequilibrium. Disequilibrium within the MHC linkage is known to occur not only between A and B alleles but also between B and D. If the immune response system does indeed have genes in linkage disequilibrium with HLA, and especially D locus genes, this would explain the HLA antigen associations with disease. The strength of such an association would depend in part on the degree of linkage disequilibrium between a particular HLA gene and the appropriate immune response genes, and this linkage might differ in separate racial groups.

Our continuing ignorance of the biological significance of the HLA system should warn us against ill-considered demands for large-scale population screening, at least in the short term. The diagnostic usefulness of HLA typing remains strictly limited and more detailed mapping of "disease associated genes" must be the next goal. The specificities of the immune antigen system and its genetic relation to HLA will be the subject of the 7th International Workshop to be held at Oxford in 1977.

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Contaminated infusion fluids

So commonplace is the setting up of intravenous infusions that familiarity may breed contempt. Most residents would be frankly sceptical of the suggestion that it is a potentially dangerous procedure which may cause death. The major risk is from infection. Organisms may gain access at the drip site,[1] especially if there is leakage from the development of phlebitis, and a wide range of pathogens may be responsible for such individual episodes.

We have come to expect that commercial firms will provide guaranteed sterile fluids for infusion, and, indeed, it is most unusual for fluids to be contaminated. Breakdowns may occur in the sterile preparation procedure, however, but their very