

These reports on thrombosis stimulated a great deal of investigation into the mechanism of the untoward clotting tendency brought about by the oral contraceptive steroids. Many changes in various clotting factors have been found but there is little to be gained in enumerating them now since no certain description of the abnormality brought about by oral contraceptives can yet be given. I would like to draw attention, however, to an especially important abnormality induced by oral contraceptives. This concerns the abnormal behaviour of the small formed elements in the blood called the platelets. Abnormally in platelet function is thought by many to initiate the clotting process in arteries and probably in veins. An abnormal tendency of the platelets to stick to each other and to the lining of the vessel wall has been described in several clotting disorders including occlusive vascular disease and thromboembolism. This platelet abnormality occurs in women taking oral contraceptive steroids (see review by Doctors Marion Dugdale and A. T. Masi in Appendix 2D in the Second Report on the Oral Contraceptives).

Space does not permit me to deal at any greater length with the clotting abnormality, perhaps the most important single disorder which is so far known to be associated with the use of oral contraceptives. I must emphasize, however, that the incidence of serious clinical thrombotic episodes in women taking oral contraceptives is very low, only a few fatal cases occurring in 100,000 users every year. The non-fatal attacks, of course, are much more frequent, those requiring hospitalisation of the patient being about ten times commoner than the fatal attacks. But the *potential* significance of the abnormal clotting tendency is far greater than this, as will be mentioned later.

I shall refer briefly now to hypertension. This was first definitely identified with the use of oral contraceptives by Dr. J. H. Laragh of New York in 1967. A recent report by Dr. J. H. Luetscher (*Annals of Internal Medicine*, Vol. 71, November 1969, p. 891) gives a comprehensive account of the subject. Although this is an uncommon complication of oral contraceptive medication, these drugs caused, or substantially contributed to, the development of high blood pressure in about one third of the young women currently being referred to Dr. Luetscher's hypertension clinic.

With this cursory glance at two important problems, namely abnormal blood clotting and elevated blood pressure, induced by oral contraceptives, I now return to consider some implications of the carbohydrate and lipid abnormalities which I have previously described.

Atherosclerosis, popularly known as hardening of the arteries, is responsible for a great deal of mortality and morbidity (sickness) in human beings and accounts for the majority of deaths in many countries, including Great Britain and the U.S.A.

The incidence of the disorder varies within a country and from country to country and herein lies a great deal of its interest because it is obvious from the epidemiological study of the disease, that environmental (and hence probably modifiable) factors are very important in causing the disease, as well as hereditary and constitutional factors. The precise causes of atherosclerosis are not known. We do know that the accelerated development of the disease is associated with a number of factors and these are referred to as "risk factors". The disease is of earlier onset and of far greater prevalence in men below the age of 50 compared to women. Hypertension, obesity, heavy cigarette smoking and physical inactivity increase the risk. Diabetes mellitus is associated with a greatly increased risk and this is especially true in the case of women. Certain metabolic abnormalities are strongly associated with the disease and believed by many to be important risk factors. The best known is an elevated serum cholesterol level, but in more recent years, the importance of elevated triglyceride values has begun to be appreciated. I have previously referred to the serum lipoprotein pattern. Elevation in the low density and very low density lipoproteins, is thought to be an undesirable metabolic abnormality so far as atherosclerosis is concerned. Impairment of glucose tolerance, high insulin levels and, paradoxically, low insulin levels, are also thought to increase the risk of the accelerated development of atherosclerosis. Studies of insulin and triglyceride levels have only become possible on a large scale during the past few years and they have given us new insight into the problem of the development of atherosclerosis.

How important are these abnormalities of carbohydrate and lipid metabolism, and blood clotting in causing coronary occlusion and stroke? Medical opinion is far from being unanimous but the evidence implicating them in the disorder