of oral contraceptives on carbohydrate and lipid metabolism. The findings of Professor WYNN and Dr. DOAR in general confirm their observations of impaired oral and intravenous glucose tolerance, raised blood-pyruvate levels, and increased serum lipid and lipoprotein levels in previous cross-sectional studies (8, 9). The present longitudinal observations provide additional information. Firstly, relative impariment of glucose tolerance was common, being observed in 78% of oral and intravenous glucose-tolerance tests respectively. Plasma-insulin levels were raised and 13% of women had chemical diabetes mellitus during treatment. Fasting serum-triglyceride levels increased in 95% of women tested before and during therapy. Secondly, the impaired oral and intravenous glucose tolerance and the raised seurm lipid and lipoprotein levels returned towards normal after contraceptives were stopped. Thirdly, no characteristic, such as age, parity, degree of obesity, or family history of diabetes, was detected which correlated significantly with the changes in glucose tolerance or serum-lipid levels.

It seems that the oestrogen component alone of the combined oral contraceptive can produce most of these metabolic changes, (2) though further work on the effects of oestrogens and progestagens given singly is clearly required. Earlier WYNN and DOAR (8) proposed that the raised plasma-glucose and blood-pyruvate levels during glucose-tolerance tests in subjects receiving combined oral contraceptives might be "steroid diabetes" caused by high plasma-cortisol levels secondary to the oestrogen component, rather than a primary effect of either the oestrogen or progestagen. This view is supported by the finding of increased non-protein-bound plasma-cortisol during oral contraceptive therapy (10) and also by the fact that protein-bound plasma-cortisol exerts biological activity in certain tissues with protein-permeable vascular beds, such as the liver. (11) While circulating growth-hormone and thyroxine levels are also increased during the taking of oral contraceptives, (2) the patterns of plasma-glucose and blood-pyruvate levels during treatment do not resemble those associated with increased levels of these hormones (12, 13). We have recently discussed (14) possible mechanisms for the increase in serum-triglyceride levels during the administration of oral contraceptives. Although changes of glucose tolerance and serum-lipid levels were observed in most of the women, WYNN and DOAR were unable to find any correlation between the changes of various indices of carbohydrate and lipid metabolism in individual subjects.

The clinical significance of these findings is unknown, but clearly they cannot be ignored, since they raise the possibility of irreversible structural changes, such as atherosclerosis, after ten or twenty years on oral contraceptives. Both raised serum-lipid levels and chemical diabetes mellitus are associated with an increased incidence of occlusive vascular disease (15, 16). The risks of venous thrombosis, pulmonary embolism, and cerebral thrombosis have already been shown to be increased in women taking oral contraceptives (17, 18). It is too early to say whether the incidence of clinical diabetes mellitus and the rate of development of atherosclerosis will be increased by years of treatment with oral contraceptives, and, as an F.D.A. report (1) emphasises, the safety of long-term use of these drugs cannot be predicted (1). Prospective studies of morbidity and mortality in women taking oral contraceptives have only lately been started by the Royal College of General Practioners in Great Britain and the Kaiser Permanente group in the United States, and their results may not be conclusive for twenty or forty years. The risk of potential carcinogenicity of synthetic gonadal steriods will be equally difficult to determine. In view of these doubts, the wisdom of administering such compounds to *healthy* women for many years must be seriously questioned.

References

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