With what may fairly be described as a high index of suspicion, I started to study the metabolic effects of oral contraceptives in 1964. In 1966, with my colleagues Dr. John Doar and Dr. Gervaise Mills, two papers were published in which we described some effects of oral contraceptives on carbohydrate (publication 71) and lipid metabolism (publication 72). Briefly, what we found was this. We studied two large groups of women—one group was using oral contraceptives (the test group) and the other group was not (the controls). The average ability of the test group to metabolise glucose during the course of a glucose tolerance test was significantly impaired compared to the control group. Fig. 1 shows the mean curves for both groups during the oral glucose tolerance test. About 18 per cent of the subjects in the test group had oral glucose tolerance curves which were abnormal as judged by generally accepted criteria. Only two per cent of the control group had such abnormal curves. This abnormality, which was mild in most cases, may be described as "chemical diabetes" to distinguish it from severer examples of the disorder which are found in symptomatic diabetes mellitus. Another abnormality which we found at this time was that the blood pyruvate levels were significantly elevated in the test group compared with the controls. For reasons which need not be expounded now, we considered that the glucose and pyruvate abnormality was most likely due to the oral contraceptive potentiating the metabolic effect of cortisol, the hormone, popularly called 'cortisone', produced in the body by the adrenal gland. As I shall mention later, further research supports this view. As the result of our early studies, therefore, we concluded that the oestrogen-progestagen contraceptives impair glucose tolerance and produce "chemical diabetes". Moreover the mechanism was probably to bring about a biological excess of cortisol, so that the disorder could be further categorized as "steroid diabetes".

The changes we found in the serum lipids (fats) were somewhat complex and need some prior expanlation. The fats circulating in the blood plasma or serum, when the subject has fasted for more than 12 hours, consist of cholesterol, triglycerides, and phospho-lipids. These three substances are associated together with a serum protein to form macro-molecular complexes referred to collectively as the lipoproteins. Various lipoproteins can be separated from the serum using a variety of physical or chemical methods. One method, employing the principle of ultra centrifugation (high-speed centrifuging) can be used to separate the lipoproteins into three classes referred to as high density (H.D.), low density (L.D.L.) and very-low density (V.L.D.L.) classes. The relative proportions of protein, cholesterol, triglyceride and phospholipid varies in each of these three classes of lipoproteins. With this preamble, I can now return to our serum lipid results. We found that the average serum cholesterol in the users was somewhat higher than in the controls, although not significantly so, while the serum triglyceride levels were much higher in the test group compared to the controls. Fig. 2 displays this effect.