Oral contraceptives, in their most widely used form, are mixtures in various proportions, of two types of synthetic steroid, an oestrogen and progestagen. The female hormones, oestradiol and progesterone, are not active when taken by mouth. This disadvantage can be overcome by modifications of the parent steroid. In each case, the modification protects the steroid from inactivation in the liver, so that if given by mouth it passes through the liver and can therefore reach the target issues in an active form. The idea that steroid hormones could be chemically modified in order to make them active when given by mouth is not new. In 1938 it was found that by adding a methyl radical to the 17 carbon of testosterone, an orally active form of this male hormone could be produced. The compound, methyl testosterone, became a prototype for similar modifications to the other gonadal steroids. For example, it was soon followed by the introduction into clinical practice of the orally active oestrogen, ethinyloestradiol. In this drug, the ethinyl radical is added to the 17 carbon of oestradiol, rendering the parent hormone orally active. At about this time, another interesting discovery was made by the synthetic chemists. It was shown that if the ethinyl radical was added to the 17 carbon of testosterone, the resulting compound (ethisterone) ceased to be a strong androgen, but became quite a potent progestagen. This was the beginning of the use of the testosterone molecule to produce hormonal-like steroids simulating the action of progesterone. The next major discovery in the synthetic sex steroid field occurred early in the 1950s when it was found that by removing the methyl group attached to the 10 carbon in testosterone, a compound with novel characteristics was produced, the 19 nor-steroid. 19-nor-steroids can be used to produce two classes of drugs, namely potent anabolic steroids and very effective orally active progestagens. An anabolic steroid may be described as a compound which retains the protein-building anabolic effects of testosterone but has much reduced virilising action. The orally active progestagens have already been described as mimicking the effects of progesterone. Amongst the earliest of the orally active anabolic steroids exploiting the 19-nor-steroid configuration was Nilevar (17-α-ethyl-19-nortestosterone). Norethynodrel (17-α-ethinylestrenalone) was one of the first of the 19 nor-steroid progestagens. Both of these compounds were synthesised in the research laboratories of G. D. Searle and Company.

My studies of the clinical effects of orally active enabolic steroids started in 1957 and went on for several years. I began hoping to find justification for the claims made by their promotors that these compounds were effective remedies in the treatment of many distressing conditions, especially those associated with protein depletion, debility, cachexia, wasting, osteoporosis, post-operative weakness, steroid induced protein catabolism, and even the infirmity of old age. I found instead, that these compounds seemed to have little clinical usefulness but that they produced many metabolic side effects. These effects have been described in the publications numbered 36 to 45 in my curriculum vitae, which is appended with this statement. I draw attention particularly, to publication No. 44, entitled "Anabolic Steroids and Protein Metabolism" and published in *Modern Trends in Endocrinology*, 1967, by Butterworths in London. This article summarises several years experience of the clinical use of anabolic steroids. We found, for example, that these compounds could impair glucose tolerance, cause plasma cholesterol levels to rise, modify the function of the liver in several ways, alter the metabolism of the adrenal hormone, cortisol, produce salt and water retention and were even quite effective oral contraceptives! The reason for most if not all of these changes in metabolism stems from the fact that these drugs modified the function of the liver and that this was brought about by an untoward effect on certain important liver enzymes and organelles, an effect attributed to the alkyl substitution in the 17 carbon position of the parent hormone testosterone. It should be pointed out that these orally active anabolic steroids proved to be far more toxic than testosterone itself. Indeed, even large doses of testosterone have little if any effect on liver function or on the metabolic functions listed above, with the exception of salt and water retention. My experience with anabolic steroids, given perhaps to 100 patients, who were closely supervised, taught me two lessons. The first was, that the patient, while taking the medication could feel quite well. Nevertheless, in many of these subjects, untoward metabolic changes could be demonstrated which made the continued administration of the compound unwise on medical grounds. It should