nisolone molecule, and claimed that it had fewer side effects than other corticosteroids, while having the same general field of use. Upjohn obtained the patent and then licensed Schering to produce the drug.

Lederle brought out triamcinolone in 1958, another molecular modification of cortisone, with a potency about equal to that of methylprednisolone, with the same general therapeutic applications as the other steroids, and with the same claim of fewer side effects. Lederle obtained the patent, and licensed only Squibb.

The latest modification of the cortisone molecule to be marketed is dexamethasone, brought out by Merck and Schering in 1958. This drug is said to be the most potent of the corticosteriods, being about seven times as potent as prednisone,[79] and is also claimed to have fewer side effects. No patent has yet been awarded. Merck, Schering, and CIBA were producing this drug in 1959.

A Survey of worldwide experience with these newer drugs prompted the opinion that their side effects are ". . . certainly no less than those of prednisone and prednisolone. . . . With the newer drugs, digestive accidents, fractures, adrenocortical inhibition, and indfections are still the main dangers. In contrast to the manufacturers' statements, risks are in no way eliminated by the new derivatives." [80] Since it takes years to determine the true incidence of side effects for a given drug, medical opinion is as yet inconclusive, but the most frequently expressed view is that all the corticosteroids will prove to have the same side effects in the long run.[81] Thus product improvement has here taken the form of product competition by means of trial-and-error molecular manipulation, and product differentiation by means of massive selling efforts, rather than by revolutionary advances which would make all previous corticosteroids obsolete.

In other drug markets, the development of new products also relies heavily upon the devising of molecular variations on former products. In oral anti-diabetic drugs, tolbutamide was found in Germany and licensed by Upjohn for sale in the United States as "Orinase." Upjohn carried out extensive clinical testing, and the drug was released for general prescription use in the United States in June, 1957. Other firms conducted research in order to produce a patentable substitute compound. Lilly and Pfizer came up with chlorpropamide, a slight molecular modification of tolbutamide, and Pfizer began to market this product as "Diabinese" in November, 1958. Lilly withdrew its patent application in favor of Pfizer; at present no patent has yet been awarded. United States Vitamin and Pharmaceutical Corporation later discovered phenformin, a molecular modification of certain compounds subjected to study by many scientists prior to the discovery of insulin in 1920, and marketed it as "DBI." [82] Tolbutamide appears to be unusually free from side effects. Chlorpropamide, on the contrary, is not; nor is phenformin.[83] Some physicians are of the opinion that advertising, rather than therapeutic superiority, is responsible for the sales of the later oral antidiabetic drugs.

In the tranquilizers market, the basic research on the more potent tranquilizers was done largely in France, with the development of certain phenothiazine compounds with sedative effects. Smith, Kline and French was licensed to sell chlorpromazine ("Thorazine") and prochlorperazine ("Compazine") in the United States. "Thorazine" was released for sale in 1954 as an anti-emetic; the tranquilizer properties were advertised only later when it was found that a market existed in the mental institution area. "Compazine" was introduced in 1956 as a tranquilizer, and is a phenothiazine compound similar to chlorpromazine. The market for tranquilizers grew, and so did the number of such drugs. Promazine was marketed as "Sparine" by Wyeth in 1957; again the drug is a molecular modification. Amusingly, Wyeth began to advertise promethazine hydrochloride ("Phenergan"), an antihistamine originating in France, as a tranquilizer.[84]

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[79] Report from Pharmaceutical Manufacturers Association, Hearings on Administered Prices, pt. 19, at 10845.

[80] Meyler, *op. cit. supra* note 73, at 148.

[81] Testimony of Dr. Russell Cecil, consulting medical director of the Arthritis and Rheumatism Foundation, Hearings on Administered Prices, pt. 14, at 7985.

[82] Subcomm. Report 123.

[83] The use of chlorpropamide is associated with liver damage and other mischief. Dr. Henry Dolger, in testifying at the Hearings, concluded: "I deplore the premature prosecution of unnecessary and inadequately investigated modification of sound drugs and their indiscriminate and unsubstantiated promotional campaigns." Hearings on Administered Prices, pt. 20, at 11149.

[84] In 1952, 20 per cent drowsiness was noted as a side effect. In 1959, it was stated in an advertisement that "Phenergan relieves apprehension, relaxes the patient, and produces light sleep." *Id.*, pt. 16, at 9272.