AN OVERVIEW OF NONSTEROIDAL ANTIINFLAMMATORY AGENTS (NSAIA)

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Abstract—Since the rediscovery of willow bark extract (salicin) in 1763, there has been a continuing effort to improve efficacy and reduce the side effects of antiinflammatory agents through chemical modification and innovation. The second-generation NSAIA's, phenylbutazone and indomethacin, provided clear support for the idea that these objectives were obtainable. The success of steroid programs in enhancing potency and modifying side effects, coupled with the development of effective screening techniques for identifying anti-inflammatory activity, stimulated an enormous effort to develop new NSAIA's. The products of this effort are now coming to the clinic.

Although less successful than the steroid program in enhancing potency, the effort has succeeded in changing and reducing side effects. As a result, the clinician has a greater choice of agents for dealing with individual patient variability and achieving greater patient acceptance.

INTRODUCTION

The first rational development of a nonsteroidal antiinflammatory agent (NSAIA) should probably be credited to the Rev. Edward Stone (1). In search of a treatment of ague, and reasoning from the Doctrine of Signatures, he rediscovered salicin in the aqueous extract of willow bark in 1763. In 1876 MacLagan reported its particular usefulness in rheumatism (2, 3).

Salicin was largely replaced by salicylic acid following the synthesis of the latter compound in 1859 by Kolbe and Lautemann.

After preparing and testing many analogs of salicylic acid, the Bayer Company introduced aspirin in 1899. According to Martin (4), the objective of the chemical manipulations was to reduce the frequency of gastric intolerance encountered with salicylic acid. The success of aspirin, however, may have been related to its greater efficacy.

The next major advances in antiinflammatory therapy took place in the
1940's. The wartime effort to find effective agents for the treatment of shock gave impetus to the development of steroids. It was largely for their effects on rheumatoid arthritis, however, that Kendall, Reichstein, and Hench received the Nobel Prize in 1950. Sarett of Merck synthesized cortisone in 1946. As with the discovery of salicin in the eighteenth century, an era of molecular manipulation was initiated, this time for the purpose of selectively enhancing the varied biologic properties of corticosteroids. The quest still continues a quarter of a century later, reflecting the successes in developing extraordinarily potent steroids with a relatively narrow spectrum of effects. These successes were dependent not only on the virtuosity of the chemists but also on the availability of suitable biological assays for compounds. The principal screening procedure for antiinflammatory action was inhibition of granuloma formation, first in the "pouch" assay and later in the subcutaneous cotton pellet system (5-7).

Phenylbutazone had been developed in the 1940's by Stenzel of Geigy (8) at the same time as the development of steroids but unrelated to them or the antiinflammatory concepts that have subsequently determined the course of drug development. Amidopyrine, an alkaline compound, was mixed with an acid analog, phenylbutazone, to enhance solubility. During clinical testing it became apparent that the solubilizing agent was therapeutically more active than the principal. This finding, inelegant as it was, provided insight and the conviction that nonsteroidal antiinflammatory drugs were achievable.

By the early 1950's antiinflammatory properties of steroids were apparent, and phenylbutazone was an example of a new NSAIA. With this background, T. Y. Shen, C. A. Winter, and their co-workers at Merck developed indomethacin using granuloma inhibition and foot edema assays (9). Also during the 1950's, C. V. Winder and co-workers at Parke Davis explored the activity of anthranilic acids by using a UV erythema model (10). These efforts represented the first truly rational development of new antiinflammatory agents in two centuries.

The successful introduction of indomethacin into clinical medicine in the early 1960's provided a sustained stimulus for a reenactment of the processes learned in the steroid programs. Now, 10 to 15 years later, the third-generation NSAIA's have appeared and are still appearing in the pharmacy. It is too early to make a final judgment on the importance and clinical usefulness of these newer compounds, but it should be possible to arrive at some modest conclusions and generalizations.

GENERAL CHEMICAL CLASSIFICATION

Since the structural basis of clinical activity is unknown, the grouping