However, the development of a multitude of useful medicinal agents over the past 20 years—some of them, like indomethacin, for disease entities still beyond our capability for understanding—provides evidence that one does not need to know all about a biological function to alter it beneficially.

The development of indomethacin does not suggest that we have moved any closer to understanding the factors that precipitate or are involved in the rheumatoid process. What the successful application of the compound does imply is that, with the benefit of accrued knowledge and experience, Merck scientists were able to formulate a working hypothesis as to what initiated and sustained the inflammatory process; and also able to develop methodologies for the discrete examination in laboratory animals of the effects of candidate compounds on the basic factors of the disease.

While the search for more potent corticosteriods continued in the early 1950's, a group of Merck scientists and biochemists started what was to be a 12-year search in another direction—to find a compound that was not hormonal in nature, but that would still provide the benefits of the steriods.

Early in 1957 the attention of the scientists in this program turned to compounds with an indole nucleus. This was because an indole metabolite, serotonin, was thought to play a role in initiating and sustaining inflammation. A number of serotonin antagonists were synthesized by Merck chemists and made available for pharmacologic assessment as anti-inflammatory agents.

The serotonin theory eventually proved to be wrong, but it did provide the first promising chemical lead in our nonsteriod program.

The program began to achieve full focus later in 1957, when Merck scientists observed the first promising indole derivative after evaluating hundreds of unsuccessful agents, but it did not live up to the expectation of Merck scientists and physicians and was dropped.

In March 1961, another promising derivative was finally synthesized. That compound, too, was effective in preclinical studies, but even as clinical trials were being planned, our scientists developed another indole derivative, indomethacin, which appeared to have greater potency with less toxicity than any of the previous compounds.

Before indomethacin could be studied in man, it had to undergo lengthy and comprehensive testing in animals. More than 100,000 animals were used during the nonsteroid anti-inflammatory program leading to the development of the compound.

While animals themselves do not suffer from rheumatoid arthritis as a disease entity, we have been able to utilize a number of animal models to define, reproduce, and control in the laboratory fundamental phenomena involved in arthritic diseases.

Through the capability of developing methodologies for the control of biological phenomena in animals, our pharmacologists achieved the ability to strip arthritis down to its essential elements of inflammation, swelling, pain, and heat or fever, so that the action of potential compounds could be examined unfettered by the imponderables created clinically as patient, disease, and drug interact.

Some examples of animal models to test for antiarthritic activity are the carrageenin assay, which helps in the assessment of a drug's ability to reduce inflammation, pain, and swelling; the granuloma cot-