ton pellet assay, for measuring a drug's ability to inhibit inflammation and fibroblast proliferation; and still other tests which provide an indication of the analgesic and anti-inflammatory properties of compounds.

Additional control of these animal models is afforded by a comparison of the dosage of the drug with the response. Moreover, such dosage-response relationships are further compared with those of compounds commonly employed in the management of arthritic disorders. These comparisons are more than comparisons of potency, for we are able to compare the qualitative characteristics of the compounds as well.

The sizable and comprehensive animal studies with indomethacin provided clinicians with demonstrative evidence of the safety and efficacy of the compound, warranting tests in man.

The anti-inflammatory activity of indomethacin was demonstrated in the cotton pellet granuloma inhibition test in mice in which granuloma inhibition was observed following both oral and local administration. It was also demonstrated in the inhibition of edema induced by injection of the irritant, carrageenin, into the hind paw of rats.

Fever-reducing activity was demonstrated by inhibiting the fever produced by injection of a bacterial endotoxin in both rabbits and rats, as well as yeast-induced fever in rats.

In these and other tests, the potency of indomethacin was significantly greater than that of the anti-inflammatory compounds with which it was compared. It must be noted, however, that these studies comparing indomethacin with other known compounds, though serving as valuable indicators to the clinical investigator, are based on phenomena measured in animals and are not directly translatable to disease in man.

As part of the pharmacologic assessment, indomethacin was examined in the laboratory for its effect on the heart, the cardiovascular system, and autonomic reflex mechanisms, as well as for its effect on excretion, renal function, and animal behavior. Indomethacin did not affect any of these organ systems and processes.

When methodology was needed to examine a specific effect, we devised it if it was not available. Just as the Porter-Silber test, for example, bearing the name of two members of our staff, has become standard procedure in steriod measurement, so we devised new methodology to enhance reliability of metabolic studies with indomethacin. To do this required meticulous knowledge of the physiology of the animals employed in the studies and the synthesis of indomethacin compounds labeled with radioactive carbon. Such advances in methodology not only furthered our own indomethacin studies, but also contributed to the studies of scientists in other laboratories, since much of our methodolgy was published in detail.

Tests in several species to determine the metabolic fate of indomethacin indicated that in the dog, the drug present in the plasma is essentially all unchanged indomethacin. In other animals, metabolism of the drug differs. In the guinea pig, a significant amount of the drug is present in the plasma as a metabolite, with a small amount of indomethacin present in the cerebrospinal fluid. The route of excretion depended on the species and not the dose or the route of administration.

The influence of indomethacin and hydrocortisone on resistance to