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This Week's Citation Classic

Winter C A, Risley E A & Nuss G W. Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs. *Proc. Soc. Exp. Biol. Med.* **111**:544-7, 1962. [Merck Institute for Therapeutic Research, West Point, PA]

This paper presented a method for testing compounds for antiinflammatory activity. It was the first technique available which permitted an assay after single oral doses at nontoxic levels within a single day, and which yielded linear and parallel log dose responses. [The *SCI*® indicates that this paper has been cited in over 1,000 publications since 1962.]

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"In the absence of full knowledge of the etiology of inflammatory diseases, antiinflammatory drugs seem to offer the best treatment for the relief of symptoms, but at the time of this research, the only generally useful nonsteroidal antiinflammatory drugs were aspirin and phenylbutazone. Medicinal chemists, eager to proceed with synthetic programs looking for safer and more effective compounds, were hampered in their study of structure-activity relationships by the failure of pharmacologists to provide adequate guidance. Assays of antiinflammatory activity based upon the cardinal signs of inflammation included the classic method of Meier and co-workers[1] which tested for the inhibition of granuloma formed around a cotton pellet inserted subcutaneously in the rat. The biological activity of indomethacin was discovered in this way.[2]

"Indomethacin soon established itself as the antiinflammatory drug by which others were judged, and we at the Merck Institute for Therapeutic Research felt increased urgency to improve our methods of testing new compounds. The usefulness of the granuloma inhibition assay was limited to compounds available in sufficient quantity to treat a group of animals daily for a week. We therefore sought a method responsive within hours and requiring only a single administration. A technique based upon swelling induced by acute inflammation seemed to offer a potential solution.

"Others had found that antiinflammatory drugs could inhibit the edema produced by a phlogistic agent,[3] but responses were. nonspecific, reacting to compounds of various classes, and often not to antiinflammatory compounds except in toxic doses. A more specific phlogistic agent was found in carrageenan. The finding was empirical; at first we had little knowledge of the properties of carrageenan but we soon found that it induced reproducible edema which responded in a fairly specific way to nontoxic doses of antiinflammatory drugs, yielding parallel linear log dose-response data. We were now able to test small samples of new compounds and report results within hours. Eventually, an expanded study of large series of newly synthesized agents became possible,[4] which earned the Directors' Award for scientific achievement given by the directors of Merck & Co., Inc.

"Our publication apparently filled a need, for it soon became the procedure most widely used for assay of antiinflammatory activity.[5] In our original publication, our preferred antiinflammatory compound, indomethacin, was not mentioned, although by that time, investigation of indomethacin was well under way. Not until the following year were the wraps taken off this compound.[2] It later developed that not all samples of carrageenan were the same, that edema induced by carrageenan was biphasic, and that antiinflammatory compounds inhibit only the second phase.[5] It wasn't until a decade later that Vane[6] proposed the hypothesis that antiinflammatory drugs owe their activity to inhibition of prostaglandin synthesis. At last it became clear that carrageenan releases prostaglandins, and that in using our method for seeking new drugs, what we are actually looking for are new inhibitors of prostaglandin synthesis. This offers a reasonable explanation for the fact that antiinflammatory drugs are useful in treating symptoms but do not attack the fundamental causes of rheumatic disorders; the latter requires a new approach, and such research is well under way."

1. **Meier R, Schuler W & Dcsaulles P.** Zur Frage des Mechanismus der Hemmung des Bindgewebswachstums durch Cortisone. *Experientia* **6**:469-74, 1950.
2. **Winter C A, Risley E A & Nuss G W.** Anti-inflammatory and antipyretic activities of indomethacin. l-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-indoie-3-acetic acid. *J. Pharmacol. Exp. Ther.* **141**:369-76, 1963.
3. **Domenjoz R.** The pharmacology of phenylbutazone analogs, *Ann. NY Acad. Sci.* **86**:263-91, 1960.
4. **Shen T Y & Winter C A.** Chemical and biological studies on indomelhacin. sulindac and their analogs. *Advan. Drug Res* **12**:89-245, 1977.
5. **Swingle K F.** Evaluation for antiinflammatory activity. (Scherrer R A & Whitehouse M W, eds.) *Antiinflammatory agents, chemistry and pharmacology*. New York: Academic Press, 1974. Vol. 2. p. 33-122.
6. **Vane J R.** Inhibition of prostaglandin synthesis as a mechanism of action of aspirin-like drugs. *Nature New Biol.* **231**:232-5, 1972 [Citation Classic. *Current Contents/Life Sciences* **23**(42):12. 20 October 1980.]