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The Pharmacology of Inflammation. I. Technic.

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In the induction of inflammatory reactions, two desiderata should be satisfied: (1) The reaction produced must be readable and fairly quantitative. (2) It should be repeatable a number of times in the same animal. For this purpose the conjunctival mucus membrane of the rabbit offers a sensitive surface well supplied with nerves and blood vessels; easily observed without undue disturbance to the animal, and anatomically constructed into a pouch capable of holding drugs for a relatively long time. The experiments of Amberg, Loevenhart, and McClure,¹ and Chiari and Januschke² show conclusively that pure mustard oil so injures the conjunctival mucus membrane and the cornea that only one experiment can be performed on any individual animal. It is obvious that a technic which would not produce a permanent damage to the structure of the eye would permit a more reliable study of the effects of drugs on the inflammatory process.

In the experiments here reported, the objections to the use of pure mustard oil as the irritant were obviated by substitution of a 15% solution of essential oil of mustard in mineral oil. One drop of the latter instilled into the conjunctival sac of a rabbit produced a reaction which was readable, and from which the animal recovered completely in from 7 to 14 days, at which time the experiment could be repeated. Some of the animals were used for as many as 14 experiments, without permanent injury to the eye. In 114 instillations made in 27 rabbits, the following phenomena were

¹ Amberg, Loevenhart, McClure, *J. Pharm.*, 1917, **10**, 209.

² Chiari and Januschke, *Arch. f. exp. Path. u. Pharm.*, 1911, **65**.

constantly observed: (a) blepharospasm which lasted about an hour; (b) lachrymation for about 15 minutes; (c) immediate injection of the conjunctival blood vessels, which reached a maximum in 15 minutes, but was still present after 48 hours; (d) pin-point miosis, the pupil attaining the size of the control pupil in about one hour; (the miosis was unaffected by atropine); (e) edema of the conjunctival mucus membrane, which constituted the most constant and readable phenomenon of the inflammatory reaction. The edema was first observed 5 minutes after the instillation, and reached a maximum in one half hour, at which time the sac-like swelling of the lids caused their palpebral margins to bulge from the globe of the eye. The reaction was read as "4 plus" only when all 4 components of the conjunctival mucus membrane—namely, upper and lower lids, nictitating membrane, and scleral portion, were maximally involved. If only 3 of these components were involved, the reaction was marked "3 plus". A total absence of edema was recorded as "no reaction", regardless of the appearance of any of the other phenomena enumerated above.

It now seemed desirable to try to induce this inflammatory reaction in animals injected with drugs known to inhibit inflammatory processes. Sodium salicylate and quinine bisulphate were the drugs chosen.^{3,4} Nine rabbits were injected intravenously with a 10% solution of sodium salicylate, a total of 17 times, the dose each time being 300 mg. per kilo of animal. Ten rabbits were injected intravenously with 1% solution of quinine bisulphate a total of 22 times, the dose each time being 30 mg. per kilo of animal. The number of "inhibition" experiments per animal was limited by the deleterious effects of the dose of drug necessary for the production of complete inhibition; the factor of safety is small, for the dose necessary to inhibit inflammation is very close to the minimal lethal dose.

The technic employed in these experiments was as follows: (a) One drop of 15% mustard oil in mineral oil was instilled into one conjunctival sac of a rabbit. The animal was observed until the edema reached a maximum (one half hour), (b) inhibitor drug was then injected intravenously, (c) within 5 minutes, one drop of irritant was instilled into the conjunctival sac of the other eye.

This technic permitted a direct comparison between inflammatory reactions produced on the same day, as well as a comparison of the reactions produced from day to day. It also furnished data as to any possible "curative" effect that inhibitory drug might have on the

³ Januschke, *Weiner Klin. Woch.*, 1913, **26**.

⁴ Yasko, Ikeda, *J. Pharm.*, 1916, **8**, 137.

"normal control" reaction in the eye first instilled. In 39 experiments, "curative" effect was observed only once.

The appended table enumerates the results obtained in 75 control experiments, as compared with 17 experiments in which sodium salicylate was administered, and 22 experiments in which quinine bisulphate was used. It also furnishes an adequate indication of the readability of the edematous reaction, and the faithfulness with which it may be reproduced. This method is being used to investigate a number of other drugs.

TABLE I.
The incidence of edema elicited by 15% mustard oil in mineral oil, and its suppression by sodium salicylate and quinine bisulphate.

Reaction	Controls (75)	Sodium Salicylate (17)	Quinine Bisulphate (22)
(++++) max.	55	0	0
(+++)	15	0	0
(++)	5	5	1
(+)	0	5	10
No reaction	0	7	11

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Protein Sulfhydryl Groups.

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The importance of the sulfhydryl (SH) groups of proteins in cellular respiration has been clearly recognized (deRey Pailhade,¹ Heffter²) and the appearance of these groups in some proteins as the result of denaturation has been demonstrated (Arnold³). For the study of both cellular respiration and protein chemistry, therefore, a means of measuring protein sulfhydryl groups is desirable. Investigation of them has depended mainly on the color reaction they give with nitroprusside. For this test the groups must be in the reduced (SH) and not in the oxidized (S-S) form. Heffter² supposed that since many denatured proteins, the denatured serum

¹ deRey Pailhade, *Recherches Experimentales sur le philothion, etc.* Paris, Masson, 1891.

² Heffter, *Med. Naturwiss. Arch.*, 1908, **1**, 81.

³ Arnold, *Z. Physiol. Chem.*, 1911, **70**, 300, 314.