LETTERS TO THE EDITOR

A Biochemical Distinction Between Non-Steroid Anti-inflammatory and Analgesic Drugs

SIR,—As alternatives to steroids, phenylbutazone (Butazolidine) and acetylsalicylic acid are prescribed extensively for the management of rheumatic diseases. It is well known that these two drugs are moderately potent analgesics and exhibit antipyretic activity. These facts have lent credence to a belief that anti-inflammatory (potential antirheumatic) activity amongst non-steroid drugs is either synonymous with, or largely overlaps, analgesic activity in non-narcotic drugs. This belief has been strengthened by recent reports that mefenamic acid possesses antipyretic, antinociceptive and anti-inflammatory activity in animals (Winder, Wax, Scotti, Scherrer, Jones and Short, 1962) and is a promising analgesic for clinical use (Cass and Frederick, 1963).

TABLE I

SOME PROPERTIES OF NON-NARCOTIC ANALGESICS
DATA FOR ANTI-INFLAMMATORY ACTIVITY WERE DRAWN FROM PUBLISHED REPORTS (see text)

Analgesic	Anti-inflammatory activity	Effect on	
		Oxidative phosphorylation (liver)	Phosphate metabolism (cartilage)
Phenylbutazone	†	†	†
Oxyphenbutazone	†	†	†
Amidopyrine	†	—	—
Antipyrine	—	—	—
Paracetamol	—	—	—
Acetanilide	—	—	—
Acetophenetidine	—	—	—
Salicylic acid	†	†	†
Salicylamide	—	—	—
2 and 4-Hydroxyisophthalic acids	—	—	—
Mefenamic acid	†	†	†
3-Hydroxycinchophene	†	†	†

† Indicates activity.

Adams (1960) suggested that it was not justifiable to classify all analgesic-antipyretic drugs as a single group. He presented pharmacological data which indicated that non-narcotic analgesics could be divided into two groups: (i) those including salicylic acid, aspirin and phenylbutazone which suppressed inflammation in laboratory animals and (ii) other analgesics including several derivatives of salicylic acid, which were inactive in an anti-inflammatory test (ultra-violet-light induced erythema). It has now been found that this subdivision of the non-narcotic analgesics into at least two groups according to their anti-inflammatory properties, is wholly supported by biochemical data.

Oxidative phosphorylation in isolated liver mitochondria is uncoupled by non-steroid anti-inflammatory drugs (Adams and Cobb, 1958; Whitehouse and Haslam, 1962) and certain anti-inflammatory steroids (Gómez-Puyou, Pěna-Díaz, Guzman-García and Laguna, 1963). There is evidence that these compounds will also uncouple oxidative phosphorylation in extrahepatic tissues, notably in connective tissues (Whitehouse and Boström, 1962; Whitehouse and Haslam, 1962). Table I correlates the anti-inflammatory activity of some

non-narcotic analgesics (Adams, 1960; Cutting, 1962; Winder and others, 1962) with their effects upon (a) oxidative phosphorylation in respiring liver mitochondria with succinate as substrate and (b) upon phosphate metabolism in a connective tissue (cartilage), determined *in vitro* according to procedures described elsewhere (Whitehouse and Haslam, 1962). A compound was considered to have no significant effect upon oxidative phosphorylation or phosphate metabolism if the P/O quotient, or phosphate incorporation by cartilage slices, in the presence of the drug (2mM) was not less than 85 per cent of the value obtained in parallel incubations without added drugs. These results confirm and extend Brody's (1956) observations of the effect of certain analgesics on oxidative phosphorylation.

The only compound which failed to uncouple oxidative phosphorylation *in vitro* but which is known to have some anti-inflammatory activity *in vivo*, was amidopyrine. Two of its metabolites, 4-aminoantipyrine and 4-*N*-acetylaminopyrine (Brodie and Axelrod, 1950; Halberkann and Fretwurst, 1950), were also tested and found to be as inactive *in vitro* as amidopyrine. Amidopyrine is approximately one-eighth as potent as phenylbutazone in the guinea-pig ultraviolet light erythema assay for anti-inflammatory activity (Adams, 1960).

Several other analgesics were tested and found not to uncouple oxidative phosphorylation at a concentration of 2mM. These included salicoylpiperidine (Profft and Hogel, 1962) phenyramidol hydrochloride, morphine sulphate, pethidine (meperidine) hydrochloride and carisoprodol: none of these is known to exhibit significant anti-inflammatory activity in laboratory animals.

On the other hand, sodium aurothiomalate (Myochrysin) and gold sodium thiosulphate (Sanochrysin) which are not analgesics but are sometimes prescribed as antirheumatic drugs, uncouple oxidative phosphorylation in liver mitochondria at concentrations of 3mM and 0·3mM respectively. Their gold-less chemical analogues, sodium thiomalate and sodium thiosulphate had no effect on oxidative phosphorylation at 5mM concentration. Antimalarial aminoquinolines such as chloroquine and hydroxychloroquine which manifest antirheumatic activity only after prolonged administration, could be distinguished biochemically from other non-steroid anti-inflammatory drugs by their failure to uncouple oxidative phosphorylation at concentration up to 5mM, even after pre-incubation with liver mitochondria for 4 hr. at 2°.

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