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When is a drug inactive? Concerning the uricosuric activity of some anti-inflammatory drugs

Many acidic drugs are extensively bound to plasma proteins and it has been generally accepted that the bound fraction has no pharmacological activity (Goldstein, 1949; Brodie, 1965). This concept certainly needs modifying in the light of recent reports that one drug may displace another from a common binding site on the albumin molecule; for example, salicylate and phenylbutazone can displace thyroxine and certain sulphonamides, sulphonylureas and oral anticoagulants (Solomon & Schrogie, 1967; Meyer & Guttman, 1968).

Such an interaction between two drugs *in vivo* can be formulated as follows:

Species A + Albumin–Species B combination $\rightleftharpoons$ Species B + Albumin–Species A.

Thus one drug (A) may have an "adjuvant," or potentiating, action on the pharmacological activity of another drug (B) by either increasing its effective concentration (as unbound drug B) or otherwise making it more readily available to its responsive receptors. Drug A would, however, acquire and demonstrate this adjuvant activity only when it was itself bound to the albumin. We wish to extend and further illuminate this concept that when albumin-bound, a drug entity may "acquire" pharmacological activity, which need not necessarily be that of enhancing the activity of another drug or shortening its biological half-life.

Experiments in our clinic showed that the oral ingestion of certain drugs by healthy adult volunteers significantly lowered, in a reversible manner, the capacity of the plasma proteins to bind uric acid (Bluestone, Kippen & Klinenberg, 1969). Most of this urate-binding capacity (*ca* 70%) is associated with the albumin fraction. When the urate-binding capacity of human albumin preparations both in the presence and absence of added drugs *in vitro*, was measured (Table 1) it was found that a number of anti-inflammatory acids effectively inhibited urate binding to human albumin *in vitro*, and that in man, aspirin and phenylbutazone could probably displace uric acid from its albumin binding site(s) *in vivo*.

These observations suggested that phenylbutazone and salicylates are useful uricosuric drugs because they displace some of the albumin bound urate and so augment its renal clearance. When albumin bound, phenylbutazone and salicylate may well be inactive as analgesics, antipyretics or anti-inflammatory agents; but at the same time they could also have a uricosuric effect, quite apart from any other uricosuric activities they might have when not bound to albumin, e.g., acting directly on the kidneys. In fact it may now be helpful to subdivide drugs, currently classed as "uricosurics" according to whether they (*a*) can inhibit tubular reabsorption of urate, (*b*) can displace urate from its binding sites in plasma or other tissues, or

Table 1. *Displacement of urate from its albumin-binding site(s) by some anti-inflammatory anions and probenecid*

Drug	ED50 *in vitro** (mM)	Efficacy *in vivo*†	
		Dose (g/day)	Response
Aspirin	0·3	3·0	+++
Sodium salicylate ..	0·1		N.D.
Phenylbutazone ..	0·15	0·4	++
Sulphinpyrazone ..	0·25	0·4	—
Indomethacin	0·3	0·15	—
Mefenamic acid ..	0·1	1·5	+
Probenecid	0·3	1·5–3·0	++

N.D. = not determined.

* Concentration of drug inhibiting urate binding by 50% in PIPES buffer, pH 7·35 containing 0·75 mM crystalline human serum albumin (Pentex Inc., Kankakee, Illinois) and 0·9 mM uric acid, determined by equilibrium dialysis at 4° (Klinenberg & Kippen, 1970). Saturated solutions of colchicine and allopurinol were almost devoid of activity.

† Ability to reduce plasma urate-binding capacity (determined *in vitro*) after ingestion of drug by at least 3 normal healthy adults for at least 2 days; see Bluestone & others (1969). Key: +++ = over 70% inhibition, ++ = over 40% inhibition, + = over 20% inhibition.

(*c*) facilitate urate excretion by yet some other means—while recognizing that a given uricosuric drug may enhance urate excretion by more than one of these actions at the same time.

To summarize: we would like to re-emphasize that whilst a drug is retained within the body, it should *always* be considered potentially active, even when bound to "silent-receptors" such as the albumin drug-binding sites. A drug might still cause some unexpected and apparently unrelated pharmacological (or pathological) effects by displacing certain hormones, other drugs or even normal metabolites (e.g., bilirubin, uric acid) from their usual binding sites, including the appropriate catabolic enzymes.

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