Platelet activating factor and asthma

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First encounters

David Gordon joined me at the Kennedy Institute of Rheumatology, bringing with him a newly developed radio-immunoassay for E-type prostaglandins (PGs) and an experience of industrial pharmacology. The prospect of having an immunoassay for PGs was especially attractive, for it provided an opportunity to determine whether a particular inflammatory cell population might serve as the major source of E-type PGs in inflammation. At that time, the prevailing and authoritative view was that neutrophils subserved that function [1, 2]. However, our examination of the abundant neutrophils that were collected from the synovial effusion from an untreated patient with acute rheumatoid arthritis was unrewarding. Inconsequential levels of PGs were produced by synovial neutrophils following short term culture, an observation in marked contrast with the substantial amounts of E-type PGs present within the synovial fluid [3]. These results prompted culture of macrophage-rich populations as a control, thereby revealing the production of substantial quantities of E-type PGs by this cell type [3]. Our conclusions, derived initially from bioassay and radioimmunoassay were confirmed subsequently by definitive chemical techniques [4]. These observations led to the recognition that PGE₂ formation by macrophages can regulate lymphokine secretion [5], an interpretation which has survived the vagaries of immunological nomenclature [6]. My academic bias was to pursue the regulation of lymphokine production, whilst David Gordon favoured use of macrophage cultures for the study of drug effects and he made the novel observation that glucocorticosteroids resembled non-steroidal anti-inflammatory drugs by inhibiting PG formation [7]. In addition to introducing me to glucocorticosteroids, these experiments marked my first encounter with the anti-asthma drug cromoglycate. Cromoglycate had been included in these studies, since David Gordon was already (in 1973) aware that the mode of action of this drug in asthma was uncertain; hence, he reasoned that a new pharmacological test might detect a relevant property of cromoglycate. In the event, his observations were negative and this outcome is echoed a decade later in analogous studies of thromboxane formation [8]. However, the idea was not unreasonable and in the interim, it has been reported that lysosomal enzyme release, following IgE-dependent activation of macrophages was reduced by cromoglycate [9].

Cromoglycate and the mast cell

Discovery of cromoglycate was not a consequence of some profound insight into asthma; rather, it resulted from empirical self-medicating by Dr. Roger Altounyan. This unconventional approach was vindicated by the detection of a wholly novel substance, that is effective in asthma prophylaxis [10]. In such circumstances, it is proper that pharmacologists must consider whether cromoglycate
is unique, or whether this drug represents one of a series of compounds with properties more favourable to therapy (e.g. increased solubility, increased potency, oral absorption). Amongst pharmacologists with an active interest in such drugs, there was initially a rapid acceptance that the efficacy of cromoglycate in asthma derived from an ability to inhibit mast cell activation, as had been inferred from the capacity of cromoglycate to inhibit expression of passive cutaneous anaphylaxis in the rat [11] and to inhibit mediator release from fragments of human lung in vitro [12]. However, the validity of this hypothesis was soon questioned, since compounds related to cromoglycate were without efficacy in clinical asthma, despite increased potency in laboratory tests. Thus, when we joined the Brompton Hospital in late 1975, there was adequate published data to question the dogma that surrounded the mode of action of this drug; such doubts were re-inforced by the opinion of physicians who had experience of clinical studies of potential successor compounds with a negative outcome, or had discussed informally the studies and findings of fellow investigators. Hence, even though there was paucity of published reports on the clinical efficacy of compounds analogous to cromoglycate, it was already a widely-held view that such drugs might not emerge, despite the extensive efforts of many pharmaceutical companies. Reading the clinical literature on cromoglycate in early 1976 served to reinforce that interpretation, an outcome which was a personal disappointment, since I thought that our extensive laboratory experience in the measurement of increased vascular permeability of anaphylactic and other cutaneous responses would be an advantage in this area of research.

Evaluation of the mast cell concept

The realisation that cromoglycate was not effective by virtue of an effect upon mast cell activation led me into the position of a dissident, making occasional negative comments and writing nothing of substance on this topic, since the net result of critical utterances was to encourage public opprobrium. Detailing the deficiencies of the mast cell concept of cromoglycate efficacy was undertaken together with, and at the suggestion of, Dr. Tom Stokes. As a research registrar, he had the laborious task of co-ordinating a large scale trial of oxatomide in asthma, which I had predicted would be negative notwithstanding the preclinical data that established the capacity of this drug to inhibit mast cell activation. Subsequent to the study [13], we reviewed the clinical and experimental evidence that favoured mast cell stabilisation as a basis for efficacy of cromoglycate in asthma and concluded that cromoglycate analogues selected by reference to cromoglycate in asthma and concluded that cromoglycate analogues selected by reference to mast cell stabilisation would not be effective in asthma [14]. Although regarded by many as presumptuous in 1976, the conclusion was not hotly disputed in 1981 and, with the passage of time and the demise of further cromoglycate analogues, has become conventional wisdom. It is interesting to consider why the concept of mast cell stabilisation became so strongly established to the extent that it is still promulgated in academic medicine [15], even though in the pharmaceutical industry these tests have been widely accepted as inappropriate [16].

The clinical evidence

Early clinical experience of cromoglycate in allergic asthma coupled with evidence that there was inhibition of allergic responses in rat skin [11], or human lung [12], prompted evaluation of cromoglycate efficacy in patients subject to allergen inhalation, in order to test more formally the conclusion that cromoglycate inhibited allergic responses in asthma. It could be shown that administration of cromoglycate thirty minutes prior to allergen inhalation often fully inhibited the acute bronchospasm [17]. To some extent, such an observation accords with the ability of cromoglycate to inhibit PCA reactions in the rat, on the other hand, an absence in man of the self-tachyphylaxis that is so characteristic of the action of cromoglycate in the rat does not support the proposition that mast cell stabilisation is the property of cromoglycate that determines asthma efficacy. Such anomaly should have attracted more attention, but presumably was overshadowed by the evidence that, in addition to the acute response to allergen, cromoglycate could inhibit late-onset reactions, a property hitherto only observed with steroids [18]. In this way, an anti-allergic action of cromoglycate could be clearly demonstrated; for cromoglycate has no bron-