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Drugs for asthma: mast-cell stabilisers

Mast cells are present in connective tissue throughout the body. Their name was taken from the German *masten* (to feed) when their cytoplasmic granules were believed to be products of phagocytosis. In fact, the granules are composed of complex macromolecules of many biologically active substances formed by intracellular synthesis, which are released into the extracellular space when "degranulation" occurs in response to immunological and histochemical stimuli.

The survival of mast cells in higher organisms seems to imply that they have some vital physiological function, possibly concerned with the homoeostatic control of the metabolism of connective tissue and protection against damage by noxious agents. At all events, mast cells are well equipped to serve this purpose, since their granules contain vasoactive agents (which are also bronchoconstrictors) such as histamine, serotonin, slow-reacting substance of anaphylaxis, and prostaglandins; enzymes and other substances, such as heparin, which may be implicated in both tissue damage and tissue repair; and chemotactic mediators in some types of inflammatory reaction.[1]

Paradoxically, no physiological mechanism has been identified which promotes or regulates the release of any or all of these substances in healthy persons. Yet the sudden (and apparently unphysiological) degranulation of mast cells may have damaging consequences when, for example, large amounts of histamine or slow-reacting substance of anaphylaxis are discharged into the extracellular space. In clinical terms, the most common trigger of degranulation appears to be a type I antigen-antibody reaction on the surface of mast cells which have been sensitised by cell-bound IgE antibody as a result of previous exposure to antigen.[2] If large numbers of mast cells throughout the body are sensitised in that way, acute and even fatal anaphylaxis can result from subsequent exposure to the same antigen.[2] More often, however, mast-cell degranulation is confined to one or more "target" organs, such as the bronchi, the nasal mucosa, the gastrointestinal tract, or the skin. This is now widely assumed to be the mechanism responsible for most of the common "allergic" disorders in atopic subjects.

Studies in animals have shown that an IgE-mediated reaction promotes degranulation through the influx of calcium ions into the mast cells and by the activation of membrane-associated enzymes.[3] This is the basis of the hypothesis that in patients with extrinsic asthma the prophylactic value of sodium cromoglycate is related to its "stabilising" effect on the mast-cell membrane, which prevents degranulation and the subsequent release of substances which stimulate bronchial smooth-muscle contraction.

Pretreatment with sodium cromoglycate by inhalation in patients with extrinsic asthma can certainly prevent bronchoconstriction after antigenic challenge,[4] and laboratory experiments have shown that the same drug inhibits the release of histamine and slow-reacting substance of anaphylaxis from preparations of chopped human lung sensitised by reaginic antibody and incubated with the appropriate antigen.[5 6] Yet, while these observations provide indirect evidence that the release of bronchoconstrictor agents present in mast cells can be inhibited by sodium cromoglycate, they do not necessarily prove that the drug acts specifically or solely on mast cells. The term "mast-cell stabiliser" used in the context of laboratory studies in animals could indeed be applied with equal validity to several other drugs such as beta-adrenergic agonists, methylxanthines,[7] and ketotifen,[8] but with the possible exception of ketotifen (whose therapeutic efficacy is still in dispute[9]) there is no clinical evidence that the mast-cell stabilising properties of these drugs are of any real value in the long-term "prophylactic" control of extrinsic asthma. Indeed, sodium cromoglycate seems to exert more potent therapeutic effects, particularly in children with extrinsic asthma, than if its only action were to inhibit the release of mediators from mast cells.[10]

Despite heavy research investment pharmaceutical firms have so far failed to discover any "mast-cell stabiliser" given by mouth which even remotely approaches the efficacy of sodium cromoglycate in asthma (and Fisons have had to withdraw[11] their candidate (proxicromil) on the brink of marketing). A new drug of this type would be of great potential value in the treatment of all diseases attributable to type I allergic reactions, without the limitations imposed by the purely topical action of sodium cromoglycate; the research efforts will undoubtedly continue.

Until recently these attempts to discover a new generation of antiallergic drugs to succeed sodium cromoglycate may have been unduly influenced by preconceived ideas about its actions on mast cells. Too little attention may have been paid to some of its other properties which cannot be satisfactorily explained on that basis.[10] The part played by the mast-cell

system in health and disease remains an enigma, but it is not one which simplistic expositions on the pharmacological actions of sodium cromoglycate can do much to resolve. The concept of mast-cell stabilisers may have narrowed perspectives in this important field of research activity—perhaps the term should be discarded.

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Left hand, right hand

Why are some of us left-handed? Suspicions about such individuals run deep in folklore and philology.[1] Dexterity (from the Latin dextra, right hand) is an admirable trait quite different from being sinister (Latin sinister, left). Left-handedness is illegal in Albania. While this may appear to be an excessive desire for conformity on the part of a totalitarian government the collective prejudice is nourished by morsels of truth. Left-handed people are overrepresented among populations of psychotics and epileptics—a finding that may be relevant to the causation of these conditions.[2] Left-handedness by itself, however, is of no clinical significance since almost all left-handers are otherwise (in a statistical sense) normal.

As human behaviour has become more complex lateralisation of cerebral function has been accentuated. The bilateral symmetry of the brain has been modified both structurally and functionally. The region between the primary auditory cortex and Wernicke's association area for speech is recognisably larger on the left in most fetuses from the 20th week of intrauterine life. Similarly, though both cerebral hemispheres are concerned during speech, the increase in blood flow in Broca's area for speech on the left is greater than on the right. The evolution of the neural substrate for language must have been both complex and vital for evolutionary survival, so its lateralisation might be expected to be genetically specified. Around 95% of right-handed individuals have left cerebral dominance for speech—so the choice seems not to be arbitrary. By analogy, the advancing complexity of voluntary hand function may have demanded similar lateralisation. The proximity of the language centres to the centres for preferred hand function cannot be accidental and should be (but has not been) a fruitful area for research by developmental neurobiologists.

One way in which left-handedness may arise is from some disturbance of development of the left hemisphere in an individual genetically destined to be right-handed. Examination of the function of the non-preferred hand might allow an estimate of the proportion in whom this switch has occurred. In an ingenious extension of this suggestion Bishop has recently argued that since the lateralisation of the disturbance is likely to be arbitrary more right-handers will have become left-handers than vice versa simply because most people are initially right-handed. Thus, study of a group of children with particularly poor function of their non-preferred hands should show an increased representation of left-handers, an increased incidence of potentially damaging events in their past, and more cognitive impairment. Any such group of left-handers with particularly poor function of their right hands should also have the same proportion of left-handed relatives as a group of right-handed children (and a lower proportion than a group of left-handed children with good function of their right hands). These expectations were realised in a study[3] which, though small, is particularly convincing because the second and third predictions were valid irrespective of whether the preferred hand was the left or the right.

If these observations can be repeated elsewhere in a larger study more emphasis in the future will have to be given to proficiency with the non-preferred hand. Do the left-handers found in increased proportion among children with poor reading ability[4] have more right-handed clumsiness than left-handers who are proficient readers? How efficient is the switch in hemispheric lateralisation, and does the efficiency depend on sex or the timing in development? Does a poorly performed switch explain the increased proportion of left-handers among generally clumsy children? The claims for "mixed laterality" (when the preferred hand and the preferred foot are not on the same side) as a sign of neurological dysfunction will become more convincing when examined in the light of these findings.

Finally, if some individuals can switch more efficiently than others, what effect does this have on the language function? Can we, for example, predict recovery in right-handed aphasics by studying their proficiency with their left hands? The specification of cerebral asymmetry is of great importance in human behaviour and should no longer be regarded as the province of eclectic psychologists.

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Do fetal movements reflect fetal wellbeing?

Interest in fetal movement is as old as the written history of mankind: "The children struggled together within her," referring to Rebekah's twins (Genesis xxv, 22). The specific interest of the physician has an equally long history; Hippocrates[1] believed that the fetus began moving 70 to 90 days after conception and maintained that male fetuses moved more vigorously than females. Soranus of Ephesus[2] (first