The Role of Adrenoceptors in Bronchial Asthma

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Bronchial asthma is characterised by variable airflow obstruction and hypersensitivity of bronchi to specific and non-specific trigger factors. Thomas Willis (1679) described this feature of asthma 300 years ago and Salter (1859) later attributed the cause of asthma to the release of humoral agents into the circulation and the morbid sensitiveness of the pulmonary nervous system to these agents. Bronchial hyper-reactivity to histamine (Weiss *et al.*, 1929; Curry, 1946), bradykinin (Varonier and Panzani, 1968) and prostaglandin F_2 alpha (PGF_2 alpha, Mathé *et al.*, 1973) is now well established. The cause of this bronchial hyper-reactivity in asthma is still not clear. However, considerable progress has been made in our understanding of some of the basic biochemical, immunological and physiological processes of this disease and, in particular, the role of adrenoceptor function.

Biochemical Processes

Szentivayni (1968) postulated that the atopic state and bronchial hyper-reactivity in asthma results from a reduced beta-adrenoceptor function and a relative increase in alpha-adrenergic activity. This contention was based on observations of reduced $beta_2$ metabolic responses such as hyperglycaemia and peripheral vasodilatation in asthmatic patients following administration of beta agonists as compared to these responses in non-atopic normal subjects (Cookson and Reed, 1963; Middleton and Finke, 1968). This resistance to adrenaline or 'adrenaline fastness' increases with the severity of the asthma (Inoue, 1967).

The association of membrane bound adenyl cyclase (AC) activity with beta-adrenoceptor function (Robison *et al.*, 1967) and the presence of this enzyme system in peripheral human leucocytes and lymphocytes has provided an excellent *in vitro* system for more basic and fundamental research in adrenoceptor function in asthma. It is believed that the biochemical abnormality in asthma is not localised to target organs but is generalised, and therefore studies on isolated viable leucocytes may provide meaningful information.

Logsdon *et al.* (1972) reported reduced leucocyte AC responsiveness to isoprenaline in their asthmatic patients, whereas Gillespie *et al.* (1973) failed to show any significant difference in AC activity between normal subjects and patients with asthma. In a more detailed study Parker and Smith (1973) demonstrated a diminished lymphocyte AC activity only in patients with acute asthma and this reduced beta-receptor function returned towards normal once the patient was in remission.

In a study of 14 patients with extrinsic asthma, we observed diminished leucocyte AC responsiveness to isoprenaline and cyclic 3′ 5′ adenosine monophosphate (cAMP) formation in patients with active asthma, whereas the leucocyte AC activity was normal in patients in remission (Table 1: Alston *et al.*, 1974; Patel *et al.*, 1974). All our patients had stopped oral and aerosol beta agonist bronchodilators for at least 24 hours and none were on corticosteroids. More recently, Conolly and Greenacre (1976) have reported diminished lymphocyte AC activity in normal and asthmatic subjects following prolonged administration of the $beta_2$ agonist, salbutamol. A similar desensitisation can occur in the lymphocytes of patients with phaeochromocytoma who

Table 1. The leucocyte adenyl cyclase response to isoprenaline in normal subjects, asthmatic patients in remission and those with acute asthma.

	Control value	Isoprenaline 10^{-4} M
Normal subjects (n = 10)		% Increase
Mean	1.15	44.3
SEM	0.26	11.8
P		0.005
Asthmatic patients in remission (n = 7)		
Mean	0.64	92.6
SEM	0.08	11.1
P		0.001
Patients with acute asthma (n = 7)		
Mean	1.48	12.4
SEM	0.21	10.6
P		0.20

The control value represents the basal level of incorporation of ^{3}H-adenine into cyclic AMP and the result of the drugs are given as a percentage increase from the basal or control value.
SEM = Standard error of mean.

are exposed to high levels of circulating catecholamines (Greenacre and Conolly, 1978) and also in the lymphocytes of normal subjects after prolonged incubation of cells *in vitro* with isoprenaline or PDE (Greenacre *et al.*, 1978). The role of cAMP phosphodiesterase (PDE), which is responsible for hydrolysing cAMP in this desensitisation process, remains uncertain. The cytosol PDE activity and the PDE activity in whole cell homogenate do not appear to be increased in asthmatic patients (Greenacre *et al.*, 1978; Haddock *et al.*, 1978).

In various tissue preparations, including human lymphocytes, prolonged incubation with beta agonist has been shown to result in reduction in the number of beta-adrenoceptors (Romero *et al.*, 1975; Mukherjee *et al.*, 1975). Sokol and Beall (1975) failed to show any difference in the number of ^{3}H DL-adrenaline binding sites in leucocytes of asthmatic and normal subjects. However, agonists may bind to many other sites apart from receptors and this is especially true of the neurotransmitter itself, which binds to uptake sites, degenerative enzymes and neuronal storage sites (Lefkowitz, 1976). Receptor labelling with antagonists seems to be more specific, due to the high affinity of antagonists to adrenoceptors. Kariman and Lefkowitz (1977), using (−) ^{3}H alprenolol, have shown a reduction in binding sites in the lymphocytes of asthmatic patients, which is also apparent in patients not on beta agonists. There is now cumulative evidence that a diminished beta-adrenoceptor function does exist in some patients with asthma and this may be caused by prolonged and persistent exposure to endogenous or exogenous beta agonists. A regular administration of oral and aerosol beta agonist has been shown to cause a similar desensitisation of bronchodilator response in normal subjects (Holgate *et al.*, 1977) and also in bronchial smooth muscle preparations (Davis and Conolly, 1977).

Corticosteroids and alpha-adrenoceptor blocking drugs (phentolamine and thymoxamine) have been shown to potentiate cAMP formation in peripheral human leucocytes and particularly to restore towards normal the beta adrenoceptor function in patients with acute asthma (Logsdon *et al.*, 1973; Alston *et al.*, 1974—Table 2). Alpha-adrenoceptor activation appears to involve a net increase in transmembrane Ca^{2+} movement (Kalsner *et al.*, 1970) and inhibition of AC activity, particularly when previously stimulated (Robison *et al.*, 1971; Yamashita *et al.*, 1977). The effect of alpha-adrenoceptor blocking drugs in patients with acute asthma would support this observation. Belleau (1967) on theoretical grounds proposed that membrane-bound adenosine triphosphatase (ATPase) was related to alpha-adrenergic activity. The stimulation of cationic-dependent ATPase by alpha-adrenoceptor agonists and inhibition by alpha-adrenoceptor antagonists would support this contention (Coffey and Middleton, 1973). Ouabain, an inhibitor of $K^{+}Na^{+}$ ATPase also increases cAMP formation in leucocytes in response to beta agonists (Alston *et al.*, 1974). The 'permissive' effect of corticosteroids remains unclear. It is unlikely that a steroid effect is mediated through an increase in protein synthesis related to hormone receptor sites or inhibition of PDE (Logsdon *et al.*, 1972). The inhibitory effect of corticosteroids on leucocyte ATPase (Coffey *et al.*, 1973) and on alpha-adrenoceptor bronchoconstriction in human and guinea-pig isolated respiratory smooth muscle (Townley *et al.*, 1972) may suggest a common mechanism of action of corticosteroid and alpha-adrenoceptor antagonists. The reduced beta-adrenoceptor function in asthma, either drug-induced or inherent, has an important bearing on the mediator release in the Type I allergic reaction and the effects of these mediators on the bronchial smooth muscle (Fig. 1).

Table 2. The effect of thymoxamine and phentolamine on leucocyte adenyl cyclase response to isoprenaline in normals and patients with asthma

	Thymoxamine 2×10^{-4}		Phentolamine 2×10^{-4}	
	Alone	+ Isoprenaline 10^{-4} M	Alone	+ Isoprenaline 10^{-4} M
Normal subjects (n = 10)	% Increase	% Increase	% Increase	% Increase
Mean	12.3	81.5	9.8	107.8
SEM	7.9	16.5	10.8	27.5
P	0.10	0.001	0.40	0.005
Asthmatic patients in remission (n = 6)				
Mean	19.5	163.1	28.8	189.2
SEM	9.0	16.5	11.0	21.0
P	0.10	0.001	0.20	0.001
Patients with acute asthma (n = 5)				
Mean	3.3	85.5	32.0	74.3
SEM	10.5	15.0	22.0	12.0
P	0.80	0.001	0.20	0.001

The results of drug action are given as a percentage increase from the basal or control value.

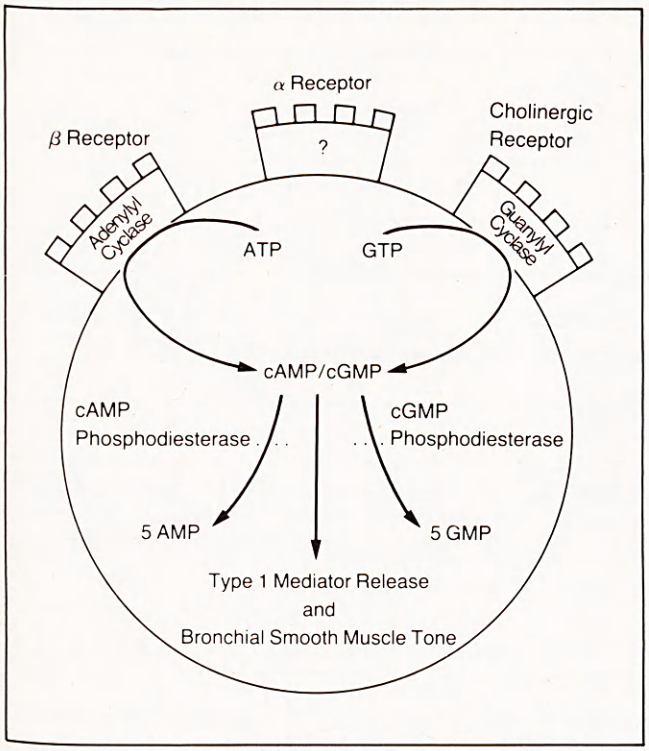

Fig. 1. *The membrane enzymes and their relationship to adrenoceptor and cholinergic activities and probable modulating effect on the Type I allergic reaction and the bronchial smooth muscle.*

Physiological Processes

The bronchoconstriction in asthmatic patients following administration of beta-adrenoceptor antagonists is now well established and has been attributed to unopposed vagal (MacDonald *et al.*, 1967) or alpha-adrenoceptor bronchoconstriction activity (Patel and Kerr, 1973). The role of the parasympathetic reflex mechanism involving the rapidly adapting or 'irritant' sensory vagal receptor in the pathophysiology of obstructive airways disease has been proposed by Gold (1975), Nadel (1977) and Widdicombe (1977). This contention is derived mainly from observations in animal models of asthma, and the relevance to human asthma is based on the blocking of muscarinic cholinergic receptors with atropine or atropine-like agents (Empey *et al.*, 1976). Although the local anaesthetic bipuvacaine hydrochloride produces reversible anaesthesia of airways and inhibits both the citric acid induced and mechanically induced cough reflex in man, it does not affect the resting bronchomotor tone (Jain *et al.*, 1973; Cross *et al.*, 1976). This suggests that the parasympathetic bronchomotor fibres are unaffected by the anaesthesia of irritant receptors and makes it unlikely that citric acid induced bronchoconstriction in asthmatic patients (Simonsson *et al.*, 1967) is mediated through stimulation of these receptors. In addition, sodium cromoglycate (SCG), which has been reported to reduce irritant receptor activity in canine models (Jackson and Richards, 1977), has no effect on methacholine and PGF_2 alpha-induced bronchoconstriction in patients with asthma (Patel, 1975). It therefore appears that although the irritant receptor stimulation and vagal reflex may play an important part in the pathophysiology of airways obstruction in animal models, a similar reflex mechanism in human asthma is less convincing. This is further supported by the variable effect of anticholinergic agents in allergen (Itkin and Anand, 1970; Yu *et al.*, 1972; Altounyan, 1974) and exercise-induced asthma (Godfrey and Konig, 1976; Tinkelman *et al.*, 1976). This variability of anticholinergic agents may be related to the main site of airways obstruction, as has been shown in exercise-induced asthma. Exercise-induced asthma can be inhibited both by atropine and ipratropium if the main site of airflow obstruction is in the large airways (McFadden *et al.*, 1977; Thomson *et al.*, 1978), suggesting the relevance of cholinergic mechanisms only in the large and central airways.

The presence of alpha-adrenoceptors in the lung has created considerable interest recently. There is increasing evidence that pharmacological alpha-adrenoceptor stimulation causes bronchoconstriction in animals and man (Castro de la Mata *et al.*, 1962; Everitt and Cairncross, 1969; Simonsson *et al.*, 1972; Prime *et al.*, 1972; Patel and Kerr, 1973). This bronchoconstrictor response to alpha-adrenoceptor stimulation can be demonstrated particularly well in patients with extrinsic asthma (Patel and Kerr, 1973; Snashall *et al.*, 1978).

In six patients with extrinsic asthma, 5 mg of phenylephrine hydrochloride (50g/litre) given by inhalation through a Wright's nebuliser resulted in bronchodilatation and a rise in specific airways conductance (sGAW). Phenylephrine is a powerful alpha agonist with a weak beta-adrenoceptor stimulating property. The bronchodilatation produced by phenylephrine reflects the predominance of beta-adrenoceptor activity in the human lung. However, when phenylephrine inhalation was repeated 60 minutes after 20 mg of propranolol given orally, it had a reversed effect, resulting in bronchoconstriction and a fall in sGAW. This bronchoconstriction response could be inhibited by the alpha-adrenoceptor blocking drugs, phenoxybenzamine and thymoxamine, given by inhalation (Tables 3 and 4) but not by atropine (Fig. 2). A similar effect of phenylephrine could not be demonstrated in normal subjects, even after 120 mg of propranolol given orally (Patel and Kerr, 1973). Snashall and colleagues (1978) have confirmed these observations using the alpha agonist, methoxamine.

In 10 patients with extrinsic bronchial asthma, thymoxamine hydrochloride given intravenously (100 mg/kg body weight) partially inhibited the allergen-induced fall in sGAW (Fig. 3). Although the overall inhibition in the allergen-induced fall in sGAW was significant, a fair degree of intra-subject variation in response suggests that the action of thymoxamine may be predominantly on the bronchial smooth muscle rather than on the mast cell and mediator release (Patel and Kerr, 1975 b).

In addition, 15 mg of thymoxamine (15 g/litre) given by inhalation also inhibited exercise-induced asthma in 12 of the 13 patients and this preventive effect in exercise-

Table 3. Effect of phenylephrine and isoprenaline on sGAW after prior beta blockade with propranolol in 6 patients with extrinsic asthma

		Change in sGaw (s^{-1} kPa^{-1})						
			Propranolol		Phenylephrine$_2$			Isoprenaline
n = 6	Baseline	Phenylephrine$_1$	45 min	60 min	2 min	5 min	10 min	10 min later
Mean	1.65	2.09	0.94	0.81	0.52	0.50	0.56	0.94
SEM	0.29	0.27	0.15	0.11	0.11	0.09	0.13	0.23
P		0.005	0.05	0.025	0.001	0.001	0.025	

SEM = Standard error of mean.

Table 4. Effect of phenylephrine and isoprenaline on sGaw after prior alpha- and beta-adrenergic blockade in 6 patients with extrinsic asthma

		Change in sGaw (s^{-1} kPa^{-1})						
			Propranolol plus phenoxybenzamine or thymoxamine		Phenylephrine$_2$			Isoprenaline
n = 10	Baseline	Phenylephrine$_1$	45 min	60 min	2 min	5 min	10 min	10 min later
Mean	0.31	1.69	0.16	1.06	1.18	1.24	1.24	1.53
SEM	0.25	0.26	0.26	0.26	0.26	0.26	0.26	0.28
P			N.S.	N.S.	0.025*	0.025*	0.01*	0.025

SEM = Standard error of mean.
*The effect of phenylephrine in the presence of alpha- and beta-blockade is compared to the effect of phenylephrine in the presence of beta-blockade alone at 60 min.

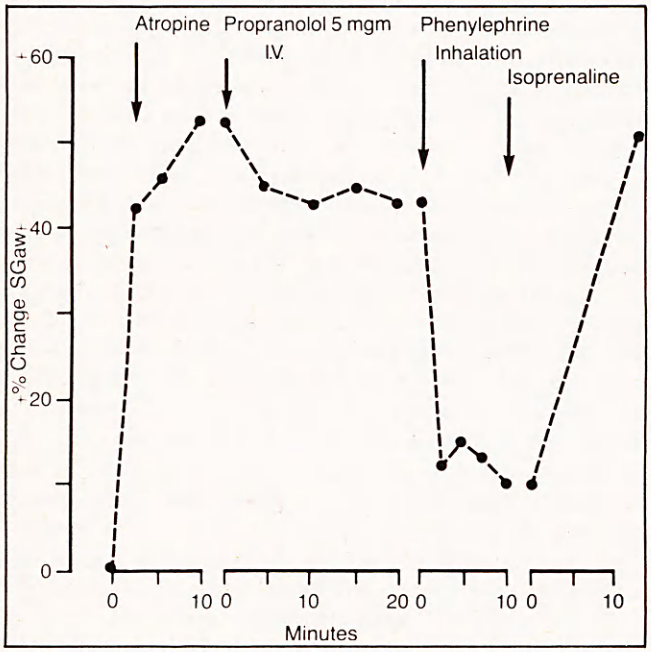

Fig. 2. *Effect of 5 mg of phenylephrine given by inhalation in the sGAW after atropine (1.2 mg by inhalation) and propranolol in 6 patients with extrinsic bronchial asthma.*

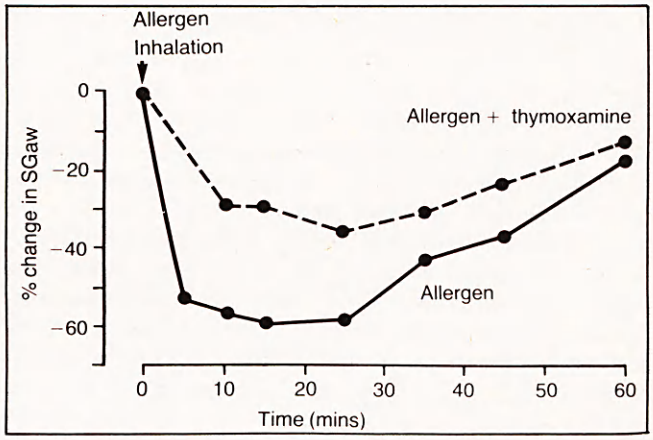

Fig. 3. *Effect of thymoxamine (100 mg/kg body weight) given intravenously on the allergen-induced fall in the mean sGAW in 10 patients with extrinsic asthma.*

induced asthma was comparable to SCG (Fig 4, Patel *et al.*, 1976). Bianco *et al.* (1974) have also demonstrated inhibition of exercise-induced asthma with indoramin, an alpha-adrenoceptor blocking drug with weak bronchodilator properties.

Thymoxamine has also been shown to potentiate the bronchodilator effect of isoprenaline in asthmatic patients. Thymoxamine 15 mg (15 g/litre) given by inhalation in combination with isoprenaline 1 mg (1 g/litre) through a Wright's nebuliser produced significantly greater bronchodilatation and a rise in sGAW (203 per cent from the baseline) in 10 asthmatic patients, compared with the bronchodilatation produced by isoprenaline alone (122 per cent, P<01). Phentolamine and isoprenaline (Fig. 5) or thymoxamine and orciprenaline have a similar effect (Griffin *et al.*, 1972; Patel and Kerr, 1975 a; Patel, 1976). In *in vitro* experiments, alpha-adrenoceptor antagonists, dihydroergo-

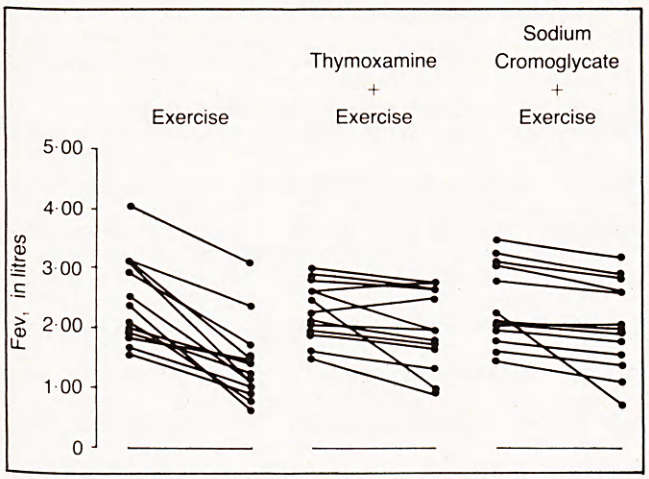

Fig. 4. *Values of FEV_1 before and after treadmill exercise in 13 patients with asthma, and the effects of thymoxamine (15 mg) and SCG (40 mg).*

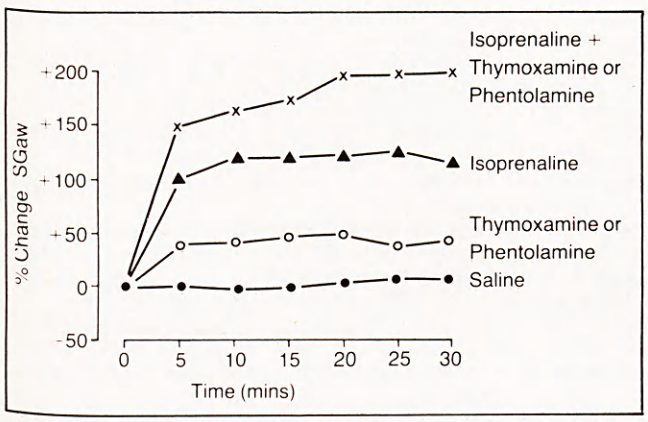

Fig. 5. *Effect of saline, thymoxamine (15 mg) or phentolamine (5 mg), isoprenaline (1 mg) and isoprenaline + thymoxamine or phentolamine on the mean sGAW in 10 patients with asthma.*

toxine, phenoxybenzamine and phentolamine have been reported to potentiate the bronchodilatation induced by adrenaline, isoprenaline, terbutaline or salbutamol in guinea-pig and human bronchial preparations (Said *et al.*, 1974; Nousiainen *et al.*, 1977).

Dopamine is a naturally occurring catecholamine and an immediate precursor of noradrenaline. Dopamine is found in the lungs of ruminants (Von Euler and Lishajko, 1957) and is located in the mast cells (Falck *et al.*, 1964). Its release from isolated calf lung sensitised with horse serum by specific antigen and compound 48/80 suggests that it may have an important role in the Type I allergic reaction (Eyre and Deline, 1971). Further, dopamine stimulates cAMP synthesis in post-synaptic ganglia (Greengard, 1976) and is an important neurotransmitter in the peripheral autonomic nervous system. However, dopamine infused at a rate of 5 $\mu g\ kg^{-1}\ min^{-1}$ for 10 minutes or given by inhalation for 2 minutes (1 g/litre and 2 g/litre) failed to have any significant effect on sGAW in normal and asthmatic subjects, suggesting an absence of specific dopamine receptors in the human lung (Thomson and Patel, 1978).

The improvement in lung function of patients with chronic asthma who were treated with the specific dopamine agonist, bromocriptine (Newman Taylor *et al.*, 1976) may be related to the ability of bromocriptine to cross the blood-brain barrier and stimulate the intracerebral dopamine receptors (Dray and Oakley, 1976).

Immunopharmacology

In human lung fragments, beta-adrenergic agonists have been shown to inhibit mediator generation and release by increasing cAMP levels. Conversely, alpha agonists decrease tissue levels of cAMP and enhance mediator release. Thus, there appears to be an inverse relationship between tissue concentration of cAMP and the degree of mediator release observed (Austen and Orange, 1975). Cholinergic stimulation with acetylcholine causes enhancement of release of chemical mediators and this is associated with increase in cyclic 3′ 5′ guanosine monophosphate (cGMP, Fig 6).

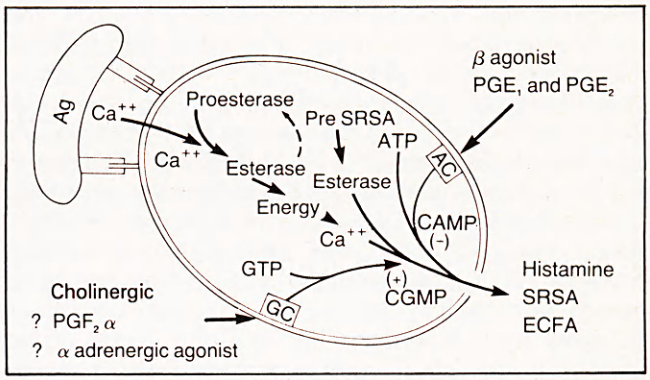

Fig. 6. *Schematic sequence of mediator release in the Type I allergic reaction and modulation by cAMP and cGMP.*

Although the definite biochemical events of cell activation immediately upon antigen bridging of the membrane IgE molecule have not been delineated, studies of the reaction sequence link Ca^{2+} ion influx and the activation of serine esterase from its precursor form. The secretion of mediators is also initiated by the application of calcium ionophore, A23187 (Foreman *et al.*, 1973) in the absence of antigen. The effective common stimulus to the mast cell and many other cells is the entry of Ca^{2+} ions into the cytosol (Amer and Byrne, 1975; Kunos *et al.*, 1976). Certain flavones, notably quercetin, interfere with the membrane transport adenosine triphosphatases (ATPases), including the calcium-dependent ATPase which is associated with exclusion of Ca^{2+} from the cytosol of cells. The flavones that interfere with transport ATPases inhibit antigen-induced histamine release from the rat mast cells (Fewtrell and

Gomperts, 1977). The flavones (2 phenylcromones) have some structural resemblance to SCG, whose activity is also implicated at the calcium entry pathway (Foreman and Garland, 1976).

The mechanism by which alpha activation draws forth various tissue responses is not known. Alpha-adrenoceptor activation appears to involve a net increase in transmembrane Ca^{2+} movement (Robison *et al.*, 1971), and an increase in intracellular Ca^{2+} may also increase cGMP concentration in response to the alpha-adrenoceptor agonists observed in some tissues (Schultz *et al.*, 1975). In contracting cardiac muscle, the rise in cGMP in response to alpha sympathomimetic amines can be inhibited by alpha-adrenoceptor antagonists (Amer and Byrne, 1975; Kunos *et al.*, 1976). A similar effect in the mast cell and bronchial smooth muscle may explain the alpha and cholinergic effects in patients with extrinsic asthma and these may be related to intracellular levels of cAMP, cGMP and enzyme activities concerned with transmembrane Ca^{2+} channels.

Conclusions

Cumulative evidence suggests that there is diminished beta-adrenoceptor responsiveness to beta agonists in patients with acute asthma. This beta-adrenoceptor desensitisation may be the result of prolonged and persistent exposure to endogenous and exogenous beta-adrenergic agonists. The diminished beta-adrenoceptor function in the lung mast cells may enhance both the generation and release of mediators of the Type I allergic reaction and the effects of these mediators on the airways. In the presence of diminished beta receptor function, alpha-adrenoceptor agonists may cause broncho-constriction. Hydrocortisone and alpha-adrenoceptor blocking drugs have been shown to restore beta-adrenergic sensitivity both in the leucocytes and in the bronchial smooth muscle. The mode of action of the alpha-adrenoceptor antagonist may be similar to the 'permissive' effect of steroids, and the common link is perhaps the enzyme systems involved in the control of transmembrane Ca^{2+} ion channels and the intracellular levels of cAMP, cGMP and Ca^{2+} ions.

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The College In Clubland

A Club, said Dr Johnson, was an assembly of good fellows, but he did not define good. Boodles and Whites were perfect examples of an eighteenth century social coterie. Small numbers, big dinners and much wine were required at any new club of the time. The College of Physicians could not fail to get in on this scene; rather, a few Fellows made themselves more exclusive by forming the College Club. Anthony Askew was the pattern of founding members. A man of fashion, intimate of the great, physician cherished by Queen Anne, he was famed for his library, if not for his medicine.

The club dined in Pall Mall, then in Bond Street, ending up at the Thatched House, St James Street, in 1774, after ten years of existence. In that year the eleven members paid 5s. each for a dinner that seven ate. Their wine bill was £1 18s 0d for five bottles of wine including one of champagne for 9s. Bottled and strong beer came to 2s. and coffee and tea cost 7s. Whether or not champagne should be served was a point hotly debated. 'Damn champaign W. Cadogan.' is written in the records. Dr Cadogan, an authority on gout, did not wine. Later, when the club had become the Social Club, new rules were laid down in 1816 to limit the membership to fifteen, to have dinner on the table at 5.30 pm and coffee served at 8.00 pm and to fine the president for non-attendance one bottle of champagne. The wine was less popular by 1836 when Dr Chambers, celebrating his appointment as Queen Adelaide's physician, gave a turtle feast in lieu of champagne.

All clubs of that day kept a book to record members' bets. The College Club was no exception, but its bets tended to be political rather than medical or sporting. Someone had a lingering suspicion of an ex-colony when in 1812 he took on a bet that there would be no war with America for the next six months. Napoleon dominated the bets for some time. On April 28th, 1812, a bet was laid that the French would not cross the River Oder during the campaign. Communications may have been abysmally slow or the taker of the bet knew he was on a winner and kept quiet as the French had crossed the Oder on February 21st. Social historians would be interested in a bet made in 1844 that the old deep champagne glasses were more capacious than the new shallow glasses. It dates exactly a change in fashion; but the old glasses did not contain more wine than the new.

It was inevitable that members of the club would want a history written and this was lovingly done in 1909 by Dr J. F. Payne. His book was printed privately on sumptuous paper and bound in Edwardian style, more opulent than artistic. The cost of such a publication today would be prohibitive. The club gave thanks to Dr Payne at a dinner on February 28th, 1910. The eighteen members present signed the fly-leaf of the book and the signature of William Osler stands out boldly.