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COMMENTARY

PROSPECTS FOR THE INHIBITION OF LEUKOTRIENE SYNTHESIS

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The synthesis and elucidation of the structures of the thiol ether leukotrienes, LTC, LTD, and LTE, and the demonstration that a mixture of these substances represents the classical Slow Reacting Substance of Anaphylaxis (SRS-A), have created a vast array of opportunities for research on the biosynthesis and metabolism of these materials and on their multiple physiologic, pathologic, and pharmacologic actions. Here I shall briefly review some of the indications in which the inhibition of leukotriene synthesis may be desirable. I shall then examine some potential sites for intervention and the risks which may be associated with these. I shall conclude this commentary with the inevitable list of caveats which must be born in mind in any attempt to intervene in the arachidonate cascade in general and in the 5-lipoxygenase pathway in particular.

WHY IS INHIBITION OF LEUKOTRIENE SYNTHESIS DESIRABLE?

Role of leukotrienes in asthma. The hypothesis that SRS-A plays an important role in eliciting the symptoms of asthma, which was first advanced by Brocklehurst [1], was based on indirect evidence. In the last few years, several lines of direct evidence have been presented in support of this hypothesis. Synthetic leukotrienes were shown to be potent spasmogens on human bronchioles and somewhat less active on human parenchymal tissue and pulmonary venules [2]. It was shown several years ago that anaphylactically-challenged, chopped human lung fragments can produce large amounts of leukotrienes. More recently [3], it was found that lung fragments, which were obtained during surgery for pulmonary carcinoma from the lungs of patients having extrinsic asthma, generated large amounts of leukotrienes when they were challenged with the relevant antigen *in vitro*. The bronchioles from the lungs of these same patients contracted upon exposure to antigen in a Schultz Dale reaction. These contractions were not antagonized by combinations of an antihistamine and indomethacin but were inhibited markedly when a selective inhibitor of leukotriene synthesis, U-60,257, was added to this mixture. In fact, it was calculated that the leukotrienes which were produced by the lung fragments could account for much, if not all, of the contraction which was seen.

The administration of aerosols of leukotrienes to both normal volunteers and to asthmatic subjects has been shown to elicit symptoms of bronchoconstriction which resembled the symptoms seen in asthma, and which persisted for relatively long periods of time [4, 5]. In contrast to observations in the guinea pig, the responses in the human volunteers were not affected when the subjects were pretreated for 3 days with sufficient aspirin to block the platelet aggregatory activity of arachidonic acid in the same subjects [6]. It is of considerable interest that the sensitivity of the asthmatics to the leukotrienes was no greater than that of the normal volunteers. This must be contrasted to the marked hyperreactivity of asthmatic patients to other aerosolized agonists [e.g. histamine, mecholyl, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), and PGD_2].

In addition to the smooth muscle-contracting activity of the leukotrienes, their effects on mucus production [7, 8] and on mucus transport may further link them to the etiology of asthma. The potent stimulation of mucus production in human lung explants by leukotrienes, and the observation [8] that this effect is primarily on the mucous rather than the serous component of the mucus, are particularly relevant. At the same time, the apparent lack of dependence on a specific structure within a broad range of synthetic leukotriene analogues [8], and the observations that mucus secretion in the cat occurs only *in vivo* [9] while the stimulation of mucus secretion by leukotrienes in the dog involves ganglionic stimulation [10–12], add complexity to the situation. Evidence for a role of leukotrienes in mucus transport is indirect at this point and consists of observations with purportedly selective inhibitors of leukotriene action [13].

The final critical element in the proof of the hypothesis that leukotrienes are important in the elicitation of the symptoms of asthma, following Dale's criteria, remains the demonstration that symptoms can be alleviated with a selective inhibitor. It has not been possible to seek this evidence thus far for lack of a truly representative animal model, on the one hand, and lack of a suitable drug for use in humans, on the other.

Role of leukotrienes in other diseases. The availability of synthetic leukotrienes has led to the recognition that these substances may play important roles in a large number of other inflammatory con-

ditions. There is considerable evidence linking the production of LTB_4 to the accumulation of leukocytes at sites of inflammation and, thereby, to the development of characteristic symptoms of inflammation. More recently, the production of LTC by polymorphonuclear neutrophils has also been reported [14, 15]. A role for the products of the 5-lipoxygenase pathway in the chronic aspects of acute respiratory distress syndrome (ARDS) is currently receiving attention from a large number of laboratories. It has been reported recently that there are elevated levels of leukotrienes in psoriatic skin [16], and benoxaprofen, a non-steroidal anti-inflammatory drug which also has some inhibitory activity

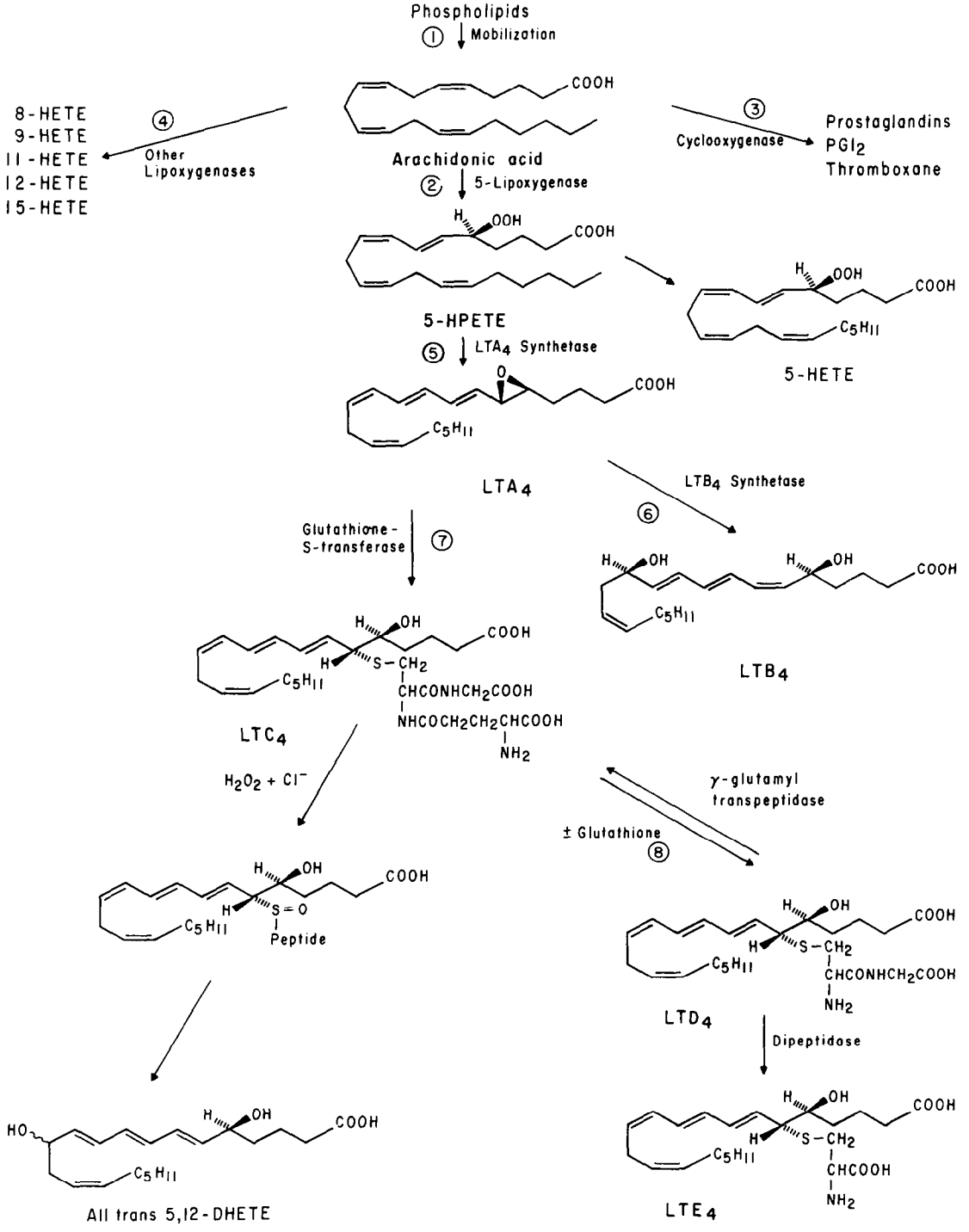

Fig. 1. Schematic for the biosynthesis of the leukotrienes.

against the 5-lipoxygenase, has been found in a double blind trial to be helpful in the treatment of psoriasis [17]. Though arguments are presented against this, the possibility exists that the inhibitory actions of the drug were due to its known photosensitizing activity. Elevated levels of LTB were also found in inflammed bowel scrapings, and sulfasalazine, a commonly used medication for the management of inflammatory bowel disease, has been shown to inhibit the 5-lipoxygenase at concentrations which are commonly found in bowel contents [18]. Finally, products of the 5-lipoxygenase pathway appear to modulate secretion of pituitary hormones [19], and LTD_4 was shown to have complex effects on blood pressure in spontaneously hypertensive rats [20].

POTENTIAL SITES FOR INHIBITION OF LEUKOTRIENE SYNTHESIS

The biosynthesis of the leukotrienes is represented schematically in Fig. 1. In principle, each step in the pathway is a candidate for inhibition. However, the choice of site of inhibition may have to be influenced by a number of considerations over and above the element of luck which still governs our ability to synthesize useful and selective inhibitors for specified reactions.

Arachidonate mobilization. An implicit assumption in these remarks is that we desire an inhibitor which will selectively block the formation (or actions) of products of the 5-lipoxygenase pathway without affecting other pathways of arachidonate metabolism. It is not yet clear if any level of selectivity exists in the mobilization of arachidonic acid in any given cell for metabolism via one or another major pathway. Indirect evidence has suggested that such compartmentalization may indeed exist, but much definitive work remains to be done. In this regard, the role of apparently selective factors, such as the peptide Prostaglandin Generating Factor of Anaphylaxis, which can induce the production of products of the cyclooxygenase pathway without, apparently, activating the 5-lipoxygenase pathway [21, 22], remains to be elucidated.

5-Lipoxygenase. All the products of the 5-lipoxygenase pathway have pro-inflammatory actions. 5-Hydroperoxyeicosatetraenoic acid (5-HPETE) and 5-hydroxyeicosatetraenoic acid (5-HETE) have been shown to stimulate histamine release from basophils [23]. LTB is associated with the inflammatory response, and the thiol-ether leukotrienes have potent actions on smooth muscle and on mucus. Thus, it is logical to attempt to block this pathway *in toto* by inhibiting the 5-lipoxygenase itself. It certainly appears to be possible to find compounds which can inhibit this enzyme and, depending on the cell or tissue being affected, some of these compounds appear to be quite selective. In one sense, U-60,257 is such a selective inhibitor in that it inhibits the 5-lipoxygenase without affecting the cyclooxygenase of the 12-lipoxygenase of platelets.

It must be stressed that, at least to a first approximation, the inhibition of the first irreversible step in a pathway which begins at a branch point can lead to the shunting of the precursor molecule toward the other branch in the pathway. Indeed, this tendency has been recognized for many years; the addition of indomethacin to incubations has been used to block the cyclooxygenase pathway and thereby maximize the yield of leukotrienes in an incubation. Similarly, incubation of rat peritoneal mononuclear cells with the calcium ionophore in the presence of U-60,257 has resulted in a moderate increase in thromboxane formation while inhibiting the production of leukotrienes [24].

The effect of shunting of arachidonate to the cyclooxygenase pathway from the 5-lipoxygenase pathway may be desirable or undesirable depending on the cell or tissue in which this takes place and the nature of the predominant cyclooxygenase products which that cell or tissue is programmed to produce. Thus, in the case of the rat peritoneal mononuclear cells, thromboxane formation appears to be increased; on the other hand, in the endothelial cells, PGI_2 formation would most likely increase.

Superimposed on these considerations, it is also unclear if complete systemic inhibition of the 5-lipoxygenase pathway is a desirable goal *in vivo*. It may be, for example, that local delivery of the inhibitor to the intended target tissue, such as the lung in asthma, will help to minimize the undesirable consequences that would otherwise follow from the inhibition of a pathway which leads to products which appear to have so many homeostatic control functions.

LTA synthetase. Little is known about this enzyme. It would clearly be an ideal enzyme to attempt to inhibit if total inhibition of all leukotriene synthesis were to be achieved. There was a suggestion that diethylcarbamazine, which has been known for a long time to be a "selective inhibitor of SRS-A formation", was a specific inhibitor of this enzyme [25]. More recent results from my laboratory (M. K. Bach and J. R. Brashler, unpublished observations) have shown that such is not the case since this compound also inhibits at least one other step in the pathway.

LTB synthetase. This enzyme has not been studied in any detail thus far. It is present in the high speed supernatant fraction from homogenates of rat basophil leukemia cells. Studies by Lewis *et al.* [26] have suggested that the conversion of LTA to LTB is not rate-limiting in either human neutrophils or mouse bone marrow-derived mast cells (E cells) since, in both instances, little LTA appears to be degraded nonenzymatically.

LTC synthetase. Formally, the reaction of LTA with glutathione is the typical reaction which is catalyzed by the glutathione *S*-transferases. Indeed, the mixed glutathione *S*-transferases in the high speed supernatant fraction from rat liver homogenates are capable of generating LTC when they are incubated with LTA and glutathione [22]. However, liver is not ordinarily recognized as a rich source of leukotrienes. When cells that are known to synthesize leukotrienes were examined, it was found that the high speed supernatant fractions, which contained glutathione *S*-transferase activity as determined with chromogenic substrates (e.g. 3,4-dinitrochlorobenzene), were devoid of leukotriene C-generating activity. Instead, the LTC-generating activity resided

Table 1. Comparison of some of the properties of the LTA:glutathione *S*-transferase of rat basophil leukemia cells and the soluble and particulate glutathione *S*-transferases of rat liver

	RBL		LIVER	
	SOLUBLE	PARTICULATE	SOLUBLE	MICROSOMAL
PHYSICAL				
Freeze-Thaw	Stable	20-30% Loss/Cycle	Stable	Stable?
Subfractions	4?	?	6 or more	Single peak
pI	Mostly < 8.5		7-10. mostly > 8.5	
Effect of N-ethyl maleimide	None	1.8X activation	None	Up to 7X activation
Effect of Triton X-100	None	Solubilizes, activates	None	Solubilizes*
SUBSTRATE SPECIFICITY (mixed enzymes)				
DNCB	+ +	0	+ + +	+ + +
DCNB	+	0	+ +	+ +
ENPP	+ + +	0	+ +	0*
Leukotriene A_4	0	+ + +	+ +	+ + +
INHIBITOR PROFILE (EC_{50}, μM)				
Bilirubin	1.3	Inactive at 500‡	3.8	496
Bromosulfophthalein	9.0	60‡	100	28
Estrone-3-SO_4	9.4	1200 ‡	75	7.2; 1600‡
U-60257	3.9*	Inactive at 1000‡	54	409 ; 1200‡

*Morgenstern et al., *Eur. J. Biochem.*, *128*:243, 1982.
*Only 80% inhibition can be achieved even at 1000μM inhibitor
‡Leukotriene A_4 substrate.

in the high speed particulate fraction, an observation which confirmed earlier reports from Dr. Jakschik's laboratory [27]. Further investigation revealed that, in rat basophil leukemia cells, the particulate fraction that was capable of coupling LTA to glutathione was devoid of any glutathione *S*-transferase activity when any of the usual chromogenic substrates were employed. This, combined with extensive inhibitor studies, has led to the conclusion that the LTC synthetase is a unique enzyme. The same also appears to be true in rat peritoneal mononuclear cells and in homogenized human lung (M. K. Bach and J. R. Brashler, unpublished observations). A comparison of some of the salient features of the LTC synthetase and various glutathione *S*-transferases is shown in Table 1.

Glutathione *S*-transferases are ubiquitous enzymes and play an important role in detoxification reactions. Thus, as long as the enzyme responsible for the generation of LTC was thought to be a typical glutathione *S*-transferase, there was good reason to question whether inhibiting this step in the biosynthesis could be medically useful [28]. However, with the finding that the susceptibilities to inhibition of the LTC synthetases and the traditional *S*-transferases are quite different, there may be an opportunity to affect the synthesis of leukotrienes selectively if a good inhibitor of this enzyme could be found.

Generation of LTD and LTE. The sequential conversion of LTC to LTD and to LTE is catalyzed by a gamma glutamyl transpeptidase and a dipeptidase respectively. The transpeptidase is located in the particulate fraction, and the dipeptidase appears to be granule-associated. Neither enzyme is necessarily present in the cells which actually produce the leukotrienes. For example, E type mast cells produce only LTC and do not metabolize this substance further [29]. There is little reason to consider either of these enzymes as interesting subjects for inhibition since, on the whole, the relative potencies of LTC and LTD are very nearly the same and that of LTE is not much smaller so that interference with their interconversion would be expected to have little practical import.

Some thoughts on the utility of inhibiting multiple steps in the pathway. U-60,257, which has already been referred to several times in this paper, is a selective inhibitor of leukotriene formation. Mode of action studies have convinced us that this compound inhibits at least two distinct steps in the pathway. It is an inhibitor of the 5-lipoxygenase ([30]; Fig. 2) and, at the same time, it also appears to inhibit the activity of the LTA:glutathione *S*-transferase, at least in certain cells and tissues. This latter inhibition appears to exist in the E type mast cells from mice where formation of LTC is much more susceptible to inhibition than is formation of LTB (E. Razin, personal communication). The apparent stimulation of 5-HETE and LTB formation in the presence of high concentrations of arachidonate and low concentrations of the inhibitor in human polymorphonuclear neutrophils (Fig. 2) may also be examined in this manner if one assumes that the inhibition of the 5-lipoxygenase by this compound

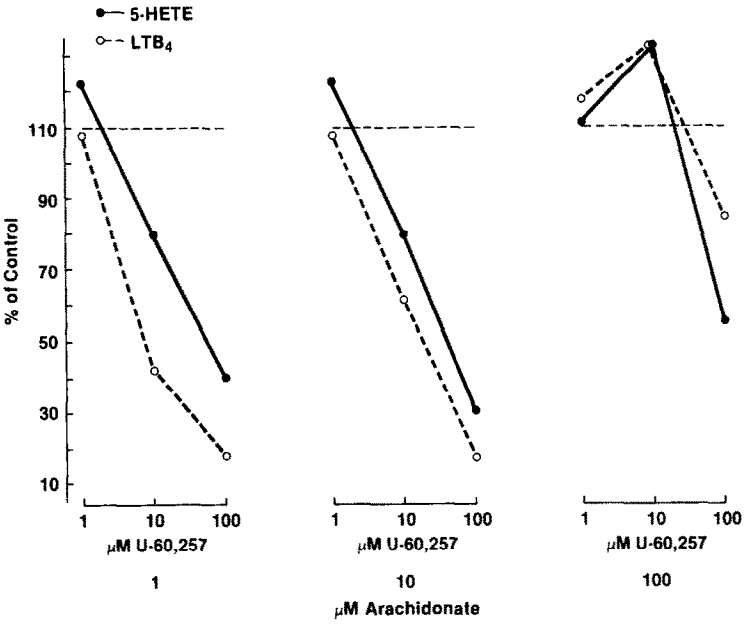

Fig. 2. Effect of U-60,257 on the conversion of arachidonate to 5-HETE and LTB_4 in human polymorphonuclear neutrophils. Data are shown for three different arachidonate concentrations and for three concentrations of U-60,257 at each arachidonate concentration (from Sun and McGuire [29]).

is competitive with arachidonate. Preliminary results suggest that the LTC synthetase of human lung may also be susceptible to inhibition by this compound although we do not yet know what the nature of this inhibition is (M. K. Bach and J. R. Brashler, unpublished observations).

As already indicated (see results with the E type mast cells, above), the capacity to affect two steps in a pathway can mean a much more profound inhibition of the formation of the final product of this pathway than the inhibition of an earlier product. If the inhibition of the second step is competitive with substrate, one can envision a situation where a relatively minor effect on the first step in the pathway, leading to a small reduction in the steady-state pool size of the precursor for the last affected step, might be translated into a nearly total inhibition of the second step and thus of the formation of the end product. Such a situation could have the advantage of preventing much of the shunting of the branch point intermediate (arachidonate in this instance) into another pathway and yet down-regulating moderately the amounts of all the products of the affected pathway which might be produced. At the same time, a key metabolite (LTC in this case) would be nearly totally eliminated. A mechanism such as this may explain why U-60,257 appeared to be much more active when given by aerosol to Ascaris-sensitive monkeys than it was with rat mononuclear cells *in vitro* [31].

SOME THOUGHTS ON THE LIMITATIONS ON THE DEVELOPMENT OF INHIBITORS OF LEUKOTRIENE SYNTHESIS

There are a number of ways of looking at the topic of this commentary. Implicit in all that has been said thus far is the assumption that we are interested in *selective* inhibitors of leukotriene synthesis. First, we have to define what we mean by selectivity. For my purposes, the term has a dual meaning and both meanings are important to my goals. One meaning is selectivity within the arachidonate cascade. Thus, a selective inhibitor of leukotriene synthesis should affect leukotreine synthesis and not prostaglandin synthesis, 12-HETE synthesis or 15-HETE synthesis. The other meaning involves functional selectivity, and by this I mean selectivity for leukotriene synthesis as compared to the synthesis or secretion of other mediators which may be involved in the condition which I may wish to study.

But whether or not we want a *selective* inhibitor is really part of the answer to the next question we have to address and that is the purpose for which we want the inhibitors in the first place. On the one hand, we may wish to have such compounds as laboratory tools in order to study certain reactions *in vitro* or *in vivo*. On the other hand, we may want the compounds as potential therapeutic modalities for the treatment of human disease. From my own point of view, we would want selective inhibitors in either instance, at least at this stage in our knowledge. Clearly, for mechanistic and laboratory studies, it will be essential to have compounds that are as selective as possible if we are to be able to interpret our results with any confidence. At the same time, and as already indicated in the first section of this commentary, we must view the application of an inhibitor of leukotriene synthesis to the treatment of asthma as an experimental application too, since the critical experiment to prove the role of these mediators in asthma is yet to be run. But once this question has been answered it may well prove advantageous to devise compounds having certain specific combinations of activities.

Two quite distinct series of reservations must enter

our evaluation of the prospects for the development of inhibitors of the leukotriene pathway. One series deals with the complexity of the arachidonate cascade and the other deals with the complexity of the diseases which may be affected by imbalances in the cascade. A few closing words on both of these may be in order.

The complexity of the arachidonate cascade. As anyone following the ever-present schemas of the arachidonate cascade over the past 10 years knows, the number of pathways that are known to occur is large indeed and, seemingly at least, the end is not yet in sight. But, beyond this first order of complexity, there are second and third orders of complexity, and it is these which must receive more attention if we are to succeed in the development of selective inhibitors. I am referring to the complex of interactions that appear to take place among the enzyme(s) of one pathway in the cascade and the products from other pathways, on the one hand, and the interactions between products of arachidonate metabolism and the systems responsible for the production of other mediators, seemingly outside the arachidonate cascade, on the other.

Some of the interactions between different branches of the arachidonate cascade have been the subject of a recent commentary in this journal [32] and will not be discussed in any detail. Suffice it to state that the 12-lipoxygenase product of platelets, 12-HPETE, has been shown to be a potent activator of the 5-lipoxygenase pathway in leukocytes and that 15-HETE, especially, is an inhibitor of this enzyme in many cells while, under certain conditions, it can actually act as an inducer [33]. In fact, products of all three major lipoxygenase pathways appear to feed back on each other [34].

Superimposed on these interactions among products of different lipoxygenase-initiated pathways, there are interactions with products of the cyclooxygenase pathway. I already mentioned the well-established ability to enhance leukotriene synthesis in the presence of inhibitors of the cyclooxygenase which has been interpreted as being due to shunting of the precursor arachidonate. However, this explanation may not be the whole story since selective inhibition of thromboxane synthesis by a variety of selective inhibitors can also cause an increased production of leukotrienes [35]. Perhaps this is due to the inhibition of leukotriene synthesis by elevated levels of cyclic AMP which may be induced in the systems being studied by the thromboxane, but this is not clear at the moment. The reverse situation also appears to hold. Thus, production of leukotrienes, or stimulation of tissue with leukotrienes, can result in the formation of thromboxane which can augment the physiologic response since it, too, is a smooth-muscle-contracting substance. Again, it is not clear if this effect is a direct or indirect one, although the finding that the addition of leukotrienes to isolated macrophages can cause them to release thromboxane [36] suggests that the effect may be relatively direct.

Finally, it must be kept in mind continuously that the arachidonate cascade, complex as it is, interacts at many levels with other systems. The effects on cyclic AMP (above) are just one example of this. The apparent ability of H_1 antihistamines to partly antagonize the responses of the airways of monkeys to administered leukotrienes [37], and the observation that the responses of dog tracheae to leukotrienes can be antagonized by atropine and synergized by dimethyl phenyl pyperazinium [12], suggest the existence of other interactions which are not yet fully understood.

Some thoughts on the complexity of asthma. Implicit in much of what has been said about the presumed role of leukotrienes in eliciting the symptoms associated with asthma is the assumption that there exists, more or less, a linear relationship between a given etiologic agent and the elicitation of symptoms. As our knowledge of disease has increased over the years, this simplistic assumption has often been challenged. Such is certainly the case in asthma. It may well turn out to be true that the leukotrienes play a role in causing the symptoms of this disease although the observation that, uniquely, asthmatics are not more sensitive to these spasmogens than are normals [5] strongly hints that the role of these mediators may be more complex. In fact, asthma may not be a single disease at all but rather may represent a collection of patients who have reversible, hyperreactive airways which may be caused by any one of a number of underlying causes or, more likely, by combinations of these. The role of chronic irritation, chronic production of low levels of various mediators, damage to the epithelial lining of the airways and ensuing loss of tight junctions (which could be caused directly or indirectly by the chronic overproduction of mediators in the airways), or a genetic predisposition, are but some of the contributing factors which we now recognize.

The consequences of these realizations are that the prospects for the inhibition of leukotriene synthesis, from a practical point of view, are a bit less certain than they might have been a few years ago. Dale's criteria require that there be a single cause-and-effect relationship, and the multiple paths to the same end, which the picture of asthma now emerging suggests, may or may not be sufficiently dependent on the leukotrienes, representing just one of the paths, for there to be a demonstrable effect on the disease once the contribution of these agonists is eliminated. Only time, and experience over the next few years, will tell which way the answer lies. But, regardless of the outcome, the availability of selective inhibitors should prove of great value in the further dissection of the pathophysiology of this and other diseases in which the leukotrienes may play a role.

REFERENCES

1. W. E. Brocklehurst, *Prog. Allergy* **6**, 539 (1962).
2. C. J. Hanna, M. K. Bach, P. D. Pare and R. R. Schellenberg, *Nature, Lond.* **290**, 343 (1981).
3. S. E. Dahlén, G. Hansson, P. Hedqvist, T. Björck, E. Granström and B. Dahlén, *Proc. natn. Acad. Sci. U.S.A.* **80**, 1712 (1983).
4. J. W. Weiss, J. M. Drazen, N. Coles, E. R. McFadden, Jr., P. F. Weller, E. J. Corey, R. A. Lewis and K. F. Austen, *Science* **216**, 196 (1982).

5. M. Griffin, J. W. Weiss, A. G. Leitch, E. R. McFadden, Jr., E. J. Corey, K. F. Austen and J. M. Drazen, *New Engl. J. Med.* **308**, 436 (1983).
6. J. W. Weiss, J. M. Drazen, E. R. McFadden, Jr., P. Weller, E. J. Corey, R. A. Lewis and K. F. Austen, *J. Am. med. Ass.* **249**, 2814 (1983).
7. Z. Marom, J. H. Shelhamer, M. K. Bach, D. R. Morton and M. Kaliner, *Am. Rev. resp. Dis.* **126**, 449 (1982).
8. S. J. Coles, K. H. Neill, L. M. Reid, K. F. Austen, Y. Nii, E. J. Corey and R. A. Lewis, *Prostaglandins* **25**, 155 (1983).
9. A. C. Peatfield, P. J. Piper and P. S. Richardson, *Br. J. Pharmac.* **77**, 391 (1982).
10. H. G. Johnson, R. A. Chinn, D. R. Morton, M. L. McNee, M. D. Miller and J. A. Nadel, *Agents Actions* **13**, 1 (1983).
11. H. G. Johnson, M. L. McNee, M. A. Johnson and M. D. Miller, *Int. J. Immunopharmac.* **5**, 391 (1983).
12. H. G. Johnson, M. L. McNee, M. A. Johnson and M. D. Miller, *Int. Archs Allergy appl. Immun.* **71**, 214 (1983).
13. A. Wanner, S. Zarzecki, J. Hirsch and S. Epstein, *J. appl. Physiol.* **39**, 950 (1975).
14. G. Hansson and O. Rådmark, *Fedn Eur. Biochem. Soc. Lett.* **122**, 87 (1980).
15. U. Aehringhaus, R. H. Wöbling, W. König, C. Patrono, B. M. Peskar and B. A. Peskar, *Fedn Eur. Biochem. Soc. Lett.* **146**, 111 (1982).
16. S. D. Brain, R. D. R. Camp, P. M. Dowd, A. K. Black, P. M. Woollard, A. I. Mallet and M. W. Greaves, *Lancet* **II**, 762 (1982).
17. K. Kragballe and T. Herlin, *Archs Derm.* **119**, 548 (1983).
18. W. F. Stenson and E. Lobos, *J. clin. Invest.* **69**, 494 (1982).
19. Z. Naor, J. Y. Vanderhoek, H. R. Lindner and K. J. Catt, *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **12**, 259 (1983).
20. Z. Zukowska-Grojec, M. A. Bayorh, I. Yaar, I. J. Kopin and G. Feuerstein, *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **11**, 407 (1983).
21. L. Steel and M. Kaliner, *J. biol. Chem.* **256**, 12692 (1981).
22. M. K. Bach, J. R. Brashler, D. R. Morton, L. K. Steel, M. A. Kaliner and T. E. Hugli, *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **9**, 103 (1982).
23. S. P. Peters, I. M. Siegel, A. Kagey-Sobotka and L. M. Lichtenstein, *Nature, Lond.* **292**, 455 (1981).
24. M. K. Bach, J. R. Brashler, H. W. Smith, F. A. Fitzpatrick, F. F. Sun and J. C. McGuire, *Prostaglandins* **23**, 759 (1982).
25. W. R. Mathews and R. C. Murphy, *Biochem. Pharmac.* **31**, 2129 (1982).
26. R. A. Lewis, J. M. Mencia-Huerta, C. W. Lee and K. F. Austen, *Proceedings of the Workshop on Asthma III, Nuneham Park, England, May 1983,* in press.
27. B. A. Jakschik and C. G. Kuo, *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **11**, 141 (1983).
28. E. Razin, J. M. Mencia-Huerta, R. A. Lewis, E. J. Corey and K. F. Austen, *Proc. natn. Acad. Sci. U.S.A.* **79**, 4665 (1982).
29. F. F. Sun and J. C. McGuire, *Prostaglandins* **26**, 211 (1983).
30. C. W. Parker, G. M. Fischman and H. J. Wedner, *Proc. natn. Acad. Sci. U.S.A.* **77**, 6870 (1980).
31. H. G. Johnson, M. L. McNee, M. K. Bach and H. W. Smith, *Int. Archs Allergy appl. Immun.* **70**, 169 (1983).
32. P. Borgeat, B. F. Laclos and J. Maclouf, *Biochem. Pharmac.* **32**, 381 (1983).
33. J. Y. Vanderhoek, N. S. Tare, J. M. Bailey, A. L. Goldstein and D. H. Pluznik, *J. biol. Chem.* **257**, 12191 (1982).
34. J. Y. Vanderhoek, R. W. Bryant and J. M. Bailey, *Biochem. Pharmac.* **31**, 3463 (1982).
35. D. M. Engineer, P. J. Jose, P. J. Piper and J. R. Tippins, *J. Physiol., Lond.* **281**, 42P (1978).
36. N. Feuerstein, M. Foegh and P. Ramwell, *Br. J. Pharmac.* **72**, 389 (1981).
37. M. K. Bach, J. R. Brashler, M. L. McNee and H. G. Johnson, in *Advances in Clinical Immunology* (Eds. M. Condorelli, G. Marone and L. M. Lichtenstein). O.I.C. Medical Press (in press).