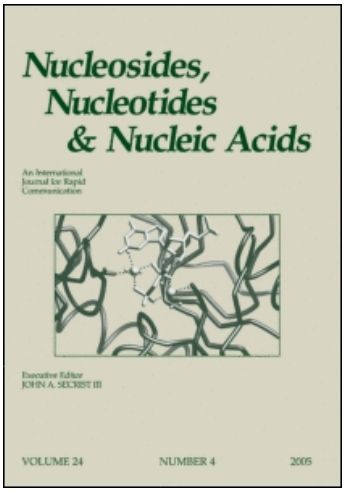

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Purinergic Receptors, Past and Future (Closing Remarks)

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PURINERGIC RECEPTORS, PAST AND FUTURE (CLOSING REMARKS)

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At the end of a symposium, it is useful to look back, both at the symposium itself and the developments that led up to the symposium. In this spirit, I thought it would be appropriate to tell the story of how I first became interested in purinergic receptors. I am recounting this story not because I believe that my audience has a burning interest in the history of my intellectual development, but rather because it illustrates the power of ideas.

Purkinje Nerves. In 1973, I was a second-year graduate student in Neurosciences looking for a dissertation topic. At the time, I was taking a course entitled Comparative Neuroanatomy. As part of the course, the students were expected to choose a scientific article from a list provided by the professor and present that article to the class. The title of one article was very puzzling to me: "Purkinje Nerves". When I asked about the article, it turned out that the professor (Dr. T.H. Bullock) was an authority on the cerebellum, so his secretary had heard of the word "Purkinje" before, but had never heard of the word "Purinergic". The actual title of the article was "Purinergic Nerves".[1] I looked up the article in the library and found it to be very interesting. Some madman named G. Burnstock was actually proposing the crazy idea that ATP was a neurotransmitter! Of course, I instantly recognized that any idea that audacious had to be correct, so I began looking for a way to do my dissertation on purinergic nerves. One thing led to another, and I started down what is now known as the P_1 branch of the purinoreceptor family tree, with results that will be familiar to many in the audience.[2-4] This story shows how ideas (or paradigms, if you will) can influence the

course of science and scientific careers, in this case ultimately resulting in my presenting these closing remarks.

Purinergic Receptors, Past. It is also useful to look at the course of research leading up to this symposium. To give the audience some idea of the growth of the field, I counted the number of articles from the BIOSIS database mentioning purinergic receptors (FIG. 1). The first article to mention the phrase "adenosine receptor" in the title or abstract appeared in 1975.[5] The adenosine receptor literature began to grow quite rapidly in the early 1980s, probably in response to the publication of the first adenosine receptor binding assays by four laboratories in 1980.[6-9] Activity in the field showed signs of leveling off in the late 1980s, but at the rate of over 250 publications per year.

The ATP receptor literature also stretches back to the early 1970s. A 1970 article mentions ATP-sensitive chemoreceptors in tsetse flies,[10] and the first mention of a mammalian ATP receptor was in 1975.[11] The growth of the ATP receptor field has been slower than for adenosine (note that the scale in FIG. 1B is 10x smaller than the scale in FIG. 1A), but shows signs of entering an exponential growth phase in the last two years. The acceleration in growth is probably due to the development of ATP receptor binding assays,[12] coupled with the recent identification of a swelling host of ATP receptor subtypes.[13] Judging from the rate of discovery of new ATP receptors, in the end there may turn out to be even more ATP receptor subtypes than serotonin receptors. The ATP receptor field may show the same rate of growth in the 1990s that the adenosine receptor field enjoyed in the 1980s.

I have already mentioned the power of ideas. Now I would like to suggest an idea: someone should work on the ADP receptor! The ADP receptor would seem to be an ideal topic for research. The role of ADP in providing positive feedback in platelet aggregation is well-established, a receptor binding assay has been available since the early 1980s,[14] and competitive ADP antagonists have existed for even longer.[15] Like adenosine and ATP receptors, ADP receptors have been recognized since the early 1970s (FIG. 1C).[16] Yet despite these attractive features, research on ADP receptors appears to have lost momentum in the 1980s. Although neglected at present, the ADP receptor holds significant therapeutic promise because of its role in thrombosis.

Purinergic Receptors, Future. The developments from this symposium point toward the future of purinergic research. Due to the number of presentations, I will not mention each by name, but rather will attempt to spotlight a few of the major trends that have emerged. A protective role for adenosine is one such unifying theme. Besides being the explicit focus of my presentation and that of Dr. Deckert, this idea is implicit in several other presentations. Compounds that increased the effectiveness of the

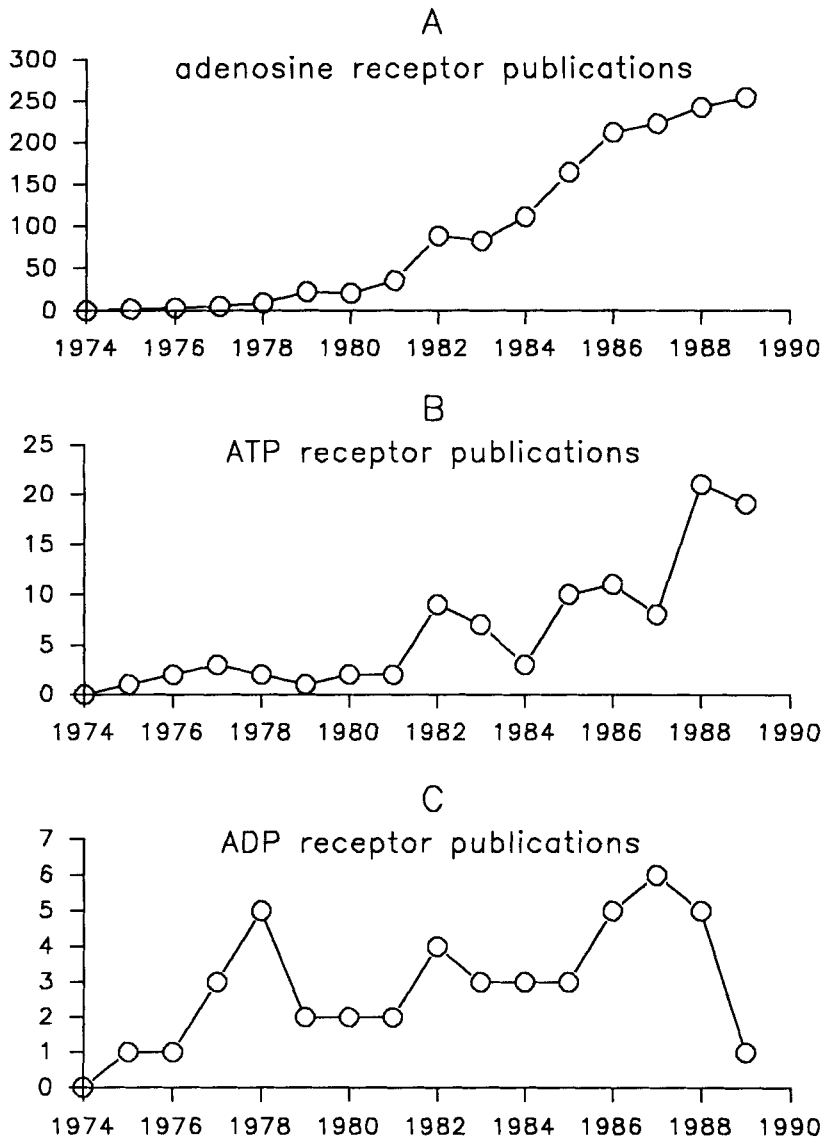

FIG. 1. Publications mentioning purinergic receptors in the title or abstract. Searches were carried out using the BIOSIS database with the keywords "adenosine receptor" (A), "ATP receptor" or "adenosine triphosphate receptor" or "P2 receptor" (B), and "ADP receptor" or "adenosine diphosphate receptor" (C). Additional publications from before 1980 were identified from the Medline and Ringdoc databases.

adenosine system would very likely be useful in ischemia. Dr. Olsson described several very potent and A_2-selective agonists, while Dr. Quinn described molecular modeling of agonist binding modes. Although side-effects may limit the therapeutic usefulness of agonists (see presentation by Dr. Williams), selective agonists continue to be very useful as pharmacological tools. Several speakers described various molecular mechanisms for potentiating adenosine, an approach that may provide better physiological control and therefore avoid side-effects. Drs. Miras-Portugal, Van Belle, and Hammond described various modulators and inhibitors of nucleoside uptake systems. In addition, Gensia Corporation is attempting to develop the ATP precursor AICA-riboside as a potentiator of adenosine production,[17] and adenosine receptor enhancers have also been described.[18] Conversely, adenosine antagonists may be useful when endogenous adenosine causes an unwanted depression of function. In this regard, Dr. Schingnitz described KFM-19, a potent, orally active A_1 antagonist with memory-improving effects.

Purinergic Nerves. It has now been very well proven that ATP really is a neurotransmitter,[19] vindicating Geoffrey Burnstock's controversial hypothesis. The focus now turns to the question of just what the roles of ATP and ATP receptors may be. New pharmacological tools, as described by Drs. Cusack and Leff, will be essential.

Concluding Remarks. In closing, I would like to thank the organizers for an enjoyable symposium that has focused attention on therapeutic opportunities in the field of purinergic receptors.

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