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I. International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification

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Preface

Since Ahlquist (1948) introduced the concept that cell membrane receptors for norepinephrine exist in distinct types, mediating separate functions, pharmacologists have attempted to characterise the receptors for many neurotransmitters and hormones. Rigorous attention to receptor characterisation and the identification of selective synthetic ligands have led to major therapeutic advances, as exemplified best by the introduction of β-adrenoceptor and H_2-histamine receptor-blocking drugs (Black et al., 1972; Black and Prichard, 1973). Nevertheless, until the advent of modern molecular biology techniques, pharmacologists were sceptical about data from functional studies in whole tissues that suggested a multiplicity of receptor types for a given mediator. However, as many as 10 adrenoceptor subtypes, 8 prostanoid receptor types, and 14 types of receptors for 5-hydroxytryptamine have been identified. This potential for receptor diversity for all neurotransmitters and hormones has been confirmed by the cloning of many genes for multiple receptor types and the study of the function of the recombinant receptor proteins for which they code. Because receptor gene cDNAs are now being cloned so rapidly, new receptor types are being proposed before their function in intact tissues, if any, is known. This creates problems for those interested in the classification and nomenclature of receptors potentially relevant to therapeutics. As a consequence of a strong international desire among pharmacologists to rationalise the information provided by techniques of molecular biology in relation to drug-related data concerning receptor function, at the General Assembly of the International Union of Pharmacology (IUPHAR), which met during the International Congress held in Sydney, Australia, in 1987, a committee was created whose mission was to discuss and clarify the criteria of acceptance of receptor (sub)types and the classification of drugs acting at these receptors. The General Assembly of the IUPHAR in its meeting during the next International Congress held in Amsterdam, The Netherlands, in 1990, reemphasized the importance of this Committee for Receptor Nomenclature and Drug Classification (NC-IUPHAR) and clarified its role as dealing primarily with an orderly nomenclature for receptor subtypes rather than with drug classification, in view of the paramount priority of the task.

The current composition of the NC-IUPHAR is listed in table 1. To provide the necessary scientific expertise, the committee has branched out into 19 subcommittees, most dealing with a specific task related (thus far) to a family of cell membrane receptors or cell membrane channels; the main NC-IUPHAR is represented in most subcommittees to ensure continuity and cohesiveness. The individual subcommittees, their current chairpersons, and their membership are listed in table 2. The subcommittees meet as frequently as possible, usually in association with an international meeting or symposium devoted to their area of particular interest.

Each subcommittee is required to prepare a document, compatible with the overall view of the main NC-IUPHAR, in which its recommendations in terms of classification are summarized. At a biannual meeting, the main NC-IUPHAR discusses and amends the proposal of the subcommittee. If the main committee believes that major adjustments are required, the document is sent back to the subcommittee for further input. The final decision concerning the content of the document rests with the main NC-IUPHAR, which sends it to the Executive Committee for official approval. At that stage, the document represents the official view of the IUPHAR and is submitted for publication in *Pharmacological Reviews*. Indeed, the IUPHAR has signed an agreement with the

TABLE 1
Current Membership of the IUPHAR Committee for Receptor Nomenclature and Drug Classification

Member	
Alison Abbott	München, Germany
Eric A. Barnard	London, United Kingdom
Tom I. Bonner	Bethesda, Maryland, USA
Phillip B. Bradley	Birmingham, United Kingdom
George J. Cosmides	Bethesda, Maryland, USA
B. N. Dhawan	Lucknow, India
C. T. Dollery	London, United Kingdom
C. R. Ganellin	London, United Kingdom
T. Godfraind	Bruxelles, Belgium
J. P. Green	New York, USA
M. Hamon	Paris, France
P. P. A. Humphrey	Cambridge, United Kingdom
D. H. Jenkinson	London, United Kingdom
T. Kenakin	North Carolina, USA
S. Z. Langer	Paris, France
T. Masaki	Kyoto, Japan
R. Paoletti	Milano, Italy
M. Spedding (Secretary)	Suresnes, France
U. G. Trendelenburg	Tübingen, Germany
P. M. Vanhoutte (Chairman)	Courbevoie, France

TABLE 2
*Subcommittees of the IUPHAR**

Subcommittee	Chairperson(s)	Members
Adrenoceptors	**S. Z. Langer** Vice-President Biological Research, Synthelabo Recherche (L.E.R.S.), B.P. 110, 31, avenue Paul Vaillant Couturier, 92225 Bagneux Cedex, France Tel: 33 1 45 36 24 11 Fax: 33 1 45 36 20 12	D. B. Bylund D. C. Eikenburg J. P. Hieble R. J. Lefkowitz K. P. Minneman P. B. Molinoff A. D. Strosberg R. R. Ruffolo **U. G. Trendelenburg**
Angiotensin receptors	M. de Gasparo Ciba-Geigy, CVS Research Department, K125-1015, 4002 Basle, Switzerland Tel: 46 61 696 3747 Fax: 41 61 696 2651	A. Husain W. Alexander K. J. Catt A. Chiu M. Drew T. Goodfriend J. W. Harding T. Inagani P. Timmermans
Calcium channels (calcium channel modulators)	**R. Paoletti** Istituto de Scienze Farmacologiche, Univesita de Milano, Facolta di Farmacia, Via Balzaretti, 9, 20133 Milano, Italy Tel: 39 2 294 04672 Fax: 39 2 294 04961	**M. Spedding** (co-chair) F. R. Buhler S. Ebashi C. Fieschi **T. Godfraind** S. Harigaya B. E. G. Johansson S. Kazda R. Kretzschmar R. J. Miller J. Moss J. Olesen L. H. Opie A. Schwartz B. K. Siesjo R. W. Tsien **P. M. Vanhoutte** P. A. Van Zwieten
Dopamine receptors	J. C. Schwartz Unité de Neurobiologie, Inserm U109, 2ter, rue d'Alésia, 75014 Paris, France Tel: 33 1 45 89 8907 Fax: 33 1 45 80 7293	**S. Langer** O. Civelli M. G. Caron A. Carlsson J. W. Kebabian B. Scatton P. Sedvall P. Seeman P. F. Spano
Endothelin receptors	**T. Masaki** Dept. of Pharmacology, Kyoto University, Faculty of Medicine, Yoshida-Konoe-Cho, Sakyo-Ku, Kyoto 606, Japan Tel: 81 75 753 4391 Fax: 81 75 753 4402	J. Vane J. A. Angus **T. Godfraind** T. F. Lüscher G. M. Rubanyi **P. M. Vanhoutte**
Excitatory amino acid receptors	D. Lodge Dept. of Veterinary and Basic Sciences, The Royal Veterinary College, Royal College Street, London NW1 OTU, UK Tel: 44 71 387 2898 Fax: 44 71 388 2342	G. L. Collingridge A. C. Foster J. Garthwaite S. F. Heinemann T. Honore M. L. Mayer P. Seeburg J. C. Watkins A. B. Young

TABLE 2
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Subcommittee	Chairperson(s)	Members
$GABA_A$ receptors	**S. Z. Langer** Vice-President Biological Research, Synthelabo Recherche (L.E.R.S.), B.P. 110, 31, avenue Paul Vaillant Couturier, 92225 Bagneux Cedex, France Tel: 33 1 45 36 24 11 Fax: 33 1 45 36 20 12	**E. A. Barnard** G. Biggio C. Braestrup **G. J. Cosmides** H. Molher R. Olsen D. Pritchett P. H. Seeburg W. Sieghart P. Skolnick H. I. Yamamura
Histamine receptors	**J. P. Green** Dept. of Pharmacology, Mount Sinai School of Medicine, Box 1215, One Gustave L. Levy Place, New York, NY 10029-6574 Tel: 212 241 7014 Fax: 212 831 0114	**R. Ganellin** H. L. Haas D. P. Healy S. J. Hill R. T. Premont J. C. Schwartz N. Shankley H. Timmerman J. M. Young
Leukotriene receptors (eicosanoid receptors)	R. A. Coleman Peripheral Pharmacology, Glaxo Group Research Ltd., Park Road, Ware, Hertfordshire, SG12 ODP, UK Tel: 920 882544 Fax: 920 883 159	S. E. Dahlén J. M. Drazen P. J. Gardiner R. D. Krell W. T. Jackson T. R. Jones S. Nicosia **R. Paoletti**
Muscarinic acetylcholine receptors	N. J. Birdsall Division of Physical Biochemistry, National Institute for Medical Research, The Ridgeway, Mill Hill, London, NW7 1AA, UK Tel: 81 959 3666 ext. 2058 Fax: 81 906 4477	N. Buckley H. Doods K. Fukuda A. Giachetti R. Hammer H. Kilbinger G. Lambrecht E. Mutschler N. Nathanson A. North R. Schwartz **T. I. Bonner**
Opioid receptors (opiate receptors)	**B. N. Dhawan** CSIR Emeritus Scientist, Head, ICMR, Centre for Advanced Research in Traditional Remedies, Central Drug Research Institute, Chattar Manzil, P.O. Box 173, Lucknow-226 001, India Tel: 91 0522 244 156 or 234 219 Fax: 91 0522 243 405	**P. B. Bradley** C. J. Evans **M. Hamon** H. Loh R. Raghubir R. S. Rapaka T. Reisine
Prostanoid receptors (eicosanoid receptors)	R. A. Coleman Peripheral Pharmacology, Glaxo Group Research Limited, Park Road, Ware Hertfordshire, SG12 ODP, UK Tel: 920 882 544 Fax: 920 883 159	**P. P. A. Humphrey** R. M. Eglen R. L. Jones S. Narumiya **R. Paoletti** P. W. Ramwell T. Shimizu W. L. Smith

TABLE 2
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Subcommittee	Chairperson(s)	Members
Purinoceptors	B. B. Fredholm Dept. of Physiology and Pharmacology, Karolinska Institutet, S171 77 Stockholm, Sweden Tel: 46 8 728 79 39 46 8 732 29 04 Fax: 46 8 733 16 53	**A. Abbott** G. Burnstock J. W. Daly P. Leff T. K. Harden U. Schwabe M. Williams
5-Hydroxytryptamine receptors (5-HT or serotonin receptors)	G. R. Martin The Wellcome Foundation Ltd., Langley Court, South Eden Park Road, Beckenham, Kent BR3 3SB, UK Tel: 081 658 2211 Fax: 081 663 3645	**P. B. Bradley** T. Branchek D. E. Clarke M. L. Cohen J. R. Fozard J. P. Green M. Göthert P. Hartig D. Hoyer **P. P. A. Humphrey** J. E. Leysen D. N. Middlemiss E. J. Mylecharane S. J. Peroutka P. R. Saxena **P. M. Vanhoutte**
Somatostatin receptors	T. Reisine University of Pennsylvania, School of Medicine, Dept. of Pharmacology, 36th Street & Hamilton Walk, Philadelphia, Pennsylvania 19104 Tel: 215 898 1750 Fax: 215 573 2236	**P. P. A. Humphrey** D. Hoyer M. Berelowitz J. Epelbaum W. Feniuk A. M. O'Carroll
Tachykinin receptors	R. M. Snider Clinical Neurosciences Department, Burroughs Wellcome Company, 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709 Tel: 919 315 0680 Fax: 919 248 4781	M. Biernert **T. I. Bonner** E. Burcher S. H. Buck J. Glowinski H. Hagan J. L. Henry J. E. Krause S. E. Leeman F. Lembeck B. Livett C. A. Maggi I. K. M. Morton M. Otsuka D. Regoli Z. Selinger J. M. Stewart K. Watling
L-Arginine: Nitric oxide pathway	R. F. Furchgott Dept. of Molecular and Cellular Pharmacology (R-189), University of Miami School of Medicine, P.O. Box 016189, 1600 N. W. Avenue, Room 6079, Miami, Florida 33101 Tel: 305 547 3982 Fax: 305 548 4555	M. Feelisch R. Garthwaith J. Gillespie J. B. Hibbs Jr. L. J. Ignarro T. F. Lüscher M. A. Marletta S. Moncada M. J. Rand S. H. Snyder N. Toda J. Vane **P. M. Vanhoutte**

TABLE 2
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Subcommittee	Chairperson(s)	Members
Imidazoline receptors	P. Bousquet Université Louis Pasteur, Faculté de Médecine, Dept. de Pharmacologie cardiovasculaire et rénale, 11 rue Humann, 67000 Strasbourg, France Tel: 88 35 87 49 Fax: 88 24 14 72	M. O. Christen P. Ernsberger G. Göthert B. Guardiola A. Parini D. Reis **P. M. Vanhoutte** G. Vauquelin J. E. S. Wikberg
Technical Subcommittee	**P. P. A. Humphrey** Glaxo Institute of Applied Pharmacology (GIAP), University of Cambridge, Tennis Court Road, Cambridge CB2 1QJ, UK Tel: 44 0223 334 078 Fax: 44 0223 334 178	**E. Barnard** **T. I. Bonner** D. Hoyer **D. H. Jenkinson** P. Leff J. Lomasney N. P. Shankley *Corresponding members:* R. B. Barlow J. W. Black D. E. Clarke D. Colquhoun R. F. Furchgott **J. P. Green** **T. Kenakin** R. J. Lefkowitz D. R. Waud

* The members of the IUPHAR Committee on Receptor Nomenclature and Drug Classification are identified by bold type.

American Society for Pharmacology and Experimental Therapeutics and has agreed to provide manuscripts prepared by the Subcommittees and recommended by the NC-IUPHAR. The Secretary-General of the IUPHAR forwards the manuscripts to the Editor of *Pharmacological Reviews* and they are published in that journal at no cost to IUPHAR. *Pharmacological Reviews* recognizes the Committee as the source of reviewers for these manuscripts.

When a Subcommittee is sanctioned by the IUPHAR, it is listed in an electronic directory developed by the United States National Library of Medicine. This database is known as DIRLINE (Directory of Information Resources OnLINE) and can be accessed from many biomedical libraries worldwide. The contractor, American Type Culture Collection, contacts the Subcommittee chairpersons, usually every year, requesting a review of the online record for currentness and accuracy.

The NC-IUPHAR is now established and provides a forum for debate on approaches to receptor characterisation to develop guidelines and recommendations for their classification and nomenclature. Of general interest is the Technical Subcommittee working toward the standardisation of terms and symbols used in pharmacology. The Technical Subcommittee works through a panel of distinguished corresponding experts and invites input from those interested in drug receptor theory to ensure that all views are considered. The principles of receptor characterisation considered so far are based on an integrated approach to classification that relies on three essential criteria for receptor characterisation: structural, operational, and transductional information (Kenakin et al., 1992; Humphrey et al., 1993). None is considered pre-eminent, although at present transductional information is limited and its relative importance for definitive characterisation of a receptor is still unclear. Operational criteria describe the drug-related characteristics of a receptor, namely, recognition characteristics for agonists and antagonists. Structural data, although providing definitive identification, may provide limited information regarding the interaction of drugs with receptors and how this leads to the modulation of intracellular events. The knowledge of whether a receptor is a ligand-gated ion channel or a G-protein-linked receptor, or neither (Barnard, 1992), is fundamental, providing critical information regarding receptor identity and function. Beyond this, present understanding of transduction mechanisms is limited, but it is interesting to speculate that each receptor type may have subtly different modes of operation; for example, each G-protein-linked receptor might recognise different G-proteins according to the structure of the intracellular domains of the given receptor. The NC-IUPHAR will, during the next year, sanction the detailed guidelines from the Technical Subcommittee. An urgent issue is how to consolidate the rapid progress made by molecular biology techniques, which

can produce new receptor structures faster than they can be either defined according to classical pharmacological techniques or assigned to existing classifications. To address this problem, the NC-IUPHAR has developed the philosophy of using a simple numbering system (Kenakin et al., 1992) and also proposes a practical differentiation of nomenclature, in which lower case should be used for recombinant receptors for which the pharmacology either has not been performed or does not conform to the accepted pharmacology of the receptor in an appropriate tissue (e.g., α_{2a} or 5-HT_{1a}). However, where the receptor is clearly defined according to the NC-IUPHAR's criteria, then it may be termed α_{2A} or 5-HT_{1A}.

The first two official documents of the NC-IUPHAR were published in *Pharmacological Reviews* in 1992. One (Kenakin et al., 1992) was a discussion, written by individual members of the committee but endorsed unanimously by the others, of the principles that should govern proper classification, both in pharmacological and molecular terms, of receptors (and channels) and of the drugs that interact with them. The other (Spedding and Paoletti, 1992) was the summary of the classification of Ca^{2+} channels and of Ca^{2+} channel activators and inhibitors as proposed by the subcommittee on Classification of Calcium Antagonists, amended by the NC-IUPHAR and approved by the Executive Committee of IUPHAR. In the past 2 years, as several subcommittees have progressed toward final documents, the same procedure has been followed; the official documents published are now presented in this special issue of *Pharmacological Reviews*.

This issue contains three distinct categories of reports. First, the NC-IUPHAR recognizes that the fields of adrenoceptors, 5-hydroxytryptamine receptors, and prostanoid receptors have reached maturity and that enough information is available to propose an official nomenclature to be recommended for usage as such in all journals and books dealing with the pharmacology of cell membrane receptors. Second, in new areas of science, represented in this issue by the article concerning endothelin receptors, the NC-IUPHAR has made every possible effort to interact early with the major contributors in the field, to prevent ill-considered attempts at unsuitable classifications and to implement its general principles of nomenclature. Articles such as these also represent the official IUPHAR nomenclature, which may be elaborated and extended as more knowledge is accumulated but should not change in terms of general design. Third, the article concerning purinoceptors describes a classification that is accepted by the NC-IUPHAR *only* until more information allows the development of a more logical framework and system of classification; this type of document is recognized by a Prefatory Statement from the Committee, as well as by a special footnote on the title page. It is the conviction of the NC-IUPHAR that, although such documents cannot be considered definitive, they nevertheless provide an important forum accessible to the whole pharmacological fraternity for a debate that should lead to improvements based on scientific grounds alone.

As the members of the subcommittees and of the main committee continue their voluntary contribution to the issue of receptor nomenclature and classification, they are confident that their efforts will ultimately help to provide a clearer understanding of the nature of cell membrane receptors, in their amazing diversity. They are proud of the unique interface that they have created between classical pharmacology and molecular biology, with the sole purpose being clarification of scientific thinking.

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