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Amino
Acids

Editorial

Amino acids: holding centre stage more strongly than ever, and continuing to spring surprises

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The widening importance of amino acids – as if their role as constituents of peptides and proteins was not enough! – is emphasised by the increasing number and diversity of research papers covering their chemistry, and their involvement in all subject areas in biology.

This new Journal is launched on the crest of a current huge wave of new knowledge of the behaviour of amino acids and of their uses, and will focus on growing points in amino acids science. This policy will benefit a considerable number of scientists, and especially those eager to see their own work appearing in print by the side of cognate material from related areas of amino acids research.

Where are these areas in which amino acids are creating such excitement?

New research topics based on amino acids are developing under all the major subdivisions of science *[General references are given covering each of the following sections. Specific references are given in the sections, for the more dramatic highlights from recent literature that are mentioned there]*:-

Organic Chemistry – new, efficient methodology in asymmetric synthesis leading to known and new amino acids; easily-available homochiral protein amino acids can be used economically for the stereoselective synthesis of important compounds outside the amino acid field; more routine uses in heterocyclic chemistry and in main areas of synthetic organic chemistry; *["Amino acids, Peptides, and Proteins", Vols 1–16, 1969–1985, continued as "Amino Acids and Peptides", Vols*

17–22, 1986–1991, Royal Society of Chemistry, London; "Synthesis of Optically-Active -Amino Acids", Williams RM, Pergamon Press, Oxford, 1989; "Chemistry and Biochemistry of the Amino Acids", Barrett GC, Chapman and Hall, London, 1985; "Asymmetric Synthesis: Construction of Chiral Molecules using Amino Acids", Coppola GM and Schuster HF, Wiley, New York, 1987; "Amino Acids", Lubec G and Rosenthal GA., ESCOM Press, Leiden, 1990];

Inorganic Chemistry – complex formation and novel ligand processes of relevance to *in vivo* metal ion binding, and as models for metal – protein complexes; cysteine and other thiol-containing amino acids and their analogues are used as chelators in different toxicological applications – they are known to be radioprotective and can moderate the deleterious effects of chemical warfare *["Amino acids, Peptides, and Proteins", Vols 1–16, 1969–1985, continued as "Amino Acids and Peptides", Vols 17–22, 1986–1991, Royal Society of Chemistry, London];*

Physical Chemistry – scanning tunnelling microscopy actually showing single molecules of simple amino acids (and molecular aggregates in the case of glycine) adsorbed on highly oriented pyrolytic graphite *[Feng L, Hu CZ, Andrade JD (1988) J Microsc 152: 811];* spontaneous resolution of racemic amino acids as their arenesulphonate salts (much of this has to do with the purification processes associated with the large scale production of amino acids); transfer across liquid membranes *["Chemistry and Biochemistry of the Amino Acids", Barrett GC, Chapman and Hall, London, 1985; "Amino acids, Peptides, and Proteins", Vols 1–16, 1969–1985, continued as "Amino Acids and Peptides", Vols 17–22, 1986–1991, Royal Society of Chemistry, London];*

Analytical Chemistry – usually thought of as the more routine side of chemistry, but fascinating new techniques are emerging, such as capillary zone electrophoresis and isotachophoresis that show astonishingly efficient separation profiles and are capable of handling attomole levels (10^{-18} M) of amino acids *[Cheng YF, Dovichi NJ (1988) Science 242: 562];* the newer branches of mass spectrometry operate on nearly the same low levels, but with underivatized amino acids; homochiral amino acid derivatives grafted on to g.l.c. and h.p.l.c. stationary phases for chiral analysis; *["Chemistry and Biochemistry of the Amino Acids", Barrett GC, Chapman and Hall, London, 1985; "Amino acids, Peptides, and Proteins", Vols 1–16, 1969–1985, continued as "Amino Acids and Peptides", Vols 17–22, 1986–1991, Royal Society of Chemistry, London].* Refined mass spectrometric analysis techniques now available, allow the pursuit of isotopically-labelled amino acids through their metabolism in patients in a wholly non-invasive fashion;

Biochemistry, Pharmacology, Cell Biology – there is a crucial role for up to six amino acids to act as neurotransmitters, and a role for nearly all amino acids to act as a simple buffering system in physiological fluids. Much remains to be

discovered, when it comes to the roles of these simple compounds – why is there so much *N*-acetylaspartic acid in the brain, and what is its role?

Considerable promise is being shown by newly-developed simple amino acid derivatives that are enzyme inhibitors *[Jung M, in "Chemistry and Biochemistry of the Amino Acids", Barrett GC, Chapman and Hall, London, 1985];* L-arginine is the source of a second messenger in smooth muscle relaxation and other contexts, established *[Palmer RMJ, Ashton DS, Moncada S (1988) Nature: 333: 664; Marletta MA, Yoon PS, Yengar RI, Leaf CD, Wishnok JS (1988) Biochemistry 27: 8706]* to be nitric oxide (possibly *via* L-N^G-hydroxyarginine) *[Feldman PL (1991) Tetrahedron Lett 32: 875–878]* and this extraordinary role for a protein amino acid is sure to lead to important consequential new understanding in cell biology *[see also "Amino Acids", Lubec G and Rosenthal GA, ESCOM Press, Leiden, 1990];*

Nutrition – the supplementation of foods by "safe and ideal" amino acids, and the belief held strongly by some people, that a diet enhanced by high levels of added amino acids is beneficial, has generated evidence of side effects. *L*-Tryptophan (produced by fermentation by Showa Denko K. K., Japan) was recently subjected to U.S. Government controls when it was linked with an outbreak of eosinophiliamyalgia syndrome, or EMS, largely in the US, in 1990 *[News Report, Chemistry in Britain (1990) 26: 1050].* It has now been established that a contaminant at levels less than 0.01%, 1,1-bis(N^{im}-*L*-tryptophanyl)ethane, *alias* 1,1′-ethylidene-bis(*L*-tryptophan), is the cause of the problem *[Mayeno AN et al., (1990) Science 250: 1707 working at the Mayo Clinic, Rochester, New York; also Smith MJ, Mazzola EP, Farrell TJ, Sphon JA, Page SW, Ashley D, Sirimanne SR, Hill RH, Needham LL, (1991) Tetrahedron Lett 32: 991 working at the Food and Drug Administration, Washington D.C., describe its preparation from acetaldehyde and L-tryptophan; see also Morbidity and Mortality Weekly Report (1990) 39: 789].* This side-product is presumably generated in the fermentation, quite unexpectedly – or more likely, in the work-up stage of the production.

Replacement additives for incorporation into specialist diets for people who show low sodium ion tolerance can be mixtures containing amino acids and their derivatives such as amino acid methyl ester hydrochlorides, that taste "salty" *[Tamura M, Seki T, Kawasaki Y, Tada M, Kikuchi E, Okai H (1989) Agric Biol Chem 53: 1625];*

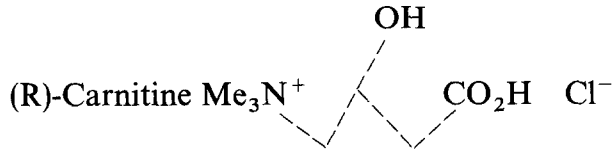
Geology and Archaeology – uses of perfected analytical techniques for determining small amounts of amino acids in terrestrial and extra-terrestrial samples; the former for age estimation of young fossils through determining the degree of racemization, the latter for speculations on the existence of life "out there", now or at some time in the past *[Barrett GC, in "Amino acids, Peptides, and Proteins", Vols 1–16, 1969–1985 from Vol. 6, and in "Amino Acids and Peptides", Vols 17–22, 1986–1991, Royal Society of Chemistry, London];*

Environmental Control – aminoisobutyric acid, not known to occur in Nature, is nevertheless effective in inhibiting the development of the dry rot fungus, *Serpula lacrimans*; this is one of a range of roles of amino acids in metabolic control (beyond the simplest form of control – the availability or non-availability of essential amino acids to individuals of a species); many seeds contain non-protein amino acids (e.g. *L*-DOPA constitutes about 8% of the dry weight of *Mucuna* and *Griffonia*, which also contain 5-hydroxy-*L*-tryptophan) whose role is the subject of speculation, but may have something significant to tell us about molecular evolution – the plant has a way of deterring predators from destroying its seeds *[Bell EA, Janzen DH (1971) Nature 229: 136];*

Medicine and Physiology – Apart from the use of amino acids in neuropharmacology (GABA analogues exerting inhibition and excitation are in use for antiepileptic therapy as well as for Parkinsonism), amino acids and their derived biogenic amines are useful tools in psychopharmacology. Highlights are microdialysis experiments showing amino acid metabolism and its changes *in vivo* in a dynamic system; metabolism of amino acids in different states of awakeness, behavioural changes and psychological situations can be monitored as reflected by the alterations of the excitatory or inhibitory amnino acid patterns. *[Amino Acids in Health and Disease: New Perspectives"", UCLA Symoposia in Molecular and Cell Biology, New Series, vol. 55, in: Kaufman S (ed) Liss AR Inc., New York, 1987; "Amino Acids", Lubec G, Rosenthal GA, ESCOM Press, Leiden, 1990].*

There are many simpler therapeutic uses for amino acids and derivatives; *N*-acetylcysteine is an antidote for paracetamol poisoning, and it is also a potent bronchosecretolytic agent. Proline derivatives are effectively reducing collagen synthesis in fibrolytic diseases, such as lung fibrosis and hepatic fibrosis; stereoisomers of substutited prolines are able to induce differentiation of astrocytoma cells into cells resembling the original morphological structure and dignity with reduced mitotic potential.

A few years ago, arginine only seemed to have a role in promoting insulin release, providing a basic test in diabetology. But it is now being used as an immunomodulator in critically-ill patients, also showing useful side-effects – it significantly reduces cholesterol levels generally, and reduces the incidence of glucose-mediated cross links in collagen (a role for glucose in diabetic long term complications).



(R)-Carnitine is a "vitamin-like" amino acid (some call it Vitamin B_T) that plays an important role in converting stored body fat into energy. Its primary role is to transport large fat molecules into cellular compartments where the fats

can be converted into energy. In the absence of *R*-carnitine, many fats cannot be "burned" and accumulate within the cell and in the bloodstream as fats and triglycerides *[Friedman S, Fraenkel GS (1972) The Vitamins, 2nd edn, In: Sebrell WH, Harris RS (eds) Academic Press, New York, 1972, Vol. 5, p. 329; Bremer J, Trends Biochem Sci 2: 207. Engel AG (1980) Carnitine Biosynthesis, Metabolism, and Functions, Eds. Frenkel RA and McGarry JD, Academic Press, New York, 1980].* Supplemental (R)-carnitine has proved to be beneficial to heart patients *[Thomsen JH, Sug AL, Yap VU, Patel AK, Karras TJ, De Felice SL (1979) Am Cardiol 33: 300]* and its effectiveness in systemic and myopathic deficiencies is now well recognised *[Borum P (1981) Nutrition Revs 39: 385; Chapoy PR, Angelini C, Brown WJ, Stiff JE, Shug AL, Cederbaum SD, N Engl J Med 303: 1389]* and moreover, this compound has been used successfully as a hypolipidemic agent in haemodialysis patients *[Vach GM, Giarcelli G, Siliprandi N, Corsi M (1983) Am J Clin Nutr 38: 532; Guarneri G, Ranieri F, Toigo G, Vasile A, Cinam M, Rizzoli V, Morachiello M, Campanacci L (1980) Am J Clin Nutr 33: 1489].*

Positron emission tomography can give information about a patient's local morphology and about dynamic cell processes such as receptor studies (in contrast with NMR imaging, which gives static structural features only); synthesis of ^{11}C-labelled amino acids and neurotransmitters for positron emission tomography challenges the development of rapid synthesis of chiral amino acids containing this short-lived isotope, and requires close collaboration between the organic chemist and the clinician.

Safety aspects of new pharmaceuticals – advantages and disadvantages of using amino acids and their derivatives in clinical and environmental situations

Many applications of simple chemicals in everyday life have developed as a consequence of the belief that something natural and familiar, such as a common amino acid that is essential to life processes as a constituent of proteins, should be safe in any way that it may be used. The term "safe" is used here in the sense of having no side-effects if used topically or environmentally, and accidentally ingested by humans and other species.

This is especially the case with the casual use of amino acids as food additives, in cosmetic formulations (*L*-tyrosine in sun-tan lotions; other amino acids in shampoos etc), even uses in environmental control (-aminoisobutyric acid for inhibition of dry rot fungus), where relatively large quantities may be employed.

It is now clear that these assumptions are unwise as starting positions, and may need to be verified. Even well-understood biotechnological production processes for amino acids can lead to unexpected problems, as in the case of *L*-tryptophan, and toxicological and other protocols should be developed and encouraged.

Conclusions

Reviews of the chemistry of the amino acids, and aspects of their biology, have been based on more than 500 papers each year *[Barrett GC, in "Amino acids, Peptides, and Proteins", Vols 1–16, 1969–1985 from Vol. 6, and in "Amino Acids and Peptides", Vols 17–22, 1986–1991, Royal Society of Chemistry, London].*

Even such a substantial number of papers could have been ten times larger, if results of biological research based on routine distribution of common amino acids, and all the pharmacological and clinical literature, and so on, had been included.

There is much of interest to come, from dedicated and well-directed research now going on in the science and applications of the amino acids and their derivatives. We confidently predict the outcome of continuing research with amino acids to be new fundamental understanding in neurophysiology in particular, but in clinical and other allied areas in general, with the support of new knowledge gathered at an increasing pace on their chemistry, especially their synthesis and physical properties.