several treatments were based on each of these approaches.

The need for reconciliation of the classification of "inert" gases in the periodic table with their demonstrated ability to form simple molecules was stressed by L. C. Allen (Princeton). He emphasized the role of instantaneous electron-electron correlations.

R. J. Gillespie (McMaster University, Hamilton, Ontario) presented predictions, based on the localized electron-pair theory, for molecular geometries and bond lengths of xenon oxides, fluorides, and oxyfluorides. In particular, his arguments suggest that XeF_6 is unlikely to be octahedrally symmetric in the vapor phase.

Evidence was presented (J. Hinze and K. S. Pitzer, Rice) that unoccupied *d*-orbitals for the noble gas atoms are of little importance to their formation of stable compounds. The unimportance of *d*-orbitals and the similarity of the halogen fluorides and inert gas fluorides was emphasized by R. E. Rundle and A. J. Serewicz (Iowa State) and the reverse argued by Smith (Oak Ridge Gaseous Diffusion Plant).

A comparison of six possible geometries for XeF_6 (L. L. Lohr, Jr., and W. N. Lipscomb, Harvard) indicates that the octahedrally symmetric structure is the most stable form considered, as judged by semiempirical molecular orbital calculations.

Finally, J. Jortner discussed absorption spectra in the near and the vacuum ultraviolet for XeF_2 and XeF_4 (Jortner, E. G. Wilson, and S. A. Rice, University of Chicago). He concluded that the semiempirical molecular orbital description of these compounds is in good agreement with their physical and chemical properties.

The alternative prediction of symmetrical versus non-symmetrical arrangements for xenon hexafluoride deepened the apparent conflict between the alternative approaches to the formulation of chemical bonds.

It is clear that additional refinement can bring either approach into agreement with the experimental observations as they are ultimately established. Nevertheless, many chemists prefer concepts that come closer to reality with fewer ad hoc adjustments.

The experimental observation and the remaining uncertainty has been discussed previously. The difficulties are formidable but do not appear insuperable. This particular discrepancy may well be resolved before this report appears in print.

All of the contending parties agreed that few discoveries in recent years have been more stimulating to the application of modern concepts of chemical binding to inorganic chemistry than the synthesis of simple xenon compounds. The weaknesses of available theoretical tools have been sharply emphasized; perhaps their strength will appear with more thorough investigation.

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Anticholinesterase Agents

An intersociety symposium on anticholinesterase (anti-ChE) agents was held at the meetings of the Federation of American Societies for Experimental Biology on 18 April. Since the mid-1940's approximately 250 publications have been issued annually on the subject of these agents. Because of this wide coverage and the broad scope of the topic, participants were requested to concentrate on two aspects of these agents: the possible physiological functions of acetylcholine (ACh) and acetylcholinesterase (AChE), and the dissociation between the effects of anti-ChE agents attributable to inhibition of AChE and those due to other actions.

G. B. Koelle discussed current theories of the physiological functions of acetylcholine and acetylcholinesterase. It has been proposed that acetylcholine, in association with the enzyme, serves (i) as a neurohumoral transmitter at synaptic and neuroeffector junctions; (ii) as the triggering agent for the propagation of conducted impulses in nerve axons and striated muscle fibers; (iii) as a local hormone, released by and acting upon various types of muscle fibers; and (iv) in regulating permeability and active transport in several non-excitable membranes.

The classical concept of acetylcholine as a neurohumoral transmitter, as proposed by Loewi, Dale, Feldberg, and others, assumes that this agent is released at the axonal terminal by a nerve impulse and combines with postjunctional receptors, thereby initiating a localized depolarization (the postsynaptic or endplate potential), which in turn triggers electrogenically the propagated action potential. Others (for example, Masland and Wigton, Abdon, W. R. Riker) have emphasized the prejunctional actions of cholinomimetic and cholinergic blocking drugs and have implied a function of acetylcholine at this site. Two general histochemical findings in the speaker's laboratory could not be explained satisfactorily in terms of the classical concept: nearly exclusive presynaptic localization of the enzyme occurred in sympathetic ganglia, in contrast to its predominantly postjunctional localization at the motor endplate, and varying concentrations were present in presumably noncholinergic neurons. On the basis of this and certain pharmacological evidence, it was proposed that acetylcholine has a dual neurohumoral role: an immediate action, at the axonal terminals from which it is released, which prolongs the depolarization of these terminals and hence promotes the release of (i) enough additional acetylcholine to act postjunctionally or (ii) another transmitter. The latter concept is consistent with Burn and Rand's hypothesis of the participation of acetylcholine in adrenergic transmission.

According to Nachmansohn's hypothesis, the propagation of the nerve action potential is dependent upon the electrogenic release of acetylcholine at successive sites along the axon, where it initiates the permeability changes which produce a reversal of the membrane's polarization. The same sequence is claimed to occur at junctional sites, where transmission would therefore also be electrogenic. Evidence along five general lines is difficult to reconcile with this proposal: (i) extreme variations in the concentrations of acetylcholine, acetylcholinesterase, and choline acetylase in various types of axons (for example, primary afferent versus motor); (ii) extremely high concentrations of anticholinesterase, cholinomimetic, and cholinergic blocking agents required to modify axonal conduction; (iii) irreducible latent period for junctional transmission; (iv) insufficient ionic content of axonal terminals to provide the current necessary for electrical transmission; and (v) electrical inexcitability of most postjunctional sites.

A local hormonal function of acetylcholine was inferred by Burn, Feldberg,

and others on the basis of evidence that a considerable proportion of this agent released by such organs as the isolated heart and ileum arises from non-nervous, and hence, muscular sources. In this capacity, acetylcholine is considered to regulate the tone and rhythmicity of its cells of origin, presumably by modifying their membrane permeability. At present, this concept has not been sufficiently tested to allow its reasonable acceptance or rejection.

Acetylcholine has been proposed to regulate permeability or transport in a wide variety of "non-excitable" membranes, including erythrocytes, amphibian skin, invertebrate gills, and placenta. While this possibility seems reasonable, particularly in the case of the placenta, which contains very high concentrations of both acetylcholinesterase and choline acetylase, the supporting evidence to date is not convincing. It is based largely on the effects of drugs at concentrations so high that their specificities of action are questionable. More direct approaches to this problem should prove fruitful.

A. G. Karczmar, in collaboration with L. C. Blaber and K. C. Kim, considered the actions of anticholinesterase agents at the neuromyal junction. Mono- and bis-quaternary inhibitors exhibit two types of pharmacological action at the cat and frog neuromyal junction; these actions include those associated with enzyme inhibition and those independent of the latter. In the first group occur (i) prolongation and augmentation of the endplate potential and of miniature endplate potentials; (ii) increase and prolongation of depolarization of the twitch response produced by exogenously applied acetylcholine; and (iii) potentiation of muscle twitch in response to nerve stimulation, concomitant with repetitive muscle action potentials. As would be expected from these actions, anticholinesterase agents antagonize *d*-tubocurarine, sometimes increasing the amplitude of the muscle twitch to levels above control height, and frequently increasing blockade produced by succinylcholine and decamethonium. All these effects of acetylcholinesterase inhibitors are consistent with a cholinergic mechanism of neuromyal transmission operating by the release of acetylcholine from synaptic vesicles present in the motor nerve terminals, which induces postjunctional bioelectrogenesis.

However, these compounds exhibit other actions which are not dependent on acetylcholinesterase inhibition. This is indicated by the fact that in several series of analogues there is incomplete correlation between acetylcholinesterase inhibition, acetylcholine twitch, *d*-tubocurarine antagonism, and muscle twitch potentiation. Direct evidence points in the same direction. Many quaternaries show an action similar to that of *d*-tubocurarine which can be antagonized by tetanic stimulation of the nerve and also by decamethonium. Others exhibit action similar to that of acetylcholine. An interesting phenomenon is that of augmentation without prolongation of acetylcholine depolarization, endplate potential, and miniature endplate potentials. Nerve terminal actions are also characteristic for many of these compounds. Some bisquaternary agents (ambenonium) and a hydroxyanilinium compound (edrophonium) show this action at an intra-arterial dose of 5 to 10 μg. Other hydroxyanilinium and related agents show this effect at much higher doses. It is not at present clear whether this effect depends upon acetylcholinesterase inhibition at the nerve terminal.

It is clear, however, that anticholinesterase and related agents act at several sites at the neuromyal junction. Hydroxyanilinium compounds increase endplate potential and acetylcholine depolarization, produce nerve terminal effects, and exhibit actions both similar and dissimilar to that of *d*-tubocurarine. The final effect observed differs from species to species and depends on an interplay between these actions. It sometimes leads to paradoxical effects such as, for example, antagonism of both *d*-tubocurarine and decamethonium blockades. This interplay may be considered due to cholinoceptive actions at post- and prejunctional membranes and to inhibitory effects on acetylcholinesterase at these sites.

R. L. Volle described the effects of anticholinesterase, cholinomimetic, and cholinergic blocking agents on synaptic processes in sympathetic ganglia. It was found that an excitatory mechanism which differed from the usual process of transmission could be activated by the anticholinesterase agents and by acetyl-β-methylcholine. The postganglionic firing produced by these agents and the ganglionic depolarization produced by acetyl-β-methylcholine were sensitive to blockade by small doses of atropine. Conversely, ganglionic blockade by hexamethonium had no effect on responses induced by these drugs. In addition, treatment of the ganglia with anticholinesterase agents unmasked a component sensitive to atropine in the ganglionic responses to injected acetylcholine. Thus, the ganglionic cholinoceptive sites appear to be of two types; one sensitive to blockade by traditional ganglionic blocking agents, and the other sensitive to blockade by atropine.

The studies of the ganglionic actions of acetyl-β-methylcholine indicated also the presence in the ganglia of an inhibitory process. Unlike acetylcholine, the ganglionic potentials evoked by acetyl-β-methylcholine were characterized by an initial period of hyperpolarization. The transmission of ganglionic action potentials evoked by preganglionic stimulation was depressed during this phase of the drug-induced ganglionic potentials. Although the nature of the hyperpolarization is unknown, the blockade by small doses of atropine of both the ganglionic potentials and the depression of transmission produced by acetyl-β-methylcholine suggests that a cholinoceptive site is involved. Similar studies with acetylcholine indicated also that the blockade of transmission produced by this agent may not be related always to ganglionic depolarization.

R. D. O'Brien presented evidence concerning cholinergic transmission at synapses of arthropods and other invertebrates. Arthropods and mammals are equally sensitive to poisoning by most organophosphate anticholinesterase agents; one may assume that this reflects the presence of vital cholinergic sites in both. However certain organophosphates containing basic nitrogen atoms are far more toxic to mammals than to insects; they are selective mammalicides. In accounting for this selectivity, the speaker and his associates first demonstrated with the American cockroach that the central nervous system has an ion-barrier to Amiton (a basic organophosphate) by showing that the rate of its penetration into the nerve cord has the predicted *p*H-dependence. In this way the mammal and insect are similar.

Extensive biochemical and histochemical work by others has shown that the insect central nervous system contains acetylcholine, cholinesterase, and choline acetylase, and that acetylcholine levels increase with synaptic excitation. However, the neuromuscular junction has no cholinesterase, and it is not sensitive to atropine or to anticholinesterase agents. Consequently the insect has all its vital cholinesterase protected by an ion barrier; by contrast, the vertebrate has a vital cholinesterase (the acetylcholinesterase at its neuromuscular junction) freely available to ions. This

accounts for the selective mammalicidal activity of Amiton. In confirmation, O'Brien prepared six fluoro derivatives of Amiton whose *p*Ka's varied from 8.9 to 4.2, and found that selectivity was markedly *p*Ka-dependent.

The neuromuscular junction of the crustacean is probably noncholinergic also. The nature of the neuromuscular transmitter in arthropods is unknown.

B. Holmstedt spoke on the pharmacology of the quaternary alkylphosphate anticholinesterase agents. In past years a number of studies had indicated that such agents have actions independent of their cholinesterase-inhibiting power. It has also frequently been observed that many quaternary ammonium bases are relatively potent, reversible inhibitors of cholinesterase. Several of these reversible inhibitors are also potent neuromuscular blocking agents; less active drugs are, in general, far less efficient cholinesterase inhibitors. Strangely enough, it was not until more than 20 years after the discovery of the organophosphorus compounds that anyone investigated seriously the pharmacological potentialities of such compounds that contained also a quaternary ammonium group.

Compounds of this type can be conveniently grouped in the following categories: (i) phosphostigmines and related compounds, (ii) phosphorylthiocholines, (iii) phosphorylcholines, and (iv) fluorophosphorylcholines.

1) Burgen and Hobbiger (1957) reported a series of alkylphenolphosphates in which the carbamate grouping of neostigmine was replaced by various phosphates. All compounds in this series, including the completely reversible analogues, are more active against butyrocholinesterase than acetylcholinesterase.

2) The compounds in this group show reactivation curves (activity/time) identical with those of the corresponding organophosphoryl fluorides or anhydrides, when pyridine-2-aldoxime methiodide is used as a reactivator. Furthermore these compounds are relatively stable to hydrolysis, are not attacked by phosphorylphosphatases, and are also extremely toxic. There is probably a partial casual relationship between the latter two factors.

3) These compounds are weak, reversible inhibitors in vitro. In animals they produce effects similar to those of some synthetic choline esters. They are characterized by their production of respiratory stimulation, but not of bradycardia.

4) The compounds in this group include both potent inhibitors of acetylcholinesterase, and agents which have a direct choline ester-like effect in preparations in which the enzyme has been completely inhibited. Accordingly, there are three different types: those with only indirect, or anticholinesterase, cholinomimetic effects, represented by the sulfur analogues; those with mainly direct effects in vivo, exemplified by the oxygen analogues; and an intermediate group with both direct and indirect cholinomimetic effects, such as the fluorophosphorylcholines.

The dual qualities of the organophosphorylcholines of being both cholinesterase inhibitors and choline esters is striking. It is likely that the study of this interesting group of compounds will yield even more profitable results in the future. In the efforts to elucidate the action of drugs at a cellular and subcellular level, the property of some of them of being positively charged irreversible cholinesterase - inhibitors should make them suitable for intracellular application through microiontophoresis.

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Meeting Notes

The following are scheduled meetings to be held in the U.S.S.R. and other Eastern European countries. Similar lists will appear quarterly in this section. In cases where the dates, location or organizers and their addresses are not known, the Academy of Sciences of the nation in question is given as a source of information.

July 1963

10–14. Czechoslovak **Chemical** Soc., Zilina, (Czechoslovak Chemical Soc., Hradcanske nam. 12, Prague 1-Hradcany)

15–17. Technique of **Compacting by Vibration**, Scientific Soc. for Mechanical Engineering, Budapest, Hungary. (Architectural Inst., Dioszegi ut. 37, Budapest 11)

22–27. Molecular **Spectroscopy**, 7th European congr., Budapest, Hungary. (I. Kovacs, Dept. of Atomic Physics, Polytechnical Univ., Budafoki ut. 8, Budapest 11)

July 1963 (no dates)

Prevention of **Blindness** in Rumania, Bucharest. (Acad. of the Rumanian People's Republic, Calea Victoriei 125, Bucharest)

August 1963

5–12. **Peat**, 2nd intern. congr., Leningrad, U.S.S.R. (Executive Committee, Presidium of Organization Bureau, Gorky St. 11, Moscow)

15–1. High Energy **Particle Accelerators and Instrumentation**, 3rd conf., Intern. Union of Pure and Applied Physics, Moscow, U.S.S.R. (Acad. of Sciences of the U.S.S.R., Lenin Prospekt 7, Moscow)

19–25. **Photogrammetry**, East German Soc., intern. colloquium, Dresden. (Dresden Technical Univ., George-Baehr-Strasse 7, Dresden A-27)

20–23. **Pharmacology**, 2nd intern. congr., Intern. Union of Physiological Sciences, Prague, Czechoslovakia. (H. Rašková, Charles Univ., Albertov 4, Prague 2)

26–30. **Nephrology**, 2nd intern. congr., Prague, Czechoslovakia. (Inst. of Cardiovascular Research, Budejovicka 800, Prague 4-Krc)

27–31. Scientific and Applied **Photography**, 4th Hungarian conf., Budapest. (A. Polster, Secretary for Photochemistry, Hungarian Soc. for Optics, Acoustics and Cinematography, Szabadság ter. 17, Budapest 5)

August 1963 (no dates)

Lubricants, 5th symp., East German Technology Soc., Chemnitz, Karl-Marx-Stadt. [Scientific-Technical Center, Chemical Industry for Lubricants and Lubrication, Krumpa (Geiseltal) East Germany]

August–September 1963

Microelements of the Far East, 2nd conf., Vladivostok, U.S.S.R. (Acad. of Sciences of the U.S.S.R., Lenin Prospekt 7, Moscow)

Hemoglobins, symp., Berlin, East Germany. (East German Acad. of Sciences, Mohrenstrasse 38, Berlin W. 8)

Summer 1963

International Technical and Scientific Organization for **Soaring Flight**, world congr., Poland. (Polish Acad. of Sciences, Palace of Culture and Sciences, Dworkowa 3, Warsaw)

September 1963

1–2. **Metallurgical** congr., 30th, Prague, Czechoslovakia. (Czechoslovak Acad. of Sciences, Narodní Tr. 3, Prague 1)

2–5. Non-classical **Shell Problems**, symp., Warsaw, Poland. (A. Sawczuk, Intern. Assoc. for Shell Structures Symp., Wspolna 32/46, P. O. Box 155, Warsaw 1)

2–6. Fluid **Dynamics**, 6th symp., Zakopane, Poland. (W. Fiszdon, Inst. of Basic Technical Problems, Polish Acad. of Sci-