JOURNAL OF Pharmaceutical Sciences

December 1965 volume 54, number 12

Review Article

Quantum Chemistry in Drug Design

By R. S. SCHNAARE* and A. N. MARTIN

ONE OF the major goals of medicinal chemistry is an understanding of the action of drugs based on a knowledge of their structure and physical-chemical properties. Empirical methods of reaching this goal have led in the past to a large number of highly useful medicinal agents; however, the techniques are admittedly time consuming and uneconomical. It is estimated that out of every 3000 to 5000 compounds synthesized today only one is ultimately found to be a useful therapeutic agent. It should be possible to improve this proportion with the aid of certain recently developed biophysical and theoretical methods.

With the increasing knowledge of the structure and physical-chemical properties of drug molecules and biochemical substances it is now possible to investigate how a drug acts at the molecular level in the body. One attempts to determine the sites, called receptors, at which a drug acts and the mechanism by which the action is brought about when the drug interacts with the receptor. A knowledge of the interaction forces involved in the binding of drug molecules to receptor sites is critical for an understanding of drug action; but unfortunately, the experimental determination of these forces is difficult, and little has been accomplished along these lines.

On the theoretical level, quantum mechanical calculation of the electronic characteristics of molecules should prove to be a fruitful approach to the determination of drug–receptor interactions. Quantum mechanics has been found to be an exceedingly difficult technique when applied to the determination of electronic characteristics of large molecules. However, the use of certain simplifying assumptions and the application of high-speed electronic computers have permitted the application of quantum theory to the study of chemical problems. A beginning has now been made in the application of quantum theory to the study of drug action, stabilization of medicinal agents, and the interaction of drugs in solution (1, 2). These applied fields of quantum mechanics are currently referred to in the literature as quantum chemistry, quantum biochemistry, or quantum pharmacology. The term "quantum chemistry" will be used throughout this report to refer to the applications of quantum theory in the study of the electronic properties of large organic molecules.

QUANTUM CHEMICAL CALCULATIONS

π Electron Systems.—Many drugs are composed wholly or in part of aromatic or π electron systems. To develop the quantum chemical interpretation of π electrons in a molecule, let us first consider benzene. In Fig. 1, *A* is the familiar Kekule representation of benzene with its alternating double bonds; *B* is a more detailed representation. The basic skeleton of benzene is composed of σ bonds which make up the rigid framework of the ring. In addition to the σ-

Received from the School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Ind.

* Present address: St. Louis College of Pharmacy, St. Louis, Mo.

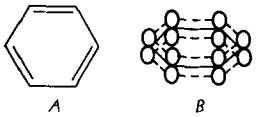


Fig. 1.—Structure of benzene. Key: *A*, Kekule structure; *B*, delocalized structure.

bonds, composed of electrons moving in the plane of the ring, each carbon atom contains a valence electron in a π orbital perpendicular to the plane of the ring. The π electrons are not localized between alternate adjacent carbon atoms as Kekule had proposed; rather, the π electrons may be diffused over the entire molecule to produce a doughnut-shaped electron cloud above and below the plane of the ring. The cloud contains six electrons, a contribution of one electron from each of the six carbon atoms of benzene. This distribution of electronic charge over the aromatic ring is known as delocalization.

Substitution by a radical, such as an amino or hydroxyl group, on the benzene ring will have two effects. First, the substituent may enlarge the π electron cloud. In phenol, for example, the oxygen atom of the hydroxyl group provides a π orbital, perpendicular to the benzene ring, which contains two π electrons. As a result, these two π electrons can blend with those in the π cloud of the benzene ring. The delocalized π cloud of phenol therefore extends over both the benzene ring and the hydroxyl group and is composed of eight π electrons (six from the aromatic ring and two from the hydroxyl group).

Second, a substituent attached to an aromatic ring may distort the π cloud of the ring. The direction of the distortion depends on whether the substituent is an electron donor or an electron acceptor. In the example just given, the hydroxyl group is an electron donor and will tend to push electrons into the ring.

We may consider one π electron to reside on each carbon atom in benzene. Therefore, a diagram of the electronic charge distribution would show 1.000 electronic charge on each carbon atom. But when a substituent, such as a hydroxyl group, is added to the ring, the charge of the mobile π electrons at any given atom may increase to say, 1.050, or decrease to say, 0.944. This change of electronic character can markedly affect the properties of the molecule during chemical reaction or biological activity.

The electronic charge distribution of such π electron systems, including highly complex molecules such as barbituric acid and riboflavin, can be calculated by the techniques of quantum chemistry. The development of this new science has been greatly facilitated by the advent of computer science. Calculations which would normally require weeks or months of work by hand can now be done in a few seconds by a modern digital computer.

It should be pointed out that quantum chemical calculations for complex molecules are approximations and should not be considered absolutely quantitative. They are, however, reliable in a relative sense and may be used quite conveniently as the basis of comparison for the electronic properties of similar molecules.

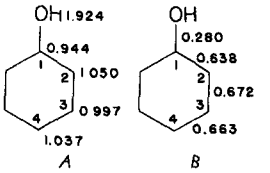


Fig. 2.—Some calculated electronic characteristics of phenol. Key: *A*, electron densities are shown at the atoms of the molecule; *B*, bond orders are shown at the various bonds of the molecule. HOMO coefficient = 0.729. LEMO coefficient = 1.000.

Some of the calculated electronic characteristics of phenol are given in Fig. 2. The results were obtained by the method of calculation described in the *Appendix*.

Figure 2 illustrates the quantum chemical interpretation of electronic structure. It is seen (Fig. 2*A*) that the electronic charge, called electron density, at each atom differs from the number of electrons that the atom contributes to the π cloud. For example, the carbon atom in position 1 contributes one electron to the π cloud; however, owing to the effect of the hydroxyl substituent, an electronic charge of 0.944 resides on this atom. One observes that the electron density or charge need not be a whole number. This does not imply that electrons can be split, but rather that electron density should be interpreted as a measure of the probability of finding an electron at a certain atom.

Bond order (Fig. 2*B*), another useful concept of quantum chemistry, is a measure of the probability of finding a pair of electrons in a bond between two atoms. It is related to the strength of the π bond between the atoms.

π Electrons in a molecule may be thought to be in energy levels just as the electrons about the nucleus of an atom are considered to be in the K, L, M, . . . shells or energy levels. The HOMO coefficient in Fig. 2 (HOMO stands for highest occupied molecular orbital) gives the relative energy of the two paired electrons in the highest molecular orbital where electrons are found and is related to the ionization potential of the molecule, that is, the ease with which an electron can be removed from the molecule. The LEMO gives the relative energy of the lowest empty molecular orbital and is related to the affinity of the molecule for an electron.

Application of these calculated electronic characteristics to pharmaceutics, medicinal chemistry, and pharmacology will now be illustrated by several examples.

SOME APPLICATIONS TO DRUG SYSTEMS

Complexation.—The binding of drugs with certain small molecules or polymeric materials has been studied as a means of preserving drugs in various dosage forms. One such example is the use of caffeine to stabilize solutions of benzocaine (3) and riboflavin (4). The writers and their associates have employed quantum chemical calculations to investigate the orientation of these two molecules within the drug complex and to study the nature of the intermolecular forces involved. The formal π charge distributions for caffeine and benzocaine, as calculated in our laboratory, are given in Fig. 3. The *formal π charge* for an atom is obtained by calculating the electron density according to the methods of quantum chemistry and then subtracting the calculated electron density from the number of π electrons initially donated to the π cloud by the atom. Thus, a positive formal charge indicates a deficiency of electrons, while a negative formal charge indicates an excess of electrons on an atom. For example, the formal π charge of +0.156 on the amino nitrogen of benzocaine, as seen in Fig. 3, indicates that the amino group has donated electrons to the aromatic ring resulting in a deficiency of electrons on the nitrogen atom.

These formal π charge distributions suggest a possible orientation of the molecules within the complex as depicted in Fig. 4. Here it is postulated that the benzocaine molecule lies on top of the caffeine molecule.

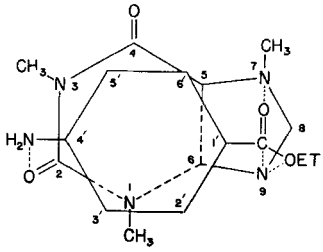


Fig. 4.—Proposed orientation of the benzocaine – caffeine complex.

The specific orientation of the two molecules is controlled by several electrostatic interactions. First of all, the formally negative oxygen at carbon 2 of caffeine interacts with the formally positive amino group of benzocaine. Similar interactions are possible between the carbonyl oxygen of benzocaine and nitrogen 7 of caffeine, and between the carbonyl carbon and the ester oxygen of benzocaine with nitrogen 9 of caffeine. These interactions thus form a three-point attachment between the two molecules in the complex.

In addition, several localized charge–transfer interactions are possible.[1] Positions 1, 5, and 6 of caffeine have large electron-donor or $S^{E\prime}$ indices (see *Appendix* for a more detailed definition of $S^{E\prime}$), as calculated by quantum chemical means, indicating that these positions are good electron-donor centers. Corresponding positions on the benzocaine molecule, positions 6′, 1′, and 2′, have large electron-accepting or $S^{N\prime}$ indices (see *Appendix* for the definition of $S^{N\prime}$), indicating that these positions on the whole are good electron-accepting centers. Localized charge–transfer interactions between these positions on the two molecules would supplement the electrostatic interactions and add to the total binding force. Stuart-Briegleb models of benzocaine and caffeine show that the distances between the various reactive centers of the two molecules are consistent with the proposed orientation.

It should be pointed out that other configurations of the complex which allow for efficient

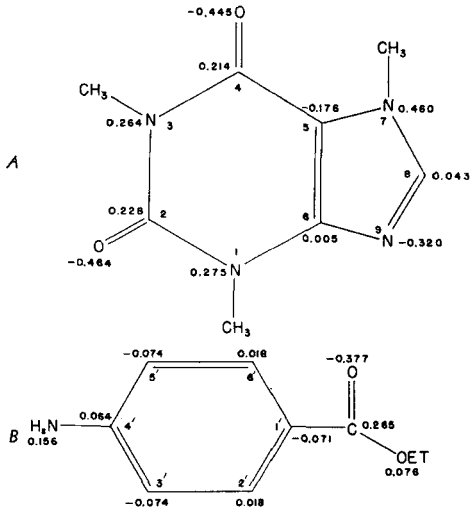
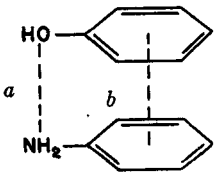


Fig. 3.—Formal charge distributions of caffeine (A) and benzocaine (B).

[1] Localized charge–transfer interactions refer to transfer of electrons between specific atoms or groups in the two molecules. This is in contrast to generalized charge–transfer interactions which involve transfer of electrons between molecules as a whole (5).



(*a*) Localized charge–transfer interaction between two specific groups and (*b*) generalized charge–transfer interaction between the two π clouds of the molecules.

electrostatic and localized charge–transfer interactions are possible, but that the results of the quantum chemical calculations suggest that the proposed orientation is the most probable.

Studies of this type should be important in understanding the forces involved in complexation and the effect of structural changes on complexation. Application of this information can be useful in the design of dosage forms from the standpoint of the solubility and stability of drug molecules.

Metabolism.—Quantum chemistry should prove a useful tool in conjunction with experimental studies for solving some of the problems of metabolism.

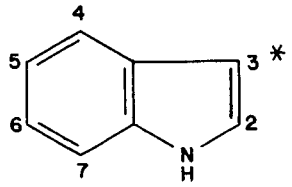
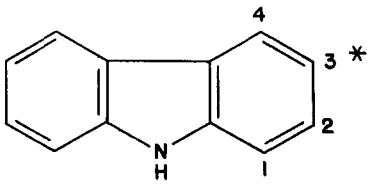
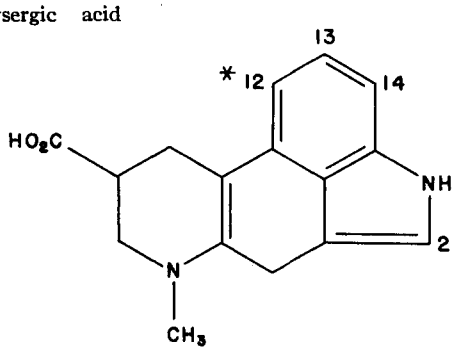
Johns and Wright (6) have recently studied the metabolism of several indole derivatives by an experimental technique. They have shown that these compounds undergo metabolism by hydroxylation in the aromatic ring of the indole skeleton, followed by conjugation with glucuronic acid. Hydroxylation was shown to occur in ergometrine and lysergic acid at position 12 and in carbazole at position 3. Indole itself is metabolized mainly to 3-hydroxyindole (7).

Hydroxylation in carbazole occurs at the position of highest electron density as determined experimentally by Brown and Coller (8). These workers determined the order of reactivity of carbazole for electrophilic attack by the OH ion to be $3 > 1 > 2 > 4$. Johns and Wright have shown that such information would be of value in experimentally determining the structure of metabolites.

In Table I are listed the electron densities for indole, carbazole, and lysergic acid as calculated in our laboratory. Indole and lysergic acid are indeed metabolized at the position of highest electron density; however, there is a discrepancy in the case of carbazole. Contrary to the order of reactivity found by Brown and Coller (above), the calculated electron densities suggest that the order is $1 > 3 > 2 > 4$.

This contradiction shows that our calculated electron density, while being successful for indole and lysergic acid, is inadequate for predicting the reactivity of carbazole. The results suggest that other factors may have to be considered or perhaps other δ and γ parameters (see *Appendix*, Table I*A*) must be chosen to bring the calculated

TABLE I.—ELECTRON DENSITY AND REACTIVE INDEX, *N*, OF INDOLE, CARBAZOLE, AND LYSERGIC ACID

Compd.[a]	Position	Electron Density	Reactive Index, *N*
Indole			
	2	0.999	−0.812
	3	1.170	0.378
	4	1.023	−0.874
	5	1.039	0.306
	6	1.031	−0.610
	7	1.037	−0.830
Carbazole			
	1	1.049	−0.484
	2	1.010	−0.593
	3	1.045	0.020
	4	1.005	−0.608
Lysergic acid			
	2	1.017	−0.506
	12	1.089	0.356
	13	1.026	0.260
	14	1.078	−0.544

[a] The asterisk indicates the position of hydroxylation.

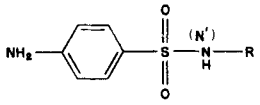


Fig. 5. — General structure of N'-substituted sulfonamides.

results into correspondence with the experimental findings. Further study will be required before this question can be answered adequately.

Dewar (9) has developed an index, N, for reactivity of these compounds based on π electron energy considerations. The index, N, has been calculated in a slightly modified form for indole, carbazole, and lysergic acid. The results are listed in Table I. For carbazole this index suggests the order of reactivity of $3 > 1 > 2 > 4$, which is consistent with Brown and Coller's results and correctly predicts the site of metabolism for indole and lysergic acid.

This preliminary study shows that quantum chemistry can afford a readily available method of predicting the site of metabolism for certain indole derivatives. Johns and Wright have pointed out that such a method could greatly decrease the amount of work necessary to prove the structure of metabolites by experimental methods. The theoretical technique is quite general in nature and can be extended without difficulty to other classes of drugs. In addition to shedding light on the structure of metabolites, the calculations should prove useful in suggesting possible mechanisms involved in metabolism.

Activity of Sulfonamides.—The bacteriostatic activity in a series of N'-substituted sulfonamide derivatives, having the general structure shown in Fig. 5, has recently been the subject of a quantum chemical study (10).

Bell and Roblin (11) showed a relationship between the bacteriostatic activity of a series of sulfonamides and the acid dissociation constant of the molecule. The sulfonamides are weak acids because the amide (N') nitrogen of these compounds is sufficiently positive in solution to liberate a proton. As a consequence one would expect to find a relationship, (*a*) between pKa of the sulfonamide and the electronic charge on the ionizing (N') nitrogen, and (*b*) between bacteriostatic activity and the charge on the N' nitrogen. Kumler and Daniels (12), however, reasoned that the bacteriostatic action was primarily associated with the *p*-amino group.

It should be possible to solve this conflict, or at least to shed some light on the problem, by obtaining the electronic charges of the sulfonamide derivatives by quantum chemical calculations. By such an approach, one might hopefully account for the bacteriostatic action of these compounds and predict why one is more effective than another.

The electronic charges for a series of 50 sulfonamides have been calculated (10). The formal π charge distribution of sulfanilamide (Fig. 6*A*) indicates the following general results.

(*a*) A deficiency of π electrons exists at the *p*-amino group resulting from donation of electrons to the aromatic ring; (*b*) due to their high electronegativity, the oxygen atoms of the sulfonyl group withdraw electrons from the sulfur atom and also from the N' nitrogen resulting in a large excess of electrons at these oxygen atoms; and (*c*) the N' nitrogen is deficient in π electrons and as a result has a positive formal π-electronic charge.

Substitution of a phenyl group at the N' nitrogen of sulfanilamide (Fig. 6*B*) results most dramatically in an increase in the positive formal charge of the N' nitrogen. This is reflected in the change in pKa from sulfanilamide (pKa = 10.43) to N'-phenylsulfanilamide (pKa = 9.60). Since the R group is the only variable in the structure of the sulfonamides, it must be the factor controlling the acid dissociation constants of these compounds. The observation of the variation of pKa with the variation of the charge on the N' nitrogen is consistent with the chemical facts.

The R groups of the 50 sulfonamides studied were of widely varying types. It has been found by experience that the quantum chemical technique used here (see *Appendix*) gives good comparisons with experimental data only for closely related series of compounds. For this reason the 50 sulfonamides were broken down into groups dependent on the type of substituent R attached to the N' nitrogen atom. Under this classification, satisfactory relationships were found between pKa and calculated electronic charge on the N' nitrogen.

It was observed in our work that the electronic charge of the *p*-amino group did not vary with a change in the R group. Although the *p*-amino group may be necessary for activity, we were not able to obtain a correlation between degree of activity and the electronic charge density at this position.

Work is now going forward to correlate various

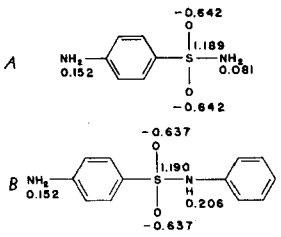


Fig. 6.—Formal π charge distributions of sulfanilamide (*A*) and N'-phenylsulfanilamide (*B*).

bond orders in the molecule, the electronic characteristics of the SO_2 group, and the charge on the N' nitrogen with biological activity.

The correlation between pKa and the charge of the N' nitrogen suggest that quantum chemical calculations may have value for theoretically predicting the pKa of certain types of complex drug molecules. The possibility of a biological activity–electronic charge correlation for drug molecules suggests an interesting application for quantum chemical calculations. The calculations may be useful as a screening technique for predicting biological activity of untested or even unsynthesized compounds.

SUMMARY AND CONCLUSIONS

The approach to the theoretical calculation of electronic structure has been described in relation to π electron systems, and it is suggested in this report that such studies can be of importance in the study of physical chemical properties and drug action.

Three applications have been presented. First, quantum chemical calculations yielded information about the electronic interactions involved in the benzocaine–caffeine complex which suggested a possible orientation for the molecules of the complex. Intermolecular forces controlling the orientation were concluded to involve electrostatic and localized charge–transfer interactions.

Second, the application of quantum chemistry in determining the atomic position of hydroxylation of indole derivatives confirmed experimental data and should be useful in predicting the structure of metabolites.

Third, a preliminary investigation of the electronic structure of a series of sulfonamides showed a satisfactory relationship between pKa and calculated electronic charge. Further work is now in progress to investigate calculated electronic characteristics and biological activity of the sulfonamides.

Such investigations concerning the effect of electronic structure on physiological action and chemical reaction should prove to be a useful tool in developing a rational approach to understanding molecular properties and pharmacological actions leading to subsequent improved methods of drug design.

APPENDIX

LCAO–MO Method.—The method of calculation used in this paper is known as the linear combination of atomic orbitals–molecular orbital (LCAO–MO) method. Since a detailed development of the mathematics involved in the method is beyond the scope of this paper, it will be sufficient here to give a discussion of the parameters needed for calculation and the type of data obtained.

TABLE I*A*.—δ AND γ VALUES[a]

Atom[b]	δ	Bond	γ
$=\dot{C}-$	0.0	C=C	1.0
$=\dot{N}-$	0.4	C=N	1.0
$-\dot{N}-$	1.0	C—N	0.9
$\lvert$			
$=\dot{O}$	1.2	C=O	2.0
$-\ddot{O}-$	2.0	C—O	0.9
$-CH_3$[c]			
$-\dot{C}\equiv$	0.0	$C\equiv H_3$	2.0
$\equiv\dot{H}_3$	−0.2		

[a] *Reference 2.* [b] The dots above the atoms refer to the number of π electrons initially assigned to the atom. [c] Treated by hyperconjugation.

The calculations are based on the assignment of two parameters: δ_x which is characteristic of an atom, x, and γ_{xy}, which is characteristic of the bond between atoms x and y. The values of these parameters for certain atoms and functional groups are listed in Table I*A*. The input data for the computer is composed of an array of these parameters corresponding to the chemical structure of a given molecule.[2]

In general, for a π electron system containing n atoms, the LCAO–MO calculations will yield n molecular orbital (MO) energy levels and n^2 atomic orbital (AO) coefficients. These two sets of data are obtained directly from the computer and are used to calculate various electronic characteristics.

The MO energy levels are a measure of the energies of the π electrons. According to the Pauli exclusion principle, two π electrons are assigned to each MO, beginning with the lowest energy level until all the π electrons have been assigned. The energy of the highest occupied MO, designated by the abbreviation HOMO, is then a measure of the ionization potential of the molecule. Likewise, the energy of the lowest empty MO, abbreviated as LEMO, is a measure of the electron affinity. These two energy levels are important in determining electron donor–acceptor properties.

The AO coefficients are used to calculate electronic characteristics associated with specific atoms within the molecule. Among these are the π electron density at an atom and the bond order which is a measure of the π electron bonding between two specific atoms.

Other electronic characteristics depend on both the MO energy levels and the AO coefficients such as the superdelocalizability indices (13). The approximate superdelocalizability nucleophilic index, $S^{N'}$, is a measure of the ease with which a particular atom can accept electrons. The approximate superdelocalizability electrophilic index, $S^{E'}$, is a measure of the ease with which a particular atom can donate electrons.

Readers interested in the mathematical development of the LCAO–MO method and the precise method for calculating the various electronic characteristics should consult *References 14–16.*

[2] The calculations were performed on an IBM 7094 digital computer.

REFERENCES

(1) Inouye, A., Shinagawa, Y., and Takaishi, Y., *Arch. Intern. Pharmacodyn.*, **144**, 319(1963).
(2) Pullman, B., and Pullman, A., *Rev. Mod. Phys.*, **32**, 428(1960).
(3) Higuchi, T., and Drubulis, A., *J. Pharm. Sci.*, **50**, 905(1961).
(4) Guttman, D. E., *ibid.*, **51**, 1162(1962).
(5) Karreman, G., Isenberg, I., and Szent-Gyorgyi, A., *Science*, **130**, 1191(1959).
(6) Johns, S. R., and Wright, S. E., *J. Med. Chem.*, **7**, 158(1964).
(7) Baumann, E., *Hoppe-Seyler Z. Physiol. Chem.*, **1**, 60(1877); Master, B., *ibid.*, **12**, 130(1888).
(8) Brown, R. D., and Coller, B. A. W., *Australian J. Chem.*, **12**, 152(1959).
(9) Dewar, M. J. S., *J. Am. Chem. Soc.*, **74**, 3357(1952).
(10) Foernzler, E., and Martin, A. N., to be published.
(11) Bell, P. H., and Roblin, R. O., *J. Am. Chem. Soc.*, **64**, 2905(1942).
(12) Kumler, W. D., and Daniels, T. C., *ibid.*, **65**, 2190 (1943).
(13) Fukui, K., Chikayoshi, C., and Yonezawa, T., *ibid.*, **80**, 2267(1958).
(14) Daudel, R., Lefebvre, R., and Moser, C., "Quantum Chemistry," Interscience Publishers, Inc., New York, N. Y., 1959.
(15) Streitwieser, A., Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961.
(16) Pullman, B., and Pullman, A., "Quantum Biochemistry," Interscience Publishers, Inc., New York, N. Y., 1963.

Research Articles

Relationship of Antral Motility to Gastrin Activity in Surgically Prepared Dogs

By DONALD D. ABBOTT*, ALFONSO R. GENNARO, and G. VICTOR ROSSI

Chemical secretagogues and insulin-induced vagal stimulation were utilized to evoke gastrin release in dogs prepared with vagally denervated fundic pouches. For comparative purposes a gastrin extract was prepared from hog antral mucosa, using the method of Gillespie and Grossman. Gastrin activity was assessed in terms of the total acid content of periodic samples aspirated from the fundic pouch. Movements of a magnet, affixed surgically to the pyloric antrum, were remotely monitored using a magnetometer. Antral motility was monitored during the stimulation of endogenous gastrin release and the infusion of exogenous gastrin in anesthetized animals. These studies indicated that there is not a direct correlation between endogenous gastrin release and antral motility. The intravenous infusion of exogenous gastrin elicited gastric acid secretion and antral motility; the responses bore a relationship to infusion rate.

RELEASE OF THE hormone, gastrin, from the mucosa of the pyloric antrum is apparently mediated by a mechanism responsive both to chemical secretagogues and mechanical stimulation. The existence of a local neural mechanism, cholinergic in nature, is supported by the observations that topical application of local anesthetic and atropine solutions (1, 2) to the antral mucosa effectively inhibits gastrin release, whereas locally applied acetylcholine (3) evokes release of the hormone.

Several investigators (4–8) have associated vagal activity, a major determinant of gastric motility, with the release of gastrin. On this basis, two mechanisms may be postulated: (*a*) gastrin is released as a direct consequence of vagal nerve activity, and/or (*b*) antral motility, elicited by vagal stimulation, evokes the release of gastrin. Nyhus (9) considered the effect to be primary, based upon studies in which innervated antral mucosa, devoid of musculature, responded to vagal stimulation.

Few studies have been directed toward the relationship of antral motility and gastrin release due, in large measure, to the limitations of available techniques for assessing gastric motility *in vivo*. The most commonly used methods for evaluating gastrointestinal motility, *i.e.*, the balloon and open-end tube procedures, provide only a gross indication of motor activity. In both instances the pressure changes (intraballoon or intraluminal), which are interpreted as reflections of motor activity, are influenced by the presence of the indwelling system which serves as

Received April 2, 1965, from the Department of Pharmacology, Philadelphia College of Pharmacy and Science, Philadelphia, Pa.
Accepted for publication September 2, 1965.
Presented to the Scientific Section, A.PH.A., Detroit meeting, March 1965.
* Present address: LaWall and Harrisson Research Laboratories, Inc., Philadelphia, Pa.