# TECHNICAL PAPERS

## Pathogenicity and Isosterism

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The influence of stereochemistry on modern scientific thinking has led to many interpretations of physical, chemical, and physiological phenomena in terms of molecular structure. This has been true in the search for a chemical interpretation of toxicity. If toxicologists are asked about a possible correlation between pathogenicity and molecular structure, they are likely to say that the evidence is mostly negative. No one questions that the like toxic effect of such diverse substances as alcohol, ether, chloroform, and acetone, for example, all of which produce a state of anesthesia, may be due to similar chemical properties; they are all fat solvents. But this is not a correlation between anestheticity and molecular structure. That there is evidence of a relationship between toxicity and molecular properties is suggested by some biological chemists; for example, the effectiveness of sulfanilamide and *p*-aminobenzoic acid as insecticides is said to be due to the $C_6H_4N_2$ group present in each.

In the search for a correlation between pathogenicity and the physical-chemical properties of the responsible reagents, certain significant properties may have been overlooked. Nothing, so far as I am aware, has been said on the possible relationship between pathogenicity and isosterism.

Throughout my work on the anesthesia of protoplasm, the similarity in the anesthetic effects of carbon dioxide and nitrous oxide was so close and so constant, in comparison to the varying effects of other anesthetic agents, that I, knowing of no chemical properties common to these two gases, sought comparable physical qualities. Such qualities would be particularly appropriate to a theory of anesthesia which attributes unconsciousness to a physical change in the protoplasm, namely, to gelatinization. This theory, which is a slight modification of that of Claude Bernard (*2*), I have supported with considerable visual evidence (*4*).

Certain other agents also gave parallel results. Similarity in the effects of the ordinarily highly toxic carbon monoxide and the relatively inert nitrogen (with a trace of oxygen) was particularly striking. Five hours of constant application of either one of these two gases had no effect on the primitive form of living material used.

When a beginning is made on an hypothesis as broad as the possible correlation between pathogenicity and isosterism, an experimenter is forced to ask his reader to limit his thoughts, for the moment, to the particular material worked upon and the particular reagents under consideration. I am well aware that when other organisms, especially those of higher complexity, and other toxic agents are considered, the hypothesis may not hold. It should be borne in mind, however, that complexity in an organism does not necessarily vitiate—it may only obscure—a correlation. Work on a lowly form of life has the advantage of simplifying the situation sufficiently for the correlation to be revealed.

The living material studied in the experiments reported here was the myxomycete or slime mold, *Physarum polycephalum*. As a slime mold is probably as close an approach to a primordial ooze as any form of life on earth today, *Physarum*, therefore, lacks many of the characteristics of higher organisms; there is no cellular tissue, no well-defined nervous system, and no hemoglobin. However, any protoplasm of lowly form is, after all, living matter—a fact too often minimized. A slime mold is in itself a nervous system. Its response to reagents will be very similar to that of our own protoplasm when the latter is divested of all the intricate accessory mechanisms of higher organisms.

The reactions of *Physarum* to carbon dioxide and to nitrous oxide are identical. The slight variations which occur in the response of the protoplasm to the two gases are no greater than the variations seen in the reaction of two separate cultures of the same species to one of the gases. The protoplasm ceases all visible activity within $\frac{1}{2}$ min. when gas is administered at the rate of 0.2 cc/sec. Recovery, indicated by normal active flow, occurs within $\frac{3}{4}$–1 min. after the gas is shut off. The rapidity with which the gas is administered and the time the culture is kept under the influence of the gas determine, in part, the time required to produce anesthesia and the time of recovery. Both gases, when judiciously administered, cause no visible injury, no syneresis, no surface breakdown, and no coagulation.

Substances of close chemical relationship are generally grouped on the basis of molecular composition, e.g. the alcohols, the aldehydes, and the esters. Nothing is usually said of the possible similarities of such properties as crystal form, spectrum, surface tension, viscosity, and electronic pattern. Certain of these are collectively known as isosteric properties. When they are given due consideration, an extraordinarily close agreement is found to exist between substances which show no close chemical relationship in either composition or molecular structure. Physical relationships which run counter to chemical ones are present among many substances; thus, Barker (*1*) has shown a great number of cases of isomorphism among crystalline substances, which, according to the usual valence theory, are not closely related. Isosteric substances owe their similar physical properties to similar electronic arrangement. Carbon dioxide and nitrous

[1] I am indebted to my colleague, Marvin Carmack, for suggestions pertaining to certain problems discussed in this article—in particular, the significance of isosteric properties in chemistry.

oxide, which have a like effect on protoplasm, are isosteres. That this is true is shown in Table 1.

It is thus obvious that in their isosteric properties as in their anesthetic or pathological effects on certain lowly organisms, carbon dioxide and nitrous oxide are nearly identical.

TABLE 1

THE ISOSTERIC PROPERTIES OF CARBON DIOXIDE AND NITROUS OXIDE*

| | $CO_2$ | $N_2O$ |
|---|---|---|
| Number of exterior electrons | 22 | 22 |
| Molecular weight | 44 | 44.02 |
| Viscosity, at 20°C and 1 atm | $148 \times 10^{-6}$ | $148 \times 10^{-6}$ |
| Critical pressure (atm) | 77 | 75 |
| Critical temperature | 31.9° | 35.4° |
| Heat conductivity, at 100°C | 0.0506 | 0.0506 |
| Density of liquid, at –20°C | 1.031 | 0.996 |
| Density of liquid, at 10°C | 0.858 | 0.856 |
| Refractive index of liquid, D line, 16°C | 1.190 | 1.193 |
| Dielectric constant of liquid, at 0°C | 1.582 | 1.598 |
| Magnetic susceptibility of gas, at 16°C and 40 atm | $0.12 \times 10^{-6}$ | $0.12 \times 10^{-6}$ |
| Solubility in $H_2O$, at 0°C | 1.780 | 1.305 |
| Solubility in alcohol, at 15°C | 3.13 | 3.25 |

* Certain discrepancies appear to exist between the values in the foregoing table (in part from Langmuir, *3*) and other recent work. Where the values given by authors differ, the agreement between the two gases $CO_2$ and $N_2O$ is, nevertheless, surprisingly close. Thus, the dielectric constants in Lange's *Handbook of physics and chemistry* (5th ed.) are 1.000985 for $CO_2$ and 1.00116 for $N_2O$, at 0°C and 1 atm. As temperatures and pressures are not always stated, I have kept strictly to the Langmuir values, except for several additions.

Nitrogen and carbon monoxide have no effect on slime mold protoplasm (except for a brief initial injury due to shock, which is not uncommon in treating protoplasm with reagents). These two gases, both the biologically inert nitrogen and the usually active carbon monoxide, have closely similar isosteric qualities. Carbon monoxide poisoning in mammals is due to combination of the gas with hemoglobin. This is a different matter than the effect of the gas on protoplasm which lacks most mammalian characteristics.

That certain properties of protoplasm, not only purely physical qualities such as viscosity and elasticity but complex chemical ones such as respiration, are similar in primitive forms of protoplasm and in higher forms of life, including man, is indicated by the following experiment: A 3- to 5-day chick heart reacts to carbon dioxide in a manner identical to the protoplasm of a slime mold. The chick embryo contains blood not yet distributed in an organized system extending throughout the tissue; yet, though blood is present, the embryo, unlike the adult chick as a whole, reacts as does a primitive form of living matter (*5*).

The correlation between pathogenicity and isosterism may ultimately prove to hold for only a few isolated cases. Gases and other reagents may be found which are not isosteres but to which protoplasm shows similar reaction. However, such a correlation will not have been proved false until two isosteres are found which have wholly different effects on living matter.

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## Control of Hemorrhagic Syndrome and Reduction in X-Irradiation Mortality With a Flavanone[1]


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A hemorrhagic diathesis is now believed to be characteristic of the mammal exposed to the ionization of single-dose radiation and, to a lesser degree, to repeated radiation. Following sub- or midlethal doses of total body radiation this bleeding is uncontrollable and is a primary factor in mortality. The disturbance is one of generalized bloody extravasation with oozing into practically every organ and tissue. In the dog, exitus is usually preceded by profound intrapulmonary and/or intraintestinal hemorrhage.

A direct influence of ionizing radiation on vascular integrity has not been proved. Earlier studies have implicated thrombocytopenia as a causal factor in the hemorrhagic picture (*5*).

Recent investigations indicate the presence of an increased quantity of heparin or heparin-like material in the blood of dogs following acute whole-body exposure to ionizing radiations. In these animals certain antiheparin substances, such as toluidine blue and protamine, restored prolonged *in vitro* and *in vivo* coagulation time to normal (*2*). This technique served to halt the hemorrhagic tendency, although all treated dogs succumbed about 22 days after being exposed to 450 r, while control untreated dogs usually died after 11 days (*1*).

As the result of studies in this laboratory it was felt that control of vascular integrity might be of benefit to the organism in which hypocoagulability exists. In this condition, prevention of vascular damage might reduce the hemorrhagic extravasation. It would appear that the function of critical organs already suffering from some degree of direct destruction by ionizing irradiation is further impaired by the bloody ooze of capillary destruction. By maintaining the vascular structure, an in-


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