Bioelectronics

Intermolecular electron transfer may play a major role in biological regulation, defense, and cancer.

Albert Szent-Györgyi

Many years ago, working with J. A. McLaughlin, I came to the conclusion that, in animal tissues, cell division may be controlled by two antagonistic substances, an inhibitor and a promotor (*1*). In plants, growth is known to be controlled by such antagonists, which have been isolated and identified (*2*). My arduous efforts to isolate the inhibitor of animal tissues failed, and this made it necessary to look more deeply into the problem.

Present-day biology is dominated by the molecular outlook—the view that living systems are built of isolated small units, molecules, and that in order to understand life we only have to know these molecules, the rest will take care of itself.

Joseph Weiss discovered in 1942 (*3*) that in certain molecular complexes an electron can go spontaneously from one molecule (the donor) to another (the acceptor), a reaction he called "charge transfer." Weiss worked with complexes formed by strongly oxidizing and reducing agents. Later, attention was given to charge transfer in which the energy of light moves electrons from one molecule to another. This was called a "weak transfer" to distinguish it from the "strong" transfer studied by Weiss, in which the transfer was spontaneous. R. S. Mulliken cleared up the quantum mechanics of these reactions (*4*) and systematized them. He preferred the name "DA [donor-acceptor] interactions" to "charge transfer."

Though in several instances DA interactions between biological substances have been produced in vitro, the idea of charge transfer found no real place in biology. Strong charge transfer could play no role because the presence of strong oxidizing agents is incompatible with life, and we have no light in our body to move electrons (except in the eye and skin). So charge transfer remained, for the biologist, more or less a chemical curiosity.

Using the method of electron spin resonance (*5*), I could show that even molecules with low reactivity, which play a major role as metabolites or hormones, can give off a whole electron, forming a free radical; this suggested that charge transfer may be one of the most common and fundamental biological reactions. Such considerations led to the study of the nature of the various donor and acceptor atomic groups.

Donor and Acceptor Groups

The cell has a rich source of transferable electrons in its nitrogen, sulfur, and oxygen atoms, which all have pairs of "lone" electrons—electrons which do not take part in bonding and are thus available for transfer. Not so with acceptors. The cell is poor in these. I could find one acceptor group only, CO, the carbonyl. This is a "ketoid acceptor" which, as shown by Mulliken, can accept in its double bond an additional electron, acting as a "π acceptor." As an acceptor, CO is very weak. However, if its acceptor ability is due to its double bond, then it should be possible to boost this ability by inserting into the molecule another double link in the α-β position. This produces good acceptors, but no substance of this composition is known to play a role in biology.

Another way to extend the double bonding and thereby increase the acceptor ability is to introduce a second CO on the neighboring carbon atom, in the α position. If we also link a hydrogen atom to this atom, and give the molecule, as HCO, the character of an aldehyde, then we also lend the molecule a greater chemical reactivity, aldehydes being, on the whole, more reactive than ketones. So the question was: Could keto-aldehydes play a major role in biology as acceptors?

L. G. Együd found indication of the presence of a keto-aldehyde in our growth-retarding preparations (*6*). The simplest α-keto-aldehyde is methylglyoxal (pyruvic aldehyde) (Fig. 1); this fact seemed most exciting (*7*) because, as far as we know, all cells contain a very powerful enzymic system for the conversion of α-keto-aldehydes into the corresponding unreactive oxyacids—for converting, for instance, methylglyoxal into lactic acid. This enzymic system, called the "glyoxalase," occupied the attention of several of the most outstanding biochemists in the first half of this century, but the interest later faded out, for no glyoxal derivative could be found on the main metabolic pathways, nor could such a substance be isolated from tissues under normal conditions. And what is the use of an enzyme without a substrate?

Should the inhibitor of growth prove to be a dicarbonyl, like methylglyoxal or a compound thereof, then I had an excuse for not having been able to isolate it, for the isolation of the expected trace amounts of such a very reactive substance would be very difficult indeed.

To investigate this matter, Együd synthesized a greater number of different α-keto-aldehydes and studied their action on cell division in bacteria (*8*) and other cells. At a low concentration they all inhibited cell division reversibly, in a specific way (*9*), inhibiting protein synthesis (*10*) on the ribosomal level (*11*).

All this suggested that cell division may be regulated by DA interactions and that the DA balance may be an important parameter of cell life.

One of the most active donor groups is the sulfhydryl (SH), and SH is known to have an important function in cell division. So the regulation may actually rest on a DA interaction of a keto-aldehyde and SH. Együd found that the inhibition, induced by methylglyoxal, could be released instantaneously by the addition of an equivalent quantity of cysteine or other SH-containing substances (*12*), a finding which strongly supported the assumption that the in-

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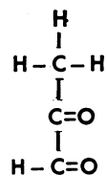

Fig. 1. Structure of methylglyoxal.

hibitory action of the keto-aldehyde was actually due to its interaction with SH groups. These groups are known to play an important role in many biological reactions, but the SH groups involved in cell division appeared to be especially reactive, and to open the way to a specific inhibition of proliferation.

Regulatory Systems

If one double bond, introduced in the α-β position, increases the acceptor ability of a molecule, then the introduction of a more widely conjugated system of double bonds must do so even more strongly. Such a system is found in aromatic molecules. Accordingly, two CO groups, in an aromatic molecule, must make a very good acceptor. Aromatic quinones actually are known to be strong oxidizing agents. They are much too strong to be compatible with life. If not compatible with life, they could be used by an organism for killing, in self-defense, invading microorganisms. This thought led me back to one of the earliest pieces of biochemical research I did as a beginner. As is generally known, many plants discolor if they are damaged; about half of all plants do so. If you drop your pear or apple, the next day you find a brown patch on it. This reaction is very sensitive; the slightest damage may induce such a change. Figure 2 shows a banana which, on the previous day, had been dipped up to its middle in chloroform for 1 minute. The underlying mechanism of the pigment formation is as follows. The intact plant contains, side by side, a polyphenol and a polyphenoloxidase, which can oxidize the phenol into a quinone (Fig. 3). The two are separated and cannot interact. This is a most subtle situation; the slightest damage will disturb it, releasing the oxidase which, then, will oxidize the phenol, eventually producing the dark color. The biological meaning of this is simple: the reaction serves as a defense and has a great survival value. Suppose a bacterium penetrates the plant. By the damage it induces it releases the phenoloxidase from its bondage; the enzyme oxidizes phenols to quinones, and the quinones kill the bacterium. Nature has set, cunningly, a trap and makes the invading microorganisms commit suicide by activating the enzymic system. The quinone has other functions, too. It "tans" the proteins. If the plant is damaged by a cut, the tanned proteins form a protective film over the cut, closing the wound. There is thus a regulatory system in the plant which functions in such a way that damage activates it, whereupon it corrects the damage. There are many such mechanisms; they seem to represent one of nature's widely applied principles. Take, for instance, sunlight. Ultraviolet radiation damages our skin, the damage releases the "tyrosinase," the tyrosinase produces pigments, and the pigments protect us against sunlight. In blood coagulation, damage to blood and blood vessels releases an enzymic system which produces fibrin, which plugs up the damaged vascular system. If damage is deep, it is desirable that the damaged cell be eliminated. Such damage releases cathepsin, a proteolytic enzyme, which digests and eliminates the damaged cell.

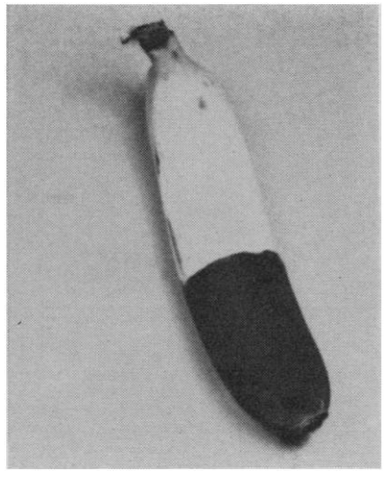

Fig. 2. A banana which, on the previous day, had been dipped in chloroform for 1 minute.

Living matter has an inherent drive to proliferate. In monocellular organisms it may be simply the quantity of food available which sets limits to growth, but, in multicellular organisms, cell division had to be subjected to strict regulation in the interest of the whole organism. A brake had to be put on,

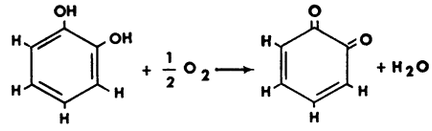

Fig. 3. Oxidation of a diphenol to an *o*-quinone.

but put on loosely, for, if I cut myself, my cells have to start multiplying at short notice to fill the gap and heal the wound. If it is methylglyoxal which acts as a brake, then, in the resting cells, the glyoxalase must be kept separated from the methylglyoxal. Cell division would be induced by liberation of the glyoxalase. The glyoxalase, by decomposing the keto-aldehyde, would release the brake and start up cell division which, then, would continue until the gap was filled—until the wound was healed—whereupon, with balances restored, the glyoxalase would be bound again, and the system would return to its initial resting state. If we suppose that the damage induced by the cut liberates the glyoxalase, then the whole system comes into line with other regulatory systems in which a damage induces the changes which lead to its correction.

A Tentative New Theory of Cancer

One could ask what would happen if a cell lost its ability to bind its own glyoxalase? Then it would have to go on multiplying senselessly and endlessly, behaving like a cancer cell. As far as we know, the only difference between a normal cell and a cancer cell is the fact that the latter divides when no proliferation is needed. All this leads, tentatively, to a new theory of cancer: a cancer cell is a cell which has lost its ability to bind its own glyoxalase. Whether this theory is right or wrong remains to be demonstrated. It recommends itself by its clarity, its simplicity, and its ability to explain why such a great variety of noxious influences can lead to the same end, cancer. The theory also has the earmark of a good theory: it can be proved or disproved. What may lend it additional value is the fact that it suggests various ways of seeking a therapy for cancer. It is regrettable that, owing to cuts in the budget, this research will have to be discontinued, killing now having precedence over healing.

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13. The experimental work discussed in this article was supported by grant GM10383 from the National Institutes of Health.

NEWS AND COMMENT

Smog: Los Angeles Running Hard, Standing Still

Los Angeles. The Los Angeles basin, which is said to have the most vigorous air pollution control program in the nation, has made little progress in recent years in its struggle to cleanse the air of smog.* Though the Los Angeles County Air Pollution Control District (APCD) has pioneered in imposing stiff curbs on industrial polluters, and the state of California has pioneered in cracking down on motor vehicle emissions, the gains made thus far have been offset by new pollution stemming from the growth of population, automobile traffic, and industry. As a result, air quality in Los Angeles has shown no appreciable improvement in this decade, though pollution authorities now profess to see "light at the end of the tunnel."

The continuing high level of pollution, coupled with the likelihood that it will be many years before air quality is significantly improved, has led some medical leaders here to warn people away from the Los Angeles area. They have taken such drastic action despite what many scientists regard as a lack of solid scientific proof that existing levels of pollution constitute a serious health hazard.

Early in August some 60 members of the UCLA medical faculty issued a statement to the Los Angeles *Times* asserting that "air pollution has now become a major health hazard to most of this community during much of the year." The statement advised "anyone who does not have compelling reasons to remain to move out of smoggy portions of Los Angeles, San Bernardino, and Riverside counties to avoid chronic respiratory diseases like bronchitis and emphysema."

The statement has been criticized privately by some UCLA faculty members as being unduly alarmist and based on insufficient evidence. But William Hildemann, professor of microbiology and immunology, who circulated the statement for signatures, told *Science*: "I'll be the first to admit the evidence implicating smog as a major health hazard falls far short of conclusive scientific proof at the present time. But the evidence strongly suggests that long-term exposure to polluted air presents a very real and serious hazard indeed. Common sense should dictate that we take vigorous community action soon before a smog catastrophe is at hand. Twenty years from now we might have lots of hard evidence, but by that time it may be too late for hundreds of thousands of people."

The statement from the UCLA medical faculty members echoed similar warnings expressed in recent years by the medical profession here. In a survey conducted in 1960–61 it was estimated that Los Angeles physicians had advised more than 10,000 patients to leave the area for reasons of health during the previous year, and nearly all the doctors interviewed cited air pollution as a reason for the recommendation. At least 2500 of the patients acted on their doctors' advice and left the area. Since the survey, the doctors have expressed increasing concern about smog. Last October the Los Angeles County Medical Association asserted that "air pollution is becoming increasingly worse and may lead to great lethality in this community." The doctors' group said air pollution posed an especially serious threat to "those who are ill, the very young and the aged," but added that it also endangers "those who are presently in good health."

Much of the smog problem is caused by climatic and geographic factors peculiar to this area. These include frequent temperature inversions which trap pollutants near the ground; mountains that hem the pollutants in; breezes too gentle to push the pollutants away; and abundant sunshine, which converts the individual pollutants, notably hydrocarbons and nitrogen oxides, into the peculiar blend of photochemical smog† for which Los Angeles is noted. Photochemical air pollution exists in some other cities, but it is particularly identified with Los Angeles, where it occurs 200 or more days a year and affects more than 80 percent of the population, often causing people's eyes to sting and tear. Smog is so common here that local broadcasting stations and newspapers provide smog forecasts along with the daily weather report.

Almost all pollution experts agree that automobiles are the chief source of noxious pollutants in the Los Angeles basin, but there is disagreement over how serious a problem is caused by pollutants from industry and other stationary sources. The local APCD claims it has largely controlled stationary sources and says 85 to 90 percent of the remaining problem (in terms of the weight of pollutants emitted) is caused by automobile emissions, an

* Though *smog* was a word apparently coined to describe a particular form of pollution—smoke plus fog—it has become the word popularly used to describe air pollution in Los Angeles.

† The action of sunlight on a mixture of hydrocarbons, oxides of nitrogen, oxygen, and other materials results in a series of complex reactions leading to a variety of intermediate and end products which, together, are called smog. Among the products reported, according to a prepublication review by Irving R. Tabershaw and his colleagues at the University of California, Berkeley, are aldehydes, ketones, alcohols, alkyl nitrites and nitrates, acids, ethers, peroxylacyl nitrates and nitrites, carbon monoxide, carbon dioxide, and particulate matter.