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Melvin Calvin and G. J. Calvin

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ABSTRACT

An answer to the question of how the molecules which constitute today's living organisms may have arisen on a prebiotic earth is being sought within the context of moern experimental science.

We begin with the primitive atmosphere as it is presently conceived by a consensus of astronomers and geochemists, namely, a reducing one, and introduce various forms of energy into this system to determine the nature of the molecular changes whuch might occur and which do occur. Experimental demonstration shows that the atoms which constitute the primitive atmosphere are of such chemical character that they give rise to molecules of biological interest almost immediately under these conditions. Autocatalytic mechanisms, beginning with the crude catalytic properties of the mineral surface of the earth, then select among these molecules certain classes as favored.

The basic problem of the generation of macromolecules of two general types is discussed. The first, resulting from carbon-carbon linkage, comes via vinyl polymerization. The second, resulting from dehydration condensation, has been more difficult to demonstrate experimentally as possible in an aqueous medium. However, certain dehydrating agents are now being discovered which show signs of functioning specifically in the aqueous milieu to give rise to the protein, nucleic acid and carbohydrate types of polymers.

Then the question of a higher degree of order, leading ultimately to visible structure resulting from the construction of macromolecules, is discussed. It is shown that a sequence of thermodynamically controlled processes may be expected to give rise to secondary, tertiary and even quaternary structure in such systems, the last eventually reaching the range visible under suitable microscopic conditions. The question of membrane formation and boundary enclosures is still moot.

However, the evolution of macromolecules, according to the present laws of molecular evolution, are now visible to us. These can be seen to lead to the kind of organization we now recognize as living, and new chemistry is daily derived via the attempt to understand the reproduce such systems.

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INTRODUCTION

The course of the social history of man from the time he became capable of recording his progress is popularly considered the only "recorded" history. This "day" in the history of mankind is so brief in relation to all history, and has been so exaggerated in importance as to obscure the long course of evolutionary development preceding this period. Because man has emphasized his own personal history, much as an individual views the importance of his own brief years in relation to recorded history, the natural laws -- which govern the development of man and the countless life forms which exist with him -- are frequently isolated from those laws which govern other matter in the universe.

It is difficult to consider living things as a far product on the long continuum from organic element to Einstein. However, as we learn even more details of the composition of living things, the course becomes clear, and the experimental evidence more corroborative, that the entities known as "living" follow the simple molecular laws of chemistry and physics, just as do the chemicals on the shelf. It becomes clear, too, that atoms can be combined into molecules and macromolecules in test tubes today in much the same way as was possible under the conditions when the earth was new.

The expanded knowledge about the atomic and molecular constituents of which living things are made, together with an increased understanding of the way molecules interact with each other, i.e., communicate with each other, so as to produce what we now recognize as living organisms, has had

two very interesting results. The first has been to stimulate scientists to create hypothetical schemes leading from the primeval nonliving earth to the present day[1-10]. The second has been to induce scientists to devise experimental ways to test some of these schemes in points at which they might be amenable to experimental laboratory tests. A certain degree of success in a variety of these laboratory experiments has, in turn, modified the original theories and has even led to new experiments in both chemistry and biology.

TERRESTRIAL CHEMICAL EVOLUTION

Conjecture as to the origin of life on the earth must involve knowledge of the behavior of molecules in the prebiotic period as well as a detailed and intimate understanding of the composition and function of living matter. The complexity of the problem is both simplified and exaggerated by contemplation of the quantities which distinguish nonbiotic systems from those we call "alive". There is a high level of disagreement among scientists who try to define the minimum requirements for living systems. This fact is in itself significant for it demonstrates that the borderline between the living and the nonliving is a difficult thing to recognize. There is no problem in distinguishing the living from the nonliving at the extremes of the scale; there is difficulty only at the borderline.

At this borderline a living system has no sharply defined characteristic, easily distinguishing it from a nonliving system. Rather, a living system is a molecular aggregate possessing a sequence of properties which make it indisputably recognizable as "living" at one end of the scale and as "nonliving" at the other end of the scale. But somewhere in between the nature of these

properties is such that there are those who will say that the system is "alive" and those who will say it is not.

Of these various properties, I am going to choose two which I think everyone will accept as necessary, although perhaps not sufficient, attributes of a molecular system in order for it to be called "alive." These two properties are (1) the ability of such a molecular aggregate to transfer and transform energy in a directed way and (2) its ability to remember how to do this, once having learned it, and to transfer, or communicate, that information to another system like itself which it can construct. The two are, restated: (1) The transfer and transformation of energy and (2) the transformation and communication of information. In a sense the second -- that is, information transfer -- may be thought of as including the energy transfer problem as well, but I like to think of them as separate problems.

Molecular Construction

There seems to be a fairly general agreement that the primitive earth is approximately 4.7 billion years old and that it was originally surrounded by an atmosphere which was composed primarily of reducing material, that is, the atoms of hydrogen, oxygen, carbon and nitrogen in their fully reduced, or hydrogenated state. This corresponds to the relative cosmic abundance of the very same elements -- hydrogen being the most abundant ($>99\%$ exclusive of the rare gases helium and neon)[10a] oxygen the next, etc. Thus the atmosphere of the primitive earth is envisioned as containing mostly the atoms of hydrogen, carbon, nitrogen and oxygen combined only with the overwhelmingly dominant hydrogen giving molecular hydrogen, methane, ammonia and water.

What kinds of compounds can we make from these primordial molecules? Ultimately we will recognize these molecules to be the main metabolic materials which now are the sources of energy and structure in living organisms, but, most importantly, we have to make the chief components of living organisms which are three polymers which we recognize as essential, namely, the proteins (derived from amino acids), the nucleic acids (composed of a heterocyclic base, a sugar and a phosphate) and the polymeric substances known as polysaccharides, cellulose, starch, etc. (composed of simple sugars made of carbon, hydrogen and oxygen with relatively small amounts of nitrogen and a few other elements). (Fig. 1) We have tried to devise ways and means of making the monomeric materials of which these polymers are constructed and then of finding ways of evolving the polymers themselves by nonbiological routes. It is at this level that we can inject experimental observation, and this has been done not only in our laboratory but elsewhere as well.

We thus have to accomplish two stages of chemical evolution, i.e., (1) we have to transform the primeval molecules made of carbon, oxygen and nitrogen, attached to hydrogen, into the small primitive molecules which are the monomers from which (2) the polymers are eventually evolved.

The time scale which is available to perform these transformations is given in Fig. 2. The formation of the present earth took place somewhere around 4.7 billion years ago. Overlapping with this period begins the period of chemical evolution which covers almost the entire time scale. The earliest known generally accepted fossils are less than one billion years

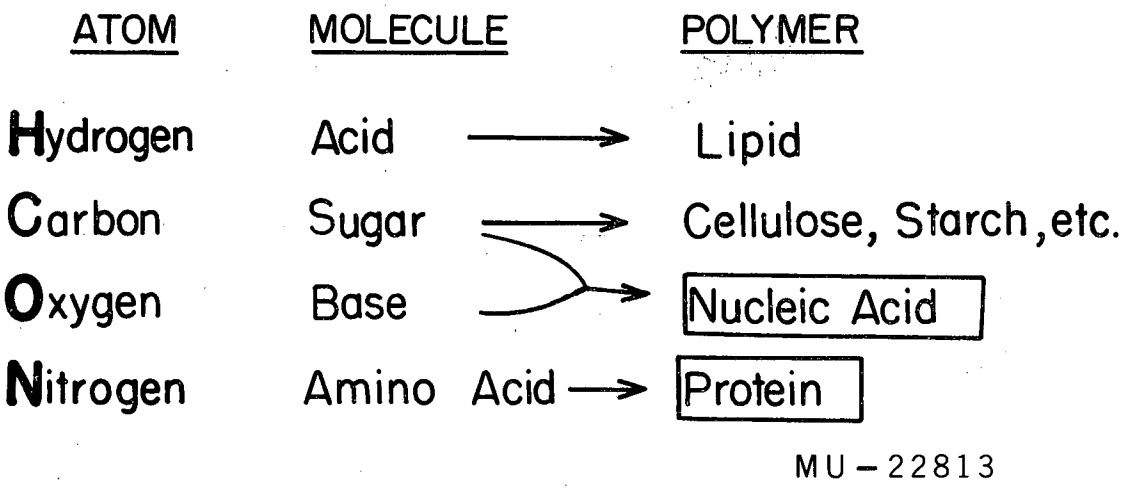

Fig. 1. Schematic representation in chemical terms of the set of formations which have to be accomplished from the atoms to produce the structure of the cell.

old. However, it has been reported that there is organic matter -- formed elements and even recognizable structures -- in formations about 2 billion years old in the Gunflint chert of Northern Michigan.[11] This chert is a carbonaceous formation in which one can, in section, see formed elements which appear to be primitive blue-green algae. The earliest known fossils in an unequivocal sense appeared in the Cambrian period, but I believe that the primitive blue-green algae formations in the Precambrian material from Michigan might push the dating of the early fossils back about another billion years. Therefore, the period of chemical evolution is probably shorter than it appears in Fig. 2, but organic evolution as it is commonly defined must have begun approximately 2 billion years ago. The moment that living organisms appear, the processes which we describe as nonliving or chemical (evolution) may have had a rather sharp decline because the living material would rapidly absorb and convert the primitive molecules and the relatively slow non-biological chemical change would be cut off.

You will notice from Fig. 2 that the evolution of mammals is relatively recent, and the evolution of man himself by the process of random mutation and selection occupies an even still shorter period of the time scale. What I have called "Social Evolution" is so small that it can't be represented on this time scale; in fact, it is a matter of only a few thousand years. One might say a new kind of social evolution has only just begun in the last century or two, since man has had in his own hands the ability to manipulate a living organism in a directed way.

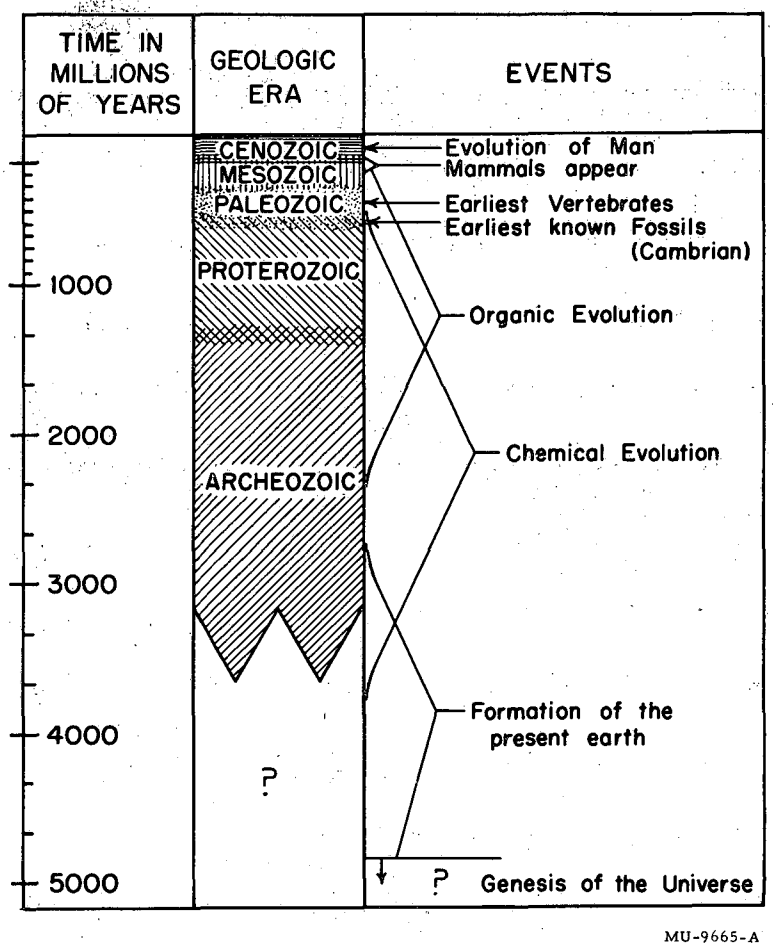

Fig. 2. Time scale for total evolution.

We will concentrate on the period of chemical evolution and the borderline period of biological evolution, during which living cells first appeared. Photosynthesis must also have begun at this time[12] and as soon as this phenomenon appeared, the whole scheme of animal evolution and plant evolution as we now see it in the fossil record began and really "exploded" at an enormous rate.

I am not going to be concerned too much with this intermediate region of organic evolution except to describe its principles of direction which were determined (and still are) by the principles of chemical evolution which gave rise to the living organisms in the fiwst place.

Fig. 3 depicts the primeval (methane, ammonia, hydrogen and water) and primitive organic molecules with which chemical evolution began. The energy sources that were used in the transformation were any of several: Ultraviolet light from the sun, cosmic radiation, radioactive minerals on the surface of the earth, and the streaming of the atmosphere due to thermal convection giving rise to the generation of electrostatic potentials and electric discharges. These various sources of energy induced the fracturing of the carbon-hydrogen, hydrogen-oxygen, hydrogen-nitrogen and hydrogen-hydrogen bonds in the primeval atmosphere to give high energy intermediates which were then recombined to intermediately stable forms shown in the second row of Fig. 3. In the last dozen or so years this kind of evolution has been demonstrated in the laboratory. In our first experiments in 1950 using ionizing radiation from an accelerator, we showed the conversion of carbon dioxide in water and hydrogen to produce formic acid, formaldehyde, etc.[13] Within a couple

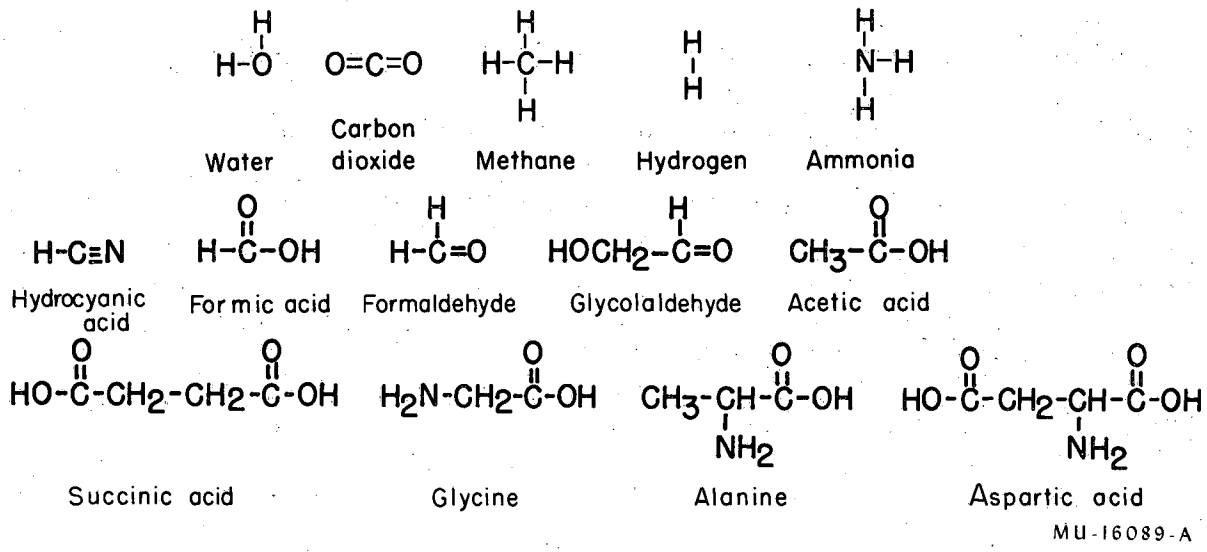

Fig. 3. Primeval and primitive organic molecules.

of years after that, Stanley Miller used methane and ammonia in the reaction mixture with the resulting appearance of amino acids -- glycine, alanine, aspartic acid.[14] This started the search for all of the primitive monomeric molecules which are the constituents of the three polymers so essential for the construction of living organisms.[15]

In general these processes of energy transformation of the primeval to primitive molecules took place in a random way. The same forces which disrupt the primeval molecules can also disrupt the primitive monomeric molecules as well. One must therefore seek autocatalytic processes which would select among the various possible recombinations and which would favor one or another of these primitive molecules.[16] By adding mineral catalysts, for example, iron, zinc, etc. (which may give rise to more complex substances) to such reaction mixtures, porphyrins show up quite early in the evolutionary scheme and, in turn, these are catalytic for their own formation, thus giving rise to a molecular selection in the course of chemical evolution.

It is possible to produce from the primeval atmosphere a collection of primitive monomeric molecules in solution. It has recently been shown that HCN is formed in this way,[17] and the pentamer of HCN, adenine, as well, even in this dilute solution.[18] From adenine (a nucleic acid constituent) it is possible to make other heterocyclic bases which are necessary for the construction of the nucleic acids. Not only adenine but sugars are also formed from the formaldehyde which comes directly from carbon dioxide, or from methane, hydrogen and water. Thus in this mixture there is already present the base and the sugar.

In the last several months, Ponnamperuma has obtained adenosine upon ultraviolet irradiation of a dilute solution of ribose[19] (the five-carbon sugar which is required for the formation of riboside). If this adenosine is irradiated with ultraviolet light absorbed by the adenine in an aqueous solution of pyrophosphate, adenylic acid is obtained and even ATP as well.[20] This demonstrates that not only can building blocks of today's organisms be generated by abiogenic processes, but the basic "energy currency" used by all organisms can be formed in a similar abiogenic conversion of the prime energy sources, ionizing energy and light.

Polymerization

Thus the whole sequence of events from methane to the mononucleotide has now been carried out by the random supply of energy of the right kind to the primeval molecules. We can make the monomers which are the requirements for the polynucleotides. Is it possible to construct, under similar circumstances, the polymers which are required both for structure and for information storage and transfer? The nucleotide is still not a polymer -- it is only the monomeric unit which ultimately has to combine with another one through phosphate linkages. In order to get the polymer from, for example, adenylic acid, it will be necessary to do another condensation reaction between the phosphoric acid group of one molecule and one of the alcohols on another adenylic acid molecule; thus a bifunctional unit is maintained which can be used in further condensation leading eventually to the useful polymer.

In the case of the amino acids we also have a bifunctional form (the carboxyl at one end of the chain and the amino group at the other), and there are a variety of R groups, depending on the molecules with which one starts.

These bifunctional molecules can then be combined into a polymeric form by a dehydration reaction. Fig. 4 shows the nature of the dehydration reaction of the precursors which lead to the proteins, polysaccharides and nucleic acids, the biopolymers.

The question now is: What kind of dehydrating agent(s) is (are) necessary to bring this sequence of events about in a nonbiological system in a dilute water solution? This kind of thing was recently done in the laboratory by using HCN itself as a dehydrating agent. HCN is an anhydride of formamide and it may behave as a specific dehydrating agent, even in dilute aqueous solution. By heating amino acids in solutions of HCN, one is able to obtain not only adenine but polymers of the amino acids as well.[21] Fig. 5 shows a possible mechanism by which HCN might function as a specific dehydrating agent. The analogy of this reaction to the established synthetic reaction using carbodiimide is apparent.[22] The possible more or less specific dehydration condensation function of the wide variety of phosphoric anhydride derivatives has long been under exploration,[22] and their more recent[23, 24, 20] application in aqueous solutions is even more promising.

There are also other means of obtaining polypeptides, polyphosphates, esters, etc., for example, in a nonaqueous medium such as one might get in tidal pools by evaporation and concentration.

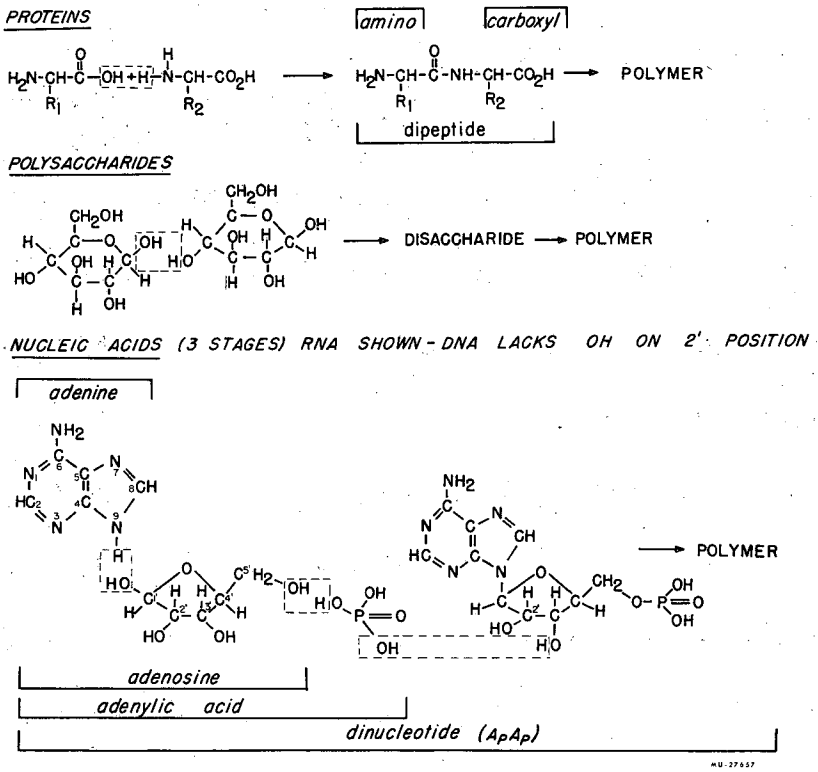

Fig. 4. Dehydration reactions leading to biopolymers.

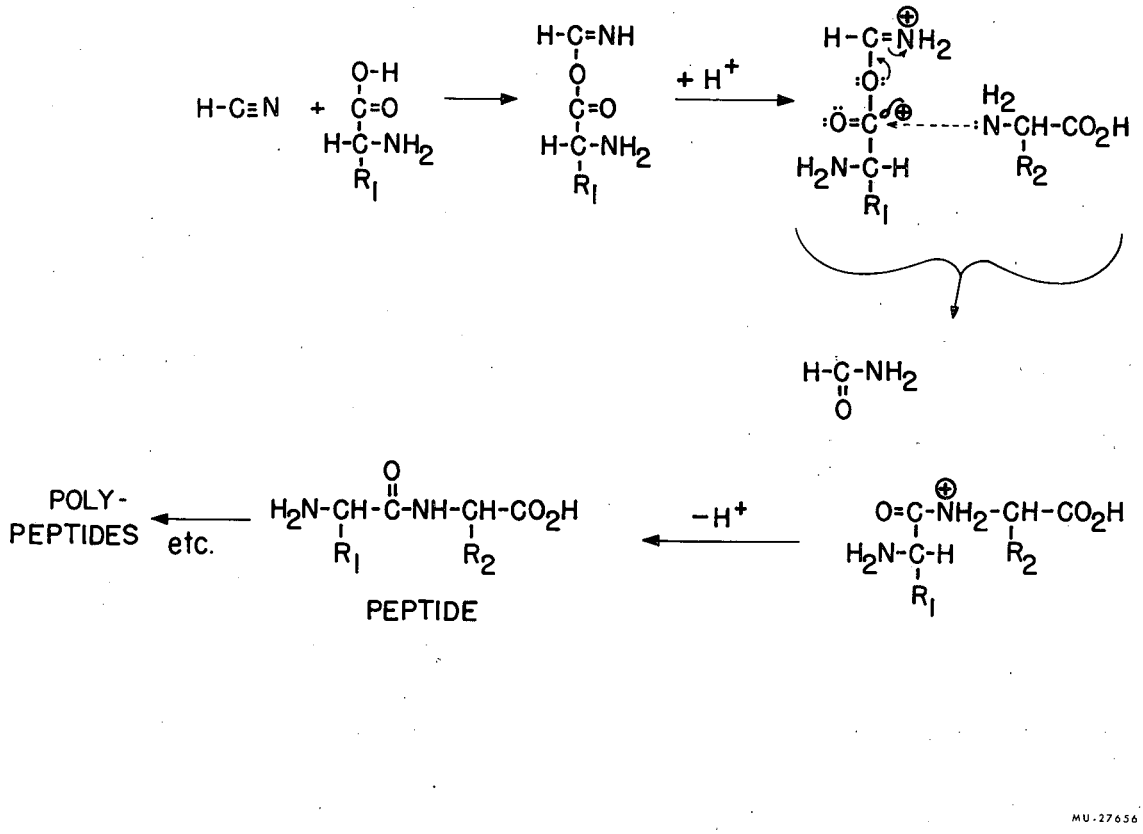

Fig. 5. Possible mechanism of peptide formation with HCN as dehydrating agent.

GENERATION OF ORDER AND NEW INFORMATION

If it is accepted that we can construct polypeptides, polynucleotides and polysaccharides by nonbiological methods, this is itself is a major step toward the structured features which are required for organized energy conversion and information transfer. In the primary structure of these polymers is contained the necessary dements for energy and information transfer. Evidence is accumulating that the secondary, tertiary and even quaternary structure of proteins and nucleic acids are thermodynamically stable forms of a particular primary structure. I would like to make some experimental points which will help demonstrate that such structural information which is required for both efficient energy conversion and for information transfer are contained ultimately in the monomeric sequences that one finds in either of these two principal types of polymers, namely, nucleic acids and the proteins.

Protein Structure and Function

From amino acids one can make a polypeptide of some particular amino acid sequence, and this polypeptide will assume a definite structural arrangement which is not random in solution. The structure assumed depends upon the various atoms of which it is constructed, particularly on the amide carbonyl and the amide NH group, and upon an interaction between the R groups themselves. These latter may be any of a variety of types; hydrophobic bonds, van der Waals' interactions, electrostatic interactions, hydrogen bonds, etc.

For our purposes it is enough to know that there are forces which hold the polypeptides in definite conformations, such as shown in Fig. 6. The polypeptide contains within it, just from the sequence of bonds, the necessary structural information to give rise to the well known alpha helix. This alpha helix of the protein is a macrostructure of a higher degree of order than that defining the amino acid sequence alone. The helix is a secondary structure of the protein which is spontaneously taken up by the primary structure. The information on how to do this is contained in the primary structure (polypeptide) itself.

Evidence for this is abundant. For example, it is possible to destroy the secondary structure and then see if it will reform. This phenomenon is demonstrated in Fig. 7, which shows it for polyglutamic acid. At pH 8 the gamma-carboxyl groups on the end of each glutamate are ionized to produce negative charges which repel each other strongly enough to destroy the alpha helix structure. This is manifested in the form of the optical absorption of the amide linkage. When the amide linkages are randomly oriented with respect to each other (random coil at pH 8) there is a higher optical absorption. At pH 4.9, when the carboxyl groups are not ionized, the alpha helix is reformed and there is a new optical transition in the ordered array of the amide linkages. The effect is reversible.[25] This demonstrates that the secondary structure of the polymer is already contained in the primary amino acid sequence.

Much more than the limited information required for the secondary structure is contained in the primary amino acid sequence. The socalled tertiary structure is contained as well. The tertiary structure may be considered as

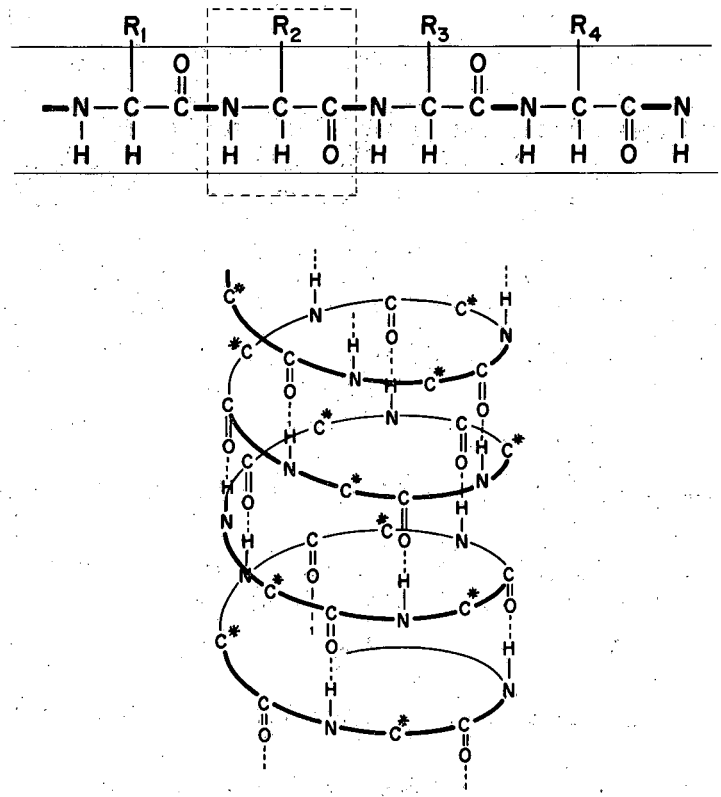

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Fig. 6. Protein structure.

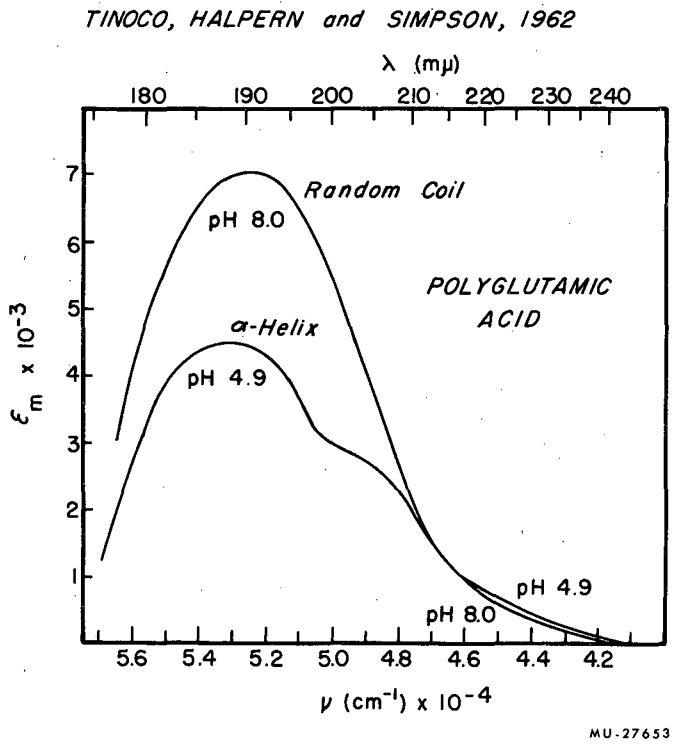

Fig. 7. Absorption spectrum of polyglutamic acid in both helical and random coil forms.

the folding of the alpha helix coil on itself in some special way. In general, the way in which tertiary structures are arranged with respect to each other could be called quaternary structure. The definition of this fourth level of order is at present under lively discussion by chemists, physicists and biologists.[26]

The evidence for the fact that the tertiary structure is contained in the primary amino acid sequence is just coming to hand. (It appears to have existed for some time, but not recognized as such.) The primary form of that evidence is the reversible denaturation of enzymes. Enzymes in general are proteins which not only require a particular amino acid sequence and a helical structure but need helical sections structurally related in space to each other in the proper way. For example, it is not uncommon to have the functional groups of an enzyme consist of an imidazole group of a histidine residue and a hydroxyl group of a serine residue and they may be in different parts of the protein chain. In the active form of the enzyme they function together, side by side, on the same substrate. Since we know the primary sequence, we therefore know that the helical part must have tertiary structure which brings the histidine and serine residues together so that the two groups can function cooperatively, for example, in the hydrolysis of an ester. Thus we know that there is tertiary folding.

Recently it has been demonstrated in a number of cases that one can inactivate an enzyme and show that this inactivation involves the destruction of the tertiary structure, or the quaternary structure in which subunits are packed together but not linked by primary valence. By suitably incubating the inactive

material, as much as 95% of the enzymatic activity can be recovered. This means that the tertiary and quaternary structures (depending upon what the enzyme is) have been reformed spontaneously.[26] One can carry this denaturation clear down to the random coil level, that is, go all the way down to the primary structure, and can climb almost all the way back through the alpha helix into the tertiary folding and even into the quaternary aggregation. This last has indeed been achieved in the case of the enzyme aldolase.[26]

The whole purpose of this discussion is to demonstrate that the primary sequence of the R groups in a polypeptide contains all of the enzymatic information -- enough to construct a whole active functioning structure as a thermodynamically stable form.

Nucleic Acid Structure and Function

The same phenomenon which was discussed for the structured arrangement in the polypeptide holds true for the polynucleotide as well -- having formed the linear array the helical structure follows from it. Fig. 8 shows the construction of the polynucleotide itself. It is a 2-desoxyribose phosphate-3, 5-polymer, and to each desoxyribose sugar molecule is attached one of the heterocyclic bases (thymine, cytosine, adenine and guanine) by 1-glycoside amino linkage. Two of these desoxyribose phosphate chains are specifically paired by a hydrogen-bonded matching of the heterocyclic bases (thymine-adenine; cytosine-guanine). The base pairs each form a flat plane aromatic system, and the two polymer chains are held together by the hydrogen bonds. If the chains are twisted, a helix is formed as shown in Fig. 9. The same sort of base

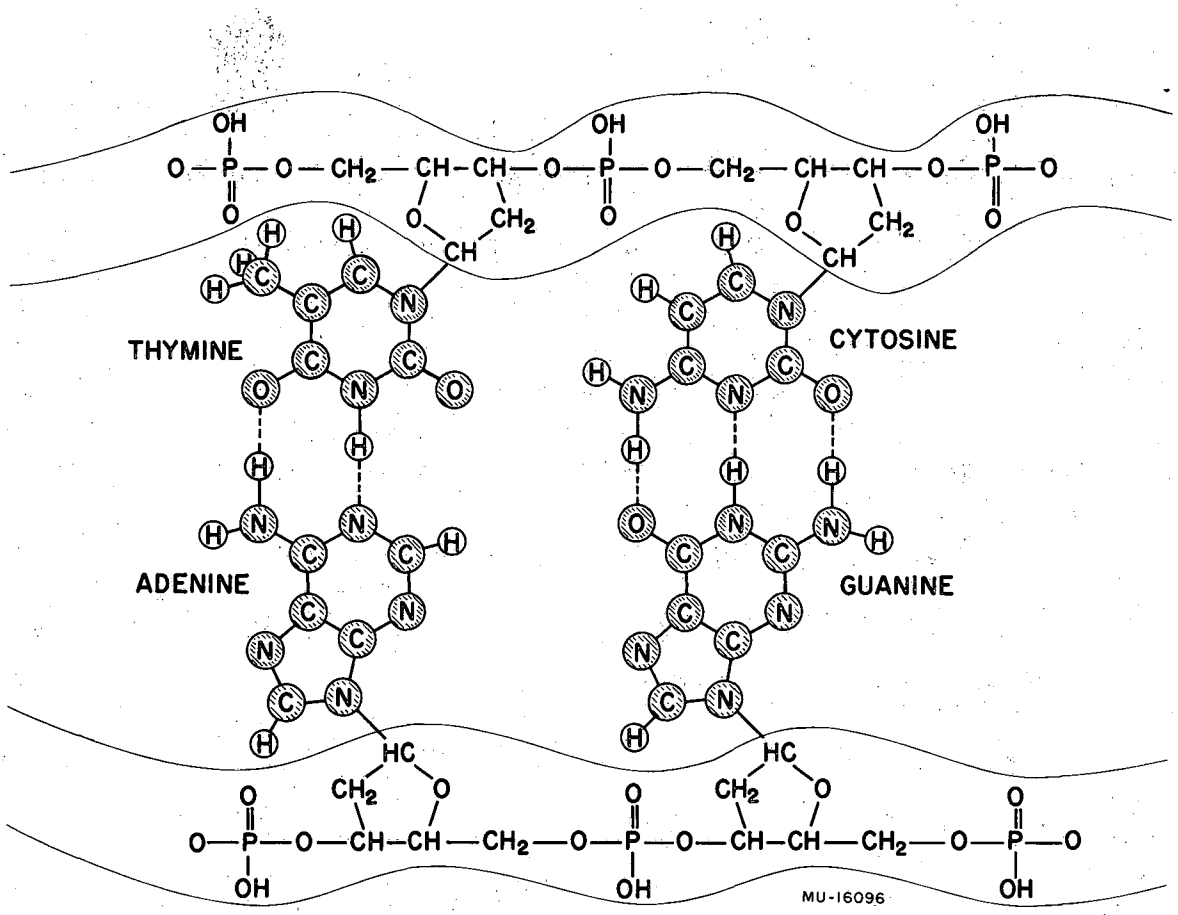

Fig. 8. Molecular drawing of components of DNA.

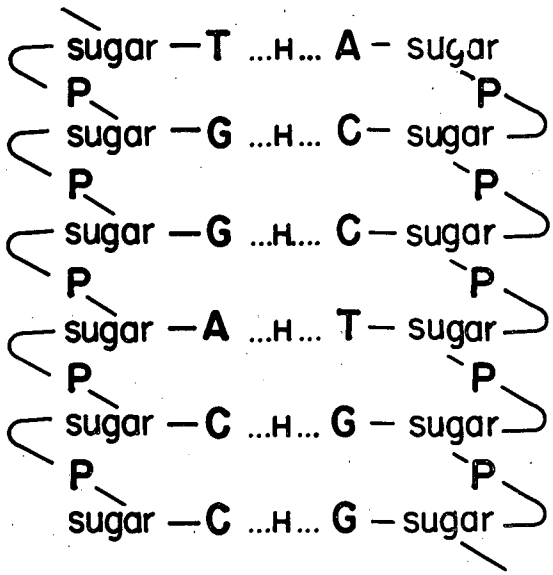

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Fig. 9. Base pairing for DNA replication and RNA template formation.

pairing seems to occur for the ribonucleic acids as well as for the desoxyribonucleic acid.

It now seems clear that one of the principal functions of this simple type of linear polymer is the storage and transfer of information which is coded into the base sequence in the linear array.[27, 28, 29]

While adenine, cytosine, guanine and uracil are the principal bases in RNA, there are some half-dozen methylated bases as well which are present in trace amounts and which undoubtedly represent informational marks along the RNA chain. There are probably a variety of rare special bases in the DNA as well, but this information is only now beginning to appear. One can see that the occasional presence of trace bases would give rise to much additional information in such a linear array.

Here the double helical structure is something which is the permanent and stable form determined solely by the base sequence. One can demonstrate this in a fashion similar to that used for the polypeptide -- disorganization with random coil formation, and recoiling (helix formation) as a spontaneous process depending on the thermodynamics of the situation. Fig. 10 shows data for such a demonstration in nucleic acid. Here at the absorption maximum at 2600 A^{o}, the random coil has larger absorption than the helix. One can go back and forth between the two types, in this case by simply changing the temperature. This is one more bit of experimental evidence to show that the structural information required for energy transfer in an ordered system[30] and for information storage and transfer from one system to another is contained in the linear structure of the polymer.

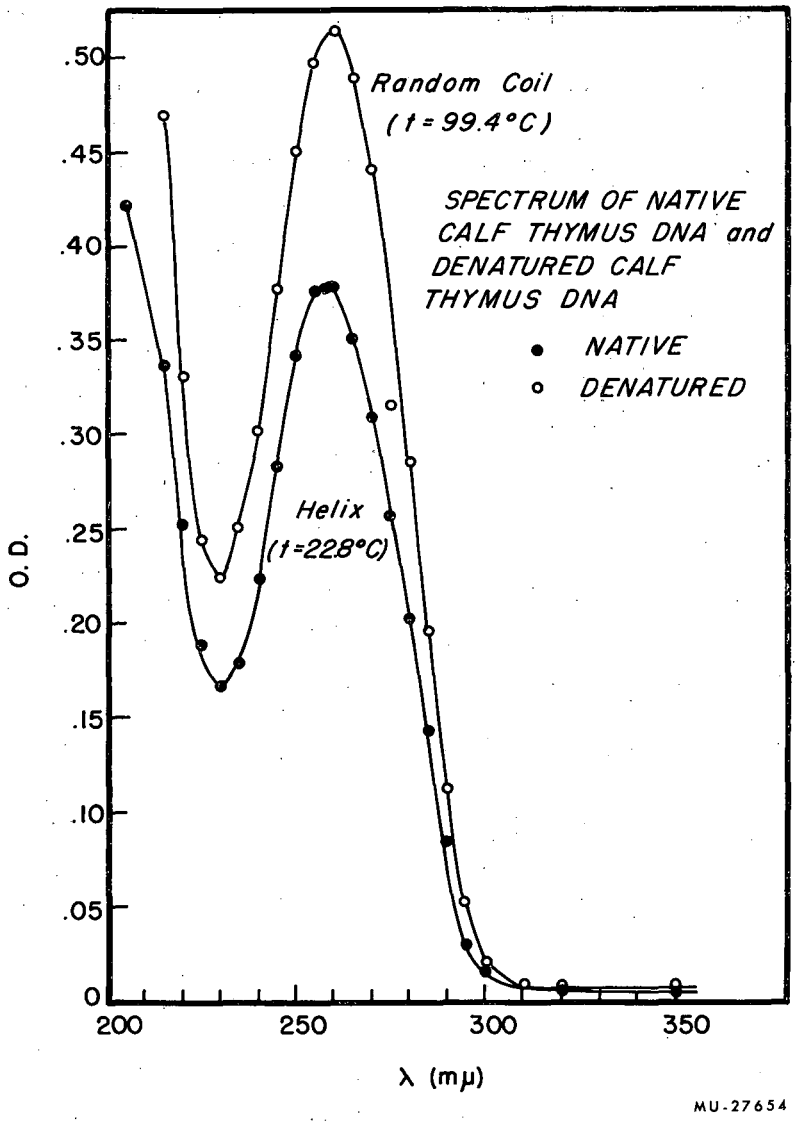
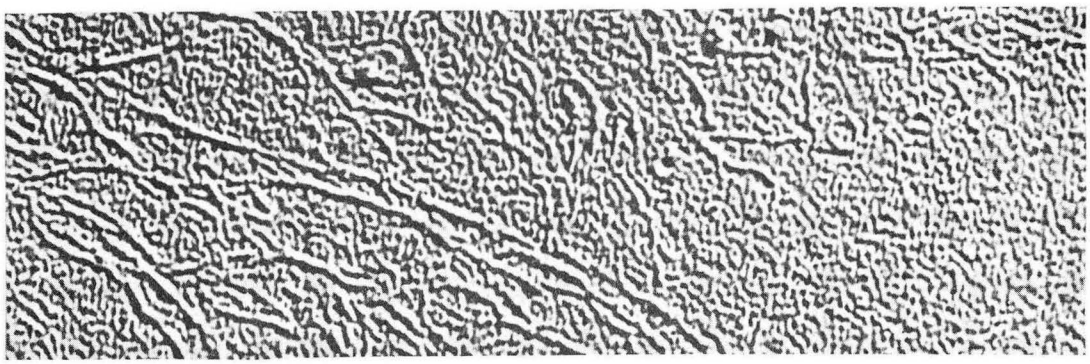


Fig. 10. Hyperchromism on nucleic acid.

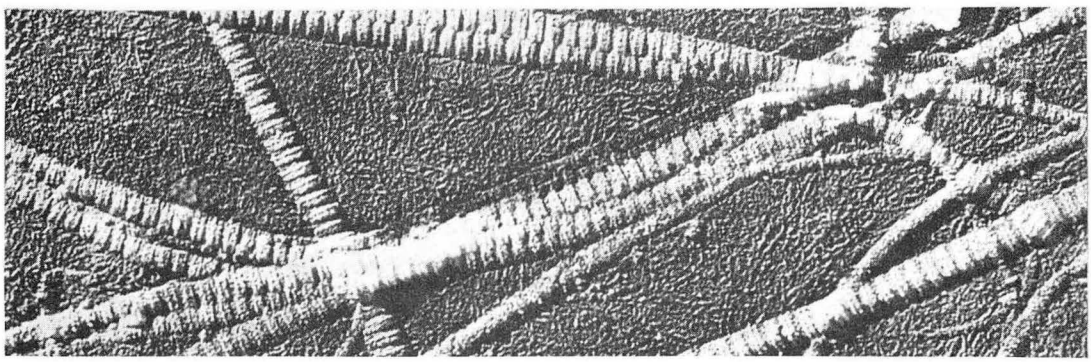
The Next Level of Organization

Finally I would like to say something about the next higher order of structure reaching into the range of the visible -- structures that can actually be seen either by electron or optical microscopy. This structure also may be the ultimate resultant of the primary structure of the polymer. Fig. 11 shows some collagen filaments. In the upper part of the figure they are separated into individual helices. If the proper type and amount of salt is added to a solution of these helices, they will aggregate and collagen fibrils appear which look exactly like the natural collagen fibrils. The lower part of the figure shows some of the reconstituted fibrils. We are now getting into the visible region of structure.

Thus we have outlined a possible sequence of events to traverse the entire route from methane, ammonia and water into visible biological structures. The point is that the information required to build visible biological structure may be contained in the electronic structure of the constituent atoms and the resulting molecular structure itself.[31] The possibility that some of the visible organizations of macromolecules (such as the lamellae of chloroplasts) may themselves be the templates (analogous to crystallization nuclei) for their own reproduction remains. There is some suggestion of the existence of such nonchromosomal information transfer not only in the fact that once lost from certain cells[32] they do not return, but in more subtle changes as well.[33]



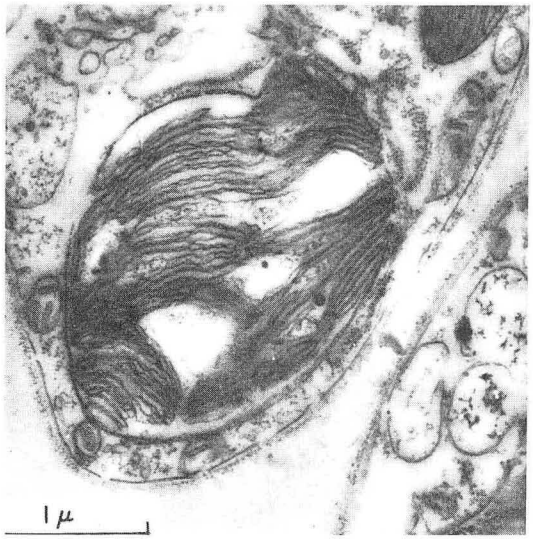
FILAMENTS OF COLLAGEN, a protein which is usually found in long fibrils, were dispersed by placing them in dilute acetic acid. This electron micrograph, which enlarges the filaments 75,000 times, was made by Jerome Gross of the Harvard Medical School.



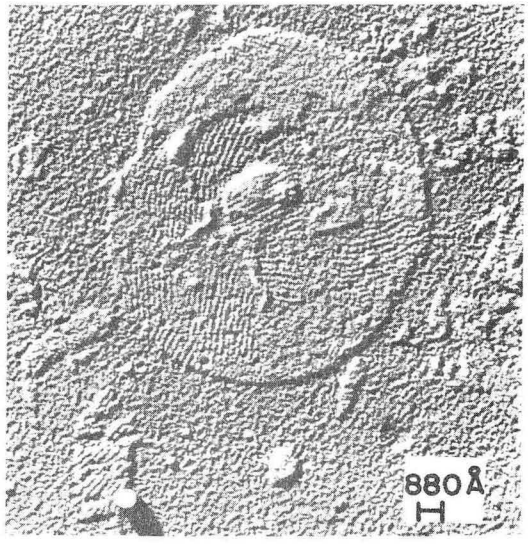
FIBRILS OF COLLAGEN formed spontaneously out of filaments such as those shown above when 1 per cent of sodium chloride was added to the dilute acetic acid. These long fibrils are identical in appearance with those of collagen before dispersion.

ZN-3215

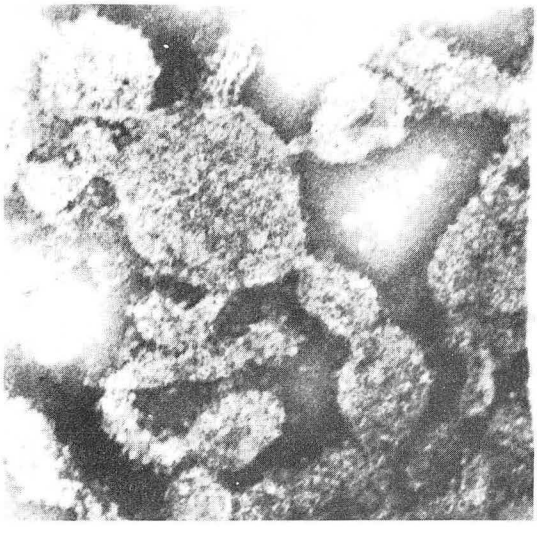
Fig. 11. Structure of collagen.



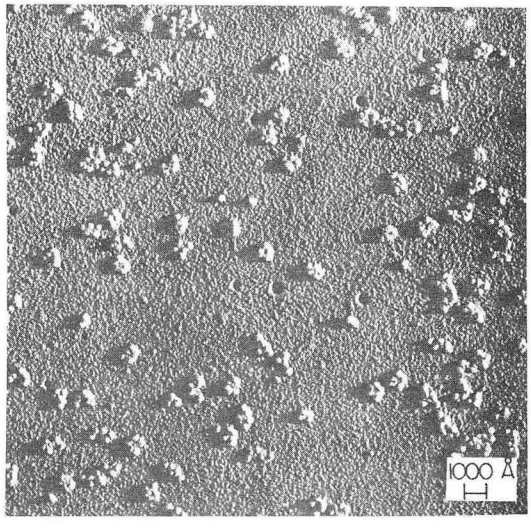
CHLOROPLAST WITH MITOCHONDRIA
CHLAMYDOMONAS (SAGER)



QUANTASOMES FROM SPINACH
(PARK and HEALEY)



NEG.-STAINED MITOCHONDRIA
(PARK and PACKER)



POLYSOMES MAKING HEMOGLOBIN
(WARNER, RICH and HALL)

ZN-4070

Fig. 12. Electron micrograph showing the "fundamental particles" of biology: ribosomes, electron transport particles of the mitochondria, quantasomes of the chloroplasts and unit lipoprotein membrane.

a. Chlamydomonas cells showing chloroplasts, mitochondria, ribosomes and membranes.[35a]
b. Spinach chloroplasts showing quantasomes.[35b]
c. Negative-stained mitochondria.[35c]
d. Polysomes making hemoglobin.[35d]

We will not discuss here the organization of these macromolecules (proteins, nucleic acids, carbohydrates) into cellular units since experimental information is lacking. We know that such units exist, and may even have a certain limited number of forms common to all living cells -- the "fundamental particles" of biology.[34] Fig. 12 is a composite electron micrograph of various origins[35] which purports to show four of these units: the ribosomes, the electron transport particles of the mitochondria (more recently called oxysomes), the quantasomes of chloroplasts and the unit lipoprotein membrane so essential to the enclosure of the cell organelles as well as the cell itself. There is little information about the physics and chemistry of the organization of the macromolecules into closed, membrane bounded packages which we call cells.[36] A good bit of work is going on in surface chemistry, particularly of surface active materials which tend to spread out on the surface of an aqueous layer in a two-dimensional ordered way. The gradual evolution of biologically active membrane structures from such materials can as yet only be imagined and remains to be experimentally demonstrated.

INFORMATION TRANSFER

We have now arrived at the stage of enclosing the energy transfer and information communication apparatus within a cell wall. The next problem is to pass this structural and operational information from one cell to another. Here we introduce two subdivisions of the information transfer process; (1) the transcription of information from one cell to another, in which the language is still the same, i.e., simply passing knowledge from one place to another without using it, and (2) the translation of the instructions which may be contained in the transcription into the construction of a new cell, i.e., following

the instructions to create the machine which can manufacture a new set of instructions. In this last instance information may be transmitted from one cell to another coded in a linear sequence of bases in a nucleic acid (transcription), and then that linear sequence of bases is translated into a linear sequence of amino acids which gives rise to the structure of the cell itself. How is this translation accomplished?

Fig. 13 shows the two kinds of linear arrays: the bases in the nucleic acid which contain the coded genetic information which is handed on from one cell to another, and the proteins (used by the cell in structural and enzymatic functions) which require only the specification of a linear array of amino acids. The coded transcription is made by simply zipping up another set of bases complementary to the first one, following which two strips are separated with one going to the daughter cell for information transfer. The transfer of one kind of linear array into the other is a much more complex operation. All sorts of information-handling machinery exists in the cell for this purpose, and the control apparatus which determines when to read, translate and carry out a particular bit of the available instructions is only now becoming slowly known to us. In the last few years it has become possible to begin the compilation of the "dictionary" for the translation. How the actual translation is accomplished is more complex.

Fig. 14 summarizes some current thoughts of how the translating mechanism functions. In the parent cell, DNA replication (transcription) takes place by matching the bases in one helix to produce another polynucleotide which is then transferred to the daughter cell. The upper left

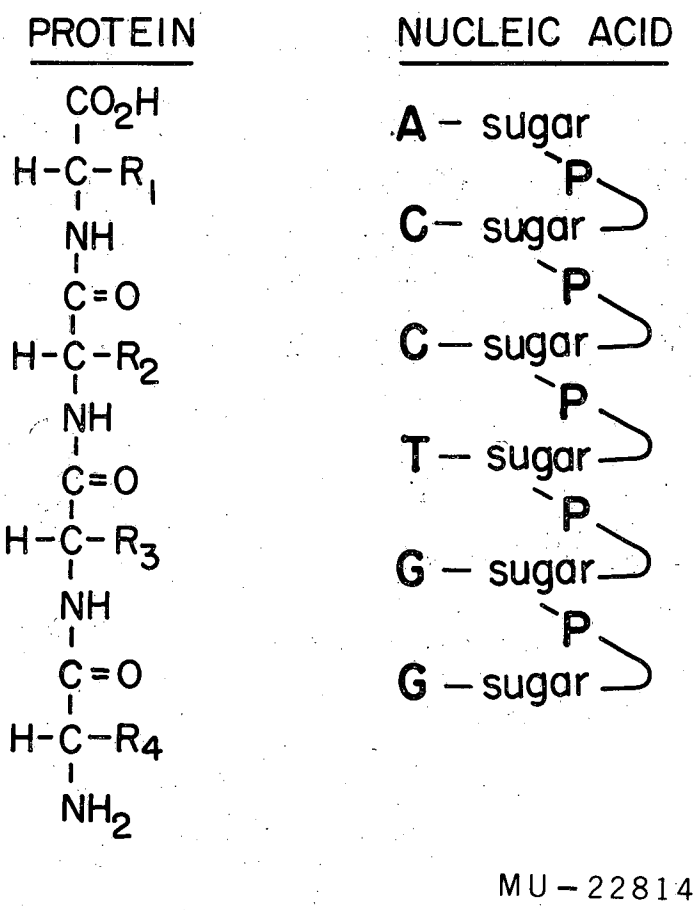


Fig. 13. Structure of protein and nucleic acid.

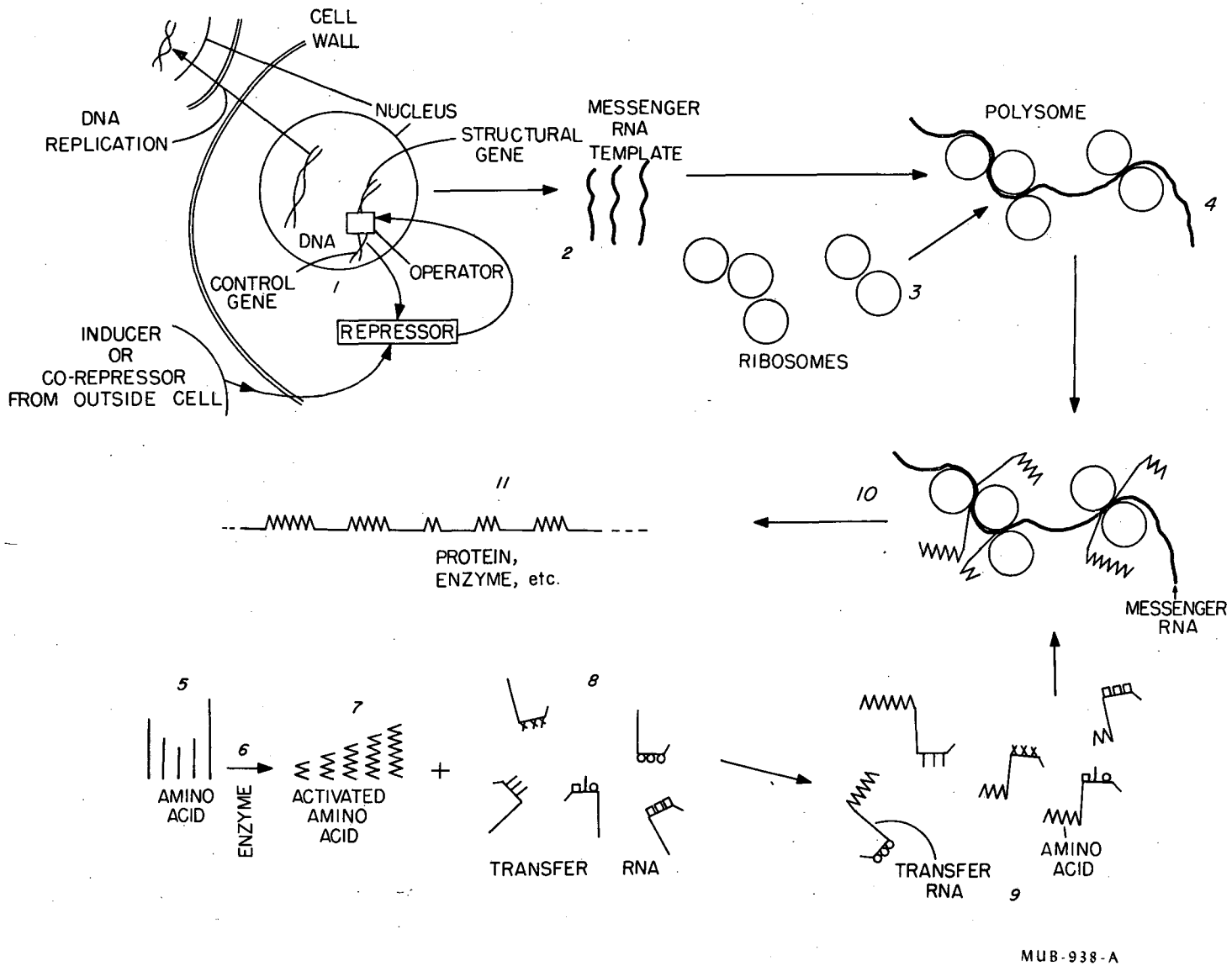


Fig. 14. A sequence of events of the molecular communication problem.

hand corner depicts the new daughter cell containing the new DNA which is now ready to be translated into the formation of a whole organism. How is the linear array of bases translated into protein molecules which are both structural and enzymatic? From the DNA a linear array of complementary bases can be made which are hooked together by ribose sugar molecules into an RNA molecule, thus forming a complementary template to the DNA or some particular part of it. This template which is made in the cell nucleus, and which presumably comes out of the nucleus in some unknown fashion, is called "messenger" (template) RNA. It is the material which reads the coded message off the nuclear translating and construction apparatus in the cell cytoplasm, enabling it to make the proper material. The messenger RNA is a linear sequence of bases corresponding either to the whole or part (we believe it is part in the higher cells but it may be the whole nucleic acid in the simple viruses) of the genetic nucleic acid. The "factory" or "assembly line" is a combination of nucleoproteins which is in a small particle, about 200 Å in size, the ribosome.

It is now quite clear that it is not possible to get the rate of construction that is necessary with only one ribosome working on a single messenger RNA. The situation now appears to be that the messenger RNA can have several ribosomes rolling along it simultaneously.[37,38] The ribosomes contain various amounts of polypeptides, and if the RNA messenger has information for several proteins, presumably there are certain punctuation marks along it which induce the detachment of the ribosome with its completed protein

molecule for release. The protein molecule, having come free, folds up into its secondary and tertiary structure, and takes up its function. The ribosome then goes back to pick up more messenger.

Correspondingly at each one of these punctuation marks an entire synthetic apparatus begins. Recently I have seen electron micrographs of polysomes, which are collections of seven or eight groups, which start at different points along the messenger,[26,39] each one of these points presumably being punctuated in some way, as yet unknown. The messenger evidently is making many things simultaneously.

How do the ribosome and messenger collaborate to make a polypeptide of a particular variety? Here it is necessary to have a translation mechanism. Up to this point the DNA has only been transcribed into RNA; the translation must now be accomplished. The amino acids in Fig. 14 (5) come in from the medium outside and they are transformed by enzymes,, Fig. 14 (6) into activated amino acids (7); the special enzymes which do this seem to form an enzyme ester, generally on the carboxyl group of the amino acid, which is then transferred to a specific small molecule of what is called "transfer" (or soluble, i.e., s-RNA) RNA (8). This molecule has a very specialized character; it is small, only about eighty bases long. Each of the s-RNA's has somewhere on it a three-base sequence which corresponds to a specific amino acid. While the literature suggests that the transfer RNA which is made up of some eighty bases is a hairpin-like structure whose ends form a complementary double helix, this has recently been called into question.[26] However, for the moment let us accept this hypothesis. The s-RNA then

contains three bases, presumably at the bend in the hairpin, which are not paired. These unpaired bases have been called the "codon" for a particular amino acid. The special enzyme (6) to activate the amino acid which is transferred to the specific s-RNA containing the specific codon also has amino acid specificity. Several of the various transfer RNA's have been isolated as pure substances -- alanine transfer RNA, serine transfer RNA, etc. -- and work is rapidly progressing now toward the determination of the complete base sequence in the transfer RNA's. There may be two or three codons for one amino acid, but it is also clear that there are differences in the "handle" structure of the different transfer RNA's from different organisms.[26]

This transfer RNA (s-RNA) is really the translating mechanism within the cell. The relation between the three bases and the amino acid is contained in the transfer RNA. The three bases match up with the corresponding three bases in the messenger RNA and thus put the amino acids in the right sequence as directed by the messenger. The amino acids, thus suitably activated and placed, then "zip up" and the proper protein emerges, by an as yet unknown mechanism.

There must exist a control apparatus within the cell that determines which parts of the DNA should be read at a given time. Every cell of a particular organism contains the same kind of DNA (genetic material) but every cell does not manufacture the same things -- the cells that make the brain make different things from the cells which go to make up other organs and tissues such as fingers, liver, etc. This is the basic

problem of control of growth and differentiation. How do the different cells know that they have different functions? What tells the individual cells what parts of the DNA to read? Here must operate the control mechanism which determines how a cell behaves even though its genetic constitution is predetermined by the base sequence of its inherited DNA. How the genetic constitution of the cell is to be expressed; when and in order, is determined not merely by the DNA but by the environment. Here we come to a point at which social evolution, the control of evolution by man, can really take hold, certainly on a cellular level and probably on an organismic one as well.

FROM CHEMICAL TO SOCIAL EVOLUTION

We are now just beginning to learn the mechanisms which control the way in which a cell can develop. It is the variety in this development which can give rise to a brain cell, an eye cell, etc., all from the same initial cell. Of more direct and immediate concern is what happens if the cells go wild, as they do if the control mechanism is faulty, and they become malignant. We are here in the region of theory based upon a combination of bacterial and virus genetics, on the one hand, and some enzyme chemistry on the other. The control of the reading of the DNA is exercised through, or can be influenced by, something from outside the cell. For example, a small molecule outside the cell can determine whether a certain particular part of the DNA molecule inside the cell can be transcribed into messenger

or not. This promises to give us a handle on the control of development.

If we can already do this with one type of material and organism, it is not an improbable extrapolation to believe that, as chemists, we can make a large variety of materials, some of which could, for example, produce a new or abnormal type of organism. At birth the human has a certain number of brain cells, $\sim 10^{10}$, which is normally all it will ever have. The brain cells make a great number of connections -- excitatory, inhibitory, etc., -- which are the basis for behavior of this computer which is the human brain. If it be possible to control the growth of various developing cells in the brain (and there should be chemicals which can accelerate or decelerate the growth of certain specific kinds of cells), it is quite clear that we might change their number or at least their distribution. If the computer is limited by the number of connections it can make, and if one could go from 10^{10} to 10^{11} brain cells, there is a chance that the capacity of the brain could be increased. This is theoretically now within our range.

We are approaching not only the means of selectively transforming the gene but what is even closer, the means of deciding which ones to read and which ones to not read, and how long to read them. What effect might this have on social evolution?

Social evolution, on a physiological level, up until now has been determined primarily by the same processes of random mutation and selection that gave rise to the human race in the first place. We now have coming into our hands the tools for the control of genetic information itself, and

closer still may be the ability to control the genetic expression of information which is in any existing cell. This would not entail any change in the information (mutation or recombination) but merely to control how it is used.

On the bacterial level both things have already been done; transduction in microbes has been achieved. One can introduce genes into the chromosome of a bacterium (almost at will) which can be incorporated eventually into the bacterial chromosomes. This is what happens with lysogenic viruses; they get into the cell and remain there, and eventually some of them do get attached to the chromosome and become part of the bacterial chromosome. This is changing the bacterial chromosome by introducing new information. More easily done is the control of the expression of the existing bacterial gene by simple molecules,[40,41] by the environment itself. These can penetrate into and out of the cell almost at will and can, in turn, exercise controlling function on the ability of that cell to express its genes.

Through this mechanism it may be possible for us to control virus disease, cancer, and perhaps even change the adaptability of men, thus leading to directed social evolution. The moment we start thinking about things of this nature, we cannot escape the enormous problems involved. Who is going to decide to change men, and how many of them, and in what way?[42,43] This is a problem which we will face and we should begin thinking about it now.

One of the most far-reaching developments in social evolution will come about from this new knowledge of the manipulation of the basic polymeric materials of which all living substance is composed. We are laarning the chemical composition of the genes, and their constituents, the chromosomes, and their structural arrangement. We are learning how to alter genetic material deliberately to produce types with predetermined characteristics. This is being done with microorganisms in the laboratory right now. But in the future, as our knowledge grows, we should have the same power with plants and animals and man himself.

Two aspects of this situation should be considered from the human point of view. Many of the studies of genetic material are being carried out in the interest of controlling virus diseases and cancer. There is little doubt that eventually success will be achieved. The same genetic knowledge will con tain the information we need for controlling both the "quantity" and the "quality" of the population. We may have the power to intensify certain human traits, delete others, and perhaps even develop new ones.[43] An important corollary of this is the approaching power to control men's minds by chemical means, bringing with it the major problem of how and by whom this power should be exercised.[42,43]

The distance from Atom to Adam covers billions of years. By following natural laws of the behavior of matter, the process has been orderly, even in its infinite complexity. But during these years the laws

of nature have functioned in a laboratory in which each atom had its destiny, but within which no encompassing comprehension of the whole could sway the course of experiment.

Today the world is quite as awesome to contemplate as it must have been in its beginnings, for today man has a little knowledge! With each thread of new truth, the responsibility to weigh the consequence of its application becomes more critical. The rate of evolution can change tremendously with man's new knowledge, and the responsibility to control the rate and the direction of change must depend on wisdom. As it has to this day, time will record our success -- or our failure.

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