

From Aharon Katchalsky

Reply

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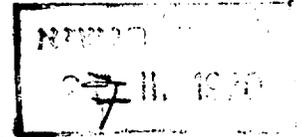
SANTA BARBARA • SANTA CRUZ

DIVISION OF MEDICAL PHYSICS
DONNER LABORATORY

BERKELEY, CALIFORNIA 94720

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Posted Feb. 20



Professor Albert Sabin
President of the Weizmann
Institute of Science
Rehovoth, Israel

Dear Albert,

I did not write you for such a long time since it has taken me several weeks to run in my research project and the lecture courses, which I am giving in Berkeley. Now that my lectures on membrane biophysics are well under way, I can sit quietly and write you in more detail a report on the activities and the plans of my department for the near future.

Let me start with some biological aspects. 1: One of the major interests of molecular biologists is in the polymerization of amino acids and nucleotides under prebiotic conditions. For many years my co-worker, Dr. Mela Horowitz, and myself studied the poly-condensation of amino acid phospho^{ph}anhydrides in aqueous solution at pH 7 and at room temperature. We have developed synthetic methods for the preparation of the highly unstable anhydrides on amino acids with free orthophosphoric acid, as well as the anhydrides with the substituted phosphoric acids. All the anhydrides polymerize in aqueous solution to give low polypeptides, up to hexa or hepta peptides. A few years ago we turned our attention to the adenylates of amino acid which are well-known precursors of protein synthesis and which might be the initial step in the prebiotic synthesis of proteins. Indeed as was shown by various authors, both amino acids and ATP are formed spontaneously under primeval conditions so that amino acid adenylates could form readily under primeval conditions. All experiments, however, on the polymerization of amino acid adenylates in a physiological medium were disappointing. In a homogeneous medium we succeeded to get only low peptides, since hydrolysis was the predominant reaction which competed effectively with chain formation. About a year ago we started a new series of experiments in which we added heterogeneous catalysts to the polymerization

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mixture. After scanning a wide range of catalysts, including colloidal metals, ion exchanges, and silicious earths, we found at long last the real stuff: in the presence of clays, and in particular montmorillonite, we got a rapid and strong polymerization to chains of 25 to 40 amino acids with practically no hydrolysis. This was particularly gratifying since it provided experimental evidence for the correctness of the Biblical statement that life started with clay... At the present moment we know that alanine adenylylate, proline adenylylate and dialanine adenylylate give very similar results and extensive experiments are now being carried out by Dr. Mela Horowitz and her co-worker, Dr. Berger, on the effect of the nature of the montmorillonite particles, the temperature and the ion strength. There are a few interesting side lights to these experiments. First, we found that the major fraction of the peptides coming off the clay particles still carry bound adenylic acid and presumably form short poly-adenylic acids. If the analysis will substantiate the fact that adenylic acid polymerizes too, then we will have in hand the clue not only to primeval polypeptide synthesis but to a simultaneous formation of polynucleotides. This will resolve the question "What precedes what - proteins the nucleic acids, or visa versa?" for the answer would be that both form simultaneously. Secondly, we found to our amazement that the distribution of the molecular weights of the polypeptide chains is not Gaussian or Poissonian, as found in all regular polymerizations, but has a spectral structure. The molecular weights segregate around sharp peaks which may be the reason why proteins started off with a relatively sharp molecular weight distribution. This finding is also of special theoretical interest and seems to indicate that on the montmorillonite surfaces we have simultaneous operation of polymerization and diffusion processes, which have recently been shown to create "dissipative structures." I am now working on the theory in Berkeley, together with a young doctorant, Alan Perelson, and we hope that in a short while we shall be able to interpret quantitatively the results of Mrs. Horowitz's experiments. The theory is important not only for intellectual reasons but since it may provide us with a plan for the preparation of higher polypeptides and indicate how to carry out poly-condensation experiments which will lead to structures closer to those of the proteins.

I reported on these results at two closed meetings. The first meeting was arranged by the Council of the European Molecular Biology Organization, of

which I am a member, and was attended by Crick, Watson, Kendrew, Perutz and Klugg. Their response to the lecture was very warm and Crick and Perutz told me that this seems to be the first important break-through in molecular biology after the discovery of the double helical structure of DNA. The second meeting was organized by the Neuro-Research Program at the American Academy in Boston and was attended, among others, by Manfred Eigen, Melvin Calvin, Jerry Edelman, and Frank Schmitt. They were as excited as the EMBO group and Melvin Calvin, who has just published a book on chemical evolution, told me that this is the step to which all the workers in the field were looking during the last twenty years. Indeed, Calvin and Eigen want to organize a special symposium on chemical evolution in which we could discuss the consequences of our discovery.

Encouraged by the support of eminent specialists, I feel that it would be advisable to extend the group of Mela Horowitz and to add to the equipment which will facilitate her work and will allow us to proceed more quickly with those fundamental experiments which should be published as soon as possible.

2: My other field of interest here is the application of non-equilibrium thermodynamics to mechanochemical conversions. You might know that some ten years ago Professor Ora Kedem and myself introduced the thermodynamics of irreversible processes into biophysics and by now it has become an integral part of biophysical teaching and study throughout the world. Our primary interest at that time was the thermodynamic description of membrane phenomena and we succeeded to establish the correct equations for both passive and active transport in cellular membranes and tissue covers. At about the same time, I developed with my co-worker, Oplatka, mechanochemical convertors which transformed directly chemical energy into mechanical work. Although the models worked out by us have no direct significance for the interpretation and the work of the muscle or of cilia and flagella, the physical principles underlying the conversion are identical, so that mechanochemical studies have an important bearing on the biophysical understanding of living motility. They are also of technological interest, and I hope that by now you have seen the machine shown at the Weizmann Institute exhibition of scientific innovations. Indeed, Professor M. Sussman of the Tufts University, who worked for some time in my

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laboratory and developed a different mechanical model which I published together with him in Science, made quite a fuss about the invention and published it in most important American daily newspapers. But from a fundamental point of view, our theoretical analysis of mechanochemical conversions was always based on reversible-equilibrium processes. It is evident, however, that both in the muscle and in the technical models the conversion is irreversible and should be treated by the thermodynamics of irreversible processes. It appears, however, that the classical non-equilibrium thermodynamics, on which I have written a biophysical book, published by the Harvard University Press, is not good enough for the study of mechanochemistry. It should be extended in some new directions related to the network and graph theory successfully developed by the electrical engineers and by the specialists on general systems theory. I am now working with a young post-doc, Dr. George Oster, on a new thermodynamics of flow processes which should be able to describe both linear and non-linear processes in steady and non-steady states. Such a thermodynamics should comprise biophysical phenomena as well as technical processes and adequate for the description of organismic systems. During this month, we made considerable progress and indeed we started already to write a monographic article describing the new approach and its application to numerous systems. Among the applications the most important case is mechanochemical systems which we feel could now be described in sufficient detail and full generality. Since the theory imposes new experiments, it would be advisable to help also Dr. Oplatka in my department to strengthen his group by additional equipment and manpower. The international interest in mechanochemistry and the fact that not only technical firms but also cell physiologists are recognizing mechanochemical processes as fundamental in cellular and membrane transport makes the experimental and theoretical study of these phenomena of real significance.

3: The last item of a biological nature is the study of membranes. The original intention of developing biological non-equilibrium thermodynamics by Dr. Kedem and myself was the interpretation of membrane behavior. Professor Kedem, together with Professor Vofsi, the leader of the Plastics Laboratory, have developed rather successfully a series of membranes for desalination and for the separation of various materials from industrial mixtures. Their

achievements will be surely brought to your attention in the proposals of the Plastics Laboratory. Here I would like to mention primarily the biological aspects and, in particular, the possibility of analyzing active transport and related biophysical phenomena. During the last years, we have published several papers in this field, and my department has become a recognized center for the study of biological membranes. Since from a certain point of view we are new-comers to the field, the experimental set-up is lagging behind the theoretical knowledge, and we are very eager to supplement our equipment with additional apparatus which will allow us to study some fundamental membrane aspects. I would like to mention in particular two directions of research: the classical studies of membranes were devoted primarily to stationary state flows. The results from stationary state measurements, however, provide only limited information about the details of the transport of matter across membranes. During the recent years, powerful relaxation methods were developed for the study of chemical processes, in particular by Manfred Eigen and his group, and I would like to introduce these methods for the investigation of membrane behavior. I discussed the matter several times with Eigen and it is his feeling that despite the fact that relaxation methods are rather expensive, they are within the range of the Weizmann Institute. Another group of investigations which I would like to introduce into my department is connected with the thermal behavior of membranes. A true thermodynamic analysis of biological membranes requires some information on the dependence of the transport coefficients on temperatures and on the flow of matter under a temperature gradient. Indeed, some work on these lines was initiated under my guidance in the Laboratory for Marine Biology in Miami, Florida. Recently, however, an important advancement was made by my friend, Professor Isador Edelman of the Medical School in San Francisco, which indicates that the active exchange of sodium-potassium in mammalian tissue may be responsible for the temperature regulation of homiothermic animals. This relation between membrane transport and thermal homostasis of higher organisms makes the investigation on the temperature dependence of biological membrane transport of particular interest, and I feel that installing the suitable experimental facilities in my laboratory is timely.

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I would like now to turn your attention to the non-biological aspects of the work going on in my department. For many years we have been involved in the study of charged polymers -- the so-called polyelectrolytes. The electro-chemistry of polyelectrolytes is of fundamental biophysical interest since the nucleic acids, polyuronic acids and some of the proteins are typical polyelectrolytes, whose solution properties are determined by the strong electrostatic field surrounding the polymer molecules. My colleague, Dr. Alexandrovich, who is working for several years on the statistical mechanics of polymer solutions in general and polyelectrolytes in particular, obtained rather interesting results by treating the effect of excluded volume on equilibrium and transport properties of macromolecules. Among others, particularly important is the evaluation of the viscosity of polyelectrolyte solutions, which could not be explained adequately hitherto. Since his work is by and large theoretical, no additional equipment is asked for at this instance. Very interesting research on polyelectrolyte solutions is carried out by my colleague, Professor Eisenberg, of this department. Eisenberg has developed a thermodynamic treatment for multicomponent mixtures which permits the analysis of biological systems, which generally comprise three components: a biopolymer, salt and water. In addition to his important theoretical contributions, Eisenberg, who is primarily an experimentalist, carried out precise and careful studies on the light scattering and centrifugation of polyelectrolyte and biopolymer solutions which are recognized internationally. For his experimental work he needs rather sophisticated and precise apparatus on which he will surely apply to you directly.

The last item to be discussed in this letter is the problem of polymer physics. As is the case in the historical development of other branches of chemistry, the research workers on polymer systems started with the study of solutions. During the last few years, however, the interest in solid polymer systems has grown appreciably. One has developed a larger number of experimental methods which allow the interpretation of the crystalline structure of polymers and provide a fundamental basis for the interpretation of the physical properties of plastics, fibers and rubbers. Indeed, polymer physics is today the basis of the modern developments in plastic industries leading to some of the remarkable materials found on the world market. It is an old dream of

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Israeli industry to enter the field of plastics and synthetic fibers and
although some important beginnings were made in the production of certain
brands of nylon, Israel is lacking in the scientific foundations on which an
advanced industry of this type could grow. In line with the ideas advanced by
you at the meeting with the senior staff of the Institute, we feel that a
section on polymer physics would be a logical development of the polymer depart-
ment. We are fortunate that Professor Alex Silberberg, who is the acting head
of the department in my absence, is a specialist in some aspects of polymer
physics. Professor Silberberg worked for many years on rheology of polymer
solutions and gels; he is one of the leading personalities in the International
Society for Biorheology. I was happy to discover that Professor Silberberg is
ready to help in the establishment of a section for polymer physics, for which
his competence in statistical mechanics and in the general mechanics of polymer
systems will be of great value. At the same time, Professor Vofsi is very
interested in promoting the development of polymer physics as a basis for the
further development of his work on the synthesis and application of new plastic
materials. A laboratory for polymer physics is a rather expensive enterprise,
since it should be provided with X-ray equipment and a series of apparatus for
mechanical and electrical measurements. There is no need, however, to start at
once on a large scale, and we feel that a small group of, say, five workers
attached either to the Polymer Department or to the Plastics Laboratory could
be an adequate beginning. If you feel inclined to look into this proposal, I
am sure Professors Silberberg and Vofsi will be happy to meet with you and
discuss in some detail the project.

This is about all that I wanted to tell you in this instance. I hope I
didn't exhaust your patience in reading through this too-long letter. It is my
intention to be back home in several weeks' time so that we could continue our
discussion in a friendly meeting.

With cordial regards and best wishes.

Yours,

Sharon

Prof. A. Katzir-Katchalsky

AK/mlq