CHEMISTRY-BIOLOGY

Constitution of Protein

"A Classic of Science"

Analysis and Synthesis of Proteins Will Aid Biology In Understanding the Mechanism of All Life Processes

UNTERSUCHUNGEN ÜBER AMINOSÆUREN, POLYPEPTIDE UND PROTEINE (1899-1906) *von Emil Fischer. Berlin, Julius Springer,* 1906. *Translated for the Science News Letter by Helen M. Davis. This is a literal translation of extracts from the original publication.*

SINCE protein materials are concerned in one way or another in all chemical processes in living organisms, we may expect from the determination of their structure and their metamorphoses reactions of the greatest importance to biological chemistry. It is therefore no wonder that the study of this material, which chemists for more than a generation have avoided almost entirely, because they found satisfaction in perfection of synthetic methods or in the study of simpler natural compounds, was kept up by physiologists in ever increasing numbers and with unmistakable success. Nevertheless, the initiated have never doubted that organic chemistry, which was cradled close to the proteins, would finally turn back to them again. But opinion was and is still today divided over the point where co-operation between biology and chemistry would be successful.

While cautious professional colleagues fear that rational work upon this class of substances, on account of their complicated structure and their most inconvenient physical properties, even today will meet with insurmountable difficulties, other optimistically minded experimenters, among whom I will count myself, incline to the view that at least the attempt should be made, with the aid of all modern methods, to attack the impregnable fortress; for only through the venture itself can the limit of power of our methods be ascertained. The sober critic will at any rate not be able to gainsay the right to discuss the prospect of success when it compares the present knowledge with that which is necessary to reach the goal.

In respect to the determination, isolation and biological characterization of the numerous natural proteins, physiological chemistry has accomplished remarkable things. We know several dozen sharply differentiated members of this class, which can be arranged in groups according to their solubility and rate of precipitation, and of these many can be obtained in crystalline form. We know further that the several individuals are carriers of different biological functions. We know, finally, that all these bodies under the influence of different ferments undergo deeprooted, characteristc decompositions.

In spite of all this, our knowledge of their chemical composition is quite limited. If we look for the results of elementary analysis, they are confined essentially to the results of hydrolysis, which can sometimes be accomplished by acids and alkalies and at other times by the digestive ferments. All proteins are made up of ammonia and from it, one after another, of albumins, peptones and finally amino acids. About the nature of the first two cleavage products we are scarcely better informed than about the protein itself.

So successful has the study of amino acids been hitherto that for many, not only has the structure been determined, but the synthesis has been effected. On this basis therefore chemical investigation, which has set itself the task of clarifying and artificially reproducing the peptones, albumins and proteins, must build further.

Filled with this conviction, when I made the resolution six years ago to devote myself to study of the proteins I began with amino acids, in order to get from a better knowledge of them new viewpoints and methods for their complex derivatives.

The outcome has not disappointed my expectations. It was successful first through use of the ester in finding a new means of separation for the monoamino acids, which has become a worthwhile method for hydrolysis of protein, and not only aids in isolation of known amino-acids, but also has made possible the discovery of new members of that class.

Still more important seem to me the methods found in the same way for the conversion of amino-acids into their amid-like anhydrides, for which I have chosen the collective name "polypeptides". The higher members of this class of synthetic bodies are in respect to external properties, definite color reactions, behavior toward acids, alkalies and ferments, so similar to the natural peptones that they may be considered their nearest relatives, and that I may reckon their production as the beginning of the synthesis of natural peptones and albuminoses. . . .

Structure and System of Proteins

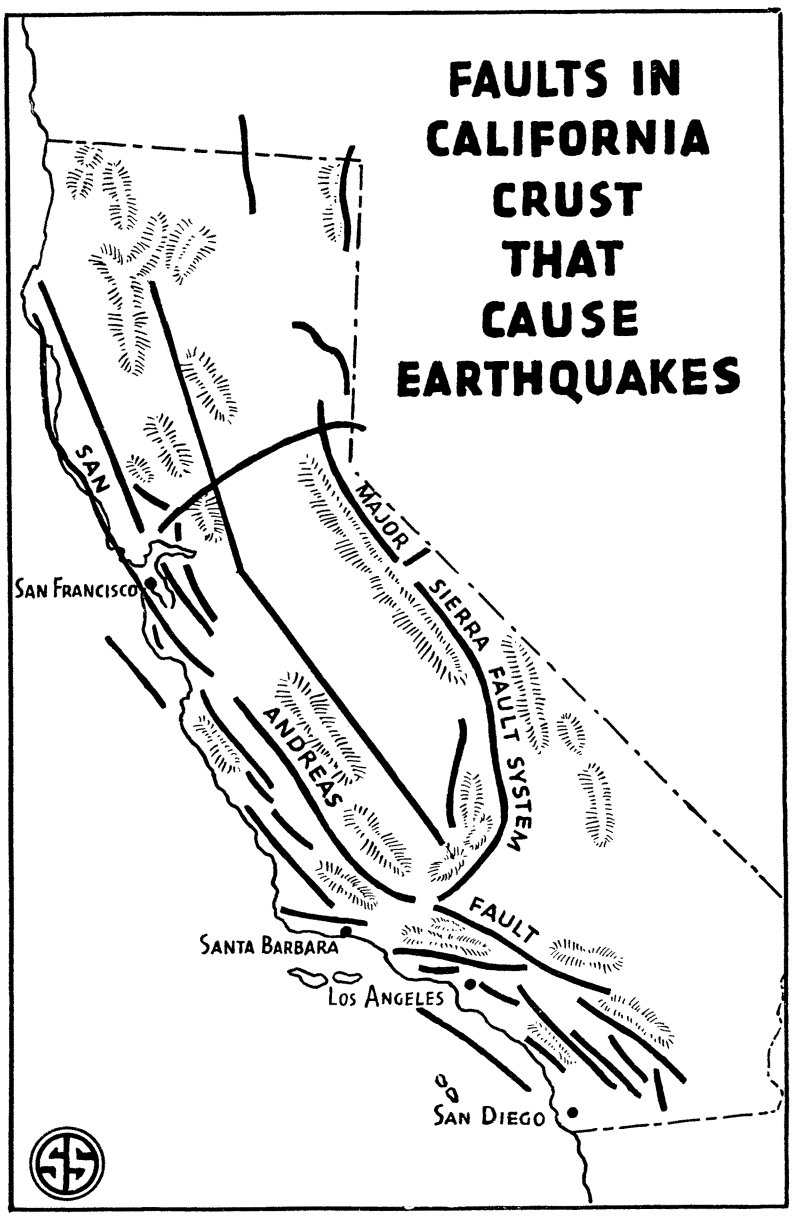
Chemical and physiological literature is not lacking in consideration of the constitution of albuminous bodies. We meet all gradations from modest remarks about the linkage of amino acids to pretentious, highly fantastic structural formulae. So far as I have been able to form an opinion, most of the views agree that in the protein molecule the amino acids are linked as amides.

Emil Fischer (1852-1919) worked for years to clear up the complex relationships of organic chemical groups occurring in the tissues of living matter. In 1906 he succeeded in synthesizing a true protein formed of a chain of 18 amino acids. Ten years later another group of workers using his methods succeeded in introducing one more amino acid group into the molecule. Some one remarked at the time that at that rate synthetic beefsteak would cost $250 per lb. As Fischer shows here, the value of such work lies elsewhere than in the mere complexity of compounds which can be built up.

This idea in most detailed form is well treated by Hofmeister, but he would not in the least wish to advance a claim to being its originator, for all synthetic researches on the linkage of amino acids, among others the discovery of glycyl-glycin which occurred shortly before his publication, are based upon the same hypothesis.

In the great similarity of artificial polypeptides to peptones, especially with respect to their behavior toward pancreas-extract, also in the preparation of glycyl-*d*-alanin-anhydride from silk, one may find a new, strong support for this idea. The possibility that from the already known natural amino-acids one may by this sort of linkage alone build up, theoretically, quite a splendid number of proteins is at hand and is fully explained in popular form by Hofmeister. The structure naturally becomes even more complex through the participation of amino-dicarbon acids (asparagin- and glutamin-acids), as well as diamino acids (eysin, arginin, etc.).

But here I might call to attention that the simple amide formation is not the only possibility of linkage in the protein molecule. On the contrary, I consider it even quite probable that sometimes piperazin rings occur there, whose easy disruption by alkali and reformation as dipeptides or their esters I have so frequently found in artificial products, and that at other times the many hydroxyls of the oxyamino acids are by no means indifferent groups in the protein molecule. The last can by intramolecular anhydride formation go over into ester- or ether-groups, and the multiplicity would still be increased if we consider poly-amino acids as true components of albumins. There is no reason to spin out these considerations, but still it seems to me important to refer to the various possibilities, to prevent the all too one-sided views which the experimental investigation might leave behind.



EARTHQUAKE MAP

The Long Beach earthquake of March 10 had its center along the fault, shown by black line, in the ocean floor that lies offshore from Los Angeles. Other black lines on the map show slipping planes or faults in California's earth crust that have caused earthquakes in the past or are likely to cause them in the future. The famous 1906 San Francisco earthquake was along the San Andreas fault. This map is based on data collected by H. O. Wood, Carnegie Institution of Washington seismologist.

In the formation of protein and its various complex derivatives, nature has, so far as we know, reached her highest chemical performance, and it would contradict all experience of organic chemistry and biology if she had here limited herself to only a few types.

As the great number of amino acids and their constantly changing composition already shows, there occurs in the composition of protein a disproportionately greater complexity than in the carbohydrates and the fats. If to that is yet added the various possibilities of linkage, which I have indicated above, the proteins have a chemical character which is equal to the extremely complex purpose for which they are used by nature, for the structure and the functions of the organs. . . .

The methods of building the polypeptides depicted above are so manifold that they will permit synthesis of numerous and quite complex combinations of the natural amino acids, if we do not count the work and expense.

But the indiscriminate increase of forms would perhaps not be worth the trouble. More important seems to me the need, which practice in experimental treatment of the synthetic products supplies, of discovering newer methods of separation of their natural relatives from the peptones. The synthesis of glycin-*d*-alanin-anhydride from silk serves as the first example of this. Hope

seems to me therefore established that it will belong to the not too distant future to isolate and artificially reproduce the most important members of the natural peptones and even the albumoses. But in order to handle a great number of single individuals in the very diverse combinations of the proteins the work of many hands will be necessary. Far more difficult is the problem, naturally, for the true albumins, since, for their reconstruction out of the first products of hydrolysis, wholly new methods must be produced, and even when these principles are established, their application in each separate case will most probably be a tedious work. We may therefore question whether the ultimate success will correspond to the labor spent. That in my opinion depends upon the use which biological research can make of it, and this is again limited by the means by which the synthesis will be effected.

If today, through a lucky accident, by the aid of a violent reaction, e. g., by melting together amino acids in the presence of a dehydrating agent, it should happen that a true protein should be formed, and if it were further possible, which is still more unlikely, that the artificial product could be identified with a natural substance, little for the chemistry of the albuminous substances would be gained thereby, and practically nothing at all for biology.

Such a synthesis I might liken to a traveller who passes through a country on a quick trip, and can tell scarcely anything further about it. The case is entirely different if the synthesis is compelled to go forward step by step and build up the molecule substance by substance, as was pointed out above for the polypeptides. Then it is like a foot traveller who seeks out his way step by step with intense attention, who must try out many roads till he has found the right one. He learns from his long, tiresome wandering not alone to know the geography and topography of the country, but he will also be conversant with the language and customs of its inhabitants. When he has finally reached his goal, he is able to find the right direction in every corner of the country, and if he writes a book about it, other people will be able to do so too.

I might therefore consider it an absolute blessing that synthesis has to devise many new methods of formation, recognition and isolation, and to study accurately hundreds of intermediate products, before it may reach the proteins. For these methods will in the end serve not alone to produce all the proteins of nature and many more still than they have produced; they will presumably also serve to clarify the numerous and important transformation products of protein which play so great a role as ferments, toxines, etc.

We may shortly expect that through thoroughgoing and far extended synthetic work the whole region now still so dark will become a land of chemical culture from which biology can draw a great deal of the help which it needs for the solution of its chemical problems.

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ARCHAEOLOGY

Prehistoric Measuring Cups Studied in Vienna Museum

A PAIR of measuring cups used by some tribe that inhabited the Danube Valley in Bronze Age times, about 2000 years before Christ, have been presented to the National Museum of Lower Austria. So far as can be determined, they represent the only liquid measures of a people in the prehistoric stage of culture that have so far been discovered.

The two earthenware cups were excavated near Vienna about 19 years ago, but did not come into possession of the museum until recently. Dr. Friedrich Wimmer, struck by their similarity in shape and by their lack of resemblance to other pottery from the same locality, conjectured that they might be measures, and made an accurate examination of them.

They are both cylindrical in general outline, and each has a small handle near the top, very much like the handles of measuring cups in modern kitchens. The smaller of the two contains a trifle less than a sixth of a pint, and its larger companion almost exactly twice that quantity.

When these cups were in use in the prehistoric neighborhood of Vienna, the high civilizations of Egypt and Babylonia had elaborate systems of measurement; but so far Dr. Wimmer's investigations have not shown any definite relations between these two cups and their contemporaries to the southeast.

Science News Letter, March 25, 1933

From Page 181

to furnish the West with a supply of Yogi for the sole purpose of fleecing succulent ladies for silly lecture courses in unworkable hokum philosophies. Again, she seems best suited to keep the British lion alive by giving him something to worry about. Then again one wonders if India does not have something to say which is worthy of thought; but when one matches that idea with the squalor and wretchedness of many phases of Hindu life he turns away and faces west again. No, India seems doomed to sterility. The world will not look kindly upon her offerings until she pulls herself out of her (*Turn Page*)