quality—experiments are made in the production of that quality on a commercial scale. The farmer as an individual producer would be wholly unable to supply such standardized products without the aid of investigation.

These things make clear the reciprocal interests of farming and manufacturing and the direct benefit of research to both lines. The great manufacturing state of Massachusetts, in addition to drawing its food very largely from sections quite remote, is dependent on agriculture outside its borders for most of its raw materials. Measured in value, considerably more than half the total output of its factories is manufactured from products of the soil. Its industries could not survive a single year without these supplies drawn from the south, the west and foreign lands, and the maintenance of both volume and quality is absolutely vital. Thus the benefits of agricultural research are not bounded by state lines; they are no less real to this commonwealth than in the regions where its raw materials are grown.

Research is itself a process of learning, but not all centers of teaching are likewise centers for enlarging the field of knowledge. A conspicuous feature of the group of institutions to which this one belongs is that they are fulfiling the double mission of centers of teaching and agencies for learning. It is this that has made them truly democratic—not merely for the few who come to their halls, but for all who will take advantage of the practical results of their research spread broadcast.

The people of this country have built up the most comprehensive and effective system for agricultural research to be found anywhere, represented by the federal department of agriculture and the state experiment stations. The station system started in Connecticut fifty years ago, with an appropriation of less than $3,000, and it is interesting to note that plans are under way for a national observance of this important anniversary at New Haven a few months hence.

In the development which has taken place in the half century, the New England states have had a leading place, noticeably so in the earlier stages. The names of Atwater, Johnson and Jenkins in Connecticut and of Jordan in Maine will stand out as pioneers who supplied ideals on which the American stations rest; while our own Goessmann, Fernald and Brooks will be remembered with great honor for their notable contributions which led the way in channels that were new.

From these small beginnings the experiment stations have grown to a national system, with an aggregate maintenance fund of $10,000,000 a year, equivalent to the income from an endowment of $200,000,000—this for a twenty-five billion dollar industry from which half the entire business of the country, half the tonnage value of the railroads and a large share of the commerce arise. To-day these stations, with the federal department of agriculture, constitute one of the most powerful agencies for the benefit of human welfare in any line.

If some great aggregation of wealth should announce the provision of an endowment of $200,000,000 for research, it would call for the largest type the newspapers had and would be heralded as a great benefaction. Such an endowment would be a remarkable tribute to the appreciation of this type of service—and it is, the more so because it expresses the judgment of the people in forty-eight states. The latest congressional measure, to go into effect next month, came as a response for relief of the agricultural industry. It is a great endorsement, for it represents the mature judgment that agricultural prosperity can not be assured through special legislation, but that safe advancement must rely on sound knowledge of scientific and economic principles to be worked out through research.

Out over the country, stretching from this eastern boundary to the Pacific and beyond, is a small army of zealous, faithful workers spending their lives in research for agriculture—for the benefit of the consumers as well as the producers in that field. They represent an infinitesimal proportion of those to whom their labors mean very much. Many of them have come from this institution. They are a product in which to take genuine pride. They have helped to make agriculture what it is, and they look forward to increasing usefulness. For they are builders of vision, the men who can!

We glory in the man who can;
  We glory in his might and mastery.
We glory that within the sullen clod
  His eyes have read the secrets of our God;
That his own hands have grappled with the key
  For fellowmen to set those secrets free.
We glory of his deeds to tell;
  And it is well.

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RESEARCHES ON INSULIN[1]

I. Is Insulin an Unstable Sulphur Compound?

In the early autumn of 1924 we were invited by Professor A. A. Noyes, director of the Gates Chem-

[1] From the Gates Chemical Laboratory, California Institute of Technology, Pasadena, California. Carried out under a grant from the Carnegie Foundation.

ical Laboratory of the California Institute of Technology, Pasadena, California, to investigate the chemical and other properties of insulin in his laboratory under a grant from the Carnegie Foundation. Commercial insulin as prepared by the Lilly Research Laboratories of Eli Lilly and Company, Indianapolis, Indiana, has served as the material for our investigation. Two forms of commercial insulin have been used by us; one a dry powder evaluated at approximately 8 rabbit units per milligram; the second a highly concentrated aqueous solution (2.44 per cent. solids) containing approximately 300 rabbit units per cubic centimeter, and with 120 milligrams of hydrochloric acid per 100 cubic centimeters.

The usual methods of fractioning and purifying bodies of protein or proteose nature have been of no service in purifying this commercial insulin, which has already been submitted to four or five isoelectric precipitations. Salting out with ammonium sulphate or sodium chloride, precipitation with tannic acid in the presence of electrolytes or precipitation with any one of a long list of metallic compounds, with phosphotungstic, phosphomolybdic or picrolonic acid, to name only a few of the many reagents that have been employed, throws down practically all the constituents of the commercial insulin and leaves only an insignificant residue of inactive material, consisting almost entirely of inorganic matter. And yet it is easily demonstrated that the above commercial insulin, even the one containing 12 rabbit units to the milligram, is a mixture of many different compounds. The details of our procedures will be found in a recent number of the *Journal of Pharmacology and Experimental Therapeutics,* 1925, XXV, No. 6, p. 423.

Neglecting inorganic constituents, we have separated from this iletin crystalline amino acids, protein-like fractions of varying sulphur content and low phosphorus content, and such as have a medium or relatively low sulphur content and a high phosphorus content. All these fractions have either no or only relatively little insulin-like action and all of them, no doubt, are capable of further differentiation. The insulin becomes concentrated in one particular fraction (fraction IV). The active insulin can be almost completely removed from all the others. These separations have been effected by the use of simple and non-injurious methods. In the course of the purification the insulin rabbit unitage was raised from 8 and 12 to more than 40. We regard our purified preparations (fraction IV) with the high unitage only as excellent material for further fractionation, and additional data on this point will appear later. We possess many data in regard to several reactions of the active preparations (as the ninhydrin reaction, for example) which we prefer to present, after more study, in a subsequent paper for the reason that some uncertainty always attaches to such data as long as the chemical individuality of the principle in question has not definitely been established with certainty. We are, however, making an exception in giving thus early our findings in respect to the highly unstable sulphur of our active preparations and its relation to the hormone, insulin, present. We have found that when an "insulin" of relatively high unitage is boiled for a short time with N/10 Na_2CO_3, the resulting physiological inactivation is always associated with an alteration in the linkage of a part if not all of the sulphur that properly belongs to the hormone. *After such treatment with an alkali a new property appears in the altered insulin in that it shows extraordinary sensitivity to very dilute acids which now liberate hydrogen sulphide from it.* Previous to this alkaline treatment these same acids applied in greater concentration and with heat fail to evolve even a trace of hydrogen sulphide from insulin. We have lately observed that boiling an insulin preparation with very much weaker alkali than N/10 Na_2CO_3 still produces the above described alteration in the linkage of its sulphur.

While crude insulin always liberates ammonia on being boiled with a dilute solution of sodium carbonate, in consequence of the destruction of certain amino acids still present in it, our purified preparations of relatively high unitage evolve no ammonia when similarly treated. We have also found that our insulin preparations of a unitage 40,[2] are more sensitive to boiling with weak acids (N/10 to N/15 H_2SO_4) than was supposed by previous investigators who worked with cruder products. We have very recently observed that neither ammonia nor CO_2 is removed from the insulin by such treatment, and at the moment we are endeavoring to learn just what changes in insulin fractions of even higher unitage are associated with its inactivation at the lowest hydrogen-ion concentration at which the inactivation can be effected. Phosphorus is not a constituent of insulin, as has been maintained by Ganassini and Gerbino, who have gone so far as to assert that the quantity of phosphorus in insulin prepared in different ways was always strictly proportional to the degree of physiological activity.

It was found that our inert fractions contain very little of the labile sulphur, referred to above, *and that in all fractions the content of labile sulphur, more especially what we have called the "sodium carbonate*

[2] Our unit is that fraction of a milligram of insulin per kilogram of rabbit which will reduce the blood sugar to the convulsive level or produce a convulsion.

sulphur," appears to be directly proportional to the degree of hypoglycemic activity. In other words, the higher the amount of sodium carbonate sulphur present in a given preparation the greater is its potency. In our paper above referred to will be found a table of chemical analyses and biological measurements in proof of our statement that the hypoglycemic activity of insulin goes hand in hand with the amount of easily split-off sulphur. Another point worthy of notice is that the total sulphur of an insulin preparation also rises with increasing purification.

It has been known for some time that insulin is readily inactivated by alkali and that even boiling for ten to fifteen minutes with so weak an alkali as N/10 Na_2CO_3 suffices to deprive an insulin preparation entirely of its sugar-lowering property. But it has not hitherto been shown that an alteration in the affinities of the element sulphur occurs coincidentally with this inactivation. Is there a causal connection between the chemical and biological events? The results of our work lead us to believe that this unstable sulphur is an integral part of the insulin molecule and that the alteration in its condition consequent upon heating with sodium carbonate bears to the destruction of the physiological activity of the hormone the relation of cause to effect.

It is not our purpose at this time to discuss the mode of action of insulin, but we do, however, wish to point out that if the labile sulphur is a pivotal element of insulin, then we possess in it a sulphur compound of high specificity, and one that plays a paramount rôle in the normal metabolic changes which the carbohydrates undergo during their utilization in the animal economy. In this connection, too, the question suggests itself as to what extent, if any, the islets of Langerhans are dependent upon the presence in our food of a special labile sulphur compound, a precursor indispensable for the elaboration of the hormone, in the absence of an adequate supply of which pathological alterations in the cells of the islets of Langerhans would take place. Should a connection of this nature be ultimately established, there would come to light an important and hitherto unrecognized etiological factor in the causation of diabetes mellitus.

Up to the present it was not possible to give an explanation of the mechanism of the physiological inactivation of insulin by weak alkalis. Our findings seem to us to correlate for the first time certain chemical properties of insulin, more especially the hitherto unsuspected extreme lability of its sulphur, with its biological activity, and we hope that our observations may serve as the basis of a method for the chemical assay of the hormone—a method of assay which is urgently needed as an adjuvant, if not as a substitute for the present costly, time-consuming and unsatisfactory rabbit method. The action of very dilute acids at various temperatures upon highly purified preparations of insulin will also lead to the discovery, we hope, of chemical methods for evaluation.

It is now only a matter of time, we believe, when this unstable hormone must yield to the investigator the secrets of its composition and the rationale of its operations within the body. A host of investigators have already made many significant and valuable contributions in reference to the influence of insulin upon the various stages of carbohydrate metabolism, but an explanation of the biochemical mechanism involved in the action of the hormone (at strategic points and moments, so to speak) must wait upon the more definite information along chemical lines such as that referred to above.

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EXPEDITION OF THE CALIFORNIA ACADEMY OF SCIENCES TO THE REVILLAGIGEDO ISLANDS

As already announced in SCIENCE (issue of April 3, 1925), the California Academy of Sciences recently sent an expedition to the Revillagigedo Islands for the purpose of studying their fauna, flora and geology. The Secretary of the Navy detailed the U. S. S. *Ortolan* for the purpose, and the expedition sailed on April 15 from Mare Island Navy Yard.

On the way south the *Ortolan* touched at San Diego to receive on board three Mexican biologists, whom the California Academy of Sciences had invited to be its guests on the cruise. They are Professor Francisco Contreras, director of the National Museum of Mexico, Dr. Octavio Solis, director of the Botanical Garden at Chapultepec, and Professor José Maria Gallegos, chief of botanical explorations, National Museum of Mexico.

From San Diego the expedition proceeded to Guadalupe Island, which lies about 180 miles to the southward, thence to Alijos Rocks, about 200 miles further south. Large and valuable collections were made at each of these stations.

From Alijos Rocks the vessel proceeded direct to Clarion, the most westerly of the Revillagigedo group, where several days were spent making collections. The other islands of the group—Roca Partida, Socorro and San Benedicto—were then visited in turn, and as