Cape Town for eighteen months; on account of the military situation, its effective eradication was neglected, and now the disease has roused into active form. It is this risk which San Francisco has been running, and this risk no community has the right to assume.

THE DESTRUCTION OF SEA LIONS IN CALIFORNIA.

PROFESSOR WOODWARD'S wholesome address on the necessity of verifying theories by the observation of facts finds an excellent illustration in the sea lion question in California. These animals, which have long been prized by lovers of nature as one of the great attractions of the coast, have fallen into disrepute among the fishermen because their presence was supposed to account for the deterioration of certain fishing grounds. So confident was the belief in their fish-devouring habits that their destruction—or at least a great reduction of their numbers—was advocated and in part accomplished by the State Commission of Fisheries. But it now appears that this belief was without substantial foundation. The appeal to fact has been made by the critical examination of the stomachs of slaughtered sea lions, and it has been found by Professor Dyche that the twenty-five animals examined had eaten only squids and other cephalopods, eschewing fish altogether. The case is suggestive of the old philosophical puzzle: Why is it that a live fish adds nothing to the weight of a bucket of water? and would be amusing but for the sad fact that the unfounded theory has already led to the killing of many of these graceful creatures.

The investigation of food-habits by means of stomach examination is of far-reaching importance. Dr. Merriam, whose letter on sea lions we print on another page, is engaged, through the Biological Survey, in the most elaborate study of animal foods ever made. For many years the stomachs of wild birds and mammals have been systematically collected and laboriously studied, to the end that the favorite and the occasional foods of each species in each season of the year, and in each part of the country, may become known. As each group is worked up the facts are published by the Department of Agriculture, and farmers and legislators are thus informed what species may properly be regarded as friendly, and what as hostile, to the interests of the people. In many instances it has been found that popular impressions, almost necessarily founded on a comparatively small number of facts, are altogether erroneous, so that war has been waged on our friends and protection given our enemies.

*ON THE VITAL ACTIVITY OF THE ENZYMES.**

IN spite of the vast amount of work that has been done on the soluble ferments, since the discovery of diastase by Kirchoff, in 1814, the exact chemical nature of these substances is, perhaps, even more of an enigma to-day than the nature of albumen itself. Indeed, beyond the fact that the enzymes, or at least the greater number of them, are albuminous, that they probably belong to the group of nucleo-proteids and that they contain phosphorus, and probably iron, in addition to carbon, hydrogen, oxygen and nitrogen, we know but little more concerning their exact chemical composition than was known to Payen and

* In slightly different form this paper was read before the Cincinnati Section of the American Chemical Society, December 15, 1900.

Many of the biological memoirs referred to in the following were inaccessible to the writer in the original. He, therefore, desires to acknowledge his indebtedness to the following authorities: 'The Soluble Ferments and Fermentation,' Green; 'Die Fermente und Ihre Wirkungen,' Oppenheimer; 'The Cell in Development and Inheritance,' Wilson; 'Plant Physiology,' Sachs; 'Plant Physiology,' Pfeffer; Hueppe's 'Principles of Bacteriology,' Jordan.

Persoz in 1833, or to Bussy, when in 1840 he wrote that up to that time it had not been possible for him to obtain myrosin in crystalline condition. Apart from this uncertainty respecting their chemical composition, however, there has been a growing conviction in the minds of many most familiar with the peculiar and remarkable properties of these substances, that in the soluble ferments we have to deal with certain subtle and peculiar activities similar to those manifested by the living organism itself. The idea that the enzymes retain at least some vestiges of the original activity of the cell or organ of which they once formed a part is one that has appeared again and again in the scientific literature of the last twenty years with a curious persistency and under almost as many different guises as the proteid molecule itself is supposed to assume. According to Loew,* who was probably the first to advance any ideas of this kind, the enzymes are to be regarded as *active* or *labile* proteids or peptones, the activity of which is probably traceable to the presence of amido and aldehyde groups in the molecule, and whose instability is in some way connected with various molecular rearrangements involving these groups. He has also pointed out that many of the so-called protoplasmic poisons are just such substances as are known to readily attack amido and aldehyde groups in organic molecules, and it was in this connection that Loew first called attention to the silver reduction test as a means of distinguishing between active and inactive ferments and dead and living protoplasm. According to Loew† the conversion of the albumin of living into that of dead protoplasm presents a remarkable analogy to the transformation of an unstable substance into its stable modification. Such a transformation, for example, as is met with in the change of the yellow iodide of mercury into the more permanent red variety of this compound.

* Pflüger's Archiv., 27 (1882), 203, and 36 (1885), 170.

† Pflüg. A., 65, 249, 1897.

In the same way Medwedew,* like Loew, has found it necessary to assume that certain of the enzymes at least possess a residuum, as it were, of the vital forces of the living cell; and finally Armand Gautier† has gone even further in his assumptions and has taken the extreme view that the enzymes are to be regarded as *dissolved cells*, and that in addition to their other remarkable properties, they possess in common with other cells the power of assimilation and reproduction. Remarkable and suggestive as these ideas certainly are, they do not seem to have met with anything like general acceptance at the hands of biologists; indeed, in certain quarters, at least, they have encountered a very vigorous and decided opposition, and by some have been pronounced as far too vague to constitute even a satisfactory working hypothesis.‡ Apart from the fairness and justice of this criticism, there can be no doubt that, in his earlier work upon this subject, at least, Loew was inclined to lay too much stress on the silver reduction test as the basis of a sharp and accurate distinction between *active* (living) and *inactive* (dead) proteid; and while the terms *splinters of protoplasm* and *dissolved cells* may appeal very strongly to the poetical side of our nature, it cannot be denied that they are far too hazy to express with any sharpness of definition a scientific truth.

On the other hand, it would seem to the layman, particularly if he happen to be a chemist, that the whole trend of modern biology, until very recently at least, has been toward form rather than substance, and that all of the efforts of the biologist to

* Pflüg. A. 65, 249, 1897.

† See Effront, 'Les Diastases.'

‡ See Pfeffer's 'Plant Physiology,' 67, 69, 1900.

account for vital phenomena have been directed to the vital mechanism to the exclusion of the material substratum.

Indeed, it is not an uncommon thing to see the argument advanced that on account of their instability we can never hope to learn very much concerning the chemistry of those substances entering immediately into the composition of the living cell, for the reason that any attempt at their isolation from the cell contents at once results in their decomposition or permanent alteration. And yet the fact remains that even now at least fifty apparently distinct and different substances are known apart from, and independent of, the cell, which, in addition to some peculiar and characteristic property, such as the power to convert starch into sugar or split a fat into glycerin and a fatty acid, possess many of the more general properties and activities of the cell itself. These substances are the soluble ferments. In two very recent communications on the subject Bokorny* has given us some additional evidence of the sensitiveness of the enzymes and some additional reasons for believing in the inherent similarity between these substances and protoplasm. According to Bokorny, the sensitiveness of the ferments and their general similarity to protoplasm are to be observed in their conduct towards heat, light and the protoplasmic poisons. He therefore reaches the conclusion that the enzymes are substances similar to protoplasmic albumen, and that in all probability the two are only to be distinguished by the fact that the enzymes are wanting in organization. As the result of some recent work on certain aspects of enzyme action, the writer has been brought to see the necessity of these or similar conclusions from a somewhat independent standpoint; and, aside from their extreme instability and their delicate sensitiveness to their physical environment and to chemical reagents, the conclusion that the enzymes are active, in the sense of retaining certain of the vital activities of the living cell, would seem to derive considerable support from the following considerations:

First, their widespread and universal occurrence in all living things.

Secondly, their importance and necessity in metabolism.

Thirdly, their mode of origin.

Finally, in what follows it will be pointed out that the ferments exhibit a remarkably close analogy to the living non-nucleated fragments of the cell.

Since the discovery of diastase, in 1814, a large number of enzymes have been recognized, and what is of still greater interest and physiological significance, a large number of them, such as diastase, lipase, trypsin, etc., etc., have been found in both the vegetable and the animal organism, and, for that matter, in nearly every living cell. By means of diastase, starch is rendered available as a food-stuff both to the animal and to the plant. Trypsin occurs not only in the digestive fluids of the intestines, but is also found in the pineapple and the leaves and sap of the *Carica papaya*. The fat-splitting enzyme has been found not only in the pancreatic secretion, but also in the blood and liver and in nearly every organ and tissue of the hog. Its presence also has been proved in many seeds and seedlings. Myrosin, the mustard ferment, is found not only in the many species and varieties of Cruciferæ, but in many other natural orders of plants as well. Emulsin is another enzyme of the widest distribution in the vegetable kingdom. It has been aptly said, therefore, concerning the occurrence of the enzymes, that 'wherever life exists there also occurs the enzyme.' The one is the inseparable companion of the other. It is in connection with growth

* Chem. Ztg., 24, 1113–1114, Dec. 19, 1900; Chem. Ztg., 25, 1136–1138, Dec. 26, 1900.

and metabolism that the importance of the soluble ferments to the vital economy is seen to the greatest advantage. According to Thompson,* "The power of growth, of adding to itself substance of the same nature as itself, is the real mystery of living matter." So far as is known at present, it is mainly with growth that the enzymes are concerned. As a general thing they effect those changes which have to do with nutrition, *i. e.*, with the digestion and assimilation of food on the part of the organism. As a rule the enzymes bring about hydrolytic cleavages, the net result of which is to transform insoluble and non-absorbable reserve or food materials into absorbable and assimilable form. The transformation of starch into sugar, the change of inulin into levulose and that of cellulose into glucose, the hydrolysis of fats and the conversion of albumen into peptone, are all important and interesting examples of enzyme action. That the enzymes can also effect certain polymerizations and syntheses seems scarcely to admit any longer of a reasonable doubt; indeed, it seems not improbable, in the light of our present knowledge, that many changes hitherto looked upon as resulting from the vital activity of the living cell itself may in reality be accomplished through the instrumentality of a ferment.† Indeed it has been found that the soluble ferments stand in the closest possible relation to the vital activities of the animal and the plant. For example, Maquene ‡ has recently pointed out that the predominating, if not the only, rôle in the conservation and development of seeds must be attributed to the enzymes, and that the causes which retard the alteration and activity of the enzymes tend to maintain the germinating powers of seeds, and that, when preserved under conditions favorable to the enzymes remaining inactive, seeds may be kept indefinitely.

* 'The Study of Animal Life,' J. A. Thompson, p. 138.

† See the work of Croft Hill 'Reversible Zymohydrolysis.'—*Jour. Chem. Soc.*, London (1898), Trans., 634. Also, the work of Kastle and Loevenhart on the Synthesis of etheyl butyrate by lipase.—*Am. Chem. Jour.*, XXIV., 491–525.

‡ Ann. Agron., 1900, 26, 321–332.

In this connection Sachs* long ago pointed out that the so-called dormant periods of seeds and buds are probably intervals during which the necessary ferments are being produced in the cell. The vital relation of the enzyme to the living cell is also indicated by the fact that the ferment is often produced by the cell to meet some new necessity arising from a change in external conditions or environment. For example, it has been found that the molds produce no diastatic or proteolytic enzymes so long as they are freely supplied with sugar. When cultivated on an albuminous medium, however, they speedily develop a proteolytic enzyme and on starch they soon produce diastase, and in the same connection Bernard has observed that the larva of one of the common flies, *Musca lucilia*, contains a large amount of glycogen, but no diastase. As soon as the larva passes into the chrysalis stage, however, where the glycogen is required, a diastatic ferment at once makes its appearance.

Apart from the production of several of the enzymes from their corresponding zymogens by the action of dilute acids, no enzyme has ever been produced outside of the living cell. In this connection it will be recalled that the zymogens are the mother substances of the ferments and that they in turn have never been produced outside of the living cell. In the light of these facts, the mode of origin of the ferments becomes a matter of considerable interest and importance. It has been proved that just as the nucleus and cytoplasm both participate in the formation of new cells by cell-division, so also both participate in the

* Sach's 'Plant Physiology,' 1887, p. 352.

formation of the zymogen granules, and that these, in turn, ultimately give rise to the soluble ferments. In this connection, it might be well to recall the interesting histological investigations of Heidenhain on the pancreas of the dog during the different phases of nutrition. In the case of a dog that had been fasting for a little over one day, each cell of this gland was seen to consist of two zones. The inner zone, abutting on the lumen of the alveolus, was observed to be much the larger of the two and to be thickly studded with fine granules, while the outer one, towards the basement membrane, was narrow and its substance clear and homogeneous. The nucleus of the cell was observed to be considerably shrunken and corrugated and to lie at the border of the two zones. In a pancreas of another dog, that had been killed during full intestinal digestion, the same two zones were visible. The inner granular zone, however, was much contracted and the granules much less numerous, whereas the outer hyaline zone was much wider. The cell, as a whole, had become smaller, the nucleus had regained its spherical shape and was situated near the center of the cell. These changes in the cells were observed to repeat themselves during the several phases of digestion. In the same manner other observers have been able to demonstrate a close connection between the degree of granularity of the cell and the amount of enzyme secreted. In studying the secretion of diastase by the scutellar epithelium of germinating barley, Brown and Morris were able to determine that when the secretion of diastase had ceased the marked granularity of the cells had also disappeared, and, what was even more remarkable, the nucleus of the cell had disappeared also. It would seem, therefore, that for each enzyme there exists in the gland cell a distinct antecedent substance or zymogen, ready to be transformed into the ferment the moment the latter is required. That these zymogens are not enzymes has been proved by Langley, for pepsin at least, in the most masterly and convincing manner; and the same thing has been shown for other zymogens by other equally competent observers.

The most important histological studies on the formation of the zymogens have been made by Macallum. By employing nuclear stains he was able to make out that during the formation of the zymogen a part of the chromatin of the nucleus was extruded into the cytoplasm of the cell in the form of a substance which he calls prozymogen. On coming into the cytoplasm it unites with some component thereof, as the result of which combination the granules of zymogen are produced. These granules were observed to gradually increase in size, apparently at the expense of some substance in the cytoplasmic portion of the cell. It will be observed that Macallum's view of the formation of the zymogen granules enables us to understand the shrinking and disintegration of the nucleus during secretion. It should be borne in mind, however, that in the formation of the mother substance of the ferment both nucleus and cytoplasm supply their quota.

This view of the formation of the zymogens strongly supports the conclusion that the enzymes retain a part, at least, of the original activity of the living protoplasm. In the formation of a new cell or an individual, the cell nucleus and the cytoplasm, of either the same or different cells, are involved. We have just seen, however, that in the production of the zymogen granules both the nucleus and cytoplasm participate. If, therefore, we look upon the cell nucleus as the formative and directive force in the one case, it would seem logical to so regard it in the other, the only difference being, that while upon the one hand its energies go to the formation of a new cell, on the other, they are consumed in the synthesis of an exceedingly active compound. So that scrutinize the matter as carefully as we may, we are able to see no break or discontinuity anywhere between protoplasmic activity on the one hand and the activity of the enzyme upon the other, and, originating as they do, it would be very strange indeed if the enzymes were found to be inactive substances. In this connection Langley's view on the relation of pepsin to the gland cells is highly suggestive. He says, I conceive the matter thus : "The protoplasm of the gland cells does not at one swoop form zymogen as it occurs immediately previous to its conversion into pepsin, but forms certain intermediate bodies in which the zymogen radicles become more and more isolated. Since the zymogen contains the radicle of the ferment, the ferment will be obtained with greater difficulty from the imperfectly elaborated zymogen, *i. e.*, as we ascend from the final meso state to protoplasm, the ferment will be split off less and less readily. The last traces of the ferment, then, which are obtained by repeated extractions, I take it, arise from substances which are on the way to be converted into zymogen.''* From such clear and beautiful reasoning it is but a short and logical step to the modern view of Reynolds Green,† who sees in the power to produce fermentation a fundamental inherent property of protoplasm; and who sees in the secretion of a particular enzyme 'a mark of differentiation within the living substance, just as in the slow movements of amœboid protoplasm we recognize something which in the higher and more differentiated organism appears as the contraction of muscular fiber.'

The general conduct of the enzymes is such, therefore, that if, in addition to their other properties, we could invest them with morphological characteristics and with the power of growth and reproduction, even the most conservative would, I take it, be inclined to place the soluble ferments in the category of living things. If they possess morphological characteristics, however, these are beyond the reach of the highest magnifying powers in our possession to-day; and while the enzymes exhibit certain recuperative tendencies,* they have never been made apart from the zymogen granules or the living cell, and while in perfectly dry condition they are fairly stable under ordinary conditions, their solutions speedily deteriorate, and only in a very few instances has there been observed any spontaneous

* 'The Soluble Ferments and Fermentation,' Green, p. 384.

† 'The Soluble Ferments and Fermentation,' Green, p. 371.

* The tendency on the part of the enzymes to regain their activity after they have once lost it, for any cause, is very suggestive in the light of these considerations. Bussy in his investigation of myrosin long ago pointed out that after the activity of this ferment had been destroyed by small amounts of ether or weak acids it regained the same by remaining in contact with water for 24 to 48 hours.—*Liebig's Ann.*, 34 (1840), 227.

In like manner Bokorny has found that a 0.01-per-cent. solution of formaldehyd renders malt diastase inactive for 24 hours without destroying the enzyme altogether.—*Chem. Ztg.*, 24, 1113–1114, 19/12, 1900.

Quite recently Hanriot has observed that serum lipase is rendered inactive by small amounts of free acid. After neutralization, however, the ferment regains its activity. He concludes, therefore. that the acids first combine with the enzyme to produce substances no longer capable of hydrolyzing fats, and that upon neutralization these compounds are decomposed and the ferment regenerated.—*C. R.*, 132, 146–149.

In this connection it is further interesting to note that by treatment with caustic potash Scholl was able to partially restore to blood serum the antiseptic powers which it had lost as the result of heating. At present the germicidal property of serum is believed to be zymotic. Hueppe's 'Principles of Bacteriology.' —*Jordan*, p. 86.

It is further interesting to note in this connection also that during life protoplasm shows a faintly alkaline reaction. Hammarstan's 'Physiol. Chem.' Also 'Lehrbuch der Physiol. Chem.' Neumeister.

increase in the activity of such solutions. Outside of the living cell, therefore, these substances do not seem to be able to grow or to reproduce.

In this connection it has occurred to the writer that the enzymes sustain about the same relation to the living cell as do the non-nucleated cell fragments. It has been proved as the result of numerous observations that, if a unicellular organism be subdivided by mechanical means, each fragment thereof will still manifest vital activity. To the biologist, all these fragments are alive and yet their ultimate fate may be very different. Those that are nucleated have been found to have the power of completely repairing their injuries and ultimately develop into complete cells again and reproduce by cell-division. On the other hand, while the non-nucleated fragments frequently retain their vitality for days, for example, non-nucleated fragments of the amœba have been known to live for fourteen days, they ultimately perish. In some cases the non-nucleated fragments may even heal their wounds and engulf food particles; the latter, however, remain undigested and the fragment ultimately dies without reproduction. In this connection Verworn has pointed out that a nuclear fragment entirely devoid of cytoplasm can no more regenerate the entire cell than can the non-nucleated cytoplasm alone. He is, therefore, of the opinion that the formative energy of the cell cannot derive from either the nucleus or cytoplasm alone, but from both. To him the cell itself, and not merely the nucleus, is the vital unit, the activities of which are contributed to, in part at least, by both the nucleus and the cytoplasm, and that numerous exchanges of material actually go on between them is supported by the most trustworthy histological evidence of the present day. We see thus that in the formation of a new cell, whether by the natural repair of a cell fragment or by the usual process of reproduction, both the cell nucleus and the cytoplasm are concerned. It has also been shown, however, that both the nucleus and the cytoplasm are concerned in the production of the zymogens and ultimately of the ferments. It would seem, therefore, that the enzyme and non-nucleated cell fragments stand in essentially the same relation to the living cell. Both originate in much the same manner, both lack the power of growth and reproduction, and yet both exhibit certain vital activities. Would it be far from the truth, therefore, to look upon the enzyme as the chemical basis of life?

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THE PROGRESS MADE IN ENGINEERING DURING THE NINETEENTH CENTURY. *

THE progress made in engineering during the nineteenth century, on the one hand, furnishes in itself a reminder of its ultimate dependence upon mathematics and the sciences, and, on the other hand, it attests the fact that its great and growing inspiration has been the welfare of all the civilized world. A hundred years ago but little of engineering worth or prominence was in existence; so little, comparatively, that a glance at contrasting conditions then and now will reveal striking differences.

A century ago traveling in its highest development was limited on land to the horse and coach, covering perhaps a wearisome fifty miles in a day; now a day's travel is eight hundred miles. Then, a trip from New York City to Philadelphia consumed as much time and occasioned more fatigue than one from New York to St. Louis now; or a journey then from New York to St. Louis consumed the greater

* Read before the Academy of Science of St. Louis on February 18, 1901.