EDITORIAL

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"THE GOOD THAT MEN DO LIVES AFTER THEM."

THAT a scientist is not without honor, save in his own time and in his own country, is not always applicable, but it certainly is in the case of Dr. Ignaz Philipp Semmelweis, whose name and work were almost forgotten until his memory was revivified by Dr. Duka, a countryman, when he brought the name of Semmelweis to the attention of Lister at a banquet given in the latter's honor, at Pesth in 1883. The history of this unfortunate physician excited the liveliest interest of Lister, who recognized in him a true forerunner in rational antiseptic treatment, though he had evidently known little, if anything, of his success and nothing of his trials and unfortunate ending of this useful life. Since then the name of Semmelweis has been placed in "the hall of fame," and surgery of the present world war has given credit to the treatment employed by him a half century or more ago.

In some respects the lives of Lister and Semmelweis are similar, in others radically different, so also the work of the two men; both utilized the deductions of original investigations and fought the unseen enemies of disease with related weapons; Lister was supported by the scientific discoveries of Pasteur, which Semmelweis did not have for his guidance. The latter died in 1865, about the time that Lister was beginning his antiseptic studies. Briefly, soon after entering the practice of medicine, Semmelweis received the appointment to the Vienna Maternity Hospital, in 1846. Puerperal fever was then claiming a large percentage of the mothers; this observant physician not only gave his attention to cleanliness but more particularly to those attending upon the confined; many of the attendants often waited upon their patients without washing their hands. Semmelweis issued orders of cleanliness and asepsis, using chlorinated lime solution for the latter purpose. The result was that in 1848, he could report the loss by death in his department as less than one in a hundred. The jealousy, more particularly of his chief, Dr. Johann Klein, drove him from Vienna in 1849, when he came to Pesth in a like capacity and where, as far as his work is concerned, he was also successful. But here comes the difference in the character of Lister and Semmelweis; the former also had opposition and jealous enemies, but he was strong enough to ignore them, and not suffer from discouragement because others who did not understand his methods and would not become converts, made adverse reports and in jealousy antagonized him; Semmelweis went into a rage or fit of despondency if he learned of an epidemic of puerperal fever, or when others dragged down his

work to the plane of personalities. Lister lived to receive universal recognition of his work, hear and read the praises of his former doubters and enemies; unfortunate Semmelweis was bereft of reason some time before he passed away from a world that failed to appreciate his services—but succeeding generations gave him recognition.

The statement made at the beginning does not apply as well to the former as to the latter, however; though Lister was the son of an illustrious father and afterward son-in-law of a great surgeon, he was constantly hampered and himself, as well as his methods, the subjects of criticism until the evidence of the value of his work was so overwhelming that even his strongest antagonists were convicted and convinced, but nevertheless it remains a fact that England, his country, and more particularly London, was late in acknowledging Lister and his great work, and then only after the International Congress of Medical Science, held in Amsterdam in 1879, accorded him the most remarkable and unprecedented ovation ever given a medical man. When the chairman was able to secure quiet in the hall of the convention, he said: "Professor Lister, it is not only our admiration which we offer to you; it is our gratitude, and that of the nations to which we belong."

Lister always gave due credit to Pasteur's discoveries that enabled him to accomplish his great work; the climax of this acknowledgment came at Pasteur's Jubilee in 1892, on which memorable occasion Lister represented Great Britain and Ireland. Lister was embarrassed by the reception given him, when Pasteur took him by the hand, led him to the center of the platform and there embraced him; the spectators applauded and relieved their overfull hearts with sobs and tears.

To an extent this controverts the introductory of this editorial; admittedly so, but Lister was a remarkable man in every way and exceptions can be found even for rules. A reference to one of many attacks upon him will not only show that he had to contend with enemies envious of his success, but also his power in argument and restraint over his feelings. This attack was made in the *British Medical Journal* during the very year that the world did him homage at Amsterdam. The article was contributed by a fellow-professor who began his charge by disclaiming any feeling of envy or uncharitableness and then launched out into an attack of considerable bitterness, disparaging Lister's method and belittling his ability as a surgeon. The latter charge Lister dismissed with the statement that Mr. Spence had never honored him by witnessing his work as a surgeon, and regarding the other, he said, that if as a surgeon Mr. Spence was so superior to him, the fact that his (Lister's) successful results far exceeded those of Mr. Spence, could only prove more strongly the value of antiseptic surgery.

It is not only necessary for a person to know, but the important thing is the application of the knowledge, and the communication of it to others for larger

service. Herein both men were great, though Lister surpassed Semmelweis, but he had many advantages.

The thought presented is prompted by the nearness of commencement exercises in colleges of pharmacy. Students should be impressed with this important factor in their life of service; that the matter of passing an examination, while it is demanded, has comparatively little value unless the knowledge obtained is retained and made widely and continuously applicable.

There were many surgeons in the time of Semmelweis who knew of chlorine, but it was his wise application of the knowledge of its properties in conjunction with other very essential means employed by him that contributed service to humanity and saved the lives of thousands. Scheele discovered chlorine in 1774; Labarraque, in 1822, prepared the solution named after him. In *Eberle's Practice* we read in the discussion of disinfectants: "* * * * At present (1826), however, chlorine and the chlorides of lime and soda are regarded as decidedly the best disinfecting agents we possess. M. Labarraque's *disinfecting soda liquid* is a compound of soda and chlorine, and its efficacy in destroying infectious matter, has been conclusively demonstrated. * * * it is employed in surgical practice for destroying the fetor of malignant ulcers." So here in the United States, twenty years before Semmelweis came to the Vienna Maternity, the value of the preparation he employed was known and in more or less general use, but it was his observance of the cleanliness of the operators that largely made him successful, and very likely his method of practice—more than knowledge is necessary.

So also "carbolic acid" was discovered by Runge in 1834, and it was very soon thereafter employed for removing the offensive odors from drains and animal matter in the state of putrefaction, and was used by surgeons in their practice, but it remained for Lister to make successful application in surgery, aided by the purer product of Calvert, and more so by the discoveries of Pasteur. His treatise of the rationale of his practice is most interesting and shows how close an observer he was, but this presentation, even in abstract, would become too lengthy; the object of the reference is simply to impress that the ability to make right application of knowledge is equally as important as the acquisition of it, for without that qualification learning has little real value.

A final thought, and that is to show the link of pharmacy in the accomplishments of Semmelweis and Lister. The work of Scheele, Labarraque, Calvert and, more particularly, the discoveries of Pasteur contributed largely to their successful labors—they were needful; there is always an interdependence, and at the appointed time the individual comes forward who is competent to utilize the investigations of others and by the aid of his native or cultivated ability, energy and wisdom brings about the results that make of him a hero. There is no desire to dim the glory of these benefactors of humanity. Pharmacists should keep in

revered memory those in their profession who contributed lives of useful service; very often the names of pharmacists become associated otherwise, though their pharmaceutical experience may have largely influenced their later work. Whether pharmacy has been the stepping-stone to other activities or life-long occupation matters not, their records serve to encourage others to follow their excellent precepts and examples and lift others up to see higher ideals—that is the important thing. The carload of ore in Colorado may represent only the milligramme of radium in Paris, but there is power in the ore, though its potency is tremendously increased in the refined product—unquestionably that which at the last constitutes a so-called waste was essential, in one way or another, to the element.

E. G. E.

THE ASSUMED DESTRUCTION OF TRYPSIN BY PEPSIN AND ACID.

THE recent papers by Dr. J. H. Long and Mary Hull on "The Assumed Destruction of Trypsin by Pepsin and Acid"* are valuable contributions to biological chemistry and present some interesting deductions regarding the proteolytic enzyme trypsin, the important constituent of official pancreatin, and its power to resist destruction. In an editorial comment, the abstracts from these papers are necessarily limited to the more important statements and the conclusions of the authors, but the papers themselves should receive careful study.

The important part played by trypsin, as the active principle of the pancreatic juice, in the functions of digestion and the vital force make it all the more necessary that we should have definite knowledge of its functions, activities and power of resisting destruction and that the medical practitioner as well as the chemist have a clear conception of the conditions under which it performs its distinct function in life and of its sphere of usefulness in medicine. Its peculiar action on proteids, its power to rapidly form amino-acids and the end products of its digestive action have presented numerous problems in physiological chemistry that have claimed the attention of many able investigators.

This field of research investigation presents peculiar difficulties and as these authors state: "It is easy to arrange experiments *in vitro*, in which one group of ferments may appear to be readily destroyed by another, but it does not necessarily follow from these that under the conditions obtained in the body a like result should be expected." "The stability and mutual action of ferments depend on a multiplicity of conditions which are properly balanced in the animal body, but which appear to present enormous difficulties in the duplication *in vitro*."

In previously published contributions, Dr. Long had brought out the fact, which he now again emphasizes, that trypsin may be incubated with considerable quantities of hydrochloric acid without suffering appreciable loss of strength.

The investigations described in the first of these papers cover a series of experiments *in vitro* where a number of varying conditions with reference to strength

* Journal of the American Chemical Society, August 1916, p. 1620, and January 1917, p. 162.

of acid, amount and kind of protein present and resultant hydrogen-ion concentration were considered. It had been observed by several investigators that in some cases rapid destruction of trypsin took place in the presence of acid and pepsin while in others no such destruction was observed. The present authors present evidence that the fate of the trypsin depends on the relative amount and kind of protein present. "All the results secured point in the same direction and to the conclusion that the pancreatic ferment persists through the acid incubation, provided this acid is sufficiently bound by protein to bring the hydrogen-ion concentration down to certain values." "Not only does trypsin appear to resist the action of pepsin and acid under the conditions described, but it seems further likely that it is able to bring about some degree of digestion in acid solution which is more marked with some protein than with others."

The authors point out that the prior work of several investigators "had shown that there was some degree of tryptic activity in solutions of low acid concentration and that Lindberger, in attempting to account for the protein digestion in the acid duodenal tract of the dog, had shown that tryptic digestion may go on very well in the presence of lactic acid or weak acetic acid. At that period the relation of acidity to hydrogen-ion concentration was not known." "Weak lactic acid furnished the proper medium for the purpose." "The commonly accepted view that trypsin is rapidly destroyed by acids and that it can exert its peculiar behavior only in alkaline solutions follows, in part, from the assumed alkaline character of the pancreatic juice which is able to neutralize completely the acid chyme and leave a marked degree of alkalinity. Many recent observations have shown that the alkalinity of the pancreatic juice is often less than formerly considered 'normal.'" The mixed duodenal fluid in dogs is frequently found to be not alkaline at all. It is also possible, as has indeed been frequently suggested, "that for the initial solution and superficial splitting of the protein through trypsin a greater degree of alkalinity is called for than is favorable in the subsequent deep-seated loosening of peptide bonds. If the initial hydrolysis is accomplished through the action of pepsin and acid a nearly neutral medium might furnish the optimum condition for the later cleavage."

In a prior paper, Long and Fenger had shown that the press juice of the pancreas of hogs, sheep and cattle is distinctly acid and constantly so. Recent observations of Dr. Fenger and Mr. Nelson have shown that in the juice of the duct of hogs noted immediately after killing, the reaction is as often acid as alkaline. The authors express their opinion "that there appears to be no physiological necessity for the assumption that trypsin can act *only* in an alkaline medium, or that it is readily destroyed by weak acids of a concentration of physiological importance."

Summarizing the results of their extensive series of laboratory experiments *in vitro* the authors' conclusions are "that trypsin may be incubated with HCl of $P_H = 1.5$ through half an hour or longer without appreciable loss of strength. In the presence of pepsin the tryptic power is rapidly lost. However, if sufficient protein is likewise present, the acid, in combining with it, is unable to destroy in the same degree. When the acid concentration is reduced in this manner to $P_H = 2.6$, or below, tryptic activity persists, even through several hours at the tempera-

ture of the body. This is a practical condition which very commonly obtains in the human stomach. An active tryptic ferment would unquestionably pass with the chyme, in part at least, into the duodenum where the P_H value is quickly reduced to 6.5 or lower, and there be able to produce a proteolytic digestion of some degree."

The second paper deals with experiments on animals. These showed that when trypsin was not given along with the test meal the amount of nitrogen in amino combination liberated from the substrate fibrin is always minute. On the other hand, when trypsin is ingested with the meal containing some meat the tryptic activity in the aspirated liquid was very marked. The experimental data submitted give evidence that under such conditions a good part of the proteolytic power of the administered trypsin persisted after prolonged contact with acid and pepsin. "In all the animals the secretion of pepsin and acid was abundant, and from this point of view the conditions for the persistence of trypsin were not favorable. Yet, in the larger number of experiments, this latter ferment was not destroyed by the other combination where sufficient protein was present to bring the concentration of the free acid down to a certain value. Trypsin seemed to be destroyed or greatly weakened only when the acid was in excess with pepsin."

As a result of these animal experimentations, the authors' final declaration is that "these experiments appear to confirm our earlier conclusions from work done *in vitro* that trypsin, pepsin and hydrochloric acid may exist side by side under conditions which, following the ingestion of trypsin, may exist in the human stomach. It is even possible that some trypsin proteolysis may occur then in that organ when the free acid is very low from protein combination. The destruction or weakening of the trypsin is a function, probably, of the hydrogen-ion concentration."

The deductions of the authors appear to be justified by the results of their experiments and these controvert the accepted theory that has long been held and that has been commonly stated in the text-books, namely, that trypsin exhibits its digestive activity only in neutral or alkaline solutions. Likewise, do they render untenable, in its entirety, the contention that has been so broadly advanced and so energetically maintained by certain chemists, that trypsin is completely destroyed in acid medium by pepsin. Their conclusions have an important bearing upon the practical side of medicine and pharmacy as well as upon the theories of physiological chemistry.

It is stated that "these investigations were made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association." The deductions therefrom cannot be considered as being in harmony with certain views on this subject promulgated by some of the members of the same Council. It is well known how strenuously these members have criticized and opposed the administration of pancreatin along with other enzymes and dilute hydrochloric acid or lactic acid and how persistently that Association has lent its publications to the promulgation of their views. It would seem to be only fair that the readers of the medical and pharmaceutical journals, who have long been accustomed to receive literature setting forth views opposite to those now submitted by Long and Hull, should be made acquainted with this later research. While the importance of correcting fallacious theories

of biologic science is fully appreciated, it would appear that the practical application of these theories in medical practice is of paramount importance.

The use of preparations containing the mixed enzymes has been very extensive in American medical practice and many able physicians have claimed beneficial results therefrom. The problem of the pharmacist is not that of the therapeutic aspect nor that of the biologic chemist. So urgent were the demands of the Council of the A. M. A., so persistent the propaganda emanating from the same source, against such acid mixtures of enzymes "as chemical and therapeutic incompatibles" that the Committee of Revision of the National Formulary gave way to these demands and eliminated from the Revised N. F. the satisfactory formulas that had been adopted for both liquid and powder preparations of such mixed ferments and, hence, we now have no authoritative standard formulas for these extensively prescribed remedies. The proposed formulas, it is likewise to be noted, contained a small amount of hydrochloric acid, which became fixed or combined, and weak lactic acid which is now declared to "furnish a proper medium." These recent investigations would appear to substantiate the claims of the practitioner of medicine rather than those of the theoretical chemist.

The query arising from the contention of this radical wing of the Council is thus stated by Long and Hull: "Will trypsin administered by the mouth persist in the stomach and retain sufficient activity to aid in proteolytic digestion in the duodenum?" Their answer is: "It is evidently true that trypsin when given in relatively large amount and in presence of protein possesses the degree of resisting power necessary."

The nicety of the adjustment of conditions, the exact equilibrium of nature, under which the healthy body performs the functions of life cannot be duplicated in either the entirety or the exactness in the laboratory of the chemist. The ease with which bodies of such stable composition that they resist the strongest reagents and reactions of the laboratory, are broken down by changes produced by living organisms is only another evidence of the superiority of the Infinite and the limitations on human knowledge and discernment. Who can tell what is the potentiality that we denominate as catalysis and by which we attempt to explain the action of these enzymes or what are the limits of enzymic catalytic power?

It is not difficult to understand how, through the human imperfection, the results of experiments may be misleading and the judgment of the investigator perverted. This is all the more an argument why radicalism and hasty actions, which are too often based upon insufficient knowledge and incomplete experimental data, should not be permitted to displace clinical evidence and the practical exhibition of usefulness.

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