SECTION I—*Clinical Medicine: Diseases of Digestion*

The Significance of Chronic Gastritis

By

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GASTRITIS is given a prominent place in the recent studies of the causes of several diseases, and an additional attempt at an appreciation of its actual significance seems permissible. The clinical diagnosis of chronic gastritis falls into that category of things, the affirmation of which places the burden of proof upon the skeptic. Because of repeated citation, the precursory and causal relationship of chronic gastritis to other gastric diseases is coming to be regarded as established, although the facts do not warrant such categorical conclusions. In practice, the clinical diagnosis of chronic gastritis is often inferred in the reverse direction rather than demonstrated objectively. It is insufficient to assume that, because of association, gastritis has been the cause of localized organic changes, and also, because of the suppression of secretory function, that this results from gastritis.

Any search for a common denominator is always fascinating. The discovery of a factor common to several disease entities would be a boon to preventive medicine. Hurst (1) recently said, in concluding a lecture on "Achlorhydria": "I expect that this is the last time there will be a discussion on achlorhydria, for the problem has shifted, and we must in future discuss gastritis, its causation, early diagnosis, treatment and prophylaxis, just as we discuss nephritis rather than albuminuria. It is gastritis which causes achlorhydria, and gastritis, not achlorhydria, which causes Addison's anaemia, sub-acute combined degeneration of the cord and predisposes to carcinoma of the stomach. The prophylaxis of gastritis is the prophylaxis of these diseases."

Gastritis has been demonstrated in surgical material in an almost constant association with gastric cancer and with gastric, duodenal and stomal peptic ulcers. It is also assumed and affirmed that gastritis is the underlying condition of gastric hyperacidity and of gastric anacidity. Gastric hyperacidity may have an associated erythrocythemia; achlorhydria is an almost constant accompaniment of the non-hemorrhagic anemias, and frequently it has as a sequel morning diarrhea, which may be promptly corrected by the administration of hydrochloric acid. These relationships of gastritis to other intrinsic gastric pathology, to extra-gastro-intestinal conditions and to systemic disease give the problem of its possible causal relationship great importance.

The generic term 'gastritis' has been loosely used and the pathological implication of the undefined term is not always clear. Its adjective qualification upon the morphologic, functional, etiologic and clinical attributes is so multiple and varied that the consequent ambiguity shows the general inadequacy of our understanding of the condition. The term is defined, however, in reference to the operative findings associated with cancer and ulcer, by description of an oedematous, reddened mucosa which microscopically has round cell infiltration involving the lymph follicles, and also an increase of the goblet cells. Submucus diapedesis of red cells and mucosal erosions may be present. Although in general discussions it is not often made clear, an atrophic type of gastritis is found in cases without cancer which clinically have shown an achlorhydria, often associated with anemia. It is not apparent that this is or is not a later stage of the follicular type of gastritis. In other discussions, the term is loosely used. It is definitely stated that gastritis denotes, not a superficial catarrhal inflammation from direct irritation, but a disease of the glandular parenchyma caused by circulating toxins. These broad pathological connotations of the term give rise to much confusion. The pathological changes and the clinical picture of disease are not static, and remote antecedents and relations are difficult to determine. The findings of gastritis, upon which the premise of an etiological relationship is based, are late pathological data and generally lack the adequate previous clinical evidence necessary to indicate the existence of the gastritis prior to the various associated diseases.

Due to these considerations, the *clinical diagnosis of gastritis* is receiving renewed and increased interest. The roentgenological study of the mucosa by its "relief" patterns, and the gastroscopic inspection of the mucosal surfaces are the chief methods of direct examination which have been recently developed. Other than these methods, the medical history, which is exceedingly ambiguous, the findings at gastric aspiration, and the thoughtful elimination of other disease form the not too-secure foundation for the clinical diagnosis of chronic gastritis. Although a deficiency of gastric juice is the most important functional finding in gastritis, it is in no sense pathognomonic. Even the diagnosis of acute gastritis depends largely upon

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the positive clinical history of injurious ingestion and of the immediate revolt of the stomach. There is no clinical method of diagnosis which can, with certainty, indicate the extent, degree, or kind of mucosal inflammation by which the actual fundamental pathology may be known prior to direct study of operative or autopsy material. Eusterman (2) says, "personally, I would not like to make a diagnosis of gastritis in one of its various forms without either gastroscopic or roentgenoscopic confirmation and apparently only the hypertrophic forms of gastritis can be recognized by the latter procedure." On the other hand, others find that the clinical diagnosis is easily made by gastric lavage. It is apparent that there is no clinical method by which effectively to follow these associated "diseases" and to demonstrate with finality their pathological association or disassociation during their evolution.

Is *gastritis a causative factor* in gastric ulcer and in what manner could it be an etiological factor in duodenal ulcer? Konjetzny, Stoerk, Puhl, Bohmausson and others believe that gastritis precedes and is to be found in all cases of chronic peptic ulcer, and bring evidence to show that such lesions, existing even in the absence of ulcer-formation may give rise to symptoms typical of ulcer (3). Overgaard (4) finds that "on the basis of reports from numerous authors, it must be accepted as certain that the antrum gastritis with its accompanying acute and chronic changes forms the foundation on which typical ulcer develops." Johnston (5) finds, as previously recorded by Orator, etc., that, of surgically resected stomachs, there are approximately two-thirds exhibiting chronic follicular gastritis and one-third with simple chronic gastritis. "Follicular gastritis" (37) was recorded as associated with duodenal ulcer (18) two and one-half times as frequently as with gastric ulcer (8), not including stomal ulcers (4), and six times as frequently with gastric cancer. In four cases, no localized lesion was present. Simple chronic gastritis (18) was associated with duodenal ulcer (7) one and three-fourths times as frequently as with gastric ulcer (4), not including stomal ulcer (1) and two and one-third times as frequently with gastric cancer. In three cases, no localized lesion was found. No note is made of the pre-operative function of the stomach, that is, of gastric motility and gastric secretion. It may be suggested that impairment of motility and prolonged retention of secretions with the continuous gastric activity involved can well be, in this type of gastritis, the factor which is common to all the cases, even those in which no localized lesion was found. It is probable that the simple chronic gastritis merely is an earlier phase of a gastritis which later becomes chronic and follicular. The predominance of duodenal ulcer over gastric ulcer cannot be reconciled to the broad assertion of causal relationship when the reports consistently record gastritis with it as with gastric ulcer. If the anatomical pathology of gastritis is a causative factor in gastric ulcer, then gastric ulcer and gastritis should have a typical and inclusive association.

To further discuss this problem, a definition of peptic ulcer is necessary. The disease of peptic ulcer is fundamentally an alteration of the function of the gastro-duodenal segment into an unphysiological status which permits the development of and, by continuance, maintains the localized round ulcer lesion which is in fact only one of the abnormalities of the entire disease syndrome. The ulcer lesion is the end result of intralumenal chemical conditions produced by multiple and varied factors which allow, at the site of some injury which otherwise would heal promptly, the progressive localized destructive excavation of the wall of the stomach by necrosis and digestion. Thus is created, according to location, either duodenal ulcer or gastric ulcer. The lesion occurs and continues by reason of interference with the native healing resident in these tissues. Healing is prevented because of the prolonged digestive activity during the abnormally lengthened digestive phase which has become disproportionate to the reduced or absent quiescent phase of gastric function. Healing of the lesion is effected when the prolonged chemical processes are successfully restricted to their normal physiological period and cure of the disease is attained when the normal interdigestive phase of gastric function is restored. The fallacy of the conception that the primary agent or reason for the break in the continuity of the mucosa is also the reason for the continuance and extension of the ulcer lesion has impeded the understanding of other factors and misdirected efforts of both medical and surgical therapy.

With the premises of an acid-pepsin genesis of peptic ulcer, gastritis might be considered to operate by providing the stage-setting of gastric ulcer by reason either of hypersecretion or of the gastroparesis, which usually accompanies, and the resulting abnormal lengthening of the time-factor of active acidity. Gastritis may also be conceived to be the essential injury to the tissue which precedes the excavating processes. These possibilities presume that the gastritis is prodromal, which however, is not proved. There is often an inference that the usual hypochlorhydria of gastric ulcer is an evidence of gastritis, rather than being merely an expression of the hypotonicity of the stomach. Johnson admits the possibility that chronic follicular gastritis may exist without ulceration but is inclined to believe that it may have an etiological relation to the peptic ulcer. Arafa notes a few cases of pyloric gastritis and duodenitis which were operated upon because the symptoms were precisely similar to those of ulcer. On the other hand, Hurst (6) finds that "chronic gastritis is a comparatively common condition with a fairly definite clinical picture and a very characteristic test meal, but in my (Hurst's) experience it is rarely associated with symptoms or signs of acute or chronic gastric or duodenal ulcer."

I can find no significance in the fact that chronic follicular gastritis gives the symptoms and many of the signs of chronic ulcer, as has been emphasized by Fitzgerald (7). Except for the pain of the actual lesion or of its peritoneal extension, the symptoms and signs come from the functional impairment and derangement, and take place because it is the same organ that is impaired rather than that the diseases are necessarily etiologically related. Henning (8) has said "that so-called 'ulcer complaints' are in no way pathognomonic of ulcer." He also finds that gross bleeding occurs without ulcer as frequently as from ulcer and tumors. It has not been my experience to meet with non-ulcer gastric hemorrhage which could be explained on a gastritic basis.

If gastritis supplies the tissue injury from which excavating ulcer evolves, it is strange that duodenal ulcer exists more frequently than gastric ulcer, even

among the advanced cases of ulcer represented by the surgical material studied. That a duodenitis analogous to the gastritis is associated with duodenal ulcer, does not solve the dilemma.

It appears, if we accept the theory of the acid or peptic genesis of ulcer, that functional change extends the time of active secretion and abolishes the interdigestive rest period, which is recuperative and reparative. This is all important. Gastritis may well result from this constant presence of effective gastric juice, but the absence of gastric ulcer in so many instances of gastritis seems to point at least to the necessity of an additional accessory factor for ulcer initiation, otherwise there would be found in the material reported more gastric than duodenal ulcers.

Gastritis of various types has a frequent association with *cancer of the stomach* and that is the best support given for the hypothesis that gastritis is an essential precursor to cancer. Polland and Bloomfield (9) find that anacidity in cancer of the stomach is associated with a chronic gastritis antecedent to the growth and Bloomfield (10) states that "cancer tends to develop in stomachs already the seat of chronic gastritis with anacidity." In support of the hypothesis of an inflammatory basis for cancer, it is also asserted in analogy that chronic mastitis and glossitis precede carcinoma of the breast and tongue respectively, which statement may well be challenged. The characteristic short history of primary gastric cancer must indicate that any preceding gastritis has been asymptomatic, and it is also asserted as a fact, but without demonstrated basis, that gastritis for a long time may be asymptomatic. The reported high percentages of gastritis found with cancer can mean as yet only the coordinate association of the two diseases. Certainly, any logical deductions from established facts could indicate only that the functional disturbances of cancer are more pertinent causes for gastritis rather than is the reverse. Both the acid and anacid varieties of gastritis are prevalent disproportionately to their association with cancer in any causal relationship. Even a long clinical history of dyspepsia cannot alone support the presumption of gastritis, for generally dyspeptic symptoms arise more often from intestinal than from primary gastric conditions. Certainly, in view of the many exceptions, cancer cannot be asserted, on the basis of the rare actually observed sequence, to be a liability of gastritis of any type.

Danger arises in practice not from the certainty or likelihood of any sequence in pathology but from the very great difficulty in the clinical differentiation of the nature of prepyloric pathology as between gastritis, benign ulcer and cancer, and the frequent suggestions in prominent places of radical surgery for these cases should be correctly and frankly based upon the uncertainties of diagnosis rather than upon presumptions of any sequence in pathology. The type of gastritis associated with cancer *per se* or with the several types of cancer has no constancy. Chronic productive, interstitial gastritis with atrophy is more frequent; hypertrophic gastritis is found in some cases of adeno-carcinoma (11). It is said that gastric atrophy occurs with carcinoma of other organs through a deleterious influence on the organism as a whole. However, statistics of achlorhydria fail to show any greater increase in its incidence with age, in association with extra-gastric disease or in otherwise healthy people (12). Ewing (11) states that "the inflammatory reaction frequently meets the invasion of tumor cells. It is a highly significant feature of malignant tumor growth and must be regarded as a defensive process." This direct reaction to tumor growth must not, however, be confused with the wider mucosal inflammation which is denoted by the term 'chronic gastritis.'

In what manner may gastritis be conceived as a change precursory to malignancy of the mucosal cells? Recourse to the time-honored theory of "chronic irritation" as a cause must be used unless the direct effects of inflammation are considered a stimulus which will cause cell division to escape physiological bounds. The idea of chronic irritation may, in argument, be rationalized to indicate any form of foreign physical, chemical or bacterial action, but it has doubtless been used commonly in the sense of mechanical excitation. If the conception is, however, broadened to include any continuing stimulus to increased metabolism in the mucosal cells, it will still fail to sustain an etiological relationship which would support the precursory position of gastritis to cancer. As long as we have no recurring observations of evidence of the transition of ordinary gastritis into cancer, the significance of the gastritis as a cause of cancer is wholly unproven. The assumption that long standing achylia is an indication of gastritis helps little, for the known cases of cancer occurring after years of achylia are so rare that, considering the frequency of both diseases, their coincidence can indicate no pathological relationship.

Erskin (13) has examined the conception of irritation as the cause of cancer and cannot find support for it in known facts. He says that "if the irritation theory is to be considered tenable, the incidence of cancer should conform to three postulates: (1), Cancer should develop most frequently upon irritated areas; (2), Chronic irritation should be followed by the appearance of cancer; (3), Cancer should not appear on unirritated areas."

The assumption that tar acts merely as a chronic irritant, continued application of which causes the tissue to be the subject of malignant change, is brought into doubt by the fact that only those tars which contain carcinogenic hydrocarbons have this capacity. Further, Cook and Dodds (14) demonstrated that these hydrocarbons have also an estrogenic action. This indication that the carcinogenic effect arrives from a specific stimulus characteristic of certain molecular structures, compels the conception that for chronic irritation to be productive of cancer, it must at least develop in the tissues such a specific agent. With relation to skin cancer, Somerford (15) says "the ideal method of preventing cancer in industrial workers should be beyond the control of the workers, and among oil workers it is possible now to supply oil possessed of oil-lubricating properties without any of the carcinogenic constituents."

Macklin (16) in an excellent report of statistical analyses of clinical material gives all but conclusive support to the hereditary nature of cancer. She says: "the medical profession has laid so much stress upon chronic irritation as a factor, that it neglects the evidence of inheritance which lies before it." She, however, undoubtedly believes that an acquired disease may precipitate an hereditary one for she does not wholly dismiss the idea of chronic irritation but states further that "chronic irritation undoubtedly plays a *rôle* in the production of some cancers. In others it is

absent. It speeds up a reaction that is already present, to take place sooner than it would have done without the stimulus of injury." A factor of acceleration is however, not causal. On the experimental side of cancer study, Maude Slye's work is conclusive of the hereditary transmission of cancer in animals in spite of any argument whether it may be by a recessive or a dominant factor. The question of the relationship of an hereditary factor and an acquired inflammation to a precancerous condition is also present in any polyposis of the mucous membrane. It is stated by Ewing (11) that polyposis is a "feature of the late stages of catarrhal inflammation of these tissues." It is more readily conceived how a diffuse inflammation would effect an extensive diffuse polypoid hyperplasia of the affected mucosa than that it would cause a neoplasm of localized origin.

Erskin (13) voices the growing conviction when he states that "whether gastric ulcer frequently becomes cancerous is no longer in dispute, and it is now fairly well established that the incidence of gastric carcinoma is not increased among ulcer patients. It is also a fact that cancer of the duodenum is extremely rare, although duodenal ulcer is more common than gastric ulcer." The conception of the malignant degeneration of ulcer has been fostered by the idea of chronic irritation. Upon the current conceptions of the peptic genesis of ulcer there would seem to be more reason to speak of cancer-ulcer than of ulcer-cancer, since there are essentially two distinct types of gastric ulcer, the benign and the malignant ulcer; in the latter a primary cancer may provide the point of localized digestive action in an otherwise quiescent ulcer *milieu*. Their coincidence is fortuitous. It is possible, if not probable, that the abnormlly prolonged digestive action in an ulcer *milieu* could even eradicate a primary cancer and thereby effect the change of a cancer-ulcer into a benign ulcer. This is at least as probable as is Bloomfield's (10) suggestion of "two types of cancer of the stomach of fundamentally different origins" . . . . . "to be differentiated with considerable certainty by the presence or absence of acid in the gastric secretion." This conception seems to attempt to harmonize the discrepancies which arise when gastritis, in its acid and anacid types, is considered the cause of cancer.

The association of cancer and achlorhydria has long lost its diagnostic significance since the diagnosis of cancer has become more promptly and readily made and cancer is now found in an acid secreting stomach in at least one-third of the instances. Our clinical desire to observe a patient with achlorhydria for its several common associations is in reality based upon the persisting uncertainties of diagnosis rather than upon a definite likelihood of a known sequence in pathology. The development of parallel curves of incidence in the relation of cancer and achlorhydria to age is without direct significance as to their etiological relationship, and evidence, as with other diseases, only the common increase in incidence which characterizes the degenerative period of life.

The inference of gastritis from the mere findings of an achlorhydria or of an achylia is wholly untenable. It is asserted that with achylia of long duration there are always signs of gastritis, but admitting this fact, there has been no continued clinical observation of the inception and duration of either condition which would indicate the essential etiological relationship of gastritis. Bloomfield and Polland (17) find "that a lesion, which the pathologist classifies as 'gastritis' varies in extent and severity, it may be patchy or diffuse, and in any case it is not a specific lesion of anacidity, since similar changes have been found over and over again in stomachs from patients who, during life, had normal gastric secretions." Neither has the association been proven as constant. The association of chronic inflammatory changes in the stomach and of degeneration of the epithelia and glandular structure with pernicious anemia has been a persistent finding since their recognition merely as atrophy even prior to the discovery and demonstration of achlorhydria by gastric intubation. In the long period since the introduction of gastric analysis, the question of antecedence of these associated abnormalities has not been answered, and their causal or secondary relationship remains in doubt. Jones, Benedict and Hampton (18) report observations upon the gastric mucosa in pernicious anemia cases and find that, following specific therapy, evidence of atrophy and hypertrophy of the stomach, both tend to disappear. They think the correction of the atrophy results from the successful treatment of a deficiency state and the correction of the hypertrophy represents a subsidence of a chronic gastritis. This would indicate the mucosal inflammation to be secondary or at least a co-ordinate change. It is interesting to note that in ulcer cases of long duration in which gastritis may be presumed, according to surgical findings, to have co-existed, there is no development of achlorhydria. This failure is in a way unfortunate as it would provide conditions for the healing of the localized ulcer lesion and thus make the disease of peptic ulcer self-limited.

There is little opportunity in these cases of functional failure to secure histological information concurrent with the other clinical studies. Gastroscopy may be expected to help in this deficiency; however, in its practice gastroscopy will be an accessory rather than a primary or routine method of investigation. Simpson (19) says: "it is clear that the incidence of achlorhydria increases with age whether organic disease outside the stomach is present or not. In other words, there is no evidence that disease other than that of the gastric mucosa brings about achlorhydria. If evidence of organic disease is lacking, the assumption that the increasingly frequent anacidity is due to gastritis is the only logical one." To assume that secretory failure implies gastritis is to deny that secretory failure may arise from other phenomena. The question of a failure in the normal nervous and humoral stimuli has received no attention. Analogy must also imply that the functional failure of other secretory structures both internal and external must arise from inflammation. Other evidence of gastritis is usually lacking in instances of achlorhydria. That it may occur from biological protoplasmic failure is shown by the few cases in which an achlorhydria and the absence of the 'intrinsic' factor of the anti-anemia principle have been dis-associated, (20); also by the experimental findings of Babkin (21) "that in vitamin deficiency (general) there is a great impairment of the secretory response of the (dog) stomach to sham feeding, subcutaneous injection of histamine and introduction into the small intestine of food and five per cent alcohol. By the administration of yeast, normal relations were restored in a few days." This certainly demonstrates that a biological inadequacy may cause a

secretory failure. Christy (22) calls attention to the association of achlorhydria with other manifestations of nutritional deficiency and non-inflammatory primary changes in other than gastric tissues. The conception of a biological inadequacy is further supported by the occurrence of achlorhydria as a sequel to chronic debilitating diseases,—tuberculosis, malaria, colitis, dysentery, diabetes, chronic pyogenic suppurations, and is associated with asthenia, migraine, urticaria, pellagra, scorbutus and exopthalmic goitre. However, the frequent use of the term 'gastritis' to denote these changes in the parenchyma due to malnutrition, effects of pyrexia and hypothetical toxins is at best confusing.

It is impossible to believe that the demonstration of achlorhydria necessarily implies in any or all these diseases the presence of gastritis and the increased frequency of achlorhydria during the physiological stress of pregnancy suggests in that instance a systemic rather than a local cause. The same doubt may exist, of the essential occurrence of gastritis for the failure of the hemapoietic (intrinsic) factor and of the neurotropic factor, if such exists, as for the achlorhydria, in spite of the few recorded cases in which it has been demonstrated three months to twenty years prior to the diagnosis of pernicious anemia.

Macklin (16) says: "that achylia of certain types, perhaps all, is inherited, mostly in direct line of descent, passing on from parent to child," and Connor (23) having examined a large number of blood relations of pernicious anemia patients, believes that although "the results do not prove an hereditary aspect of pernicious anemia, they strongly suggest a familial tendency in the development of one of its most important features"—achlorhydria.

Faber states that chronic achylia has an exogenous cause and is produced by external factors acting on the stomach, either by direct irritation of the mucous membrane or through the blood circulation by a toxic action on the gastric parenchyma, causing not a superficial catarrhal inflammation but an effect on the glandular parenchyma. This is plainly a hypothesis and not a statement of objective fact and even as a hypothesis indicates a bio-chemical effect rather than an inflammatory reaction. A distinction must be made between a primary inflammation and a primary cell dystrophy arising either from nutritional deficiencies or from protoplasmic poisons.

Bloomfield concludes from his studies that gastritis is not a specific lesion of anacidity and, that anacidity as a precursor of or the cause of certain diseases, is possible but not finally proved by valid statistics.

That this problem of the possible sequence of gastritis to cancer, to ulcer or to the loss of mucosal secretory function is susceptible to experimental demonstration analogous to clinical occurrence, is not conceivable. It is a weakness in logic, when a condition associated with several diseases, is considered to be etiological in each connection. Causal influences and agents usually may be expected to have certain definite and predictable effects. Nothing has yet been developed in our knowledge of gastritis, to indicate any such possibility.

Howe (24) in discussing the causal fallacy, says: "there is one point, however, which every science or art must have in common with metaphysics, and that is its dependence upon some fundamental concept or elementary working hypothesis. The imposing structure of the completed edifice sometimes hides from us the fact that there must be a foundation somewhere. It is rather shaking to our scientific certainty when we realize that the nature of that foundation is nothing more secure than a hypothesis."

"The danger of a hypothesis is that it may be taken as an axiomatic statement which is therefore assumed to require no proof. There is no difficulty in checking up the error of one hypothesis by inventing others as required to fill the gaps which the original hypothesis fails to explain. This is a very general scientific tendency and accounts for the large number of hypotheses which pass as scientific facts." "A hypothesis is never at its best when used as a part of our therapeutic armamentarium but it is an essential weapon of research."

I find it impossible to harmonize the discrepancies which are found to exist when the hypothesis of gastritis as the causal precursor of peptic ulcer, cancer, achlorhydria and its association of anemia and cord degeneration, is examined. Gastritis, however, does merit in itself the revived and increased attention which is being given it.

In reviewing this hypothesis, it appears that gastritis in the sense of primary mucosal inflammation, is more likely to be in most instances a sequel or complication of peptic ulcer. In those cases in which it may have been prodromal, additional factors must be found to account for the localization of the ulcer within or without the gastritis area, factors which would, and do, operate also in the absence of gastritis. Cancer of the stomach is not in any way dependent upon or promoted by a sub-stratum of gastritis, and there has yet to be shown that there may arise from gastritis any carcinogenic factor by which an acquired disease could promote an hereditary disease. Achlorhydria and its associated secretory failures with their remote influences are more likely to arise from primary biological failure of the gland cells than to be essentially secondary to primary mucosal inflammation.

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SECTION II—*Experimental Physiology*

Pancreatic Enzymes and Tissue Metabolism*†

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RECENT articles in this Journal have ascribed to the pancreas an extraordinarily important role in metabolism. W. Boldyreff (1) states that the non-secreting tissues of the body, such as muscle, liver, spleen, etc., are unable to produce enzymes of their own and must therefore depend upon the secretions of the pancreas and intestinal glands for their supply of lipase, amylase, protease and glycolytic enzymes. The external secretion of the pancreas, according to this author, is absorbed completely from the intestine into the blood, and thus becomes in reality its internal secretion. The enzymes are then fixed by the tissue cells throughout the body. Oelgoetz, Oelgoetz, and Wittekind (2) carry the hypothesis a long step farther and state that the blood vessels constitute the main digestive organ of the body. Food and enzymes are mixed in the intestine, and together absorbed by the blood where the major steps of digestion occur. In the case of proteins, gastric and intestinal digestion may carry them through the preliminary change to acid and alkali metaproteins, but these, along with the proteolytic enzymes are absorbed as such and are finally digested in the blood. "The blood therefore may be regarded as a more important final digestive organ than is the gastro-intestinal tract." The tissues are said to contain these same enzymes, derived from the intestinal tract, and at a concentration one hundred times that found in the blood.

The three papers cited above contain little data in substantiation of the assumptions made. Boldyreff offers no data, but cites his earlier work in proving rhythmic activity along the intestinal tract as evidence in favor of the hypothesis (3). The papers by Oelgoetz, Oelgoetz, and Wittekind describe a rough method for determining the iodine absorbing power of serum, and state that this is a test for amylase. They also state without evidence that the pancreatic enzymes are always present in the blood, and in fixed proportions, so that the determination of one of them is sufficient to determine the concentration of them all.

It is not our intention to attempt a critical analysis of the details of these papers, many of which are quite counter to data in the literature. In the following paragraphs, however, we will submit concrete evidence which bears directly upon the major premise of these papers—namely, that pancreatic enzymes are present in the tissues; that tissue cells are unable to produce their own enzymes, and must depend upon the pancreas for a continually renewed supply in order to carry on the syntheses and hydrolyses incident to metabolism. If trypsin can be found in significant amount in tissues other than the pancreas, it would appear to give strong support to the hypothesis of Boldyreff. If trypsin cannot be demonstrated, it would appear to leave the hypothesis without factual justification.

We have chosen trypsin because its properties are so unique and so well characterized that there is no danger of mistaking some other proteolytic enzyme for it if the experiments are adequately controlled. The same cannot be said perhaps for lipase and amylase of the pancreas. Similar enzymes are widely distributed, and while we believe there are differences between the lipase of the pancreas and that of the liver or kidney, they are not so convincing as the differences between trypsin and other proteases.

In an earlier publication we presented some data which at the time we felt was fairly good evidence that trypsin is not one of the proteases of liver or kidney (4). In the following experiments we have again sought this enzyme under even more carefully controlled conditions. The data appears to be unequivocal and so far as it goes should definitely set at rest the question of whether pancreatic enzymes are present normally in tissues other than the pancreas.

EXPERIMENTAL PART

Hog pancreas, spleen and liver were obtained within a few minutes of the death of the animal. They were re-

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