are undergrowth inasmuch as we do not know their ultimate effect on the other organs of internal secretion.

SUMMARY

1. Most authors agree that, at the onset of diabetes in children, the great majority of these are at or above the normal standards of height. As the disease progresses, many of these children seem to fall below the normal standards.

2. An analysis of 100 diabetic children from my own series, children who have been followed up over a period of years, almost without exception, the above statement holds. As time goes on, many of these children maintain this high normal level; others, after a period of few years, fall below the normal standard. This drop in

height is most marked in the age period between the thirteenth and the sixteenth years. Few fall definitely into a group we might call "dwarfism". There were more of these dwarfs in my own series among the boys than among the girls.

3. This relationship of over- and undergrowth, in my series of 100 children, taken at large and over a period of years, showed nearly twice as many children above the normal standards.

4. Future studies will disclose whether this stunting in the growth in the later stages of diabetes in some children successfully can be combated by the use of extracts of the endocrine glands or whether a proper metabolic balance can be attained by proper nutrition and proper control of the diabetic condition alone.

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The Nutritional and Digestive System Aspects of Pernicious Anemia (Part I)

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DURING 113 years since the recognition of pernicious anemia as an entity, countless etiological hypotheses have been offered. Although today a more inclusive viewpoint is possible than at any previous time, the cause of the disease is not yet completely demonstrated. The newer knowledge of gastric physiology is the particular phase upon which hangs the best hope of an explanation for the involved pathogenesis.

If the spinal cord changes could be as readily co-ordinated with the gastric state as can the blood changes, the problem of the cause would seem to be nearing a solution. But it is well known that the degenerative changes in the nervous system may, at times, become actively progressive while the blood system is under satisfactory control by specific treatment. For this reason it is difficult to assume that the hemopoietic system and the nervous system owe to any common cause their dissociated manifestations.

A large proportion of the total knowledge of

the disease relates to the digestive system. It has received almost as much clinical and pathological attention as has the hemopoietic system and more than the nervous system. If without reference to the literature a physician were to study the patients intensively he would be so impressed by the gastro-intestinal symptoms as to impute to them a causative role. This has been the history of the disease, for the profession has not been able to dismiss this strong intuitive attitude.

A common weakness in all etiological deliberation is to overemphasize a positive finding, even when it fails to explain the total manifestations of the disease. Again, a partially successful method of treatment, while invaluable from a practical and humanitarian standpoint, is seldom of equal value in pathological argument. While insulin gives a more striking control over carbohydrate metabolism than any known agent, it does not necessarily follow that diabetes mellitus primarily is a disease of the pancreas. Similarly, although the "x" substance found in liver,

stomach, or produced by the action of the intrinsic factor of the stomach on protein, exerts a remarkable control over the blood-forming organs, it does not of necessity follow that the absence of this intrinsic factor is the sole and sufficient cause of the disease. It must be remembered, for example, that constitutional peculiarities are unusually marked in persons acquiring pernicious anemia, so that perhaps idiosyncrasies of bone marrow and of the nervous tissues are just as essential as are delinquencies of gastric secretion. This point might be settled by finding persons without the intrinsic factor who do not develop pernicious anemia.

It is not the purpose of this monograph to claim complete etiological significance for abnormalities found in the gastro-intestinal system, although it is the conviction of the Authors that no better lead exists. It is intended rather to show what a very large amount of the total investigation of the disease has centered around the digestive tract.

EARLY INVESTIGATIONS

In 1821, Combe of Edinburg, in describing pernicious anemia for the first time, felt instinctively that a nutritional problem was involved, since he wrote: "It is probably owing to some disorder of the digestive and assimilative organs that its characteristic symptoms have their origin." Elliotson's *Practice of Medicine*, 1846, refers to certain cases of severe anemia which were, no doubt, Addisonian, and he mentions the "bad appetite" and calls special attention to a group of cases in which the digestive symptoms dominated the clinical picture—dark, fetid stools, nausea and constant vomiting.

While Addison's famous communication of 1895, *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*, placed the disease forever on a firm basis as a generic entity, it rather slighted the digestive system, though he did not neglect to mention the failure of the appetite.

As early as 1851, the discerning Barclay (1) described for the first time the glossitis, which Hunter later developed into an important diagnostic sign.

Austin Flint, in 1860, and Fenwick, in 1865, emphasized certain degenerative changes in the gastric mucosa as possibly related to the cause of the disease. This, and similar conjectures found throughout the early literature, did not indicate so much a profundity or acumen, as a well-established tendency to attribute etiological significance to every new clinical or pathological finding. Gairdner in his *Clinical Medicine*, 1862, noted fatty degeneration of the liver as one of the most striking morbid appearances, while the same finding was taken by Perroud (2), earliest of the French school to observe the disease, as the essential causal factor of pernicious anemia.

Biermer's (3) remarkably well-rounded description of the disease contained reference to

insufficient and unsuitable feeding, characterizing the lives of many victims, and the persistent diarrhea, anorexia, "weak digestion" and gastric discomfort noted during the disease.

William Hunter's studies, begun in 1885 and published at frequent intervals for many years, are of great importance, especially because they directed attention to features other than the purely hematological. His work on hepatic siderosis manifested an accuracy of observation, then too uncommon. He is responsible for glossitis as a diagnostic sign. Oral infection had been given little, or at best sporadic, thought in connection with any disease until Hunter's tireless descriptions of the mouth conditions in pernicious anemia really laid the ground work for all subsequent ramifications of the concept of "focal" infections in general.

SYMPTOMS AND SIGNS

Without counting achlorhydria, which is virtually constant, the other symptoms and signs referable to the digestive system tract are equally frequent with those of the nervous system and almost as frequent as are the blood changes. Eighty per cent of patients present definite gastro-intestinal manifestations. In view of the fact that over 99 per cent show achlorhydria (indeed, achylia) the digestive tract always is abnormal.

Panton *et al.* (4) have shown that vomiting and diarrhea are the most common symptoms, with anorexia and epigastric pain closely following in incidence. Although these symptoms occur in only 20 to 40 per cent of patients, often they are extremely impressive, especially the persistent diarrhea and the extreme anorexia. Sore mouth and tongue probably do not exceed an incidence of 50 per cent (Minot, 5), although Hunter (6) and more recently Percy (7) would regard it as almost a constant symptom at some stage of each case. Pyorrhea, apical granuloma, and dental caries seem to have an incidence higher than in most diseases.

The Mouth, Its Contents and the Oesophagus: Glossodynia, sore mouth and painful deglutition depend upon glossitis, stomatitis and a reasonably presumed oesophagitis. Barclay's case was a woman nursing her baby and he ordered her to leave off beer and meat and confine herself to slops! Muller (8) found in six out of sixty-two cases a peculiar stomatitis characterized by small whitish ulcers, "the size of a split pea" on, and under the tongue, very resistant to local treatment, disappearing spontaneously or with remissions, but tending to recur without special reason. Quinke (9), Eichhorst (10) and Laache added further reports, showing the commonness of redness and soreness of the tongue, of painful dorsal fissures, the loss of papillae, the excoriation of the angles of the mouth, the smoothness and cleanliness of the tongue, the extension of the soreness into the throat preventing the use of hot or hard

food, and an associated loss of taste and sense of smell. Ewald (11) suggested the term "follicular stomatitis".

Hunter (12), as early as 1889, began a long campaign of education of the profession, and his emphasis on the glossitis and the oral sepsis marks his chief claim to be remembered in connection with this disease. He made sections and cultures of the tongue tissues, demonstrated mucosal and muscular atrophy and recovered a virulent long streptococcus, excellent illustrations of which are to be found in his books. Hunter believed that some specific virus caused the disease, pernicious anemia, and regarded the streptococcus as a preliminary invader of the tongue and of the wall of the entire gastro-intestinal tract, which prepared the tissues for the hypothetical organism.

The glossitis has been sufficiently observed to merit its present position as an important diagnostic sign and one of the specific features of the disease.

The smoothness of the tongue, and its cleanliness and moisture prompted Evans (13) to make the striking remark: "A coated tongue and a diagnosis of pernicious anemia is a combination to excite suspicion."

In the most active stage of the glossitis, the organ is fiery red and justifies the common description of "beefsteak tongue". It may be edematous and show indentations along its border from pressure of the teeth. Vesicles filled with serum may occur near the tip on either surface, although this is not common. During phases of marked anemia, the generalized mucous membrane pallor is shared by the tongue, except along the edges, where a mottled redness persists. Simple ulcers, resembling canker sores, may be seen on the tongue borders, on the buccal surfaces of the cheeks or on the anterior walls of the *vestibulum oris*.

Later in the disease, uncontrolled by specific treatment, is to be found the small-appearing "ironed-out" atrophic tongue, with dwarfed or absent papillae, subject still to periodic attacks of marginal redness, but decidedly quiescent. Before the days of specific treatment, this atrophic tongue became a permanent hall-mark of the disease and of similar clinical significance to the permanent macrocytosis, which was to be found even in the longest of the spontaneous remissions. In those days it was abundantly proved that this glossitis resisted all forms of local treatment. It interfered with the taking of nourishment, and not infrequently drove the victim to distraction. It ran in very irregular cycles, being on the whole worse at the beginning and less severe toward the end of the disease.

Glossitis, as Riesman (14) pointed out, often is an inaugural symptom, being present from weeks to even years before the onset of the anemia. There are many patients, however, with atrophic tongues who never remember much active discomfort. Finally, an occasional patient shows a

tongue with no glossitis, no atrophy and with no indication whatever of local abnormality.

The cause of the glossitis has long been debated, and for years infection was considered to be responsible. This is by no means logically disproved today, but since the glossitis is one of the very first symptoms to yield to the administration of effective curative material such as liver, it seems to argue for a metabolic etiology.

While it is frankly rare to encounter a patient with pernicious anemia without a foul mouth, since pyorrhea is so very common, nevertheless cases are found with teeth clinically and roentgenographically normal, and, again, other cases develop in individuals long since edentulous. The state of the teeth is important for at least two reasons. Sometimes a severe septic anemia, somewhat resembling pernicious anemia, may result from dental infection *per se*: and, still more important is the fact that pernicious anemia, complicated by infection, was in the past a much more severe disease, and is today much less easily controlled by specific therapy. Doubtless, any severe infection, whether of the teeth or other organs, or whether of acute or of chronic, or focal type, can and actually does help to precipitate pernicious anemia in those individuals constitutionally predisposed thereto.

There is clinical evidence that an oesophagitis similar to the glossitis at times occurs; Schwenkenbecker has described a similar involvement of the nasal mucosa.

Anorexia, nausea, and vomiting probably depend primarily on the deficiency known to exist because they disappear very rapidly after administration of liver extract, long before any considerable blood increase is gained. But these symptoms were much worse in pre-liver days in those cases which had the added element of sepsis from teeth or from gall bladders or inflamed appendices, as Hunter (12) and Percy (7) have convincingly demonstrated. Likewise, the symptoms were worse in the instances of benign stenosis of the intestine. Jones and Joyce (15) showed the frequent association between pernicious anemia and cholecystitis. It must not be forgotten too that every case of pernicious anemia probably is a case of chronic gastritis and in this connection, it will be remembered how efficacious HCl proved in treating these particular symptoms.

Epigastric pain variously may be explained on the basis of intra-gastric disease, associated gastro-intestinal conditions or on the basis of an angina pectoris with referred sensation as Coombs has explained at length. Most deceptive when it is of the nature of a girdle pain, arising from the posterior column degeneration, such abdominal crisis has often led to fruitless laparotomy.

Diarrhea of an unusually protracted and intractable type may precede the disease by months or years or may be present for months during the disease. Cornell (16) has described a case in

which ten stools per day for two and one-half years preceded the onset of the recognizable disease. Such diarrhea has a post-prandial tendency but not the decided matitudinal tendency as in sprue. Mucus, pus and even blood may be demonstrated at times in the stools, and there is always much undigested food material. In some cases, great rectal discomfort and sense of burning precede or accompany defecation. The incidence of severe diarrhea before or during the disease is 20 to 25 per cent. It usually causes marked loss of weight. The cause has been variously regarded as (a) rush peristalsis due to the premature opening of the achylic stomach or (b) *B. Welchii* enteritis. While both factors conceivably may be of importance, it is to be noted that the symptom abates after the beginning of specific treatment so rapidly as to suggest that it too is due to the deficiency which liver supplies.

ANATOMICAL AND HISTOLOGICAL CHANGES

Stenosis of the oesophagus has been reported at autopsy, and one of us recently had a case of pernicious anemia associated with an oesophageal stricture, in whom the disease began ten years after he had caused the stricture by drinking lye. He was kept in remission with the most unusual difficulty even on large doses of liver and ventriculin and finally died from a mediastinitis following instrumental dilatation of the stricture.

Fenwick (17) in 1870 demonstrated marked general atrophy of the secretory tubules of the gastric mucosa, but found no evidence of inflammation. There was fatty transformation of the glands, this as the result of a very slow degenerative process, leading to general starvation of the body tissues. Flint (18) supported Fenwick to the extent of admitting that at least some cases of idiopathic anemia, as the disease was then called, depended upon a degenerative atrophy of the gastric glands. Schaumann (19) observed in one case a virtual absence of the stomach epithelium, the remaining glands being few and badly developed, and the mucosa being generally characterized by increase of fibrous tissue, with small sub-epithelial hemorrhages. Quincke (20) found the mucosa of the stomach very thin and the glands few in number, and in a second case a diphtheretic membrane in the colon. Bramwell noted slight intestinal ulceration. Eichhorst (10) felt that any changes found were due to the anemia and of little consequence. However, in one of his cases the mucosa of the intestine, the upper part of the jejunum, the lower part of the ileum, and the entire colon were edematous with small hemorrhages on the edge of the villi.

Nolen (21), from a study of two cases, believed the glandular degeneration to be the cause of the anemia. Nothnagel claimed to show intestinal atrophy in 84 per cent of his post-mortem cases. Pye-Smith (22), in an analysis of 103 cases in 1883, noted the frequent occurrence of fatty degeneration of the gastric glands, occasional leu-

cocytic infiltration between the tubules, and a thickening of the mucosa with parenchymatous atrophy. Henry and Osler's case (23) showed atrophy of the gastric mucosa with complete destruction of the peptic glands over the greater part. Toward the pylorus, atrophy was less marked, but a small-celled infiltration, denoting a chronic inflammation was plainly made out. They said: "A careful study of the case justifies, we believe, the conclusion that a primary atrophy of the mucous membrane does occur, and bears out the suggestion of Flint, Nothnagel and others, that certain of the cases of pernicious anemia depend upon the profound alteration in the gastric tubules." They mentioned the chronic abuse of alcohol in this case as probably a co-operative factor in producing the atrophy.

Lewy (24) thought the same histological picture resulted from ulcerative processes, responsible for the hematemesis in his case. In Kinnicutt's (25) first case, the tubules were absent over large areas, while elsewhere tubular fatty degeneration, hyalin change, and small-celled infiltration were noted, although there was no fibrosis and the sub-mucous coat appeared normal. In his second case the greatest destruction occurred in the deeper portion of the tubules, and was probably caused by a chronic inflammatory process. He could not conceive of these changes as being due to a creeping ulceration. Some cases of pernicious anemia might, in his opinion, be due to the impaired nutrition resulting from consequent functional debility of the stomach.

Rosenheim (26) noted cystic degeneration of the mucosa as well as other evidences of catarrhal inflammation. Hale-White (27), in an analysis of the gross anatomical features in 17 cases from Guy's Hospital post-mortem records, noted in six cases certain abnormalities. In the first case—edematous cecum, two blackish small spots on the mucous membrane, almost diphtheritic in appearance; in the second—numerous ulcer cicatrices in the large intestine, or newly healed ulcers, and a little recent diphtheritic inflammation with exudation in parts; in the third—thickening of the pyloric mucosa; in the fourth—the scar of a small ulcer one foot above the cecum; in the fifth—several scars in the lower part of the small intestine.

Mott's case showed no definite microscopic changes in the stomach wall, although he noted that the mucous membrane was covered by a thin layer of glary mucus. Eisenlohr (28) noted in his case not only gastric atrophy but also a *complete disappearance of glands and villi in the intestine*. He felt strongly that nutritional disturbances consequent on this extensive atrophy caused the disease, and furthermore that the process was one of primary genuine atrophy. Nonné (29) found evidence of chronic inflammation both of the mucosa and the submucosa of the stomach but could detect no glandular atrophy.

Pepper and Stengel (3) as well as Hayem

(31) noted atrophic changes in the stomach, although in one of Hayem's cases, gastritis without atrophy existed. Ewald (11) emphasized the intestinal atrophy in addition to the gastric atrophy, as the obvious cause of the disease. Martius (32) claimed to have noted pronounced atrophy of the intestinal, as well as the gastric mucosa in two of seventeen cases, and adopted the view that the intestinal changes noted were decidedly the more responsible for the disease, and acted by disturbance of food absorption.

Grawitz (33) found gastric atrophy, in one case moderate, in another marked, but was noncommittal as to its significance. Koch found atrophy in both the stomach and the intestine in five cases, thus confirming the observations of Ewald and of Martius, but felt that these findings were secondary to the anemia. Fletcher (34) discovered old inflammatory lesions of the colon, associated with patchy necrosis, hyperemia, and hemorrhages. These he regarded as due to neurotrophic disturbances.

Hunter (35) made similar observations on the occurrence of inflammation and atrophy in the wall of the stomach. Some of his descriptions are graphic as, for example the following:

" . . . I found *post-mortem*, marked inflammatory lesions, both old and recent, in the mucous membrane of the stomach. The inflammation was localized and, in certain parts, of the most intense description; the changes in the glandular cells and the infiltration with leucocytes recalled at once the similar appearances frequently presented by glandular structures, like the kidney, when the seat of a localized infection.

"Furthermore, the swollen, pinkish, translucent appearance of the small lymphatic glands, lying on the wall of the stomach itself—under ordinary circumstances scarcely visible to the naked eye—pointed to some recent as well as chronic irritation of the stomach wall itself."

Hunter's conception, which for many years had a great influence, may be summarized briefly as follows: the gastric atrophy was the result of a gastritis due to septic organisms swallowed from the mouth, but the gastric atrophy was neither the result nor the cause of the disease. It was to be regarded as an associated condition. In order to explain the disease, Hunter hypothesized a specific infection by an unrecognized micro-organism for whose successful invasion the septic influence had well prepared the tissues.

As may be surmised from this review, the problem of the gastro-intestinal pathology was in an unsatisfactory state at the close of the last century. Nothnagel, Martius and Ewald all championed intestinal atrophy as the cause of nutritional disturbances which underlay the disease. It remained for Faber and Bloch (36) to detect the fallacy of this argument, by doing away completely with the conception of intestinal atrophy. By injecting 500 c.c. of 10 per cent formalin into the peritoneal cavity immediately after death to

preserve the tissues, they found that no atrophy of the intestine existed. What had given the appearance of atrophy was the post-mortem gaseous distention of the bowel. In experiments with dogs they demonstrated how easily this distention might deceive. They showed, moreover, that the intestine in pernicious anemia harbored no inflammation in its wall. This left still unsettled the problem of the constancy of atrophy and inflammation in the gastric mucosa. Faber and Bloch, again using the technique of formalin fixation, showed that while atrophy might or might not exist, chronic inflammation (gastritis) was always present.

The observations of these workers have been confirmed by Lepehne (37). No observations on the intestinal histology should be seriously considered unless the methods of Faber and Bloch are employed. Such methods might do away with some of the more recent alleged findings of intestinal atrophy. Passey (38) has brought the method of biopsy to bear on the problem of the stomach condition. In one case of true pernicious anemia with achlorhydria, a section of the fundus, removed at operation, showed the oxyntic cells fewer than normal, very little atrophy indeed, but definite evidences of inflammation. This bears out the findings of Faber and Bloch, that whether atrophy is present or not, inflammation is always to be found.

The more recent reports on pathological findings in the intestine deal largely with strictures, obstructions, and hypertrophies of the small bowel and with disease of the large bowel. Maynard and Sturton (39) report the case of an individual who nine years before the disease had suffered from colitis, and at autopsy a fine ring of small ulcers was found at a point five feet above the ileocaecal valve. The outer surface of the gut at this point showed a sharp line just as if an end-to-end anastomosis had been performed, although there had been no operation. Microscopically, the mucous layer showed simple ulceration, while the other layers were normal. This ulcerated region caused no constriction of any kind whatever. Coates reports a case which showed at autopsy definite ulcers of the large bowel with a large ileocaecal gland draining the area of an ulcerated patch.

Chapman and Duff (40) in April, 1921, opened the abdomen of a patient on account of a diagnosis of intestinal obstruction. The colon was distended but there was no recognizable cause for the obstruction. A colostomy was done and the patient remained in perfect health until August, 1923, when she returned complaining of dyspnoea, and a diagnosis of pernicious anemia was made. They felt that the pernicious anemia was due to the same toxemia that had caused the paralytic condition of the colon.

Faber reported the first instance of intestinal stenosis with pernicious anemia in 1895. Meulengracht (41) has given particular attention to

these cases of so-called "stricture anemia." In 1921 he reviewed seven cases from his own experience and from the literature. In 1922 he (42) reported a further instance in a woman of sixty-four, with three strictures in a certain segment of the small intestine. Haden (43) has reported a case of clinically typical pernicious anemia occurring with a malignant tumor of the gall bladder and obstruction of the duodenum and colon. He considered it probable that the toxic agent responsible for the anemia had arisen as a result of the stasis or of some alteration in intestinal function, induced by the presence and perhaps pressure of the tumor.

Ross (44) attended a physician who developed pernicious anemia soon after swallowing a sharp piece of lamb bone. The bone lodged in the wall of the ileum and was afterwards passed with the stools, but the patient died of pernicious anemia.

Kleeman (45) reports the finding of simple pyloric hypertrophy in pernicious anemia. The case was operated upon for a schirrhous growth of the pylorus. Percy (7), who has operated upon more cases of pernicious anemia than anyone else, stated, in reply to a question by Gibson, that in seventy-seven laparotomies in this disease he had never encountered pyloric stenosis.

Mayo (46) has noticed the frequent development of a severe anemia, sometimes indistinguishable from pernicious anemia, in disease of the colon, particularly of the proximal half.

Whereas, a few instances of pernicious anemia show various abnormal conditions of the intestine, such as those just described, most cases do not present such findings. Surgeons will agree that similar abnormalities are frequently found at laparotomy without any associated picture of pernicious anemia. The obvious inference is that such abnormalities are not essential but may be contributory, in some way, to the development of the disease.

To sum up—it is recognized that atrophy of the gastric mucosa may or may not occur; that gastritis always occurs; that intestinal atrophy and infection are not proved and much doubted; and that a few cases show stricture, ulcer, or neoplasm of the bowel.

In summing up the information available on the subject of achlorhydria in pernicious anemia, in 1927, one of us (16) wrote: "Achlorhydria, a functional abnormality of constitutional origin, is almost invariably associated with pernicious anemia, and forms, in these cases, a necessary link in an etiological chain, to which, by the addition of *further unknown* links, pernicious anemia is made to appear." While the latter part of the present monograph will reveal how true that statement was, it is considered wise, at this point, to present the reader with some of the extensive background of investigation responsible for the 1927 attitude.

Grawitz in the late nineties listed "achylia gastrica" as a definite etiologic factor in the broad

group of cases which he, in conformity with continental custom, included under the term, "pernicious anemia". Faber and Bloch (36) collected 33 cases of the disease in which gastric analysis had been done, and in all of which the acidity was greatly diminished or absent. Similar results were obtained in their own four cases, and *post-mortem* examination showed diffuse inflammation of the stomach wall with destruction and atrophy of the glands. Faber maintained for many years that the gastric changes and the blood changes had a common cause in a general toxic-infective state of the body, though he finally came to view the achlorhydria as possibly a constitutional manifestation.

Hutchison (47) in 1909 demonstrated that since achlorhydria so often existed for years without blood changes, it could not, *per se*, be validly regarded as the cause of the disease. He admitted that achlorhydria robbed the intestinal tract of its natural antiseptic and was among the first to recommend HCl as a rational method of therapy.

The report of Levine and Ladd (48) of finding achlorhydria in 99 per cent of 150 cases of pernicious anemia was the first of a series that eventually settled the importance of the finding. Hurst (49), Faber and Gram (50), Percy (7), Panton et al (4) all made similar studies with identical results. Hurst and Bell (51) found achlorhydria to be as characteristic of "pure" cases of subacute combined degeneration of the spinal cord without anemia, as of the cases showing anemia, and their report did more than any other to unify the conceptions of neurologists with respect to this disease. Piney (52) found one case of subacute combined degeneration of the cord with free HCl present, just as Shaw, and others more recently have done in cases with anemia. These exceptional instances proved stumbling blocks to constructive hypothecation along etiologic lines until quite recently, as will be shown later.

Faber and Riley (53), Hurst and others (54), (55), (56), (57), (58), were able to show definitely that achlorhydria preceded the disease in all cases where the point could be settled, for periods of from one to twelve years. The condition of achlorhydria was more permanent than the disease, for in the instances of 20-year spontaneous remissions of Hurst's, the HCl never appeared. Achlorhydria, when not associated with pernicious anemia, often shows some degree of recoverability as in alcoholic cirrhosis or cirrhosis of the liver, but in pernicious anemia it is consistently persistent.

At first the anemia itself was regarded as the cause of the achlorhydria, and then a toxic-infective or "noxa" factor was accredited with producing a parenchymatous gastritis or perhaps an interstitial infectious gastritis which, by gradual condensation of fibrous tissue, resulted in eventual atrophy of the secreting cells. Finally the idea of achlorhydria being a constitutional, and

even an inherited, characteristic has gained so much ground that it is practically accepted today. The biopsies of Hurst and Passey proved that the gastric mucosa in pernicious anemia may be histologically normal although achlorhydria was present. The occurrence of *familial* pernicious anemia, and the high incidence of achlorhydria in close relatives of patients with the disease supports the constitutional conception.

Much recent work on achlorhydria, itself, has shown it to be much more prevalent in the general healthy population than formerly believed, and to follow, in its incidence certain age levels. Perhaps it usually causes no symptoms whatever, or at most, predisposes to diarrhoea and an absence of alkaline tide in the urine.

THE FOOD FACTORS

Much experimental work on anemias due to vitamin deficiency has been undertaken, but no reproduction of a condition resembling human pernicious anemia has been accomplished.

The voluminous work on vitamins during the past decade unquestionably suggested that avitaminosis might play some role in pernicious anemia. Falconer concluded that blood changes in vitamin A deficiency were neither striking or constant enough to constitute specific deficiency lesions. Koessler *et al.* (59) do not indicate the condition of pigment metabolism in the anemia they produced in rats by chronic vitamin A deficiency and, hence, any comparison with pernicious anemia, lacking this information, is problematical. They indicate that in this experimental anemia, produced by vitamin A deficiency, blood regeneration occurs only with, and in proportion to, the addition of vitamin A. Nothing could appear more logical, since no anemia can improve so long as the set of conditions responsible for the anemia do not change. Simmonds *et al.* (60) suggest that Koessler's rat anemia was due to deficiency in vitamin E, which is believed to play an important role in the absorption of iron. Whatever may have caused the anemia, it does not, from their description, appear to bear any necessary relationship to pernicious anemia; and in fact Koessler *et al.* propose such a vitamin A deficiency not as a sole, but rather as a co-operative factor in the etiology of the human disease.

Barker and Sprunt (61) emphasized the importance, on general principles, of treating pernicious anemia by liberal and well-balanced diets. Many others have, with no recognizable specific reason of importance, advised special diets of various kinds. Mosenthal (62) showed that forced feeding can restore a positive nitrogen balance. Gibson and Howard (63) showed in careful metabolic experiments that more favorable ni-

trogen and especially iron balances may be established in pernicious anemia when diets rich in food iron, and comparatively low in caloric and protein values are given, and urged the use of iron-rich and vitamin adequate diets in the treatment of this disease. This was an intentional, clinical application of high food iron diets which had been found by Whipple *et al.* (64, 65) so valuable in causing blood regeneration in dogs rendered anemic by hemorrhage. Elders (66), fully convinced of the possibility that sprue and pernicious anemia possess a common etiology, and equally convinced that sprue is a deficiency disease, suggested that pernicious anemia might be found at least amenable to improvement by well-chosen food. Minot and Murphy (67) found it permissible to speculate "on the possible partial rôle that some nutritional excess or deficiency may play in the etiology of the disease". With a special diet rich in proteins of good biological value, particularly liver, low in fat and carbohydrate and with vitamins well supplied, these investigators obtained remarkable therapeutic results, more constant and more lasting than those obtained by any other form or forms of treatment. The published work of Minot and Murphy brought the whole problem of nutrition in pernicious anemia to a sharp focus of interest. Their results suggested the possibility that dietary factors may actually play a rôle in the production of the disease. No studies of the pre-disease diets of patients had as yet appeared.

In 1927, Cornell showed by a study of the pre-disease diets of twenty-five persons, later developing pernicious anemia, that it was not a true deficiency disease in the ordinary sense of the term because these individuals, prior to their disease, had regularly eaten diets which could be regarded as of average type.

BACTERIA AND PARASITES

As might be expected, most of the intestinal bacteria and most of the parasites occurring in the stools of patients with pernicious anemia have received rather extensive study. The streptococci, *B. Welchii*, and *B. Coli*, have all been formally suspected of causing the disease. Hurst, in England, led the streptococcus hypothesis, receiving the mantle from Hunter. Herter (68), of New York, in 1906, initiated the *B. Welchii* hypothesis followed years later by Cornell (69), Kahn and Torry (70), Reed, Orr, and Burleigh (71) and others. Adami (72) in Montreal in 1900 started the "subinfection by *B. Coli*" conception and further work on this phase was done by Lowenberg (73), Percy (7) and Nyfeldt (74).

(To Be Continued)

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ABSTRACTS

JOSLIN, E. P., AND LAHEY, FRANK H.

Diabetes and Hyperthyroidism. Ann. Surg., October 1934. Boston, Mass.

The authors stress the fact that glycosuria is so related to hyperthyroidism that care must be taken not to make the diagnosis of true diabetes in hyperthyroidism when it actually does not exist. Raised blood-sugar levels are

suggested to avoid this common error. Dr. Lahey states that the important part of the successful care of diabetes and hyperthyroidism is the management of the diabetes.

The authors believe that the combination of diabetes with hyperthyroidism increases the risk and, therefore, demands more conservative operative approach if the mortality is to be kept low.