was readmitted on January 7, 1945, following development of a discolored area of the skin of the right, large and second toes. On admission, the fasting blood sugar was 258 and the blood counts revealed hemoglobin 13.0 grams, erythrocytes 4,340,000 and leucocytes 8,500. The patient was admitted to the hospital for the third time on December 4, 1945. Nausea and vomiting had begun two days previously and she was brought to the hospital in a stuporous state. Physical examination revealed bilateral cervical and inguinal adenopathy, a large hard spleen and a palpable liver. The fasting blood sugar was found to be 285. Blood counts were as follows: hemoglobin 8.0 grams, erythrocytes 2,490,000 and leucocytes 19,500. The peripheral blood smear included blast cells 27%, lymphocytes 41%, neutrophils 26%, stab forms 1%. eosinophils 2% and monocytes 3%. The blast cells were lymphoid in type. Blast cells, similar to those in the peripheral blood, predominated in the sternal marrow. On the basis of the clinical findings and the hematological picture, a diagnosis of subacute lymphatic leukemia was made. On January 14, 1946 the leucocyte count was determined at 52,000. The diabetes was controlled by a daily dose of 30 units of protamine-zinc insulin and 10 units of unmodified insulin. Three blood transfusions were administered but she continued to fail and expired on January 15, 1946.

Discussion

Of the seventeen cases of coexistent diabetes and leukemia recorded in the literature eight were of the myeloid type, seven lymphatic and one was monocytic. Twelve cases were known to have been diabetic prior to the development of leukemia. The time of onset of diabetes or leukemia was not definitely established in the remaining five patients. Eleven of the patients were fifty years of age or older and males predominated eleven to six.

Our group of ten cases of diabetes and leukemia consisted of seven females and three males. Eight of the patients were fifty or more years of age. The types of leukemia represented were as follows: six cases of chronic lymphatic, three cases of chronic myeloid and one case of subacute lymphatic. Diabetes mellitus was known to have existed prior to the onset of leukemia in eight cases. In two cases the diagnosis of diabetes and leukemia was established at the same time.

The diabetic state did not seem to affect the course of leukemia. Two patients survived for two years after the diagnosis of leukemia was made and three patients were known to be alive one year later.

Summary

The association of diabetes mellitus and leukemia in the same patient is infrequent. Ten cases of coexistence of these two diseases are reported. This group is part of a series of 805 cases of leukemia studied.

REFERENCES

1. Rebitzer, A.: Ein fall von leukamie und Diabetes. Prag. med. Wchnschr., 17:356, 1892.

2. Schwarz, E.: Ein fall von myelamie mit diabetes mellitus und miliartuberculose. Wien. med. Wchnschr., 55: 414-19, (Feb. 25) 1905.

3. Fitz, R.: Diabetes mellitus and myelogenous leukemia. J. A. M. A., 75:1331-32, (Nov. 13) 1927.

4. Glaser, J.: Diabetes mellitus and concomitant leukemia. J. A. M. A., 88:1626-27, (May 21) 1927.

5. Rapaport, H.: Diabetes Mellitus with myelogenous leukemia and miliary tuberculosis. California & Western Med., 27:802-03, (Dec.) 1927.

6. Wright, F. R.: Diabetes Mellitus and leukemia. Clifton Med. Bull., 14:1-3, (Jan.) 1928.

7. Elman, C. and Marshall, S.: Anemia of Pernicious Type Complicated by Diabetes Mellitus and Termination in Acute Myeloid Leukemia. Lancet, 2:1094-96 (Nov. 7) 1936.

8. Hart, J. F., Lisa, J. R. and Riedel, P. A.: Diabetes Mellitus Complicated with Lymphatic Leukemia. J. A. M. A., 113:1222-23 (Sept. 23) 1939.

9. Levi, J. E. and Friedman, H. T.: Insulin Resistance In a Case of Diabetes Mellitus and Chronic Lymphatic Leukemia. Report of a case. New Eng. Jour. of Med., 225: 975-78 (Dec. 18) 1941.

10. Joslin, E. P., Root, H. F., White, P., Marble, A. and Bailey, C. C.: Treatment of Diabetes Mellitus, Eighth edition, Philadelphia, Lea & Febiger, 1946, P. 609.

ACHYLIA GASTRICA: KEYSTONE IN THE DEVELOPMENT AND ERADICATION OF MACROCYTIC ACHYLIC ANEMIA (PERNICIOUS ANEMIA, ADDISON-BIERMER).

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TODAY, ACHLORHYDRIA, anacidity and achylia gastrica are regarded as synonymous, and the terms are used interchangeably. It is the assumption that these three names define the same clinical conditions: Lack of hydrochloric acid in the gastric juice. Achylia gastrica, in addition, supposedly implies the absence of pepsin and ferments. For clinical purposes this distinction shall be of no significant importance.

Since there are apparently different forms of 'lack of hydrochloric acid', one has been forced to introduce a division among achlorhydria, anacidity and achylia gastrica as to 'true' and 'false' conditions; thus, each writer has to explain what he wishes understood by his use of a particular expression.

Submitted June 21, 1951.

Up to now we have found an unbelievable number of names in medical literature for what has been apparently considered the same condition: Idiopathic achlorhydria, achlorhydria constitutionalis (Schmidt); achylia gastrica simplex (Martius); achylia gastrica constitutionalis (Schmidt); pseudo-achylia gastrica (Henning); unexplained achylia gastrica (Bloomfield and Polland); histamine refractory achylia gastrica, apparent achylia gastrica (Bockus); partial achylia gastrica (Forsgreen); esential achlorhydria (Winkelstein), and more.

One has been led to believe that the introduction of the fractional gastric test with histamine stimulation has brought about a clearing up between the abovementioned *'true'* and *'false'* conditions. The claim is

that we can speak of a 'true' achlorhydria, anacidity or achylia gastrica only when at no time during digestion is free hydrochloric acid found by means of the fractional alcohol method and histamine injection. The 'false' condition exists when the gastric contents show no free hydrochloric acid with the Boas-Ewald test meal, or with fractional withdrawal, but when, after histamine injection, free hydrochloric acid will be found.

Henning, however, has seen in many cases of histamine refractory achlorhydria the proof become positive some time later, and Faber writes that in complete anacidity, and even in histamine refractory cases, it is by no means unusual for the acid secretion to return. Therefore, Henning and Norpoth make this appraisal: "Is the histamine test able to differentiate between the functional achylia gastrica and the organic one?" They conclude that the different forms of achylia gastrica cannot be distinguished by the alcohol-histamine test.

Of what value, then, for the diagnosis of achylia gastrica is the fractional alcohol test with histamine injection? So Bockus is seemingly refuted in his opinion that all diagnoses of achylia gastrica *before* the introduction of the fractional gastric analysis and, more particularly, *before* the use of histamine must be discarded.

Of course this was a very singular point of view, because achylia gastrica was discovered and diagnosed incontestably before the introduction of these tests; we can say, in fact, that all the important papers about achylia gastrica were written *before* these tests were used. I will venture further by stating that, in my opinion, with the advent of the fractional alcohol and histamine tests, our previous knowledge of achylia gastrica has today been set aside as inapplicable and the present confusion has come about. The abundance of terms alone is a clear sign of the obscurity surrounding the problem and our ignorance of it. The history of diseases shows that the moment there is certainty about a given disease, all the different terms like 'true', 'false', 'pseudo' disappear immediately.

How could this 'hopeless' situation have arisen, and why is it apparently impossible to bring clarity to these simple and uncomplicated conditions, anacidity, achlorhydria, achylia gastrica? Our first and most important question, therefore, is one of definition.

Today's definitions are:

Achlorhydria: Lack of hydrochloric acid

Anacidity: Lack of acid

Achylia gastrica: Lack of hydrochloric acid and ferments.

We are at a point where achylia gastrica must be rediscovered. It is always helpful and enlightening, if there is something obscure about a disease, to go back to the papers of those who first described it. In his excellent monograph, published in 1897, Martius writes: "Achylia gastrica exists only when, besides hydrochloric acid, there is lack of the ferments. Yes, strictly speaking—and this will prove to be very important—there must be proof that there is *no secretion at all.*" What does this mean: That, for a diagnosis of achylia gastrica, there must be lack of *all secretions*—rennin, pepsin, lipase, mucin, the intrinsic factor, water and whatever may be found in the future. It is what the name, exquisitely coined by Einhorn expresses—a-chylos—the stomach does not produce gastric juice; it is free from any juice whatsoever, and therefore the emphasis should not be placed merely on lack of hydrochloric acid.

Does it not seem paradoxical to diagnose with a liquid test (alcohol) a condition the most important symptom of which is the absolute lack of gastric juice? Originally this entity was worked out by means of the Boas-Ewald test meal. When an easier method of testing for the intrinsic factor is found, the differentiation between achylia gastrica and achlorhydria will prove to be very simple.

The entity 'achylia gastrica' shows three strictly circumscribed signs:

1) Absolute lack of gastric juice, with lack of all the constituents of the gastric secretion.

No free HCl; chloride concentration very low; reaction is often alkaline. The quantity of liquid is minimal; only a few cc, presumably from the intake of tea during the test meal.

2) Disturbance of chymification.

There is no pulpy digestion of the gastric content, so the expressed residue of the test meal consists of what seems to be only chewed crumbs. There is little mucus; often traces of blood and particles of the mucous mucosa, due to the vulnerability of the mucosa.

A *liquid* anacid gastric content, even if it contains coarse bread particles, does not permit the diagnosis of achylia gastrica.

3) Disturbance of motility.

Increase of the expulsion phase of the stomach. The stomach expels the test meal generally in half the normal time up to a few scanty remnants. Normal expulsion time after Boas-Ewald's test meal is about 45 minutes; but in achylia gastrica it is accomplished in 20-25 minutes; the stomach is almost empty 40-45 minutes after intake of the test meal. One can observe the rapid emptying of the stomach on x-ray examination (it is just the contrary in achlorhydric conditions where we find a slow emptying time).

These three changes (in secretion, chymification, motility) are such typical findings after expulsion of the Boas-Ewald test meal that it is almost possible to make the diagnosis "achylia gastrica," as Martius once said, with the naked eye.

The alcohol test with histamine injection gives us information only on the hydrochloric acid secretion. Histamine refractory cases have been described where some time later free hydrochloric acid has been found; therefore the test no longer decides the differential diagnosis between achylia gastrica and achlorhydria (Henning, Henning and Norpoth, Faber). With these tests we cannot prove lack of secretion (although diminished secretion has been found by Goldhamer, Wintrobe; Bloomfield and Polland) and certainly not the chymification and motility of the stomach.

Only the Boas-Ewald test meal gives us proof of these three conditions and therefore must, of necessity, be used for a diagnosis of achylia gastrica.

II

All writers who consider achylia gastrica, achlorhydria and anacidity an identical condition because there is no free hydrochloric acid state that a *gastritis* with

inflammatory and atrophic changes is the cause of this condition.

In their opinion, the changes in the gastric mucous membrane are caused by a great number of 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 parenchyme (Faber).

The causes of this gastritis can be:

Gastric carcinoma, chronic gastritis, gallbladder disease, tuberculosis, Graves' disease, chronic arthritis, alcoholism, subacute combined sclerosis, pernicious anemia, hypochromic anemia, pellagra, sprue, anorexia nervosa, Simmond's disease, gastric lues, gastrogenous diarrhea, nephritis, diabetes mellitus, gastrogenous intestinal disturbances.

Mouth infections, focal infections, any infection (local and general), circulating toxins, allergic toxins. Acute infections: Typhoid, paratyphoid, pneumonia, influenza, dysentery, appendicitis, morbilli, diphtheria. Defective denture.

Irritants: Strong tea, coffee in excess; curry, pickles, pepper, mustard.

Drugs, such as: bromide, iodine, mercury, digitalis, quinine, salicylates; too many cigarettes.

Hot food, cold food, improper food, coarse food, decomposed food; too much food, too little food; rapid eating.

On the basis of this evidence, merely taken from textbook after textbook, one can only ask: Is there anyone who has no gastritis? Bloomfield and Polland rightly state that such a concept obviously reduces the whole subject to an absurdity! One might also ask: Is there such a thing as normal stomach mucosa? Guiss and Stewart have ascertained that 82 per cent of apparently normal persons who died within the cancer age (over 40) show, microscopically, evidence of chronic atrophic gastritis. Only at birth, and during the first and second decade did they find no pathological changes. In adults, the round-cell infiltration is actually to be considered *normal* (Benedict and Mallory; Paschkis and Orator; Hebbel, Hamperl, Hillenbrand, Jones, Magnus, Crohn).

The main advocate of the gastritis theory is Knud Faber. His idea is that primarily there is a gastritis which is produced by external factors, and this leads secondarily to the absence of free hydrochloric acid (Kuttner, Boas, Henning and others). Also, according to *Faber,* achylia gastrica or achlorhydria is always, and under all circumstances, a disease which develops in a stomach heretofore apparently absolutely normal, at any time of life, and as a result of external factors.

Martius has exactly the opposite point of view. He considers achylia gastrica a separate entity, having nothing in common with achlorhydria but the absence of free hydrochloric acid. He repudiates the exogenic factor for achylia gastrica. He sees in it a definite, permanent and unalterable condition without any gastritis. In his opinion, the glandular cells of the stomach develop histologically apparently normally, but they function poorly or not at all. It is this primary achylia gastrica simplex or constitutionalis—and it alone—this is closely connected with pernicious anemia.

In other words, there are two entirely different fundamental opinions: According to the prevailing opinion, achlorhydria or anacidity or achylia gastrica are the same disease—merely different names for the same condition. The opposite opinion differentiates between achylia gastrica and achlorhydria or anacidity: 1) *Achlorhydria* is lack of free hydrochloric acid; a symptom found in many conditions and of no clinical significance; secondary to exogenic causes. 2) *Achylia gastrica,* on the other hand, *is complete absence of gastric juice; primary, constitutional and the precursor of pernicious anemia.*

To prove the accuracy of the supposition that achylia gastrica differs from achlorhydria, it was of the greatest importance to know whether a gastritis is really always the cause of the disappearance of free hydrochloric acid, and whether the pathological changes are the same in achylia gastrica as in achlorhydria.

The first who contradicted Faber's opinion was Weinberg (1918), after the examination of eleven stomachs of patients with achylia gastrica who died of pernicious anemia. He stated that there was no gastritis at all in any of his eleven cases.

He divided his cases into three groups: Group 1. Three cases: No changes of gland cells; only very slight round-cell infiltration; no atrophy. Group 2. Five cases: Slight atrophy; slight gland cell changes in cardia and fundus; pylorus free. Group 3. Three cases: Intense atrophy of cardia and fundus; pylorus free.

The result of these examinations was:

1) The pathological changes were limited to fundus and cardia; pyloric region showed no changes, even in cases with intensive atrophy.

2) In three of eleven cases there was no change whatever of the gastric mucosa which was normal.

There were cases with only slight atrophy, others with progressive atrophy.

There was *no* inflammatory gastritis in the eleven cases of achylia gastrica in pernicious anemia. A gastitis, consequently, cannot have been the cause of lack of gastric juice. Achylia gastrica can exist with normal gastric mucosa.

Einhorn, Lubarsch have described the same phenomenon on the basis of examinations of mucosal particles; Ricker, in 1906, described the postmortem findings of the stomach mucous membrane of a patient with achylia gastrica, who died of pernicious anemia, as *"absolutely normal"* ("no gastritis, no atrophy"). Lubarsch and Borchardt showed that in 16.5 per cent of their 121 cases of pernicious anemia even roughly recognizable pathological changes of the stomach did not exist. Passey (1922) found normal oxyntic cells and no evidence of inflammation in a fragment of gastric mucous membrane removed during an appendectomy on a patient with Addison's pernicious anemia; Madeleine Brown found one case of pernicious anemia with entirely normal mucosa. Crohn, Hurst speak of simple achylia gastrica with normal gastric mucosa; Wallgren among 18 cases, in three cases "no atrophy could be traced out."

The findings of Weinberg—no inflammation and no pathological changes of the pylorus—are confirmed

by Magnus and Ungley (1938), Meulengracht (1939), Cox (1942), Wallgren (1943).

Magnus and Ungley examined seven cases in which they found severe atrophy but no evidence of past inflammation. In all seven stomachs there was atrophy of fundus and cardia, but no suggestion of atrophy or inflammatory lesions in the pyloric mucosa. They conclude that the gastric lesion present in pernicious anemia is not the end result of an inflammatory gastritis; it is regarded as an atrophic process, the cause of which is not known. Cox saw the same picture in six, Meulengracht in eight cases. Cox found the lesions in the cases of pernicious anemia different from those of so-called "chronic gastritis," to the extent that the changes and distribution may represent a "specific change."

Wallgren, on examination of 18 cases of pernicious anemia, found atrophic changes in the fundus. Contrary to the results of the other examiners, however, he saw pathological changes in the mucosa of the pylorus, too. But the atrophy was much more evident in the fundus than in the pylorus. While all authors found only high atrophy, Weinberg and Wallgren saw a gradual transition—from normal to intensive atrophy:

	No atrophy	*Mild atrophy*	*Intensive atrophy*
Weinberg	3	5	3
Wallgren	3	4	8

Bockus, Bank and Willard; Jones, Sturgis and Goldhamer; Doig and Wood confirm the findings that it is not a question of an inflammatory process. It is an atrophic degeneration of the secretory structure. In my opinion, it is a progressive *inactivity atrophy;* "disuse of structure results in atrophy" (McCallum). If we have inflammatory changes in cases of achylia gastrica, and no doubt there can be such, they are of secondary nature and have nothing to do with the presence of achylia gastrica.

An explanation for the peculiar findings, that only the cardia and fundus of the stomach show atrophic changes whereas the pylorus is free, has been given by Fox and Castle. They proved "that, in men, the important sites of secretion of the intrinsic factor are in areas containing the fundus type of glands and that the observations suggest that the source of the intrinsic factor in the normal human stomach coincides with the site of the degenerative process seen in histologic preparations of the stomach in pernicious anemia;" confirmed by Landboe-Christensen and Plum.

III

Although it has been known for a long time that free hydrochloric acid is absent from the stomach in cases of pernicious anemia, there have been attempts to prove otherwise. Wintrobe speaks of lack of free hydrochloric acid in at least 97.6 per cent of cases; he finds "at least 36 cases have been described in which free hydrochloric acid was found in the gastric secretion of otherwise typical cases of pernicious anemia." Naegeli estimates that achlorhydria is found in 98 per cent of all cases of pernicious anemia.

When I started my work on pernicious anemia, I was astonished to find that in *all* my cases (105 at that time) hydrochloric acid was absent; but the condition was not merely absence of free hydrochloric acid—it was typical achylia gastrica simplex or constitutionalis. Martius (1897) had already recognized the association of achylia gastrica—not achlorhydria—with pernicious anemia.

The question was: Is pernicious anemia regularly, and without exception, accompanied by achylia gastrica? With this in mind, a careful study was made of all cases of pernicious anemia described with *normal* gastric juice. Not a single case was found which was an actual case of pernicious anemia (1918).

Since that time, a number of cases of pernicious anemia with free hydrochloric acid again have been described. In his critical analysis of these cases, Askey reported on 47 cases with free hydrochloric acid, but "none of these 47 cases has been proved by complete precise criteria to be Addison's pernicious anemia" (1944). Again and again, certain cases are quoted which attempt to demonstrate the existence of Addison's pernicious anemia with free hydrochloric acid. Such are Castle's two cases. But Castle himself diagnosed one of these cases as sprue; the other as "macrocytic anemia with chronic diarrhea following operations resulting in multiple intestinal anastomoses." In addition, there are the two cases by Barnett, of which Bloomfield and Polland say "they are a stumbling-block to the categorical acceptance of the theory of achylia gastrica with pernicious anemia." In my opinion, both cases are sprue although Barnett calls one of them "atypical primary anemia."

Recently, two more cases have been published as Addison's pernicious anemia, with normal gastric acidity and no intrinsic factor. In A. Murphy's case, however, the sternal biopsies first undertaken after the beginning of liver treatment and for the second time during relapse—did not show the typical picture: "failure to disclose a megaloblastic marrow picture." All the "logical and adequate reasons to explain it" for the second sternal biopsy cannot be considered valid. In this case of Murphy's we do not find a typical example of the disease, and the picture is more normocytic than macrocytic. To draw such an important conclusion, i.e. that achlorhydria (he does not say achylia gastrica) is not essential to the development of Addison's pernicious anemia, one must describe an absolutely incontrovertible case. Here only facts and not explanations count.

Benjamin's case (infantile form of pernicious anemia), with normal gastric juice and no intrinsic factor, differs from the normal picture of pernicious anemia: There was no tendency to the development of spontaneous remissions, so characteristic of pernicious anemia—not only in adults, but also in typical cases of childhood. As a result, today, no doubt, all who write with authority are of the opinion that a diagnosis of Addison's pernicious anemia with normal gastric juice must be an error (Martius, Weinberg, Askey, Ewald, Zadek, Wintrobe; Bloomfield and Polland; Bockus, Bank and Willard; Wilkinson, Goldhamer, Sturgis, Crohn, Schwartz etc.). The fact is stressed that the disturbance of the gastric secretion (achylia gastrica) in pernicious anemia never changes, in spite of liver therapy and an absolutely normal blood picture; the achylia gastrica is unchangeable.

In the future it must be determined whether the gastric content in dubious cases shows a typical picture of achylia gastrica, or whether it is only achlorhydria. The work of Castle has given us a better understand-

ing of the connection between achylia gastrica and pernicious anemia. He proved that the gastric juice contains a substance—the intrinsic factor—which acts on an element present in protein food—the extrinsic factor—to produce the normal stimulant, the anti-anemic substance, for the formation of red blood corpuscles in the bone marrow. The result of the absence of the intrinsic factor is the blood defect characteristic in pernicious anemia.

No diagnosis of pernicious anemia should be permitted when there is no achylia gastrica; in the absence of achylia gastrica, pernicious anemia (Addison-Biermer) does not exist.

That achylia gastrica is something totally different from achlorhydia can be proved when we compare the achlorhydria in other conditions (such as cancer of the stomach, tuberculosis or alcoholism) with achylia gastrica in pernicious anemia.

Let us give some statistics. In tuberculosis of the lungs, Permin and Hansen saw in 658 cases: Achlorhydria (and hypochlorhydria) in 38 per cent, divided as follows:

Stage I: 23 per cent, Stage II: 34 per cent, Stage III: 47 per cent. In cases that died at least six months later: 75 per cent. We see, therefore, that the frequency of anacidity depends upon the stage of the disease. Torning saw only 6 per cent, Henning 26 per-cent anacidity.

The same picture is evident in cancer of the stomach. Hydrochloric acid diminishes during the course of the disease from normal to zero (Riegel).

	1) *Hartman*	2) *Mimes and Geschickter*
Among 551 cases of stomach cancer:		Among 339 cases
Anacidity	54 per cent	64.6 per cent
Hypoacidity	16 per cent	35.9 per cent
Normal values	17.5 per cent	6.7 per cent
Hyperacidity	4.5 per cent	——

Bloomfield and Polland saw loss of hydrochloric acid (with histamine test) in 69 per cent; Kelling, 75 per cent (622 cases); Hurst, 65 per cent (74 cases); Brunschwig, Schmitz and Rasmussen in about 60 per cent: Hebbel and Gaviser, 65 per cent. That the increase of achlorhydria is concurrent with the progress of cancer is shown in White's statistics:

Anacidity in group of earlier cancer: About 50%.

Anacidity in group of later cancer: About 75% up to 80 or 90%.

The presence of free hydrochloric acid is closely related to operability (White, Katsch, Eusterman and Bueerman).

Let us consider another condition very often associated with achlorhydia: Alcoholism. In 128 patients who were confirmed alcoholics, Vogelius found in 56 per cent of them achlorhydia on admission. In a large number of patients this achlorhydria disappeared quickly with treatment.

On the other hand, the development of achylia gastrica has never been observed (Weinberg, Cornell, Wilkinson and others). Not one case of pernicious anemia has been reported where normally functioning gastric mucosa was demonstrated before the start of the disease. Many cases have been documented in which achylia gastrica has been found up to 40 years before the manifestations of pernicious anemia (Einhorn, Schauman, Martius, Weinberg, Sturtevant, Queckenstedt; Cornell, Riley, Faber, Eggleston, Cobert and Morawitz; Johannsen, Askey, Strandell, Meulengracht, Vanderhof; Rozendaal and Washburn, Jorgensen and Warburg, Beebe and Wintrobe, Lichty and others).

CONCLUSION

Achlorhydria in cancer, tuberculosis and other diseases can be observed in its origin. There is a gradual, progressive diminution of free hydrochloric acid which parallels the progressive severity of the disease. Achlorhydria, therefore, is to be found only in a certain percentage of the cases. When the benign condition is cured—as in alcoholism and bad teeth—it is reversible.

Achylia gastrica, in sharp contrast, is to be found in pernicious anemia 100 per cent. It is never progressive. It is present not only at the onset of the disease but prior to it.

IV

There is no longer any doubt that achylia gastrica precedes the rise and development of pernicious anemia; but there is no agreement about the significance of this pre-existent achylia gastrica.

There are two opposing points of view: 1) Achylia gastrica is the earliest prodromal symptom of pernicious anemia, often present before the onset of pernicious anemia. (Both of coordinate origin, Faber; collateral phenomenon, Meulengracht.) 2) Achylia gastrica is the basis for the rise of pernicious anemia. Without achylia gastrica there is no pernicious anemia.

If observations were correct—that achylia gastrica always precedes pernicious anemia and that pernicious anemia cannot exist without achylia gastrica—then it should be possible to demonstrate the development of pernicious anemia, and to make an early diagnosis by systematic blood examinations of the cases of achylia gastrica.

It is evident that pernicious anemia must have a beginning and not, as formerly has been asserted, an *end* but *no beginning*. Of course there have been attempts to make an early diagnosis by the most exact observation of all signs and symptoms of pernicious anemia, but without any success (Plehn).

In my examination of 77 cases of achylia gastrica with 110 blood tests, I found four different types:

1) Cases with normal findings=22 per cent

2) Cases with hypochromic anemia (of chlorotic type)=26 per cent

3) Cases with hyperchromic ('normal') blood picture (latent cases)=17 per cent

4) Cases with pernicious anemia blood picture (early cases)=12 per cent

Of interest to us are groups 3 and 4 only.

These examinations showed that in a great number, the hemoglobin content was over 100 per cent and the amount of erythrocytes above 5,000,000.

In four cases we saw the findings of polycythemia (hemoglobin 130, 130, 135, 139; erythrocytes 6.1, 6.1, 6.4, 6.9 millions). Polycythemia has been found so often in connection with ulcus ventriculi that Bing be-

lieves it is due to the gastric secretion. On the other hand, there has been observed a transition from polycythemia to pernicious anemia (Freund; Minot and Buchman, Makarevicz, Avery; Delhougne, Gotschlich and Froboese, Christian). In Christian's case there was a longstanding achylia gastrica; Risak and Schur saw achylia gastrica in polycythemia.

The following is a case of achylia gastrica with very high hemoglobin and transition to pernicious anemia.

Female—56 years old

	Achylia gastrica	*Hemoglobin*	*Erythrocytes*	*Color Index*	*Leucocytes*
1919		120	5,000,000	1.2	6,100
1920		110	4,000,000	1.4	6,400
1921		67	2,400,000	1.4	5,400

Patient died in 1924. Autopsy revealed pernicious anemia.

The leucocytes in our cases (108 examinations) were:
Normal (6,000-9,000) in 56 cases=52%
Increased (above 9,000) in 22 cases=20%
Diminished (below 6,000) in 30 cases=28%
The diminished amounts are distributed:
6—5,000 in 18 examinations
5—4,000 in 7 examinations
4—3,000 in 4 examinations
Below 3,000 (2,885) in 1 examination

The percentage of lymphocytes was increased (over 30 per cent) in 54 examinations (from 67 cases), equaling 82 per cent.

Let me give the picture of several blood examinations in personally observed cases of achylia gastrica.

TABLE I.

	Sex	*Age*	*Hemoglobin*	*Erythrocytes*	*Color Index*	*Leucocytes*	*Lymphocytes %*	*Monocytes*
1.	M	31	92	4,300,000	1.1	11,000	43	3
2.	F	30	98	4,100,000	1.2	7,300	34	3
3.	F	45	106	5,000,000	1.1	7,800	30	2
4.	M	56	103	4,400,000	1.2	8,800	44	4
5.	F	47	90	4,000,000	1.1	4,700	34	0.75
6.	F	31	90	4,000,000	1.1	6,200	54	6.5
7.	M	46	105	4,900,000	1.1	6,200	40	3
8.	F	40	100	4,350,000	1.2	5,000	41	4
9.	M	56	86	3,800,000	1.1	5,700	43	1
10.	F	32	93	4,300,000	1.1	6,100	32	5.5

In case 1: Father died from pernicious anemia.
In case 2: Mother suffered from pernicious anemia.
In case 3: One brother has pernicious anemia.

The most striking feature in all these cases is the *macrocytosis*. With color index above 1 we see polychromacy sporadically, but very often poikilocytosis and anisocytosis. In all these cases there was relative lymphocytosis, often leucopenia with hypersegmentation; diminished monocytes, diminished platelets. In separate instances we saw normoblasts, in a few cases myelocytes and promyelocytes, even myeloblasts. The diagnosis in our cases was *latent* pernicious anemia. There are changes in the blood picture in microscopically small form, which, increased, would show the typical picture of pernicious anemia.

These ten cases were potential cases of pernicious anemia. In fact, seven of them developed pernicious anemia during the next six years. Three could not be followed.

Here are some of our cases (described by Stahl) with special consideration of the platelets.

TABLE II.

	Sex	*Achylia gastrica*	*Hemoglobin*	*Erythrocytes*	*Color Index*	*Leucocytes*	*Platelets*
1.	F	—	110	4,000,000	1.4	4,900	365,800
2.	F	+	106	4,200,000	1.3	5,800	125,000
3.	F	+	100	4,700,000	1.1	5,100	90,000
4.	F	+	96	4,700,000	1.0	4,700	122,000
5.	F	+	94	4,100,000	1.2	5,100	126,000

The following case is an example of transition from normal to pernicious anemia observed for sixteen years. The patient was sent regularly by the state insurance company for examination at the hospital.

Male—32 years old in 1906

	Diagnosis	*Hemoglobin*	*Erythrocytes*	*Color Index*	*Leucocytes*
1906	Achylia gastrica: neurasthenia	Tallquist 90-100	—	—	—
1908	Achylia gastrica	—	—	—	—
1909	Achylia gastrica	—	—	—	—
1915	Achylia gastrica	104	4,500,000	1.2	13,300
1918	Achylia gastrica	65	2,600,000	1.3	5,600
1921	Achylia gastrica	47	1,400,000	1.7	2,600
1922	Achylia gastrica	35	850,000	2.1	1,300

The patient died in 1922 (9 remissions). Autopsy showed pernicious anemia.

Achylia gastrica was only an incidental finding because in our hospital the gastric analysis was as routine an examination as urinalysis. In 1915, when I saw the patient for the first time, as in every case of achylia gastrica, the blood was examined. It was a so-called 'normal' specimen. Who would have thought of latent pernicious anemia with 104 per cent hemoglobin? Nevertheless, this diagnosis was entertained in view of past experience. Seven years later the patient died of pernicious anemia.

It was O. Schauman who first (1912) described a case that was at this time a very early case of pernicious anemia. Hemoglobin: 85 per cent; erythrocytes: 2,400,000; color index: 1.75; leucocytes: 3,700 with

30 per cent lymphocytes; poikilo-anisocytosis; strongly marked megalocytosis, and of course, achylia gastrica. The hemoglobin content was extremely high for a diagnosis of pernicious anemia at this time. It caused Schauman to establish the very important fact (not yet totally understood and valued) that there can be pernicious anemia with normal and above normal hemoglobin content. Naegeli's and Zadek's early cases show the same picture.

Naturally there exist examinations of the blood in achylia gastrica, but, strange to say, very few and of only two kinds: Normal cases and cases with hypochromic anemia. All writers have been interested only in studying the connection between achylia gastrica and hypochromic anemia. All the non-anemic cases are registered as 'normal'.

Among Einhorn's cases of achylia gastrica, two showed pernicious anemia; eleven were 'normal'. But two of his 'normal' cases are of particular interest:

	Age	*Hemoglobin*	*Erythrocytes*	*Color Index*	*Leucocytes*
1.	30	100	4,235,000	1.2	5,700
2.	25	100	4,580,000	1.1	7,600

Among Polland's 56 cases I find eight described as 'normal', with a color index above 1 (hemoglobin in 3 cases: 100, 105, 107). Meulengracht described a case of a child with achylia gastrica, a blood relative in a family with pernicious anemia. The examination showed: Hemoglobin, 98; red cells 3,000,000; color index 1.6; megalocytosis; average red cell diameter, 8.8μ; leukopenia, bilirubinaemia, urobilinuria; glossitis. Cary found in 4 out of 23 cases a high color index. Askey writes about 'normal' blood findings, but in six cases the color index is above 1, and in three there is macrocytosis. He considered 10 of his 61 cases with achylia gastrica "potential cases of pernicious anemia who in later years might develop the disease." Over a six year period, four in fact developed apparent incipient pernicious anemia (relatives of patients with pernicious anemia). Borgbjärg and Lottrup saw the color index over 1 in 22 among 134 patients; megalocytosis was found in 15 per cent, most often in patients with high color index.

In 18 of his white counts, Carey found the total average of leucocytes less than 7,000; in 3 cases, less than 5,000. Kohn saw a low number of leucocytes in 10 cases. In the last few years, further observations have been published of achylia gastrica with color index above 1, and megalocytosis (Frank; Ungley and Suzman; Chevallier, Lehmann—these French authors call it métanémie; Warburg and Jorgensen; Beebe and Wintrobe). Only Rozendaal and Washburn obtained different results: Among 36 cases with achlorhydria, they found the color index above 1 in only 2 cases; in all others, within the normal range.

The transition from achylia gastrica to pernicious anemia has been seen by Strandell who examined 117 cases of pernicious anemia. In 22, the gastric juice was searched several years before pernicious anemia appeared. Of course, there was no indication or even suspicion of pernicious anemia at that time. All 22 cases had achylia gastrica and a few years later pernicious anemia. Unfortunately, only two blood examinations were made in these 22 cases:

		Hemoglobin	*Erythrocytes*	*Color Index*	*Leucocytes*	*Achylia Gastrica*
Case 1.	1916	80-90	5,000,000	—	5,900	+
	1917	40	—	—	—	+
	1918	56	1,763,000	1.6	5,888	+
Case 2.	1922	95	5,000,000	.95	6,200	+
	1924	38	1,400,000	1.4	5,800	+

Diagnosis in both cases was pernicious anemia.

One case by Schauman:

	Hemoglobin	*Erythrocytes*	*Color Index*	*Leucocytes*	*Achylia Gastrica*
1911	93	3,660,000	1.2	3,660	+
12/19/1919	67	2,530,000	1.3	2,100	+
12/26/1919	52	2,240,000	1.3	2,000	+

Martius (1897) described among 17 patients with achylia gastrica two who under his observation developed pernicious anemia. There are other cases by Hutchinson, Meulengracht; Schneider and Cary (4 cases); Schemm, Frank (twins), Askey, Strandell; Kaufmann and Thiessen.

Bloomfield and Polland reject the connection between achylia gastrica and pernicious anemia, because they have observed 64 patients with total anacidity for varying periods up to five years without the development of pernicious anemia. Barnett, Crohn; Wilkinson and Brockbank are of the same opinion.

Wills points to the importance of the time factor: After total gastrectomy, there may be a period as long as ten to fifteen years between the time of operation and the development of symptoms. The time element is again indicated in Schemm's record: Mother and son had achylia gastrica; the mother developed pernicious anemia at the age of 63, the son at 24.

V

For a long time there was a controversy as to whether achylia gastrica occurs among infants and children. One believed it to be nonexistent so early in life.

In recent years, however, numerous cases have been described which prove beyond a doubt that achylia gastrica does occur among newborn infants and children. Among infants it has been described by Lehmann—1 out of 30, 12 months old, histamine-fast achylia gastrica; Faber and co-workers—6 out of 10, ages from 7 months to two years; Cutter—4 out of 10 healthy infants in the neonatal period with histamine; Miller—6 out of 50 normal infants examined

daily for the first ten days of life; Peterson and Dunn—girl, 13 months old; Zuelzer and Ogden—9 out of 10 infants, ages 2 to 16 months with histamine; Dedichen—girl, 9 months old.

Zuelzer and Ogden call our attention to the fact that achlorhydria in infants must be interpreted with a great deal of caution. In many cases it cannot be definitely decided, on the basis of the histamine test alone, whether it is a case of achylia gastrica or achlorhydria. Several cases, however, have been described where achylia gastrica still existed when reexamination was made after many years: Miller, 2 years later; Faber, first examination at 8 months, reexamination 7 years later; Peterson and Dunn, from 13th month, followed to the age of 5½ years.

As long ago as 1913, Albu described achylia gastrica among children: 34 cases of achylia in children under 10 years; his youngest was four years old. He observed family occurrence seven times. Martius, Queckenstedt, Weinberg have long ago shown the occurrence of achylia gastrica among children of parents with pernicious anemia; later, Wilkinson and Brockbank, Siemsen; McLachlan and Kline; Moschcowitz and Crohn, Martinez and others. Copeman and Hill reported 7 cases in 66 normal children between the ages of 12-15; Wright saw only 1.6 per cent in children from 6-15 years. (Others by Katsch, Schmidt.)

Achylia gastrica is accompanied in children by the same changes of the blood as in adults: Hypo- and hyperchromic anemias. From a remark of Leonard Findley, however, we learn that he has come across children in whom he found an "idiopathic achlorhydria" with *no obvious anemia.*

In hypochromic anemia the achylia gastrica persisted after the anemia had been cured by the administration of iron (Hawksley, Lightwood and Bailey, Wilson; Dacie and Elman, Ogilvie and others). In cases of hyperchromic or macrocytic anemia, we must distinguish between two separate types. There are those with macrocytic blood picture, normal gastric secretion or temporary achlorhydria; complete and permanent recovery can be brought about by diet or liver or folic acid (Zuelzer) treatment, spontaneous recovery; no tendency to relapse (Zuelzer and Ogden, Veeneklaas). The others have achylia gastrica, marked tendency to relapse and need continuous treatment. Only these cases should be considered pernicious anemia Addison-Biermer. Peterson and Dunn want "the use of the term 'pernicious anemia in childhood' to be restricted, as it is in general medicine, to those cases of macrocytic anemia in which there is a complete and continuous achlorhydria, in which the patient shows a specific response to liver therapy, and in which continuous therapy is required to maintain the patient in a state of remission." In order to obtain absolute clarity, we shall, in future, speak of achylia gastrica instead of 'complete and continuous achlorhydria.' Parson and Hawksley, Davis; Karlström and Nordenson share this view on achylia gastrica.

If we consider these rigid and justified demands as a basis, we can regard only a few cases as typical pernicious anemia. Peterson and Dunn: Girl, with anemia from 8th month, followed from the age of 13 months to 5½ years; Dedichen: Boy, followed from the age of 9 months to the age of 3 years; Edgren and Segerdahl: Boy, aged 1½ years, under observation to the age of 3 years; Langmead and Doniach: Boy, 13 months, follow-up period 3 months; Pohl: Girl, 13 years old, follow-up period 3 years; Kade: Boy, followed from 7 to 14 years of age; Murphy: 11 years old, observed 3 years; Jacobsen: Boy, 14 years old.

We have four cases of pernicious anemia occurring in infancy which satisfy the strictest critic. Among older children, more cases are to be definitely regarded as pernicious anemia, even though they do not meet the requirements of Peterson and Dunn, since they had been described prior to liver therapy (Kusunoki, von Seht, Hotz, Brückner).

Stewart is of the opinion that achylia gastrica is not found in healthy children. Miller emphasizes that his infant with achylia gastrica was a "strong healthy child" from birth. Cutter mentions expressly that his children were healthy ones. It is to be assumed that Stewart confuses achlorhydria with achylia gastrica. There is no "cause" of achylia gastrica; it is inborn, as Miller's case proves.

To penetrate deeper into this question, we must make systematic stomach examinations of the children of parents suffering from pernicious anemia or achylia gastrica.

VI

An important element in achylia gastrica is *heredity.* P. White and G. Pincus have stated four factors in favor of the theory that the potentiality for developing diabetes is inherited. In a separate paper, I have shown the likeness of the conditions in diabetes and achylia gastrica. The four factors prove the same for achylia gastrica.

First Factor: Almost simultaneous occurrence of achylia gastrica and pernicious anemia in both members of identical twins.

Second factor: The greater incidence of achylia gastrica and pernicious anemia in the blood relatives of patients with achylia gastrica and pernicious anemia than in those of a control.

Third factor: The demonstration of Mendelian ratio.

Fourth factor: The demonstration of expected ratios for achylia gastrica and pernicious anemia in presumably latent cases.

The *first factor:* The occurrence of achylia gastrica and subsequently of pernicious anemia in uni-ovular twins proves the influence of heredity. We have knowledge of seven definite cases of identical twins with achylia gastrica (Strandell, Ellis, Frank, Werner; Kaufmann and Thiessen, Bremer, Stamos). Four pairs had achylia gastrica with pernicious anemia; in the three other pairs, one twin had pernicious anemia and the other achylia gastrica developing into pernicious anemia.

Frank's case is a good example of the development from achylia gastrica to achylia gastrica with macrocytosis to pernicious anemia:

Twin brothers—aged 57. One has achylia gastrica with pernicious anemia. Other twin has achylia gastrica. *Blood is normal.*

Ten months later: Second twin, hemoglobin normal; color index 1.13. Achylia gastrica with *macrocytosis.*

Fifteen months later: Both brothers have *pernicious anemia.*

The *second factor:* The familial occurrence of pernicious anemia is a fact. In the course of recent years, many single cases and family observations have been published in which the appearance of the disease in several members of one family has been shown. Complete statistical studies have been given by Wilkinson and Brockbank, and by Stamos. Further evidence is shown by MacLachlan and Kline in four generations; Mustelin, Schwartz in three generations; five members in one family by Bramwell, Wilson, Askey, Patek, Dorst, Schemm, Moschcowitz and many more.

What of the familial occurrence of *achylia gastrica?* Biedert, as early as 1895, pointed out the possibility that the lack of gastric secretion is a familial attribute, inborn by predisposition or hereditary in its origin.

Weinberg, led by the fact of the invariable occurrence of achylia gastrica in pernicious anemia, for the first time systematically examined relatives of patients with pernicious anemia for achylia gastrica and found it in 29 per cent. Conner saw familial achylia gastrica in 25.9 per cent, Askey in 16 per cent, Wilkinson and Brockbank in 24.1 per cent.

Askey, Werner, Kaufmann and Thiessen saw achylia gastrica in relatives of pernicious anemia patients to be twice as high in *near* relatives as in *distant* ones.

	Near Relatives	*Distant Relatives*
Werner	19 per cent	9 per cent
Kaufmann and Thiessen	17.1 per cent	9.4 per cent

Among the general population, the number of achylia gastrica was 13.7 per cent by Hartfall; Andreasen, Eggleston saw it in 10 per cent, Jeffrey in 11.8 per cent, Conner in 15.2 per cent. In contrast, Bennett and Ryle found it only in 4 per cent among 100 healthy medical students; Lander and MaClagan in 1 per cent; Doig and co-workers in only 1 out of 134 students.

The comparison of the findings shows:

1) Occurrence of pernicious anemia in relatives of patients with pernicious anemia.

	Per Cent
Schemm	18.70
Castle and Minot	18.00
Schwartz	18.00
Kaufmann and Thiessen	16.70
Werner (about)	9.00
Schneider and Carey (between 6 and 12%)	9.00
Wilkinson and Brockbank	8.75
Naegeli (about)	8.00
Stamos	7.90
Levine and Ladd	6.30
Average	12%

2) Occurrence of achylia gastrica in relatives of patients with pernicious anemia.

	Per Cent
Weinberg	29
Conner	25.9
Wilkinson and Brockbank	24.1
Zadek	21.7
Askey	16.4
Schneider and Carey (at least)	12
Kaufman and Thiessen (near and distant relatives)	13.25
Werner (near and distant relatives)	14
Average about	19.6%

Of the *third factor* we can only say that a definite conclusion regarding the mode of hereditary transmission cannot yet be stated. We lack real demonstrable scientific hereditary research. Mustelin, Weitz; Kaufmann and Thiessen, Werner are of the opinion that achylia gastrica is transmitted as a dominant characteristic.

Fourth factor: Demonstration of expected ratios in presumably latent cases. The blood examination of my 77 cases of achylia gastrica showed 29 per cent had changes which allowed the diagnosis of latent or early pernicious anemia. In a great number of such cases it is possible to observe the transition to pernicious anemia.

Another factor, to which Colwell called attention in diabetes mellitus, is the so-called "anticipation." This means that a hereditary disease in three generations of a single family appears from generation to generation at an earlier age. In Mustelin's case, pernicious anemia appeared in the mother at 67, daughter at 42, grandchild at 24; all had typical achylia gastrica. We assume that, due to the congenital achylia gastrica, there is a diminished storage of the antianemic principle in the liver, and that the exhaustion becomes effective at an earlier age in each successive generation.

Additional interesting evidence for heredity has been given by Horsters and Krohn: In one family in which mother and oldest son had pernicious anemia, there was at the same time an inheritance bound to blood group A. Besides these two manifest cases, all members of the family with blood group A had a hyperchromic blood picture.

Further proof of heredity is given by the pathological findings. We have seen cases of achylia gastrica who died of pernicious anemia without atrophy of the gastric mucosa; the gastric mucosa was normal (Weinberg, Wallgren).

In their comprehensive statistics, Wilkinson and Brockbank differentiate among three groups:

1) Families with two or more members affected with pernicious anemia.

2) Families in which pernicious anemia and achylia gastrica existed simultaneously.

3) Families in which achylia gastrica was found without pernicious anemia.

In reality there is only *one* group: The families with achylia gastrica. Some of these achylic members will develop pernicious anemia. Wherever there is a family tree with achylia gastrica, there is a mixed occurrence of achylia gastrica and pernicious anemia. I, personally, have never seen families where the members had nothing but pernicious anemia or achylia gastrica (groups 1 and 3); careful and extensive examination always showed that achylia gastrica and pernicious anemia existed simultaneously.

VII

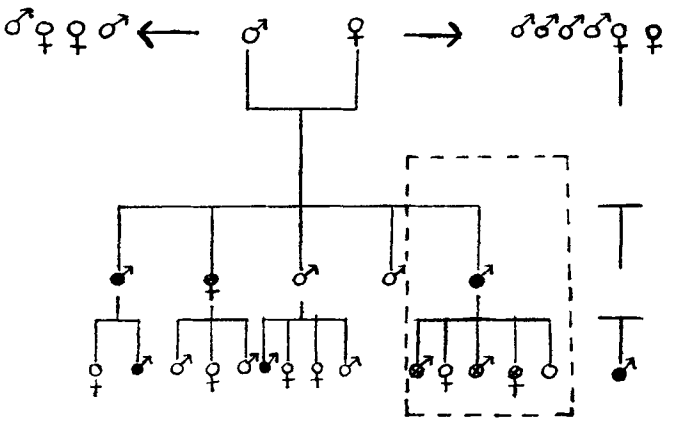
What is the practical value of true hereditary incidence in achylia gastrica?

We have seen that it is possible to make the diagnosis of pernicious anemia in its latent stage with normal or above normal hemoglobin and erythrocytes. We are familiar with the deficient factor in the form of liver or other substances; we know persons with achylia gastrica are potential cases of pernicious anemia: Is it not then logical to give such persons the lacking substance as soon as possible, thereby

forestalling the development of pernicious anemia and subacute combined degeneration of the cord?

The task is to find these cases with achylia gastrica constitutionalis. The procedure is systematically to examine all the relatives of a patient suffering from pernicious anemia or of a patient with achylia gastrica constitutionalis. Otherwise, it is a chance finding because people with achylia gastrica do not 'suffer'; they rarely have complaints. They do not visit a physician's office, especially not the gastro-enterologist's. To get valuable results, there must be an examination of every patient's genealogical tree—of all the living antecedents and descendants. It must cover all collateral relatives, including aunts, uncles, cousins, etc. It has to be a clan-examination, so-called 'Sippschaftstafel,' which means all blood-relatives near and distant, first described by Crzellitzer.

Figure I.



Genetic Diagram

Open circles: No gastric change
Filled circles: Macrocytic achylic anemia
Crossed circles: Achylia gastrica
Clan-examination: 21 relatives, indicating the familial incidence of achylia gastrica with macrocytic achylic anemia

Let us examine an actual case: In a patient with pernicious anemia, five children could be examined. Three had achylia gastrica. The family examination showed that, of the 21 relatives, 8 had achylia gastrica, and 4 out of those 8 had pernicious anemia. This examination did not reveal the source of the inherent factor. A thorough examination of sisters and brothers of the parents (four from his father's, six from his mother's side) gave no clue—the gastric examinations were normal. But an aunt (his mother's sister) had married a man whose name was on our list of patients with pernicious anemia, and a grandson of hers actually had pernicious anemia.

For the detection of other cases of achylia gastrica or pernicious anemia, all the descendants of the six uncles and aunts of our patient should have been examined. This is the only way to find the persons with achylia gastrica. It is a formidable task. But it must be done and it has already started in Germany and Italy.

The method of procedure should be as follows: A certain institution in a given district is appointed, to which every case of pernicious anemia should be reported, by the physician or by the hospital: Name, address, diagnosis. From here the work starts: The institution must search the whole genealogical tree of the patient with all the collaterals. (A similar but more comprehensive method was followed in diabetes mellitus which proved very successful, Wilkerson and Krall). A gastric analysis and blood examination have to be performed upon each of these relatives. Those with achylia gastrica are potential cases of pernicious anemia as long as they live (see case of Schemm, page 357).

What should we do with these persons with achylia gastrica constitutionalis who seem to be absolutely healthy and have 'normal blood?' There are two possibilities. The first is the scientific way: To examine these persons at regular intervals, for instance every six months, to find out how many of them show blood and nerve changes in the course of time, and the rate of development. The second way is to treat these potential cases prophylactically, with liver or the other helpful substances, so as to prevent the development of pernicious anemia.

I am convinced that in all the cases of achylia gastrica constitutionalis, in which we have seen the transition to pernicious anemia, well-timed treatment with the antianemic principle would have averted the manifestation of the deficiency disease (see the cases of Strandell, Askey, Frank's twin brother, Meulengracht, Dorst, our own cases).

It is a 'mass experiment' and will achieve its goal only after a long period of time. But the goal will be worth while: The prevention or eradication of pernicious anemia. To achieve this goal we must enlighten physicians and patients alike. The physician must have more knowledge about the heredity of achylia gastrica and its connection with pernicious anemia, and he must convince the patient with pernicious anemia of the necessity for family examinations. It was never a difficult matter to explain this to our patients; most patients are interested in the facts of heredity and are grateful for enlightenment. While there were never any difficulties in obtaining consent for the blood examinations, there were sometimes objections to the gastric examinations; but these objections must somehow be overridden since, of the two, gastric examination is the more important.

The blood examination should not be just routine; it should be effected with special care and with appreciation of all useful methods (platelets, erythrocyte diameter, bone marrow puncture).

Originally the disease was named progressive pernicious anemia. To distinguish it from the other macrocytic anemias, it is at present known as pernicious anemia Addison-Biermer. It is time to give the disease a more accurate name, since the word 'pernicious' fortunately no longer applies; the disease is one of deficiency marked by an inborn, constitutional lack of gastric juice—achylia gastrica. Therefore the most significant designation for this disease is *'macrocytic achylic anemia.*

SUMMARY AND CONCLUSIONS

Achylia gastrica and achlorhydria are not synonymous.

Achlorhydria is lack of free hydrochloric acid, a symptom found secondarily in many diseases and conditions, and of no clinical significance.

Achylia gastrica is complete absence of gastric juice, primary and constitutional.

The differentiation is of greatest importance because achylia gastrica—not achlorhydria—leads to pernicious anemia.

The entity achylia gastrica shows three strictly circumscribed signs:

1) Absolute lack of gastric juice

2) Disturbance of chymification

3) Disturbance of motility

These three signs, necessary for the diagnosis of achylia gastrica, can be determined only by the Boas-Ewald test meal.

For the diagnosis of achylia gastrica the alcohol test meal with histamine injection is of minimal value, because it shows only the presence or absence of hydrochloric acid.

Achylia gastrica is not based upon a gastritis atrophicans. It can exist with normal gastrica mucosa. The changes are not inflammatory; they are atrophic—not in the pylorus, only in cardia and fundus—leading to the final stage of inactivity atrophy.

Blood examinations in achylia gastrica often show hemoglobin and erythrocyte values above normal. In many cases so-called 'normal blood' has been found, but there were changes which permitted the diagnosis 'latent or early penicious anemia.' There is macrocytosis with Color Index above 1, lymphocytosis, leukopenia with hypersegmentation, diminished monocytes, diminished platelets. From this stage the development of pernicious anemia has been seen.

The achylia gastrica is unchangeable. The development of achylia gastrica has never been observed.

Achylia gastrica has been detected in infants and children, especially in families where one parent had pernicious anemia. There is a familial occurrence of achylia gastrica; it is inborn, hereditary.

Our goal is to find these cases of achylia gastrica. For this reason all the relatives, antecedents and near and distant descendants, must be examined; a so-called clan-examination. It is suggested that these examinations be made at the central institution of a given district which collects all the names of patients with pernicious anemia and directs the examinations.

As potential cases of pernicious anemia, all persons with achylia gastrica must be under steady observation.

The question is: Shall we not give these people with achylia gastrica the factor necessary to forestall the development of pernicious anemia, and thereby, perhaps, eradicate the disease?

The name "pernicious anemia" is now misleading, since the disease is no longer pernicious. Furthermore, we have shown the importance of achylia gastrica which alone leads to "pernicious anemia." Therefore, because this disease belongs in the group of macrocytic anemias, I suggest that it be henceforth designated *macrocytic achylic anemia.*

BIBLIOGRAPHY

Albu, A.: Therapie der Gegenwart, 54:433, 1913.
Andresen, A. F. R.: Ann. Clin. Med., 5:472, 1926.
Askey, J. M.: Ann. Int. Med., 14 1:593, 1940.
Askey, J. M.: Gastroenterology, 2:1, 1944.
Avery, H.: Lancet, 1:342, 1930.
Barnett, C. F.: Am. J. M. Sci., 182:170, 1931.
Beebe, R. T. and Wintrobe, M. M.: Arch. Int. Med., 51:630, 1933.
Benedict, E. B. and Mallory, T. B.: Surg. Gynaec. & Obst., 76:129, 1943.
Benjamin, B.: Am. J. Dis. Child., 75:143, 1948.
Bennett, T. L. and Ryle, J. A.: Guy's Hosp. Rep., 71:286, 1921.
Biedert and Langermann: Diatetisches Kochbuch fur Magen und Darm Kranke, 1895, Stuttgart, F. Enke.
Bloomfield, A. L.: Stanford M. Bull., II:5, 1944.
Bloomfield, A. L. and Polland, W. S.: Gastric Anacidity, 1933, The McMillan Co., New York.
Bloomfield, A. L. and Polland, W. S.: J. Clin. Invest., 14:32, 1935.
Bockus, H. L.: Gastro-Enterology, Vol. I, W. B. Saunders, Phila. and London, 1943.
Bockus, H. L., Bank, J. and Willard, J. H.: Am. J. M. Sci., 184: 185, 1932.
Borgbjarg, A. and Lottrup, M. C.: Acta Med. Scand., 72:539, 1929.
Bramwell: cit. Stamos.
Bremer, F. W.: Der Erbarzt, 1:17, 1934.
Brown, M. R.: New Engl. J. Med., 210:473, 1934.
Brueckner, M.: Jahrb. Kinderhk.; 114:370, 1926.
Brunschwig, A., Schmitz, R. L. and Rasmussen, R.: J. Nat. Cancer Inst., 1:481, 1941.
Carey, J. B.: Minn. Med., 9:385, 1926.
Castle, W. R., Townsend, W. G., Heath, C. W. and Strauss, M. B.: Am. J. M. Sci., 182:741, 1931.
Castle, W. R.: New Engl. J. M., 226:903, 1942.
Castle, W. R. and Minot, G. R.: Oxford Medicine, Oxford Univ. Press, New York, Vol. II, Part 2, 589.
Chevallier, P.: Prat. Med. Franc., 15:583, 1934.
Cobet, R. and Morawitz, P.: Z. angew. Anatomie und Konstit., 6:244, 1920.
Colwell, A. R.: Arch. Int. Med., 70:523, 1942.
Conner, H. M.: Staff Meet. Mayo Cl., 4:200, 1929.
Conner, H. M.: J. A. M. A.: 94:606, 1930.
Copeman, W. S. C. and Hill, N. G.: Lancet, 1:718, 1929.
Cornell, B. S.: Medicine, 6:375, 1927.
Cornell, B. S.: Pernicious Anemia, Duke Univ. Press, 1927.
Cox, A. J.: Am. J. Path., 19:491, 1943.
Crohn, B. B.: 52 Meet. Assoc. Life Ins. Directors, 29:74, 1942.
Crohn, B. B.: J. Mt. Sinai Hosp., N. Y., 11:75, 1944.
Crzellitzer: Familienforschung in Grotjahn und Gaupp: Handwoerterbuch der Sozialen Hygiene, Leipzig, Vogel, P. 326.
Cutter, R. D.: J. Pediat., 12:1, 1938.
Dacie, J. V. and Elman, P. H.: Brit. J. Child. Dis., 39:97, 1942.
Davis, D. and Vanderhoof, D.: Virginia Med. Monthly, 57:250, 1930-31.
Davis, L. J.: Arch. Dis. Childh., 19:147, 1944.
Dedichen, J.: Acta Med. Scand., 111:90, 1942.
Delhougne, F., Gotschlich, E. and Froboese. Deutsches Arch. Klin. Med., 160:257, 1928.
Doig, R. K., and Wood, I. J.: Med. J. Australia, 37: 566, 1950.
Doig, R. K., Motteram, R., Weiden, S. and Wood, I. J.: Lancet, 1:948, 1950.
Dorst, S. E.: Am. J. M. Sci., 172:173, 1926.
Edgren, G. and Segerdahl, E.: Acta Med. Scand., 134:235, 1949.
Eggleston, E. L.: J. A. M. A., 97:1216, 1931.
Einhorn, M.: Med. Record, 41:650, 1892.
Einhorn, M.: Med. Record, 45:780, 1894.
Einhorn, M.: Arch. Verdauungsk., 9:147, 1903.
Einhorn, M.: Diseases of the Stomach, Wm. Wood Co., New York, 1929
Ellis: cit. Hurst, Brit. M. J., 2:665, 1934.
Eustermann and Bueerman: quoted by White.
Ewald, C. A.: Kraus-Brugsch, Specielle Path. und Therapie, Vol. VIII:1216, 1920.
Ewald, C. A.: Berlin. Klin. W., 32:527, 1886.
Faber, H. K.: Am. J. Dis. Childh., 36:1121, 1928.
Faber, H. K., Mermod, G., Gleason, A. C. and Watkins, P. R.: J. Ped., 7:435, 1935.
Faber, K.: Berlin. Klin. W. 1:958, 1913.
Faber, K.: Gastritis and its Consequences, Univ. Press, Oxford Med. Publ., 1935.
Faber, K. and Lange, G.: Zeitschr. Klin. Med., 66:53, 1908.
Findley, L.: cit. Dacie and Elman.
Forsgreen, E.: Nordisk Medicine (Hygeia), 31:1603, 1946.
Fox, H. J. and Castle, W. R.: Am. J. M. Sci., 203:18, 1942.
Frank, H.: Deutsches Arch. Klin. M., 175: 96, 1933.
Freund, H.: Muench. Med. W., 66:84, 1919.
Goldhamer, S. H.: Am. J. M. Sci., 191:405, 1936.
Guiss, L. W. and Stewart, F. W.: Arch. Surg., 46:823, 1943.
Hamperl, H.: Wiener Kl. W., 45:515, 1932.
Hartfall, J.: Guy's Hosp. Rep., 82:13, 1932.
Hartman, H. R. and Sager, W. W.: J. A. M. A., 83:1976, 1924.
Hartman, H. R. and Sager, W. W.: Med. J. and Rec., 124:96, 1926.
Hawksley, J. L., Lightwood, R. and Bailey, U. M.: Arch. Dis. Childh., 9:359, 1934; 10:143, 1935.
Hebbel, R.: Am. J. Path., 19:43, 1943.
Hebbel, R. and Gaviser, D.: Surgery, 24: 512, 1940.
Henning, N.: Die Entzuendung des Magens, Leipzig, 1934, J. A. Barth.
Henning, N. and Norpoth: Kl. W., 11:159, 1932.
Hillenbrand, K.: Beitr. Path. Anat. und Allg. Path., 85:1, 1930.
Horsters, H. and Krohn, W.: Deutsche Arch. Kl. Med., 173:271, 1932.
Hotz, A.: Jahrb. Kinderhk., 105:161, 1924.
Hurst, A. F.: Lancet, 1:111, 1923; 1:719, 1929; 2:1023, 1929.
Hutchinson, K.: Clinical Journ., 33:193, 1909.
Jacobsen, A. K. F.: Nordisk Medicine, Hospitalstidende, 35:1469, 1947.
Johannsen, A. H.: J. A. M. A., 92: 1728, 1929.
Jeffrey, J. R.: quoted by Eggleston.
Jones, C. M.: Am. J. Dig. Dis., 8:205, 1941.
Kade, H.: Zeitschr. Kinderhk., 65:47, 1947.
Karlstrom, F. and Nordenson, G.: Acta Paed., 32:58, 1944-45.
Katsch, G.: Handbuch der Inneren Medizin, Vol. 3, Berlin, J. Springer, 1938.
Kaufmann, O. and Thiessen, K.: Zeitschr. Klin. Med., 136:474, 1939.
Kelling, G.: Arch. Verdauungsk., 15:568, 1909.
Kohn, E.: Wiener Kl. W., 41:1221, 1928.

Kusunoki, M.: Korresp. Schweizer Aerzte, 44:533, 1916.
Kuttner, L.: Zeitschr. Klin. Med., 45:1, 1902.
Kuttner, L.: Kraus-Brugsch, Handb. der Spez. Path. und Ther., Vol. 8, 1920.
Landboe-Christensen, E. and Plum, C. M.: Am. J. M. Sci., 215:17, 1948.
Lander, F. P. L. and MaClagan, N. F.: Lancet, 2:1210, 1934.
Lange, G.: Arch. Verdauungsk., 10:1, 1904.
Langmead, F. S. and Doniach, I.: Lancet, 1:1048, 1937.
Lehmann, H.: Berichte ges. Physiologie, 87:347, 1935.
Lehmann, R.: Thesis, Paris, E. Le Francois, 1936.
Levine, S. A. and Ladd, W. S.: Bull. Johns Hopkins Hosp. 32:254, 1921.
Lichty, J. A.: J. A. M. A., 2177, 1907.
Lubarsch, O.: in Martius, Achylia Gastrica, 1897.
Lubarsch, O. and Borchardt, H. in Henke & Lubarsch: Handb. Spez. Path. Anatomie und Histologie, 4/3:1, 1929.
MacLachlan, W. W. and Kline, F. M.: Am. J. M. Sci., 172:533, 1926.
Magnus, H. A.: J. Path. and Bact., 58:325, 1946.
Magnus, H. A. and Ungley, C. C.: Lancet, 1:420, 1938.
Makarewicz, V.: Klin. W., 7:1054, 1929.
Martinez, F. F.: Medicina Ibera, 1:118, 1927.
Martius, F.: Achylia Gastrica, 1897, Leipzig und Wien, F. Deuticke.
Martius, F.: Med. Klin., 1:8, 1904.
Martius, F.: Med. Klin., 12:481, 1916.
Meulengracht, E.: Am. J. M. Sci., 169:177, 1925.
Meulengracht, E.: Med. Welt, 12:132, 1938.
Meulengracht, E.: Am. J. M. Sci., 197:201, 1939.
Miller, R. A.: Arch. Dis. Child., 16:22, 1941; 17:198, 1942.
Minot, G. R. and Buchman, Th. E.: Am. J. M. Sci., 166:469, 1923.
Moschcowitz, E.: Arch. Int. Med., 48:171, 1931.
Moschcowitz, E.: J. Mt. Sinai Hosp., N. Y., 10:796, 1944.
Murphy, A.: Med. J. Australia, 35:521, 1948.
Murphy, W. P.: Anemia in Practice, Phila., 1939.
Mustelin, O.: Acta. Med. Scand., 56:411, 1922.
Naegeli, O.: Deutsches Arch. Klin. M., 124:221, 1917.
Naegeli, O.: Fol. haemat., 58:320, 1937.
Ogilvie, J. W.: Arch. Dis. Childh., 9:327, 1934; 9:93, 1935; 10:143, 1935.
Parsons, L. G. and Hawksley, J. C.: Arch. Dis. Childh., 8:143, 1933.
Paschkis, K. and Orator, V.: Z. Anat. und Entwicklungsg., 67:494, 1923.
Passey, R. M.: Guy's Hosp. Report, 72: 172, 1922.
Patek,: J. A. M. A., 56: 1315, 1911.
Permin, G. E.: Gastritis ved Lungetuberkulose, Kobenhavn, 1909.
Peterson, J. C. and Dunn, S. C.: Am. J. Dis. Child., 71:252, 1946.
Pincus, G. and White, P.: Am. J. M. Sci., 181:1, 1933.
Plehn, A.: Berlin Klin. W., 44:742 & 748, 1907.
Pohl, C.: Monatschr. Kinderhk., 84:192, 1940.
Polland, W. S.: Arch. Int. Med., 2:903, 1933.
Queckenstedt, H.: Deutsche Med. W., 39:883, 1913.
Ricker: cit. Martius, Med. Klin., 1:8, 1904.
Riley, W. H.: Battle Creek Sanit. and Hosp. Bull., April, 1923.
Riley, W. H.: J. A. M. A., 85:1908, 1925.
Risak, E.: Wiener Ges. inn. Med., Febr., 1932.
Rozendaal, H. M. and Washburn, R. N.: Ann. Int. Med., XI:1834, 1937-38.
Schur: Wiener Ges. inn. Med., Febr., 1932.
Schauman, O.: Deutsche M. W., 26:1228, 1912.
Schauman, O.: Z. angew. Anat. und Konst., 6:258, 1920.
Schemm, F. R.: Am. J. M. Sci., 199:167, 1940.
Schmidt, R.: Med. Klin., 15:595, 1912.
Schmidt, R.: Klin. W., 2081 and 2117, 1932.
Schneider, J. P. and Carey, J. B.: J. A. M. A., 91: 1763, 1928.
Schwartz, H. O.: Med. Clin. in North America, 28:214, 1944.
Siemsen, W. J.: Am. J. Dis. Child., 44:1013, 1933.
Stahl, R.: Z. angew. Anat. und Konst., 6:301, 1920.
Stamos, H. F.: Am. J. M. Sci., 200:586, 1940.
Stewart, A.: Brit. J. Child. Dis., 34:1, 1937.
Strandell, B.: Acta Med. Scand., Suppl., 40:1, 1931.
Sturgis, C. C.: Ann. Int. Med., 10:283, 1936.
Sturgis, C. C., and Goldhamer, S. H.: Ann. Int. Med., 12:1245, 1939.
Sturtevant, M.: J. A. M. A., 85:1638, 1925.
Torning, K.: Klin. W., 18:1261, 1929.
Ungley, C. C.: Newcastle Med. J., 10:14, 1929.
Ungley, C. C. and Suzman, M. J.: Brain, 52:271, 1929.
Veeneklaas, G. M. H.: Fol. haemat., 65:303, 1941.
Vogelius, F.: Arch. Verdauungsk., 24:278 and 346, 1918.
von Seht, L.: Z. Kinderhk., 18:15, 1918.
Wallgren, J.: Nordisk Med., 20:2061, 1943.
Warburg, E. J. and Jorgensen, H.: Acta. Med. Scand., 70:193, 1929.
Weinberg, F.: Deutsches Arch. Klin. Med., 126:447, 1918.
Weinberg, F.: Z. angew. Anat. und Konst., 6:289, 1920.
Weinberg, F.: Muench. M. W., 5:165, 1925.
Weinberg, F.: Proc. Rudolph Virchow Med. Soc. in City of N. Y., 5:8, 1946.
Weinberg, F.: Am. J. Dig. Dis., 17:398, 1950.
Weitz, W.: Vererbung innerer Krankheiten, Stuttgart, 1936, F. Enke.
Werner, M.: Verh. Deutsche Ges. inn. Med., 50 Kongress: 303, 1938.
White, F. W.: Nelson Loose-Leaf Medicine, Vol. 5, p. 2993, Thos. Nelson and Sons, 1946.
Wilkerson, H. L. C. and Krall, L. P.: J. A. M. A., 135:209, 1947.
Wilkinson, J. F.: Quart. J. Med., 361, 1932.
Wilkinson, J. F.: Lancet, 1:293, 1949.
Wilkinson, J. F. and Brockbank, W.: Quart. J. Med., 24:219, 1930-31.
Wills, L.: Blood, 3:36, 1948.
Wilson, R.: Canadian M. A. J., 41:176, 1939.
Winkelstein, A.: Am. J. M. Sci., 203:419, 1942.
Wintrobe, M. M.: Clinical Hematology, Lea and Febiger, Phila., 1943.
Wright, C. B.: Arch. Int. Med., 33:435, 1924.
Zadek, J.: Berlin Klin. W., 58:1253, 1921.
Zuelzer, W. W.: J. A. M. A., 131:7, 1946.
Zuelzer, W. W. and Ogden, F. N.: Am. J. Dis. Child., 71:211, 1946.

EFFECT OF A LYSOZYME INACTIVATING ANION EXCHANGE POLYMER IN TREATMENT OF PEPTIC ULCER: EXPERIMENTAL AND CLINICAL STUDY

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REGARDLESS OF THE various psychic factors that are invoked in the pathogenesis of chronic peptic ulcer, it is generally agreed that the combined action of hydrochloric acid and pepsin are determinant factors both in its persistence, the failure of healing, and the production of symptoms. In 1910 Schwartz (1) enunciated the dictum "No acid—no ulcer," a statement confirmed as recently as 1949 by the work of Palmer and his school (2). As stated by them, "Chronic peptic ulcer occurs only in association with acid gastric secretion; achlorhydria lasting longer than 3 months produces complete healing of peptic ulcer, irrespective of the age of the patient or the duration of the disease; and spontaneous or induced achlorhydria, if present, produces permanent healing of peptic ulcer." (2b).

Standard in all regimens of treatment of peptic ulcer has been the use of bland diets and antacids. Of the latter, a plethora of preparations is available. While some have produced satisfactory results, none are free of unpleasant side effects, and some, chiefly sodium bicarbonate, have actually shown serious toxic effects over prolonged periods such as ingestion alkalosis (3), and increased blood urea nitrogen (4). Thus, also, protein hydrolysates as recommended for ulcer therapy (5) have induced progressive rises in gastric acidity and prolongation of gastric emptying time (6). Even multiple cream and Sippy powder feedings have been shown to evoke an increased volume of gastric secretion, with increased acid and pepsin activity as compared with a single feeding (7).

The untoward effects have led to further search for potent antacids without these undesirable side effects. Adams and Holmes (8) first called attention to the adsorptive properties of synthetic resins in 1935, and these were first employed by Segal and associates (9) ten years later to reduce gastric acidity in rats. They, however, found such large amounts necessary as to make the clinical use of resins for this purpose of doubtful value. The difficulty was overcome by Martin and Wilkinson (10) who, by reducing the size of

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Submitted June 13, 1951.