In conclusion, I would call attention to the work of the nurses and attendants at our large mental institutions. I have been impressed by the quickness and the sureness with which they detect the onset of bodily illness in the inmates under their charge. Usually it is by some very slight change in behaviour or appearance, either not eating their dinner or being less irritable, or perhaps some change in their colour. This is noted and reported at once. Their duties are often exceedingly trying, and if anything goes wrong public sympathy is not usually on their side. It is therefore a pleasure to take this opportunity of stating that those with whom I have come in contact have shown a care and interest in the patients under their charge which is in every way worthy of praise. I am much indebted to members of the medical staff of the South Yorkshire Mental Hospital for help in preparing this paper, especially to Drs. Gillespie and Mathieson for clinical records, and to Dr. Thorpe for pathological notes. For permission to make use of the material and for every assistance in so doing, my thanks are due to Dr. W. J. Vincent, medical superintendent of that institution at the time.

SOME OBSERVATIONS ON ACHLORHYDRIA AND ANAEMIA *

BY

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We define achlorhydria as the condition in which there is an absence of free hydrochloric acid in the gastric juice. Actually we do not often test directly for this acid. Knowing that a certain degree of acidity (pH 3) can, in practice, only be due to hydrochloric acid, the direct chemical test becomes unnecessary. If no portion of the gastric juice is acid to a certain indicator (that is, red to Töpfer's reagent) no free acid can be titrated: this is achlorhydria in the usually accepted sense, and in this sense is employed here.

TESTING FOR ACHLORHYDRIA

We have at once to recognize that failure to secrete acid on carrying out a test upon the stomach may vary to some extent in the same individual and also with the stimulus to secretion which is employed. By applying a powerful stimulus to gastric secretion we may call forth acid which a milder stimulus may fail to provoke.

An ordinary meal is presumably the most natural physiological stimulus to the secretion of gastric juice, and the earlier tests of gastric secretion made use of 2 oz. of dry toast and 8 oz. of unflavoured tea (Ewald), or 1/2 oz. of boiled rolled oats reduced to a pint (Ewald-Boas). This material, after remaining in the stomach for three-quarters of an hour, was withdrawn and tested. This form of test is still in vogue on the Continent, and many of the older statistics relating to achlorhydria, both here and in America, are based upon it. The principal objection to this test is that all the stomach contents are withdrawn after they have remained in the stomach for, say, three-quarters of an hour, and we learn nothing about secretion after this. In some persons there may be a considerable delay in the production of acid, and it is easily possible that a case which is achlorhydric according to the Ewald test, may not actually be so. The incidence of achlorhydria, using this test, therefore tends to be high.

The fractional test meal, popularized by Rehfuess in America and Bennett and Ryle in this country, and used in this hospital, consists in withdrawing samples of the gruel meal, administered after the fasting juice has been withdrawn, at quarter-hour intervals for three hours. Each sample may be analysed, and a dynamic picture of the fluctuations of gastric

secretion during digestion is obtained. Delayed acid secretion will usually be revealed, and statistics demonstrating the incidence of achlorhydria based on this test show that it is rather less common than the Ewald test would suggest.

Recently the introduction of a powerful stimulant to gastric secretion which can be administered subcutaneously has given considerable impetus to further studies. This drug—histamine—administered in suitable dosage, according to body weight of the individual, causes, within a very few minutes, a copious flow of gastric juice unaccompanied by any other disturbance. The gastric juice so obtained is pure and uncontaminated by food, and is eminently suitable for analysis. Histamine is probably the most powerful stimulant to acid secretion we possess, and when a case fails to secrete acid following the appropriate dose of histamine, it is truly achlorhydric. A proportion of cases achlorhydric in the fractional test meal do produce acid on histamine stimulation.

ITS DISTRIBUTION

The incidence of achlorhydria as shown by these various tests by different workers, for all age periods, is probably about 14 per cent. My own series, collected from patients under Dr. A. F. Hurst at the New Lodge Clinic, is comfortably average (13.7 per cent.).⁶ I think the inference we can draw is that *about 14 per cent. of the average population of all ages is achlorhydric*. Nearly all observers have found that achlorhydria is commoner in females than in males. This was so in my series for all age periods, except between 20 and 40 years. This higher incidence among healthy females is disclosed also when histamine is used. The influence of age has become of considerable importance because of its bearing upon the hereditary, constitutional, and acquired factors which predispose or actually induce achlorhydria and related disturbances in gastric secretion. All types of tests of gastric secretion (including the most recent ones with histamine) show that the incidence of achlorhydria increases with age. This was especially noteworthy in my own series among females beyond the age of 40. Information about achlorhydria in infants is a little uncertain, but beyond the age of infancy we know that the incidence slowly and surely increases. When large series of investigations are put together this increase occurs with a regularity and smoothness which suggests that a true biological fact is revealed.

ITS PATHOLOGY AND SIGNIFICANCE

We have next to consider how, or by what mechanism, achlorhydria develops, and what is its significance. Complete proof does not exist that changes in the mucous membrane of the stomach always and necessarily accompany achlorhydria. The necessary correlations between impaired gastric secretions and the histology of the cells of the mucous membrane of the stomach at all ages have not yet been made. The association of achlorhydria with so many diseases, however, strongly suggests that in a large majority of cases it must have a very definite pathological significance. At the same time we must recognize that its presence may be compatible with apparent normal health, although there are many who believe that achlorhydria always has a serious significance, if not at the moment, then certainly in the future. We cannot ignore the nervous factor. We know that nervous influences, emotional upsets, and psychological factors may play a part in inhibiting gastric secretion. The very emotional upset which may accompany the passing of the stomach tube in a nervous subject may be sufficient to inhibit the acid secretion for a time. In such a patient, employing the older methods, achlorhydria might result according to the first test, and free acid would be obtained

* A lecture delivered to the Leeds and West Riding Medico-Chirurgical Society, November, 1933.

when the test was repeated. Acid secretion can also be suppressed by suggestion, as, for example, fear suggested under hypnosis. If such are the effects of transient emotional stimuli, it is possible that more permanent changes may be induced through the visceral nervous system by prolonged emotional stimuli, such as the fear element which is associated with psychoneurotic states. For many years it has been maintained that constitutional factors play an important part in the aetiology of achlorhydria. The evidence afforded by test meals carried out on newborn or very young babies is at present equivocal. On the whole, the incidence of achlorhydria is sufficiently high to suggest that some (genotypical) inherited factor is at work. Further support for this view, however, is found by the tendency of achlorhydria to occur in many members and several generations of one family. Thus Conner found 25.9 per cent. achlorhydria among 154 blood relatives of patients suffering from pernicious anaemia. This constitutional factor becomes of importance when we consider those instances of familial pernicious anaemia, simple achlorhydric anaemia, and families which show both these diseases and symptomless achlorhydria (Gram,⁵ Witts,¹⁶ Heath,¹¹ Witts and Hartfall⁷).

ACHLORHYDRIA AND CHRONIC GASTRITIS

Having considered achlorhydria from the point of view of heredity, the next point is to consider the definite underlying pathology of the gastric mucosa which most commonly accompanies achlorhydria—namely, chronic gastritis. The view that chronic gastritis accounts for the development and persistence of achlorhydria was first put forward by Hayem and Faber,⁴ and has many supporters. It is well established that all stages of chronic gastritis, even to complete atrophy of the gastric glands, may be found in the gastritis of pernicious anaemia, and to a less extent in simple achlorhydric anaemia, Graves's disease, etc. It is possible that alterations in the functional secretory capacity of the stomach may precede demonstrable chronic gastritis. Inspection of the gastric mucous membrane in cases of achlorhydria during life by means of the gastroscope, however, frequently reveals a changed appearance of the mucous membrane which is interpreted as chronic gastritis. There is one other aspect of the aetiology of achlorhydria which must be mentioned. Vanzant and Alvarez,¹³ and also Pollard,¹ have shown that the average acidity for healthy individuals is higher in males than in females. In both sexes, as age advances, this average or mean acidity is progressively lowered. Finally, achlorhydria is reached, and among females it is reached, on an average, earlier. The higher incidence among women is accounted for by the above findings carried to their logical conclusion. If gastritis cannot account for these phenomena the alternative is to regard them as "involutional changes," the secreting mechanism becoming "played out" upon slight provocation, or spontaneously (Bloomfield and Pollard¹).

My own belief, which I find most useful in understanding this difficult problem, is as follows. I believe that there exists a hereditary predisposition to the cessation of normal gastric secretion, the basis of which is a gastric mucous membrane of functionally subnormal type. This subnormal mucosa may easily be disturbed by various factors. Many of these injurious agencies are exactly those which cause gastritis, and, in this particular inherited hyposecretory type, achlorhydria quickly results. The multiplication of these injurious factors as age advances accounts for the increasing incidence with age. The higher incidence in females can only be accounted for by the strain which the reproductive functions—menstruation, pregnancy, and lactation—throw on the economy of the female organism.

ITS CLINICAL APPLICATIONS

What, then, is the clinical importance of this condition of achlorhydria? The best evidence of its importance is obtained by a consideration of those diseases with which it is associated and especially those which it precedes, where it is regarded as an essential predisposing condition to the disease in question.

1. It almost invariably precedes and accompanies true Addisonian pernicious anaemia and subacute combined degeneration, and it persists after the cure of the blood and nervous condition.

2. It precedes, accompanies, and persists after the cure of the simple achlorhydric anaemia—the most important member of the chronic microcytic group of anaemias.

3. It precedes and accompanies the commonest type of carcinoma of the stomach—that is, carcinoma *ex gastritis*.

4. It is present in an ill-defined group of conditions of ill-health where chronic gastritis often exists; it accompanies frequently the asthenic neurotic diathesis, conditions of gastro-intestinal irregularity and upset, debility, and, often, soreness of the mouth and tongue. It is also present in a significant proportion of cases of rheumatoid arthritis, asthma, and allergic diseases, Graves's disease, diabetes, etc., where its exact significance is disputed.

5. It may result from a variety of gastric operations (to be considered later), and in a proportion of them seems to account for certain post-operative conditions of chronic ill-health.

6. It may be encountered in normal health, when its prognostic significance is disputed.

It is important to realize that the suggestion is not made that mere lack of hydrochloric acid secreted in the stomach is directly responsible for every symptom associated with these various disorders; sometimes this may be the case, but more often the achlorhydria is simply an indication that something is wrong with the secretory apparatus, and that combined with this defect in acid secretion are other defects which are more directly concerned with the particular pattern of ill-health which may be present. So far as the blood is concerned with these gastric secretory changes, the loss of acid is not always the most important thing.

CLASSIFICATION OF ANAEMIAS

A simple classification of anaemia based on modern work is given in Table I. It shows us that the two forms of anaemia in which achlorhydria is commonly found are closely related from the aetiological standpoint. Both are examples of failure of proper maturation or development of red cells, due to the lack of some agent or principle necessary for their complete development. This incomplete development has been called by Witts "anhaemopoiesis," and the whole group of anaemias, the "anhaemopoietic anaemias."¹⁵

TABLE I.—Classification of Anaemia

<i>Blood Loss :</i>	<i>Blood Destruction :</i>
Acute.	Haemolytic anaemias.
Chronic.	Acute (Lederer), poisons, of pregnancy, etc.
	Chronic acquired, acholuric jaundice, etc.
<i>Inhibition of Blood Formation :</i>	
Anhaemopoiesis: Complete—aplastic, anaemia.	
	Incomplete—arrested maturation of red blood cells due to deficiencies. (A) Megalocytic anaemia—for example, Addisonian pernicious anaemia (due to deficiency of anti-pernicious anaemia factor). (B) Microcytic anaemia—for example, simple achlorhydric anaemia (due to failure of absorption or utilization of iron).

Anhaemopoiesis

Group A.—Classical Addisonian pernicious anaemia is characterized by a tendency for the majority of the circulating cells to be larger in size, and often carrying more haemoglobin per cell. The bone marrow shows megaloblastic degeneration. The colour index is high. The anaemia is therefore megalocytic, and is also called hyperchromic, though the latter is a bad name. The anaemia develops when the anti-anaemic principle, as found in the liver, is deficient. This principle, in turn, depends upon the presence of an active ferment-like substance in the gastric juice, called haemopoietin,¹⁴ and its interaction with certain extrinsic substances associated with the proteins of the diet. The product must be satisfactorily absorbed through the gastro-intestinal mucous membrane, stored in the tissues (especially the liver), and utilized according to the demands on the bone marrow. It is possible that an anaemia of pernicious type may develop when any of the phases in the formation and absorption of the anti-anaemic principle fails. Thus, in Addisonian pernicious anaemia the intrinsic factor of Castle (haemopoietin) is absent; in tropical megalocytic anaemia the extrinsic factor is absent. In the megalocytic anaemia of sprue, fatty diarrhoea, multiple stenoses and strictures, and intestinal parasites, either the gastric digestion or the absorption of the factor fails. In gastric carcinoma and in Graves's disease the intrinsic factor occasionally disappears and a megalocytic anaemia develops, and similar changes may occasionally be encountered after severe gastric operations. To recapitulate: broadly speaking, in the Addisonian-pernicious-anaemia-subacute-combined-degeneration syndrome the most important and fundamental defect is a gastric one—the loss of the intrinsic factor of Castle (haemopoietin), which is a product of the normal gastric mucous membrane.

Group B.—The second, or microcytic, type of anaemia contrasts in many respects with pernicious anaemia; for the majority of the circulating red cells tend to be slightly smaller than normal, and their haemoglobin content per cell is reduced in much greater proportion. The colour index is low. The bone marrow shows normoblastic reaction. The anaemia is therefore microcytic and hypochromic. It does not respond to liver or stomach preparations, but, being due to a deficiency in iron, it responds to treatment with certain iron preparations, though they must be given in large doses. Achlorhydria is very common in this anaemia, which is largely confined to women. It includes simple achlorhydric anaemia and the Plummer-Vinson syndrome; the microcytic anaemias secondary to pregnancy, Graves's disease, etc.; the anaemia of cancer of the stomach; and that following gastric operations.

Comparison of Two Groups

The next problem is to consider how far the defects in gastric secretion are comparable, and whether they have an equal significance in this second microcytic form of anaemia, as they appear to have in pernicious anaemia. It was with this aspect of the problem that Dr. Witts and I were chiefly concerned.^{2,7,8,9} It soon became apparent that for practical purposes achlorhydria (with gruel test meal and histamine) occurred in 100 per cent. of cases of true Addisonian pernicious anaemia; in chronic microcytic anaemia, although more than 80 per cent. were achlorhydric in the gruel fractional test meal, a proportion of cases could be made to secrete small quantities of acid with histamine, and thus were really hypochlorhydric. The cases investigated were therefore subdivided into true simple achlorhydric anaemia, and a small group of chronic microcytic anaemia with hypochlorhydria.

Our principal findings in the gastric secretion of these groups of cases are shown in a summarized form in Table II. Briefly, it will be seen that there is a striking

TABLE II.—*Histamine Secretion in Anaemia with Achlorhydria*

	Normal	Addisonian Pernicious Anaemia (25 Cases)		Chronic Microcytic Anaemia			
				Simple Achlorhydric Anaemia (36 Cases)		Hypochlorhydric Group (12 Cases)	
	Average	Range	Average	Range	Average	Range	Average
10-minute volume ...	c.cm. 35	c.cm. 1-20	c.cm. 10.5	c.cm. 2-25	c.cm. 12.3	c.cm. 2-42	c.cm. 19
Free acid (N/10 NaOH per 100 c.cm.)	100	—	—	—	—	0-75	16
Total acid (N/10 NaOH per 100 c.cm.)	110	0-10	5	2-14	5.6	12-90	30.5
Chloride (N/10 HCl per 100 c.cm.)	135	18-38	38	20-71	48	28-5	64
Pepsin (Grosche units' ...)	40	0-15	1.75	0-15	2.4	5-40	20
Insol. mucus (mg. N) ...	9%	26%		19%		3%	
per 10-minute vol. ...	2.4		1.6		1.4		0.3
Soluble mucoprotein (mg. N) ...	26%	56%		48%		40%	
per 10-minute vol. ...	7		3.5		3.6		4.5
Intrinsic Castle factor	Present	Absent		Traces?		Reduced	

gradation in the severity of the gastric defect in all three groups of cases as shown by examination of the histamine gastric juice. This is seen to affect all the elements of gastric juice investigated—the ten-minute volume secretion, the hydrochloric acid, total chloride, pepsin, insoluble mucus, and soluble mucoprotein. It was noteworthy that sometimes the gastric secretion of simple achlorhydric anaemia might be indistinguishable from pernicious anaemia, but whereas the defects in pernicious anaemia were *constantly* found to be most severe, occasionally in simple achlorhydric anaemia the changes would be less severe. In the hypochlorhydric group the changes were found to be least severe, although deviating widely from the normal.

If, then, the gastric secretions in these anaemias in so many respects closely resemble one another, in what respects do they differ? Experiments were carried out to demonstrate the presence or absence of the intrinsic factor in the gastric juice of patients suffering from simple achlorhydric anaemia. Witts and I were able first to confirm the absence of the intrinsic factor in the gastric juice of pernicious anaemia as first shown by Castle, but in the case of simple achlorhydric anaemia our results were not entirely in conformity with the original Castle hypothesis. Briefly, we found that the factor was present, but much reduced—sometimes to the point of absence. When we considered the details of the analysis of the gastric juice of those cases of simple achlorhydric anaemia which apparently possessed practically no intrinsic factor, we were impressed by the fact that they were always those cases in which gastric secretion was most impoverished, and they usually secreted no pepsin. When we repeated the experiments, using selected cases which secreted no pepsin, the result was negative. We therefore suggested that the reduction of the intrinsic Castle factor is parallel with that of other gastric ferments, but it was evident that, in general, there must be sufficient intrinsic factor secreted somewhere in the economy of these patients to hold off the development of megaloblastic degeneration of the marrow, and to prevent pernicious anaemia. If this were not so, the transformation of simple achlorhydric anaemia into pernicious anaemia would be commonly observed. Although occasionally recorded, the transformation of one type of anaemia into another in its clinical and haematological entirety is not common.

What relation, then, has the defect in gastric secretion to the anaemia of this chronic microcytic type, and why is it almost exclusively confined to women? The achlorhydria can best be considered, as Davidson³ suggests, as one of several grave disabilities which predispose to its development. The other disabilities are conditions which strain, as it were, the internal mechanism of blood formation by an excessive demand. They are conditions of chronic blood loss, and especially of excessive menstruation, repeated pregnancies and parturition, and the drain of lactation. If such disabilities operate together, and especially if the diet is only of minimum iron content (but adequate in the absence of these disabilities), then this microcytic hypochromic anaemia results.

To summarize this view. In a mixed population on an iron minimal diet the high incidence of achlorhydria and the drain of the reproductive functions accounts for the incidence of this anaemia in women. When we can reproduce such factors in men a similar type of anaemia develops.

As to the exact mechanism by which the achlorhydria interferes with the iron absorption, it has been shown by Mettier and Minot that iron is not easily absorbed from the upper gut in the absence of hydrochloric acid and pepsin. The question of the alteration of the pH of the duodenum by the iron salts employed may also be of importance (Langmead). I personally believe that other dietetic factors play a part, but this is not the place to discuss my results.

OTHER EXAMPLES OF ANHAEMOPOIESIS

The anaemias of carcinoma of the stomach and Graves's disease, and that following certain gastric operations, also provide examples of anaemia of anhaemopoietic type, and they may be megalocytic or microcytic.

Anaemia of Carcinoma Ventriculi

Cases of carcinoma of the stomach which present as examples of severe anaemia, often like pernicious anaemia, are familiar to all of us. These patients are not anaemic because of a large haemorrhage, for most surgeons will agree that such a catastrophe is a rare incident in cancer of the stomach. At the same time it is quite certain that continuous oozing of blood from the ulcerated growth surface commences at an early stage in its development, and is responsible for that valuable diagnostic finding—a positive occult blood test. This type of patient will not admit to a long dyspeptic history, and often the dyspepsia is minimal, the impairment of appetite being all that is complained of. The test meal examination of the stomach shows achlorhydria. Here, then, we have exactly those factors called "disabilities" which in women predispose to the development of chronic microcytic anaemia. The commonest type of anaemia associated with cancer of the stomach is of this type, and really is a simple achlorhydric anaemia. This is the type of cancer which develops on the basis of an unhealthy gastric mucous membrane—a gastritis, in fact—the gastritis and achlorhydria preceding the development of the carcinoma. If the anaemia in cancer is of gastrogenous origin it might be expected that anaemia of pernicious type would occasionally be associated with cancer of the stomach, and such cases have been recorded (Wilkinson has recorded two, and collected twenty-five others). In these individuals, irrespective of the presence of the growth, the intrinsic factor is lost, and the megalocytic pernicious anaemia develops. The importance of this is that both anaemias may for a time respond to their respective remedies, and the growth may be unsuspected. The pernicious type responds to liver for a time, and the microcytic type to large doses of iron. I have reported several such cases.¹⁰

Anaemia associated with Graves's Disease

Anaemia associated with Graves's disease is not rare. It is usually of the secondary microcytic type. Occasionally Graves's disease and pernicious anaemia are associated. I believe the achlorhydria and the associated defects in gastric secretion, which are common in cases of prolonged thyrotoxicosis, play an important part in the production of the anaemia. Among ten cases of pernicious anaemia associated with Graves's disease, and mentioned in a paper with Dr. Meulengracht of Copenhagen,¹² all were achlorhydric, and all were females.

Anaemia associated with Stomach Operations

Lord Moynihan's case of complete gastrectomy, ultimately resulting in death from severe anaemia, thought to be pernicious, was one of the first recorded examples of anaemia due to operative interference with the stomach. Since that time a number of similar cases have been reported, and it is now known that frequently such patients do develop anaemia, and that in complete gastrectomy its onset may not be long delayed. In partial gastrectomy, in proportion to the extent of the removal of the acid-secreting area of the stomach, so will achlorhydria result. The development of anaemia may be long delayed. After gastro-enterostomy achlorhydria does not as a rule follow, though the abnormal conditions present in the stomach frequently result in gastritis, which may ultimately cause the cessation of acid secretion. The free regurgitation of duodenal contents, and rapid neutralization of small quantities of acid, makes the certain demonstration of achlorhydria difficult in many of these cases. I have twice found achlorhydria after a faulty gastro-enterostomy has been undone, although free acid was present in normal quantities before the original operation. The type of anaemia which occurs after these operations again belongs to the anhaemopoietic group, and is frequently of the chronic microcytic type. Occasionally a case of partial-gastrectomy pernicious anaemia is encountered.

Anaemia after gastric operations seems to occur most frequently among those unfortunate individuals who are suffering from what may be called the ill results of gastro-enterostomy. If such a group of individuals be investigated, in addition to their innumerable abdominal discomforts, a proportion of them will be found to be definitely anaemic.

In a small group of twenty patients (ten male and ten female) investigated by me, who had become chronic abdominal invalids following operation upon the stomach, seven females had anaemia of secondary type, and five of these had developed gastro-intestinal hurry, as shown by x-ray examination. It is possible that the disturbed physiology of the gastro-intestinal tract had so interfered with digestion and absorption of iron that adequate quantities could not be absorbed and utilized for the manufacture of haemoglobin. In only one case had traces of occult blood, due to gastro-jejunal ulceration, been found.

Among 112 traced cases of gastrectomy for ulcer there were twenty-one deaths and thirty-six patients who complained of some degree of unfitness, and whose blood was examined. Among the thirty-six, twenty-two had some microcytic anaemia, and one was a case, since dead, of ? pernicious anaemia.

Of thirty traced cases of gastrectomy for cancer, twenty-one patients were dead, and of the nine alive and seen, six made some complaint of unfitness, and their blood was examined. Two of them, both females, had chronic microcytic anaemia.

Putting all these cases together as examples of individuals unfit after gastric operations, there were sixty-two unfit persons among 168 cases of gastric operations. Of this number (sixty-two), thirty-one were anaemic—that is, 50 per cent. of the unfit patients were anaemic. When the sex of the affected patients was considered

80 per cent. were found to be females. Here again there seems to be evidence that when the female organism is subject to the added disability of disturbed gastric physiology consequent upon unsatisfactory gastric operations, anaemia of the anhaemopoietic type develops.

TREATMENT OF ACHLORHYDRIA AND RELATED ANAEMIAS

I cannot hope to deal with every aspect of treatment which concerns achlorhydria and the related anaemic states which have been mentioned. With regard to achlorhydria much depends upon the view we take of its aetiology and the part we believe it to play in producing the associated condition. While the associated disease is obvious and urgent we treat *it*—for example, the anaemia—and we are well content to cure *it*. But we may well question whether this is sufficient, for our patients are left with the achlorhydria and the pathological condition of the stomach which underlies the achlorhydria. How far does this predispose to further complications or even new diseases? What will be the incidence of carcinoma of the stomach among patients cured of pernicious anaemia, in ten or twenty years' time? How many of them will develop biliary infections if the achlorhydria is ignored? Hurst suggests that we must always consider the treatment of achlorhydria as well as the associated disease, and also we must try to prevent these diseases by early treatment of the achlorhydria. This implies the prevention of gastritis by the elimination of all preventable forms of gastric irritation, a complete overhaul for all sources of open or focal sepsis, especially in the mouth, pharynx, and accessory sinuses. The restoration of gastric acidity may often be brought about by the old treatment of gastric lavage. Thus among thirty-four cases of achlorhydria at New Lodge Clinic³ treated by daily gastric lavage (one ounce of hydrogen peroxide to the pint) acid returned in 82 per cent. of cases.

Hydrochloric Acid

In those cases where general slackness and debility with gastro-intestinal symptoms accompany the achlorhydria, astonishing results may sometimes be brought about by the substitution of hydrochloric acid. The remarkable fact is that the dose of hydrochloric acid given is often quite insufficient materially to affect the reaction of the achlorhydric stomach, yet the abrupt cessation of gastro-genous diarrhoea, perhaps of years' duration, seems little short of miraculous. Larger doses, well diluted, and flavoured suitably with the addition of pepsin, are often useful where dyspepsia and gastro-intestinal upsets are present. In the treatment of the anaemias associated with achlorhydria, as in the case of pernicious anaemia, the problem is to select from the innumerable preparations offered to us the most economical remedies consistent with full activity and convenience in administration.

Liver

Emergency treatment practically only exists in the case of pernicious anaemia, and the introduction of safe intravenous liver preparations has, for practical purposes, rendered transfusion unnecessary. Transfusion is now only needed when severe infection inhibits the effect of the active preparation. The dose of these intravenous liver products in an emergency is 5 c.cm., and this calls forth a reticulocyte response within twenty-four hours as a rule. From 2 to 4 c.cm. may be given the next day, followed by intramuscular preparations, 2 c.cm., according to the magnitude of the blood response and the clinical progress of the case. Within a week or ten days these patients can be given preparations by mouth, and finally, by trial, the maintenance dose determined. For less acute cases treatment can be started with intramuscular preparations

which cost only half the amount of the intravenous ones, and then preparations by mouth. It is most important that patients should be made to understand the necessity of continuing with the adequate amount of active preparation. Nothing can be more deplorable than the case which is allowed to drift on with haemoglobin below 80 per cent. and red corpuscles below 4,000,000. The risk of development of nervous symptoms, and the chance of curing them if present, depend upon the maintenance of the blood at the level of health. For maintenance treatment it is necessary for the medical man to be able to recommend active preparations in which he has absolute confidence, and at the same time to save his patient unnecessary expense—for many of the most expensive products are in no way superior to certain much cheaper and reliable preparations on the market.

Stomach Preparations

Providing the patient is on ordinary mixed diet, there is no special virtue in whole liver that is not possessed by active liver extracts and stomach preparations. Few patients will continue to take whole liver for two meals a day for the rest of their lives. The dry extract is very expensive and unpalatable; the liquid extract is not pleasant, but is less expensive. On the whole, I believe that stomach preparations are best adopted as a routine, on grounds of economy, convenience in administration, and effectiveness; there are very few cases that cannot be kept with haemoglobin between 95 and 105 per cent. upon one ounce of stomach preparation a day. They are also helpful in controlling associated dyspepsia and improving the nervous symptoms of subacute combined degeneration. The price of stomach preparations is very variable, and much money can be needlessly expended. The more elegant preparations are expensive because of the cost of removing fatty matter, which gives the cheaper preparations their unpleasant odour. Very few patients in my experience are unable, after two or three days, to tolerate even the cheap fat-containing preparations, the cost of which is even less than that of 1/2 lb. of whole liver per day. Purely from the cost point of view, at the present time, treatment by intramuscular preparations given twice weekly would be only half that of treatment by mouth preparations. Large doses of the intramuscular preparations have been injected to form depots without ill result. These depots are slowly used up, and need replenishing at longer intervals of time.

Infection and septic foci retard the effect of treatment. I have seen a case fail to respond while an infected antrum was untreated. In females I would stress the frequency of *B. coli* pyelitis as a cause of unsatisfactory progress. This was the commonest infective complication interfering with treatment among 400 cases reviewed at Copenhagen in Meulengracht's Clinic. Pregnancy and lactation are indications to increase the maintenance dose of the active preparation.

Iron

The treatment of chronic microcytic anaemia, depending as it does chiefly on large doses of iron, is fortunately cheaper than that of pernicious anaemia. Here, too, the necessity for very prolonged treatment must be emphasized, otherwise these women relapse into a miserable state of chronic ill-health. It is now common experience that ferrous salts of iron are most rapidly and uniformly successful. The cheapness of these salts makes the large dose of no account. Successful treatment may usually be achieved by the following:

Blaud's pill, fresh (ferrous carbonate), 60 grains daily.
Feronyl (ferrous chloride), 6 to 9 tablets daily.

Ferri et ammon. cit. { mixed ferrous and }
Ferri et quin. cit. { ferric in colloidal } 45 grains daily.
state

Tab. ferri carb. sac. (ferrous carbonate), 45 grains daily.

These doses of iron preparations are the *minimal* effective doses, and in resistant cases it may be necessary to double the dose here indicated. Colloidal and organic iron compounds are much less effective.

Vitamins

I usually augment this massive treatment with certain vitamin preparations such as bemax or marmite 1/2 ounce daily, or yeast compressed into 5-grain tablets. Some of these patients are almost certainly suffering from vitamin B deficiency, and I have had several cases which have improved upon these vitamin B containing preparations without any iron whatever. Infection, sepsis, pregnancy, and lactation all inhibit the response of these patients to iron, and in selected cases, where menorrhagia is present, artificial induction of the menopause may be necessary before improvement will take place.

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THE HAEMATOPOIETIC RESPONSE TO INTRAMUSCULAR INJECTIONS OF CONCENTRATED HUMAN GASTRIC JUICE

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Morris and his associates¹ recently reported that although small amounts of normal human gastric juice were ineffective when injected intramuscularly, large amounts of normal human gastric juice or hog gastric contents after concentration *in vacuo* produced maximal reticulocyte responses when injected into patients with pernicious anaemia. They described the substance in the concentrated gastric juice as being thermolabile, dialysable, and exhaustible, and therefore concluded that it was probably a hormone. Conner² reported similar results in one case of pernicious anaemia, following the injection of normal human gastric juice after concentration by vacuum distillation. Wilkinson³ was unable to confirm the findings of Morris and his associates when he injected human gastric juice that had been brought to pH 7.5 previous to its concentration *in vacuo*.

The observations here recorded were carried out in order to determine whether it was possible to separate the "active principle" in the gastric juice from the known enzymes (pepsin and rennin) by the process of ultrafiltration. This process not only offered a means of determining the relative size of the various constituents of the gastric juice, but also a possible method of concentrating the gastric juice at ice-box temperatures.

METHODS

The patients, clinically and haematologically typical of pernicious anaemia, received the concentrated gastric juice intramuscularly after preliminary control periods (average seven days). Red blood counts, haemoglobin determinations (Newcomer), and reticulocyte counts were made daily during the control and test periods. The human gastric juice used was obtained from young healthy adults following the injection of 0.5 mg. of histamine subcutaneously. It was filtered immediately after collection through a No. 1117½ Faltenfilter (Carl Schleicher and Schüll). The enzymatic content of the gastric juice to be concentrated was determined by methods detailed previously.⁴

The Bechold type of ultrafilters described by Bronfenbrenner⁵ was used in the experiments. The gastric juice (285 to 630 c.cm.) was concentrated by these ultrafilters, and twice diluted with distilled water or 0.3 per cent. hydrochloric acid, and reconcentrated before being brought to the final volume of 13 to 15 c.cm. This procedure was carried on in the ice-box. Since only negligible amounts of pepsin and rennin passed through these filters, each new filter could be tested for possible defects in the construction by determining the amounts of these known enzymes in the ultrafiltrate.

In a preliminary study it was found that the "active principle" in liver extract No. 343 passed through the ultrafilters. One patient (Case 9) had a reticulocyte peak of 25.6 per cent. (absolute reticulocyte count 620,000 per c.mm.) following the intravenous injection of the amount of liver extract derived from 100 grams of whole liver, after the extract had been passed through the ultrafilter.

In the experiments in which concentration by vacuum distillation was employed the procedure was as follows. The distilling flask (fitted with the usual capillary tube to prevent bumping) was immersed in a constant temperature bath maintained at 40°C. The vacuum was produced by a water pump. The gastric juice (500 to 600 c.cm.) was concentrated to 10 to 15 c.cm. in a period of three to five hours. The gastric juice concentrated by either or both of the above methods was sterilized by passing through an N Berkefeld filter, or by the addition of a few drops of tricresol, and was adjusted to a pH 7 (at ice-box temperature) by the addition of strong NaOH before being injected into the patients.

RESULTS

In the first group of observations (Group 1) the gastric juice used had been filtered through paper and then stored in the ice-box for approximately two months before being subjected to ultrafiltration. The effect of the two injections of the concentrated juice (that held back by the ultrafilters) is shown in Chart I, Case 1. The clinical response in the patient was only slight, and the increases in the red blood count were not sustained. A further rise in reticulocytes and a satisfactory rise in red blood cells followed the administration of extralin* by the mouth. The ultrafiltrate (the portion passing through the ultrafilters) of this juice was concentrated by vacuum distillation and injected into Case 2a. No response of the blood occurred during the following twelve days.

These reticulocyte responses were not maximal; therefore it was decided that fresh gastric juice should be used in the next group of tests (Group 2), as the storage in the ice-box might have destroyed some of the active material. However, when the fresh gastric juice was used, no reticulocyte responses followed the injection on three occasions of the portion of the fresh gastric juice held back by the ultrafilters, and on one occasion

* A potent preparation obtained by the interaction of liver or liver extract with hog gastric tissue.