Remarks

ON

A CLINICAL STUDY OF ACHLORHYDRIA*

BY

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[The lecturer first discussed, in the light of recent literature, the significance of achlorhydria in pernicious anaemia^{1 2 3 4} and subacute combined degeneration of the spinal cord, and pointed out that while achlorhydria is almost a constant finding in pernicious anaemia, yet, theoretically, this disease might possibly occur with hydrochloric acid present in the stomach secretion—he had himself met with one such case. He then continued:]

INTRODUCTION

For more than ten years I have been interested clinically in achlorhydria, and about five years ago my interest in this connexion became acute when some peculiar cases of anaemia in middle-aged women presented themselves. The anaemia in these patients appeared at first sight to be pernicious in type, inasmuch as there was atrophy of the lingual papillae associated with superficial glossitis and achlorhydria, and the patients had a sallow or subicteroid complexion. The blood examination, however, showed an anaemia with a colour index well below unity, megalocytosis was absent, and although there was anisocytosis and poikilocytosis, the average size of the erythrocytes was not greater than normal; the anaemia, therefore, was not Addisonian in type. As the standard textbooks gave no information about this syndrome, and as a superficial search of the journals furnished but little, it was evident that we were dealing with a form of anaemia not generally recognized. During the following years—namely, from January 1st, 1927, to June 30th, 1931—we endeavoured to collect, and when possible to study, cases of this form of anaemia—that is, cases of non-megalocytic anaemia with a low colour index and achlorhydria; we succeeded in collecting thirty-three such cases, in each of which the haemoglobin content of the blood was under 70 per cent. During the same period we did fractional test-meal analyses on as many other patients as was possible, with the idea of obtaining some information relative to the incidence of achlorhydria in other diseases. Naturally, we were unable to have test-meals done on all cases entering the wards, and at first we concentrated on cases which symptomatically might be likely to have achlorhydria. The incidence of achlorhydria in some of the groups—for example, diabetes mellitus—may be somewhat higher in this study than is actually the fact, because in the earlier part of the work only those cases of the group showing symptoms or signs suggestive of achlorhydria were tested, whereas, after we realized from our growing experience that absence of hydrochloric acid from the stomach secretion was a rather common finding in the disease, then all cases of that group entering the wards were tested by fractional test-meal as a routine. For this reason, and because the number of cases tested is too small, the incidence figures of the frequency of achlorhydria in this study cannot be taken as having statistical value; but, at the same time, we believe that they give some indication of the frequency of achlorhydria in certain conditions.

The three-hour fractional test-meal technique, with Ryle tube and a thin gruel, was used; if there was any doubt

about the presence of achlorhydria, or if there was much mucus present in the majority of the specimens, the stomach was thoroughly washed out, as recommended by Hurst, and the test-meal repeated. (Only cases showing complete achlorhydria, as judged by this method, are so classified.) In certain cases the fasting gastric juice was aspirated and the test-meal repeated after the subcutaneous injection of 0.5 mg. of histamine in the form of acid phosphate, which is known to be a powerful stimulant of gastric secretion,⁵ or the fasting stomach was twice evacuated twenty and fifty minutes after histamine injection. (Wherever this method was used it is mentioned in the tables.) We have made no attempt to test for pepsin in the gastric contents. The fasting blood sugar was estimated by the Folin-Wu method, and the basal metabolic rate was determined by means of the Roth-Benedict apparatus. Haemoglobin was estimated by a checked Sahli test, and a certified Bürker chamber was used for the blood counts. Table I gives a general

TABLE I

Total number of patients for whom one or more test-meal examinations were done: period 1/1/27 to 30/6/31, 1,228.
Number of these patients with initial achlorhydria, 272 (22.1 per cent.).

Description	Number with Achlorhydria	Total Number	Per cent. showing Achlorhydria
Non-megalocytic anaemia of doubtful etiology	33	47	70.2
Diabetes mellitus	33	83	39.7
Hyperthyroidism	37	47	78.7
Gastro-intestinal cases	100	—	—
Miscellaneous	74	—	—
Total	277-5=272*	—	—

* Two patients with diabetes, one with hypocalcaemia, infantilism, and spontaneous fractures, and two with hyperthyroidism had achlorhydria and non-megalocytic anaemia, and are included under two diagnoses.

summary of our results, and shows that out of forty-seven cases of so-called "secondary," "hypochromic," or non-megalocytic anaemia, thirty-three, or 70 per cent., had achlorhydria. This particular form of anaemia is probably, therefore, one of the commonest types of anaemia encountered; it is certainly surprising that so little attention had been paid to it in the literature, and that it was so seldom recognized in practice. The table also shows that out of eighty-three cases of diabetes mellitus, thirty-three, or over 39 per cent., had achlorhydria, and out of forty-seven cases of hyperthyroidism, thirty-seven, or over 78 per cent., had achlorhydria. There were 100 gastro-intestinal cases and seventy-four miscellaneous cases with achlorhydria. Out of a total of 1,228 patients tested by the fractional test-meal method during three and a half years, 272, or 22 per cent., had achlorhydria, as judged by this technique. Achlorhydria is not unknown in otherwise apparently healthy individuals. Bennett and Ryle⁶ found an incidence of 4 per cent. with the fractional test-meal, and Baird, Campbell, and Hern⁷ found an incidence of 3.5 per cent. with the same method in apparently normal persons. Connor⁸ has shown that the frequency of achlorhydria in patients increases as age advances; in patients of from 30 to 39 years of age there was an incidence of 10.5 per cent., while in those of 60 to 67 years of age it was 28 per cent.; in 5,000 patients suffering from a variety of diseases Connor found achlorhydria to be present in 15.2 per cent. by the fractional method. Faber²⁴ also found that achlorhydria increases in frequency with advancing age. It may be of interest to observe here that pylorospasm, as noted by x-ray examination, and comparatively rapid emptying of the stomach, as judged by the time required for the gastric evacuation of starch,

* A British Medical Association Lecture delivered in Kilkenny, May 28th, 1931. A synopsis of this study was given in the Section of Medicine, British Medical Association Annual Meeting, Eastbourne, July, 1931.

were frequent findings amongst our cases of achlorhydria (provided that organic obstruction and gastric hypotonia were absent).

NON-MEGALOCYTIC ANAEMIA

Of the thirty-three cases of non-megalocytic anaemia of unknown origin with achlorhydria (Table II) there were twenty-seven females and six males. The anaemia was chronic in all, and in some had lasted for several years. Weakness, palpitation, and breathlessness on exertion were common symptoms, and many of the patients complained of digestive disturbances, such as flatulence and epigastric discomfort after food, diarrhoea, vomiting after food, or loss of appetite. The complexion was usually sallow, but sometimes pale. A frequent finding, present to some degree in nineteen of the thirty-three cases, was atrophic superficial glossitis, very similar to the form so frequently found in pernicious anaemia, the tongue often being too red and the papillae having in many cases completely disappeared from the dorsum. In several cases this condition was patchy in distribution, or more advanced in some areas of the dorsum linguae than in others; furrowing of the tongue was even more common than glossitis, while some degree of regeneration of the atrophic papillae was occasionally observed after successful treatment, and frequently the redness and furrowing became less. Paraesthesia and signs suggesting subacute combined degeneration of the spinal cord were not observed, but menstrual irregularity was not uncommon. The average number of erythrocytes was about 3,700,000 per c.mm. and the average haemoglobin content of the blood was 50 per cent. before treatment; the lowest red cell count was 1,920,000 per c.mm. and the lowest haemoglobin measurement 15 per cent., both in the same patient (Case 19). In some patients the red cell count was about normal, but a considerable haemoglobin deficiency existed. The average colour index before treatment was 0.66 (lowest, 0.32, and highest, 0.95). The average colour index after successful treatment in twenty cases was 0.86 (lowest, 0.61, and highest, 1.04). The average leucocyte count before treatment (excluding Case 17, where there was a polymorphonuclear leucocytosis from severe oral sepsis, and Case 32, where there was a thyroid abscess with a leucocytosis) was 5,200; after successful treatment in nineteen cases it was 7,022 as against 5,400 on admission. The differential leucocyte count was normal in all, except in Cases 17 and 32, which showed a polymorphonuclear leucocytosis.

The degree of anisocytosis and poikilocytosis was usually proportional to the severity of the anaemia. The average diameter of the red cells was never greater than normal. Blood bilirubin, the platelet count, and the reticulocyte count, before treatment, were normal in all. No cases included in the present series were under 15 or over 70 years of age, or had a blood haemoglobin of over 70 per cent. In the series, there was one case (Case 29) of the so-called Plummer-Vinson syndrome,⁹ and the spleen was enlarged only in two (Cases 29 and 33). This variety of anaemia occurred in two cases of diabetes mellitus and in three cases of hyperthyroidism, all five of which had achlorhydria (one of the latter is not included in Table II). In all cases a haemorrhagic cause was carefully excluded.

DETAILS OF TREATMENT

Twenty-three cases submitted themselves to treatment for a period sufficiently long to show an excellent response to oral iron therapy. With the exception of one patient (Case 32) who died of infection, the blood values—haemoglobin content, erythrocyte and leucocyte counts—were restored to normal, or considerably improved, while there was at the same time great symptomatic improvement. Iron by mouth gave good results in treatment,

as shown by the table. At first we used citrate of iron by mouth in treatment, and found that 60 grains per day were necessary to get a good result in three to five months; later we found that Blaud's mass in doses of 30 to 45 grains a day gave a much quicker response, the period of time necessary for effective treatment being in some cases reduced to from four to six weeks. Thirteen of the successfully treated cases were tested for the presence of hydrochloric acid in the stomach (fractional test-meal, after the anaemia had responded to treatment, and the acid was then found to be present only in three—namely, the Plummer-Vinson case (Case 29), which showed a normal curve of gastric HCl without histamine, one case (Case 2) which showed traces without histamine, and Case 17, which had no gastric HCl with the ordinary technique, but showed it after histamine. Seven cases which showed achlorhydria with the ordinary fractional test-meal technique after successful treatment of the anaemia also had achlorhydria after histamine injection. These findings would indicate that the anaemia was not the cause, but more probably, in part at least, the result of the achlorhydria. The administration of 60 minims of dilute hydrochloric acid (*B.P.*) by mouth with pepsin, thrice daily after food, did not seem to be of any special value in restoring the blood to normal, but it was of undoubted value in relieving the frequently associated gastro-intestinal symptoms. Liver extract for pernicious anaemia and desiccated stomach proved useless. The use of cooked whole liver by mouth gave doubtful results, but I obtained the impression that its use was of some value as an adjunct to iron; however, I am not prepared to be definite on this point. Neither can I be dogmatic on the best form of maintenance treatment once the anaemia had disappeared—some patients have kept well for a year, or even more, on small doses of iron, some on moderate doses of hydrochloric acid, and at least one (Case 17) on no special form of medication; it is interesting to note that two years after successful treatment this case showed HCl in the fractional test-meal after histamine injection, but none on the ordinary technique (no histamine) before treatment. It is worth mentioning that we have had a female patient with true achlorhydria under frequent observation since early in 1928 who, in September, 1931, developed, for the first time, glossitis and non-megalocytic anaemia of a mild type, although she had been continuously taking 40 to 60 minims of dilute hydrochloric acid with pepsin by mouth, thrice daily, after food; she is not included under the heading of anaemia in this paper, for the blood changes developed after this study had ended. In this case the taking of acid as a prophylactic measure in these doses did not prevent the ultimate development of the anaemia.

It would seem probable that both iron and hydrochloric acid would have their own place in maintenance treatment in the majority of cases, iron being probably by far the more important. The achlorhydria in the majority of these thirty-three cases was probably a true and not an apparent achlorhydria, for suitable precautions were used in all the fractional test-meals—for example, several test-meals were done on the majority of the patients, the stomach in many cases being washed out beforehand, but the histamine stimulation method was unfortunately only used in a minority (eight) of the patients before treatment.

ITS ETIOLOGY

As regards the etiology of this non-megalocytic anaemia, one is at once struck by the fact that it is commonest in women from the ages of 20 to 50 years, although examples of it were encountered in male patients from the ages of 15 to 60 years. It would appear that the achlorhydria is the most important single etiological factor,

TABLE II.

No.	Sex	Age— Years	No. of Erythrocytes in Thousands		Haemoglobin Per Cent.		Duration of Treatment in Days	Treatment and Result	HCl in Test-Meal at End of Treatment	Remarks
			Before Treatment	After Treatment	Before Treatment	After Treatment				
1	F	38	3,590	5,330	54	85	277	HCl Fe L=++	—	—
2	F	36	4,420	5,070	40	90	231	HCl Fe=+	Traces	—
3	F	29	4,100	5,150	63	80	141	HCl=0. Fe=+	—	Hyperthyroidism
4	F	27	5,500	5,860	62	93	71	HCl=0. Fe=+	Absent	Traces of HCl 12½ years later after histamine
5	F	53	3,820	5,880	32	88	61	HCl=0. Fe=+	Absent	—
6	M	50	3,170	5,040	54	90	44	HCl L=+	—	Relapse on ceasing treatment (10% Hb) Results repeated
7	F	40	3,400	5,500	50	82	113	HCl=0. L=+ HCl Fe=+++	Absent	Relapse on HCl alone. HCl absent after histamine. Result repeated
8	F	43	4,090	—	60	—	30	HCl Fe L clinical +	—	—
9	F	41	4,980	—	65	—	—	—	—	—
10	F	61	4,910	4,500	58	60	21	HCl As=0	—	—
11	F	41	5,330	4,760	40	85	?	HCl Fe=+	Absent	Irregular visits
12	F	27	5,520	—	65	—	26	HCl Fe= clinical +	—	—
13	F	36	4,800	5,630	60	75	8	Fe=+	—	—
14	F	46	5,590	—	60	—	—	—	—	—
15	F	25	2,728	—	38	—	—	—	—	—
16	M	16	3,880	—	50	—	—	—	—	Blood condition same 4 years later. In- fantilism. HCl absent after histamine
17	M	50	2,290	4,120	36	80	60	HCl Fe Oral sepsis treatment=+	Absent	Purpura and oral sepsis. HCl absent 2 years later, but present after histamine
18	F	22	3,500	4,920	35	77	133	HCl=0. HCl Fe=0	Absent	Hypocalcaemia, infantilism, and spon- taneous fractures
19	F	28	1,920	5,100	15	61	91	HCl Fe L=+ HCl Fe=0 HCl Fe V=0 HCl Fe L=+	—	No meat eaten for years because of gastric discomfort. Meat given during treat- ment. Poor co-operation
20	F	38	4,000	5,000	55	50	116	HCl=+	Absent	—
21	M	15	5,760	—	65	—	—	HCl Fe=+	—	Imperfectly developed testicles
22	F	56	4,350	5,100	45	88	81	HCl=0 Fe=+	Absent	HCl absent after histamine
23	F	59	3,200	3,570	25	58	31	Fe L=++ HCl Fe=+	—	—
24	F	50	3,220	4,430	50	90	44	HCl Fe L=++	—	Diabetes mellitus under treatment for 7 years. Achlorhydia discovered in 1918 and anaemia developed about 2 years later
25	F	69½	3,100	3,410	65	75	21	HCl Fe=+	—	Pus in left maxillary antrum; palliative treatment
26	M	38	3,840	4,340	55	90	—	HCl Fe L=++	Absent	—
27	F	41	4,130	—	64	—	—	HCl Fe= Clinical +	—	Hysterectomy 4 years previously
28	F	53	3,230	5,070	40	91	29	HCl Fe=+	—	Diabetes mellitus under treatment for 2½ years before anaemia developed or achlorhydia discovered
29	F	45	3,650	5,200	54	90	39	HCl Fe=+	Normal	Plummer-Vinson syndrome. No meat for several months. Oesophagus dilated before treatment and meat given
30	M	59	2,400	4,600	38	78	72	HCl Fe L=+	Absent	Retinal haemorrhages; cleared up after treatment. HCl absent after histamine
31	F	55	4,160	5,200	65	94	40	HCl Fe=+	Absent	HCl absent after histamine
32	F	38	3,360	5,200	50	80	40	HCl Fe=+	—	HCl absent after histamine; hyper- thyroidism; thyroid abscess
33	F	47	2,880	—	45	—	—	—	—	Spleen enlarged; blood bilirubin normal; developed acute parotitis; died; post- mortem examination
16 (4 years later)	M	20	4,800	4,800	52	76	67	Fe=+	—	Returned in four years with achlorhydia and anaemia, no treatment meantime; good response to iron

27 Females, 6 Males.

EXPLANATION OF TABLE II.—By "Duration of Treatment" is meant the number of days required to obtain a definite result with the anaemia by the various forms of treatment tried; the time required became shorter as we gained more experience with the treatment. Under the heading "Treatment and Result," HCl means dilute hydrochloric acid (B.P.) in drachm doses thrice daily. Fe means iron by the mouth, + a good result with reference to the anaemia, 0 means no result, L means cooked liver by mouth, and V means ventriculin.

although probably there are others. In this connexion, one might note that recently Mettler and Minot¹⁰ have shown that "iron is more potent for blood production in secondary anaemia when absorbed from an acid than an alkaline medium within the gastro-intestinal tract"; they further suggest that "anaemia can result from failure over a prolonged period in the adjustment of the contents of the upper intestinal tract to a suitable pH for iron utilization—for example, achylia gastrica."

We have seen twelve cases of secondary anaemia of unknown origin with HCl present in the stomach contents,

and thirty-one cases of anaemia referable to a definite cause (pernicious anaemia excluded), as against thirty-three cases of non-megalocytic anaemia with achlorhydia, during the period in which the present study was carried out. This gives an idea of the relative importance and prevalence of this non-megalocytic anaemia with achlorhydia.

To summarize, one may say that one of the commonest forms of secondary anaemia, especially in females, is this non-megalocytic form, which is associated with achlorhydia; that it is probably due to deficient formation of

haemoglobin; that it is not haemolytic or haemorrhagic in origin; and that its appropriate treatment with iron gives eminently satisfactory results.

COMMENTARY ON CASES

Relevant details of these thirty-three cases of non-megalocytic anaemia of unknown origin with achlorhydria are shown in Table II. Certain of these cases require comment.

Case 3 had Graves's disease; the anaemia was refractory to treatment with hydrochloric acid alone, but readily improved on iron being given by mouth; the hyperthyroidism showed a satisfactory result from non-operative treatment; she now remains in good health three and a half years after her first visit.

Case 6 had a relapse some months after ceasing treatment, but again the anaemia yielded to hydrochloric acid and iron by mouth.

Case 7 had a relapse on a maintenance treatment of hydrochloric acid by mouth alone, but again a good result was obtained on iron.

In Case 16 treatment was refused at first examination. We asked the patient to return four years later, when the anaemia and achlorhydria was found to be present to the same degree. Thirty grains of Bland's mass a day by mouth caused the haemoglobin to rise from 52 to 76 per cent. in sixty-seven days, and it rose to 80 per cent. later. This case showed a mild degree of infantilism.

Case 17 had secondary purpura haemorrhagica and severe oral sepsis, there being a polymorphonuclear leucocytosis (10,000 per c.mm.). The treatment consisted in clearing up the oral sepsis by mouth hygiene, teeth extraction, and the giving of hydrochloric acid and iron by mouth. Both anaemia and purpura readily responded to treatment. HCl was absent from the stomach contents two years later on the ordinary technique, but was present after histamine, and neither the anaemia nor the purpura reappeared in this period, although the patient was on no special treatment for the final year. Possibly the oral sepsis was one important factor in causing the anaemia.

Case 24 is of particular interest. She had been under treatment for diabetes mellitus with diet and insulin for seven years, when symptoms suggestive of achlorhydria caused us to do a test-meal examination, which showed achlorhydria. Hydrochloric acid in 60-minim doses thrice daily, with pepsin after food, relieved the gastro-intestinal symptoms, but after a year this treatment was only irregularly carried out. Two years after the achlorhydria was discovered the anaemia developed, and this readily yielded to iron in the form of Bland's mass with HCl and liver, the haemoglobin rising from 50 to 90 per cent. in forty-four days.

Case 28 also had diabetes, and anaemia developed two and a half years after the treatment with diet and insulin was started, when she was found to have achlorhydria. The anaemia readily yielded to treatment with iron and HCl. There was no relapse in nine months on treatment with HCl alone, in combination with anti-diabetic measures.

Case 29 was the only one which exhibited the so-called Plummer-Vinson syndrome, originally described by Kelly.¹¹ The oesophagospasm was in the lower third of the gullet; atrophic superficial glossitis was present, the tongue being smooth, red, and furrowed; there were cracks at the angles of the mouth; and the spleen was enlarged. The patient was edentulous, and had eaten no meat for months. Six days after oesophageal dilatation by Dr. P. Dempsey she was able to swallow normally, and a test-meal (without histamine) showed achlorhydria. With treatment by HCl, iron, and a normal diet (including meat) the anaemia quickly disappeared, the spleen after three weeks was no longer palpable, the tongue became normal, and the cracks at the angles of the mouth disappeared. When the blood count was normal the stomach secretions were re-tested, and HCl was found to be present in normal amount without the use of histamine. It is interesting to speculate whether a similar result would have been obtained if the HCl and iron had been omitted.

Case 32 showed the rare combination of hyperthyroidism, acute thyroid abscess, achlorhydria, and anaemia. The anaemia readily yielded to treatment by HCl and iron after the thyroid

abscesses had been drained by Mr. P. J. Smyth, but the hyperthyroidism persisted until a temporary remission was obtained through iodine by mouth.

Case 33 proved refractory to treatment by HCl and iron (Bland's mass, 45 grains a day by mouth) for several weeks, and then developed acute right-sided parotitis, with a subcutaneous abscess behind the right ear. Notwithstanding surgical drainage she died, and, in my absence, my house-physician (Dr. Malley) removed the liver and spleen and some tibial bone marrow; he found the gastro-intestinal tract macroscopically normal. Dr. W. R. O'Farrell reported no significant changes in the liver beyond slight thickening of the capsule, a slight round-celled infiltration in the neighbourhood of the portal areas, and slight cloudy swelling with patchy fatty degeneration of the parenchymatous liver cells. He found a pure hyperplasia of the spleen without qualitative alteration in its structure. The tibial bone marrow he found to be erythroblastic in type, with large numbers of red corpuscles, some normoblasts, but no megaloblasts; myelocytes and lymphoid cells were also seen in normal numbers.

GENERAL DISCUSSION

In 1930, when the present study was drawing to a close, the first comprehensive account of this particular form of anaemia in the British literature was given by Wits.^{12 13} Our own results, up to date, were reported to the Royal Academy of Medicine in Ireland¹⁴ and summarized in the *British Medical Journal*¹⁵ about the same time.* As Wits^{12 13} and Davies¹⁶ have gone fully into the literature it will suffice to point out that, although Faber¹⁷ described the disease in 1913, his description did not seem anywhere to attract the attention which we now know that it deserved. As far as our cases are concerned, the clinical picture seems closely to resemble that described by Wits, except that, while he notes that koilonychia was occasionally observed, we have never seen it in any of our cases, and, further, that he encountered splenomegaly much more frequently than we have done.

A reference might here be made to terminology. Up to about eighteen months ago we frequently referred, in clinical lectures, to this disease as "achlorhydria anaemia," but we believe that we have recently encountered some examples of it with traces of HCl present in the stomach contents, and this makes it doubtful whether such a term should be employed in its designation. Consequently, for the time being, we prefer the unfortunately cumbersome name of "non-megalocytic anaemia with achlorhydria." This term will serve to distinguish the condition from pernicious anaemia, which is macrocytic, but which is, except in very rare instances, associated with achlorhydria. Again, we prefer the term "non-megalocytic," rather than "microcytic," as used by Wits, because in our series, while none showed macrocytosis, some cases did not show microcytosis. We do not like the term "secondary" anaemia, partly because the only real form of primary anaemia is probably a form of aplastic anaemia, and partly because, as knowledge grows, most forms of anaemia will probably be shown to be "secondary." For example, it is now believed that pernicious anaemia is secondary to defective formation by the stomach (or defective absorption) of an erythropoietic substance.

Achlorhydria in Diabetes Mellitus

Among eighty-three cases of diabetes mellitus, achlorhydria was found in thirty-three (39.7 per cent.), six cases had traces of gastric HCl, ten had hypochlorhydria, thirty had the acid present in normal amounts, and four had hyperchlorhydria. Histamine was not used in these cases, except in a few odd instances; whenever there was acidosis the test-meal examination was not done until several days after the ketosis had disappeared as a result of treatment.

* These results were also given before the British Medical Association Meeting in Eastbourne, in July, 1931.

To give brief details, forty-four of these patients were males and thirty-nine females. Achlorhydria was present in thirteen males and twenty females. The ages varied from 9 to 69½ years (average 42), and the fasting blood sugar from 161 to 345 mg. (average 254) per 100 c.cm. Two of the cases developed the type of anaemia referred to above, with glossitis and achlorhydria. Probably the incidence of achlorhydria in these cases is somewhat too high for the reason already mentioned, but it is clear that the condition is a frequent finding in diabetes mellitus. Curiously enough, comparatively few diabetic patients with achlorhydria complained of the gastro-intestinal disturbances which are frequently associated with absence of the gastric acid, and superficial glossitis was also rare among them, but the two patients (Nos. 24 and 28, Table II) with achlorhydria who developed anaemia, both had superficial glossitis, flatulence, and diarrhoea. The rarity of gastro-intestinal symptoms and glossitis among diabetics was probably responsible for our not realizing that achlorhydria was fairly common in diabetes until the present study was well under way.

A search of the literature showed that others have noted a fairly high incidence of achlorhydria in diabetes mellitus; Joslin¹⁸ gives a figure of 27.3 per cent. among 106 cases, and he mentions an incidence of 40 per cent. in the first 100 cases tested in the Royal Victoria Hospital, Montreal. Bowen and Aaron¹⁹ reported achlorhydria in 29 per cent. of sixty-nine diabetics, and Rabinowitch, Fowler, and Watson²⁰ found achlorhydria in 39 per cent. of 100 diabetics. It is interesting to note in this connexion the considerable number of cases of pernicious anaemia recently reported in diabetics. Joslin²¹ mentions forty-eight cases in which both diabetes and pernicious anaemia were found combined. As regards the value of giving hydrochloric acid by mouth in diabetes when achlorhydria exists, we found that this procedure was of some use in the few patients who complained of gastro-intestinal symptoms, but that it appeared to be of little help otherwise.

To summarize, one may conclude that achlorhydria is a common finding in diabetes mellitus. In two cases of the present series it was accompanied by the non-megalocytic form of anaemia above described.

Achlorhydria in Hyperthyroidism

Our attention was called to the frequent occurrence of achlorhydria in Graves's disease by the gastro-intestinal symptoms, such as flatulence and diarrhoea, of which patients with this malady so frequently complain. Moreover, the appearance of the tongue in hyperthyroidism quite frequently suggested absence of gastric HCl, although the definite degree of superficial glossitis seen in the above-mentioned form of non-megalocytic anaemia with achlorhydria was encountered only occasionally.

The fractional test-meal examination showed that amongst forty-seven definite cases of hyperthyroidism, achlorhydria was found in thirty-seven (78.7 per cent), four cases had traces of HCl, one had hypochlorhydria, and four had the normal amount of gastric HCl. Full details cannot be given owing to lack of space. Forty-one were females and six were males; achlorhydria was present in thirty-three females and four males. The ages varied from 16 to 62 years (average 38) and the basal metabolic rate from +25 to +112 per cent. (average +56 per cent.). Three of these patients had anaemia with achlorhydria, and in two the haemoglobin was under 70 per cent. Histamine was used in only five cases, but its use in these failed to stimulate the formation of HCl. In practically all of these patients a remission, with marked lowering of the basal metabolic rate, was obtained by the use of Lugol's solution in doses of from 4 to 10 drops, twice

daily by mouth, and in the majority microscopical examination of the gland removed at operation showed the changes associated with hyperthyroidism or with the iodine remission. It is without doubt remarkable that such a high incidence of achlorhydria should be found in hyperthyroidism, and our present results obtained since this study was concluded still continue to show a high incidence. Faber²² found achlorhydria in 50 per cent. of patients suffering from Graves's disease.

Two of these cases of hyperthyroidism with absence of gastric hydrochloric acid showed the non-megalocytic anaemia (with haemoglobin under 70 per cent.)—namely, Cases 3 and 32 (Table II).

Other Associated Diseases

In the gastro-intestinal group there were 100 cases whose main complaints were referable to the gastro-intestinal tract. Forty-five had such vague symptoms that, notwithstanding careful investigation, no definite diagnosis beyond the achlorhydria itself could be made. The symptoms complained of were flatulence and sensations of abdominal distension, discomfort or pain after food, nausea or vomiting, attacks of diarrhoea, soreness of the tongue, or, occasionally, superficial ulceration of the buccal mucous membrane, regurgitation of food or sour fluid into the mouth, and so forth. Fifteen other cases were diagnosed as definite or probable chronic cholecystitis, ten as visceroptosis, seven as chronic gastritis, and four as gastric carcinoma. The remaining patients of this group were given various other gastro-intestinal diagnoses, but space again forbids going into detail. All these cases were thoroughly investigated clinically; routine gastro-intestinal x-ray or gall-bladder visualization examinations were made and special laboratory and diagnostic procedures were used whenever indicated. The treatment of gastro-intestinal symptoms associated with achlorhydria by means of oral administration of hydrochloric acid has been recently gone into by Wilkinson and Oliver.²³ As we are in substantial agreement with the opinions of those authors on this subject we need not deal with the matter here, beyond saying that where achlorhydria seems to be a direct or indirect cause of gastro-intestinal symptoms the use of dilute hydrochloric acid in 15 to 60 minim doses (with pepsin, if necessary) in a suitable vehicle, thrice daily with or after food, frequently gives satisfactory results, provided that appropriate attention is paid to whatever additional therapeutic instructions may be necessary.

There were seventy-four cases in the miscellaneous group. Fourteen were labelled pulmonary tuberculosis, two amongst them having also chronic nephritis. There were thirteen cases of pernicious anaemia and ten with cardio-vascular hypertensive disease—with or without evidence of kidney involvement; various diagnoses were made in the other members of the group. The frequent occurrence of achlorhydria in pulmonary tuberculosis was noted by Faber²² in 1905.

It would be hazardous, with the information in our possession, to express an opinion on the causes of achlorhydria. Faber²⁴ thinks it is an expression of gastritis—traumatic or toxic—haematogenous in origin, and brings forward post-mortem evidence to that effect; this matter, however, should be still a fruitful field for investigation. There appears to be a good deal yet to be learned about the physiology of gastric hydrochloric acid, and it must be admitted that our present clinical methods of studying gastric secretion leave much to be desired.

SUMMARY AND CONCLUSION

Achlorhydria, besides being found in a certain proportion of apparently healthy persons, in many cases of gastro-intestinal disease, and in odd cases suffering from

miscellaneous disorders, is a frequent finding in diabetes mellitus, and a still more frequent occurrence in hyperthyroidism and in the non-megalocytic "hypochromic" anaemia above described. In the latter disease it seems to have causal relationship, direct or indirect, but in the light of recent work on pernicious anaemia even this surmised causal relationship may ultimately prove to be incorrect. At any rate, this form of anaemia is of frequent occurrence, and its adequate treatment with iron in the ferrous form, by mouth, gives satisfactory results.

It gives me great pleasure to acknowledge, in this study, the cordial co-operation of Dr. W. R. O'Farrell, pathologist to the hospital, and of Drs. L. K. Malley and M. A. Moriarty while they were my house-physicians.

The original lecture was illustrated by more extensive tables and details, which cannot be reproduced here owing to lack of space.

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SOME CLINICAL ASPECTS OF CORONARY DISEASE *

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Clinical observations of practical value in the treatment of patients with disease of the coronary arteries have in recent years been rapidly accumulated, and some of the gaps in our knowledge of the clinical manifestations of this malady have been filled in. For many years the general conceptions of coronary disease, and the events associated with it, were influenced by studies which often lacked the observational precision shown by those great physicians, Heberden, Parry, and Jenner, in their classic records of a hundred and fifty years ago. The theories advanced were based on insufficient knowledge of the anatomy and physiology of this region, and progress was relatively slow. The observation that nitrites, introduced by Lauder Brunton, controlled the pain of angina pectoris by means of vaso-dilatation has undoubtedly increased our knowledge of the clinical pathology of coronary artery disease. Head and Mackenzie made important observations regarding the distribution of pain in anginal subjects, and Mackenzie revived the theory of myocardial exhaustion, and its relation to a deficient coronary circulation, as the cause of anginal pain and heart failure. Allbutt viewed angina as a symptom of

aortic disease, and Wenckebach supported him in opposing those who accepted the coronary explanation of the anginal syndrome; others have maintained that anginal pain may be a symptom either of coronary or of aortic disease. It has long been known that pain with an anginal distribution may be due to other causes than heart disease; the term "secondary angina" has been employed to distinguish such cases from primary angina subjects with structural disease of the heart. In 1912 Herrick in America described symptoms and signs associated with acute obstruction of a coronary vessel, and stated that these patients might recover from the attack. His description of the coronary occlusion syndrome was a valuable contribution to clinical medicine, and it has helped clinicians to diagnose obstruction of a coronary vessel at the bedside, and to offer a fair prospect of recovery to the patient. To American physicians is due the credit of describing the clinical picture of this disease as we now recognize it, and their success in this field of medicine is a tribute to observational methods of research.

Shortly after the war, Pardee and others observed characteristic changes in the electrocardiogram of patients with coronary artery occlusion, which are of the greatest value in the diagnosis of this disease. Some years later Parkinson and Bedford in this country, in a series of accurately recorded cases, confirmed by post-mortem evidence, described electrocardiographic signs which have added to our knowledge of coronary infarction and thrombosis. These clinical observations, by distinguishing the coronary occlusion syndrome from angina pectoris, have established on a sound basis our present conception of some of the clinical phenomena of coronary artery disease.

Within the last three or four years observations relating to the mechanism controlling the peripheral circulation have been made by Lewis and his co-workers. By employing precise observational and experimental methods, they have brought forward evidence which explains how pain is produced in contracting visceral muscle under conditions of circulatory arrest. Their studies support the generally accepted view that ischaemia of the heart muscle, from a defective coronary circulation, is responsible for the pain in anginal subjects. Lewis has now isolated from the general group of anginal patients a distinct type with aortic regurgitation, having a high blood pressure and rapid heart rate during the paroxysms of pain. These signs suggest that widespread vaso-constrictor influences, involving the coronary circulation, are an essential feature, and they emphasize the importance of recognizing, in addition to coronary disease, other contributory factors associated with the anginal seizure. It is beyond the scope of this paper to discuss the pathology of arteriosclerosis, which is the cause of coronary disease, or the class and sex incidence of anginal pain, except to point out that vaso-constrictor influences may be a determinant factor.

There are certain characteristic symptoms arising out of an insufficient blood supply to the heart muscle from structural changes in the coronary vessels which enable us to distinguish two types of cases presenting distinct clinical phenomena: in one, angina pectoris; in the other, the syndrome of coronary occlusion. The differential diagnosis is extremely important, for upon it depends the treatment—which is quite different in the two maladies—and not infrequently the life of the patient.

ANGINA PECTORIS

The distinctive character of the pain of angina pectoris is that it can always be provoked by effort; it is paroxysmal, usually felt in the front of the chest, under the sternum, and down the left arm, and is relieved by rest and nitrites. An emotional upset, a heavy meal, exposure to cold, may initiate an attack or favour the

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