DETECTION OF ACHLORHYDRIA WITHOUT INTUBATION

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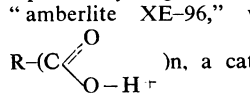
Intubation of the stomach to obtain samples of gastric juice for examination has two major disadvantages. Even with expert assistance it often proves distressing to the patient, and the act of swallowing the tube tends to alter the composition of the juice. Thus, nausea and retching inhibit the secretion of gastric hydrochloric acid in dogs even when histamine is injected every ten minutes (Grossman *et al.*, 1945), and the presence in the stomach of excessive saliva reduces the acid content (Zaus and Fosdick, 1934).

The most important information which the clinician wants from a gastric analysis is the ability or otherwise of the stomach to secrete hydrochloric acid. This can now be obtained by a simple test which does not involve the passage of a tube. This paper describes the origin of the test, its use by other workers, and some personal results.

Rationale and Development of Test

Following the work of Adams and Holmes (1935) on synthetic ion-exchange resins, H. L. Segal, of Rochester, New York, became interested in their use as antacids (Segal *et al.*, 1945). The therapeutic trials were disappointing, but in 1948 he and his co-workers began to develop the idea that an ion-exchange resin to which a special indicator cation was attached could be used to detect gastric hydrochloric acid without intubation.

The preparation and use of such a compound was first reported by Segal *et al.* (1950a). Starting with the resin "amberlite XE-96," which has the general formula  , a cation exchange indicator compound, now marketed under the trade name of "diagnex," was produced by replacing the hydrogen ions of the carboxylic acid groups with quininium ions. Studies *in vitro* showed that the displacement of the quininium cations of this compound by cations in solution depended on various factors, the most important being the hydrogen-ion concentration. Sodium, potassium, and calcium replaced quinine only slightly, but magnesium was more powerful in this respect. When the compound was given orally to patients the hope that quinine would be easily liberated by the hydrogen ions of the hydrochloric acid present in gastric juice was confirmed. The quinine set free was rapidly absorbed and approximately a third excreted in the urine (Goodman and Gilman, 1941). The time of appearance, as well as the amount of quinine in the urine, was noted to avoid misinterpretation resulting from later ionic exchange in the small intestine.

In their preliminary clinical study Segal *et al.* (1950a) gave the quininium indicator compound orally in 2-g. doses with 50 ml. of 7% alcohol to 63 patients whose gastric secretory response to alcohol had been determined by the usual intubation technique on a previous day. In 34 of the 38 patients with free gastric hydrochloric acid quinine was found, on qualitative testing, in the urine excreted during the first, second, and third hours after the administration of the compound, whereas none of the 25 with achlorhydria showed quinine in the first-hour urine and 20 also failed to excrete it in the second. They concluded that the appearance of quinine in the urine during the first and second hours indicated the presence of free gastric hydrochloric acid, and delay in its excretion until the third hour was compatible with achlorhydria. A few patients passed quinine only in the second and third hours and not in the first; quantitative testing by a photofluorimetric technique was then necessary to confirm the presence or absence of free hydrochloric acid.

Further experiences with the test were described by Segal *et al.* (1950b), Segal (1951), and Segal *et al.* (1953). It was established that achlorhydria could be differentiated from the presence of free hydrochloric acid by the total quantity of quinine excreted in the first two hours after the ingestion of diagnex. Out of 257 subjects who were known to secrete hydrochloric acid and 85 with proved achlorhydria, only four gave inconsistent results by the tubeless technique.

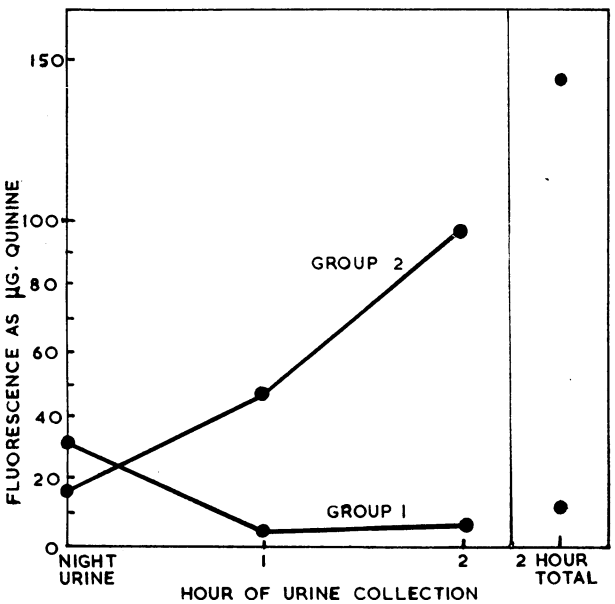
Other favourable reports, in smaller series of cases, were published by Malach and Banks (1952) and Flood *et al.* (1953). Harkness and Durant (1953) made an indicator exchange compound similar to diagnex and showed that patients with free gastric hydrochloric acid excreted considerably more quinine than those with achlorhydria.

Present Investigation

Method.—The patients, none of whom had been ingesting vitamins or drugs containing calcium, magnesium, iron, or aluminium during the previous 24 hours, were investigated in the following manner. After an eight-hour fast the bladder was emptied and the urine saved. Immediately afterwards 0.5 mg. of histamine acid phosphate was injected subcutaneously and 2 g. of diagnex, in 4 oz. (114 ml.) of water, given orally with instructions to avoid chewing the granules. Thereafter the bladder was emptied at the end of one and two hours. The volumes of all three urine specimens were noted and each was treated with ether and sulphuric acid according to the method described by Kelsey and Geiling (1942) for the extraction of quinine. The final acid extracts were compared with a standard solution of quinine sulphate in a Hilger fluorimeter; the natural fluorescence of the night urine (expressed as μg. of quinine) and the amount of quinine in each hourly specimen were then calculated.

Material.—Twenty-two patients were investigated. Intubation studies were performed, usually 24 hours before the diagnex test, in all but four, the exceptions being two with peptic ulceration, one with gastric carcinoma, and one with a partial gastrectomy. For assessing the results of the diagnex test the patients were divided into two groups. Group 1 contained 11 with proved histamine-fast achlorhydria (Addisonian pernicious anaemia, 4; iron-deficiency anaemia, 3; partial gastrectomy, 2; gastric carcinoma, 1; anxiety state, 1), and, in addition, 2 who were not examined by the intubation method (partial gastrectomy, 1; gastric carcinoma, 1). The last two patients were included in this group because it was considered that free hydrochloric acid was more likely to be absent than present. Group 2 comprised 9 patients who were known, or expected, to secrete hydrochloric acid (active peptic ulceration, 6; partial gastrectomy, 2; refractory anaemia, 1).

Results.—In group 1 the total urinary output of quinine in the first two hours after the administration of diagnex ranged from 5.1 to 19.1 μg., and for 8 patients in group 2 from 57 to 319 μg. The Chart shows the wide separation between the mean curves of the urinary fluorescence in the two groups. The remaining patient in group 2 was exceptional in that only 12.8 μg. of quinine was excreted. This patient had a partial gastrectomy, and the fasting juice, when examined previously by the tube method, contained 6.4 clinical units of hydrochloric acid.



Mean curves of urinary fluorescence.

Discussion

In this small series of cases the existence of achlorhydria coincided with an excretion of less than 20 µg. of quinine in the total two-hour urine, while, with one exception, the presence of free gastric hydrochloric acid was associated with an output of more than 50 µg. Flood *et al.* (1953) reported similar findings except that the upper limit of urinary quinine in the achlorhydric cases was 25 µg. After long experience with the test, Segal *et al.* (1953) concluded that a firm diagnosis of achlorhydria depended on an excretion of not more than 15 µg. of quinine. These slight differences in the interpretation of the significant urinary quinine level are possibly due to minor variations in the extraction technique. In the group 2 patients no quantitative relationship was demonstrated between the amount of quinine in the urine and the units of acid present in the stomach.

The diagnex test, although still in the experimental stage, promises to be a valuable clinical method of gastric investigation. The patient who refuses or fails to swallow a tube is in no way upset by a procedure which involves only the ingestion of a non-toxic tasteless compound, an injection of histamine, and the collection of urine samples. If further simplification is desired, histamine can be omitted in the first test, but without artificial stimulation a low output of quinine cannot be accepted as evidence of achlorhydria. The test must then be repeated after several days with the addition of histamine. Diagnex itself does not promote acid production to any appreciable extent, and the routine use of histamine is desirable to save time.

Apart from its convenience in patients who are apprehensive about passing a stomach tube, the test has other clinical applications. It is eminently suitable for investigating the incidence of achlorhydria in the general population (Segal *et al.*, 1953), and Malach and Banks (1952) advocate its use, in preference to the conventional tube method of gastric analysis, after recent bleeding from the upper gastro-intestinal tract and after the operation of partial gastrectomy. They report excellent correlation between the diagnex test and the ordinary aspiration technique in nine patients after gastric resection. In the present study four such patients were examined by both methods and the results were conflicting in one: hydrochloric acid was demonstrated by aspiration, but the output of quinine suggested achlorhydria. This may have been due to too rapid emptying of the diagnex, or the hydrochloric acid, from the gastric stump. The interpretation of the standard fractional gastric analysis in patients who have had a partial gastrectomy is often suspect because of doubt about the position of the tube in the gastric remnant, and it is unfortunate that the tubeless method does not appear to be a completely reliable alternative. Much more experience with such cases is required before the status of the tubeless technique can be properly evaluated.

In the laboratory the only problem concerned the possible significance of natural urinary fluorescence as a source of error. Extraction of normal urines obtained under the exact conditions of the test, except that diagnex was omitted, showed, however, that it did not have an important influence on the results. Apart from the concentrated night urines, the fluorescence did not exceed the equivalent of 3 µg. of quinine in any specimen. Segal *et al.* (1953) recommended that the night urine should be discarded and a control specimen collected an hour later immediately before the administration of the diagnex. This will serve for the recognition of fluorescence due to the ingestion of riboflavine, nicotinic acid, or quinine.

At present the diagnex test is likely to be used only in selected patients, especially those who object to swallowing a stomach tube. Eventually, however, it may become the routine method of gastric analysis, if only for the sake of the patients' comfort.

Summary

The development of a quininium cation exchange indicator compound called "diagnex" and its use to detect achlorhydria without intubation are reviewed.

Experience of the test in 22 patients is described. Achlorhydria was associated with an output of less than 20 µg. of quinine in the urine passed during the first two hours after the oral administration of diagnex.

In general, the results agreed well with those obtained by the aspiration technique, but a discrepancy occurred in a patient who had a partial gastrectomy.

The clinical advantages and applications of the test are discussed.

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The World Health Organization has published a *World Directory of Medical Schools* (1953) which lists over 500 institutions arranged under countries. Information given includes name and place of each institution; year founded; details of administration; length of the academic year; conditions governing admission of students; numbers of full-time and part-time teachers; total enrolment, by sex; number of new students admitted each year; language in which instruction is given; degrees obtainable and time required to obtain them; annual number of graduates; and annual tuition fees. Information is given in both English and French. The directory reveals that the U.S.A. has 79 medical schools, the U.S.S.R. has 61, Japan 46 (of which 21 have been created since the war), India 34, United Kingdom 27, France 25, and Italy 21. It is obtainable in Britain from H.M. Stationery Office, price 25s.