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THE TREATMENT OF PEPTIC ULCER WITH ENTERIC AND URINARY CONCENTRATES: A REVIEW

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INTRODUCTION

ANY HOPE OF CURE for the ulcer patient rests in a concept of therapy that seeks to alter the presumed metabolic or constitutional susceptibility which permits the development of a mucosal "locus minori resistentiae" to one or more exciting factors. In 1945, Sandweiss[1,2] and Necheles[3] called for further investigation of new substances that hold promise as "immunizing" agents in the treatment of peptic ulcer disease. It will be the purpose of this paper to determine how near to this realization subsequent years of chemical, physiological and clinical experimentation with enterogastrone, urogastrone, anthelone and related materials have brought us.

EXPERIMENTAL BACKGROUND

Intestinal Extracts

Ewald and Boas in 1896 made the observation that the addition of olive oil to a test meal inhibits gastric secretion. Fifteen years later, Pavlov's laboratory reported that the inhibition occurred only when the fat acted in the duodenum. The humoral nature of the process was revealed by Farrell and Ivy (1926) and by Feng, Hou and Lim (1929) who found that gastric motility and secretion were inhibited when olive oil was fed to a dog with a subcutaneously autotransplanted (completely denervated) pouch of the fundic portion of the stomach. That the humoral agent was not an absorbed product of digestion was also proved by Feng, Hou, and Lim, who showed that no constituent of the lymph collected from a thoracic duct fistula had an inhibitory effect on gastric secretion after intravenous injection. Kosaka and Lim made extracts of various tissues and found that only extracts of intestinal and colonic mucosa had an inhibitory effect on gastric secretion after intravenous injection comparable to that induced by a previous ingestion of olive oil. They named this extract enterogastrone, a term derived from entero/n, gastr/on, and chal/one.[2,4,5,6] In 1937, Gray, Bradley and Ivy prepared a potent extract of the duodenal mucosa of hogs and defined a unit of enterogastrone as that quantity, which upon intravenous injection in a dog with a total pouch of the stomach, brought about a fifty percent depression in the output of acid secretion during the two hours following histamine.[7]

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The beneficial effect of enterogastrone on Mann-Williamson (M-W) dogs was described by Hands and others in 1942.[8] This group treated M-W dogs with intravenous injections of 50 mgm. of enterogastrone extract three times a day, and although they failed to inhibit gastric secretion, they not only prevented jejunal ulcers during therapy, but three years after enterogastrone had been withdrawn six of their ten animals were still alive. Jejunal ulcers had been prevented before with aluminum phosphate gel[9] and mucin,[2] but it would be an unusual M-W dog that lived one year after such treatment had been discontinued. Two years later, it was shown that M-W dogs treated with enterogastrone responded to histamine stimulation in a fashion identical to untreated, unoperated dogs.[10] Similarly, Ivy reported that while untreated M-W dogs secrete longer in response to an alcohol meal, M-W dogs protected with parenteral enterogastrone respond like normal dogs to alcohol.[11,12] Because Ivy produced a beneficial effect on M-W ulcers without affecting gastric secretion, he attributed the effect to something other than inhibition of gastric secretion. Speculating on this interesting and unexpected outcome, Ivy concluded that "it is in the possibility of the prevention of recurrence rather than in the production of a remission of symptoms that enterogastrone concentrates derive their unique interest".[11] Years later, to determine the way in which entergastrone worked, changes in acidity and volume output in Heidenhain pouch dogs were measured and evidence was obtained by Linde et al that enterogastrone had no specific action on acid output, but it did alter secretory rates which, in turn, affected acidity.[13] Other later investigators showed that it effectively inhibited gastric secretion in cats[14] and pancreatic secretion in dogs.[15] However, it should be pointed out that efforts to inhibit ulcers in M-W dogs with *oral* gastrointestinal extracts failed.[16,17]

A few groups[18,19,20] employed the Shay rat[21] as an assay animal. Enterogastrone did not uniformly offer protection against ulceration in the Shay rat.[22,23] It was also demonstrated that intraperitoneal turpentine or blood and the intravenous injection of various substances delayed ulceration in the Shay rate, so that any non-specific influences of enterogastrone could be magnified in this animal.[24]

Urine Extracts

In 1938, Sandweiss, Saltzstein, and Farbman found that extracts of the urine of women, pregnant or not, afforded protection against M-W ulcers when injected subcutaneuosly.[25,26] One to five cc. of these extracts had no effect on gastric secretion stimulated by a meal, although it was found later that subcutaneus doses of 10-20 cc. did lower the volume of HC1 in dogs with total gastric pouches.[27] Intravenous administrations of either normal female or male urine extracts have depressed gastric secretions stimulated by histamine, however.[28] As early as 1939, Friedman et al[29] noted that the amount found effective by Sandweiss[26] for protection against the M-W ulcer was too small to reduce gastric secretion and suggested that there might be two factors in the urine extracts. Other laboratories confirmed this observation, taking care to record body temperatures to rule out non-specific pyrogenic effects.[30,31] It would appear, therefore, that "the inhibitory effect on gastric secretion of urine extracts containing APL (anterior pituitary like) hormone is due (at least, in part) to some substance other than the contained APL hormone and is a property of urine

extracts from both sexes; and that the ulcer-preventive factor in urine extracts is also independent of its content of APL hormone, being present in the urine of males and non-pregnant females".[32]

Sandweiss reported in 1942 an experience which included observations on 142 dogs: 28 untreated controls, 42 treated with pregnancy urine extracts, another 42 treated with urine extracts of normal women, and 30 treated with extracts of urine of patients with active ulcer symptoms.[33,34] He had three criteria for therapeutic effectiveness: 1) absence of an ulcer, 2) evidence of healing of the ulcer — fibroblastic proliferation and epithelialization, 3) prolongation of the life of a treated dog beyond the maximum length of life of the control dogs — 135 days. Of the 42 dogs treated with pregnancy urine, 85 percent were benefited, and of the 42 treated with normal female urine, 62 percent were benefited. Of the 30 treated with the urine of the ulcer patient, 24 percent were benefited. The degree of healing was greatest in the group treated with female urine. The postoperative survival for controls and dogs treated with the urine of ulcer patients was 71 days; the dogs treated with the normal female urine survived an average of 140 days; the group treated with pregnancy urine survived, on the average, 169 days. Sandweiss[35] administered these extracts of urine, obtained from females pregnant and non-pregnant, to a total of 282 M-W dogs and obtained remarkably good and consistent results, based on his established criteria.[33] A later report by Sandweiss[36] describes the results with oral uroanthelone (Kutrol) in 10 M-W dogs who lived considerably longer and developed fewer ulcers than M-W control dogs, though hydrochloric acid and pepsin levels were unchanged.

Inhibition of ulceration in the rumen of the Shay rat, occurred with injections of urine extract,[37] although Risely et al[38] noted that the effectiveness of these extracts paralleled the depression of acid secretion, an observation not confirmed in a similar study employing M-W dogs.[39]

The Clinical Experience

Because the administration of either urine or intestinal extracts in animals and humans had shown that the healing of ulceration occurred without lowering gastric acidity and that gastric acidity had been decreased without prolonged protection against peptic ulceration,[8,10,33,34,40,41] some investigators were compelled to believe that the urinary and intestinal extracts each contained two separate factors. Thus, Sandweiss and Friedman[40,42] worked with a purified urine extract, which they called GSD because of its powerful gastric secretory depressant effect, and also worked with a urine extract, which was given the name anthelone, because it had prevented ulceration in M-W dogs without affecting gastric secretion.[41] Similarly, although Gray, Bradley and Ivy[7] assayed enterogastrone on the basis of its secretory depressant effect, other investigators[8,11,12] found only its immunity effect significant. In terms of the nomenclature suggested by Littman,[4] there are four possible products. The gastric secretory depressant factor obtained from intestinal mucosa, called enterogastrone, received much clinical study, but a urogastrone preparation was apparently not produced for clinical use. The "anti-ulcer factor" (enteroanthelone) was either assumed to be

proportionately concentrated with the GSD factor[43] or was ignored completely since determination of its presence involved a complicated assay procedure. However, a substance labelled as enterogastrone when given orally, subcutaneously or intramuscularly was shown to have little or no affect on human gastric secretion[44,45,46,20,47] and presumably, in clinical trails, derived its activity from the enteroanthelone component.[43,48,49,50,51,52] A considerable European experience was amassed with a commercial gastrointestinal preparation, called Robuden, for which the claim was made that it had distinct anti-ulcer activity and no anti-secretory activity. A third substance was an oral uroanthelone preparation named Kutrol, which, though showing anti-ulcer activity in the Shay rat, was proven in humans to have no significant influence on the fasting 36 hour secretion of hydrochloric acid or the output of hydrochloric acid stimulated by a test meal.[36]

It should be emphasized that these extracts can be differentiated only by their physiological action and are not isolated as pure substances identifiable as chemical entities.[6] The chemical nature of enterogastrone has never been clearly defined. Grossman[4] stated that enterogastrone preparations all contain amino acids. Fonss-bech and Heintzelmann[19] described a non-dialyzable fraction which contained at least four amino acids. However, Obrink[53] upon electrophoretic analysis failed to identify any protein moiety. Electrophoretic analysis of Robuden revealed the presence of several mucous substances, pepsin in insignificant amounts, and an unknown alkaline material.[54] Urogastrone, as isolated by R. A. Gregory,[55,56] contained a golden yellow fluorescent pigment of unknown composition and a protein component of low molecular weight. His product inhibited gastric secretion and presumably is not identical with the commercial product Kutrol which is purported to be a uroanthelone. An earlier study indicated that urogastrone was probably a complex organic base.[57]

No definite relationship has been proven between enteric and urinary extracts. Although some workers[58,59] witnessed the disappearance of urogastrone in enterectomized dogs, most did not.[40,60,61,62] Differences in chemical properties also appeared to invalidate the idea that enterogastrone and urogastrone were of similar origin.[63,64] The work of Kaulberz, Patterson and Sandweiss[65,66] indicated that urogastrone was dependent on the presence of the anterior pituitary gland rather than an intact gastrointestinal tract.

Enterogastrone

Greengaard et al[67] studied 58 patients with active ulcer symptoms who acted as their own controls; that is, they all had a history of repeated attacks over several years despite treatment. Of 26 patients getting intramuscular injections six times a week for an average of about nine months, four had recurrences and six were without any improvement in x-ray findings; of the remaining 32 patients who received three injections a week for an average length of therapy of eleven months, ten experienced recurrences and twelve were unimproved as far as ulcer size was concerned. Over half the patients were without recurrences though enterogastrone injections were discontinued. Thirty-three of these same patients and thirteen additional ones were given 200 mgm. intramuscular injections of enterogastrone, which at first was Ivy's

own preparation[68] and later a commercial one. (It is noteworthy that the few batches of enterogastrone that had been assayed in M-W dogs were discovered to be ineffective in 25 percent of the dogs). Of 35 patients receiving six injections weekly, 37 percent were completely relieved of symptoms and 89 percent were improved during the five to twelve months period of injections; four patients were symptom-free 17-52 months after cessation of enteroanthelone; eleven patients had their usual recurrences after the completion of therapy.[43] The symptom-free interval on enterogastrone therapy was considered significantly longer than that prior to therapy. A trial of enterogastrone therapy was proposed "in certain patients . . . who do not have . . . pyloric stenosis, who have periods of severe distress . . . (on) adequate dietary and antacid management, and who defer or refuse operative intervention".[43]

Pollard's group gathered data on 28 patients, but the evidence was inconclusive as to the efficacy of enterogastrone in preventing recurrences.[48] In another study, Wollum and Pollard[49] treated 34 patients who had ulcer symptoms for an average of 14.2 years with two to three recurrences each year and only eight patients were significantly improved. Sandweiss[50] treated 48 intractable ulcer patients with daily intramuscular injections of 200 mgm. of enterogastrone for three months, followed by an oral preparation in a dosage of seven grams per day. Although 55 percent of his patients were symptom-free during parenteral therapy, 70 percent suffered relapses within a year. The commercial preparation used by Sandweiss later proved to be ineffective in M-W dogs as well as patients, while the beneficial effect obtained in patients by Ivy's product was duplicated in M-W dogs.[50]

Gambill[51] set up a double blind study: 77 percent of his twenty-two patients taking 6 grams of commercial enterogastrone orally were improved, but so were 59 percent of the seventeen patients taking placebos. Bone et al[52] using daily 200 mgm. injections of a commercial preparation for an average of four months, found that 60 percent of his twenty patients on entergastrone therapy improved, but so did nine of sixteen patients (56 percent) who were being injected with placebos. In the post-treatment follow-up, Bone reported 17 percent of the patients who took enterogastrone still improved after about a year as compared to 27 percent of those who received placebos. Similar observations were made in a European clinic,[19] where enterogastrone, which was assayed in Shay rats, was given by intramuscular injection in a dose of 200 mgm. every other day for six months. Five males received enterogastrone and another five water, but both groups were told that they were getting the "new American drug". The results of the treatment were "almost identical, both as regards the effect shown in x-ray findings, on the gastric secretion and on the subjective symptoms — in the course of, as well as immediately after discontinuation of the treatment, and at re-examination".[19] Another double blind study of 33 patients,[69] using a powder of duodenal extract said to contain enterogastrone and an anti-proteolytic factor, found the preparation at least as good as current therapy and better than the placebo.

Robuden

Roth[70] reviewed 16 reports appearing in European journals from 1944-1953. 67.5 percent of 911 cases treated as in-patients were said to be "cured". Of 629

out-patients 77.3 percent were considered "cured"; 379 patients were followed for about four years on prophylactic Robuden and 50.4 percent were free of recurrences. Among these trials of therapy, there may be cited the very good results of Hobacher[71] who achieved "rapid disappearance of symptoms" in 44 of 54 ulcer patients, and the rather poor results of Stoltz[72] who found placebo therapy comparable in effectiveness to Robuden therapy, whether oral or parenteral.

In an excellent review of the literature to 1952, concerning therapy of peptis ulcer with tissue extracts, Notkin[73] emphasizes that Robuden is probably not identical with enterogastrone which he believed was therapeutically ineffective because of the absence of anthelone activity. Notkin cites the experimental work of Roulet and Vallery-Radot as evidence of the high anthelone activity of Robuden which European clinicians used, as noted above, so successfully. Notkin's series of twenty patients with duodenal ulcer showed that 75 percent of patients taking Robuden "did very well".

Evans[74] obtained protein-free extracts from the stomach and small intestine of animals and administered the water soluble portion by injection and the water insoluble portion by mouth to 111 patients. After five months of therapy, he found this material, called Robaden, of no value. A similar trial of therapy[75] was offered to 136 patients, 47 of whom failed to improve after two to four years of observations, but all the patients had been chosen for Robuden therapy because they had proved refractory to other modes of medical therapy. Glass concluded from his evaluation[54,76] that "in 80 percent of the cases studied, prolonged, intermittent treatment with Robuden ameliorated the natural history of peptic ulcer by decreasing the severity, duration and/or frequency of relapses".[54] Kaludi's results[77] with Robuden were also encouraging.

Kutrol

Using an extract of pregnant mare's urine which, when tested on rats, showed a 28-53 percent inhibition of gastric secretion, Page and Heffner[78] treated 26 patients with intractable ulcer symptoms for 20 months. Only three of their patients failed to achieve complete remissions.

Together with their usual therapy, another group of 63 active ulcer patients[33] received parenteral urine extracts in decreasing frequency for about two months. A 15 percent increase in remissions was observed as compared to alkali therapy. Of 39 patients treated with urine extract after failure on a diet-alkali regimen, 64 percent became free of symptoms. A high rate of remission was also noted with injections of vaccine and distilled water. In 1952, Sandweiss and Sugarman,[79] upon analysis of 43 patients who had failed to become symptom-free on their usual therapy, concluded that one-third of patients who do not respond to conventional ulcer therapy will respond to Kutrol for at least one year.

Employing the double blind technique, a study of ten patients on Kutrol and ten patients on placebo capsules showed uniformly poor results with either mode of ulcer therapy.[80] However, Bercovitz[81] improved one-half of his patients taking

Kutrol for ulcer disease while less than 10% were improved with placebo medication. (This was a "single blind" study). Grief[81] observed a relatively rapid disappearance of x-ray signs of peptic ulcer in a study of thirty patients who were placed on urogastrone therapy.

SUMMARY

The early pioneer work and subsequent extensive animal experimentation with enteric and urinary "gastrones" and "anthelones" have been traced. Although this was followed by numerous clinical trials, these agents have not met with wide acceptance in the treatment of peptic ulcer.[82] The reasons for this are:

1. The failure to make a chemical identification or isolation of the active factor or factors.
2. The inability to reproduce consistently in man the physiologic responses to these preparations obtained in animals and
3. The mode of clinical evaluation which because it was based, for the most part, on poorly controlled therapeutic trials (necessarily remains inconclusive).

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