PROGRESS IN GASTROENTEROLOGY

VOLUME I

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Edited by

GEORGE B. JERZY GLASS, M.D.

New York Medical College, New York, N. Y.

GRUNE & STRATTON New York and London

Preface

GASTROENTEROLOGY has changed much during the past generation. Some 25 years ago a gastroenterologist studied his patients for the most part across the desk or in the darkness of the X-ray room. In 1968, the gastroenterologist holds in one hand a variety of tubes, scopes and needles, while with the other hand he manipulates complex controls of pressure recording devices, telemetering capsules, movie cameras, intraluminal pH meters, scintillation scanners, well counters, or electron microscopes. He also must know how to use the wealth of information yielded by modern physiologic, biochemical, enzymologic and immunologic research. This paragraph, taken from my previous text depicts the complexity of modern gastroenterology which is reflected in this volume.

The present text samples the "present status," "current views" or "recent developments" in gastroenterology. The title of "Progress" parallels other similar "Progress" series put out by the publisher. The editor, at the onset of this work, recognized that any attempt at a complete coverage by such a venture would be futile and impossible. Thus, the material presented reflects the bias of the editor in choosing the topics of the chapters. The other obvious consideration was to eliminate from the volume the subjects extensively treated in other related texts published during the last few years. Thus, only a few topics contained in this text have been tapped in related volumes published in English during the last few years. The list of these is appended at the end of this Preface, to help the interested reader build up his gastroenterologic library. Of the twelve texts listed, five appeared in this country, one in Canada, and six in Great Britain during the last 20 years, of which seven were the outcome of Post-graduate Courses. Of the others, only two, one American and one British, have been published in the last two years, and of these, one was surgically oriented. The question of whether there is room for publication of the "Progress," which the editor asked himself prior to accepting the publisher's invitation, thus had to be answered affirmatively.

In considering the framework for this current series, it was agreed that the text would differ from the Post-graduate Courses in that it would contain more extensive information on fewer topics. It will also differ from the monthly reviews in some gastroenterologic periodicals which, because of the limitations of the journal, are restricted in their tabular and graphic contents.

The contributing authors have built their reputations in the particular areas about which they were asked to write. This allowed them to filter the available information through their own knowledge. The authors were asked to express their concepts freely without fear of restraint by editorial reviewers. The editor attempted to achieve some balance among individual chapters, although they have varied significantly in size and the wealth of illustrations.

Twenty papers by thirty-two authors form this volume of over 500 pages, which also contains over 180 figures, 40 tables and more than 1,800 references. Among the topics covered, there is a strong emphasis on stomach, with small intestine as second best. It is hoped that there will be a shift of emphasis in the

next volume, which is expected to appear within one and a half to two years. Because of the availability of the fine series on "Progress in Liver Diseases," issued by the same publisher, all matter pertaining to the liver has been eliminated from this volume.

The editor is deeply indebted to all the authors for their generous and unselfish contribution to this volume. He is also grateful to Dr. Henry M. Stratton, President of Grune & Stratton publishing company, for his encouragement, sincere interest in this publication, and willingness to accommodate all the requests of the editor. Mr. Duncan Mackintosh, Vice President of the publishing company, has been in charge of this series, and has given us a helpful hand in producing the volume. My thanks go also to my past secretary, Mrs. Joan Corso, for her valuable help in corresponding with the authors and Publishers.

G.B.J.G.

Related Texts

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4. Recent Advances in Gastroenterology. *(J. Badenoch & B. N. Brooke, Eds.)* J. & A. Churchill, Ltd., London, 1965.
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Post-Graduate Gastroenterology Courses or Symposia on Special G.I. Topics

1. Postgraduate Gastroenterology. Proceed. of Course Given Under Sponsorship of the Am. Coll. of Physicians, Philadelphia, 1948 *(H. L. Bockus, Ed.)*.
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Contributing Authors

BANK, S.
Consultant Gastroenterologist, Groote Schuur Hospital, Observatory; Senior Lecturer in Medicine, University of Cape Town, Cape Town, South Africa.

BOLT, ROBERT J.
Professor and Chairman, Division of Medicine, University of California School of Medicine, Davis, California.

CODE, CHARLES F.
Director, Medical Research and Education, Mayo Foundation, Rochester, Minnesota.

COLCHER, HENRY
Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York.

COOKE, W. T.
Consultant Physician, Nutritional and Intestinal Unit, The General Hospital, Birmingham, England.

DEL GUERCIO, LOUIS R. M.
Associate Professor of Surgery, Albert Einstein College of Medicine, New York, New York.

DOBBINS, WILLIAM O., III.
Chief of Gastroenterology, Veterans Administration Hospital, Durham, North Carolina.

FISHER, JUNE MARION
Dernham Research Fellow, Department of Medicine, Stanford University School of Medicine, Palo Alto, California.

GALAMBOS, JOHN T.
Professor of Medicine (Gastroenterology), Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.

GLASS, GEORGE B. JERZY
Professor of Medicine and Chief, Section of Gastroenterology and Gastroenterology Research Laboratories, Department of Medicine, New York Medical College, New York, New York.

HOLT, PETER R.
Director, Gastrointestinal Unit, Department of Medicine, St. Luke's Hospital Center, New York, New York.

KATZ, DAVID
Assistant Professor, Department of Medicine, New York Medical College, New York, New York.

KOKAS, ESZTER
Department of Physiology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

LAMBERT, RENÉ
Scientific Director, Unité de Recherches de Physiopathologie Digestive, Institut National de la Santé et de la Recherche Medicale, Hôpital Edouard-Herriot, Lyon, France.

LILLIBRIDGE, CLINTON B.
Pediatric Gastroenterologist, The Genesee Hospital, Rochester, New York.

LINDNER, ARTHUR E.
Assistant Professor of Medicine, New York University School of Medicine, New York, New York.

LOUW, J. H.
Professor and Head of Department of Surgery, Groote Schuur Hospital, Observatory; University of Cape Town, Cape Town, South Africa.

MARKS, I. N.
Part-time Head, Gastro-Intestinal Service, Groote Schuur Hospital, Observatory; Lecturer in Medicine, University of Cape Town, Cape Town, South Africa.

MARSHAK, RICHARD H.
Clinical Professor of Radiology, The Mount Sinai School of Medicine, New York, New York.

PIPER, DOUGLAS W.
Associate Professor of Medicine, The University of Sydney; Honorary Physician, The Royal North Shore Hospital of Sydney, Sydney, Australia.

SESSIONS, JOHN T.
Professor of Medicine and Chief, Section of Gastroenterology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

SIEGEL, HOWARD I.
Clinical Instructor, Department of Medicine, New York Medical College, New York, New York.

SIMONS, KAI
Junior Fellow of the National Research Council for Medical Sciences, Department of Serology and Bacteriology, Helsinki University, Helsinki, Finland.

SYBERS, ROBERT G.
Assistant Professor of Radiology, Department of Radiology, Emory University School of Medicine, Atlanta, Georgia.

TANG, JORDAN J. N.
Associate Member, Oklahoma Medical Research Foundation; Associate Professor, Department of Biochemistry, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma.

TAYLOR, KEITH B.
Barnett Professor of Medicine, Chief, Division of Gastroenterology, Department of Medicine, Stanford University School of Medicine, Palo Alto, California.

VIEGAS DE ANDRADE, S. R.
Fellow, Kellog Foundation and American College of Physicians, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

VILLARDEL, FRANCISCO
Director, Escuela de Patologia Digestiva, Hospital de la Santa Cruz y San Pablo, Barcelona, Spain.

WATSON, DAVID W.
Assistant Professor of Medicine, University of Michigan, Ann Arbor, Michigan.

WINAWER, SIDNEY
Assistant Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, Memorial and New York Hospitals, New York, New York.

WOLF, STEWART
Professor and Chairman, Department of Medicine, University of Oklahoma Medical Center, Oklahoma City, Oklahoma.

ZAMCHECK, NORMAN
Assistant Clinical Professor of Medicine, Harvard Medical School; Chief, Gastrointestinal Research Laboratory, Mallory Foundation; Physician-in-Charge, Mallory Gastroenterology Laboratory, Boston City Hospital, Boston, Massachusetts.

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SMALL INTESTINE

COLON

PANCREAS

VASCULATURE

1

Gastritis

KEITH B. TAYLOR AND JUNE MARION FISHER

ANY diffuse inflammation of the gastric mucosa may be described as gastritis. The structural changes to which this term applies and the associated functional disturbances can be best understood by contrasting them with what is known of normal structure and function.

The gastric mucosa may be divided into three areas. The acid-producing mucosa constitutes the body gland or proper gastric gland area[1] and extends from the proximal part of the stomach or cardiac gland area to the pyloric gland area of the antrum. The distal line of demarcation is somewhat irregular and outcroppings of the acid-producing mucosa may sometimes be found in the proximal part of the pyloric gland mucosa. Two cell types distinguish the mucosa of the body; the parietal or acid-producing cells, and the chief or pepsinogen-producing cells. The rather specialized intracellular structure of the parietal cell has been well reviewed by Sedar and Friedman.[2] There is strong evidence that the parietal cell produces acid; this function is subserved even in the absence of superficial epithelial cells.[3] Recent evidence suggests that the functional integrity of other structures may be essential for the secretion of acid into the lumen of the stomach.[4] Parietal cells also contain and possibly elaborate blood group substances[5] and, in man and other primates, probably secrete intrinsic factor.[6,7] This double or triple function is not surprising when considered in comparative phylogenetic terms. Thus, in amphibia, the analog of the mammalian parietal cell, the *Hauptdrüsenzelle*, secretes both acid and pepsinogen. In the rat, the chief cells appear to secrete intrinsic factor as well as pepsinogen.[6] In the hog, intrinsic factor secretion is subserved by a cell-type distinct topographically and probably structurally from both the parietal cell and the chief cell.

From the Department of Medicine, Stanford University Medical School, Palo Alto, California.

We are grateful to the Editor of *The Lancet* for permission to reprint Figure 4, and to the Editor of *Science* for permission to reprint Figure 5.

Supported by National Institutes of Health Grants Nos. AM 08262 and AM 06971.

In the body of the stomach the gastric glands consist of neck and body (Fig. 1). The neck is lined with mucous neck cells and a few parietal cells. The body of the gland is lined with parietal cells and chief cells. There are, in addition, a small number of argentaffin cells, whose function is uncertain.

Inflammatory cells of all types are rather uncommon in the lamina propria of normal gastric mucosa, unlike that of the healthy small intestine, although occasional collections of lymphocytes may be seen; a few plasma cells, macrophages, and eosinophils are normally present. Any significant increase in the number of such cells justifies the diagnosis of gastritis.

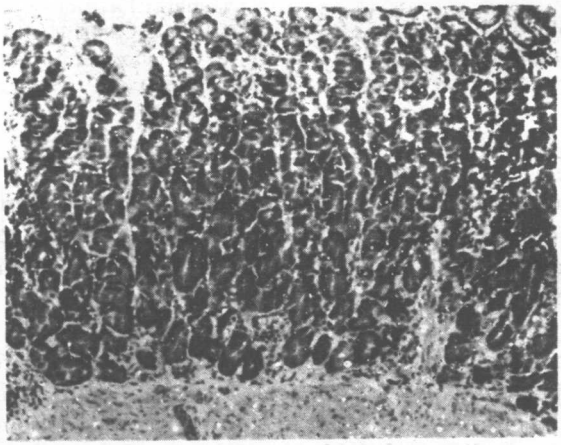

FIG. 1.—Normal human gastric mucosa, × 35.

ACUTE GASTRITIS

Most commonly, gastritis is classified as acute or chronic. Acute gastritis may be associated with symptoms of nausea and epigastric pain of a varying degree of severity or it may be wholly asymptomatic. The mucosa displays a wide spectrum of histologic changes. There may be a minor increase in the number of inflammatory cells in the lamina propria. The majority of them are neutrophilic polymorphonuclear leukocytes; eosinophils may sometimes be conspicuous. The distribution of these cells is often superficial. At the other end of the spectrum, there may be extensive and severe changes, in which the surface of the mucosa may be deeply eroded and the gastric glands distorted by edema and heavy inflammatory infiltration; often extravasated red blood corpuscles are seen in the lamina propria. These changes may be associated with widespread, punctate ulceration. Hemorrhage into the gastric lumen may sometimes be so severe that emergency gastrectomy is done as a life-saving measure.

Any part of the stomach may be affected. Ingested corrosives often exert their maximal effect on the antral region, and there is some evidence that the now rare acute, erosive gastritis seen in children with severe acute infections has a predilection for this area. Ingestion of large quantities of ethanol and staphylococcal exotoxin are other causes of acute gastritis.

It is commonly accepted that the mucosa of acute gastritis has a natural tendency to revert to normal. There have been few studies based on gastric biopsy, but a noteworthy exception is that by Palmer.[8] Most studies have been based on gastroscopy, which is not reliable,[9] or on autopsy material. The latter, unless autolysis is inhibited by fixation within minutes of death, undergoes changes which may render histologic interpretation impossible.[10]

Very little is known of the disturbances of secretory function or of histochemical changes in acute gastritis. Regeneration following acute gastritis induced in animals has not been well studied, but numerous observations have been made of the train of events following removal of areas of gastric mucosa in dogs, rats, and other animals. Regeneration of tissue, accompanied by cellular differentiation, seems to be quite rapid, according to Milton et al.,[11] Williams,[12] and Townsend.[13] However, in one recent study in mice by Myren and Torgersen,[14] it has been shown the regeneration of parietal cells did not occur within a period of twenty-five weeks following thermal injury to the mucosa. It was also shown that during the period immediately following injury, an enzyme of the parietal cells, succinic dehydrogenase, was reduced in activity, not only at the site of injury, but at some distance from it. The parietal cell mass became rapidly reduced, and did not recover within the half-year period of observation following injury. Such observations are complicated by the fact that stress lowers the mitotic indices of the gastric mucosa in the rat,[15] and the same effect may be exerted in other animals, including man.

Chronic Gastritis

In considering chronic gastritis three points should be made. First, that the acid-producing mucosa, which approximates only roughly to the anatomic body or corpus of the stomach, must be considered a separate structure from the mucosa of the antrum. The importance of the study by Magnus and Ungley[16] of the gastric atrophy of pernicious anemia lies in its emphasis on the sharp demarcation between the atrophic mucosa of the body of the stomach and the normal appearance of the mucosa of the antrum. Another study by Cox[17] showed a much higher incidence of gastritis of the antrum than of the body with advancing age in healthy subjects. The second point is that reliable information can only be obtained by rigorous tests of gastric secretory function and multiple biopsying of the mucosa. Gastroscopy, radiologic examination, and surgical biopsy can sometimes play a supporting role. Post-mortem studies have proved very misleading in the main, and it is of some interest to read Magnus'[18] own re-evaluation of his prior work,[16,19] and that of Meulengracht[20] and Cox,[21] in the light shed by the biopsy studies of the Australians.[22] Instead of severe, noninflammatory atrophy of the gastric mucosa being an invariable finding in pernicious anemia, it has become apparent that different grades of atrophic gastritis are quite as commonly to be found and that surviving foci of chief and parietal cells are not uncommon, a matter of significance in evaluating response to attempted therapy (Fig. 2). Thirdly, as in the case of acute gastritis, severe changes in the mucosa may occur without any gastrointestinal symptoms.[22,23]

Types of Chronic Gastritis

Chronic gastritis of the mucosa of the body of the stomach is usually classified as chronic superficial, chronic multifocal, or chronic diffuse. In all of these the predominant inflammatory cells are of the mononuclear types, those usually associated with delayed hypersensitivity reactions, namely, lymphocytes and plasma cells. This factor and the fact that repeated serial biopsies confirm the chronicity and relative stability of the pathologic picture justify use

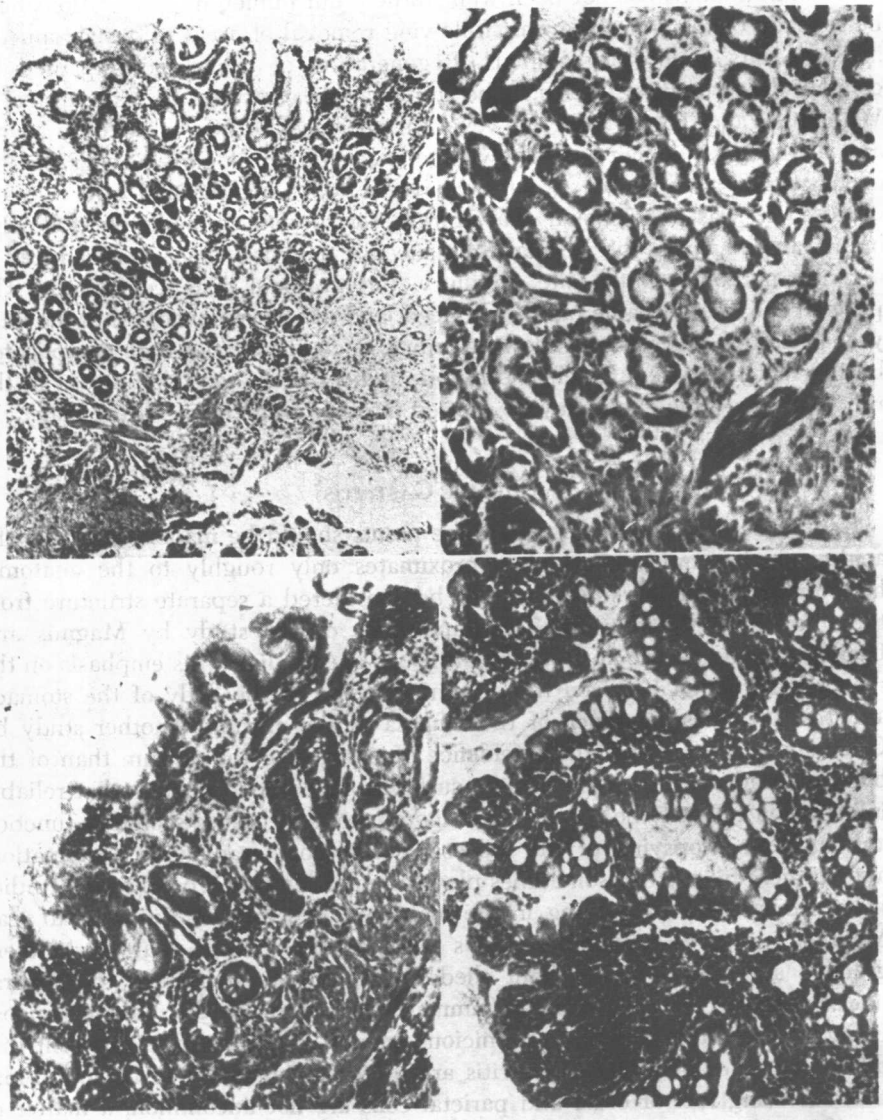

FIG. 2.—Sections from two suction biopsy specimens of gastric mucosa taken from the same patient at the same time. (A) (top left) Section showing moderate degree of chronic gastritis. (B) (top right) Same section under higher power. (C) (bottom left) Section showing marked intestinal metaplasia. (D) (bottom right) Same section under high power.

of the term chronic. To the above categories must be added gastric atrophy. Irreversibility of the pathologic changes appears to be a dominant quality in chronic gastritis; its significance will be discussed.

Chronic Superficial Gastritis

Here the mononuclear cellular infiltration is predominantly in the superficial third of the mucosa, often rather strikingly so. There may be a few polymorph neutrophils seen in addition to lymphocytes and plasma cells and occasional eosinophils. The appearances of the deeper parts of the lamina propria are within normal limits, and there is no reduction in specific glandular elements.

Chronic Diffuse Atrophic Gastritis

Inflammatory infiltration is extensive, but may not be homogeneous. Specific glandular tissue is much reduced, with reduction in mucosal thickness. The changes may show some regional variation—particularly if gastric ulceration is present, when they tend to be most severe in the region of the ulcer or ulcers. Parietal and chief cells, if present at all, are seen in small numbers and may be difficult to recognize, although special stains, such as phosphotungstic acid, may be very helpful in recognizing scanty parietal cells. Areas of intestinal metaplasia may be present.

Chronic Multifocal Atrophic Gastritis

In this rather uncommon form, infiltration with mononuclear inflammatory cells tends to be patchy. Areas of normal or only slightly infiltrated mucosa alternate with areas of heavy infiltration and loss of specific glandular elements. It should be borne in mind that chronic atrophic gastritis is often patchy (see Fig. 2), and it is therefore possible that multifocal gastritis does not constitute a separate category. There is now immunologic evidence which suggests that such a subdivision possibly has some validity.[24]

Gastric Atrophy

Here there is virtually complete absence of chief and parietal cells, with marked reduction in mucosal depth. Cellular infiltration is scanty, although foci of mononuclear cells may be seen. Intestinal metaplasia may be extensive.

Intestinal Metaplasia

This is a remarkable feature of chronic gastritis. Areas of small intestinal mucosa seem to replace normal gastric glandular tissue. The architecture is usually abnormal, the villi being thick and distorted; but the epithelium may possess a brush border, and microscopic examination of the tissue taken by biopsy after ingestion of fat reveals a picture similar to that seen in the jejunal mucosa during the process of fat absorption.[25] The impressive feature histologically is the presence of goblet cells, which are never seen in normal gastric mucosa. Paneth cells are also seen (Fig. 2C and D).

Histochemistry

Published histochemical studies of the gastric mucosa are far from compre-

hensive. Attempts to preserve the fine structure of the tissue have required methods of fixation which may alter enzyme activities. In the normal mucosa, enzymes serving glycolytic breakdown and the Krebs cycle are present; those necessary for the hexose monophosphate shunt are demonstrable in minimal amounts. Alkaline phosphatase is present only in the walls of blood capillaries in normal gastric mucosa. Acid phosphatase activity is present predominantly in the chief cells. More than twenty enzymes have now been identified by Ragins et al.[26]

The first histochemical observations in gastritis were made by Wattenberg,[27] who found aminopeptidase activity, absent from normal gastric mucosa, in the mucosa of intestinal metaplasia. Planteydt and Willighagen[28] extended this observation and showed that in intestinal metaplasia enzymes typical of the small intestinal mucosa appeared in the region of the brush border and Golgi zones; these included alkaline phosphatase, aminopeptidase, 5-nucleotidase, esterase, ATP-ase, and some oxidative enzymes. Confirmatory evidence was provided by Niemi et al.,[29] Cornet et al.,[30] and Plosscowe et al.[31] Ragins and Dittbrenner[32] have put forward the hypothesis that in intestinal metaplasia both cell turnover rate and cellular enzyme content provide evidence of conversion from a primarily secretory to a primarily absorptive mucosa.

Ragins and Dittbrenner[32] studied enzymes which stained specific cytoplasmic organelles, namely, lysosomes (PbS acid phosphatase method of Gomori), Golgi apparatus (thiamine pyrophosphatase method of Novikoff and Goldfischer), and mitochondria (nicotinamide adenine dinucleotide $NADH_2$ tetrazolium reductase method of Novikoff et al.). They found that in severe chronic atrophic gastritis, $NADH_2$ tetrazolium reductase was much reduced because of the absence of parietal cells, which are particularly rich in mitochondria, whereas thiamine pyrophosphatase was much increased in the foveolar mucous epithelial cells, and lysosomal and cytoplasmic acid phosphatase activity was somewhat increased. The methods used were, of course, only semiquantitative, but these studies suggest a change in enzyme activities proportional to the degree of mucosal damage, the most severe changes occurring when intestinal metaplasia supervenes. Graham and Schade[33] have adopted with success the novelty of applying histochemical techniques on a macroscopic scale in order to outline a total area of intestinal metaplasia.

Cell Kinetics

Neither in man nor in experimental animals have estimates of turnover of the specialized cellular elements of the gastric mucosa been made with any precision. The usual techniques have been applied to the gastric epithelial cells and fairly good agreement obtained, namely, of a turnover time of about seventy-two hours, although in gastric ulcer and gastric carcinoma it is said to be shorter than in normal or in duodenal ulcer.[34] It is generally held that the parietal cells constitute a rather fixed population; for instance, mitotic figures in them are rare. However, Messier and Leblond[35] have shown, using radioautography, that the parietal cells do divide. Further, Cox and Barnes[36] and Tongen[37] have shown a significant increase in the parietal cell mass in guinea pigs and dogs, respectively, as a result of continuous histamine

stimulation. Some studies have suggested that during regeneration and differentiation, following ablation of areas of mucosa, parietal and chief cells appear rapidly and some evidence suggests that the gastric neck cell is the toti-potential cell of their origin.[13] However, evidence on this point is not firm and not all studies are in agreement. The nature of the injury and degrees of stress constitute two possible determining factors.

One point deserves comment. Teir and Räsänen[34] have shown that in metaplastic intestinal glands in the stomach, the mitotic indices are low by comparison with gastritic gastric glands and approximate to those of the duodenal mucosa. The replacement capacity of metaplastic glands may thus be much impaired. By some,[38] this is considered to be a factor in the development of gastric ulcer. However, Cox[38] has pointed out that the migration distance is longer in intestinal glands than in gastric glands, and comparisons such as those made by Teir and Räsänen[34] may not be completely valid.

A recent study by Bannerman et al.[39] has shown that in iron deficiency in the rat, a condition which in man has been associated with the development of chronic gastritis, there is no evidence of abnormal cell kinetics in the stomach. Such deficient animals do not develop any changes of gastritis, although they show impaired secretion of both intrinsic factor and acid.

Recently, Croft et al.[40] have measured DNA in gastric juice as an index of the rate of loss of cells from the gastric mucosa. Such loss should be directly related to the rate of production of gastric surface epithelial cells. The state of the gastric mucosa was determined by multiple biopsy in all the patients studied. These authors found that patients with normal gastric mucosa had a lower turnover of surface epithelial cells per unit of gastric epithelium than patients with simple atrophic gastritis or with atrophic gastritis associated with treated pernicious anemia. These findings were supported by observations that in the surface epithelium in treated pernicious anemia and in simple atrophic gastritis there were higher mitosis rates than in normal gastric mucosa. Since there was apparently no direct correlation between DNA loss into the lumen and the degree of inflammatory infiltration in the mucosa, the authors concluded that their results were a true index of turnover of gastric epithelial cells.

Gastric Secretory Function

Reasonably satisfactory methods are now available for measuring the capacity of the gastric mucosa to secrete hydrochloric acid, pepsinogen, and intrinsic factor.

As regards acid, the demonstration by Card and Marks[41] that the parietal cell mass in man correlates with the amount of acid produced in response to a maximal dose of histamine has encouraged the widespread application of Kay maximal histamine[42] or histalog[43] tests as a measure of the potential of the gastric mucosa to produce acid. These tests, and presumably those which will now be developed using gastrin as the secretory stimulus in a similar way, have the advantage of reproducibility. It is, however, possible that they may tend to obscure the presence of minor but possibly important mucosal disease, where a less vigorous stimulus would permit its detection. At present, we have

no evidence as to whether the gastritic parietal cell is still capable of producing a secretion of the same concentration of acid as the normal cell. Another complication is that recently Davenport et al.[4] have suggested that one factor in determining the secretion of acid into the gastric lumen is the integrity of the gastric sodium barrier; this may be impaired in gastritis, so that hydrogen ions "leak" back into the blood stream—an intriguing possibility, which, if proven, will impose new conditions for the performance of acid secretory studies. Thirdly, no attempt to measure the nonacid secretions of the stomach is usually made. This secretion is not necessarily the same in gastritis as in the healthy stomach, either quantitatively or qualitatively. Nevertheless, reduction in hydrochloric acid secretion seems to be a common, though not invariable, concomitant of chronic gastritis; sometimes the degree of loss of acid secretion may seem to be out of all proportion to the degree of gastric change, as determined by gastric biopsy.

Achlorhydria, determined by the maximal histamine test, is usually regarded as diagnostic of pernicious anemia on the basis of such studies as those of Card et al.[44] However, there is evidence that in chronic gastritis without the lesion of pernicious anemia, achlorhydria may also be found.[45,46]

Pepsinogen secretion, measured directly or as plasma or urinary pepsinogen, is also impaired, and so is that of intrinsic factor, although the last may still be secreted in amounts sufficient to mediate adequate vitamin B_{12} absorption, even when extensive gastritis is present.[46] One factor here seems to be that in health the amount of intrinsic factor secreted is vastly in excess of physiologic requirements.[46a] Since observations in man have suggested that the gastric parietal cell is the source of intrinsic factor, the problem has arisen as to how in some subjects with extensive atrophic gastritis, failure to secrete acid can occur with persistence of production of adequate intrinsic factor. Gastric biopsies in such cases often reveal the presence of a few parietal cells, however, and it may well be that failure to demonstrate acid production is due to some of the causes enumerated above. It may be that surface electrodes placed on the gastric mucosa[47] may prove ultimately to be the best means of determining the capacity of the parietal cell to secrete acid. It is of interest to note that when the maximal histamine test is applied to a group of subjects with established pernicious anemia, it is found that the resultant pH of the gastric secretions may range between 3.5 and 8.9,[45,48] so that this is some expression of the resultant of nonparietal secretion and variable but very small amounts of parietal secretion.

Prevalence

No proper surveys have been made of the prevalence of chronic gastritis in a truly representative group in any population. Chronic gastritis is so often asymptomatic. It is a formidable task to undertake a large number of multiple gastric biopsies in an apparently healthy population. Yet, in the light of present knowledge, no other screening procedure can provide reliable results, since neither a finding of gastric secretory activity within the normal range nor of the absence of gastric antibodies (see below) can exclude the presence of chronic gastritis. It is still possible that immunologic studies may prove the

most practicable tool. They can be performed without difficulty. The incidence of positive serologic findings in cases of gastritis established by biopsy is becoming well established, so that, bearing in mind age, sex, racial, and regional differences, it should be possible to arrive at estimates of the prevalence of gastritis, especially as recent studies suggest that antibodies are not found in the absence of gastric mucosal disease.[49] Valencia-Parpacen et al.[50] reported 2000 consecutive gastric biopsies; gastritic changes were present in 514 (25.7 per cent). It seems likely that these subjects, of whom no details are given, were already selected by receiving prior medical attention. In a series of 1000 successful biopsies by Joske et al.,[22] only 167 biopsies were judged to be normal, but these figures do not approach a true prevalence for the same reasons as in the study by Valencia-Parapacen.

In a study biased in the opposite direction, we performed gastric biopsies on twenty-seven normal volunteers ranging in age from 21 to 42. None of these volunteers had a history of gastrointestinal disease or any chronic disease involving other organs. Three of these subjects (11 per cent) had chronic atrophic gastritis.[49] If the prevalence increases with age, the proportion in those over the age of 60 may be quite high, though Palmer's observations[8] do not support this. However, Joske et al.[22] found a trend of increased prevalence up to the age of 50, beyond which it leveled off. Cornet et al.[51] studied one hundred subjects over the age of 65 and found that only 26 per cent of biopsies were normal. However, 47 per cent of his patients had upper gastrointestinal complaints, and 30 per cent had anemia, including four with pernicious anemia.

For the reasons stated above, the sex ratio is also unknown.

Causes

Much early speculation about etiology was dependent on observations which have faded in the light of present knowledge. Many of the facts which now seem to be pertinent may also prove to be evanescent. Factors which have been considered include (1) mechanical, thermal, chemical, and radiation injury; (2) infection; (3) nutritional deficiency; (4) immunologic factors; (5) endocrine disturbances.

It is often suggested that genetic factors or other environmental factors may modify or mediate the action of any of those listed. One view had been that repeated injury to the mucosa may result in chronic gastritis.[19] If this is so, it seems likely that factors other than the quality or quantity of the injury must be operative in inhibiting recovery. Palmer[8] was not able to demonstrate such a course of events on serial biopsy; however, Edwards and Edwards[52] have shown an association between ingestion of hot fluids and chronic gastritis, thus supporting a suggestion advanced many years before by Hurst.[53] Joske et al.[22] believe alcohol to have a causal relationship with chronic gastritis, whereas Palmer[8] does not. In the case of x-irradiation, a study of Ricketts et al.[54] suggested that this might sometimes produce irreversible suppression of gastric secretion and atrophic gastritis; there were no preirradiation controls.

In recent years the possibility that infection might play an important role in causing or perpetuating chronic gastritis has been discounted. There have been