Chronic gastritis, alcohol, and non-ulcer dyspepsia[1]

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SUMMARY   An investigation of 102 men comprising alcoholics, patients with non-ulcer dyspepsia, and healthy controls is reported. It demonstrates that alcohol is a cause of chronic gastritis and the severity of the mucosal lesion is directly related to the duration of excess drinking. Contrary to popular belief, chronic gastritis does not give rise to symptoms. The effect of alcohol on the gastric mucosa is a direct one and is not mediated by malnutrition, hepatic damage, intestinal malabsorption, anaemia, ascorbic acid deficiency, or any disturbance in immune tolerance.

The natural history of chronic gastritis is described, involving an initial hypertrophy and hyperfunction of the gastric mucosa, followed by atrophy and hypofunction.

Cigarette smoking is confirmed as another cause of chronic gastritis. The non-ulcer dyspepsia syndrome is unrelated to chronic gastritis.

Chronic gastritis is a distinct histological entity for which many aetiological factors have been identified; they are discussed in detail elsewhere (Roberts, 1971). Chronic ingestion of alcohol might be expected to cause chronic gastritis and would provide a classical example of an exogenous aetiological factor. The acceptance of alcohol as a cause of 'gastritis' has been based on the frequent association of chronic dyspepsia with heavy drinking rather than on experimentally established fact. The present investigation was designed to show whether chronic ingestion of alcohol causes chronic gastritis, with or without dyspepsia, and if so to characterize it and establish any significant associations or sequelae.

Patients and Controls

The patients and controls, all males, comprised four groups.

GROUP 1
Thirty-one patients who were admitted to hospital because of the effects of prolonged excessive drinking of alcohol. Their ages ranged from 23 to 52 years (average 34·1 years).

GROUP 2
Twenty-five patients presenting with a syndrome of non-ulcer dyspepsia and who were heavy drinkers (defined as the consumption, over the immediately preceding year, of a daily average in excess of 1·5 litres of beer). Their ages ranged from 19 to 41 years (average 26·5 years).

GROUP 3
Twenty-seven patients with non-ulcer dyspepsia who were not heavy drinkers. Their ages ranged from 18 to 41 years (average 26·5 years).

GROUP 4
Nineteen volunteer control subjects who were symptom free. Four were heavy drinkers (as defined above) and were designated group 4B, the remaining 15 being designated group 4A. Their ages ranged from 18 to 28 years (average 21·1 years).

Methods

The state of nutrition of each patient during the previous year was arbitrarily assessed as adequate or inadequate, based on a dietary history. The following were estimated by standard methods: faecal occult blood (three stools); serum bilirubin, thymol turbidity, zinc sulphate turbidity, alkaline phosphatase, aspartate transaminase, iron, iron-binding capacity; glucose tolerance; d-xylose excretion; faecal fat excretion (over five days); leucocyte

ascorbic acid (LAA) level; serum vitamin B_{12}; thyroglobulin and thyroid microsomal antibodies, parietal cell antibodies (PCA). A barium meal and follow-through formed the basis of an assessment of the degree of gastric mucosal rugosity and of the presence of evidence of intestinal malabsorption. A gastric biopsy was taken by Crosby capsule from the middle of the body of the stomach. From a minority of patients a jejunal biopsy was taken from the first loop of the jejunum. An augmented histamine test was performed in all cases.

The classification of the histological appearances of the gastric mucosa is based on that of Joske, Finckh, and Wood (1955) as modified by Roberts (1971). The thickness of the mucosa was measured, using an eyepiece micrometer, from the luminal surface of the epithelial cells to the deepest part of the tubules or, in the absence of tubules, to the
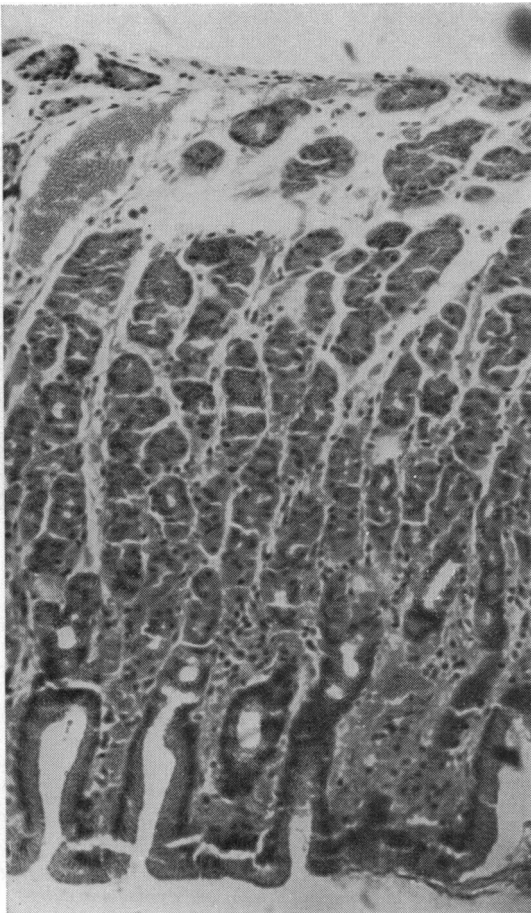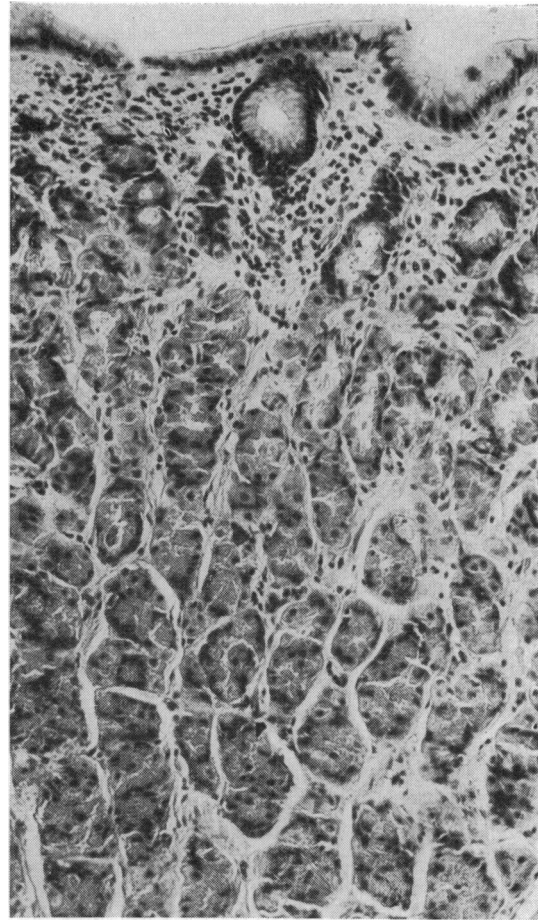

Fig. 1

Fig. 2

Fig. 1 *Grade 1: normal. The surface is made up of regular columnar cells. The foveolae are short and narrow, and the epithelial cells at their bases show a moderate degree of mitotic activity. Tubules are plentiful, regularly disposed, and more or less straight. They are composed almost entirely of parietal and zymogenic cells. The lamina propria contains only occasional lymphocytes or plasma cells, usually in the superficial part. The fibres of the muscularis mucosae are regular and separated, and some strands are seen entering the stroma of the lamina propria.*

Fig. 2 *Grade 2: mild superficial gastritis. The only deviation from normal is the presence of a slight or moderate infiltration of the superficial portion of the lamina propria by polymorphs, plasma cells, or lymphocytes.*
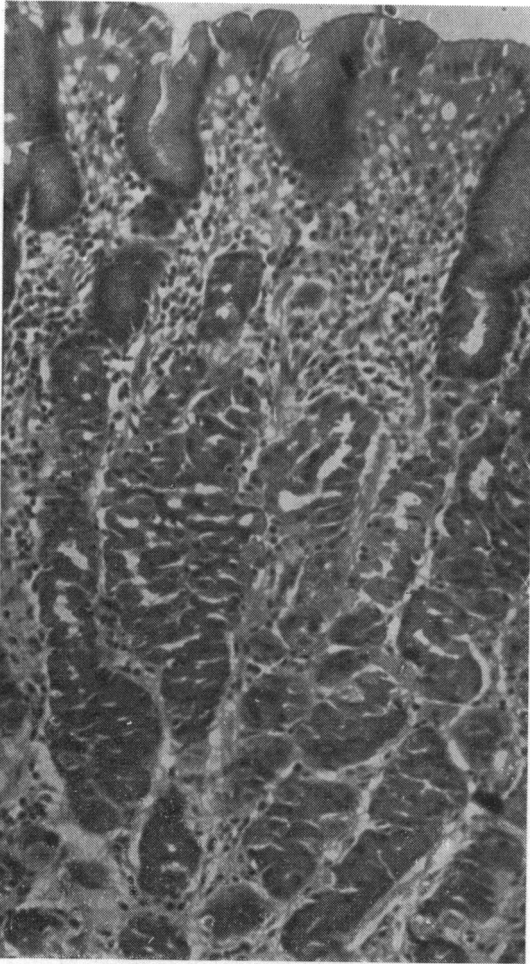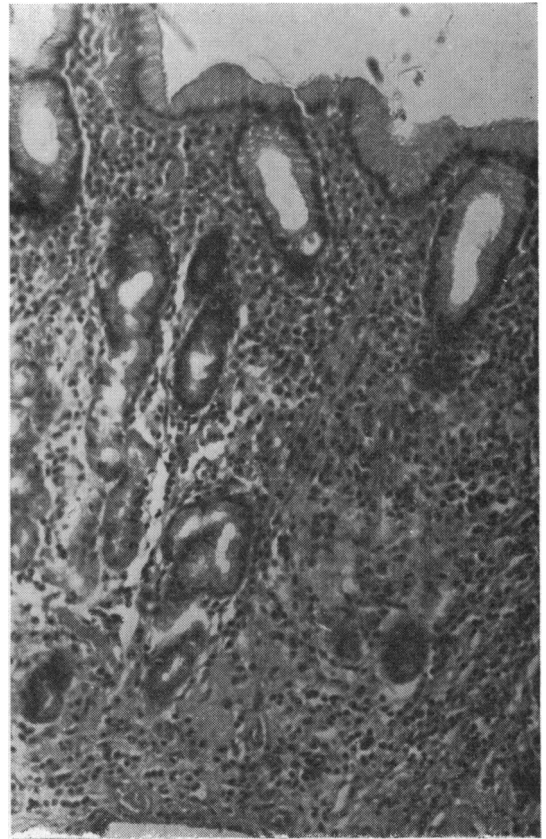
Fig. 3

Fig. 4

Fig. 5

Fig. 3 *Grade 3: superficial gastritis. Loss of tubules or of acid- or pepsin-secreting cells is not significant, but there is a more intense infiltration of the lamina propria by polymorphs, plasma cells, or lymphocytes in varying proportions predominantly involving the superficial part of the lamina propria or its whole depth. Epithelial cells may be flattened, irregular, or even shed.*
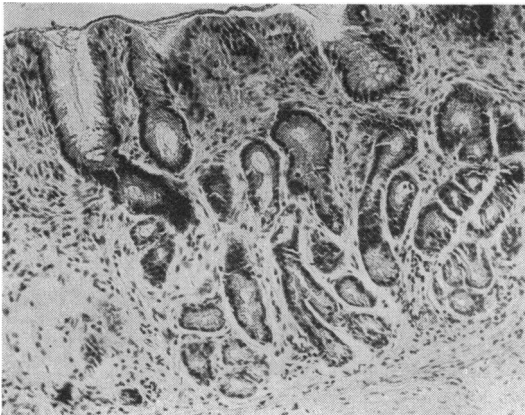
Fig. 4 *Grade 4: atrophic gastritis. The surface epithelium is abnormal, mitosis at the base of the foveolae is usually increased, and the inflammatory cell infiltration of the lamina propria is severe and extensive. Tubules tend to be tortuous and may be reduced in number to a varying extent. Within the tubules parietal and zymogenic cells may be lost and replaced by pale-staining, apparently non-specific mucus-secreting cells.*

Fig. 5 *Grade 5: Gastric atrophy. The mucosa is reduced in width, the epithelium is irregular, shed in places, and often contains some goblet cells. The foveolae are deep and wide, with increased mitosis, and there is a tendency to early villous formation in some cases. The tubules are severely atrophic and tortuous, often resembling pyloric glands. Acid- and pepsin-secreting cells are either absent or few. The lamina propria is often severely infiltrated with chronic inflammatory cells of patchy distribution.*
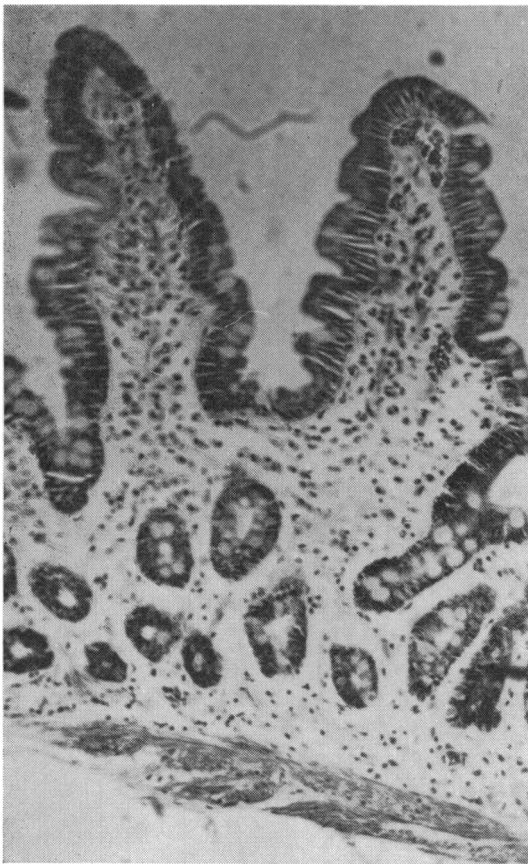
Fig. 6   *Grade 6: gastric atrophy with intestinal meta-plasia. The mucosa is reduced in width and is villous. The epithelium contains many goblet cells. The tubules are made up mainly of apparently undifferentiated cells and may contain Paneth cells at their bases. There are no cells which stain as acid- or pepsin-secreting cells. There is usually no marked cellular infiltration of the lamina propria, although a few plasma cells or lymphocytes may be present. This picture represents intestinal metaplasia.*

Fig. 7   *The relationship between the degree of gastritis and alcohol consumption. Gp 1—alcoholics. Gps 2 and 4B—heavy drinkers. Gps 3 and 4A—non-heavy drinkers.*

2 and 4B occupying an intermediate position. Moreover, a significant regression relationship exists between the histological grade and the duration of drinking expressed in years ($p = 0.05$).

RELATIONSHIP TO DYSPEPSIA
There is no evidence of an association of chronic gastritis with non-ulcer dyspepsia. Further evidence that chronic gastritis does not cause dyspepsia is provided by the lack of correlation between gastritis and dyspepsia in the alcoholics of group 1, in which 75% of subjects with a normal mucosa have dyspepia and 87% of the subjects with chronic gastritis have dyspepsia, an insignificant difference.

THICKNESS OF THE MUCOSA (FIGURE 8)
Compared with normals, the mucosal thickness is increased in the milder pre-atrophic degrees of gastritis, but is progressively decreased in the more severe degrees of gastritis with atrophy ($p = 0.05$).

inner aspect of the muscularis mucosae. Each biopsy was classified into one of six grades (Figures 1-6).

Results

HISTOLOGY OF THE GASTRIC MUCOSA
Sixty-one subjects out of 93 (63%) have an abnormal mucosa.

RELATIONSHIP TO ALCOHOL (FIGURE 7)
The differences in severity of gastritis between alcoholics and controls are highly significant ($p < 0.01 > 0.001$), the heavy drinkers from groups
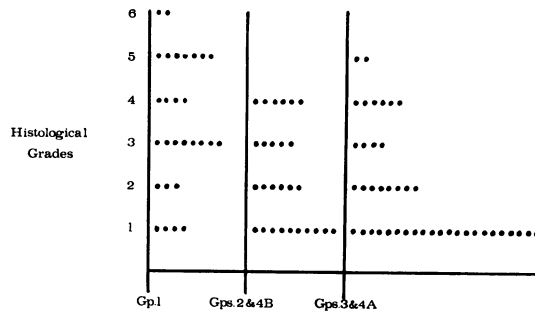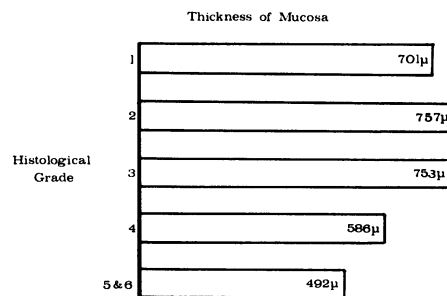

Fig. 8   *Relationship of mucosal thickness to severity of gastritis.*

GASTRIC SECRETION (FIGURE 9)

Both the mean maximal acid output (MAO) and mean basal secretion for subjects with pre-atrophic grades of gastritis are higher than in normals, but fall away sharply for those with atrophic gastritis and gastric atrophy, the lowest output being found in association with intestinal metaplasia. This trend is significant ($p < 0.05 > 0.02$).
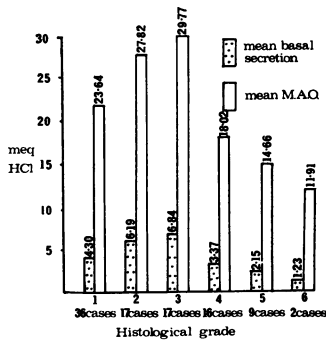
rugosity most commonly have gastritis with atrophy. Radiological evidence of intestinal malabsorption is lacking from this series.

Fig. 11 *Relationship between acid secretion and radiological appearances of the gastric rugae.*

Fig. 9 *Relationship between acid secretion and severity of gastritis.*

VITAMIN B₁₂ (FIGURE 10)

Serum vitamin B_{12} levels are higher than normal in subjects with pre-atrophic grades of gastritis and lower than normal in association with atrophic grades.
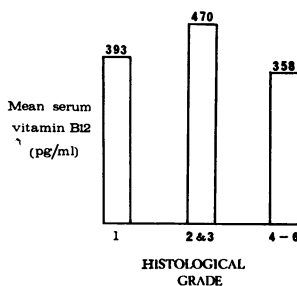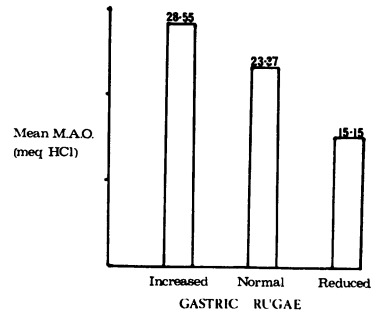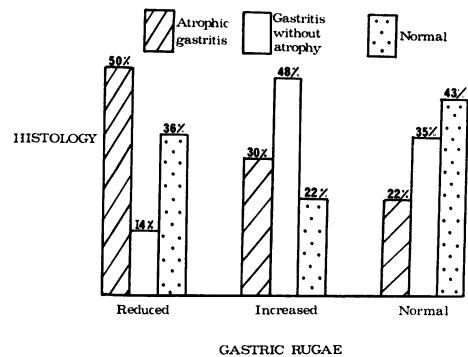

Fig. 12 *Relationship between gastric mucosal histology and radiological appearances of the gastric rugae.*

SMOKING (FIGURE 13)

The difference for grade 1 alone reaches significance,

Fig. 10 *Relationship between serum vitamin B_{12} and severity of gastritis. Grade 1, 36 cases; grade 2 and 3, 32 cases; grades 4-6, 25 cases.*

RADIOLOGICAL STUDIES (FIGURES 11 AND 12)

The MAO increases as the prominence of gastric rugae increases. Subjects with normal rugae most commonly have a normal mucosa; those with increased rugosity most commonly have a pre-atrophic grade of gastritis; those with reduced

Fig. 13 *Comparison of the incidence of each histological grade of gastric mucosa in smokers and non-smokers.*

non-smokers having a higher incidence of normal mucosa (58·8%) than smokers (32·5%) (P < 0·05 > 0·02).

NUTRITIONAL STATUS (FIGURE 14)

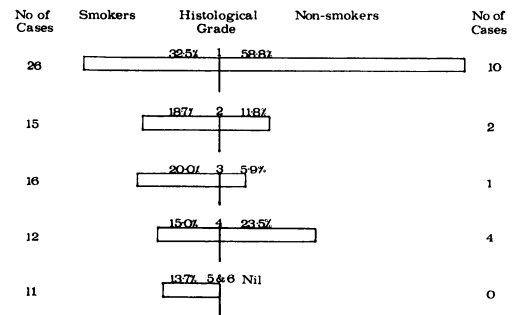Malnutrition is absent among controls, slight among non-ulcer dyspeptics who do not drink heavily, moderately severe among non-ulcer dyspeptics who drink heavily, and severe among alcoholics (P < 0·01 > 0·001). Five out of 36 subjects (13·9%) with a normal mucosa are malnourished, compared with 26 out of 61 (42·6%) of subjects with gastritis (P = 0·01). However, it is quite unjustified to assume that this is a direct relationship. It is more likely to be due to the frequency of malnutrition among heavy drinkers who, in turn, only infrequently have a normal mucosa.
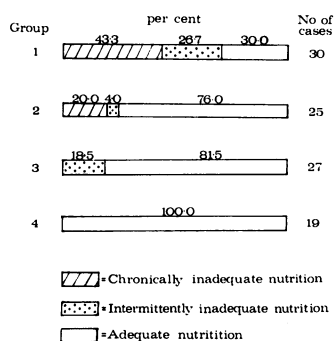

Fig. 14 *Nutritional status in each group of subjects.*

MISCELLANEOUS FACTORS

In this series no evidence emerged for an association between chronic gastritis and any of the following factors: anaemia, occult gastrointestinal bleeding, organ-specific autoimmunity, ascorbic acid deficiency, impairment of liver function, intestinal malabsorption, advancing age. The series had therefore been successfully designed to obviate the known effect of age on the gastric mucosa.

Discussion

Details of a series similar to the present one have not been published previously. In this series 63% of biopsies show some degree of chronic gastritis. Others have shown from 34 to 70·7% abnormal in variously selected series (Shiner and Doniach, 1957; Russell, Aziz, Ahmad, Kent, and Gangarosa, 1966). Previous evidence for the causation of chronic gastritis

by alcohol is conflicting (Williams, 1956). The present data show that it is unusual for an alcoholic, even a young man (average age 34 years), who has been drinking excessively for only a few years to have a normal mucosa. Only 14% do have, compared with over half the controls. The more severe degrees of gastric atrophy, with or without intestinal metaplasia, were rarely found other than in alcoholics. Moreover, the incidence of gastritis is directly related to the duration of excess drinking.

The progressive thinning of the gastric mucosa due to atrophy is to be expected, but the increased thickness in the milder degrees of gastritis is perhaps surprising and requires explanation. Three possible explanations may be considered. First, it has been suggested that inflammatory cell infiltration might account for the increase. Against this is the fact that it is not uncommon to find severe inflammatory cell infiltration in the presence of appreciable glandular atrophy and a thin mucosa. Second, the foveolar layer may increase in size in response to a need for increased surface regenerative capacity in the face of chronic inflammation. In support of this is the known increased turnover of the epithelial component in the presence of atrophic gastritis (Croft, Pollock, and Coghill, 1966). Third, there is the possibility that there may also be an actual increase in size of the glandular layer, a suggestion that may seem unlikely at first glance. If there is an increase in the gastric glandular layer, one would expect to find evidence of a concomitant increase in the gastric glandular functional capacity in the presence of the milder forms of gastritis. This is precisely what is now demonstrated, since the secretion of acid is greater than normal in subjects with superficial gastritis but falls to subnormal levels in the presence of atrophic gastritis. Hence, in early gastritis the mucosa is both hypertrophic and hyperfunctioning. It would be reasonable to expect that the capacity to secrete intrinsic factor in the presence of gastritis would be affected in the same way as the capacity to secrete acid. It is well established that the production of intrinsic factor and hence the levels of serum B_{12} are reduced in subjects with atrophic gastritis (Wood, Ralston, Ungar, and Cowling, 1964). The effect of mild, pre-atrophic degrees of gastritis on the secretion of intrinsic factor does not seem to have been previously examined separately. Since the absorption of dietary B_{12} is normally nearly complete, the fairly high levels of serum B_{12} found in association with pre-atrophic gastritis in the present series are certainly compatible with hypersecretion of intrinsic factor.

The value of radiology in the diagnosis of chronic gastritis remains unsettled (Bock, Kemp, and Richards, 1963). The present data show a broad

relationship between the radiological appearance of the gastric rugae and both the histology and the gastric secretion. These relationships are meaningful, but they provide no reliable guide to gastric secretion or histology in the individual case, since individual variation is so extreme.

One of the aims of the present investigation was to determine not only whether alcohol causes chronic gastritis but, if it does, whether other processes are involved. Evidence has been produced suggesting that anaemia, malnutrition, intestinal malabsorption, hepatic dysfunction, and a disturbance of immune tolerance play no part. It therefore seems justified to conclude that alcohol causes chronic gastritis directly, without the intervention of other processes.

The finding by Edwards and Coghill (1966) of a relationship between smoking and chronic gastritis is confirmed.

Dyspepsia is very common among alcoholics, but the dyspepsia is not due to gastritis. Similarly the evidence is that non-ulcer dyspepsia is not caused by gastritis. Indeed, there is no evidence to suggest that gastritis ever causes dyspeptic symptoms per se.

Conclusion

Prolonged consumption of alcohol causes chronic gastritis by a direct action on the gastric mucosa. In the early phase of this process there is a mild and then a severe gastritis, the inflammatory cell infiltration starting in the superficial part of the mucosa and spreading to involve the whole thickness. During this phase there are both hypertrophy and hyperfunction of the mucosa. The hypertrophy involves the foveolar layer (due partly to inflammatory cell infiltration, but mainly in response to a need for increased surface regenerative capacity in the face of chronic inflammation) and probably also the glandular layer. The hypertrophy is paralleled by hyperfunction which is evidenced by an increased capacity to secrete hydrochloric acid. During this early phase of gastritis there is also possibly an increased secretion of intrinsic factor, and serum vitamin B_{12} levels are maintained at high normal levels.

With the passage of time atrophy of the glandular elements in the mucosa supervenes, resulting in a progressive reduction of overall thickness of the mucosa, despite an even greater increase in thickness of the foveolar layer due to further increase in the demand for surface regenerative capacity. The overall reduction in mucosal thickness is due mainly to atrophy of the gastric glands proper, but also to a subsidence in the activity of the inflammatory cellular infiltration which 'burns itself out'. The atrophic process, as expected, is accompanied by a progressive reduction in the capacity to secrete hydrochloric acid and this is paralleled by a diminution of intrinsic factor secretion and hence by a reduction in serum levels of vitamin B_{12}.

When the various stages of this process are followed radiologically by barium studies of the stomach, it is seen that there is a greater than normal prominence of gastric mucosal rugae during the early pre-atrophic phase of the gastritis whereas later, during the atrophic phase, there is a tendency toward reduction of the prominence of gastric mucosal rugae seen on radiographs.

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