

Functional dyspepsia—a conceptual framework

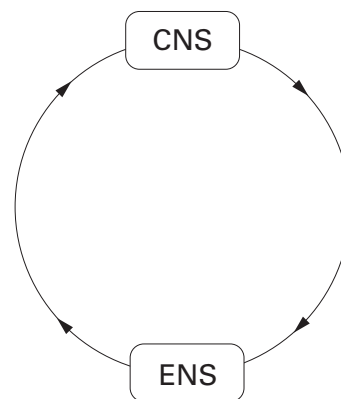
A Berstad

When the cause of tuberculosis was discovered more than 100 years ago, the relationship between the infection and disease seemed rather straightforward. Koch's postulates for the general principles of such relationships became very famous and are still valid (table 1). When there is only one cause of a disease, we are inclined to think in a linear manner, as in the case of tuberculosis. However, it became clear subsequently that most diseases have more than one cause—that is, most diseases are multifactorial with several risk factors. Today's criteria for a causal relationship between a disease and its causes are therefore much more complicated, as listed in table 2.¹

However, we are still inclined to think of a linear relationship between the cause and disease, albeit that there might be several causal factors where each contributes only a little to the final result (and not necessarily in a proportional manner). The situation might be much more complicated if all or most "effects" are the "causes". We may then apply a circular cause and effect relationship (fig 1).

When it comes to functional gastrointestinal disorders, their pathogenesis might well be described by the latter model, with the central nervous system (CNS) on one side and the enteric nervous system (ENS) on the other, connected through the spinal cord and the peripheral nerves. Abnormalities in one system are conveyed to the other without a clear cause and effect relationship.

Our working hypothesis for the pathogenesis of functional dyspepsia is illustrated in fig 2.² Most investigators agree that personality and psychological factors, such as stress and



Where does an abnormality begin?

Figure 1 Central nervous system (CNS) and enteric nervous system (ENS) interactions.

neuroticism, are important pathogenetic mechanisms. We also know that (acute) stress suppresses vagal tone which is shown to be (chronically) low in these patients. A low vagal

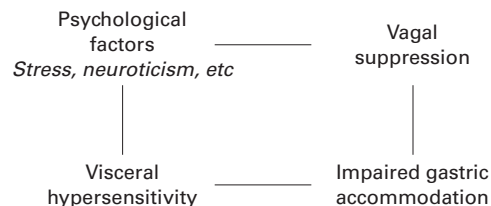


Figure 2 Vicious cycle in functional dyspepsia.

Abbreviations used in this paper: CNS, central nervous system; ENS, enteric nervous system.

Table 1 Koch's postulates (1882)

- The parasite occurs in every case of the disease in question and under circumstances that can account for the pathological changes and clinical course of the disease.
- It occurs in no other disease as a fortuitous and non-pathogenic parasite.
- After being fully isolated from the body and repeatedly grown in pure culture, it can induce the disease anew.

Table 2 Criteria for causation (Evans 1976)

- The hypothesised cause should be distributed in the population in the same manner as the disease.
- The incidence of the disease should be significantly higher in those exposed to the hypothesised cause than in those not so exposed. (The cause may be present in the external environment or as a defect in host responses.)
- Exposure to the hypothesised cause should be more frequent among those with the disease than in controls without the disease, when all other risk factors are held constant.
- Temporally, the disease should follow exposure to the hypothesised causative agent.
- The greater the dose or length of exposure, the greater the likelihood of occurrence of the disease.
- For some diseases, a spectrum of host responses should follow exposure to the hypothesised agent along a logical biological gradient from mild to severe.
- The association between the hypothesised cause and disease should be found in various populations when different methods of study are used.
- Other explanations for the association should be ruled out.
- Elimination or modification of the hypothesised cause or of the vector carrying it should decrease the incidence of the disease (for example, control of polluted water, removal of tar from cigarettes).
- Prevention or modification of the host's response on exposure to the hypothesised cause should decrease or eliminate the disease (for example, immunisation, drugs to lower cholesterol, specific lymphocyte transfer factor in cancer).
- When possible, in experimental settings, the disease should occur more frequently in animals or humans appropriately exposed to the hypothesised cause than in those not so exposed; this exposure may be deliberate in volunteers, experimentally induced in the laboratory, or demonstrated in a controlled regulation of natural exposure.
- All of the relationships and findings should make biological and epidemiological sense.

Division of
Gastroenterology,
Department of
Medicine, Haukeland
University Hospital,
5021 Bergen, Norway
A Berstad

Correspondence to:
Professor A Berstad,
arnold.berstad@
med.haukeland.no

tone may be one important mechanism by which the CNS modifies the function of the gut.

Impaired accommodation of the proximal stomach is shown by various techniques and by several research groups to be a characteristic feature of functional dyspepsia patients. This results in a relatively small proximal and a wide distal stomach in response to a meal, as illustrated in fig 3.³ Similar accommodation disturbances were seen in patients with diabetes mellitus but these patients complained of much less discomfort than patients with functional dyspepsia.⁴ Hypersensitivity to gastric distension (denoted as visceral hypersensitivity) also appears to be a characteristic feature of functional dyspepsia.

A simple “explanation” of visceral hypersensitivity could be that gastric mechanoreceptors are coupled in series with smooth muscle cells.

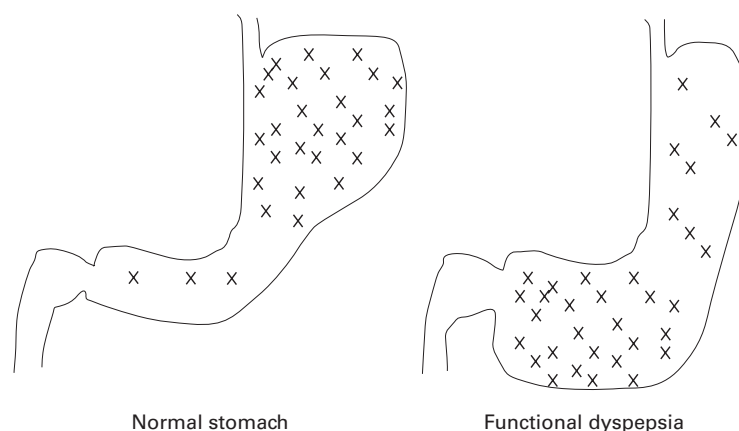


Figure 3 Gastric accommodation in the normal stomach and in functional dyspepsia.

Firing of the mechanoreceptors is then dependent on the contractile state of the smooth muscles. Distension of the stomach without prior/proper vagally-mediated relaxation may be a key mechanism by which epigastric discomfort is elicited. However, as functional dyspepsia patients complain much more than, for instance, diabetics who have more impairment of gastric accommodation, a central amplifying mechanism might be involved in patients with functional dyspepsia. Whether visceral hypersensitivity is merely a combination of impaired gastric relaxation on the one hand and “neuroticistic” amplification of afferent signals to the CNS on the other, we do not know.

We also do not know where in the body functional gastrointestinal disorders begin. Consequently, we do not know where to break into the circle for treatment. However, the advantage of such a model is that it does not matter where the disease begins or where we apply the treatments. The pathogenetic mechanisms are all connected in a web of causation, which means that correcting one abnormality, central or peripheral, may break the vicious pathogenetic circle and generate a general beneficial result.

- 1 Evans AS. Causation and disease: the Henle-Koch postulate revisited. *Yale J Biol Med* 1976;49:175–95.
- 2 Berstad A. Today's therapy of functional gastrointestinal disorders—does it help? *Eur J Surg* 1998;194(suppl 583):92–7.
- 3 Berstad A, Hausken T, Gilja OH, et al. Imaging studies in dyspepsia. *Eur J Surg* 1998;194 (suppl 582):42–9.
- 4 Undeland KA, Hausken T, Gilja OH, et al. Gastric meal accommodation and symptoms in diabetes. A placebo-controlled study of glyceryl trinitrate. *Eur J Gastroenterol Hepatol* 1998;10:677–81.