SUMMARY 2
Investigation of visceral sensation in humans

Hypersensitivity in functional gastrointestinal disorders
Patients with functional gastrointestinal disorders present with abdominal symptoms which have no apparent organic cause. It has been well established that these patients have a sensory dysfunction that affects exclusively the viscera. However, the extent of the dysfunction in the different clinical syndromes and the origin of visceral hyperalgesia remain obscure. Some data indicate that the sensory dysfunction in these patients is associated with altered reflex activity, and both mechanisms may interact to produce the symptoms, which in each clinical syndrome would depend on the particular pathways that affected. This working hypothesis would explain both the clinical pleomorphism and the frequent overlap of functional gastrointestinal disorders.

The role of the brain and sensory pathways in gastrointestinal sensory disorders
It is well known that there is a higher prevalence of current anxiety, depression, and global psychological symptoms among patients with IBS compared with patients in other medical clinics. It is likely therefore that visceral pain and limbic pathways overlap. Abnormalities that upregulate afferent signal intensity at any level in this system are likely to mediate hypersensitivity leading to pain and discomfort.

Testing the sensitivity hypothesis in practice
The series of modulatory mechanisms that operate at various levels between the central nervous system (CNS) and the gastrointestinal tract may in themselves be a cause of hypersensitivity. Their effects have the potential to confound clinical assessment. Compliance data for example, are more complex than a linear interpolation would suggest. There are also apparent anomalies in the effects of pharmacological interventions. Cisapride increases accommodation but does not reduce discomfort whereas octreotide alters perception without changing rectal compliance, implying that the drug affects visceral afferent function. Glucagon, sumatriptan, and buspirone all reduce changing rectal compliance, implying that the drug affects visceral afferent function. Glucagon, sumatriptan, and buspirone all reduce discomfort whereas octreotide alters perception without physiological changes.

Food and hypersensitivity in functional dyspepsia
It has long been known that stress affects the stomach and colon. This has been shown by brain imaging techniques and also by the very high prevalence of gastrointestinal symptoms among patients with psychiatric illness. The source may be limbic or peripheral; encoded memories or physiological changes.

The role of inflammation in IBS
It is also becoming increasingly clear that a variety of factors such as stress, inflammation, and peripheral insult produce changes in gastrointestinal function which are mediated at several levels, including the CNS. The resulting responses are thus a consequence of a "psychoneuroimmune interaction."

There is growing evidence that patients with IBS have an increased number of inflammatory cells in the colonic and ileal mucosa. Underlying causes include previous episodes of infectious enteritis, genetic factors, undiagnosed food allergies, and changes in bacterial microflora. Both human and animal studies support the concept that inflammation may perturb gastrointestinal reflexes and activate the visceral sensory system even when the inflammatory response is minimal and confined to the mucosa. It is unclear however whether these events occur only in selected subsets of patients (that is, those with diarrhoea dependent IBS with evidence of previous gastrointestinal infections).

Another promising line of investigation concerns the role played by immunocytes other than mast cells in the production of low grade inflammation, and the interactions of these cells with the enteric nervous and sensory afferent systems. The actual pathogenetic role exerted by low grade inflammation in symptom generation in patients with IBS also remains to be clarified.

The role of stress hormones
Corticotrophin releasing factor (CRF) plays a physiological role in the regulation of behavioural and autonomic responses to stress.

Cytokines have been shown to stimulate CRF release and to activate the hypothalamo-pituitary-adrenal axis. Interleukin 1β (IL-1β) and CRF in the genesis of stress induced IBS has therefore been proposed.

The role of fat and cholecystokinin in functional dyspepsia
Duodenal lipids enhance perception of gastric distension in healthy subjects and in patients with functional dyspepsia. The severity of nausea and the degree of gastric sensitivity caused by gastric distension increase in relation to the dose of duodenal lipid administered. Cholecystokinin and 5-HT, receptor antagonists reduce gastric perception and also the occurrence and intensity of lipid induced nausea. These findings suggest that both types of receptors have a modulatory role in the induction of gastrointestinal sensation during gastric distension.