**SUMMARY 1**

Basic science of visceral sensation

**Neurobiology of visceral nociception**

The gastrointestinal tract is served by a complex network of intrinsic and extrinsic sensory innervation. Stimuli are detected by afferents (vagal and spinal) which have different stimulus-response functions. Vagal afferents are responsible for low threshold activity whereas spinal afferents encode both physiological and supraphysiological levels of intestinal pressure. It is therefore likely that vagal and spinal afferents play different roles in mediating sensation.

Spinal afferents form the main pathway for radiating pain perception while vagal afferents are probably involved in emotional and behavioural aspects rather than in cognition of pain. Some vagal afferents project to the cervical regions of the spine and influence spinthalamic pathways between C1 and C3; these are thought to be involved in perception of referred pain.

**Reflex modulation of gastrointestinal function**

Prevertebral ganglia form an extended neural network which connects the lower to the upper gastrointestinal tract. Intestinofugal afferent neurones (IFANs) are a unique subset of myenteric ganglion neurones which function as slowly adapting mechanoreceptors. They relay mechanosensory information to prevertebral sympathetic ganglion neurones and function as volume detectors, thus providing a protective buffer mechanism against large increases in tone and intraluminal pressure.

Visceral spinal afferent neurones have axon collaterals which form en passant synapses with prevertebral ganglion neurones. They release substance P (SP) and calcitonin gene related peptide (CGRP) in prevertebral ganglia and evoke slow excitation postsynaptic potentials in sympathetic neurones.

Preganglionic fibres probably act as a gating mechanism. Quantitative analysis shows that the diameter of the peripheral extension (the axonal and dendritic diameter) is larger than the diameter of a central projection. This implies that a large amount of spike information is needed to activate the smaller diameter central process. This process enables low threshold activity to continue without being referred to the central nervous system, and ensures that only large distending pressures trigger perceived colonic sensation.

**Visceral perception, sensory transduction, and nutrients**

Nutrients, especially carbohydrates and lipids, in the intestinal lumen inhibit gastric function. It has been postulated that there are "sensors" in the intestinal wall which detect the presence of nutrients. Endocrine and/or enterochromaffin cells (EC) in the intestinal mucosa may therefore act as "taste" cells which respond to changes in luminal contents by releasing neuroactive mediators, such as cholecystokinin and serotonin (5-HT), which in turn activate specific receptors on primary afferent nerve terminals.

Both vagal and spinal afferent pathways are involved in intestinal feedback inhibition of gastric emptying precipitated by glucose. The response is mediated by 5-HT, receptors and also by a sodium-glucose cotransporter 1 expressed by EC. It is not known how the brain handles the signal from the afferent innervation. It may be either a process of pattern recognition or of the number of impulses. Research is underway to investigate how impulses are handled by second and third order neurones in the brain. The role of the lymph and its composition is also being studied.

**Peripheral insult and visceral afferent dysfunction**

Both low and high threshold visceral mechanosensitive fibres are involved in the response to noxious stimuli and both types of fibre contribute to the discomfort and pain arising from functional gastrointestinal disorders. All hollow organs, except the stomach and ureters, have a subpopulation of low threshold afferent fibres which also encode into the noxious range, while between 20% and 25% of the afferent population only respond at high thresholds.

Peripheral insult, such as experimentally induced gastric ulceration, has been shown to enhance peak sodium current excitability resulting in a lower threshold for action potential generation and a higher spike frequency.

The hypersensitivity that characterises functional gastrointestinal disorders is often maintained after the initiating event has disappeared. This is mediated entirely by central mechanisms which alter descending endogenous modulatory systems, dorsal root reflexes, and efferent projections to the organs which contribute to the neurochemical milieu at sensory receptors located in the tissue. Intrinsic primary afferent neurones (IPANS) of the enteric nervous system contained within the walls of organs may also contribute significantly to the excitability of the extrinsic innervation and to the development and maintenance of altered sensation.

**Inflammatory and non-inflammatory mediators of visceral perception**

Inflammatory mediators are known to sensitise primary afferents and to recruit silent nociceptors. Local tissue injury promotes the release of a variety of substances, including bradykinin, tachykinin, and CGRP, which directly activate nerve endings and trigger the release of algesic mediators (histamine, 5-HT, and nerve growth factor) from immunocytes and mast cells. At the same time other sensory neuropeptides released by axon reflexes activate neutrophils, fibroblasts, and mast cells resulting in the so called neurogenic phase of inflammation.

Recent evidence suggests that non-inflammatory mediators such as stress have the potential to trigger visceral pain or lower the threshold of neuronal responses to mechanical stimuli. Glycerol sensitises primary afferent neurones; glutamate released peripherally by neuronal stimulation sensitises nociceptive fibres, and trypsin may act directly on nociceptive fibres. These physiological actions constitute part of an alerting system.

Post-infectious hyperactivity of mast cells is linked to SP and neuropeptide release. Infection triggers either an increase in sensitivity or an increase in the population of receptors that respond to these mediators. The fact that postinfection hyperalgesia often persists after histological signs of damage have disappeared suggests that a neuroplastic response produces long term changes in the distribution of primary afferent terminals.