Chapter 2—Summary

This chapter highlights the detailed and yet limited extent of our knowledge with regard to the anatomical origins and development of the enteric nervous system (ENS), the complexity of its circuitry, and the prejunctional and postjunctional events involved in the neurotransmission process.

Enteric neurones and glial cells are derived from the neural crest and their embryonic development has been followed using a number of elegant techniques. These include: ablation of defined regions of the neural crest in chicken embryos; transplantation of neural tube regions from quail embryos to chicken embryos; and labelling of pre-migratory cells from different regions of the neural crest to see which part of the gut they finally colonise. Gene knockout studies have been used to identify which molecules are essential for the development of the ENS in particular regions of the gastrointestinal tract. An understanding of the normal ENS developmental processes should assist in the detection of abnormal development and ultimately in the therapeutic targeting of abnormalities.

The development of the ENS into a quasi autonomous part of the nervous system involves the formation of complex neural circuits. As in all nervous systems involved in sensory-motor control, the ENS comprises primary afferent neurones sensitive to chemical and mechanical stimuli, and interneurones and motor neurones that act on different effector cells, including smooth muscle, pacemaker cells, blood vessels, mucosal glands, and epithelia. The movements of the intestine are the result of the interaction between the neural apparatus and the muscular apparatus and include myogenic rhythmic activity, content dependent neural mechanisms (that is, accommodation and propulsion) and spontaneous cyclical migrating motor complexes. The relative importance of one type of movement at any one time changes, but it is not clear what controls the shift. It is known, however, that the ENS consists of an abundance of different types of neurones which innervate the wall of the gastrointestinal tract. The presence of several receptor types and several neurotransmitters on enteric neurones is an expression of their heterogeneity.

Most information has been obtained from animal studies, as the availability of human tissue is limited. Notwithstanding this, optical imaging of neuronal calcium concentration is currently being adopted for study of enteric neuroresponsiveness to neuroligands in human specimens. It has been suggested, however, that it is worthwhile to pursue research in other species, for example the mouse, to elucidate mechanisms which may well apply to the human nervous system also. Much of the fundamental research on mechanisms has been aimed at elucidating physiological responses but it must be borne in mind that pathological conditions such as inflammation may change the mechanisms, as even phenotypic changes in neurones can occur in disease states. We must look at alteration of receptors in disease states and assess the role of chemical mediators which might be released, in order to draw valid conclusions.

The activity of gastrointestinal smooth muscle is regulated by interstitial cells of Cajal and modified by inputs from nerves, hormones, and paracrine substances. In general, excitatory transmitters increase Ca²⁺ influx through non-selective cation channels while inhibitory transmitters enhance the “open” probabilities of a variety of K⁺ channels. Electrical mechanisms are supplemented and further regulated by release and uptake of Ca²⁺ from stores. Thus modulating uptake and release of Ca²⁺ offers an important control point for regulating the “open” probabilities of Ca²⁺ dependent channels.

In conclusion, this session has presented some complex challenges for researchers. By study and understanding of the development of the ENS we may be able to pinpoint abnormalities which lead to certain gastrointestinal disorders. Evaluation and mapping of the complex circuitry of the ENS will hopefully reveal whether each neurone has a predetermined function or can be “programmed” into different circuits according to its requirement. Elucidation of transmitters and ionic channel mechanisms may hopefully pave the way for the development of selective neuronal or muscle channel blocking drugs.