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Progress report

Disorders of the myenteric plexus

The nervous control of gut motility is mediated by the myenteric plexus lying between the two muscle coats. This is a rather geometrical network of nerve fibres with neurones at the angles. In animal material in which the muscle wall is thin enough to be examined as a whole mount, the plexus can be well seen whether stained by a cholinesterase technique or by silver impregnation. In man, silver methods usually have to be used but sections must be cut parallel to the plexus not transverse to the gut. Cutting thick sections in this way also helps to avoid the sampling error, as one of these 100μ sections is equivalent to about 200 5μ paraffin sections cut transversely.

There are two types of myenteric neurones, distinguished by their affinity for silver. The argyrophil cells constitute between 5 and 20% of the total number, the rest being argyrophobe. The argyrophil cells are multipolar and frequently multiaxonal, their processes terminating around other neurones either in the same ganglion or in neighbouring ones. The axons of these cells do not leave the plexus and do not reach muscle fibres. The argyrophobe cells, which are strongly cholinergic, give off axons which form the secondary and tertiary plexuses and supply the muscle fibres. From these anatomical observations it is probable that the function of the argyrophobe cells is to produce the acetylcholine which fires the muscle fibres and that of the argyrophil cells to act as a controlling device to coordinate peristalsis. They can be considered as secondary neurones in the vagal nerve supply. The important corollary to this is that the loss of argyrophil cells only will have the same clinical effect as total neuronal fallout. The two types of cells cannot be distinguished on haematoxylin and eosin preparations and the numbers of argyrophil cells are too small for their loss to be picked up on this type of section.

The general effect of myenteric plexus damage is the same wherever it may occur in the alimentary tract. There is loss of the coordinated muscle contraction which propels the bolus analwards. This tends to remain relatively stationary and may produce intestinal obstruction. As the affected segment is continually being refilled from above it dilates and the pressure within it rises. This stretch on the muscle wall is a stimulus to segmentation which is a myogenic movement and not dependent on the nerve supply. A concomitant to this is gross hypertrophy and probably hyperplasia of the smooth muscle coats. This could be simply a work hypertrophy due to the hypersegmentation, but there is also some evidence that denervated smooth muscle hypertrophies[1], in contrast to skeletal muscle. The hypertrophy is striking and is very much greater than that which is seen behind an organic obstruction. The thick muscle is useful as an aid to diagnosis and it is also probable that in some cases the muscle hypertrophy itself exacerbates the patient's symptoms.

Chagas disease is a condition in which the myenteric neurones are destroyed by the *Trypanosoma cruzi*. It can occur anywhere in the alimentary canal and thus serves as a pattern for diseases which occur in Britain due to

other unknown agents. Achalasia of the cardia, hypertrophic pyloric stenosis, megaduodenum and megacolon can all occur in Chagas disease[2,3,4,5].

Achalasia of the cardia is known to be due to a destructive lesion of the myenteric plexus in the oesophagus and gastro-oesophageal segment[6]. The loss of myenteric neurones is often extensive and may be complete. There are reports, however, that neurones have been found in biopsies taken at cardiomyotomy[7]. Considering the sampling error involved in using thin paraffin sections, even if many are taken, it is possible that the number of residual neurones is underestimated. However the ganglion cells which are left are argyrophobe[8] and therefore do not contribute either to peristalsis or oesophageal reflexes. The cause of the dysphagia appears to be due to loss of reflex relaxation of the gastro-oesophageal segment in response to stretch or increase in intraluminal pressure in the ampulla. This is the result of destruction of the nervous pathway. Following the denervation there is hypertrophy of the muscle of the sphincter region which will increase the obstructive element, although of course the sphincter is not closed and the oesophagus can still empty under gravity if the column is high enough. Some authors have described a vagal lesion in achalasia[9] and if this is established, it implies that it is a process involving primary and secondary neurones. This would narrow the field of aetiology to a system degeneration or a viral infection. Some writers have described an inflammatory infiltration of the plexus[7,10] which might make a virus the more likely cause.

Infantile hypertrophic pyloric stenosis is a condition coming on during the first few weeks of life: it is not congenital[11], and it appears to be due to a failure of the pyloric pump[12]. The pyloric canal is open most of the time and fills from the stomach largely by gravity. At intervals it contracts along its whole length forcing part of its contents into the duodenum and part back into the stomach. Reflux is prevented not by pyloric closure but because the very active duodenum sweeps the contents on. This is the usual mechanism of gastric emptying in the normal individual but it is not necessary; the stomach will empty by gravity if the distal opening is large enough. In infants with this disease the stomach empties quite well at birth but with increasing smooth muscle hypertrophy at the pylorus, probably secondary to the denervation, the canal becomes too narrow and obstruction occurs. If no surgery is performed and the child survives, the symptoms disappear, but the radiological abnormality and the pyloric tumour may persist indefinitely[13]. Cases of this condition, demonstrated radiologically, sometimes have no symptoms[14] and some of them present in adult life. The adult cases often have associated pathology such as a gastric ulcer which precipitates symptoms. The ulcer may be initiated by the impaired gastric emptying which these patients will always have.

In spite of opinions to the contrary in the literature, standard sections in hypertrophic pyloric stenosis probably show no neuronal abnormality. One pair of workers[15] have described a complete absence of argyrophil cells and this has been confirmed once[16]. This suggests that the condition is a localized maturation defect in which innervation of the pyloric canal remains inadequate.

Myenteric plexus deficiency in the small intestine may be congenital or acquired. The commonest site for congenital absence of neurones seems to be the duodenum. In cases in which the lesion is acquired[17] the presentation may be one of subacute intestinal obstruction usually recurrent. Another possible presentation is as intestinal malabsorption as the stagnant loop of bowel becomes infested by bacteria[18]. The intestinal segment affected is dilated and grossly thickened, the wall feeling almost wooden at laparotomy. Histology of the plexus shows fallout of argyrophil cells with a consequent schwannosis. The residual neurones, if any, may show considerable abnormalities with swelling of the perikaryon and deformity of the cell processes.

Excision of the denervated loop is effective in curing the patient's symptoms.

The commonest lesion of the myenteric plexus occurs in the colon. This is congenital megacolon or Hirschsprung's disease. It presents clinically as a spectrum from intestinal obstruction in the newborn, to the child with the pot belly and wasted buttocks, to the adult with obstinate constipation. The factor which decides the mode of presentation appears to be the length of the contracted segment. In the adult this may be so short that there is no aganglionic gut on the excised specimen. The histology is the same at all ages. The plexus region in the distal contracted segment shows no neurones and the plexus is replaced by a network of fine unmyelinated fibre trunks which are different in morphology from trunks seen in the normal. In addition there is a single fibre, argyrophil network in the muscle coats in an area in which normally axons are not seen. These are probably the adrenergic nerve fibres which are present in this condition[19]. Histology of the dilated segment shows that neurones are appearing but they are abnormal in morphology and often have no processes. The unmyelinated nerve trunks are still present but show fragmentation of some axons and thickening of others. In some instances poorly formed neurones lie on the unmyelinated trunks[20]. Where axons of a mature parasympathetic type are present they are often thick and uneven in calibre with axonal swellings but most important they do not have the correct anatomical connections so that they cannot function normally. This condition is usually present up to the upper cut end.

The muscle coats of both the distal contracted and the proximal dilated portion are extremely thick. There is physiological evidence of hypersegmentation in the dilated portion[21] which would support the fact that its innervation is abnormal. The cause of the symptoms in this disease is thus not only the obstruction by the distal contracted segment, which is only partial, but also the absence, above, of the necessary coordinated muscle contraction which might overcome it.

Acquired disease of the colonic myenteric plexus does occur[17] but the number of cases described is so far too small to make any useful comment. A condition which is seen frequently and which does show evidence of myenteric plexus damage, which may be severe, is cathartic colon[22]. The changes seen in these cases consist of a fallout of argyrophil cells and axons with a resultant schwannosis. The appearances of the remaining neurones are always abnormal, but seem to vary with the length of history. In young patients who must necessarily have a relatively short history they are pale and enlarged with thick and irregular processes. In the patients who give a a history of taking purgatives for 30 to 40 years the neurones are shrunken, very dark, and the processes are clubbed. The pathology is always worse on the right side of the colon as is the melanosis coli. The cause of this neuronal damage could be related to the mode of action of the purgatives. In spite of the enormous quantities of these substances which are consumed, little interest has been taken in their pharmacology. It appears, however, from experimental evidence[22] that the anthraquinone purgatives given in very large doses can damage myenteric neurones. It is possible that, since their toxic effect is to destroy neurones, their pharmacological action is to stimulate them. This would account for their purgative action and also the histological changes seen in man when they are grossly abused.

The myenteric plexus, together with the rest of the peripheral autonomic nervous system and the posterior root ganglia, is outside the blood-brain barrier. It is therefore unprotected against circulating neurotoxins. A number of drugs in modern use can damage nerve cells if they reach them in large enough quantities. The colon is more dependent on its innervation for its efficient function than the rest of the alimentary tract, and thus constipation is a side effect of many drugs. These drugs include the anticholinergics[23], particularly the tranquillizers, the spindle poisons such as the vinca alkaloids,

and the substances which impair RNA synthesis, such as many of the antimitotic drugs[24]. It must be remembered that if the neurones are damaged by drugs, they will not respond to the anthraquinone purgatives. It is therefore of little value treating a schizophrenic on large doses of chlorpromazine with syrup of senna.

Conditions affecting the myenteric plexus are rarely fatal but they do cause a considerable morbidity. Much of this morbidity can be helped by an understanding of the underlying defect and in many cases by myotomy or resection of the denervated area.

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