ISCHAEMIA : A HYPOTHESIS FOR THE GENESIS OF AGANGLIONIC BOWEL.

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ISABELLA FORSHALL ESSAY PRIZE 1968
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ISABELLA FORSHALL (1902-90)
CHM, FRCS, FRCSED

Isabella Forshall was one of the pioneers whose work did much to establish paediatric surgery as a recognised branch of surgery in the United Kingdom. It is remarkable that she should have done so at a time when women were not expected to achieve distinctions in the professions and when the surgical establishment did not encourage the development of subspecialties.

Isabella’s childhood was spent in affluent surroundings in west Sussex. She was educated privately at home and never went to school. Her education, no doubt influenced by her mother, who had read classics at Girton in the 1890s, imbued her with a keen appreciation of art and literature and particularly poetry. It is perhaps surprising that a young woman of her time and background should have embarked on a career in medicine. When asked about the family’s attitudes to her ambition she would say that she had been expected to make the observance of her social responsibilities her first priority and, although never encouraged to think of a career, was never actively discouraged.

Isabella was appointed house surgeon at the Royal Liverpool Children’s Hospital in 1929 and later at Alder Hey Children’s Hospital and worked at these hospitals until her retirement in 1965. In 1939, while retaining her registrar post, she became honorary assistant surgeon at Birkenhead and Wirral Children’s Hospital and Waterloo General Hospital. In 1942 she became an honorary surgeon at the Royal Liverpool Children’s Hospital.

It was not until the end of the war that Isabella was able to realise her ambitions for paediatric surgery. She gathered around her a group of young people in paediatric surgery and in the associated specialties, whom she fired with her own enthusiasm. This resulted in considerable advances in the surgical treatment of children and in the foundation in 1953 of the Liverpool neonatal surgical centre. During the first six years of its activity the mortality of infants with surgically treatable congenital abnormalities in the Liverpool region fell from 72% to 24%, and soon afterwards the Ministry of Health published a report on surgery of the newborn that strongly recommended the establishment of similar units in all regions.

These achievements brought Isabella widespread recognition nationally and internationally. In 1958 she became the second president of the British Association of Paediatric Surgeons; the next year she was elected president of the paediatric section of the Royal Society of Medicine. She was president of Liverpool Medical Institution in 1963, was elected an honorary member of the British Association of Paediatric Surgeons and of the British Paediatric Association, and in 1970 was awarded an honorary degree of master of surgery from the University of Liverpool. Despite having such a distinguished career she had no personal ambition and would give to her associates much more credit than they sometimes deserved for joint achievements; she fought only for the better care of children.

Those who enjoyed her friendship quickly learnt of her warmth, her delightfully mischievous humour, her abhorrence of pomposity, and her concern for all, particularly the deprived. It was this concern that caused her to be among the first to embark on the more enlightened approach to the needs of children in hospital that today is the norm: in her early days parental visiting was greatly restricted and awareness of children’s emotional needs was totally lacking.

Throughout her busy working life she devoted every spare moment to her garden, which was always a joy to see and where she loved to entertain on a summer evening. She was delighted to retire to her beloved Sussex. —JR.

Isabella Forshall, formerly senior paediatric surgeon at Royal Liverpool and Alder Hey Children’s Hospitals, died 18 August age 88. Born west Sussex; studied medicine at London School of Hospital for Women (MB, BS 1927).
INTRODUCTION

Hirschsprung's disease and achalasia of the oesophagus are similar because the ganglion cells in Auerbach's plexus are either absent or fewer than normal. The aetiology of both diseases is unknown but the surgical treatment alleviates the symptoms satisfactorily. Textbooks of surgery have emphasized that they are different, because in Hirschsprung's disease the dilated bowel is normal and the narrow segment has no ganglion cells but, in achalasia of the oesophagus, the dilated gut contains few or no ganglion cells. They are the same type of lesions because the bowel is aganglionic but the gut reacts differently in each part to this denervation. All aganglionic bowel is dilated except for the narrow segment in Hirschsprung's disease and the lower end of the oesophagus in achalasia. In megacolon, caused by Chagas' disease, there is a similar loss of ganglion cells and in those cases of Hirschsprung's disease which persist untreated into adult life, there is no narrow segment of obstruction (186, 233). This narrowed bowel, in which no co-ordinated function can occur, is caused by the failure of circular muscle relaxation after denervation and by the inability of the propulsive power of the proximal gut to dilate it. The dilatation in achalasia is inexplicable if the competence of the gastro-oesophageal junction is thought to be due to a flap-valve or pinch-cock mechanism of the diaphragm rather than a physiological sphincter (53, 59, 85). The denervation produced by the lack of ganglion cells causes a lack of co-ordinated peristalsis in the body of the oesophagus and a failure of sphincteric relaxation. The physiological sphincter can be forced open by a
column of liquid when the hydrostatic pressure is high but not by a normal swallow. Dilatation follows the obstruction. The sphincter is normally closed and the pressure may temporarily but never permanently open it, so that free reflux can occur from stomach to oesophagus. This type of sphincter does not exist in the colon or rectum to explain Hirschsprung's disease.

This essay reviews the present knowledge of the diseases and suggests a unifying hypothesis for the cause of aganglionic bowel. The rare aganglionic megaduodenum is also discussed so that a spectrum of lesions which include achalasia of the oesophagus, aganglionic megaduodenum and Hirschsprung's disease can be considered together. Many unconnected facets of the diseases are clarified and made understandable by such a hypothesis, which the majority of the evidence substantiates. However this is no conclusive proof that the ideas are correct and future experimental work, based on the hypothesis, remains to be done.
ANATOMICAL DISTRIBUTION

The term aganglionic bowel is used in American literature and has the advantage that achalasia of the oesophagus, aganglionic megaduodenum and Hirschsprung's disease can all be discussed under one heading, but it has the disadvantage of a neologism and is inexact when a few ganglion cells remain.

Sir Arthur Hurst first suggested that achalasia of the oesophagus might be a peristaltic disorder because of absent ganglion cells (125), but this was first found by Rake in 1927 (221). The body of the oesophagus is affected more than the lower end and the gastro-oesophageal junction (280). The ganglion cells at the lower end may be reduced in number or normal even when the body of the oesophagus contains no ganglion cells (3, 45, 161). The cardiac end of the stomach in achalasia may also contain fewer cells (28, 221). A re-examination of the material used by Cassella (45) in his study at the Mayo Clinic by the author showed this ganglion cell loss in some of the cases.

In 1933 the first patient with aganglionic megaduodenum was described (138) and by 1955 the number had increased to 32 (14). Megaduodenum is rare and is usually said to be caused by compression of the gut by mesenteric vessels but histological examination is rarely done. There is no sufficient information available to describe the distribution or the extent of the lesions.

Considerably more information is available in Hirschsprung's disease about the distribution of aganglionic bowel (9, 37), which was first described by Tittel in 1901 (268) although this is usually ascribed to Dalle Valle (63). In the majority, a short segment below the pelvic colon is affected but, in a minority, longer segments of colon are involved. Bodian (26, 27) gives the percentages as 82%
for the "short" segment below the pelvic colon, 17% for the "long" segment extending above this level and 1% involving the small intestine (27). 55 cases of total colonic involvement have now been described (254) and 31 cases involving both the entire colon and the small intestine up to the duodenal jejunal flexure are documented (277). A very rare "mid-zonal" variety occurs (27, 109), in which the aganglionic segment is confined to the pelvic colon but the bowel above and below is normal.

Most of the gut may lose ganglion cells but aganglionic bowel is most frequent at both ends of the gastro-intestinal tract. In more extensive cases either end is affected and the disease process extends inwards either to the stomach from the oesophagus or to the colon and small intestine from below.

In two types, megaduodenum and the "mid-zonal" Hirschsprung's disease, there is an intermediate segment without the ends involved.
EPIDEMIOLOGY

The distribution of aganglionic bowel in populations throughout the world enables individual factors such as race, age, sex or associated diseases to be compared and apparent differences may suggest aetiologies. In the absence of complete epidemiological studies, geographical, racial, sexual and environmental factors can only be incompletely assessed from patients seen in hospital.

The geographical distribution must be assessed from the isolated case reports and most series of surgical patients or those treated by dilatation represent a biased selection and a minimal incidence because the total population at risk is not examined accurately.

Willis described the first case of achalasia in 1674 (285), and by 1920 more than 1200 had been described (43). The Mayo Clinic have published two separate series of 691 (192) and 601 patients (208). The steady increase may be true due to a rise in the incidence or apparent because of more patients reported. But the number diagnosed has not increased appreciably because no real advance in diagnostic techniques have been made since the advent of radiology. The only epidemiological study of incidence and prevalence comes from the Mayo Clinic, Rochester, Minnesota, where the prevalence appears to be about 1 :100,000 with no changes over the last thirty years (79). These figures are based on small numbers in a small community but are complete.

Only thirty-two patients with aganglionic megaduodenum have been described, therefore no epidemiological study has been conducted (14). Those from Brasil have not been included in this number (219). Far more work has been done on the
epidemiology of Hirschsprung's disease. In London there is an incidence of between 1:2000 and 1:10,000 newborn children (26) and in Bremen, Germany 1:12,000 (9). A calculation of the figures from the Neonatal Surgical Unit in Liverpool, serving a population of three million, with a birth rate of 60,000 per annum, suggest also an incidence of 1:12,000 live births (92, 227).

No figures of prevalence in the population have been given but since the survival rate after successful treatment in this disease is high, the prevalence of Hirschsprung's disease must be far higher than achalasia.

Factors of race, geography and species:

Achalasia is well documented in European and North American literature in Caucasians but it is more rarely described in other cases. In one study there were twelve Negroes out of 123 patients with achalasia in Chicago (167). In South Africa only seven cases have been described in Negroes (151) and in North Africa eight (41, 47). Most of the Negroes affected were adults but one Negro infant with achalasia has been reported (223). The disease exists in Indians (5) and Japanese (205). In Europe, achalasia has been reported from Budapest (28), Coimbra (43), Graz (164), Leipzig (122), Liverpool (228), London (15, 83), Louvain (273), Lyons (237), Malmo (187), Moscow (271), Munich (299), Oslo (123), Oxford (6, 22), Wroclaw (145). Achalasia has also been described in dogs, occurring spontaneously in more than fifty of which the breed most affected is Alsation (81, 132, 133).

Hirschsprung's disease also shows no specific geographical or racial bias. Since the original description by Hirschsprung from Denmark (130) it has been described in most races and cities including Peking (51) and Cairo (98). A series from South Africa confirmed that it occurred in Whites, Cape-coloured, and Negroes (102). Megacolon without histological confirmation has occurred in the cat (62).
and in pigs (152) but not in the dog. Histological confirmation is available in the large series of inbred mice with congenital megacolon described from Australia (23, 70).

Sex and age factors:
Sex differences in achalasia were not apparent in two series (167, 299), although in one large adult series males predominated by 327 to 274 (209) and in one group of children males predominated by 16 to 11 (213). At St. Thomas Hospital, London, males predominated over females below the age of fifty but above this age the ratio was reversed (15). No definite conclusion can be drawn from the sex incidence because the figures usually given are not adjusted to the age and sex distributions in the general population. The only available epidemiological study shows a preponderance of females (79).

In Hirschsprung's disease Bodian and Carter showed that boys predominated over girls by 3.6 : 1 but that when "short" segment disease was considered alone it was 5 : 1. However in the "long" segment disease there was almost an equal incidence (26, 27). Age is an important factor in the distribution of aganglionic lesions. In the oesophagus the usual age presentation is between 45 and 55, although the onset of symptoms is a decade earlier (208, 209, 212). Approximately 10% have symptoms before the age of 14 (191), and the disease exists in the neonate (228), the first case being described in 1906 (179). The true incidence of the congenital or infantile type is probably less than 5% of the total. There were three cases in Liverpool in a ten year period during which 74 adults were treated (228).
In aganglionic megaduodenum symptoms occur usually between 17 and 74 with a mean age of 40 (14) and only one case discovered at birth has been described (138). In Hirschsprung's disease the majority are diagnosed soon after birth but occasionally they may present later (186, 198, 233).

The genetical factors involved are difficult to assess. Three families with achalasia occurring in two siblings have been described (201, 267, 270) and one with three brothers affected (74), otherwise no familial incidence is noteworthy. In Hirschsprung's disease numerous siblings and successive generations are recorded but Bodian and associates in an analysis of over 200 cases could find no simple hypothesis as to the nature of the genetic factors (26). The association of Hirschsprung's disease with achalasia has been described in two patients in a large series (212) but large series of Hirschsprung's disease contain no achalasic patients (259). No significant associated diseases are described with achalasia (209) or aganglionic megaduodenum but in 204 patients with the colon affected there were other malformations in ten, of which three had mongolism (26). Only this last association seems to be significant but in the literature it has only been reported in 19 cases (104). A disturbance of bladder function possibly connected with aganglionic bladder was found in 5% of children with this disease (257) but a very detailed study of the vesical ganglia has shown normal ganglion cells in the bladder and not a single case of megaureter in 278 cases (174).
DISCUSSION OF ANATOMY AND EPIDEMIOLOGY

The anatomical distribution of aganglionic bowel obviously affects the intestinal tract at both ends of which the lower end is more susceptible. When the disease involves a greater length of bowel it usually affects one end primarily and then extends inwards. Megaduodenum and the rare “mid-zonal” variety of Hirschsprung’s disease are two exceptions. The anatomical distribution is similar to that of intestinal atresia where oesophagus and rectum are most frequently atretic. The cause of the anatomical distribution is not known but the lesions are distributed according to the arterial blood supply. The oesophagus is supplied above by branches from the inferior thyroid artery, below by branches from the left gastric and inferior phrenic arteries, and in the middle by two to three branches from the aorta and bronchial arteries (189). When the left gastric artery is severed to facilitate gastric mobilisation, the lower oesophagus may be severely devascularised and the anastomosis between the bronchial artery and the inferior phrenic arteries may be insufficient (245, 258). The inferior phrenic arteries may be sufficiently large enough to play an important role in collateral circulation (189) but they themselves arise from the left gastric artery in about 2% of cases in which case division of the left gastric artery would be more likely to cause necrosis (189).

Whenever the blood supply is poor, such as in arteriosclerosis, abnormal arterial distributions or blockage of one of the main arterial vessels the middle of the oesophagus is most susceptible to ischaemia (258). The necrotic area will extend to involve the lower end of the oesophagus and possibly the stomach, if the blood supply is more severely compromised.
The second part of the duodenum is normally well supplied with blood from the coeliac axis and the superior mesenteric artery through the superior and inferior pancreatico-duodenal arteries and the anastomosis between them, but is susceptible if either one or both of the main aortic vessels is obstructed.

The rectum is supplied by the terminal branches of the superior haemorrhoidal artery and there is an anastomosis at the lower end with the branches of the internal iliac artery. If the whole colon and terminal ileum are involved, the distribution is that of the inferior mesenteric and sigmoid branches. When the lesion extends to the duodeno-jejunal flexure, such an area is supplied by the superior and inferior mesenteric arteries.

It is suggested that the anatomical distribution of aganglionic bowel is based on its blood supply. The bowel affected also has a distribution similar to that of the atresias. The arterial supply is contained in vascular pedicles, which, although apparently fixed, were at one stage of intra-uterine life free, mobile and involved in replacing the gut in its adult position. If they are susceptible to rotation, it is conceivable that they could be obstructed at this stage.

The epidemiology of the disease was assessed by searching through the reports of isolated cases and large series of aganglionic bowel. Apart from the epidemiological studies in achalasia (79) and Hirschsprung's disease (9, 26) showing the true incidence, the findings represent only a minimal incidence. A case report indicates the existence of the disease in a population but not its true frequency unless the disease has been excluded from the whole population at risk.
Hirschsprung's disease is more common than achalasia and has an incidence of about 1:12,000. Achalasia has an incidence of 1:100,000 and occurs in adults between the ages of 35 and 45. Hirschsprung's disease may very rarely not present until adult life, but 5% of achalasia patients have symptoms in early childhood.

There is no geographical nor racial limitation to the diseases because they have been described in most lands and races, and other species than man are affected. The sex differences in achalasia are not significant, whereas in "short" segment Hirschsprung's disease the male predomination is real. Bodian suggests that this may be associated with the advanced development that a female child has, compared with a male, at birth but this does not help to find the aetiology. There is no genetical basis for achalasia in humans although there may be in dogs. But there may be a genetical basis for Hirschsprung's disease, which is supported by the evidence of numerous siblings and families as well as the inbred strain of mice. The mechanism of such hereditary factors is not apparent.

Aganglionic bowel has a random distribution and there are no definite causative factors that can be deduced from the present available epidemiology.
NORMAL NERVE SUPPLY OF THE BOWEL

The intestine throughout its whole length is a hollow muscular tube with an inner circular and an outer longitudinal muscular layer. In the wall of the gut lies the intrinsic nervous system of Auerbach's intermuscular and Meissner's submucous plexus. The extrinsic nervous system is the cranial parasympathetic distributed in the vagus, the pelvic parasympathetic and the sympathetic nervous system. The vagus motor fibres, originating in the dorsal motor nucleus, are pre-ganglionic and synapse with the ganglion cells in Auerbach's plexus, which relay post-ganglionic fibres. The pelvic para-sympathetic fibres have similar connection with cells in the colon and rectum. The sympathetic fibres have a ganglion outside the gut and post-ganglionic fibres pass to the gut wall. The final termination of these sympathetic fibres is unknown. They may either (1) end on blood vessels, (2) directly innervate smooth muscle cells or (3) synapse with the ganglion cells. In the latter case the post-ganglionic fibres belong to the ganglion cells of Auerbach's plexus and a tri-neuronal theory of distribution for the sympathetic must be postulated (169). In the intestinal wall, six neuronal plexuses have been described, but Auerbach's and Meissner's plexuses are the most important (129). Between the layers of muscle lies a network of nerve fibres at the junction of which lie Auerbach's plexuses. These consist of about 40 ganglion cells also called enteric neurones (108), interstitial cells of Cajal, fibroblasts, pre-ganglionic non-medullated para-sympathetic, post-ganglionic sympathetic fibres, numerous inter-connecting fibres of the ganglion cells (129), and occasional sensory organs (143, 165, 250).
Meissner's plexus is situated in the submucous layer and is not so large. There is usually no Meissner's plexus in the oesophagus (108, 166, 222, 253) although one illustration in Cassella's thesis demonstrates it. The author has never seen it in the oesophagus except for this one illustration. It certainly exists in the colon and the rectum.

Dogiel (76) described three types of ganglion cells, all recognised by their large size and nucleus, cytoplasm with dark granules and their processes. Dogiel Type I is a multipolar cell with short dendrites and has one predominant axone which may end on muscle, although even electronmicroscopy can not demonstrate this convincingly. This cell is more common in the rectum and the oesophagus and is definitely motor in function (165). Dogiel Type II is a sensory cell, multipolar with long dendrites passing to the mucosa. It exists in the small intestine with Type I but is not seen in the oesophagus or rectum. Dogiel Type III is similar to Type II but has large dendrites which do not anastomose. This subdivision is based on the appearances after silver staining, and the different types may possibly be artefacts of this method. The interstitial cells of Cajal are now thought to be fibroblasts on the evidence provided by the electronmicroscope (226). The majority of the fibres are interganglionic connections of the intrinsic nervous system and also connect Auerbach's plexus with Meissner's. The generally accepted view is that Auerbach's plexus is predominantly motor and Meissner's sensory. The motor fibres to muscle are the processes of Type I ganglion cells, although an intermediate fibre plexus as well as the interstitial cells of Cajal was originally suggested as an intermediate station. The anatomical basis for a local reflex arc definitely exists independent from the extrinsic nervous system (165, 166, 276) and this has also been demonstrated.
physiologically (16, 33). Six months after a vagotomy in dogs the oesophagus may still have an intact local reflex (38, 139, 150).

The extrinsic nerve supply is predominantly parasympathetic with the sympathetic playing an unknown but relatively unimportant role. The vagus is said to supply the gut as far as the splenic flexure (105), based on experimental work in cats and dogs showing degeneration to this level after section of the vagal trunks (24). Such degeneration has also recently been confirmed (242) but the number of fibres ending in this region is very small. The distribution of the vagus on the intestinal wall ends at the pylorus and the route of any further fibres to the colon must be in the gut wall. The distal part of the gut is supplied by the pelvic para-sympathetic but the exact distribution is unknown. Evidence shows that the motor fibres of the vagus may go no further than the pylorus (272) where their distribution on the outer wall of the gut ends. The evidence from comparative anatomy in the chick may be pertinent because the vagus supplies the gut to the pylorus and then the nerve of Remak passing upwards supplies the gut distal to this point (40, 294, 295). A further fact, not sufficiently emphasized, is that the vagus is predominantly sensory and not motor (4, 134) and most of the fibres are non-myelinated (46, 134) with less than 10% efferent at the diaphragm (4).

In the cat there are approximately 3000 motor fibres at the diaphragm (4) compared with 5 million ganglion cells in Auerbach's and 15 million in Meissner's plexus (239). If the vagal pre-ganglionic fibres end on Auerbach's plexus distal to the pylorus, the distribution must be very sparse in proportion to the vast numbers of ganglion cells. More pre-ganglionic fibres end on the cells of Auerbach's plexus in the oesophagus and stomach than in the small intestine.

If structure is to be related to function this will explain why the oesophagus and
the stomach are the only parts of the gut with a true coordinated peristaltic
wave whereas the small intestine has an intrinsic rhythm with a frequency
dependent on the inherent gradient in the gut. There is also evidence that
the ganglion cells decrease in number from the pylorus to the ileo-caecal
region (173).
The motor fibres of the vagus arise in the dorsal motor nucleus of the vagus.
The central connections of the sensory fibres are in the tractus solitarius.
Retrograde degeneration has been demonstrated after peripheral nerve section
in the dorsal motor nucleus of the vagus (19, 97, 194, 260, 292). The striated
muscle of the oesophagus is supplied by fibres from the nucleus ambiguus.
Retrograde degeneration studies have also shown that the caudal part of this
nucleus is the source of these fibres (97, 261, 171). In the dog these non-
medullated pre-ganglionic fibres do not pass directly to the striated muscle but
relay in the cells of Auerbach's plexus (120). Evidence on this point is not
available in humans but Auerbach's plexus has been seen in the predominantly
striated muscle part of the oesophagus by the author.
Originally the pathological changes described in achalasia and Hirschsprung's
disease were confined to the ganglion cells of Auerbach's plexus. Recently
more detailed pathology of the changes in Auerbach's and Meissner's plexuses,
the extrinsic nerves, their central connections and the muscles has become available.
ABNORMALITIES OF THE NERVE SUPPLY

Rake was the first to describe the loss of ganglion cells in achalasia (221) and in his original description emphasized that the body of the oesophagus was affected more than the lower end. The abnormality of those remaining was noted by Botar and Rubanyi in 1965, who remarked that the plexus appeared to have been previously present but was involved in a progressive destructive process. The number of nerve fibres also appears to be decreased but the author from his experience using a modified Bielschowsky staining technique is not able to say whether this is a loss of the larger extrinsic nerve fibres or the smaller intrinsic fibres. Cellular infiltration by small mononuclear cells has been noted (28, 60, 196, 205, 221). Unpublished work by the author can find no correlation between cellular infiltration and the severity of the disease and the majority of autopsy cases do not show this infiltration. It is probably not connected with epithelial ulceration but it may possibly be related to the dilatation or surgical procedures which precede death. In some cases this infiltration may also extend into the surrounding muscle, but not to the submucous layer.

In aganglionic megaduodenum there is an absence or decrease in the number of ganglion cells and a similar small cell infiltration may also be seen. The tissue spaces representing the original site of Auerbach's plexus, are still evident but in this type of aganglionic bowel there is a marked overgrowth of nerve fibres in contra-distinction to achalasia (14).

In Hirschsprung's disease ganglion cells are usually completely absent but in achalasia a total loss is rare. This total loss is confined to the narrow segment
and then there is a zone of hypoganglionic bowel of varying length. In this transitional zone the appearance of the cells suggests a progressive progress (27, 230, 264). The spaces representing the original site of the plexus are present but filled with numerous nerve fibres (27, 183, 253). In the rarer cases where the aganglionic bowel extends to the duodeno-jejunal flexure no such nervous overgrowth is seen (277). A cellular infiltration has been rarely observed similar to that found in achalasia (36, 264).

In the extrinsic nerve supply the abnormalities discovered have mostly been in achalasia and almost no work has been done on similar lesions in Hirschsprung's disease. Reduced numbers of cells in the dorsal motor nucleus of the vagus have been found in achalasia (45, 46, 156). A similar lesion of the nucleus ambiguus, the nucleus for the striated muscle of the oesophagus, was also found in human achalasia (156). The lesions in the vagal nucleus are specific, bilateral and only of that part of the dorsal motor nucleus that supplies the smooth muscle of the oesophagus. In achalasia a lesion of the trunk of the vagus was first suggested a long time ago (126) but no evidence was obtainable by light microscopy (87, 175, 176). Recently electronmicroscopy shows a definite decrease in the numbers of fibres and a progressive destruction of both myelinated and unmyelinated fibres in the trunk of the vagus, although it is not certain whether they are efferent or afferent (45).
ABNORMALITIES OF THE MUSCLE

Little attention has been paid to the muscle changes in achalasia. The sphincteric muscle at the lower end of the oesophagus is usually of normal thickness (278) although a few cases of hypertrophy have been described. The body of the oesophagus may be normal, thickened or dilated and thin. It is possible that this represents an early stage and the latter a terminal decompensated stage of the disease process.

Rake in his original description noticed that some muscle fibres seemed larger than usual (221). In the author’s experience this usually applies only to the striated muscle. Sclerosis of the smooth muscle is on the other hand commoner (7, 8, 175, 176, 280, 281). It predominantly affects the circular layer of muscle and the muscularis mucosa (280) but this distribution is not so clear in those cases the author studied. No evidence is available as to whether the body of the oesophagus or the lower end are most affected but the sclerosis appears proportional to the ganglion cell loss.

Electronmicroscopy has shown definite changes which consist of loss of intercellular bridges, the nexus, alterations of cytoplasmic condensates, changes in the size and the shape of the cells and intercellular collagen infiltration (45, 46, 119). Occasional hypertrophy of individual smooth muscle has also been seen under the electronmicroscope (119).
PREVIOUS AETIOLOGICAL THEORIES

1. General

Many of the older aetiological theories, more frequent in achalasia than Hirschsprung's disease, are completely untenable with our present knowledge of physiology and the extent of the pathological lesions but others deserve careful consideration. Before the discovery of the ganglion cell loss, weakness of the oesophageal wall (297), compression of the oesophagus by the aorta (117), the liver (196) or diaphragm (144) were suggested but these ideas have no physiological basis.

Purton in 1821 described one of the first cases of achalasia and mentioned that the patient had received a blow on the sternum thirty years previously (218). Trauma was also considered important in the aetiology at the beginning of this century (103). The subject was recently reviewed and thought to be significant (243) but the majority of patients do not have a history of trauma. Many experienced clinicians are impressed that achalasia patients are mentally abnormal. Two studies show that the majority have some psychological abnormalities (184, 234). They were passive, shy, sensitive and lack aggression. Systematic psychotherapy helped in all twelve patients treated in one series (234). It is impossible to decide whether these disturbances are the result or the cause of difficulty in swallowing. No such study has been done on patients with Hirschsprung's disease who have had their symptoms relieved by a successful operation. Mickulicz suggested that spasm of the sphincter was the cause of achalasia (190) but oesophageal motility studies show no spasm but rather a reduced or normal pressure in the zone of elevated pressure at the lower end of the oesophagus (59, 85). As early as 1888 a failure of the sphincter to relax on
swallowing rather than spasm (82, 188) and an abnormality of the coordinating mechanisms was postulated (232), but this theory had to mature a long time before it was proved correct by oesophageal pressure recordings (59).

The discovery of the ganglion cell abnormalities made possible a more logical approach to the aetiology but although this provided an anatomical basis for the physiological changes. The cause remained unknown. To postulate that dilatation itself caused the death of ganglion cells (290) does not help unless the cause of the dilatation is known and is most unlikely to be true in the absence of experimental evidence and the knowledge that the dilated bowel in Hirschsprung's disease contains normal ganglion cells.

Bacterial invasion of Auerbach's plexus was proposed (36). A virus was incriminated (17, 199), Etzel (88) also suggested Vitamin B1 deficiency for the numerous cases seen in Brasil, based on the clinical association with malnutrition. Experimental work with vitamin B deficiency in other animals although producing motility disturbances, has not produced achalasia (54). The main argument against the infectious theories is that although a virus, such as the poliomyelitis virus, can be specific against a specific type of nerve cell, they do not explain the anatomical distribution in which only certain parts of the gut are affected. Oesophagitis as an underlying cause of the bacterial invasion might explain the cellular infiltration at the lower end of the oesophagus but does not explain why the body is more affected than the lower end.

There is usually no evidence of reflux in achalasia before treatment nor any colitis in Hirschsprung's disease.

One infective lesion definitely does cause ganglion cell loss, not confined to any one part, because Chagas' disease affects the whole gut. At this stage the present knowledge of this disease and whether it could be responsible for all cases of aganglionic bowel will be discussed.
II. Chagas' disease.

Chagas himself first suggested the possible connection between the "megas" and acute Chagas disease which he first described in 1909 (48, 49). Individuals are inoculated by the faeces of a reduviid bug, which contain trypanosoma Cruzi parasites, and suffer from the acute phase of Chagas' disease with a mortality of 10%. After the initial infection repeated inoculations take place and the individual may or may not enter the chronic phase of the disease. Previous infection can be recognised by a complement fixation test from which the number of people infected in Brasil is estimated at about four million and in Venezuela one million (160). The parasite passes into the lymphatics of the gut which are mainly between the muscular layers. Reproduction occurs through an intermediate stage in a muscle cell, which subsequently bursts and liberates parasites into the blood stream. Since Auerbach's plexus is in this region it is liable to injury and the ganglion cells are killed either by a neurotoxin (159) or an allergic arteritis (66, 206). The subsequent post-ganglionic denervation and muscle damage affects mainly the heart and gut (162) but the urogenital tract, gall bladder and bile ducts may also dilate. The fact that most patients with megacolon and megaoesophagus had a positive complement fixation test (66, 67, 69, 216) establishes some correlation and the discovery of leishmania stage in megaoesophagus was additional circumstantial evidence (163). The experiments producing the chronic form of the disease in mice (207), dogs (207) and monkeys (113) were proof that the dilated gut could be caused by trypanosomiasis. The ganglion cell loss in Chagas' disease affects the whole length of bowel indiscriminately but the colon dilates earlier and more often than the oesophagus or small bowel. Motility studies of the oesophagus revealed early changes in asymptomatic patients with proven Chagas' disease, by complement fixation test, which were more marked when a concomitant megacolon was present (215). This work indicates that ganglion cell loss in the oesophagus with or without dilatation may occur without symptoms. If the colon and oesophagus are
equally affected by ganglion cell loss, then the cause of decompensation of the colon with the production of symptoms must be due to an inherent property of the large bowel. This may be due to the solidity of its contents or the lack of normal peristalsis and the absence of the effect of gravity. On this evidence many cases of non-trypanosomal European achalasia may exist without symptoms.

The parasite itself has a wider distribution than South America and has been described in the southern states of U.S.A. (31, 121, 124, 183, 279). The reduviid bug which is the important vector, has also been found in the U.S.A. (286, 288). In one series of children in an endemic area in U.S.A. Chagas' disease was diagnosed by complement fixation test in 2.5% but no permanent defects were noted (287).

Ingelfinger has described four possible cases of Chagas' disease megaoesophagus in the indigenous inhabitants of the Southern States, of which one also had E.C.G. changes (89). This is the total extent of Chagas' disease in the Southern States of U.S.A., where both the parasite and the reduviid bug exist. There is no evidence that Chagas' disease exists in Europe (161) or Asia (131). Therefore infection by trypanosomiasis is not the cause of aganglionic bowel in countries outside South America.

III. Extrinsic nerve lesions.

Numerous theories have been based on lesions of the extrinsic nerves. Since the sympathetic system either has no effect on motility or increases the tone in the musculature, only lesions of the parasympathetic have been postulated. These could either exist in the vagal nucleus or the trunks of both vagi in achalasia or in the pelvic parasympathetic in Hirschsprung's disease. No such theory has been postulated for aganglionic megaduodenum.
The experimental evidence for such lesions is extensive and has a long history. In 1839 Reid in Edinburgh produced dilatation of the oesophagus in rabbits and dogs after section of the vagus and this was repeated by Claude Bernard in 1849. Dilatation of the oesophagus can be obtained by lesions of the vagus above the hilum of the lung, but below this level the effect is confined to the area supplied below the divided nerve (44). Recently destruction of the vagal nucleus in the medulla of cats and dogs (128, 238) and bilateral supranodal vagotomy in dogs has produced a dilatation of the whole oesophagus (127). The results have been confused by species differences and although permanent dilatation can be obtained in dogs and rabbits it is only temporary in cats and monkeys. This is almost certainly due to the return of autonomous peristaltic action in the oesophageal smooth muscle of cats and monkeys whose distribution is the same as the human, whereas the striated muscle which extends to the lower end of the oesophagus in dogs and rabbits never recovers (38, 150). Sympathectomy normally has no effect on motility (107) and after a preliminary vagotomy the return of normal activity caused by a sympathectomy (149) must be considered part of the normal recovery of function in denervated smooth muscle. The experimental evidence for extrinsic denervation in the colon and rectum is not so extensive. Removal of the pelvic parasympathetic supply may cause a dilated colon but there is usually retention of urine due to the denervated bladder and the animals do not survive (3, 142). Although dilatation of the oesophagus may be produced by bilateral vagal lesions at or above the cervical region, the condition produced has certain important differences from achalasia. First, autonomous peristalsis in the smooth muscle of the oesophagus returns after vagotomy. Secondly, when the extrinsic nerves are destroyed, there is no evidence that the ganglion cells degenerate. Although one study in monkeys has suggested a reduction in ganglion
cells in the oesophagus after vagotomy (24), the majority of evidence shows that transynaptic degeneration of ganglion cells after pre-ganglionic denervation does not occur (129, 147, 150, 172, 185, 205, 229, 242, 253, 272, 276). Most of these workers have concentrated on morphological changes but a recent study by the author using a new histochemical technique, by which the ganglion cells in large areas of oesophageal wall could be counted, showed no decrease in ganglion cells after subhilar vagotomy in dogs. If an extrinsic nerve lesion does not cause degeneration of the ganglion cells, the lesions found in the extrinsic nerves must be secondary to the primary damage of the ganglion cells. Retrograde degeneration in the vagal nucleus have been described experimentally (19, 97, 292). The probability of such a wide anatomical distribution of a primary lesion is unlikely because it would be extremely rare for a pathological process to destroy only a part of the dorsal motor nucleus of the vagus on both sides of the medulla. But if retrograde degeneration produces these separated lesions, then the primary pathological process is more likely to be in the gut wall.

IV. Neural crest lesions.

Neural agenesis has been proposed as a cause of aganglionic bowel (93) and another group of workers with great experience of Hirschsprung's disease have suggested a lesion of the neural crest (26). They base the idea on the experimental work in the chick embryo of Yntema and Hammond, who extirpated the vagal neural crest and adjacent neural fold within the first few days of development (294, 295) and this work has been repeated in a turtle (293). Complete removal caused the disappearance of intrinsic ganglia in the lungs, heart, oesophagus, stomach and intestines and the incomplete removal produced a decrease distally more than in the proximal parts of
the intestine. This idea is attractive because the degree of damage to the neural
crest changes the length of aganglionic bowel to explain the "short" and "long"
segments of Hirschsprung's disease. The lesions produced by neural crest extirpation
are widespread, involving heart and lung ganglia, absence of spinal ganglia at the
level of the lesion and a reduction or absence of sympathetic ganglia as well as the
changes mentioned above. No mention of vesical or ureteric ganglion loss was
made in this work but these would be expected. Such a widespread lesion obviously
does not occur clinically. If a lesion of the neural crest were to explain the loss
it would have to be finely localised to the neural crest of both sides and occur
between the 5th and 10th somite stage in the first week of embryonic life. In
Hirschsprung's disease, the area where Auerbach's plexus should be, are very
noticeably filled with neural fibres rather than cells. In a congenital lesion at
such an early stage one would expect no evidence of these spaces and histological
appearances are more compatible with the cells having been present and then
disappearing, than never having developed. Another objection to this theory is that
it can not explain achalasia, because this is probably an acquired disease to the
extent that ganglion cells are often seen degenerating, and a few may remain and
the distribution in this instance would be expected to involve the whole bowel.
A further criticism is that the "zonal" Hirschsprung's disease and aganglionic
megaduodenum are unlikely distributions of a centrally occurring lesion.
SUMMARY OF PREVIOUS AETIOLOGICAL THEORIES

It is valuable to summarise the argument at this point. None of the previously suggested causes fits all the known facts. The theories of neural crest abnormalities and extrinsic lesions of the para-sympathetic system are best but there is evidence that they are not true. A hypothesis is needed that will fit the random distribution of aganglionic bowel on (1) an epidemiological basis (2) the definite anatomical distribution in accordance with the arterial blood supply and (3) the associated lesions in the muscle. Lesions other than those occurring locally in the gut wall are extremely unlikely, because trans-synaptic degeneration does not occur and the ganglion cells themselves must be primarily affected. Since the arterial distribution is an outstanding feature of the disease one is left with the possible alternative that an arterial lesion producing ischaemia might be the cause.

EXPERIMENTAL ISCHAEMIA AS A CAUSE OF INTESTINAL ATRESIA

Ischaemia of the gut usually causes other lesions and a digression is necessary to discuss the effects of ischaemia both in the adult gut and at an early stage of intra-uterine development. Surgeons are familiar with the result of arterial obstruction in the gut clinically. The gangrene that develops is either due to an intrarterial obstruction due to thrombosis, embolus or compression from the outside usually by strangulation in a hernia, volvulus or intussusception. This gangrenous gut may either be removed surgically or perforate but in certain instances it recovers spontaneously with ensuing stenosis. Over eighty cases of intestinal stenosis after a strangulated hernia have been described (50). Experimental work in the dog has
elucidated the damage done by ischaemia and the time factors involved (153).

It was shown that epithelium regenerated but that the irreversibly damaged muscle became stenotic. Experimental gangrene in adult dogs produced peritonitis after perforation, but if the bowel was sterile peritonitis was unlikely. Experimentally, dead sterile bowel can be absorbed without trace from the abdominal cavity (170) but the only time when the bowel is sterile is in utero. Barnard, working with Professor Wangensteen in Minneapolis, operated on pregnant dogs to produce gangrenous gut in intra-uterine puppies and when the puppy was born fourteen days later found a stenosis, web or atresia (12, 13). In these experiments the gangrene was produced by a volvulus of the small intestine. With the proof of the basic mechanism provided by this experimental work a classification was postulated for congenital intestinal small bowel lesions depending on the severity of the ischaemia (181).

1. **stenosis**

2. Type I atresia—membrane, septum, web or diaphragm.

3. Type II atresia—proximal and distal blind ends connected by a band-like remnant with or without a V-shaped mesenteric defect.

4. Type III atresia—disconnected blind ends with or without a V-shaped mesenteric defect.

This classification of intestinal lesions is not yet universally accepted although it has appeared in a textbook (284). Previous theories were based on the concept that the once solid gut failed to recanalise. Tandler stated that the duodenum was at one stage of development occluded by epithelium (265) and this was applied indiscriminately to the rest of the gut, supportive evidence being cited that the
oesophagus of the logger-head turtle was also obliterated (148). In man this probably does not occur (146, 197) although one report describes it (182).

As early as 1901, Bretschneider provided very strong circumstantial evidence that the theory of "failure to recanalise" was untenable, because he found lanugo, epithelial cells and meconium distal to the atresia and also demonstrated an atretic area containing these tissues. This has also been confirmed by others (32, 204, 236). The occlusion must occur later than the fourth week of intra-uterine life when meconium is first secreted (284) and the gut must have been patent to allow the passage of meconium and lanugo.

In 1883 Gartner suggested that atresia and stenosis were due to volvulus because the lesions were common at the extremities of the bowel and most susceptible to rotation (95). The finding of rotational defects in a significant number of colonic atresias is circumstantial evidence for this (94). Bland-Sutton's principle that congenital obstruction and narrowing are always found at the situation of embryological events is applicable here (25). Most of the atresias and stenoses are situated where the gut is most susceptible to volvulus, intussusception or strangulation in a hernia. Duodenal atresia may be caused by the rotational mechanism involved in placing the duodenum on the right side of posterior abdominal wall, and may also be associated with malrotation (90, 110). The numerous and often multiple small intestinal atresias are more likely to be caused by obstruction in an umbilical hernia rather than the main volvulus defect, although a volvulus affecting only the small bowel could exist.

The localised colonic atresias and possibly some of the small intestinal defects may be caused by intussusception. The finding of intussusception with colonic atresia
by Parkulainen is additional evidence (21). It must be emphasized that although
Barnard's work shows that the basic mechanism of ischaemia could be a cause of
intestinal atresia this was only applied in the small intestine. The same mechanisms
for the remainder of the gut have not yet been proved experimentally.

TEMPORARY ISCHAEMIA

In atresia the ischaemia must last longer than a critical period after which most of
the tissues are irreversibly damaged. Little attention has been paid to the duration
of ischaemia or whether the volvulus corrected itself. If the volvulus untwists
itself, atresia may result without any evidence of the accident having occurred.
Stenosis and the various types of atresia probably result from a long period of
ischaemia, but the bowel could be ischaemic for a shorter time without so much
muscle damage, and it is conceivable that nerve cells could be damaged without
the other tissues being affected. Kessler and Linden found that with experimental
ischaemia of the gut 3 1/2 - 4 hours was the critical period during which the neural
tissue was destroyed irreversibly without damaging connective tissue, muscle or
epithelium (153). The original work on temporary ischaemia of the gut was performed
by Cannon and Burket in 1913 (39). They compressed the small intestine of a cat
between glass plates to render it ischaemic for at least three and a half hours and
selectively destroyed ganglion cells. This compression technique has been
successfully applied to the oesophagus (55, 61, 238). Hukuhara developed this
further by perfusing the small intestine through its arterial supply with a non-
oxygenating substance (136, 137) and Okamoto and his associates with the same
method successfully destroyed ganglion cells in the oesophagus (205). They
shortened the time of anoxia to one hour by adding mercuric chloride to the perfusion
fluid. Their procedure is open to severe criticism because it does not assess the
physiological effects of ischaemia alone, the mercuric chloride adds an unknown
factor and almost certainly produces so much tissue damage that a stricture at
the lower end of the oesophagus is formed, as demonstrated by one of their illustrations.

A recent attempt to produce ischaemia of the oesophagus by a similar method
without mercuric chloride was made in fifteen dogs by the author (80). In these
experiments the lower end of the oesophagus was freed so that the left gastric artery
provided its sole arterial supply. After washing out the blood the area was left
ischaemic for at least four hours and then the normal anatomy was reconstituted.
Early motility changes in the muscular coordination of the oesophagus were noted
but within nine months they returned to normal and there was no evidence of any
stricture. Morphological ganglion cell changes and a reduction in their number
were found. This series of experiments failed to produce a permanently dilated
oesophagus possibly because only the lower ten centimetres of the oesophagus were
made ischaemic and the ganglion cell loss was only about 50% of the normal number.
It has been suggested by Koberle with his experience in Chagas' disease that at
least 90% of the ganglion cells must be absent before incoordination of the
oesophagus leads to dilatation (161, 162). These experiments succeeded in showing
that the basic mechanism of the selective destruction of ganglion cells by temporary
ischaemia was possible. Other recent experiments with anoxia have selectively
destroyed ganglion cells without muscle damage in the small and large intestine
(137, 200, 262, 263) although one attempt has been unsuccessful in the colon of
the dog (73).

This temporary ischaemia is based on the concept that of the four basic tissues
in the intestinal wall-connective tissue, epithelium, muscle and nerve - the latter
is most sensitive to anoxia (75) and no regeneration of any remaining ganglion cells
is possible. Epithelial tissue is most easily damaged but regenerates (35), muscle
is also damaged but shows very little change by light microscopy. No electronmicroscopic change in smooth muscle or skeletal muscle are available but evidence in cardiac muscle after ischaemia shows a striking increase in the amount of intercellular separation (34). The ganglion cells themselves may be irreversibly damaged and show cytological changes in the early phases after ischaemia but may possibly take up to six months to disappear (80). Mitoses are not seen in mature ganglion cells so hyperplasia is presumed not to occur. The presence of a double nucleolus in the nucleus of a damaged ganglion cell is most likely the result of the damage and does not indicate regeneration. Although this evidence suggests that regeneration of neural tissue can not occur, ganglion cells can be grown under special conditions in tissue culture and an increase of cells has been alleged in congenital pyloric stenosis (18), regional enteritis (65), above stenosing jejunitis (114) and ulcerative colitis (255). If this hyperplasia occurs, it is at the moment inexplicable and is the only known example of neural cells in any part of the body undergoing compensatory hyperplasia. In the absence of any positive evidence to the contrary it must be presumed that once the majority of the ganglion cells are destroyed there is no regeneration of the remainder.

Experimental destruction of ganglion cells has also been achieved by placing animals in a hypobaric pressure chamber representing an altitude of 4000 metres (240) and by the use of carbon dioxide snow which causes vasoconstriction and anoxia (7, 8). The damage produced by the cold from carbon dioxide snow is not completely specific and the author thinks that strictures of the lower end of the oesophagus were probably caused in this work, but the ganglion cells were successfully destroyed. Sclerosis of the muscle such as seen in some human cases of achalasia were produced. Alnor was the first to suggest that a localised disturbance of circulation, producing ischaemia, might be the cause of ganglion cell loss (8).
There now appears to be sufficient experimental evidence that ischaemia of approximately four hours duration can produce ganglion cell loss without destroying other tissues. Obviously if the ischaemia lasts longer than four hours there is a greater chance that all the ganglion cells will be destroyed, but some muscle damage may occur (153). As long as the muscle damage is minimal no scarring and no contraction will occur, but as soon as it is severe enough stenosis will result. As atresia is probably caused by intra-uterine accidents of volvulus, intussusception or strangulation, it seems logical that aganglionic bowel could occur in the same way. A review of the present knowledge of the embryology is essential as the next step in this discussion so that the stage of development of the gut in relation to intra-uterine vascular accidents is accurately known.

EARLY EMBRYOLOGICAL DEVELOPMENT OF THE GUT

The following paragraphs contain a discussion on the development of the individual components of the intestinal wall, the development of the oesophagus and the rotation that the gut undergoes in utero before it assumes its final adult configuration.

Smooth muscle layers in the intestine are present by 33-35 days (154). In striated muscle, development can occur without innervation (2) and there is also evidence that this can occur in smooth muscle (272). In humans the growth of smooth muscle has not been as well studied as skeletal muscle but since the upper end of the oesophagus contains skeletal muscle this may be pertinent. At seven weeks the first individual skeletal muscle is differentiated, at ten weeks small identifiable cells are recognised, by sixteen weeks there is no more splitting and striations
are present. In the second half of intra-uterine life there is an increase in the
size but not the number of muscle cells. Somatic nerves are seen in the connective
tissue at 10 weeks and make contact with the muscle at eleven weeks, with the
subsequent development of motor nerve endings at 12-24 weeks. Muscle spindles
are seen by eleven weeks and all essential elements are present by fourteen weeks.
By twelve weeks there is sufficient anatomical organisation for the earliest human
embryo reflexes to be present.

There is not so much evidence about neural tissue in the human as in the chick,
but the vagus is well formed by 30 days (256) and the myenteric plexus by the
38th day (154). The ganglion cells are in fact present at an earlier stage and
myelinated fibres have been reported in the intermuscular plexus by the 18th day
(249), but at this stage are usually only represented by Dogiel Type I (165).

In the chick embryo details about the development of neural innervation are
available in great detail but obviously the time factors cannot be indiscriminately
applied to humans. At 86 hours in the chick the visceral branch of the vagus is
present and by 125 hours the vagus reaches the pylorus where it stops; by the 4th day
the sympathetic also has visceral fibres (272). If the extrinsic nerves are normal
the ganglion cells develop pari passu with the growth of the parasympathetic
from both ends (40, 272). If the vagus is divided in the chick before the ganglion
cells are seen the cells of Auerbach's plexus still develop (40, 68, 272).

In spite of much work on whether the ganglion cells of Auerbach's plexus arise
from mesoblasts (272) parasympathetic neuroblasts (202, 294) or sympathetic
neuroblasts, the probability is that they arise from the parasympathetic nervous system.
Blood vessels are found entering the human embryo intestinal wall by the 37th day (153) and definite adult type blood vessels develop later.

The development of the intestinal epithelium is controversial. In the oesophagus the majority of the opinion is that the lumen is never occluded (146, 154) although in the logger-head turtle an epithelial plug was found (148). The duodenum seems more likely to be obstructed by a relative overgrowth of epithelium (265). The rectum and colon are very rarely affected by this process in the human (182).

The development of the thorax and the descent of the diaphragm is important in relation to the oesophagus. On the 33rd day the diaphragm is attached to the caudal end of the infrahyoid mass and by the 34th day it is disconnected and descending (154). This descent is caused by differential growth in which the oesophagus markedly elongates. There is disagreement as to when the diaphragm has fully descended. Keibel and Mall say at 36 days, but it may be later.

Between the 5th and 10th week the gut enlarges in length to such an extent that there is not room in the abdominal cavity and it prolapses through a large umbilical hernia. At the 5th week there is only a single loop but with the vast increase of length the loops become more complex. Towards the 10th week the gut begins to return, undergoing a 270 degree anti-clockwise rotation, so that the duodenum reenters the abdomen first and the caecum abruptly and finally at the 10th week (10, 77, 116). This anti-clockwise rotation is still evident in the adult by the position of the bowel, the taeniae coli of the colon, the anti-clockwise spiralling of the longitudinal muscle of the small intestine (42) and the oesophagus (252) and the rotation of the vagi on the oesophageal wall.
A volvulus is most likely to occur when the gut is prolapsed through the umbilical hernia between the 5th and 10th week of intra-uterine development. Since the rotational effects of the gut are more evident towards the end of this period the chances of volvulus occurring then are greater than in the 5th to 7th week.

It is probable that a volvulus results from excessive rotation between the 7th and 10th week. By the 7th week the intestinal wall has most of its essential components. The smooth muscle cells are present but still dividing. Auerbach's plexus and the extrinsic nerve supply are in situ. If four hours of ischaemia occurred at this stage the nerve cells would be destroyed and any muscle damage would be compensated by hyperplasia of the remainder, because this process normally persists until the 16th week.

EMBRYOLOGY OF OESOPHAGEAL ATRESIA AND TRACHEO- OESOPHAGEAL FISTULA

The pathology of these early embryonic events has been described in an excellent contribution on tracheo-oesophageal fistula by Smith (247). This study and that of Streeter (256) are based on a survey of over a hundred human embryos in the Carnegie Institute. Smith studied three of the five available early embryos with oesophageal atresia (100, 112, 177, 196, 291). It was concluded that the lesion occurred at the critical stage when the trachea and oesophagus are separating before the fifth week of intra-uterine development (256) and emphasized that the separation was caused by endothelial proliferation on the inside of the common tracheo-oesophageal tube as with the endocardial cushions, rather than a constriction from the outside. Tracheo-oesophageal fistula was compared with urogenital fistula and it was mentioned that atresia of the ventral and secondary developing system was rare. Lesions of Type I or II in the oesophagus may arise from a failure of the fistula to persist or develop. Smith found no support for the epithelial occlusion theory but suggested an abnormality of differential growth.
and insufficient tissue availability. The value of this work lies in localising the formation of a tracheo-oesophageal fistula to some time before the 33rd day. Since the trachea and the oesophagus are separated after the 33rd day it would be unlikely that a developmental error would cause a fistula after this. It is suggested that those atresias of the oesophagus which are not associated with fistula must be caused by a developmental error occurring after the fifth week when the trachea and the oesophagus have already separated.

TRANSITIONAL AGANGLIONIC ZONE BETWEEN ATRETIC AND NORMAL BOWEL

Further circumstantial evidence for the connection between atresia and aganglionic bowel would be provided if they were both described in the same patient. Indeed if the same aetiology is postulated there should be a zone of transition between atresia and aganglionic bowel as well as the transition between aganglionic and normal gut. Parkulainen and his associates have described the transition of rectal atresia through aganglionic bowel to normal in 15 cases of rectal atresia (211). This does not occur in every case but is more likely to occur in Type III. The transitional zone has been reported by others (29, 214, 230) but denied by Swenson (257), although one case was discovered in a series of 150. From the records of 32 paediatric centres it has been calculated that this transition occurs in 3.4% of rectal atresia (155). But this percentage increases, as Parkulainen demonstrated, if Type III atresias alone are considered (211).

In the oesophagus there is physiological evidence of disturbed motility after the repair of a tracheo-oesophageal fistula (72, 84, 115, 178, 246). This may be the effect of the operation but deficient peristalsis has been noted in the distal blind pouch before the operation (52, 157). This abnormal and deficient
peristalsis could be caused by a deficiency of ganglion cells in the body of the oesophagus. The author studied the material available at the Mayo Clinic representing unoperated tracheo-oesophageal fistulas and found definite evidence of reduced ganglion cells in a few cases. This was rare, and if found, occurred usually in the distal segment and only for a few mm. It was quite often associated with muscle damage but no correlation to the type of tracheo-oesophageal fistula was possible. The explanation of why the lower end of oesophagus and not the upper end is involved by this loss may be due to the poorer blood supply of the lower end (18). No striated muscle was found in these cases in the distal segment, so if an extrinsic nerve lesion were to have been caused during the repair, the smooth muscle would be expected to resume autonomous control. In some cases the gastro-oesophageal junction possibly contained reduced numbers of ganglion cells but no definite conclusion can be drawn with the limitations of the present technique and in the absence of further studies.

The hypoganglionic segment in Hirschsprung's disease shows a great variation in length so the aganglionic transitional segment may be expected to show some variation. There is enough objective evidence that aganglionic and atretic bowel can occur in the same patient with a transitional zone. This is not found in every case and the reason for this is not obvious.

EPIDEMIOLOGY OF ATRESIA AND STENOSIS

It has been emphasized earlier that the anatomical distribution of aganglionic bowel had certain similarities to that of stenosis and atresia. If the same mechanism is postulated for these lesions, the incidence of the different types might help in
elucidating some of the aetiological factors. Few epidemiological studies are available to give a true incidence so the figures from hospital series must be analysed. Such numbers are more reliable when the majority of the affected patients are treated in any one centre. American and London figures are suspect because many children are treated privately or in other hospitals. Provincial centres such as Liverpool, where a neonatal unit treats almost all the patients, provide the best available comparative figures (92, 277). Forshall points out that since 75% of the children in Liverpool and the surroundings are born in hospital there are relatively few patients lost because of failed diagnosis (92).

Oesophagus.

One epidemiological study assesses that oesophageal atresia in New England occurs at the rate of 1 : 5000 or more live births (140). A calculation from the available Liverpool figures gives a rate of 1 : 4000 (92, 227). The figure of 1 : 800 pregnancies from Bristol is almost certainly biased by selection and is too high (20). Oesophageal and rectal atresia each account for 30% or more of the total number of atresias, which means that they are the most common (92, 94), although the Great Ormond Street Hospital for Sick Children figures suggest that oesophageal atresia is not so common as rectal atresia (56, 57). The usual classification of tracheo-oesophageal fistula with oesophageal atresia is that of Vogt (275) and his original figures, in which 8% are Type III and the minority have atresia alone, are still basically true. It seems logical to add the rarer tracheo-oesophageal fistula without atresia to the classification and the latest figures from Great Ormond Street indicate this group form 5% of the total (56). In 1966 only 70 of these had been described in children (195) but they are frequently not diagnosed. The so-called traction diverticulum of the mid-oesophagus with a fistula, once attributed to the traction of tuberculous glands
but whose incidence has not decreased with the reduction in tuberculosis, is now considered congenital and would be the persistent equivalent of a fistula without atresia (298). If the adult diverticula are considered to be congenital then the incidence of tracheo-oesophageal fistula without atresia is probably 5% of the total fistulas with or without fistula. Congenital stenosis of non-peptic origin has been described in children and adults (106, 115, 244). They usually consist of incomplete obstruction in the middle one-third or two-thirds extending 2-3 mm. or rarely longer. Girdany has described more than thirty such cases from Pittsburgh in a ten-year period (99). These figures result from careful work so the condition must be considerably under-diagnosed. Congenital webs are even rarer (193) although Guisez was reported having found 5 in 2000 oesophagoscopies (266). Webs and stenoses have been described together (106, 118, 135) and a web with achalasia once (235). The prevalence of achalasia is 1 : 10,000 in the one epidemiological study available and the incidence is probably 1 : 100,000 (.79).

From these figures it will be seen that atresia of the oesophagus with a fistula occurs at about 1 : 5000 live births.

Atresia alone is ten times as rare at 1 : 50,000. The figures for congenital stenosis are misleading because the condition is under-diagnosed. Achalasia is even rare and occurs at about 1 : 100,000.

Rectum.

Rectal atresia is usually subdivided accordingly to the classification of Ladd (168) but it has been pointed out that Type IV is colonic atresia and not rectal (94, 236).
although this is not universally accepted. No epidemiological study is available for this condition but it has the same incidence as oesophageal atresia, occurring at least in 1 : 5000 births (92, 94, 227). Most of the Type III, which form the majority, but almost none of Type IV are associated with fistulas. Stenosis of the rectum is rare, and it is difficult to assess the true incidence from the literature. The classification of stenoses in the ano-rectal region is not as simple as in the oesophagus. If Type IV is considered colonic then the figures for colonic atresia and stenosis can be compared. Lesions of the colon are fifty times rarer than those of the rectum (94) and the colon is more commonly affected distally than proximally. In the same series there were two zonal stenoses and three zonal atresias of the colon. Hirschsprung's disease occurs at about 1 : 10,000 and the distal colon is far more frequently affected than the proximal, with zonal aganglionosis at 1-2%.

From these figures no clear pattern arises. But rectal atresia is commoner than Hirschsprung's disease. Stenotic and atretic lesions similar to the anatomical distribution of Hirschsprung's disease occur with approximately the same proportional incidence.

Duodenum.

Duodenal atresia is about half as common as oesophageal or rectal atresia (94) and occurs in about 1 : 12,000 live births (92, 227), 15% have other lesions distally (90). Stenosis is more than twice as rare. More than half are above the duodenal papilla and the remainder are below (64, 251, 282). Aganglionic megaduodenum and the distribution is unknown. Atresia is the commonest lesion. Stenosis is rare and aganglionic megaduodenum is very uncommon.
Jejunum and ileum.

Atresia of the jejunum has about the same incidence as duodenal atresia (94). Stenosis constitutes about one half of all atresias and stenoses in the small intestine (113). Rarely stenosis may occur in the adult as a late result of strangulated hernia but only about 80 have been described (50).

Both congenital atresia and stenosis may be multiple. Aganglionic jejunum and ileum have only been described in Chagas' disease. In this disease aganglionic small bowel may exist without symptoms, so it could exist in countries outside South America without recognition. Stenosis must be of a small diameter before symptoms occur, so many may not be diagnosed.

Once again atresia is commoner than stenosis. In the jejunum and ileum the lesions are multiple and no aganglionic segment has been described.

Stomach.

To complete the spectrum 52 stenoses, webs and atresias have been described in the stomach (96) and more webs have been recently added (231). Aganglionic stomach exists in Chagas' disease and in the fundus of patients with achalasia.

Stenosis, web and atresia are usually in the middle or the antrum of the stomach.
DISCUSSION OF EPIDEMIOLOGY

The distribution of stenosis, atresia and aganglionic bowel have all been considered together because ischaemia may cause all these lesions. The overall pattern emerges that atresias are more common than stenosis or aganglionic bowel. If ischaemia, caused by a volvulus, causes all these lesions, there would be more chance of permanent than temporary damage, which would affect only the neural elements. Atresia would then be commoner than stenosis or aganglionosis caused by lesser degrees of ischaemia.

Atresia with a fistula must occur earlier in embryonic development than atresia alone because the structures concerned have separated completely. The critical stage is approximately in the 4th to 5th week. Although the gut can be subjected to rotational stresses before separation has occurred, it is more likely to occur later between the 5th and 10th weeks when the hernia is larger and the gut undergoes rotation in its return to the abdomen. The mechanism for the failure of separation in the development of a fistula with atresia at both ends of the gut is unknown, but it could also be associated with a disturbance of the blood supply. The effects of the volvulus are not due to the mechanical compression of the gut itself but to the obstruction of the blood supply. When the left gastric artery and the superior haemorrhoidal artery are obstructed, the gut situated at the distal end of the distribution of these arteries is most likely to be ischaemic. The presence of the descending diaphragm does not alter the effect of obstructed blood supply and is almost complete before the rotational stresses occur. When the gut is returning to the abdomen the secondary
rotation of the duodenum may cause ischaemia, but this is naturally rarer.
The multiple jejunal and ileal lesions are more likely to occur later when the
majority of the gut has returned to the abdomen and a small umbilical hernia,
in which gut can strangulate, remains. The zonal lesions of the colon are
probably caused by intussusception and are therefore extremely rare.

The epidemiology of these lesions offers almost no help in the search for other
causes. Although numerous familial incidences have been reported, overall
epidemiological studies comment on the relatively low position of congenital
malformations in the list of diseases with familial tendencies (158, 203). A
familial tendency to malrotation may be feasible, but the cause of this tendency
is still unknown. Allowing for the variations in diagnosis there seems to be no
change of the disease incidence in recent years, which would exclude any
environmental factors such as infection or irradiation. This comparison suggests
that more aganglionic megaduodenum and congenital stenosis of oesophagus should
be diagnosed than at present.

MUSCLE AND GANGLION CELL CHANGES IN SCLERODERMA.

Aganglionic bowel occurs randomly as achalasia or Hirschsprung's disease or with
a definite cause apparent such as Chagas' disease where destruction of the ganglion
cell is caused by the Trypanosoma Cruzi. The only other disease known at the
moment where ganglion cell damage occurs is scleroderma, which is a generalised
disease of unknown origin. The smooth muscle of the small arteries is most
affected and a Raynaud's phenomenon may exist. Although the most obvious
changes occur in the skin, the oesophagus is abnormal (58). Peristalsis is poor and there is a reduced zone of elevated pressure at the lower end of the oesophagus. A reexamination of the two cases reported from the Mayo Clinic (269) by the author showed in one advanced case loss of ganglion cells of the oesophagus and stomach, and in the other a reduction in the number as well as the marked muscular damage. This was first described in South Africa by Goetz (101). Although the neural tissue loss may be secondary to the muscular damage, it is suggested that the muscular changes and the ganglion cell loss are secondary to damage of the small arteries and subsequent ischaemia. In myotonic dystrophy and progressive muscular atrophy, there is patchy necrosis of the muscles but the ganglion cells are normal or enlarged (217). The motor abnormalities of the oesophagus in these diseases are due to muscle damage alone.

ARTERIAL LESIONS

Arterial anomalies were noted in some of the embryos examined by Smith with oesophageal atresia and tracheo-oesophageal fistula (247) and it has been said that 10% have vascular anomalies (115). Whether these abnormal blood vessels affect the blood supply of the oesophagus or not is unknown, but there is a definite relationship. Damage to the small arteries in achalasia have been previously noted (36, 175, 196) but damage to the larger arteries such as the coeliac axis or the left gastric artery may also occur. Coeliac axis compression has been diagnosed during life in 17 cases (225) and coeliac angina in 15 further patients (78). In 110 autopsies 44% had a narrowed coeliac axis (71). The older patients with achalasia may have generalised arteriosclerosis or specific
damage to the blood vessels for the nutrition of the oesophagus. Abnormalities of oesophageal motility in nonagenarians (248) and reduction in ganglion cells with increasing old age has been found (160, 175). Although arteriosclerosis and old age may be concomitant, the connection between arteriosclerosis and ganglion cell loss is mere supposition at the moment. In one case, who died after a Heller's operation, a careful study by the author of the coeliac axis and the blood vessel supply to the oesophagus revealed no abnormality, but the patient was relatively young. Each main arterial axis of the abdominal aorta and its smaller branches has its own specific syndrome and it is tempting, but possibly facile, to suggest that the left gastric artery lesions produce achalasia.

HYPOCHLORHYDRIA OF THE STOMACH IN ACHALASIA

There is a definite increased evidence of hypochlorhydria in achalasia (141), which is a true finding not due to the failure to the stomach tube to pass through the lower end of the oesophagus. A possible explanation is that this is also a lesion of the extrinsic vagal nerve supply but it is probably due to aganglionic stomach that is unable to respond to any nervous stimulation. In Chagas' disease aganglionic stomach has been found and hypochlorhydria has been noted in 20% (274) to 70% (86). When the stomach is hypersensitive to mecholyl, denoting vagal denervation, there is hypochlorhydria in 100% (274). The connection of this hypochlorhydria with aganglionic stomach, unassociated with Chagas' disease, has yet to be proved, but it is unlikely to be due to a vagal lesion because pyloric obstruction does not occur.
SUMMARY

It is considered justifiable to assess all aganglionic bowel together so that common factors, important in aetiology, might emerge. The physiological differences in the gut explain why the dilated segment of Hirschsprung’s disease contains ganglion cells and the dilated body of the oesophagus has no ganglion cells. A study of the epidemiology of aganglionic gut reveals that the diseases affect other species, most races and both sexes with a relatively random distribution, occurring with a fixed incidence in populations but no definite aetiological factors emerge. The anatomical distribution of achalasia of the oesophagus, aganglionic megaduodenum and the various types of Hirschsprung’s disease is analysed and found to be distributed according to its arterial blood supply.

The associated muscular damage, lesions of the vagus and its nuclei are discussed. It is deduced that the primary lesion must occur in the gut and that the other changes are secondary. The experimental evidence for the selective destruction of ganglion cells by four hours of ischaemia is cited and it is suggested that the areas of aganglionic gut could have their blood supply interrupted for this length of time. Between the 5th and 10th week of intra-uterine life the gut undergoes rotation through $270^\circ$ before it returns to the abdominal cavity. Temporary ischaemia at this stage would make either end of the gut ischaemic. Hirschsprung’s disease and the rare infantile achalasia would ensue and the same rotational effect could affect the duodenum. The various length of bowel affected and the numbers of ganglion cells lost are proportional to the type and severity of the ischaemia. Decompensation of such a congenital lesion, if only a proportion of the cells were destroyed, might occur 20 to 30 years later to explain some of the cases of achalasia. If the oesophagus and the rectum were equally affected by
ganglion cell loss the rectum would decompensate first and dilate, because of physiological differences partially associated with the solidity of the contents. But evidence indicates that many cases of achalasia may be caused by ischaemia occurring later in life when the blood supply is reduced by arterial obstruction from thrombosis or arteriosclerosis.

The experimental work of Barnard showed that ischaemia from an intra-uterine volvulus could cause intestinal atresia or stenosis. A common mechanism would explain the similarity of the anatomical and epidemiological distribution of atresia, stenosis and aganglionic bowel.

Oesophageal atresia associated with tracheo-oesophageal fistula occurs before the 5th week of intra-uterine life before the trachea and oesophagus are completely separated and the associated fistulas of the rectum probably occur at the same time. It is feasible but less likely that lesions with associated fistulas are associated with ischaemia and malrotation of the gut. Atresias without associated fistulas must occur later than the 5th week when the gut is separated from the surrounding structures.
The hypothesis is that temporary ischaemia for approximately four hours can
selectively destroy the ganglion cells of the gut without damaging the other tissues
permanently and cause an aganglionic segment. This may occur in the adult to
explain achalasia when the arterial supply is obstructed by thrombosis or
arteriosclerosis or as a congenital intra-uterine lesion to explain Hirschsprung's
disease. Many cases of achalasia may represent a decompensated intra-uterine
lesion. Depending on the duration of ischaemia, one of five lesions may result:

1. Aganglionic bowel
2. Stenosis
3. Type I atresia - septum, web or diaphragm
4. Type II atresia - band-like remnant
5. Type III atresia - disconnected blind end


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