CHEMICAL SPHINCTEROTOMY BY GLYCERYL TRINITRATE IN CHRONIC ANAL FISSURE A PLACEBO CONTROLLED STUDY.

THESIS

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Contents.

1. BACKGROUND.

Anal fissure is a painful condition affecting the anal canal. The majority of the acute fissures heal spontaneously. However, some of these acute fissures do not resolve but become chronic. Chronic anal fissures were treated traditionally by anal dilatation or by lateral sphincterotomy. However, both of these surgical treatments may cause a degree of incontinence in up to 30% of patients. Several recent trials have shown that nitric oxide donors such as glyceryl trinitrate [GTN] can reduce sphincter pressure and heal up to 70% of chronic fissures. **[J.H. Scholefield et al, 2003]**

2. AIM OF THIS STUDY.

The aim of this study is to clarify the role of chemical sphincterotomy by glyceryl trinitrate in the treatment of chronic anal fissure, compared with placebo in a randomized controlled trial.

3.PROLOGUE.

Anal fissure is a painful common condition of the anal region characterized by pain on defaecation, anal bleeding, and anal sphincter spasm.
Acute anal fissures are arbitrary designated as those with symptoms of less than six weeks duration. These fissures respond well to conservative treatment with stool softeners and attention to local hygiene. Most of these fissures heal spontaneously.
[Scholefield et al 2002]

However, a small proportion of acute fissures does not heal and become chronic fissures [traditionally defined as symptoms of more than six weeks duration].

The pathogenesis of chronic anal fissure is ill understood. The surgical dogma is that the passage of a hard stool bolus traumatizes the anal mucosa. This is a plausible initiating factor, but does not explain why only one in four patients report constipation, while symptoms may follow a bout of diarrhea. Alternative theories to the pathogenesis of chronic anal fissures have been postulated. **[Jonas and Scholefield, 2001]**
Manometric studies have shown that fissure occurs in patients with high resting anal pressure, this is thought to occur due to hypertonicity of the internal anal sphincter. **[Farouk et al., 1994]**
Some data suggest that anal fissure is associated with a local reduction in the blood flow, healing of anal fissures is associated with a return to normal anal canal pressures with normal blood flow measurements. **[Keighley, 2001]**

Unlike acute anal fissures, chronic anal fissures do not respond to dietary advice alone. The aim of the treatment is to alleviate sphincter hypertonia and improve blood flow to the ulcerated area.
[Watson SJ, et al 1996]

Lateral internal anal sphincterotomy has replaced anal stretching as the mainstay of treatment due to concerns over adverse effects on continence. Lateral sphincterotomy permanently lowers resting anal pressure and in doing so aids the healing of anal fissures. It may, however, be associated with minor temporary or permanent alterations in the control of gas, mucus and occasionally stool in up to 30% of patients **[Khubchandani IT, et al 1989]**

This has led to alternative therapeutic approaches, in particular, pharmacological, reversible sphincterotomy using topical agents such as botulinum toxin, calcium channel blockers and glyceryl trinitrate [GTN]. **[F.F. Palazzo, et al 2000]**

The most widely used topical agent is GTN. The latter is metabolized to nitric oxide and leads to sphincter muscle relaxation and reduction in the maximum anal resting pressure. This results in a reversible improvement in pectin perfusion and eliminates the risk of permanent anal incontinence associated with surgery. **[Schouten et al., 1994]**

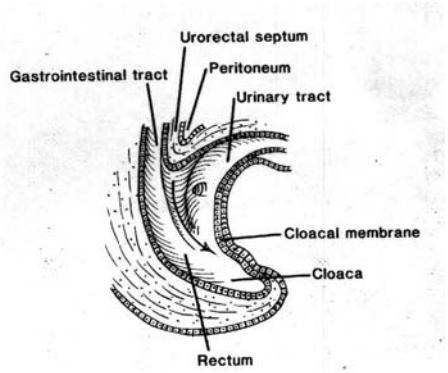
1
ANATOMY
OF THE ANAL CANAL.

1. EMBERYOLOGY

The hindgut, cloaca, proctodeal pit, and anal tubercles are the precursors of the structures of the anoderm. The hindgut forms the portion of the rectum cranial to the pubococcygeal line, whereas the cloaca forms the portion below it. The urogenital and intestinal tracts terminate in the cloaca before week 5 of gestation; fig 1-1.

At week 6, caudal migration of the urorectal septum separates the tracts. The cloacal part of the anal canal is lined by both ectodermal element [from the anal pit] and endodermal element [from the hindgut] and are separated by the anal membrane, which latter breakdown and is the origin of the anal transition zone.

FIG 1-1 the embryo at week 5 of gestation **[J.H.Pemberton, Shackelford's surgery of the alimentary tract third edition 1991]**



The anal tubercles are ectodermal in origin and become joined posteriorly and anteriorly to encircle the proctodeal pit. Anteriorly the tubercle forms part of the perineal body, which completely separates the rectum from the urogenital tract.

The external sphincter forms at the same time as the perineal body, the perineal body separate the early"cloacal sphincter" into urogenital and anal portions. The internal sphincter is formed later from enlarging fibers of the circular muscle of the rectum. During development, the external anal sphincter migrates caudally, whereas the internal anal sphincter migrates cephalad; fig 1-2.

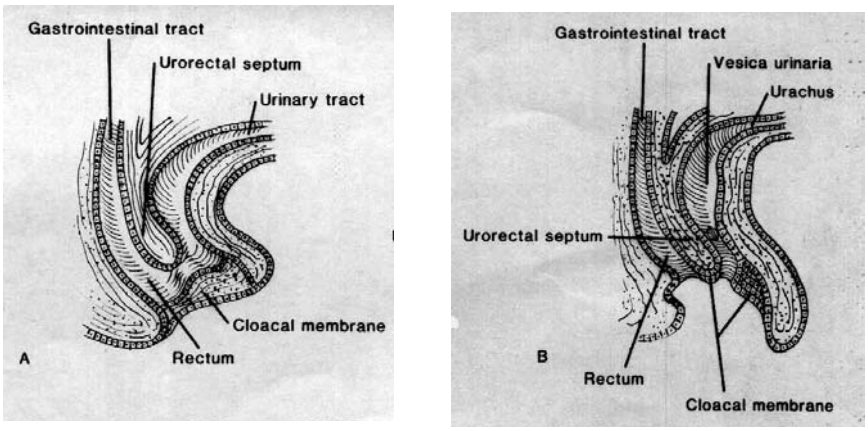


FIG 1-2; Embryo at week 6 to 7.The common cloacal membrane [A] has now been separated [B]
[J.H.Pemberton, Shackelford's surgery of the alimentary tract third edition 1991]

Finally it is generally agreed that the blood supply, venous return, and lymphatic drainage above the anal transition zone are portal in origin, whereas below this zone they are systemic**. [John H. Pemperton 1991**]

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2. THE ANUS, ANAL ORIFICE AND ANAL VERGE.

The anus is set in the diamond shaped perineum, on or just behind the transverse line which joins the ischial tuberosities. The anus has an anteroposterior direction and lies at the distal end of the natal cleft.
The skin around the anus is pigmented and is arranged in radiating folds. Normally the anus is closed, even when the patient is anaesthetized deeply, the edge of the anal orifice is known as the anal verge or margin.
[Sir Edward Hughes et al 1983]

3. THE ANAL CANAL.

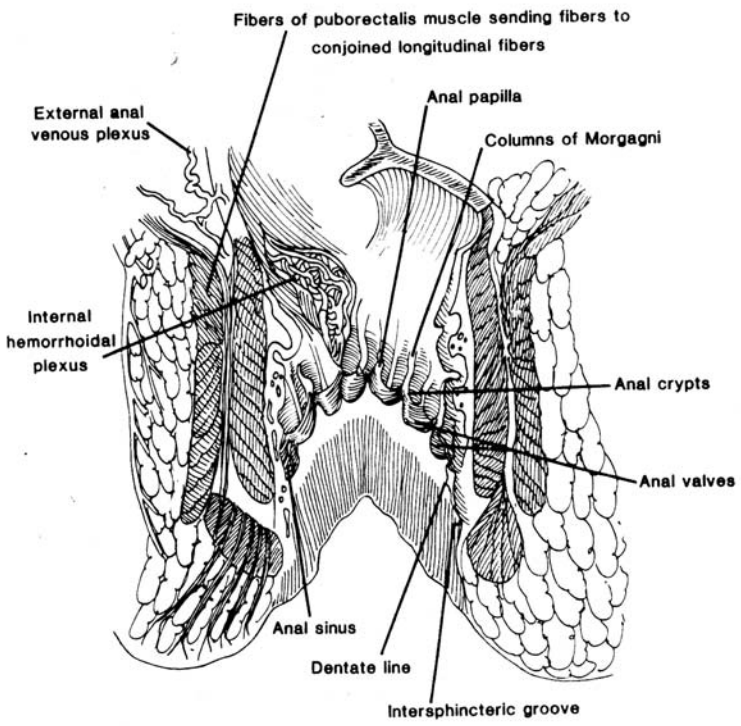


Fig 1-3: Anal canal. **[J.H.Pemberton, Shackelford's surgery of the alimentary tract third edition 1991]**

The surgical anal canal extends from the anal verge to the anorectal ring, and is 3-4 cm long [shorter anteriorly than posteriorly].

The strong, muscular anorectal rings the upper end of the sphincter muscle mass around the anal canal.

The anorectal ring is not an embryologic boundary, but it is recognized easily on clinical examination and is a landmark with considerable practical significance; fig 1-3.

The dentate line represents the upper limit of the anatomical anal canal, and the anorectal ring the upper level of the surgical anal canal.

[Sir Edward Hughes et al 1983]

4. RELATION OF THE ANAL CANAL.

POSTERIORLY: the canal is related to the coccyx with a certain amount of fibrous, fatty and muscular tissue intervening.
LATERALLY: there is the ischiorectal fossa on either side with its contained fat and the inferior haemorrhoidal vessels and nerves which cross it to enter the wall of the canal.
ANTERIORLY: IN THE MALE the canal is related to the central point of the perineum, the bulb of the urethra and the posterior border of the urogenital diaphragm [triangular ligament] containing the membranous urethra.
IN THE FEMALE: the canal is related in front to the perineal body and to the lowest part of the posterior vaginal wall.
[J.C.Goligher et al 1980]

5. EPITHELIUM OF THE ANAL CANAL.

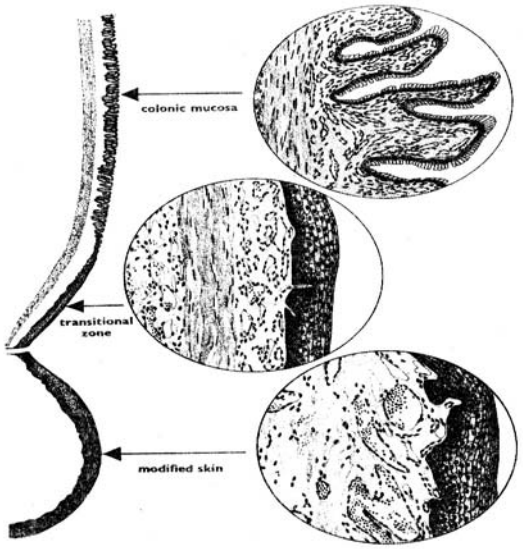
Approximately 2-3 cm cranial to the anal verge is a line of anal valves. This landmark is the pectinate or dentate line and is located at the junction of the middle and distal thirds of the internal sphincter. Above each valve is a pit or anal crypt. Connected to anal crypts are variable number of glands [four to ten] that traverse the submucosa to terminate in the submucosa, internal sphincter or the intersphincteric plane,
Cranial to the anal valves, but still in the anal canal, the mucosa is pleated into 12 to 14 columns [columns of Morgagni]. The mucosa above the valves in the area of the columns consists of several layers of cuboidal cells. This mucosa gives way, at a variable distance [0.5 cm to 1 cm] to a single layer of cuboidal columnar cells that is characteristic of rectal epithelium. The colour of the mucosa also changes: from 0.5 cm to 1 cm above the dentate line, the mucosa is deep purple changing to the characteristic pink of the rectal mucosa. This area above the dentate line is the anal transition zone.

Caudal to the dentate line, the anal canal is lined by modified squamous epithelium devoid of hair and glands, which appears smooth, thin, and stretched. Further caudally, this modified squamous epithelium changes to squamous epithelium with hair and glands at the anal verge. It is important to remember that none of the mucosal boundaries described here are at the same level at all places around the circumference of the anal canal.
[John H.Pemperton 1991]

6. MICROSCOPIC EXAMINATION OF ANAL CANAL

The lining membrane of the upper part of the anal canal has the typical appearance of colonic mucosa. The glands of Leiberkuhn are well developed, and are lined by goblet cells, although both glands and cells become fewer near the zone of modified mucosa. A fine lamina propria is separated by the muscularis mucosa from the submucosa.

Fig 1-4: microscopic features of the anal canal.
[Sir Edward Hughes, colorectal surgery, sir Edward Hughes, A.M. Cuthberston and M.K. Killingback, third edition, 1983]



At the upper edge of the opaque zone of modified mucosa the intestinal mucosa is replaced abruptly by stratified epithelium composed of cuboid or squamous cells. The stratified epithelium may contain areas of columnar epithelium. Mucous glands may be visible. The underlying connective tissue shows the same differentiation into lamina propria, muscularis mucosae and submucosa. There is no sweat or sebaceous glands or hair follicles.
At the dentate line it is common to see island of columnar epithelium. At this level anal glands extend outwards and distally into the subepithelial tissues.
Below the level of the dentate line the epithelium has a stratified squamous structure, sometimes with keratinization. There is no great difference between the epithelial layer of this zone and the previous one, although it is thicker and there are no columnar cell inclusions. The most notable difference is in the epithelial connective tissue. The lamina propria, muscularis mucosae and submucosal layers disappear at the dentate line, and are replaced by a vascular dense connective tissue containing a few muscle fibres. Sweat, and sebaceous glands and hair follicles are absent, but connective tissue papillary projections become a noticeable feature; fig 1-4.
Below this zone of modified skin the histological appearances are those of normal skin. **[Sir Edward Hughes et al 1983]**

7. THE PECTINATE LINE AND CHANGES IN THE SURGICAL ANAL CANAL

	Below the pectinate line	**Above the pectinate line**
Embryonic origin	Ectoderm	Endoderm
Anatomy		
Lining	Stratified squamous	Simple columnar
Arterial supply	Inferior rectal artery	Superior rectal artery
Venous drainage	Systemic, by way of inferior rectal vein	Portal, by way of superior rectal vein
Lymphatic drainage	To inguinal nodes	To pelvic and lumbar nodes
Nerve supply	Inferior rectal nerves [somatic]	Autonomic fibers [visceral]
Physiology	Excellent sensation	Sensation quickly diminishes
Pathology		
Cancer	Squamous cell carcinoma	adenocarcinoma
Varices	External haemorrhoids	Internal haemorrhoids

[J.E.Skandalakis et al 2000]

8. PARA-ANAL AND PARARECTAL SPACES.

There are several important potential spaces in the anorectal region that have surgical relevance

1. **The ischiorectal space** its apex is at the origin of the levator ani muscles from the obturator fascia. This space is

bounded inferiorly by the perineal skin, anteriorly by the transverse muscles of the perineum, posteriorly by the sacrotuberous ligament and gluteus maximus muscle, medially by the external anal sphincter and levator ani, and laterally by the external obturator muscle. In the lateral wall of this space is Alcock"s canal, through which the pudendal vessels and nerves course. There is a potential extension of this space anteriorly, which courses above the urogenital diaphragm. The contents of this space include fat, the inferior haemorrhoidal vessels and nerves, and the scrotal or labial vessels; fig 1-5, 1-7.

2. **The perianal space** surrounds the anal verge, is continuous with the fat of the buttocks laterally, and extends into the intersphincteric space. Its contents are the most caudal part of the external anal sphincter, the external haemorrhoidal plexus, and the inferior haemorrhoidal vessels. This space is bound down tightly because the corrugator cutis runs through it; fig 1-5, 1-7.

3. **The intersphincteric space** is a potential space between the internal and the external anal sphincter and is continuous with the perianal space; fig 1-7.

4. **The bilateral supralevator spaces** are bounded superiorly by the peritoneum, laterally by the obturator fascia, medially by the rectum, and inferiorly by the levator plate. These spaces can connect to each other posteriorly behind the rectum, deep to the anococcygeal raphe but superficial to the retrosacral fascia; fig 1-5, 1-6, 1-7.
5. **The submucous space** begins at the dentate line and extends cranially to join the submucosa of the rectum proper. The internal haemorrhoidal plexus is in this space.
6. **The superficial postanal space** is continuous with the superficial ischiorectal fossa posteriorly, deep to the skin but superficial to the anococcygeal ligament; fig 1-6.