PATHOPHYSIOLOGY AND MANAGEMENT OF DIABETIC GASTROPARESIS

Marie-France Kong
University Hospitals of Leicester
Leicester General Hospital

Gastroparesis

- ?inevitably associated with both intractable upper gastrointestinal symptoms and a poor prognosis
- once considered a rare sequela of diabetes mellitus in patients with longstanding diabetes complicated by symptomatic autonomic neuropathy

- New techniques to quantify gastric motility

- Rapid expansion of knowledge relating to gastric motor function in humans over the last 20 years

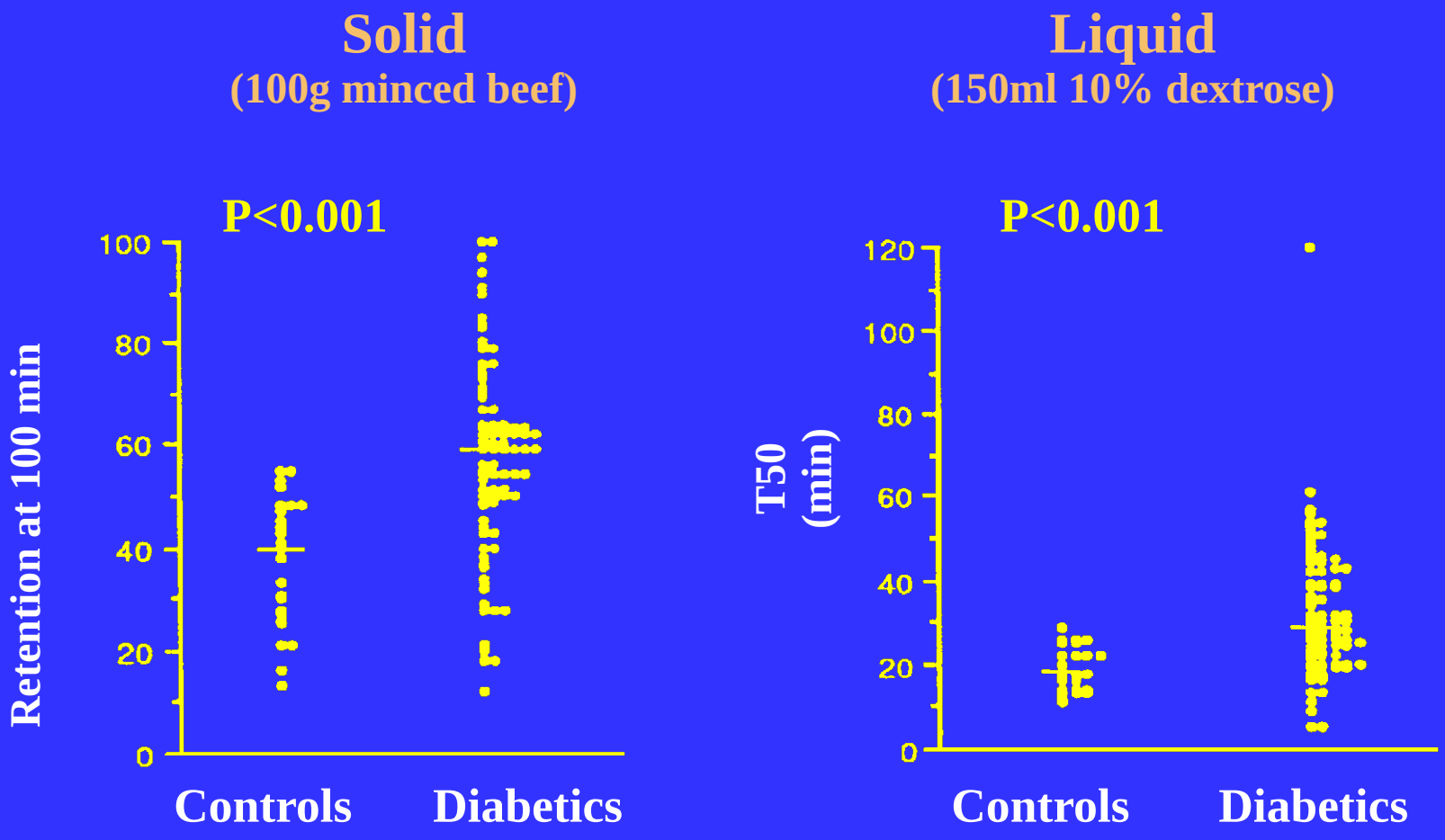
- Delayed gastric emptying represents a frequent, and clinically important, complication of diabetes mellitus

Prevalence of disordered gastric motility

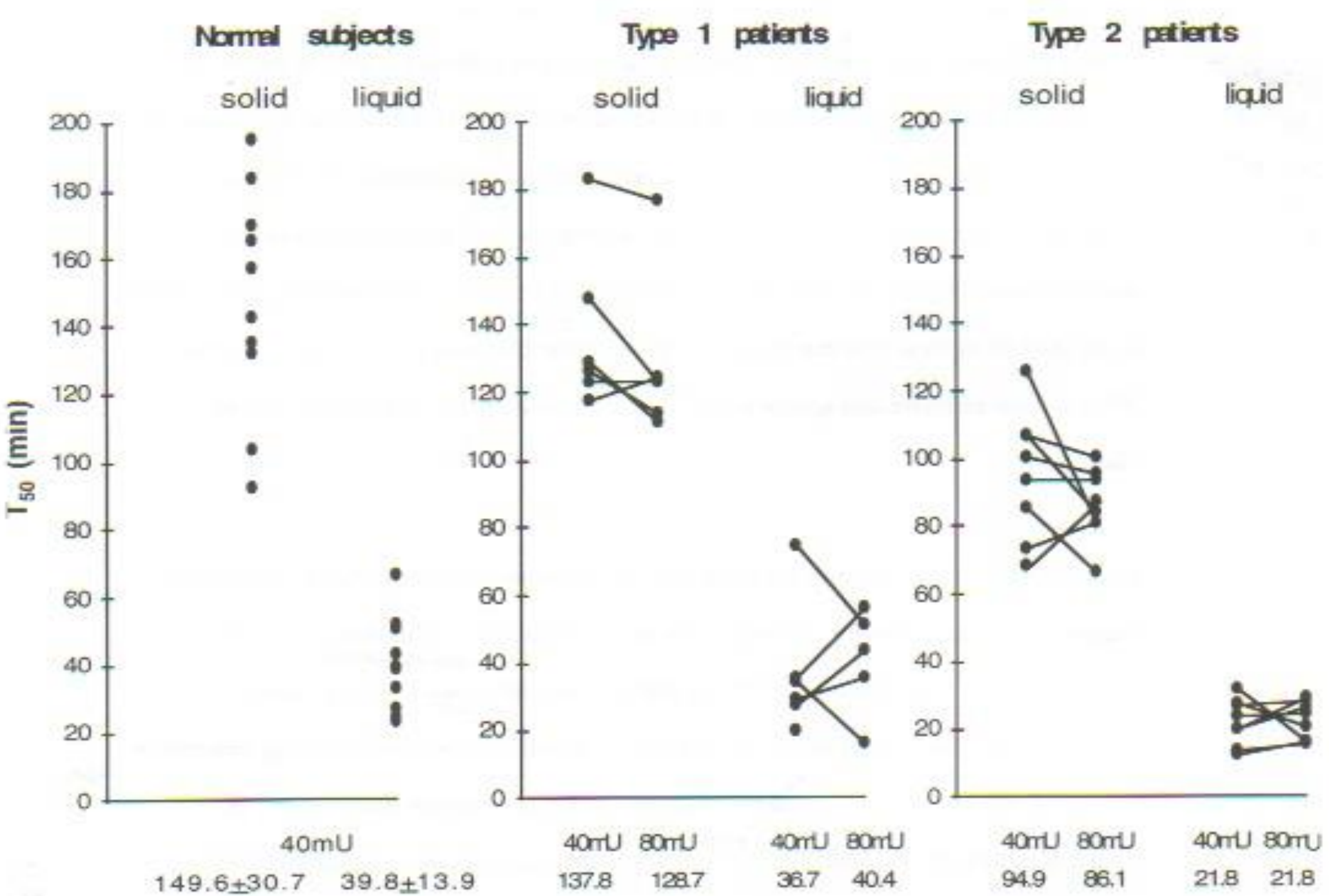
- Delayed gastric emptying in diabetes first reported by Boas in 1925
- Subsequent radiological studies by Ferroir in 1937. He noted 'X-ray examination showed that in diabetics ….the stomach motor responses are weaker than normal: contractions are slow, lack vigour and die out quickly'
- Rundles and colleagues (1945) reported that gastric emptying of barium was abnormally slow in 5 of 35 patients with clinical evidence of peripheral neuropathy

I believe that this syndrome – gastroparesis diabeticorum – is more often overlooked than diagnosed ….may adversely influence the satisfactory treatment of diabetes….. Attempts at treatment were uniformly unsuccessful.

P.Kassander, 1958



Gastric emptying of solid and liquid in both normal subjects and patients with diabetes mellitus. Horizontal lines represent median values. Gastric emptying is delayed in about 50% of patients (Horowitz et al 1991).


Normal subjects
Type 1 patients
Type 2 patients
solid
liquid
T_{50} (min)
0
20
40
60
80
100
120
140
160
180
200
40mU
149.6±30.7
39.8±13.9
40mU
80mU
137.8
128.7
40mU
80mU
36.7
40.4
40mU
80mU
94.9
86.1
40mU
80mU
21.8
21.8

Aetiology of disordered gastric emptying

- Pathogenesis of disordered GE now recognized to be multifactorial

- Dominant factors : Autonomic neuropathy and glycaemic control

Disordered gastric motility in diabetes was assumed to reflect irreversible vagal damage as patients who have had surgical vagotomy experience similar symptoms

Poor correlation between disordered motility and abnormal cardiovascular autonomic function (surrogate marker of the fn of the abdominal vagus)

?Evidence for selective autonomic impairment of the GI tract

More likely other factors are important

Blood glucose concentration

- Now recognized that acute changes in blood glucose concentration have a substantial, and reversible, effect on gastric (as well as oesophag intestinal, GB and anorectal) motility, in both healthy subjects and patien with diabetes mellitus

- Soler NG. Gastroparesis may be result of poor glycaemic control *per Diabetic gastroparesis without autonomic neuropathy.* (Diabetes Care 1980;3:200-

- Marked hyperglycaemia (BG ~15 mmol/l) affects motility in every region of the GIT

- In Type 1 patients and healthy subjects, acute hyperglycaemia (BG 16-20 mmol/l) slows GE of both solids and nutrient-liquids, compare with euglycaemia (5-8 mmol/l)

Clinical features

- Upper gastrointestinal symptoms and Malnutrition
- Changes in oral drug absorption
- Alterations in Glycaemic control

Gastrointestinal symptoms

- The prevalence of upper GI symptoms is high in both Type 1 and Type 2 diabetes, and probably exceeds that in the general population, especially in women

For e.g., in a study of 110 out-pts with long-standing Type 1 diabetes, *Schvarcz et al* reported that the prevalence of post-prandial fullness was 19%, compared with 8.5% in control subjects

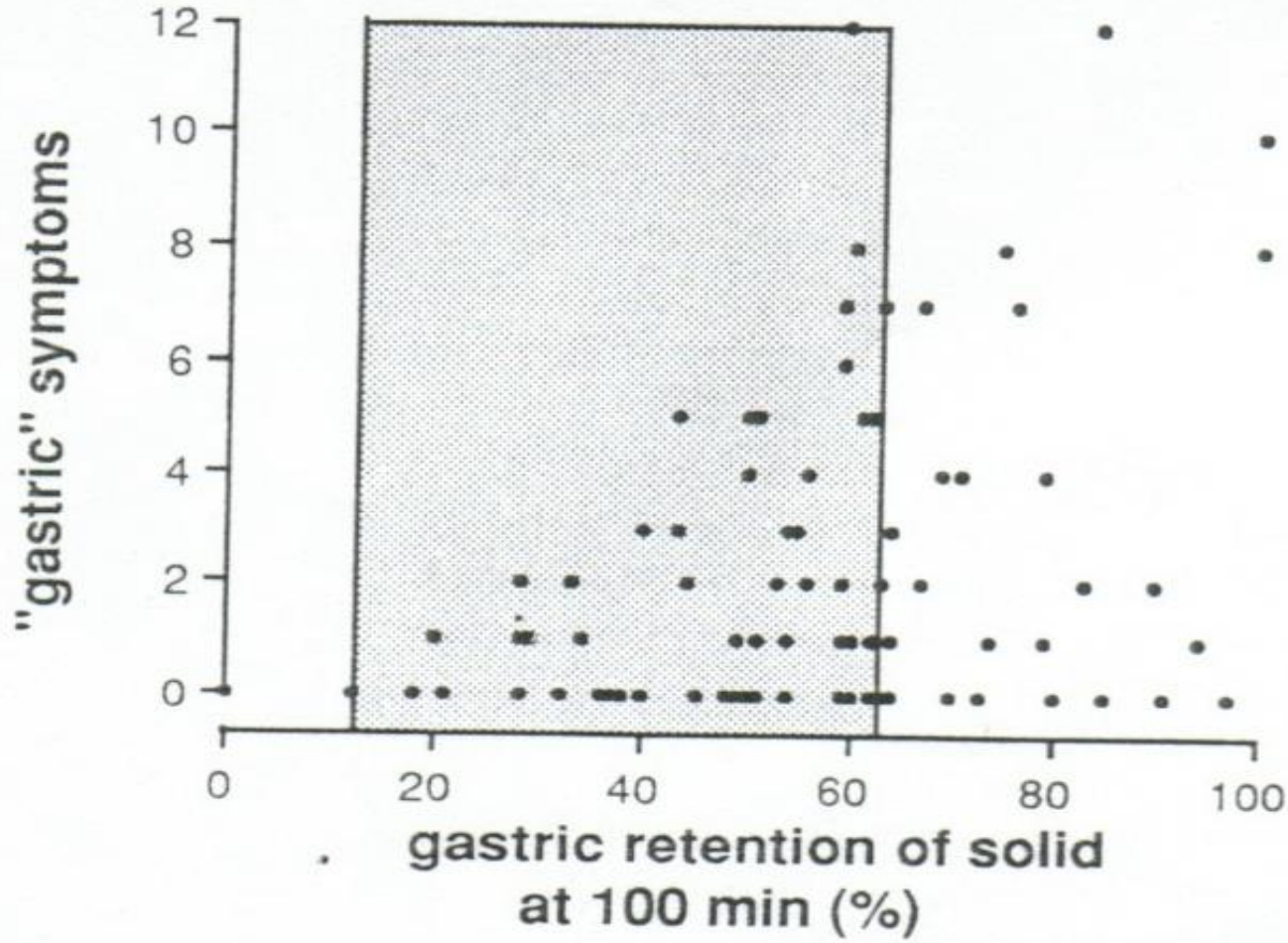


FIG 5.
The relationship ($r = 0.36$, $P < .01$) between symptoms referable to gastroparesis and the amount of a solid (^{99m}Tc–ground beef) meal remaining in the stomach 100 minutes after meal completion in 87 randomly selected ambulatory outpatients with diabetes mellitus (67 type I, 20 type II). The normal range is shown in the *shaded area*. (From Horowitz M, Maddox AF, Wishart JM, et al: *Eur J Nucl Med* 1991; 18:229–234. Used by permission.)

- Severe symptoms may remit spontaneously; may potentially relate to variations in GI motor or sensory function due to fluctuations in the BG level

- Also relatively poor relationship between the effects of prokinetic drugs on symptoms and gastric emptying

- Thus, while delayed GE occurs frequently in patients with diabetes, its role in the aetiology of GI symptoms is uncert

- Abnormal emptying should be regarded as a marker of GI motor abnormality, rather than the direct cause of symptoms

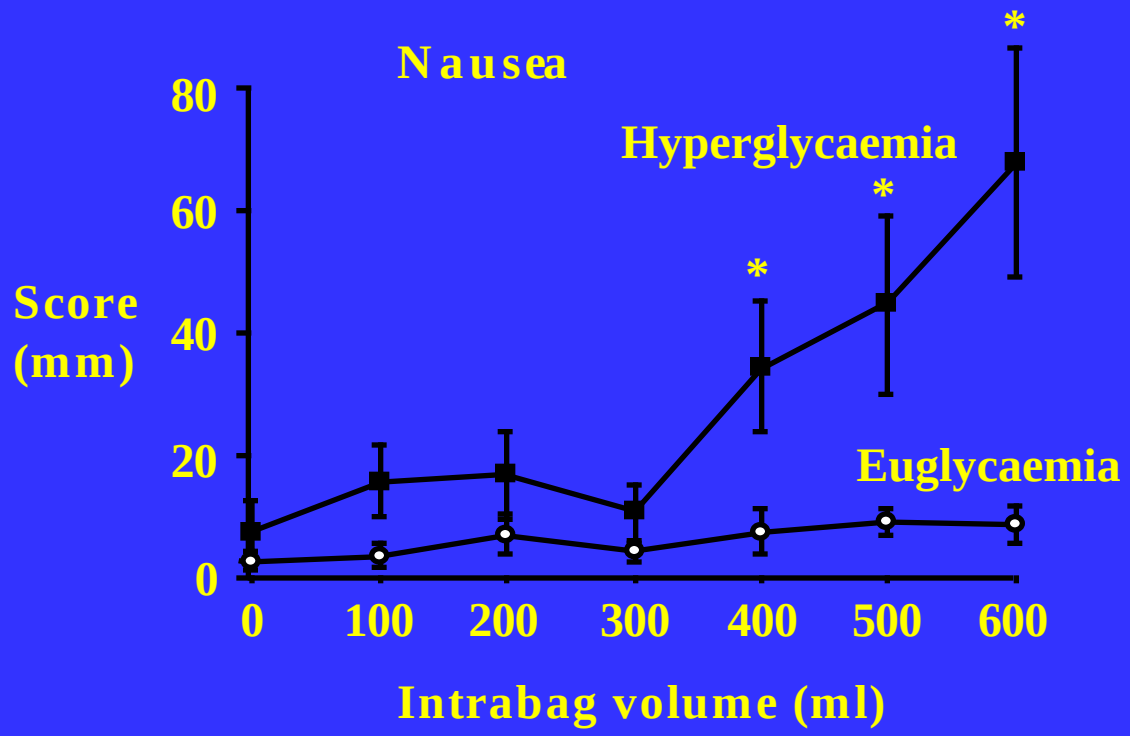
Potential determinants of GI symptoms in diabetes include

- disordered motility
- glycaemic control
- psychological and demographic variables
- autonomic neuropathy
- visceral hypersensitivity
- disordered gastric myoelectrical activity
- use of medications and
- *H. pylori* infection

- Symptoms may reflect disordered oesophageal, small intest or colonic motility, as well as psychiatric abnormality

- Psychological disorders occur frequently in diabetes and ma be associated with abnormal motility

- Uraemia may contribute to nausea and also affect gut motility
- Acute changes in BG concn have been shown to affect the perceptions of sensations arising from the stomach and duodenum



Score for nausea in normal subjects, after proximal stomach distension with a barostat during hyperglycaemia and euglycaemia. Sensations of nausea are greater during hyperglycaemia than euglycaemia (Hebbard et al 1996).

Impact of gastric emptying on glycaemic control

- *The retention of stomach contents in a diabetic obviously may cause confusion as far as food intake and utilization are concerned.*

P. Kassander, 1958

Diagnosis

- ? When to evaluate diabetic patients for disordered gastric motility
  (GI symptoms common, not strongly predictive of disordered GE or motility)

- Physical examn usually unremarkable
  In severe cases succussion splash and/or gastric distension

- Appropriate investigations to identify other causes of upper GI sympt

- Upper GI endoscopy usually required to exclude gastric outlet, or duodenal obstruction, as well as mucosal disorders

- The vomitus may contain food that has been eaten many hours earlier

Causes of gastroparesis

Transient delayed GE

- Drugs, e.g. morphine, nicotine
- Postoperative ileus
- Viral gastroenteritis
- Electrolyte abnormalities - ↑BG, ↓K, ↓Mg
- Hypothyroidism, hyperthyroidism, hypopituitarism, Addison's disease
- Herpes Zoster
- Critical illness
- Pregnancy

Chronic gastric stasis

- Diabetes mellitus
- Idiopathic/functional dyspepsia
- Post-surgical, e.g. vagotomy
- Gastro-oesophageal reflux
- Atrophic gastritis
- Progressive systemic sclerosis
- Chronic idiopathic intestinal pseudo-obstruction
- Myotonia dystrophica
- Dermatomyositis/polymyositis
- SLE
- Duchenne's muscular dystrophy
- Spinal cord disease
- Liver disease
- Parkinson's disease

Methods to assess gastric motor function

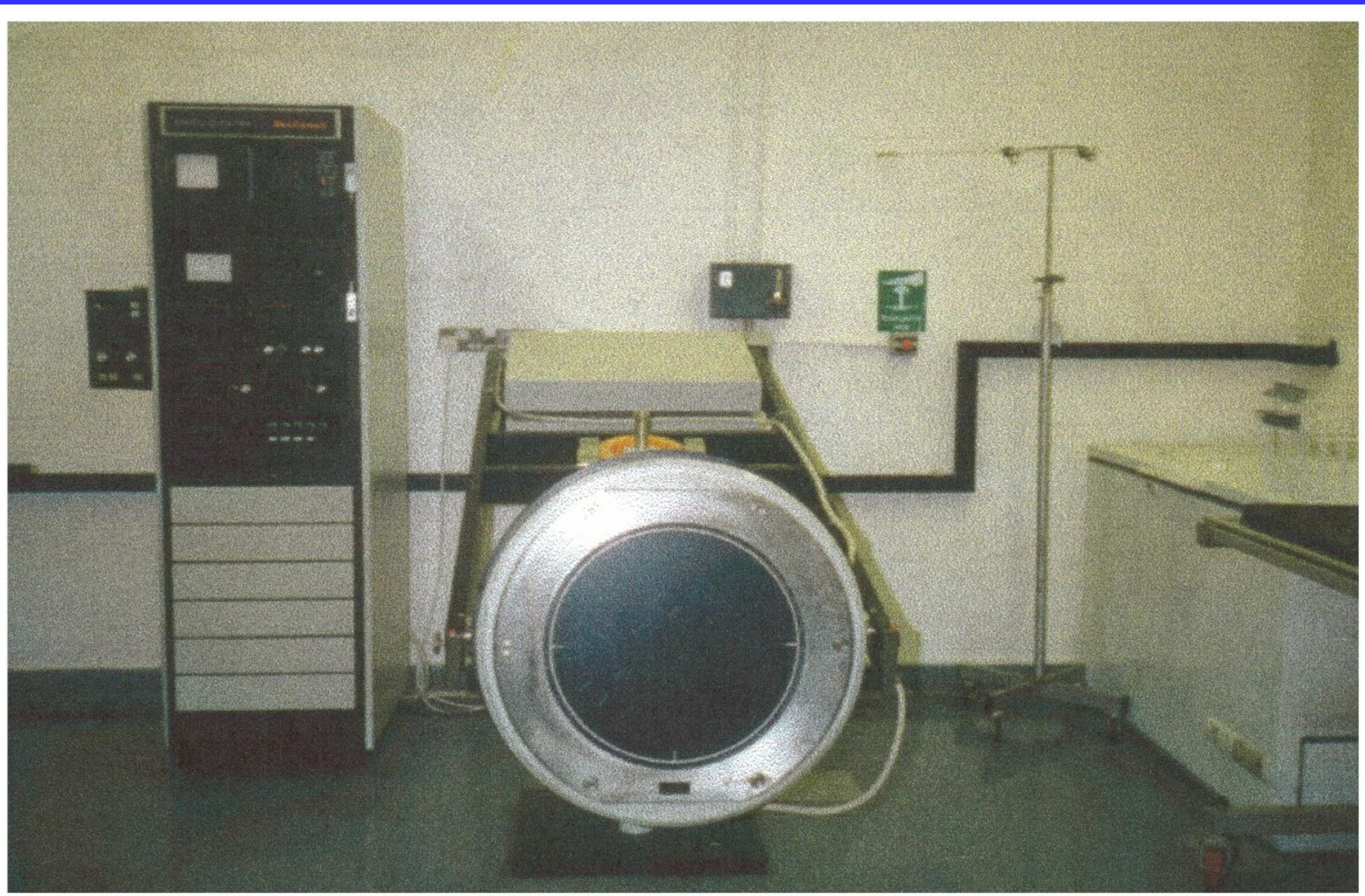
1. Measurement of gastric emptying

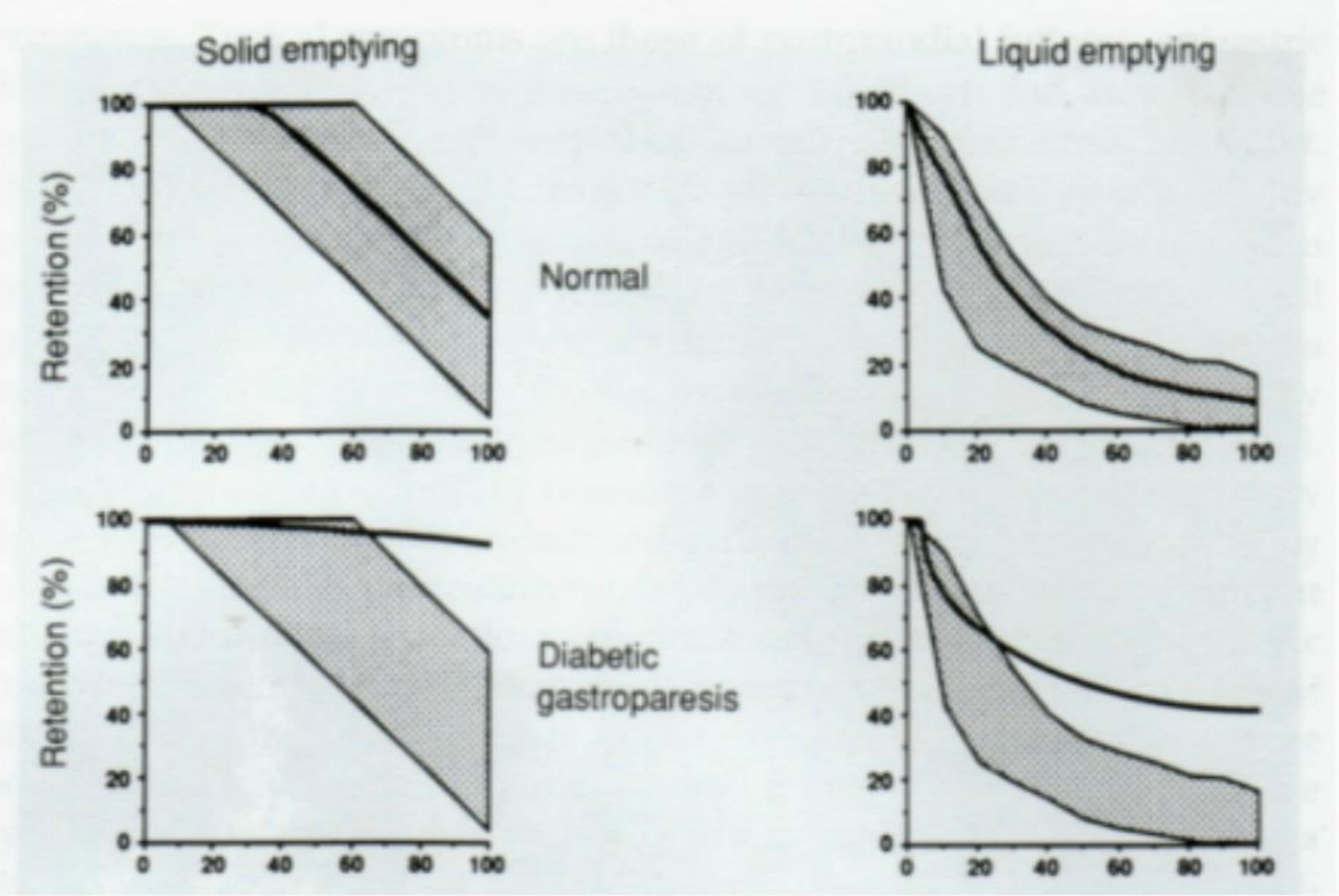
- Scintigraphy
- Ultrasound
- Radiology
  Liquid barium sulphate
  Radio-opaque markers
- Radioisotope breath tests
- Magnetic resonance imaging
- Applied potential tomography/epigastric impedance
- Pharmacokinetics of oral drug absorption
- Intubation/aspiration of gastric contents

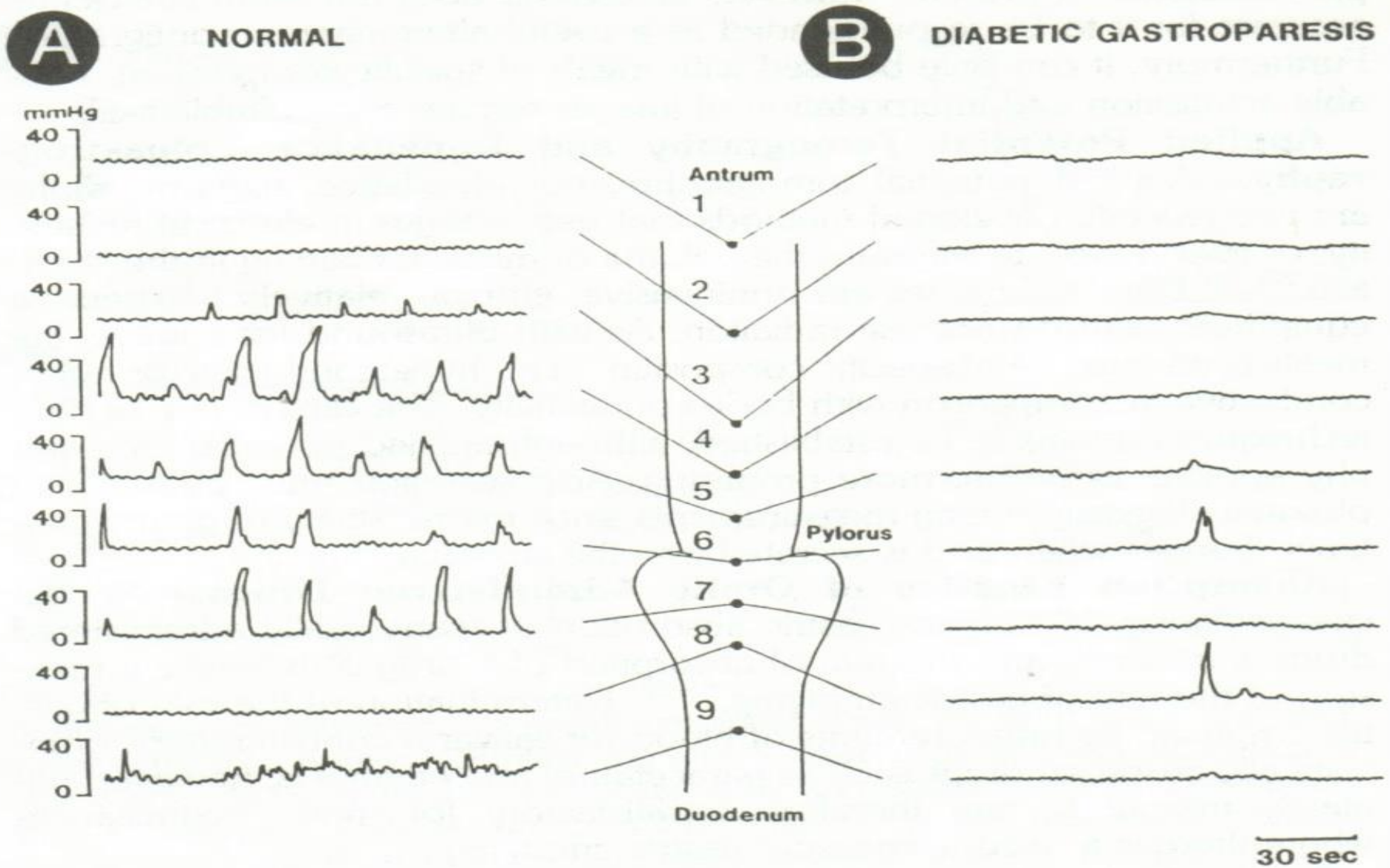
2. Manometry

3. Electrogastrography

Images acquired on computer, usually for 2-3 hours, via a gamma camera which detects radioactivity in the meal




Solid emptying
Liquid emptying
Retention (%)
Normal
Retention (%)
Diabetic
gastroparesis
0
20
40
60
80
100


A
NORMAL
B
DIABETIC GASTROPARESIS
mmHg
40
0
Antrum
1
2
3
4
5
6
Pylorus
7
8
9
Duodenum
30 sec

Modulation of GE to improve glycaemic control

- Dietary or pharmacological means to minimize post-prandial glucose excursions and optimize glycaemic control

- In Type 1 diabetes try and improve co-ordination between nutrient absorption and action of exogenous insulin

- Type 2 DM – dietary modifications to slow CHO absorption
  For e.g. an increase in dietary fibre improves glycaemic control
  Magnitude of this improvement has been shown to be comparable to t
  achieved by OHAs
  Slowing of GE likely to mediate this effect

- Pharmacological interventions
  Prokinetic drugs – e.g. erythromycin, cisapride, metoclopramide
  Agents which slow GE – e.g. CCK, pramlintide, GLP-1

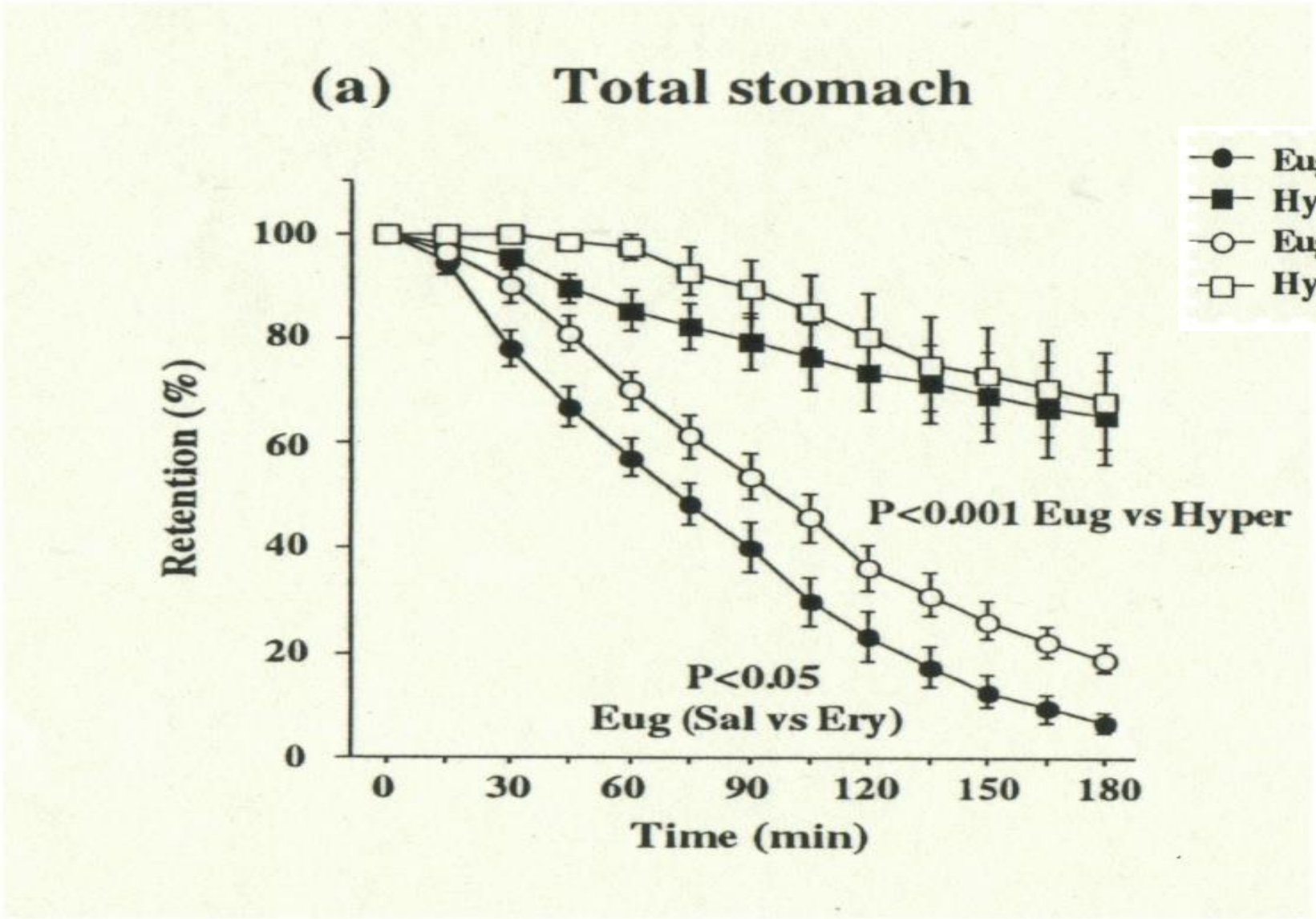
Management of gastroparesis associated with gastrointestinal symptoms

- Often challenging
- Increased prevalence of oesophageal, as well as gastric, candidiasis
- Presence of reflux oesophagitis does not exclude concurrent gastroparesis
- If above investigations unremarkable, GE should be measured, as this enables therapy to be targeted
- Because of poor predictive value of symptoms, objective measurement is required for the diagnosis of gastroparesis

Use of prokinetic drugs

- Mainstay of therapy (domperidone, metoclopramide, erythromycin)
- Dose-related improvements in GE; mechanisms of action differ
- Response tends to be greater when GE is more delayed
- Few controlled studies to evaluate effects of prolonged Rx (>8 wks)
- Improvement in symptoms but ?erythromycin
  - In general, poor correlation between effects on symptoms and GE
  - Little information whether symptomatic response differs between pts with and w/out delayed emptying
  - Likely some patients with normal GE also respond to prokinetic Rx
- Erythromycin most potent drug when given i/v (in doses of< 3mg/kg)
  - may be particularly useful in the initial phase of management
  - Oral suspension may have more efficacy than tablet

Gastric motor response attenuated markedly during ↑BG in both healthy subjects and patients with diabetes

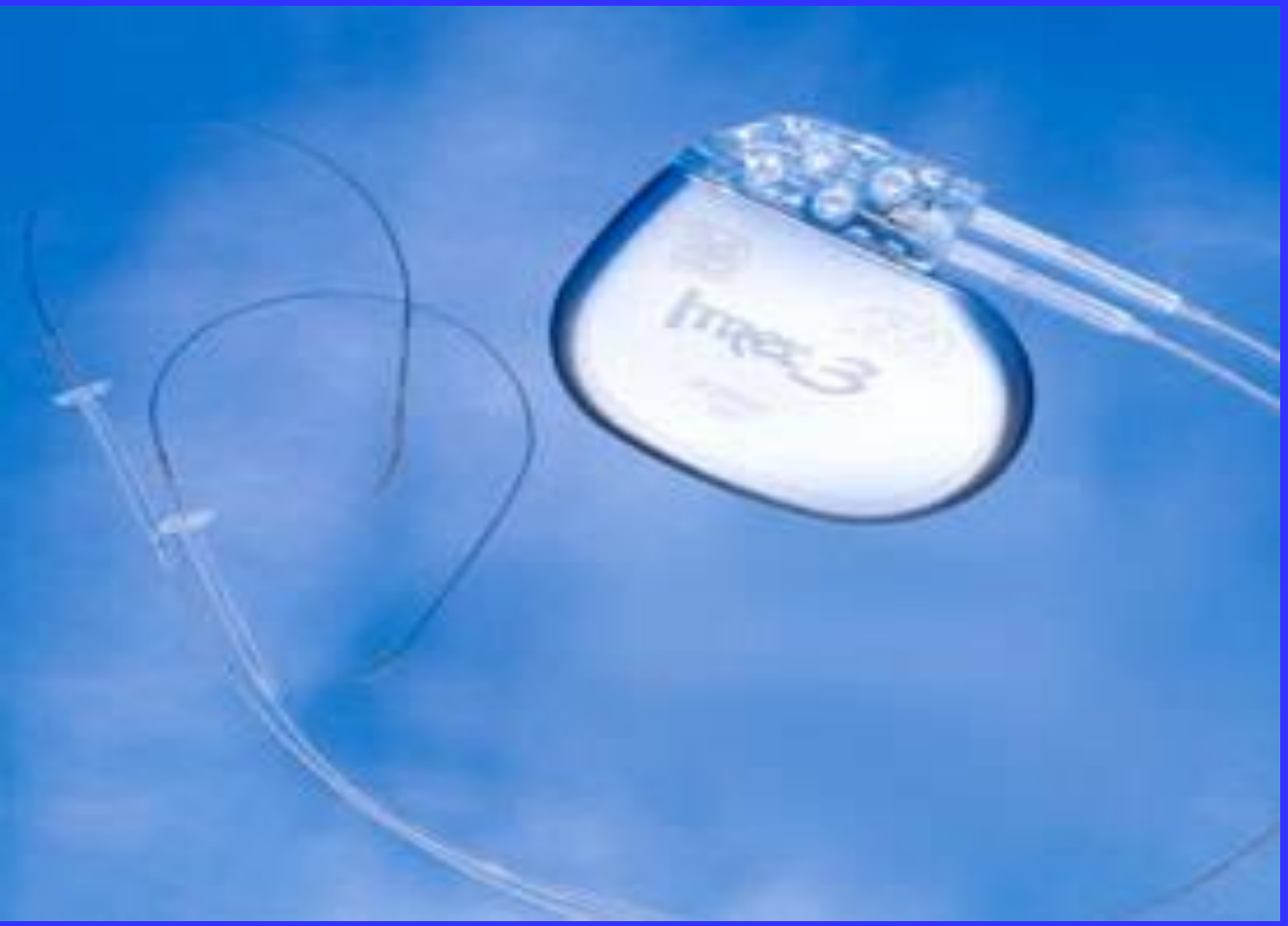


Jones et al 1999

Refractory cases

- Rx of symptomatic gastroparesis not uniformly satisfactory
- Placement of feeding jejunostomy may be required to maintain nutrit
- Surgery should be avoided; may be associated with deterioration
- Unpredictable clinical course argues vs use of aggressive therapy
- Uncontrolled data – pancreatic transplantation (known to have beneficial effects on autonomic function) may improve both GE and symptoms
- Potential role of gastric electrical stimulation

GES system with neurostimulator leads



Under GA, stimulating electrode of each intramuscular lead is implanted into the muscle wall of the antrum, 10 cm proximal to the pylorus, on the greater curvature.

The connector end of each lead is attached to the neurostimulator which is then placed s/c in the abdominal wall.

Intra-operative OGD to confirm proper lead position and to rule out mucosal electrode placement.

Device switched on by programmer, who sets the rate and amplitude of the system.

SUMMARY

- Gastric emptying is abnormally slow in ~30-50% of outpatients with long-standing Type 1 or Type 2 diabetes; the magnitude of this delay is modest in many cases

- Upper GI symptoms occur frequently and affect quality of life adversely in patients with diabetes

- The relationship between symptoms and the rate of gastric emptying is weak

- Acute changes in blood glucose concentration affect both gastric motor function and upper GI symptoms

- Gastric emptying is slower during hyperglycaemia when compared with euglycaemia and accelerated during hypoglycaemia

- The blood glucose concentration may influence the response to prokinetic drugs

- The rate of gastric emptying is a major determinant of post-prandial glycaemic excursions in healthy subjects, as well as in Type 1 and Type 2 patients

- A number of therapies currently in development are designed to improve post-prandial glycaemic control by modulating the rate of delivery of nutrients to the small intestine