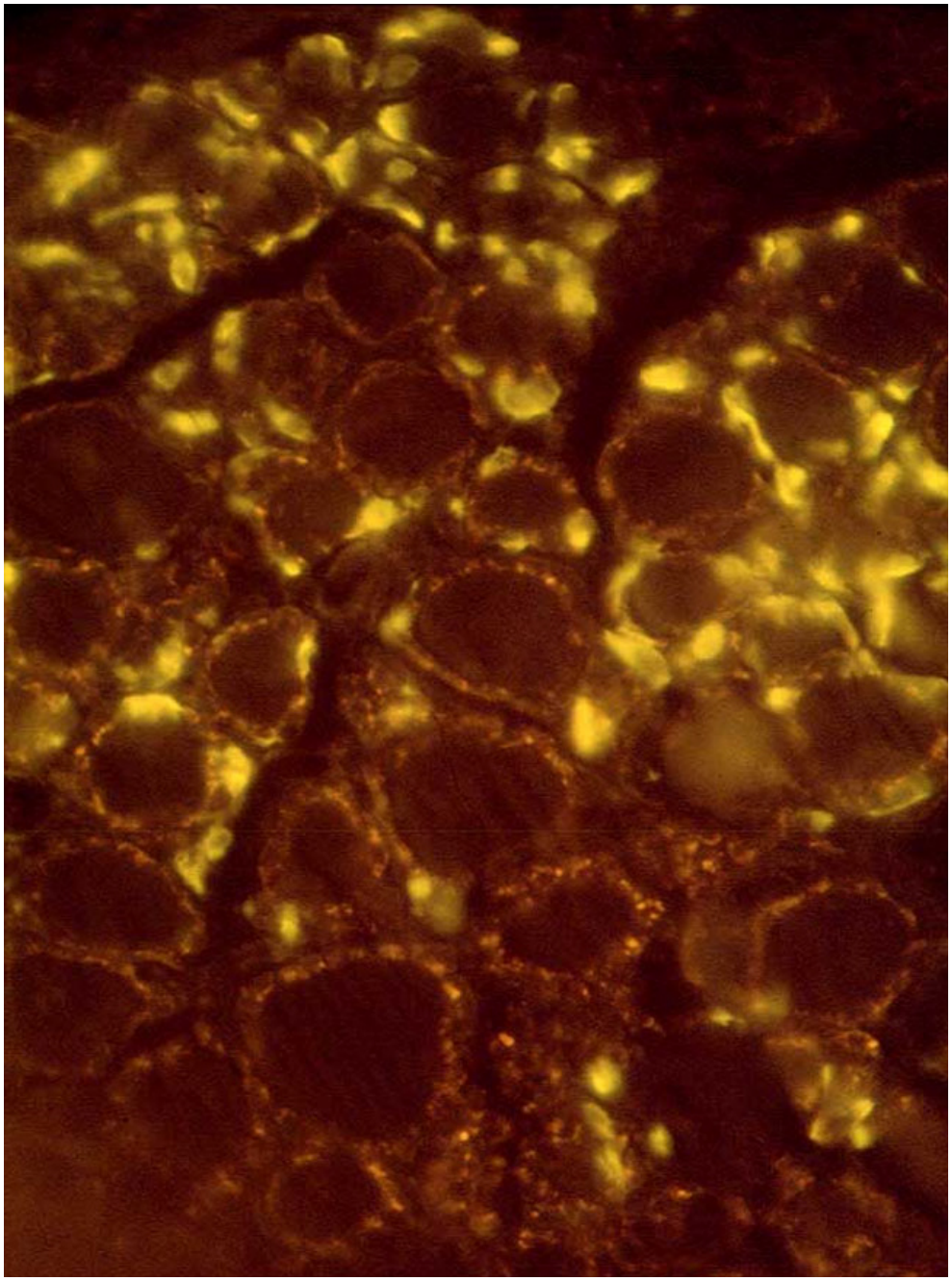
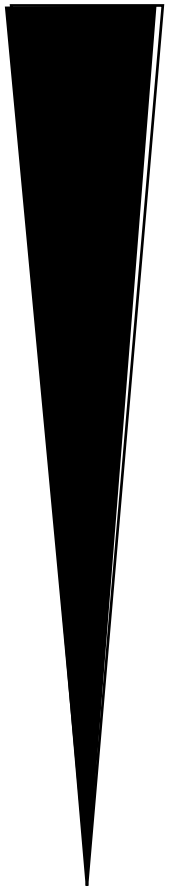
APUDoma

- Amine
- Precursor
- Uptake
- Decarboxylation

Pearse, AGE, *Vet Rec*, 79:587-590, 1966



Bussolati, *Endocr Pathol*, 25:133-140, 2014

Type	Localization	%	Frequency	Malignancy %
Carcinoid	Ileum	(90)		100
Syndrome	Pancreas	(10)		100
Insulinoma	Pancreas			5
Gastrinoma	Pancreas	(60)		50-80
	Duodenum	(25)		
	Other	(15)		
VIPoma	Pancreas	(90)		90
	Other	(10)		
Glucagonoma	Pancreas			90
Somatostatinoma	Pancreas	(56)		90
	Duodenum	(44)		
PPoma	Pancreas			90
GRFoma	Pancreas			100

Arnold et al, *Digestion*, 1994

AJCC Staging Classification

T1	**Limited to the pancreas, ≤2 cm in greatest dimension**
T2	**Limited to the pancreas, >2 cm in greatest dimension**
T3	**Beyond the pancreas but without involvement of the superior mesenteric artery**
T4	**Involvement of the celiac axis or superior mesenteric artery (unresectable tumor)**
N0	**No regional lymph node metastasis**
N1	**Regional lymph node metastasis**
M0	**No distant metastasis**
M1	**Distant metastasis**

Luo et al, *J Clin Oncol* 35:274-280, 2017

ENETS Staging Classification

T1	**Tumor limited to the pancreas, <2 cm**
T2	**Tumor limited to the pancreas, 2-4 cm**
T3	**Tumor limited to the pancreas, >4 cm, or invading the duodenum or common bile duct**
T4	**Tumor invades adjacent structures**
N0	**No regional lymph node metastasis**
N1	**Regional lymph node metastasis**
M0	**No distant metastasis**
M1	**Distant metastasis**

Luo et al, *J Clin Oncol* 35:274-280, 2017

AJCC

Stage	T	N	M
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1-3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

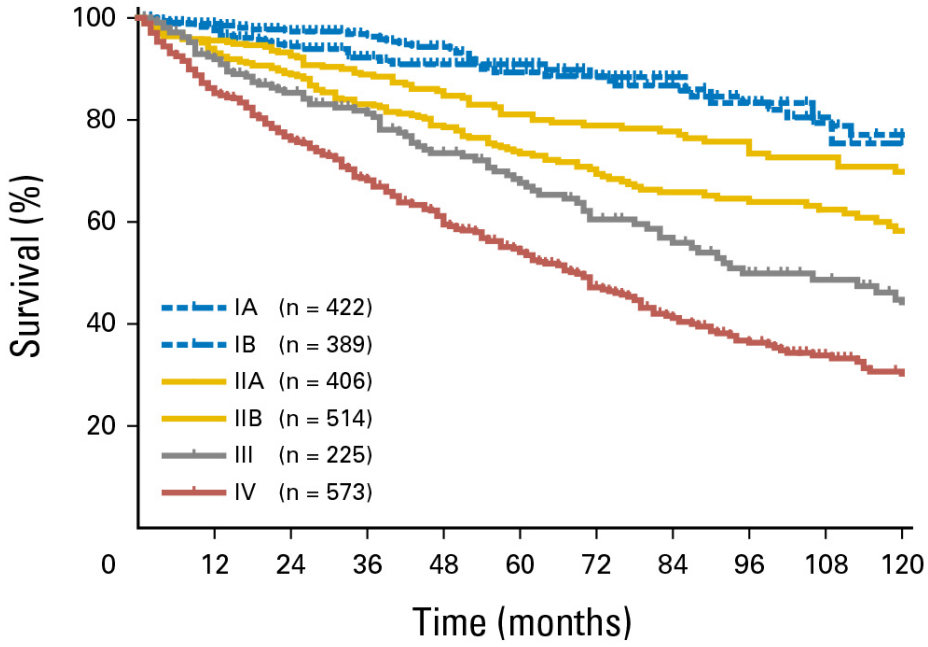
Luo et al, *J Clin Oncol* 35:274-280, 2017

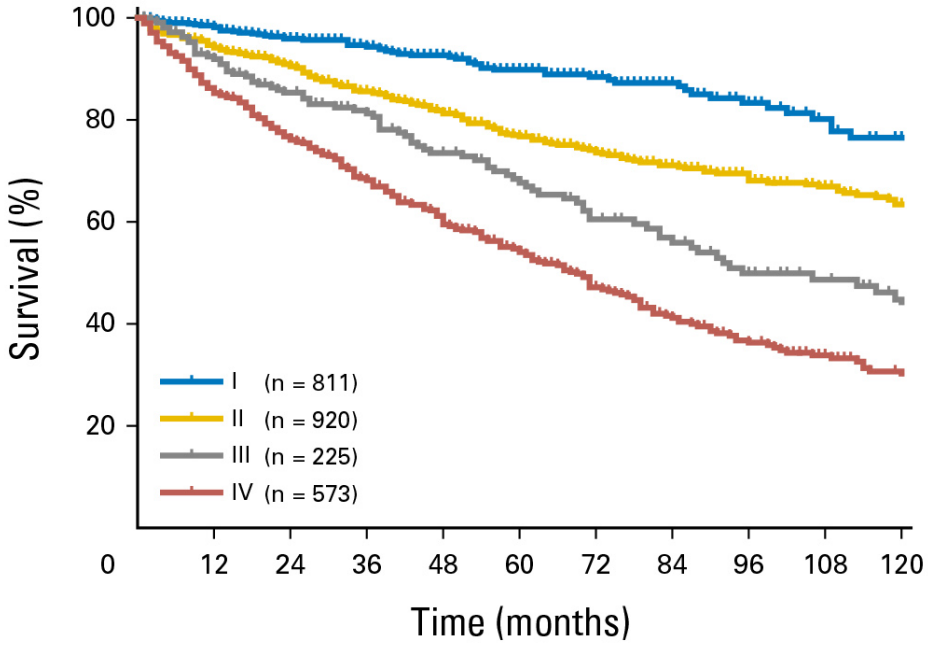
mENETS

Stage	T	N	M
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1-3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Luo et al, *J Clin Oncol* 35:274-280, 2017

mENETS





Luo et al, *J Clin Oncol* 35:274-280, 2017

WHO Grading System of pNETs

	G1	G2	G3
Ki-67 index	<3%	3-20%	>20%
Mitotic count	<2/10 High power field (HPF)	2-20/10 HPF	>20/10 HPF

Orditura et al, *Internat J Surg* 28:S156-S162, 2016

Table 2. Prevalence of common gene mutations for well-differentiated PNENs.

Gene	Jiao et al. [26]	Raj et al. [33]
MEN1	44%	61%
ATRX	18%	25%
DAXX	25%	41%
PTEN	7%	11%
TSC1/TSC2	9%	18%
PIK3CA	1%	NA
ARID1A	NA	14%
SETD2	NA	21%

pMENs, pancreatic neuroendocrine neoplasms; NA, not available.

Ohmoto et al, ***Int J Mol Sci***, 18:143-159, 2017

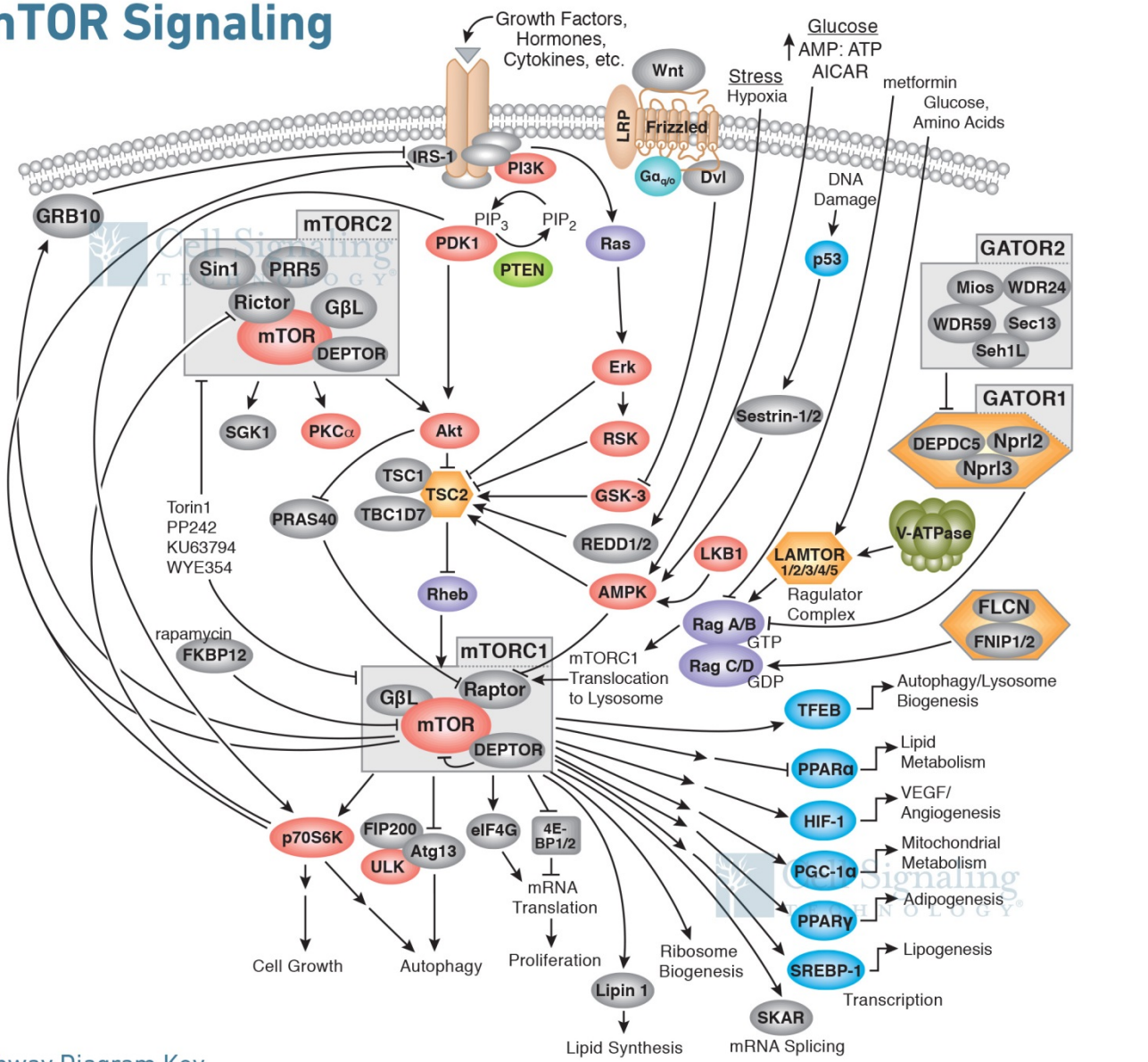
Table 3. Prevalence of common gene mutations for pNEC by targeted-sequencing data.

Gene	Yachida et al. [35]	Bergsland et al. [38]
TP53	57%	18%
RB1	71%	10%
CDKN2A	0%	21%
CDKN2B	NA	16%
KRAS	29%	7%
MEN1	NA	33%
DAXX	NA	20%

pNEC, pancreatic neuroendocrine carcinoma; NA, not available.

Ohmoto et al, ***Int J Mol Sci***, 18:143-159, 2017

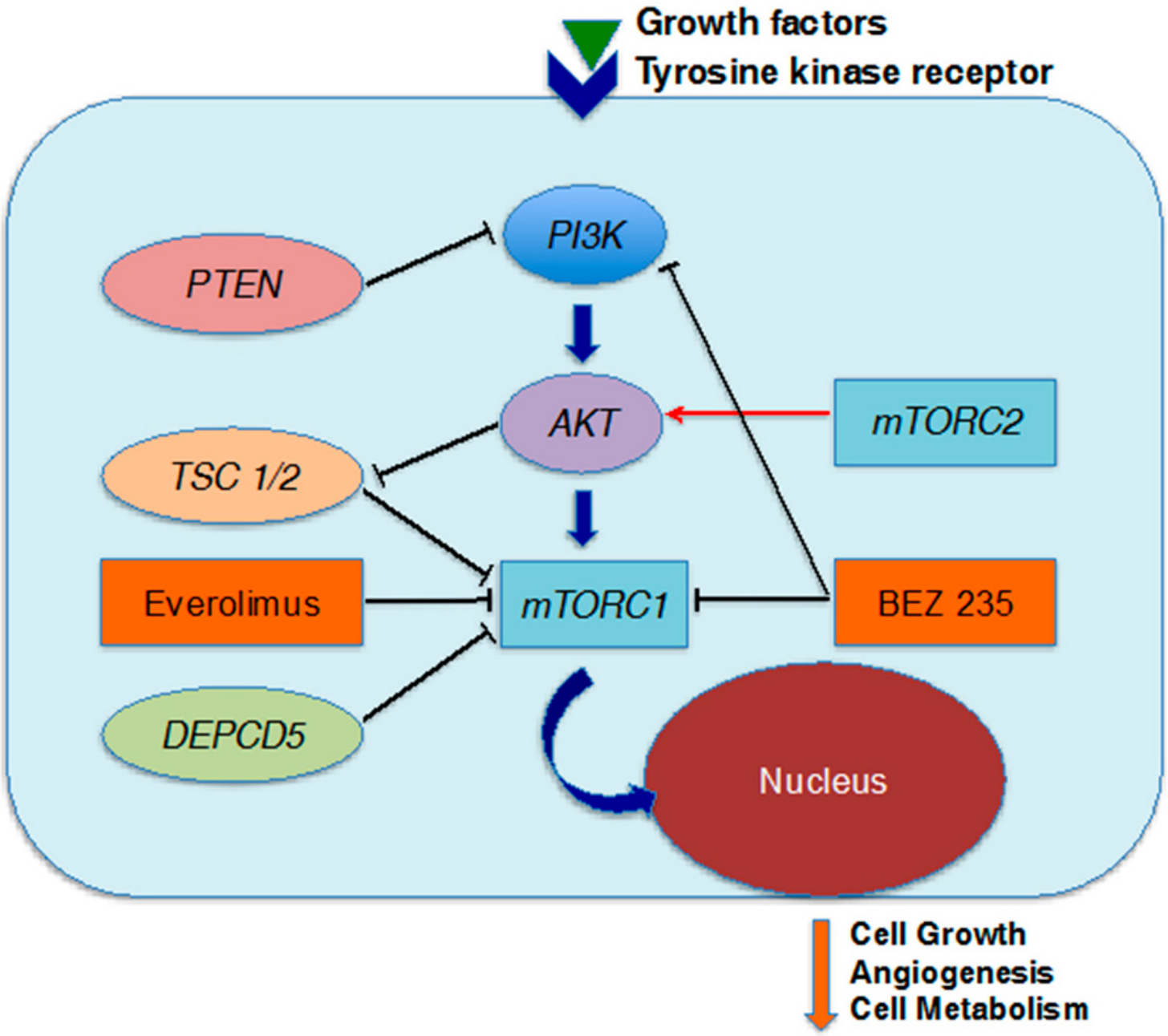
mTOR Signaling



Pathway Diagram Key

- Direct Stimulatory Modification
- Direct Inhibitory Modification
- Multistep Stimulatory Modification
- Multistep Inhibitory Modification
- Tentative Stimulatory Modification
- Tentative Inhibitory Modification
- Direct Inhibitory Modification
- Multistep Stimulatory Modification
- Multistep Inhibitory Modification
- Tentative Stimulatory Modification
- Transcriptional Inhibitory Modification

- Kinase
- Transcription Factor
- Receptor
- pro-apoptotic
- GAP/GEF
- G-protein
- Deacetylase
- Phosphatase
- Caspase
- Enzyme
- pro-survival
- GTPase
- Acetylase



Ohmoto et al, *Int J Mol Sci*, 18:143-159, 2017

Hereditary pNETs and Syndromes

Syndrome	Gene Alteration	% pNETs	Type NET
MEN1	11q13: Menin	20-80%	Gastrinoma (54%) Insulinoma (18%) Glucagonoma (3%) VIPoma (3%) Non functional pNETs
Von Hipple Lindau Disease (VHL)	3q25	10-17%	Non functional pNETs (98%)
NF-1 Von Recklinghausen	17q11.1: neurofibromin	0-10%	Duodenal NET, rare pNETs
Tuberosis Sclerosis	9q34: hamartin (TSC1) and tuberin (TSC2)	Rare	Non functional pNETs

Orditura et al, *Internat J Surg* 28:S156-S162, 2016

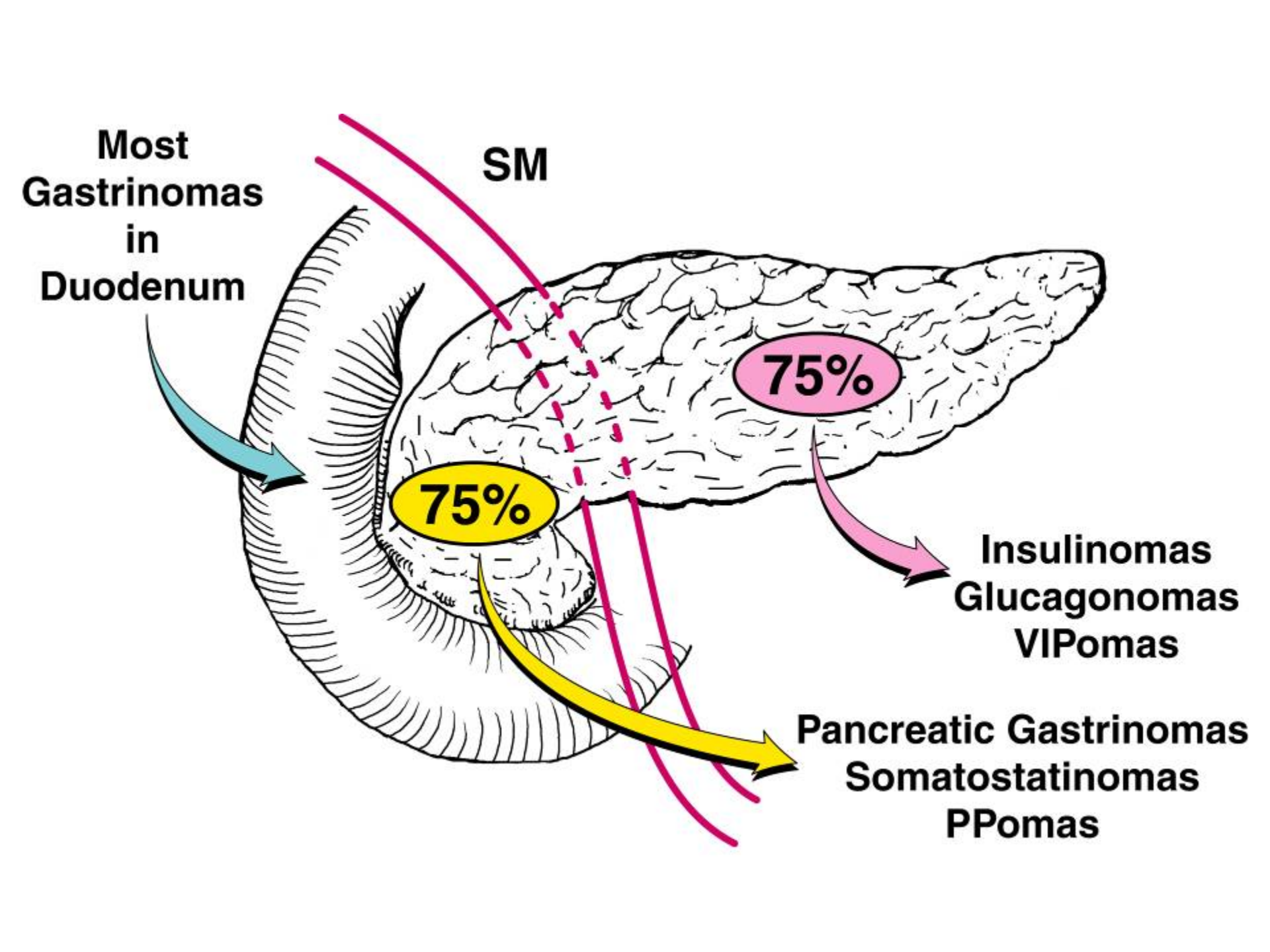
Functional pNETs

Type of Tumor	Secretion	% pNETs	Main Symptoms
Insulinoma	Insulin	30-40%	Whipple triad
Gastrinoma	Gastrin	16-30%	Zollinger-Ellison syndrome
Glucagonoma	Glucagon	<10%	Migratory necrolytic erythema, diarrhea
VIPoma	VIP	<10%	Verner-Morrison syndrome
Somatostatinoma	Somatostatina	<5%	Diabetes, steatorrhea, cholelithiasis

Orditura et al, *Internat J Surg* 28:S156-S162, 2016

Endocrine Tumors of the Pancreas

Islet Cells	Secreted Agent	Tumor and Syndrome
Alpha	Glucagon	Glucagonoma (diabetes, dermatitis)
Beta	Insulin	Insulinoma (hypoglycemia)
Delta	Somatostatin	Somatostatin (mild diabetes)
D	Gastrin	Gastrinoma (peptic ulcer disease)


Most Gastrinomas in Duodenum
SM
75%
75%
Insulinomas
Glucagonomas
VIPomas
Pancreatic Gastrinomas
Somatostatinomas
PPomas

Efficacy of Localization of Endocrine Tumors of the Pancreas and Duodenum

	True Positives (%)
Noninvasive	
Ultrasonography	23
Octreotide radioimaging (SRS)*	86
CT	43
MRI	26
Invasive	
Endoscopic ultrasonography	82
Selective angiography	56
Portal venous sampling	76
Provocative angiography†	65

*Rarely for melanoma

†Calcium for insulinoma; secretin for gastrinoma

Thompson and Townsend, *Sabiston Textbook of Surgery*, 17th Edition, p. 1003, 2004

Insulinoma

1902	Nichols	islet adenoma
1922	Banting & Best	insulin
1927	W.J. Mayo	unresectable islet carcinoma
1929	R. Graham	surgical cure of insulinoma
1935	Whipple‘s Triad	sx of hypoglycemia; low blood sugar; relief of sx with glucose

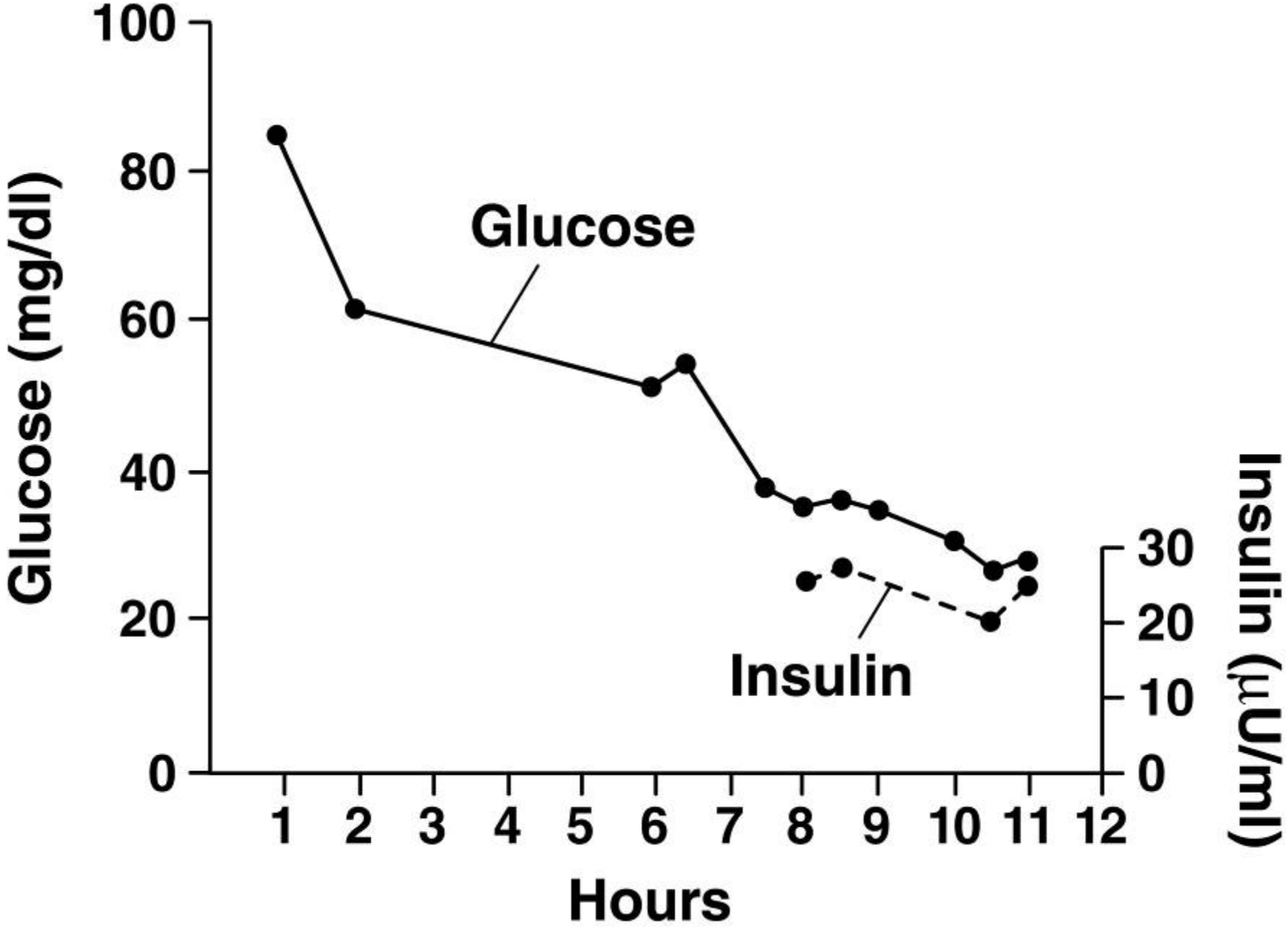
Insulinoma

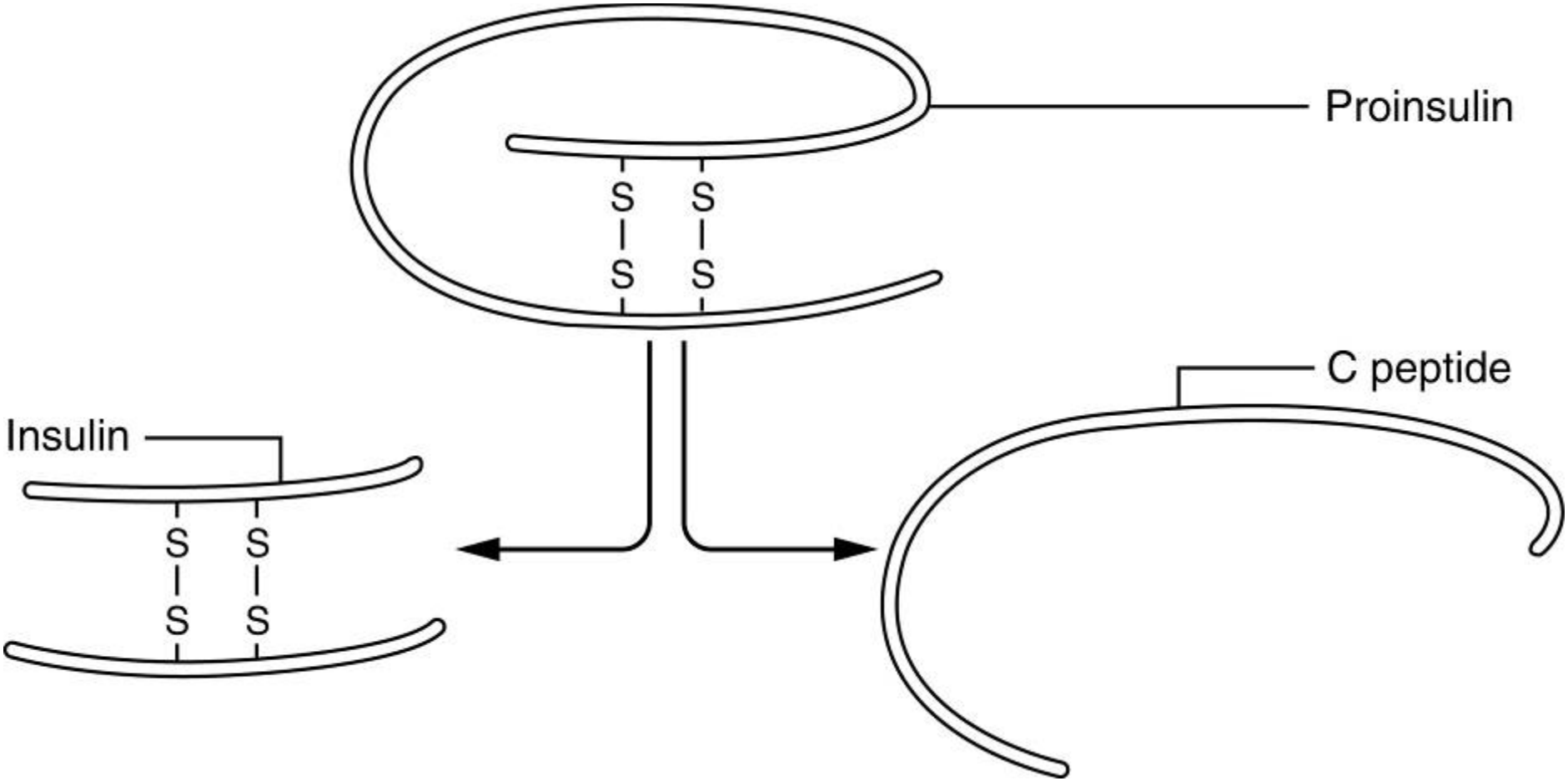
- 10% multiple
- 10% malignant
- 10% associated with MEN-I
- fasting hypoglycemia (<40 mg/dL) with elevated insulin level

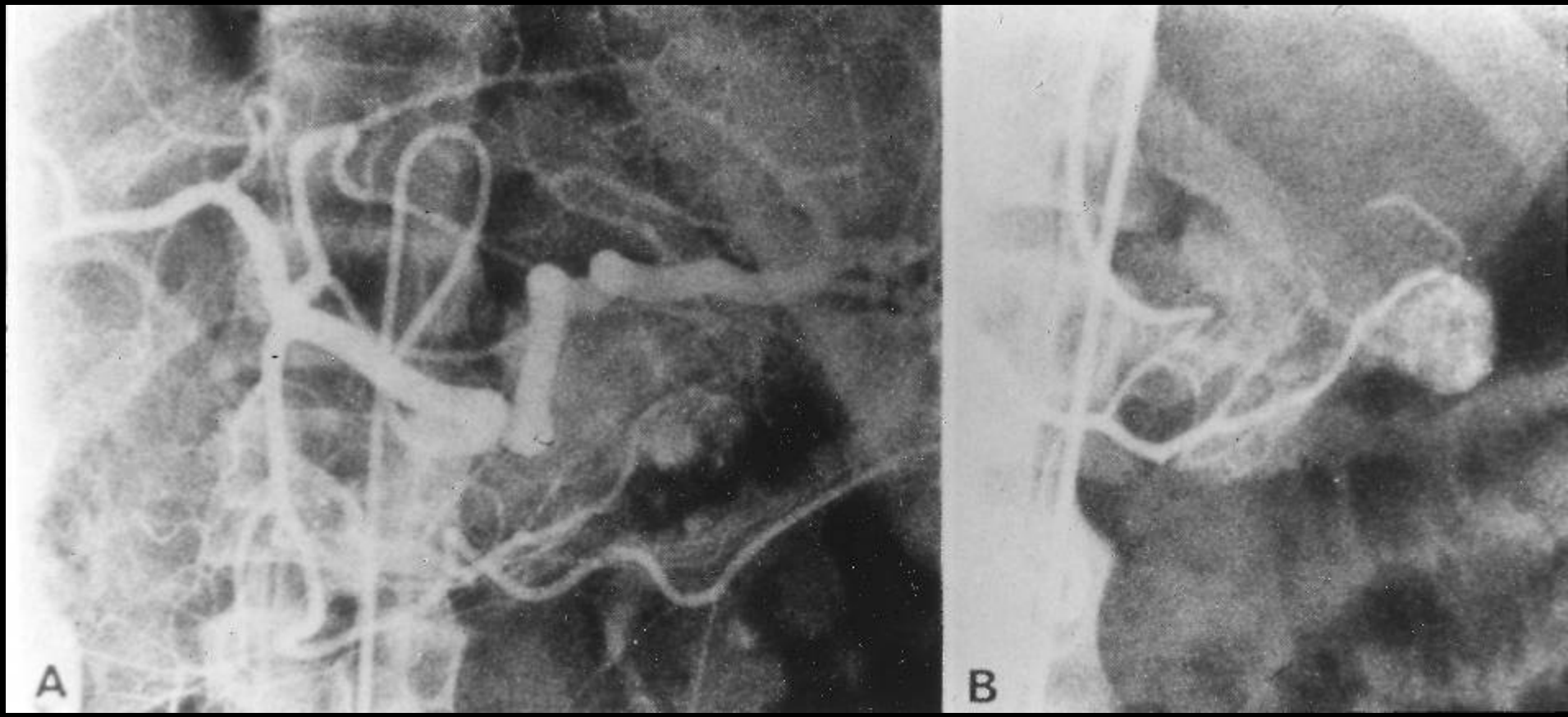
Diagnosis of Insulinoma

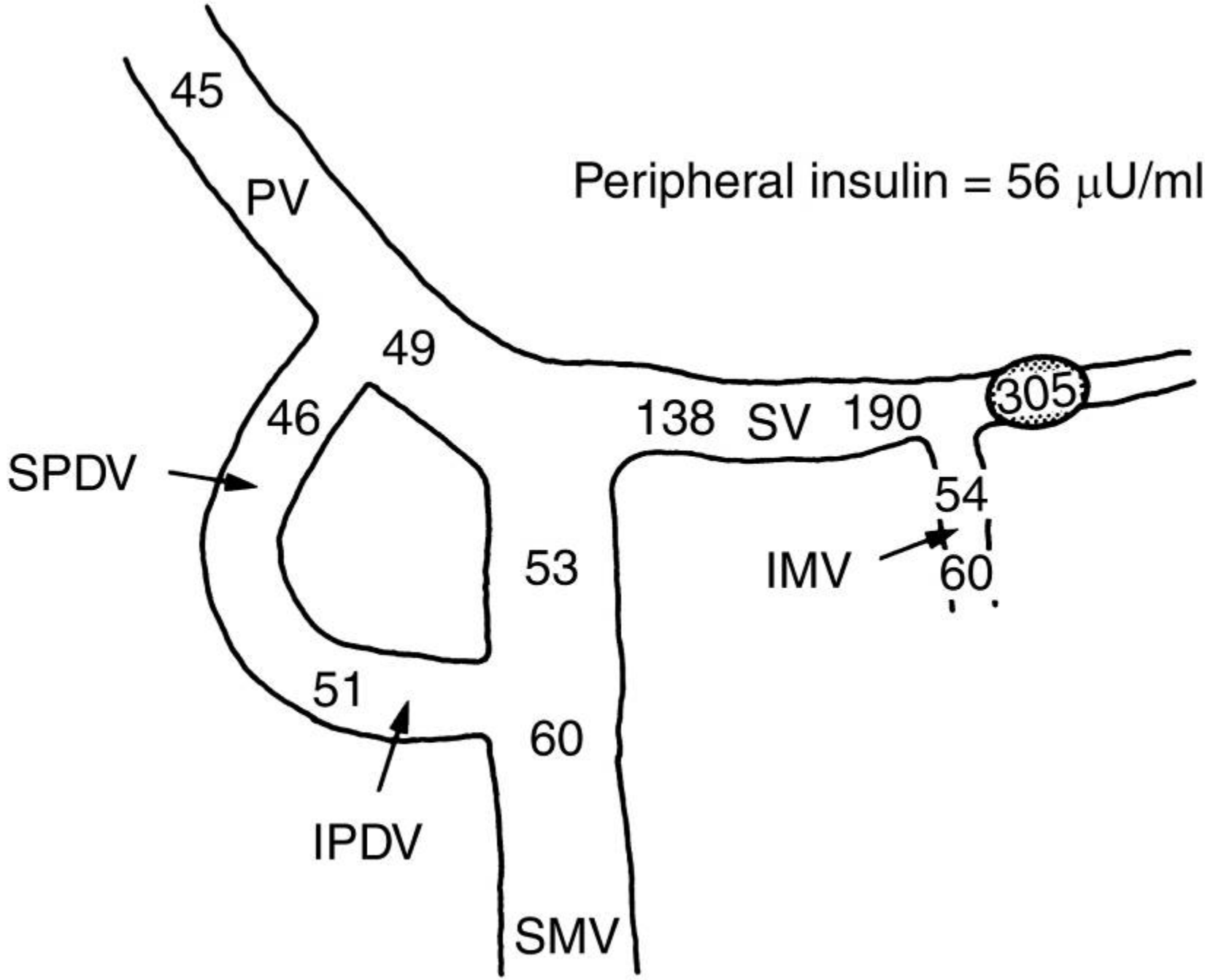
Whipple's triad:

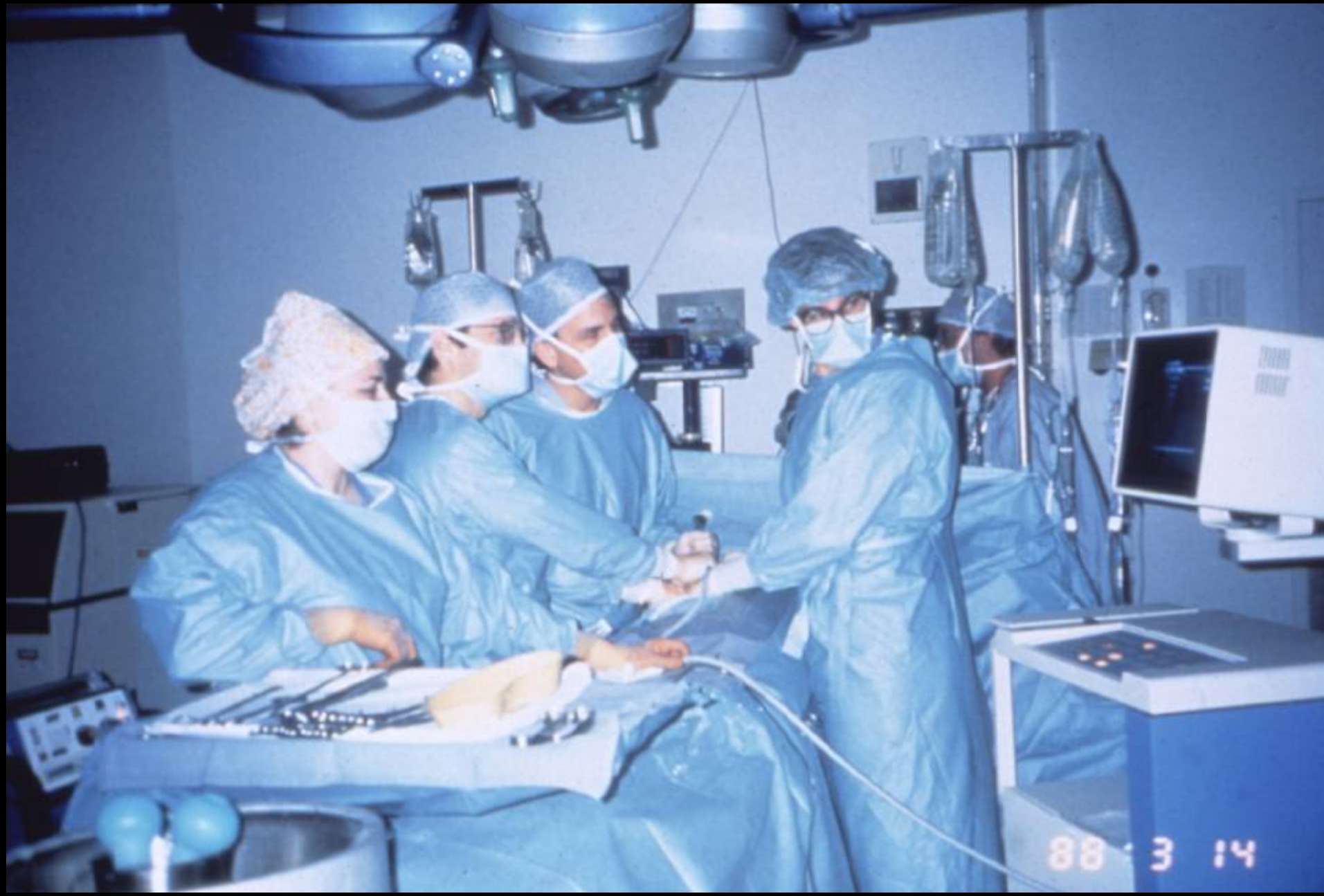
- **Symptoms of hypoglycemia**
- **Low (< 45 mg%) blood sugar**
- **Relief of symptoms with glucose**
  - **Triad ppt by 12-h fast in 37% of patients by 24-h fast in 73%**

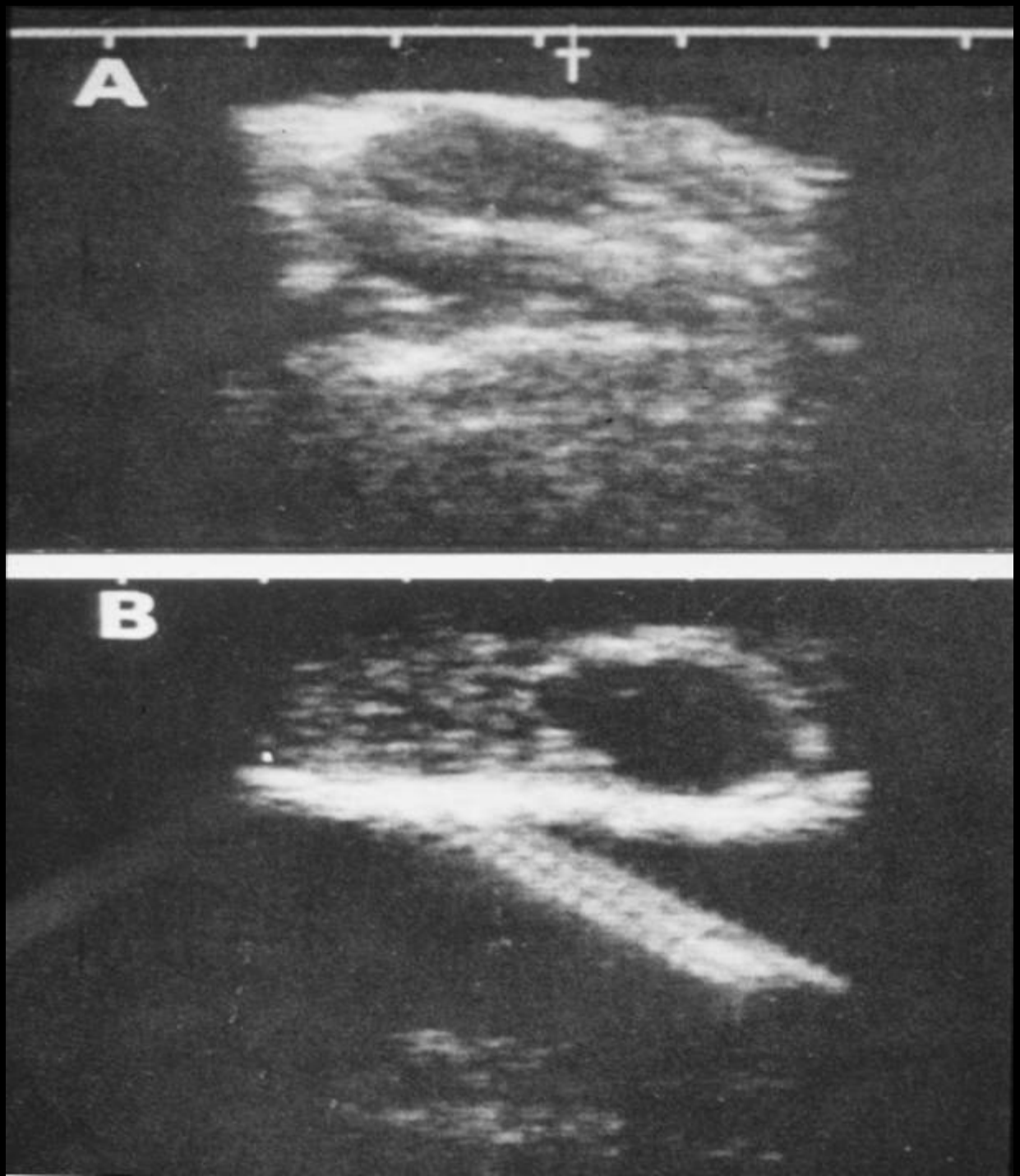

100
80
60
40
20
0
Glucose (mg/dl)
Glucose
Insulin
30
20
10
0
Insulin (μU/ml)
1
2
3
4
5
6
7
8
9
10
11
12
Hours

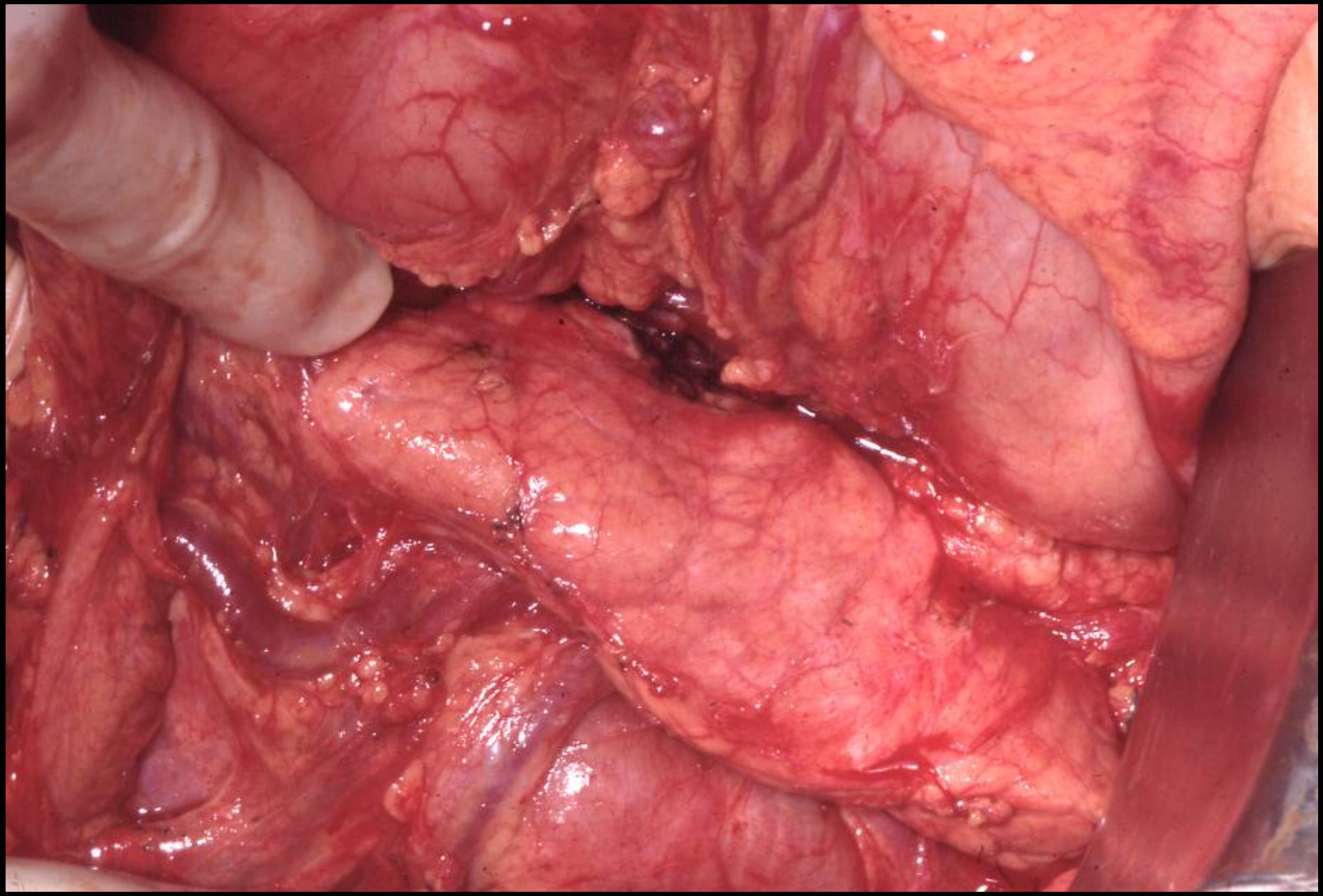

Proinsulin
S
S
S
S
C peptide
Insulin
S
S
S
S

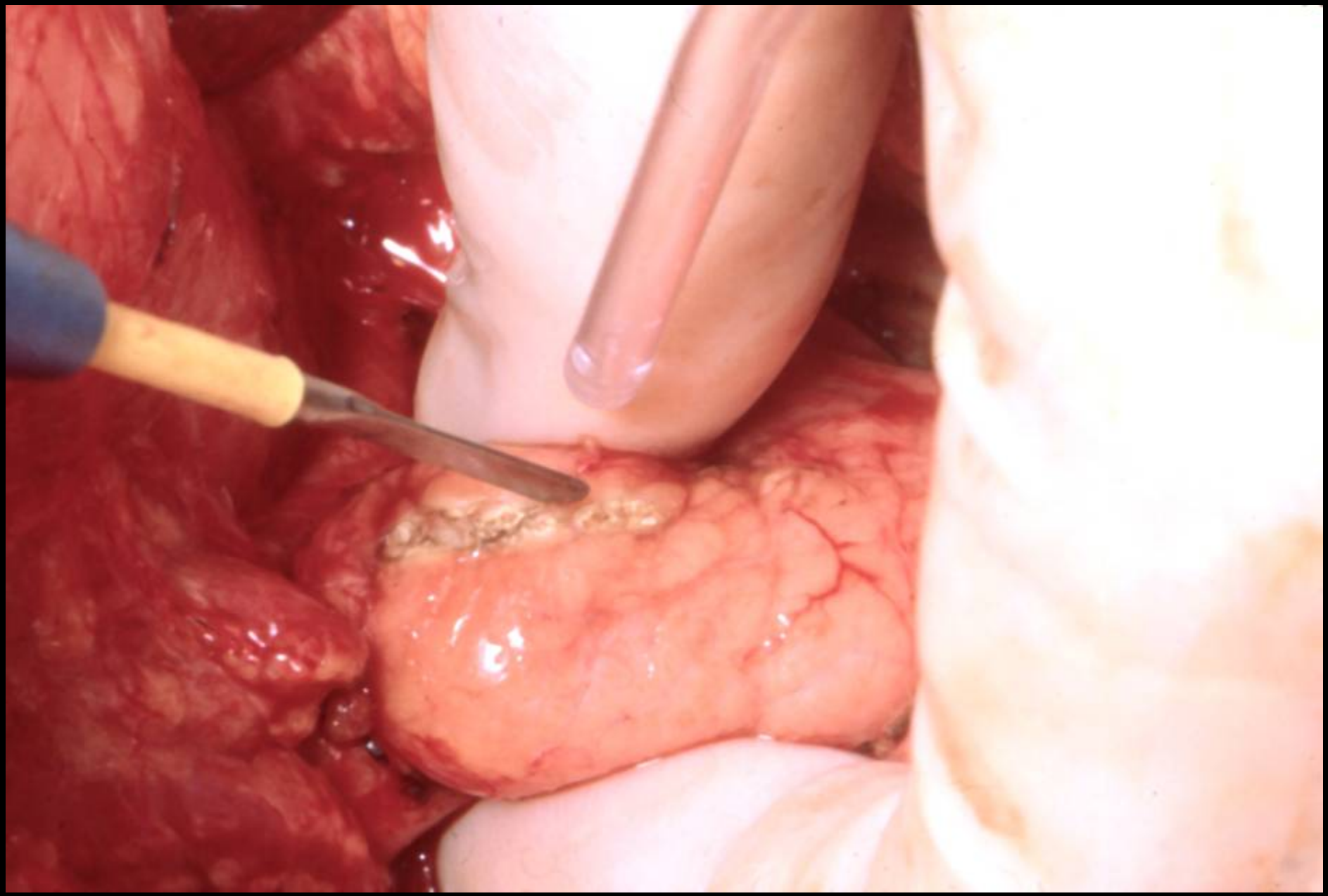

A
B

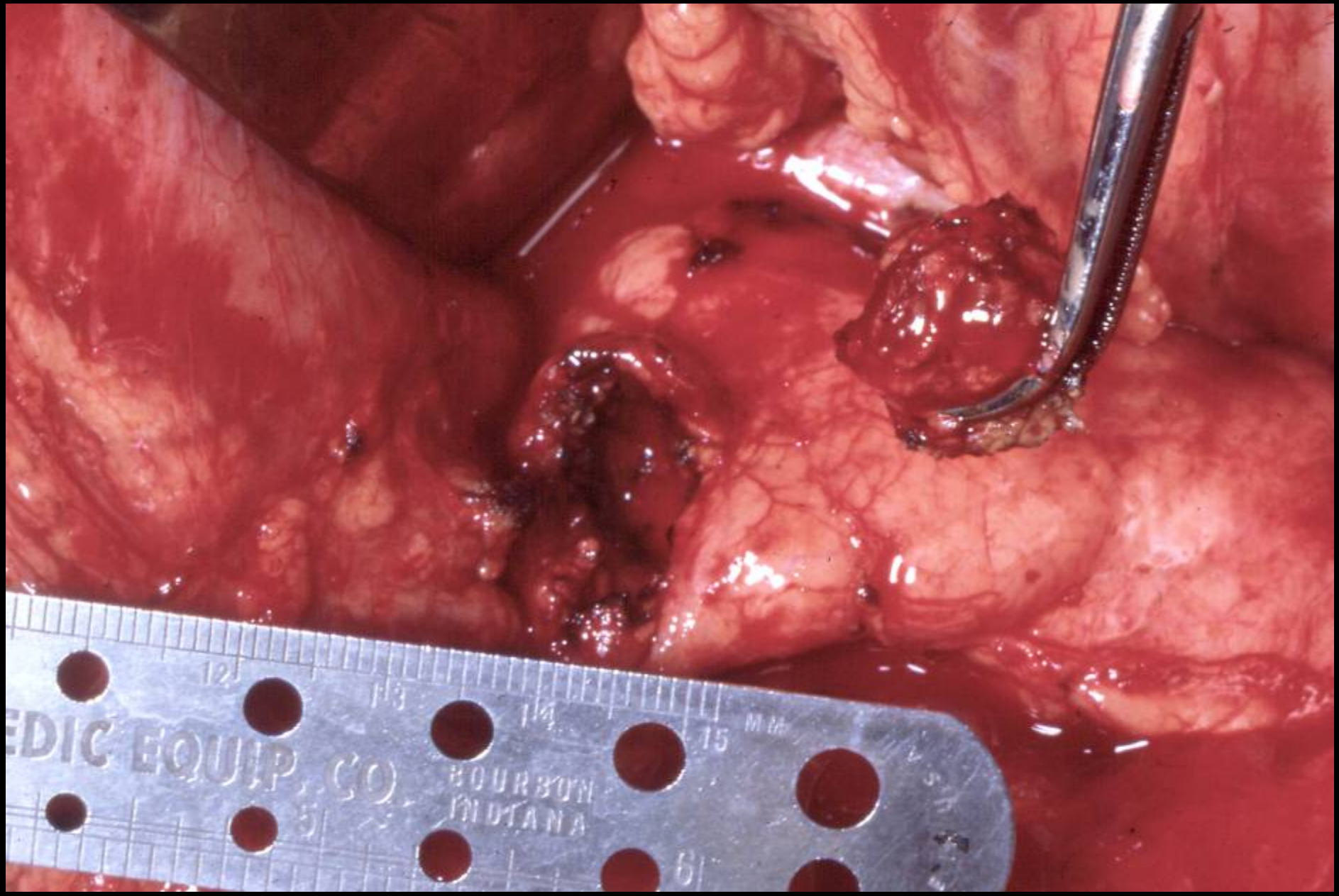

45
PV
Peripheral insulin = 56 μU/ml
49
46
138
SV
190
305
SPDV
54
IMV
60
53
51
60
IPDV
SMV

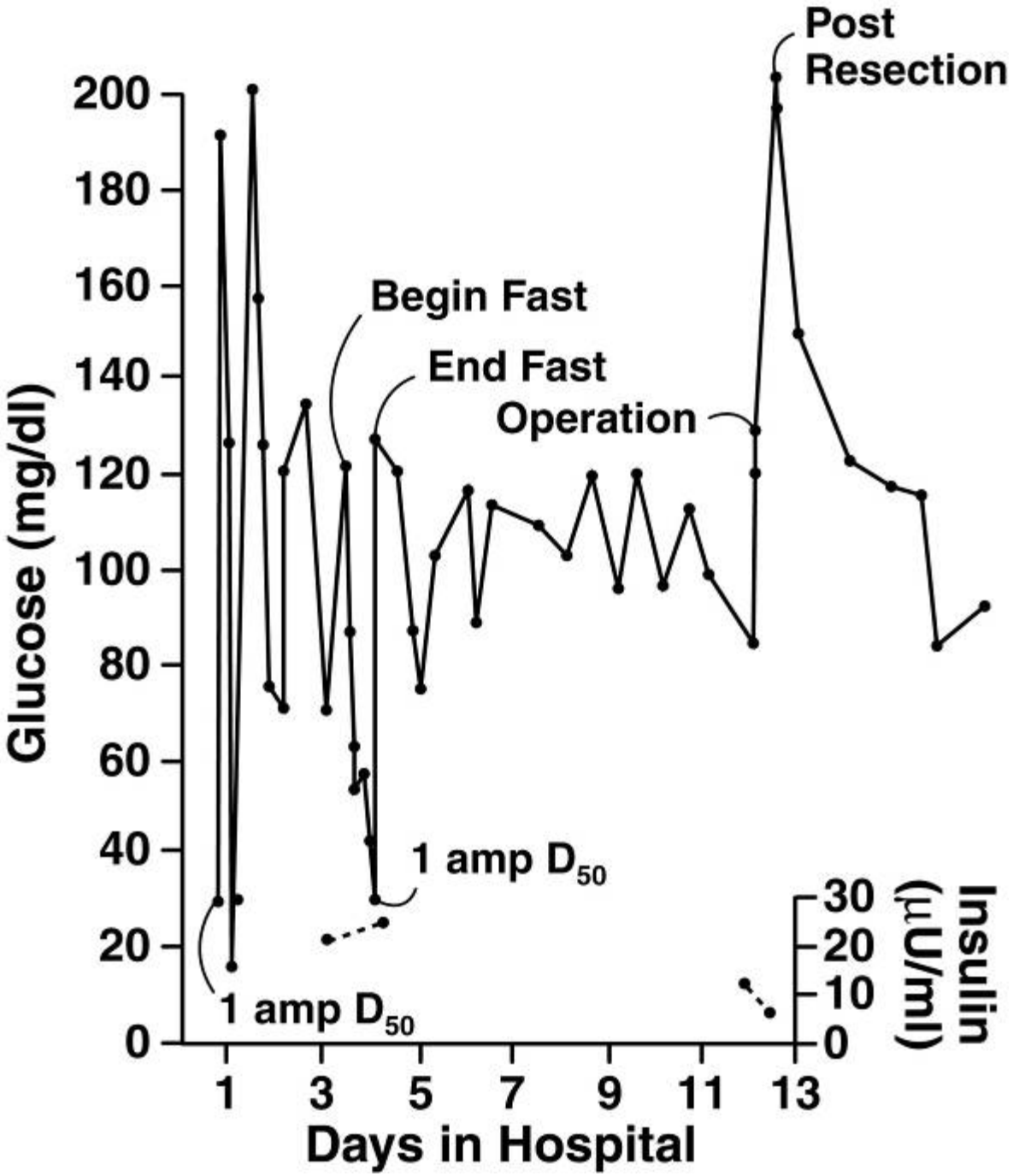

88 3 14

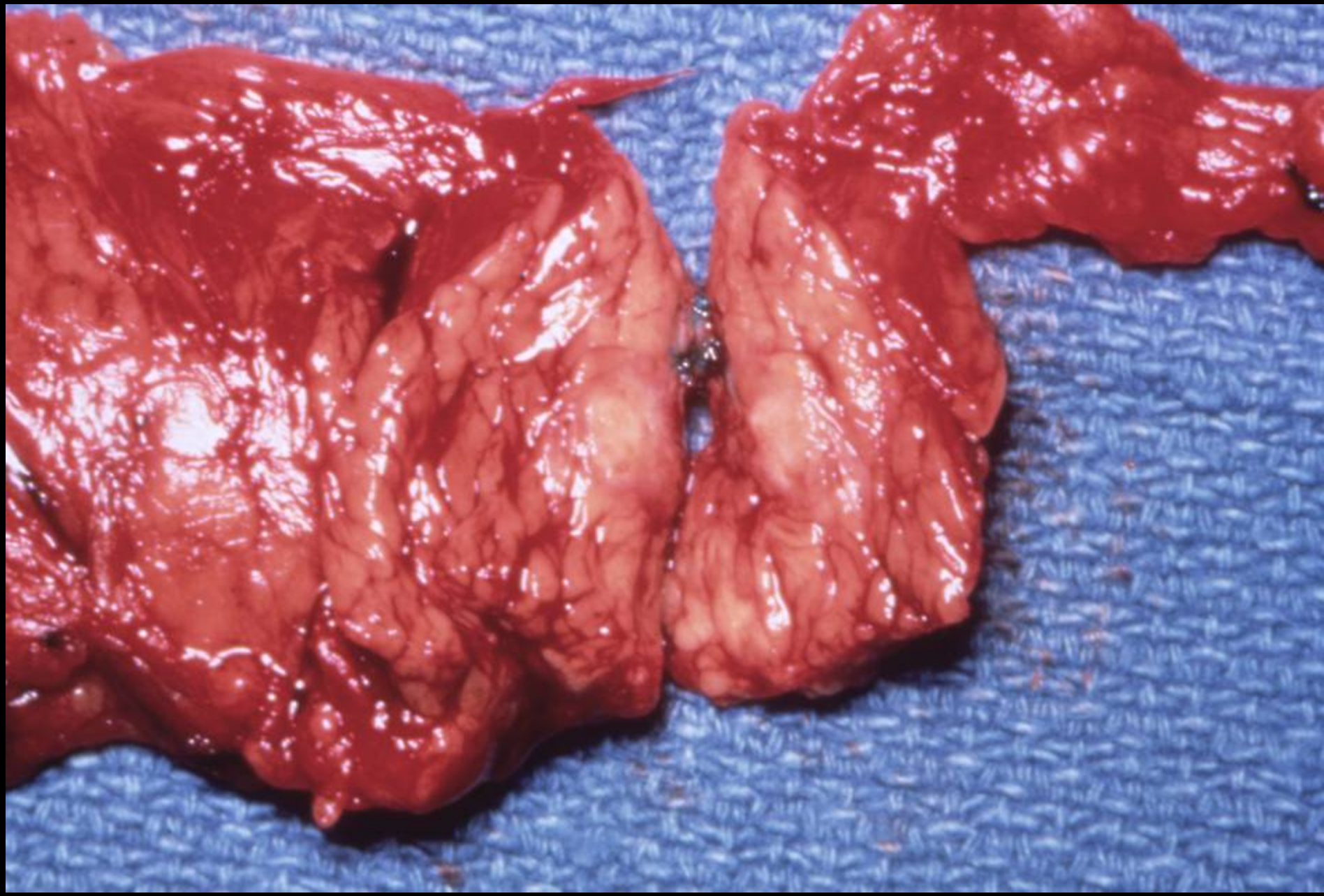

A
B






EDIC EQUIP. CO.
BOURBON
INDIANA


Post
Resection
Begin Fast
End Fast
Operation
1 amp D_{50}
1 amp D_{50}
Glucose (mg/dl)
200
180
160
140
120
100
80
60
40
20
0
Insulin (μU/ml)
30
20
10
0
1
3
5
7
9
11
13
Days in Hospital



Insulinoma Treatment Options

- **Single lesion head or < 1.0 cm in tail: enucleation**
- **single lesion in body/tail > 1.0 cm: distal pancreatectomy**
- **multiple lesions: resect body and tail**
- **metastatic lesions-lymph nodes: resect**

Zollinger-Ellison Syndrome

- unrelenting peptic ulcer disease
- gastric hyperacidity
- gastrin-producing tumor
- < 1% of all peptic ulcer disease
- 60-70% associated with MEN-I are malignant
- sporadic gastrinomas less often malignant; 70% are multicentric

Causes of Hypergastrinemia

↑ Stimulation of gastrin release

- ZES
- Antral G cell hyperplasia
- Pyloric obstruction

↓ Inhibition of gastrin release

- Hypo- or achlorhydria
  - antisecretory drugs
  - atrophic gastritis
  - pernicious anemia

Thompson and Townsend, *Sabiston Textbook of Surgery, 17th edition,* p. 1001, 2004

Causes of Hypergastrinemia (cont'd)

↓ Inhibition of gastrin release
- Hypo- or achlorhydria
  - gastric carcinoma
  - vitiligo
- Antral exclusion
- Vagotomy

↓ Catabolism
- Chronic renal failure

Unknown
- Rheumatoid arthritis
- Small bowel resection (temporary)

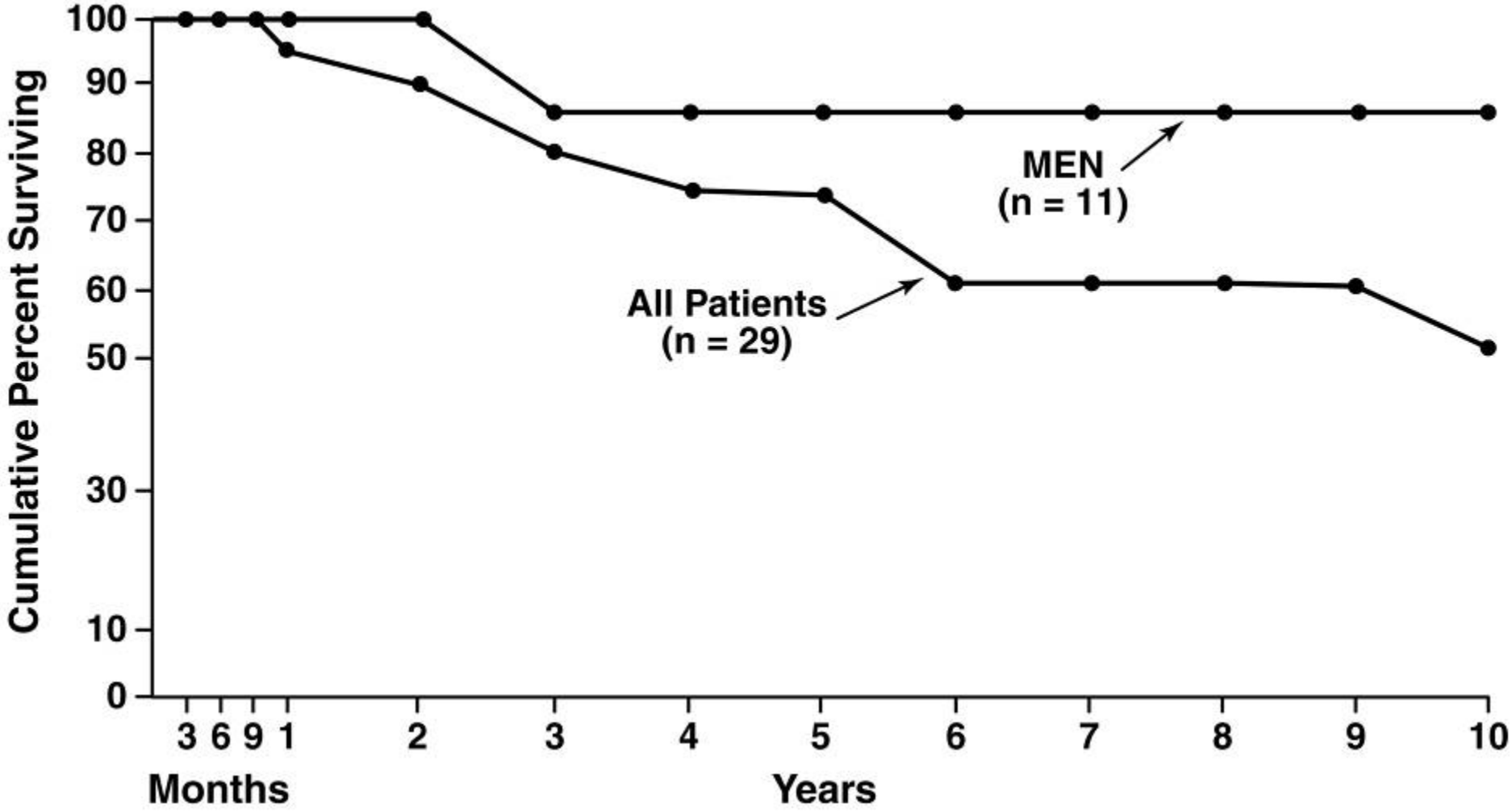
Thompson and Townsend, *Sabiston Textbook of Surgery, 17th edition,* p. 1001, 2004

ZES Diagnostic Tests

1. BAO:MAO >/= 0.6 (Basal Acid Output: Maximal Acid Output)
2. Overnight AO >/= 100 mmols
3. BAO >/= 10 mmols/hr

ZES Diagnostic Tests (cont'd)

4. Serum gastrin 10 times normal, or greater than 500 pg/mL
5. Secretin test: 2 units/kg: Positive = 100% increase over baseline
6. ↑ human chorionic gonadotropin levels


Cumulative Percent Surviving
100
90
80
70
60
50
30
10
0
MEN
(n = 11)
All Patients
(n = 29)
3 6 9 1
2
3
4
5
6
7
8
9
10
Months
Years

Zollinger-Ellison Syndrome

UTMB

34 Patients with ZES

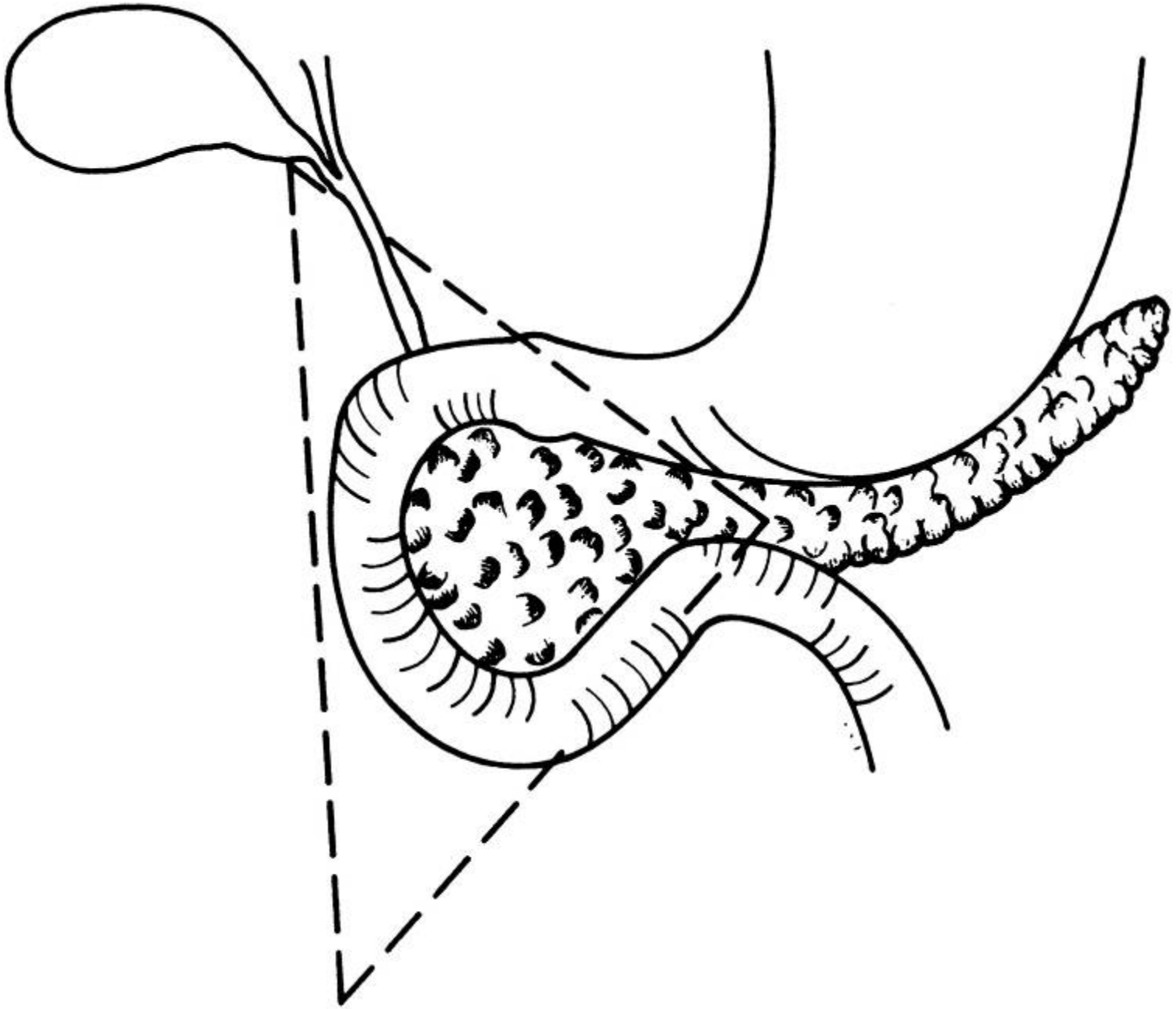
- 33 operated upon
  - 30 total gastrectomy with Roux-en-Y esophagojejunostomy
    - 1 subtotal gastrectomy, Billroth II, and vagotomy
    - 1 gastrojejunostomy
    - 1 selective proximal vagotomy + fundoplication
- 1 refused operation

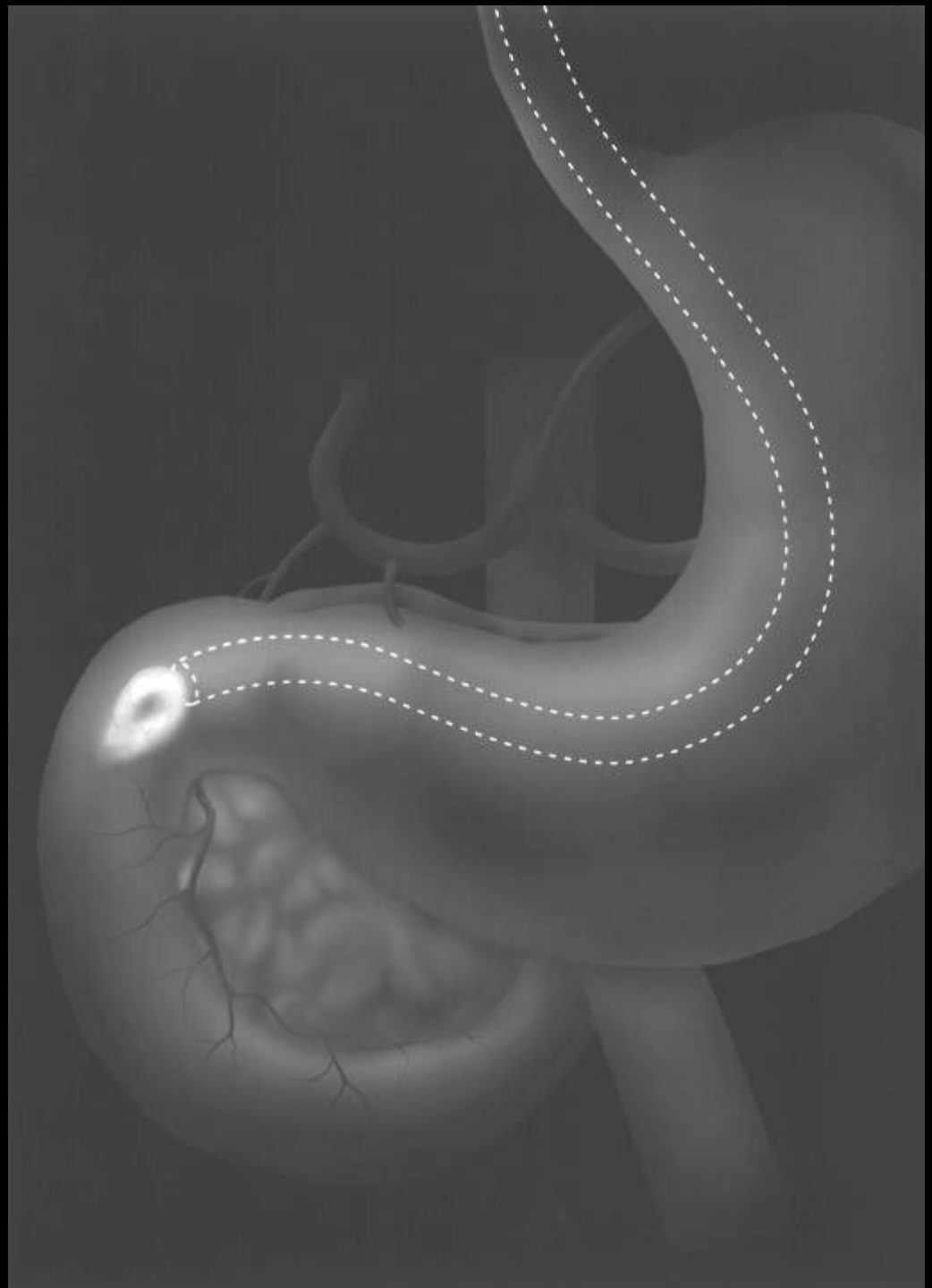
No operative deaths

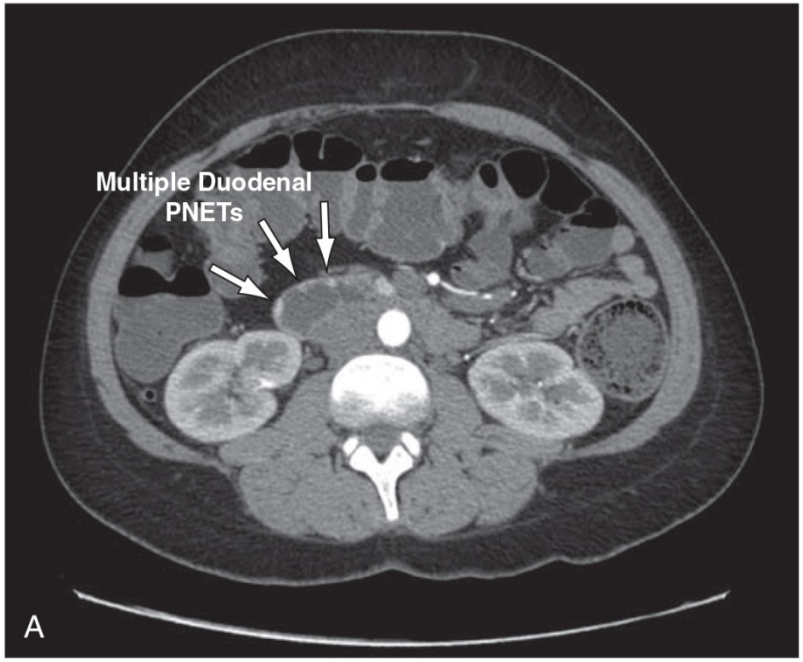
Thompson et al., *Ann Surg* 197:594-607, 1983

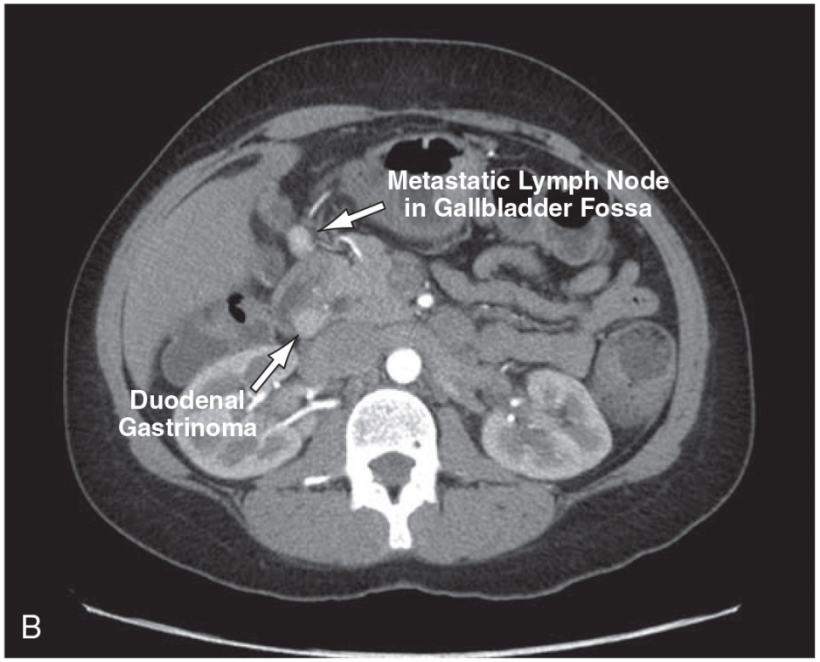
	Clinical Course (% all patients)	
	Benign (n=140)	Malignant (n=45)
Patients	76%	24%
Present with liver metastases	0%	19%
Develop liver metastases	0%	5%
Gender	68% male	67% female
MEN-I	21%	Uncommon (6%)
Onset to Dx	Long (mean 5.9 yrs)	Short (mean 2.7 yrs)
Serum gastrin level	Moderately elevated (mean 1711 pg/ml)	Very elevated (mean 5157 pg/ml)
Size of primary tumor	Small (≤1 cm)	Large (>3 cm)
Location of primary tumor	Primarily duodenum (66%)	Primarily pancreatic (92%)
10-yr. survival	Excellent (96%)	Poor (30%)

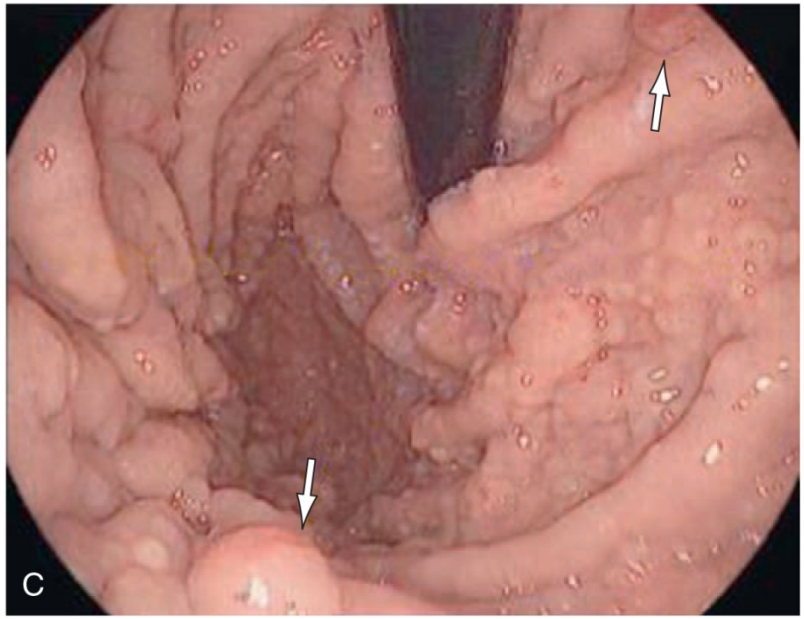
Thompson and Townsend, *Sabiston Textbook of Surgery, 17th edition,* p. 1013, 2004



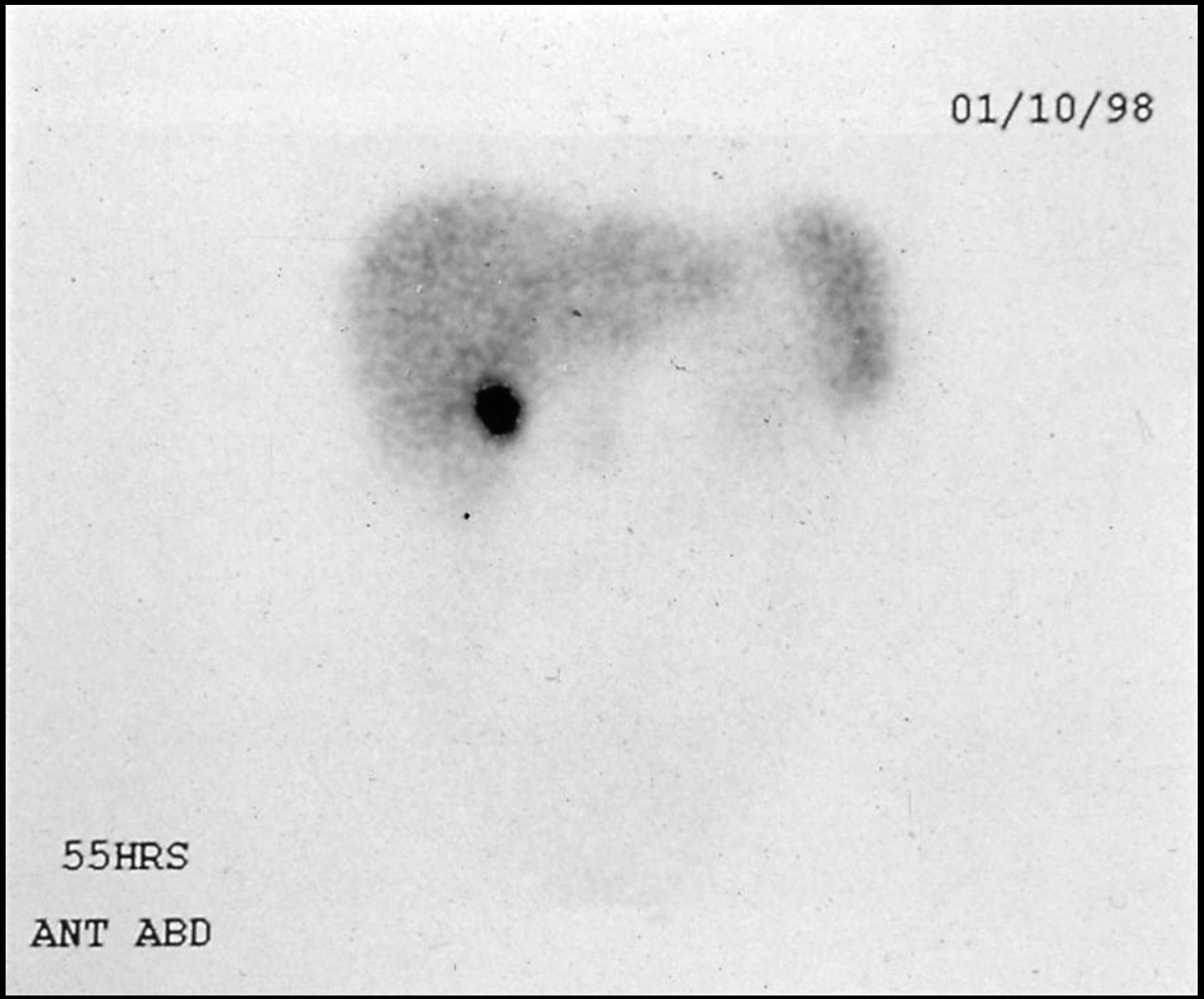


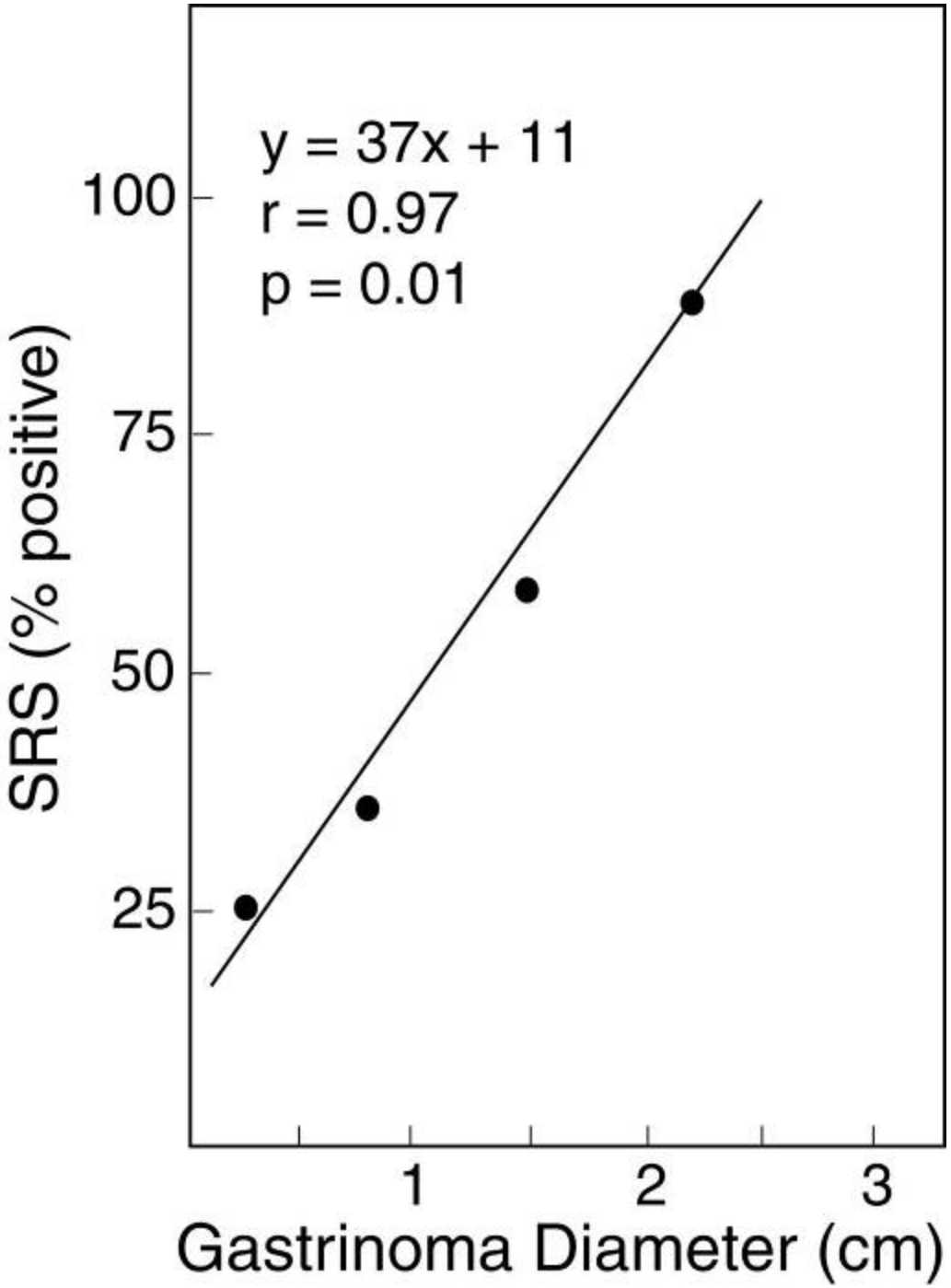


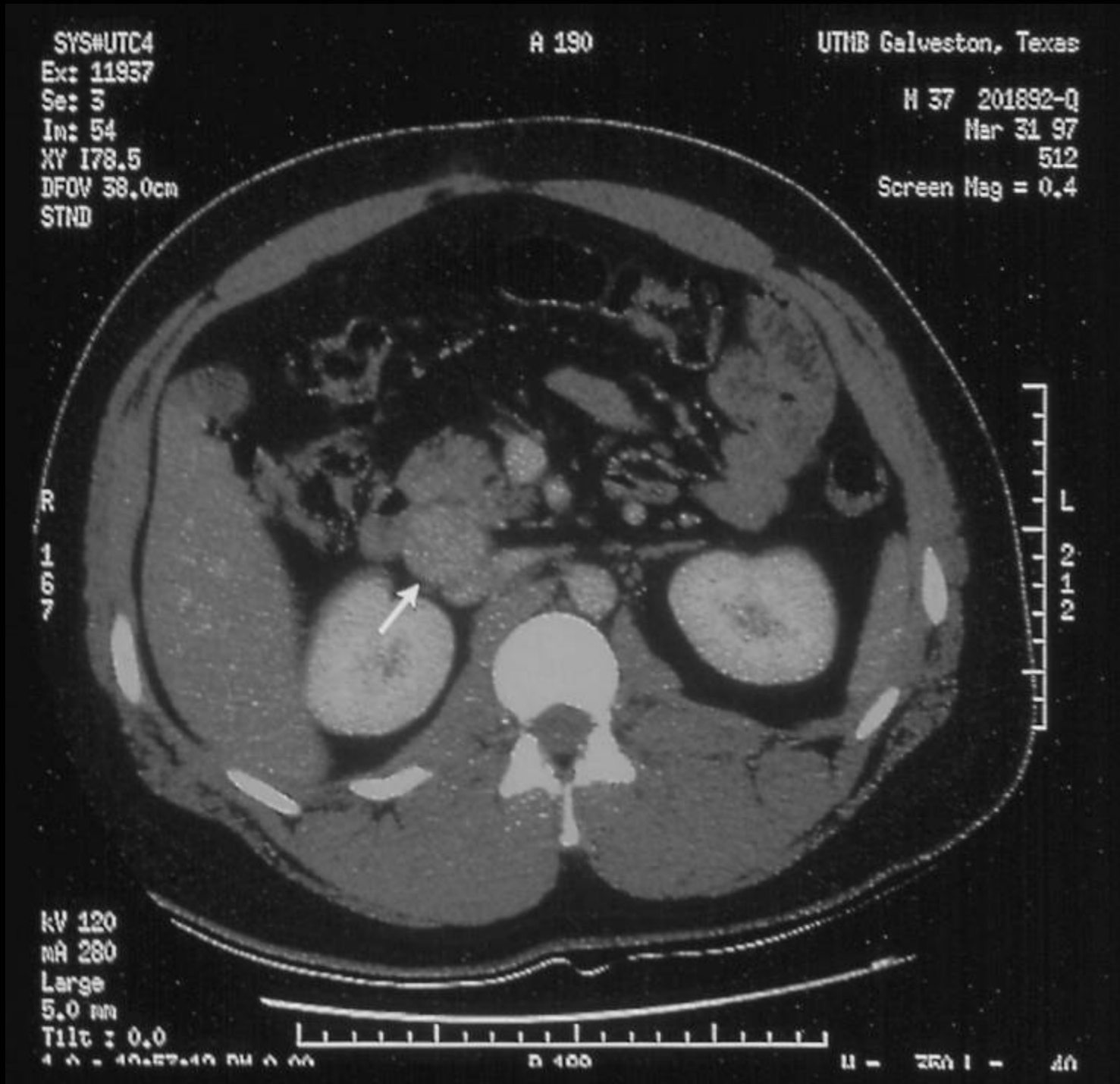


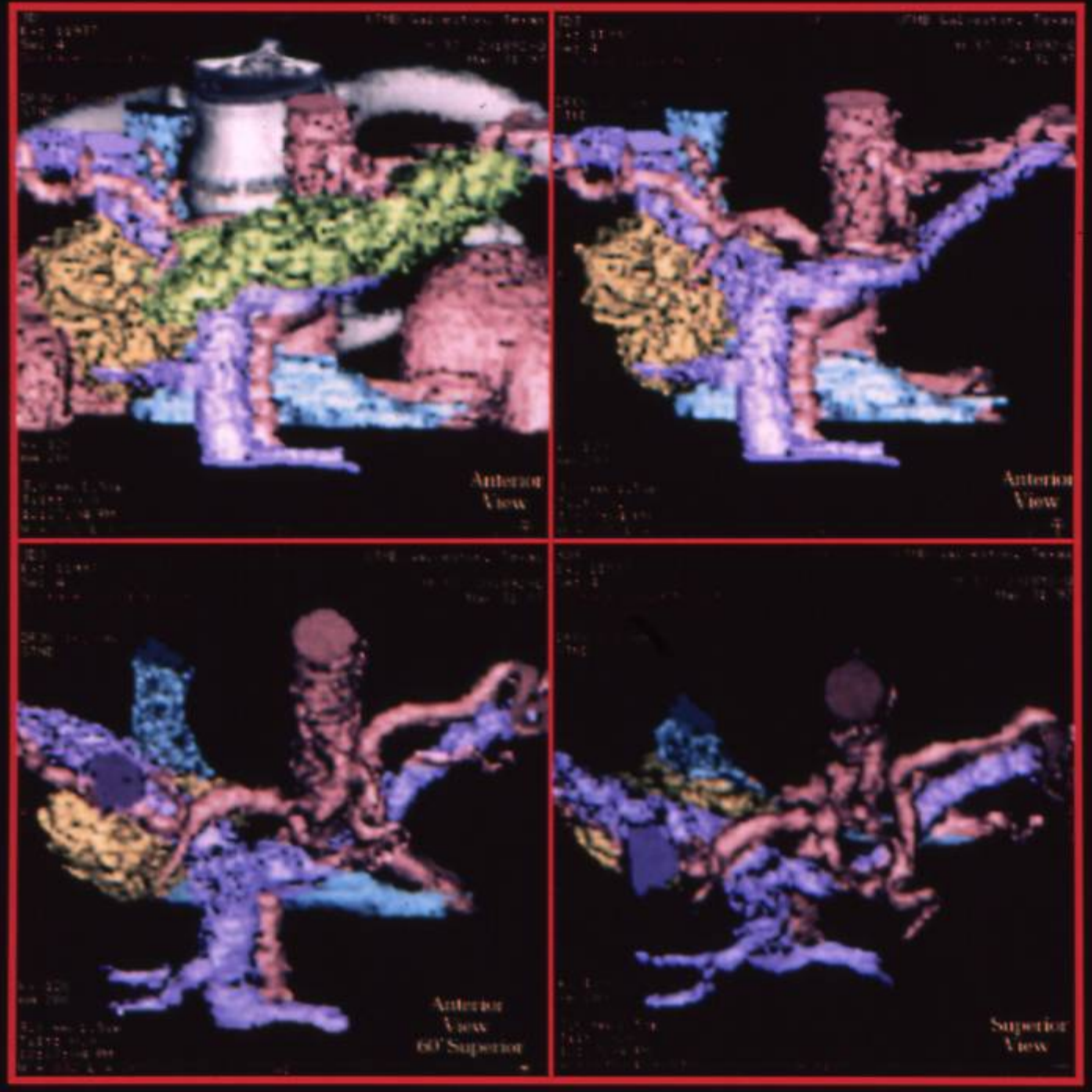


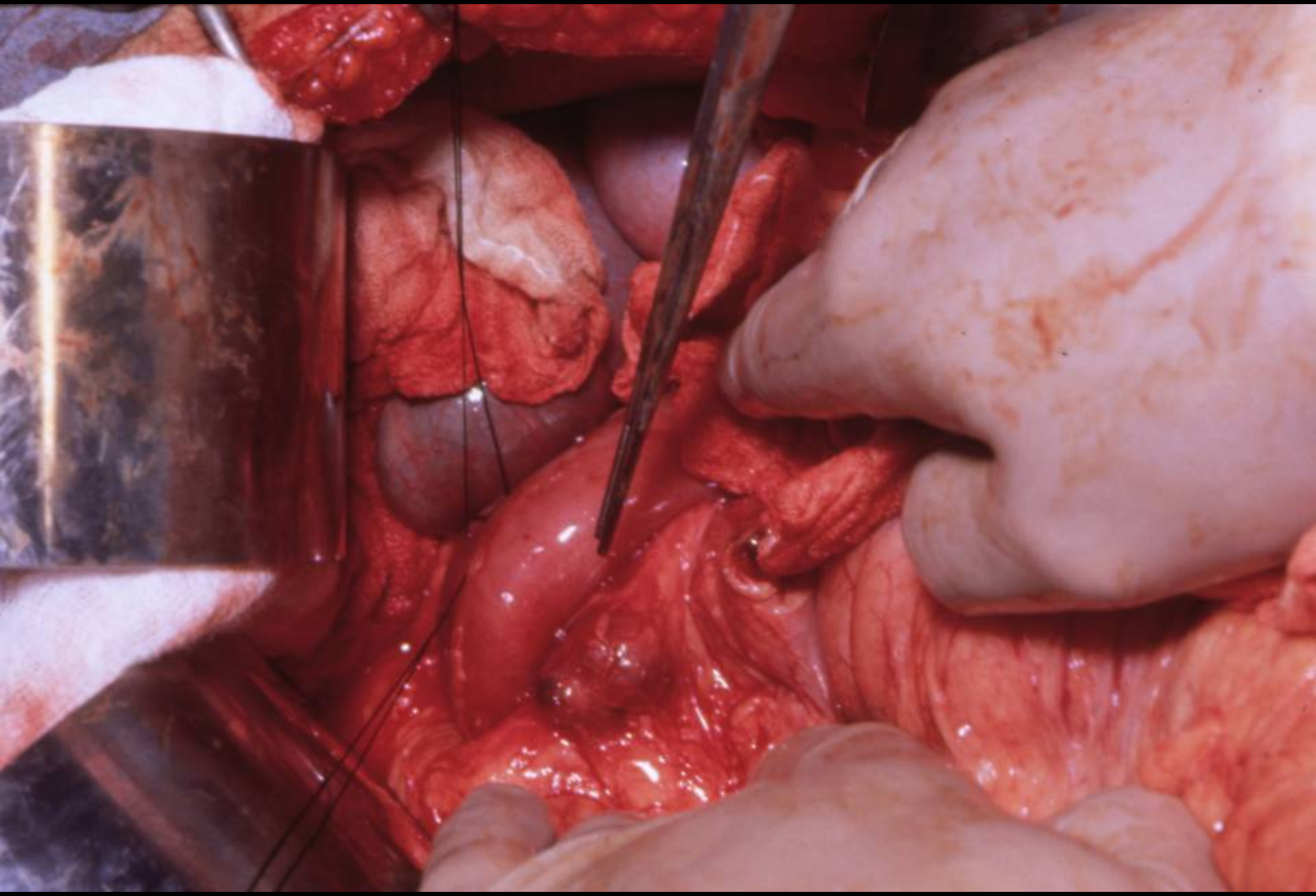
T.S. Riall, *Sabiston Textbook of Surgery, 20th Edition,* Ch 38, Endocrine Tumors, 2016

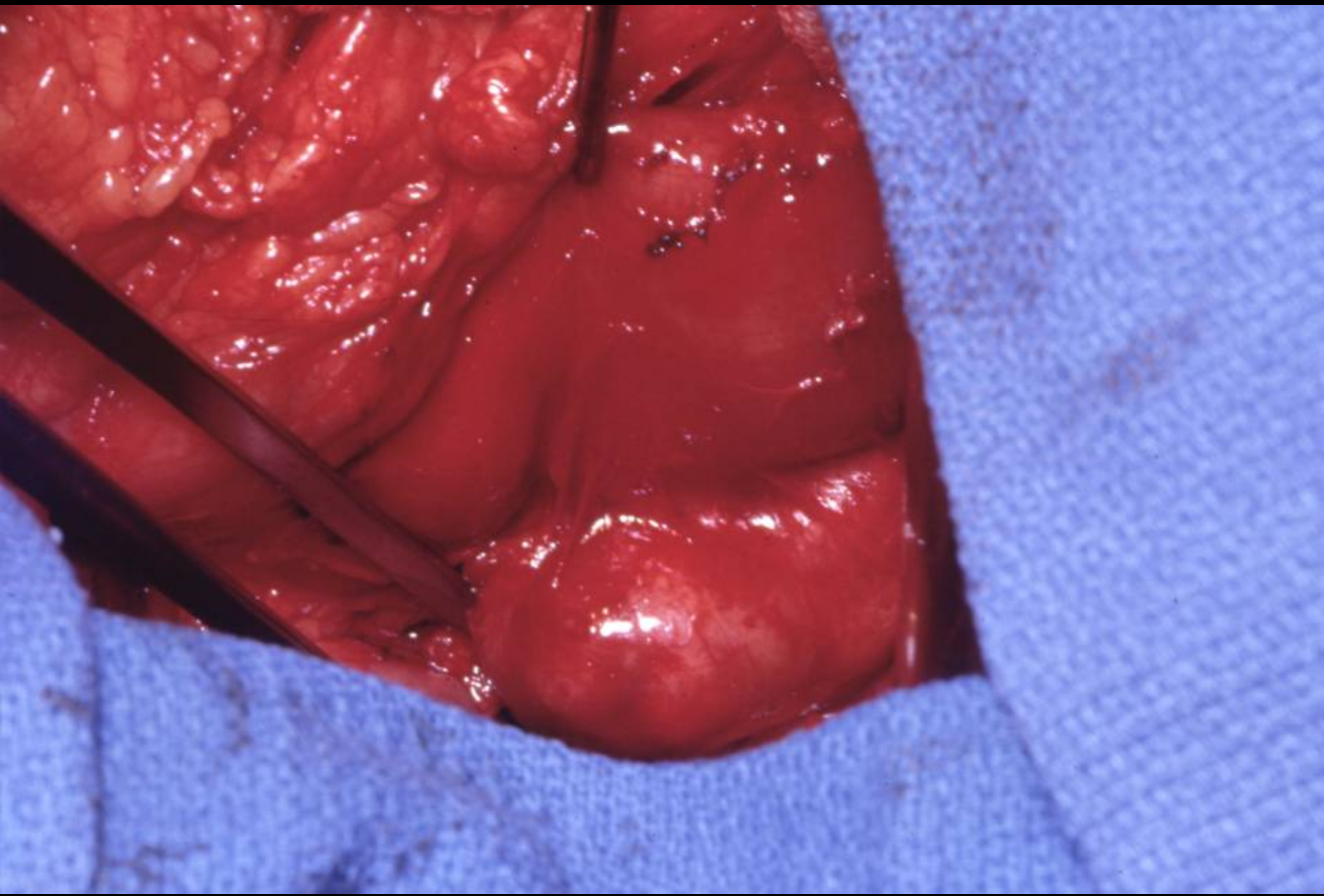

01/10/98
55HRS
ANT ABD

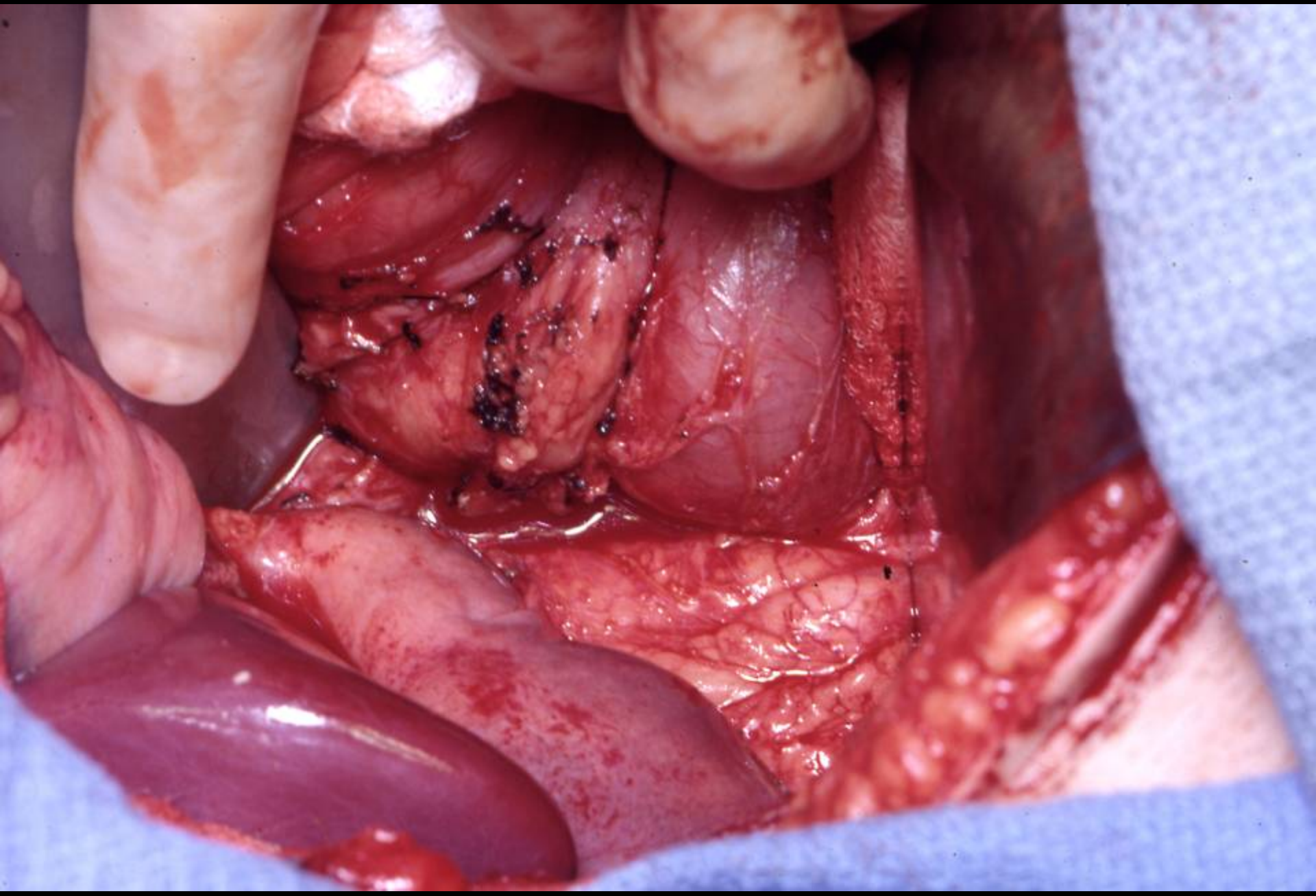

y = 37x + 11
r = 0.97
p = 0.01
100
75
50
25
SRS (% positive)
1
2
3
Gastrinoma Diameter (cm)


SYS#UTC4
Ex: 11937
Se: 3
In: 54
XY I78.5
DFOV 38.0cm
STND
A 190
UTMB Galveston, Texas
H 37 201892-Q
Mar 31 97
512
Screen Mag = 0.4
R
167
L
212
kV 120
mA 280
Large
5.0 mm
Tilt : 0.0


Anterior
View
Anterior
View
Anterior
View
60° Superior
Superior
View





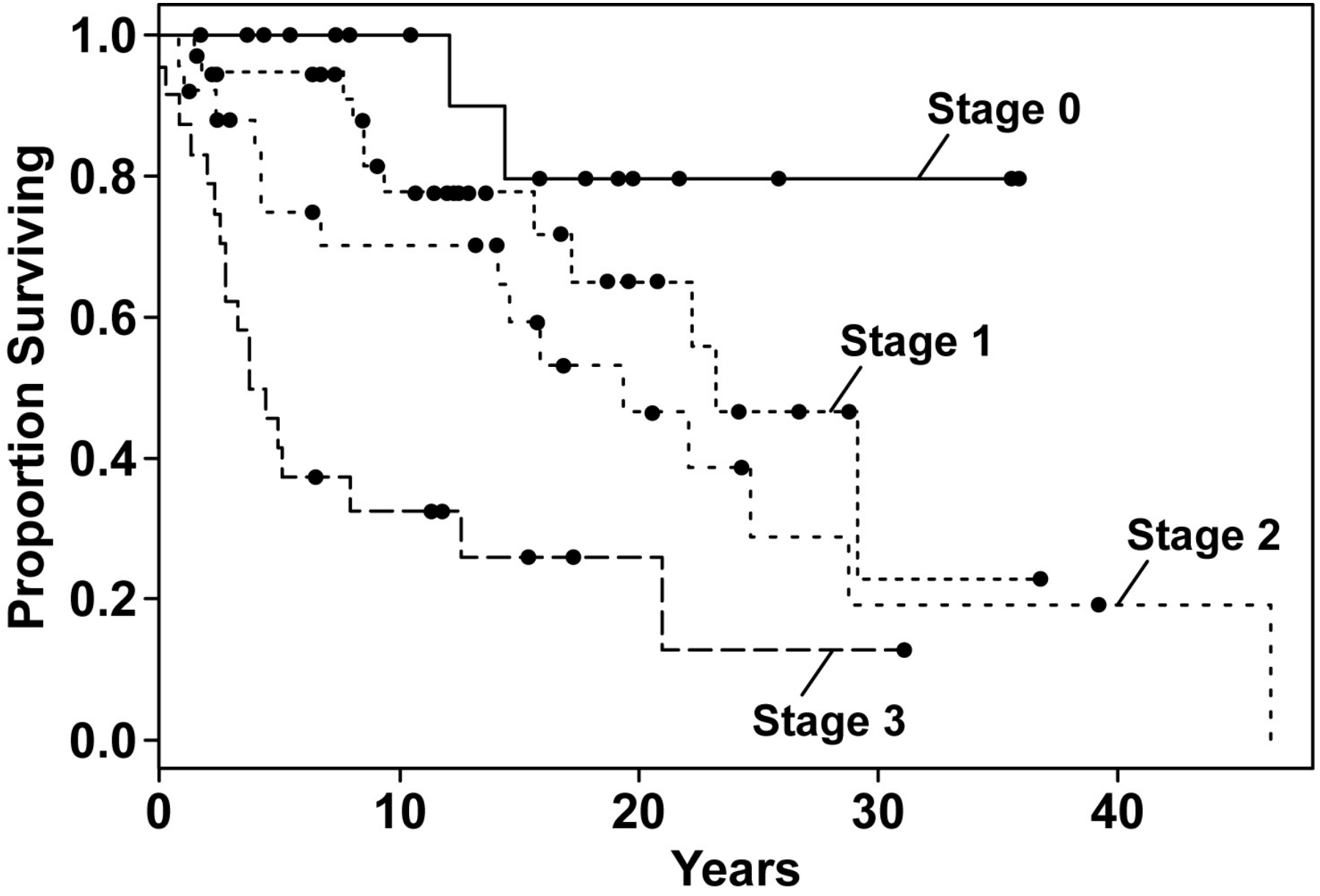


Date	Serum Gastrin (pg/ml)
8/22	1154
9/1	1340
9/17	4570
Surgery 9/18	
9/22	377
9/24	277
9/26	283

Table 3. Tumor Size and Distant Metastases

Tumor Class	Range (cm)	n	Distant Metastases (%)
T0	0	18	6
T1	0.4-1.0	21	10
T2	1.2-2.0	22	14
T3	2.2-2.6	16	12
T4	3.0-8.5	29	59

Ellison et al., *J Am Coll Surg,* 202:897-905, 2006



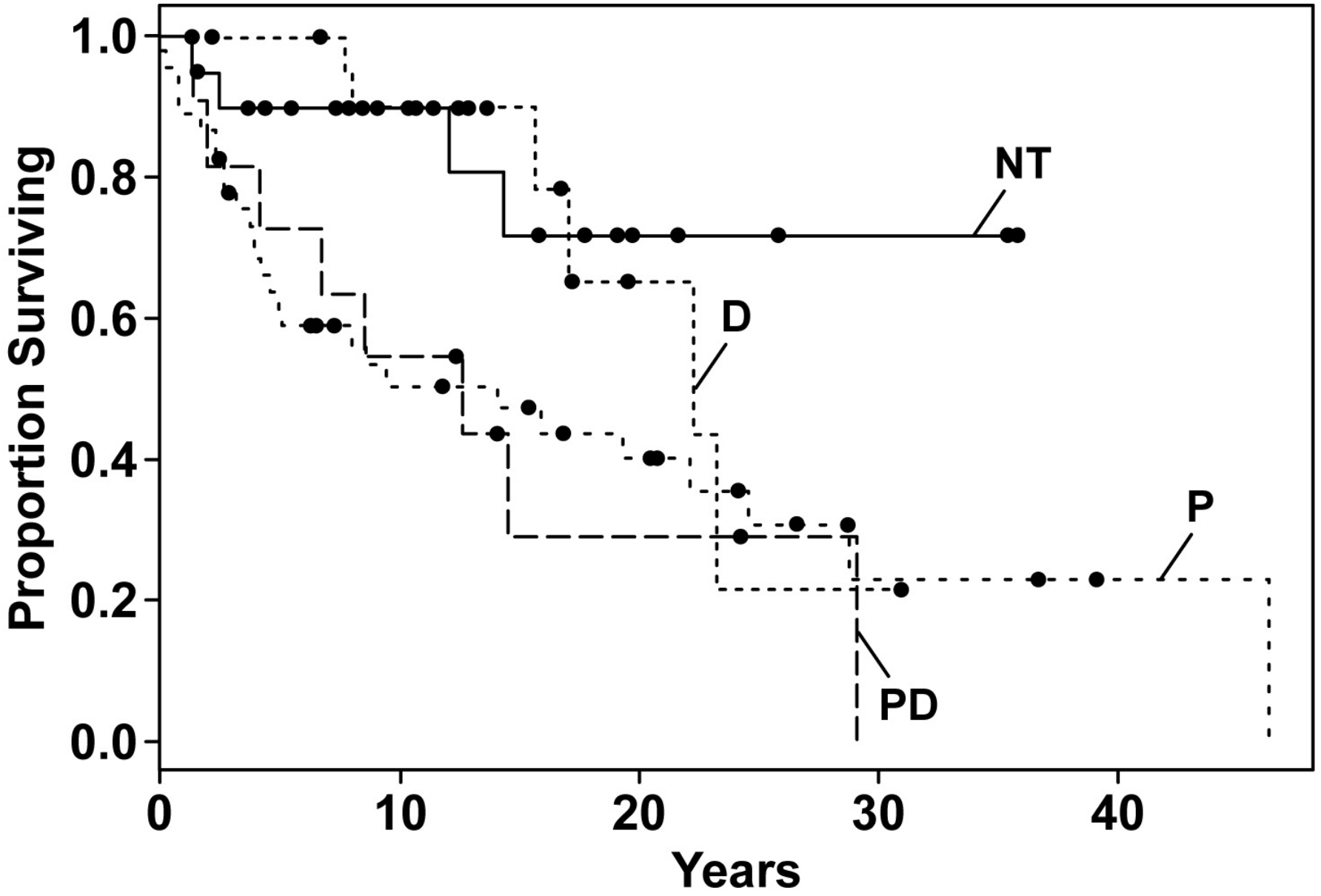
Stage was found to be predictive of DSS.

Ellison et al., *J Am Coll Surg,* 202:897-905, 2006

Table 4. Frequency Distribution of Patients by Location of Primary Gastrinoma and Stage

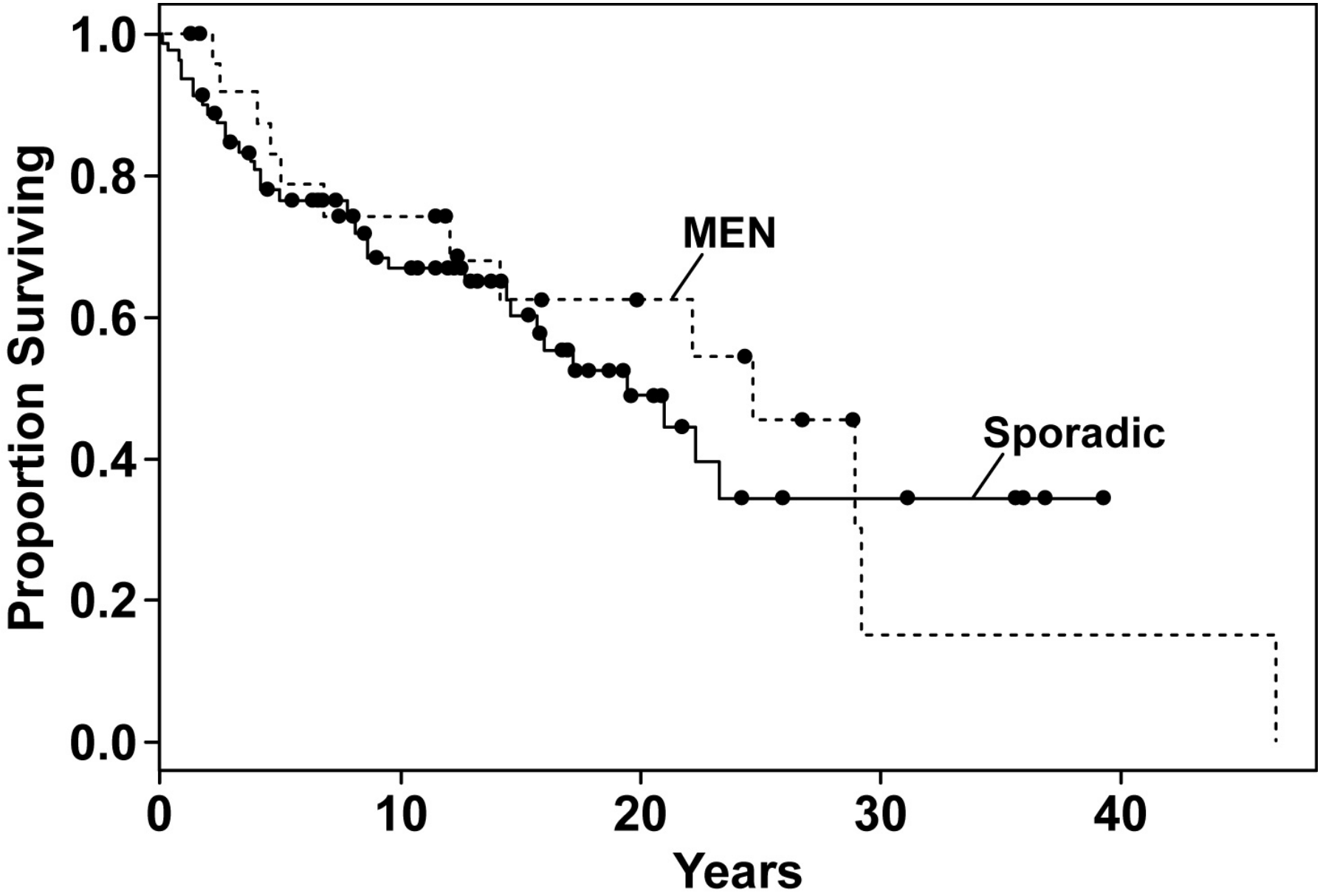
Site	Stage 0	Stage I	Stage II	Stage III	Total
Pancreas	0	12	18	16	46
Pancreas and duodenum	0	4	6	2	12
Duodenum	0	18	0	3	12
Other	0	3	2	1	6
No tumor	18	1	0	2	21

Ellison et al., *J Am Coll Surg,* 202:897-905, 2006



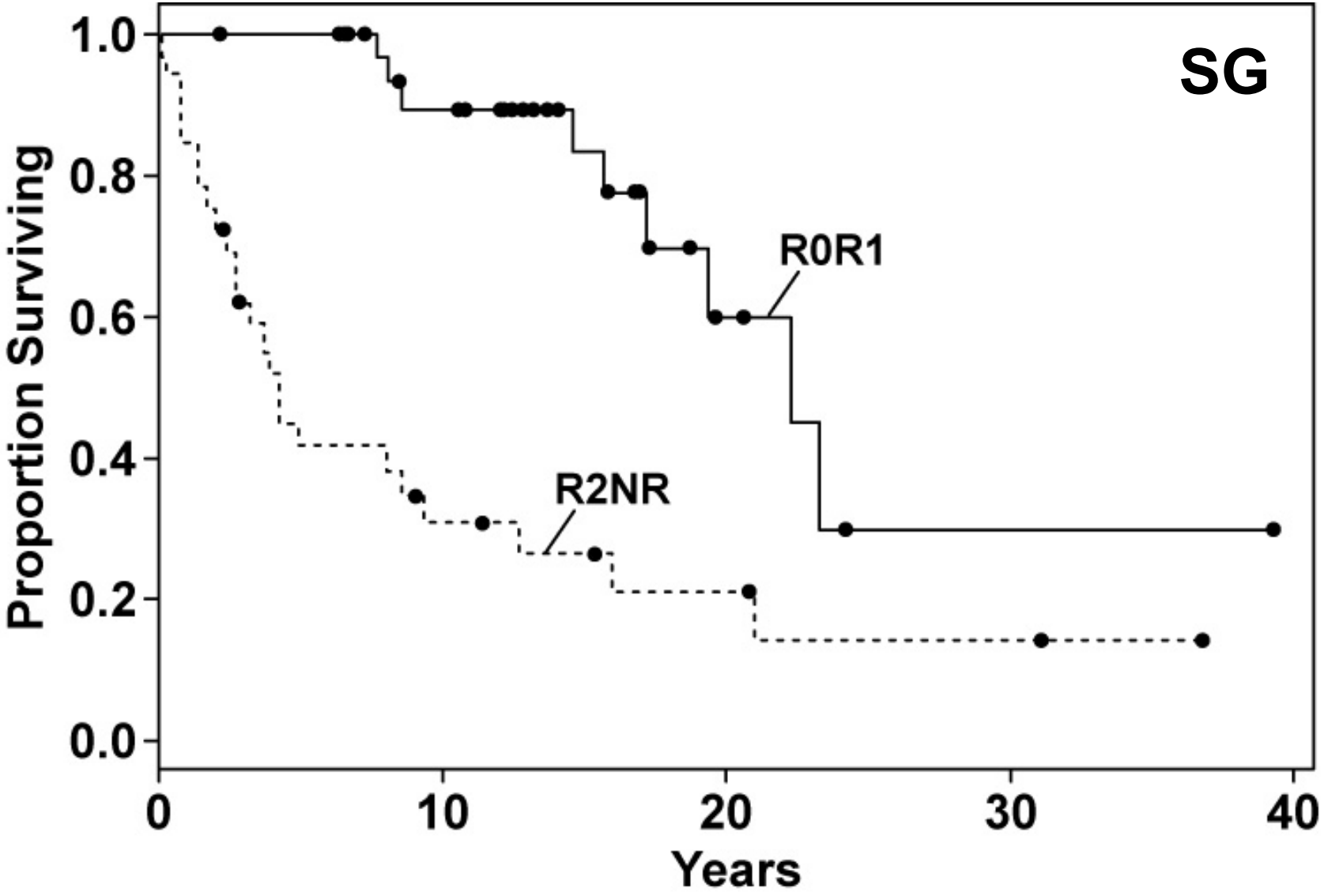
Location of the primary tumor is related to survival.

Ellison et al., *J Am Coll Surg,* 202:897-905, 2006



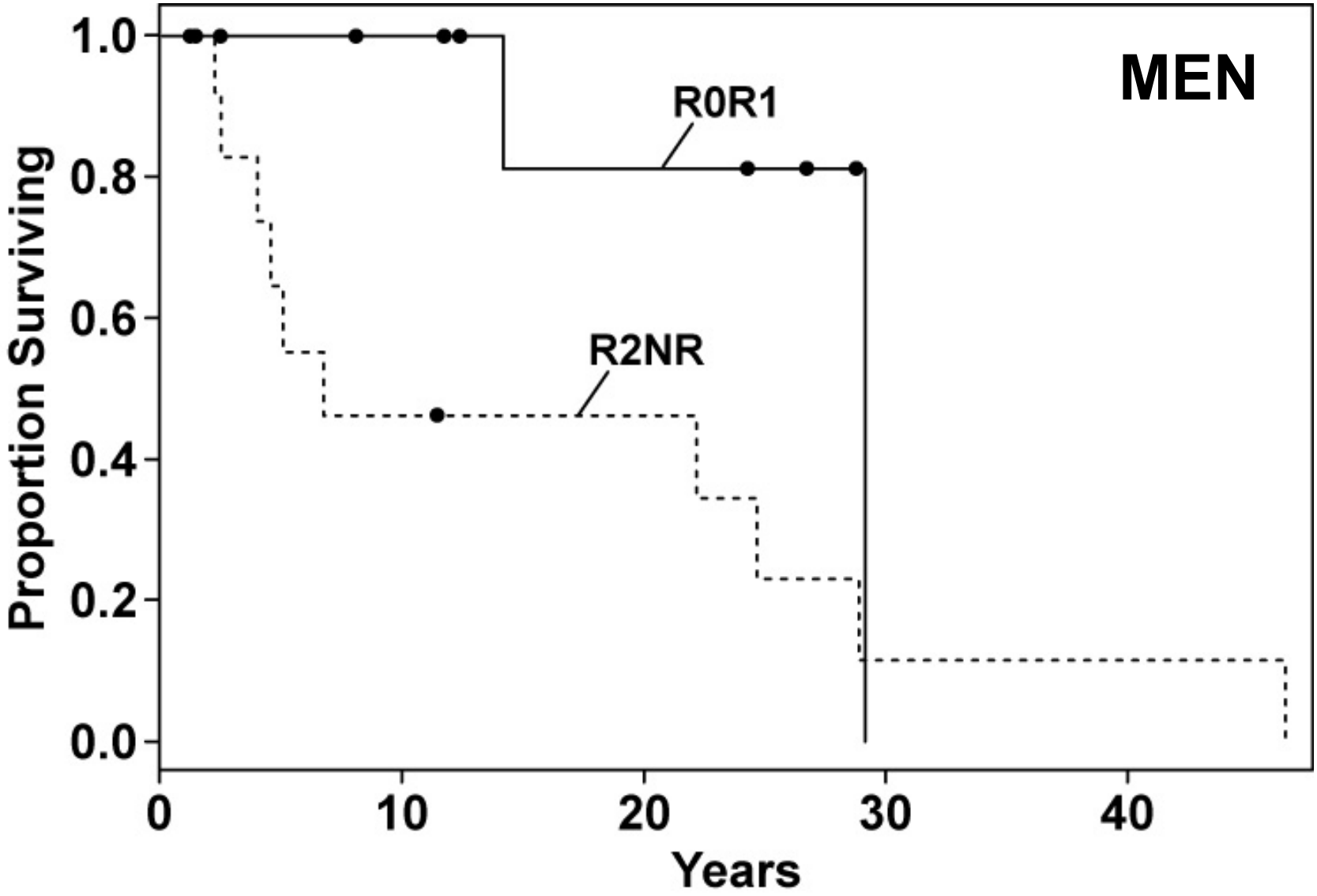
There was no difference in survival in sporadic and MEN pts.

Ellison et al., *J Am Coll Surg,* 202:897-905, 2006



Kaplan-Meier disease-specific survival curves comparing R0/R1 and R2/NR.

Ellison et al., *J Am Coll Surg,* 202:897-905, 2006



Kaplan-Meier disease-specific survival curves comparing R0/R1 and R2/NR.

Ellison et al., *J Am Coll Surg,* 202:897-905, 2006

Gastrinoma Treatment Options

- **Single lesion:**
  - **head of the pancreas: enucleation**
  - **body/tail of the pancreas: resection**
- **Single/multiple lesions in duodenum:**
  - **duodenotomy and local excision**
  - **pancreaticoduodenectomy**
- **Multiple lesions in pancreas: resection of body/tail**
  - **if residual disease, PPI**
  - **total gastrectomy**

Gastrinoma Treatment Options (cont'd)

- no tumor found: PPI; total gastrectomy
- liver metastases: resection
- metastatic disease: combination chemotherapy
  - doxorubicin + streptozocin
  - fluorouracil + streptozocin
  - octreotide

VIPoma

1958 Verner & Morrison 2 patients with watery diarrhea, hypokalemia and benign islet cell tumors

1967 Marks et al. suggested WDHA

1973 Bloom et al. high levels of VIP in patients with WDHA

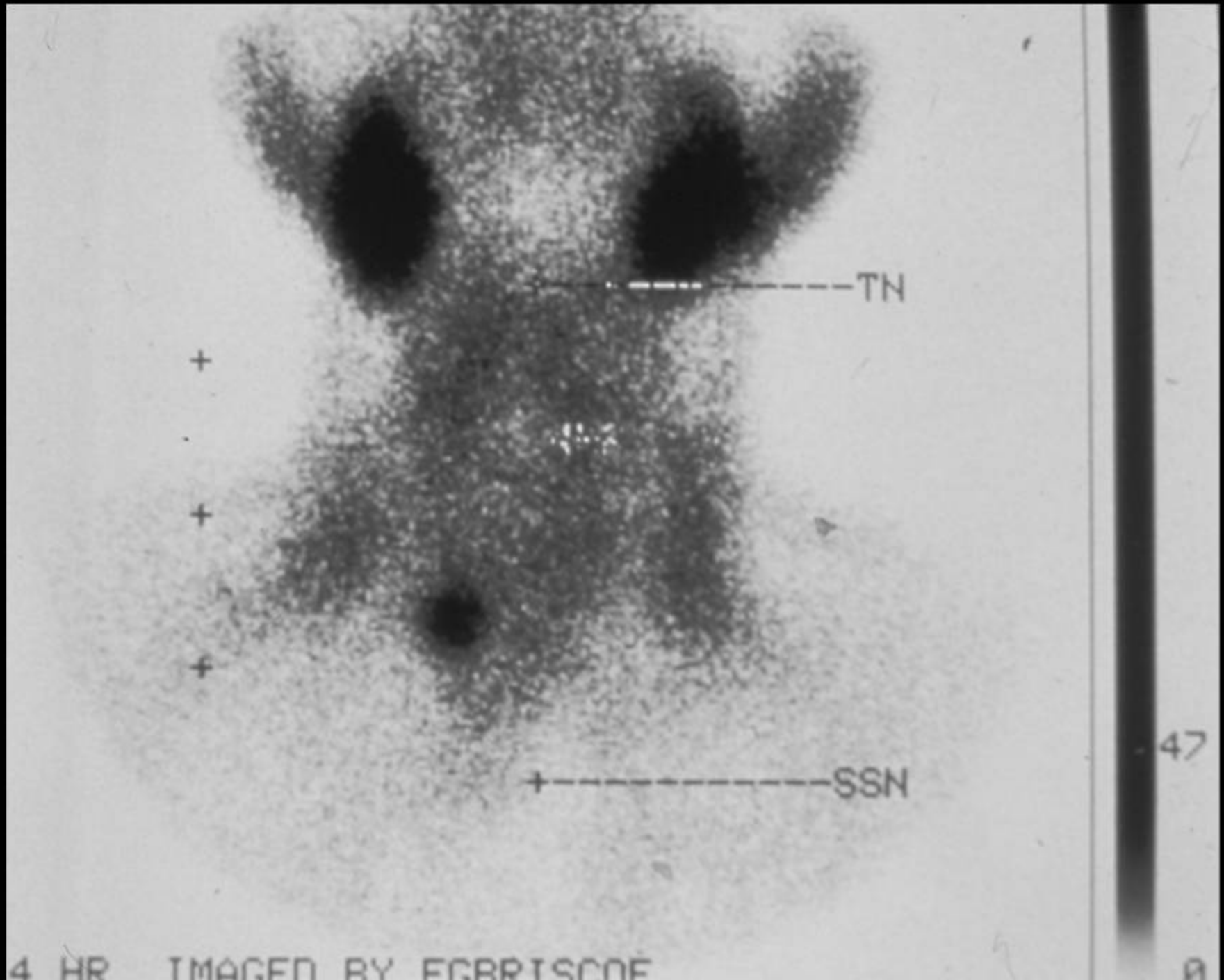
non-B cell tumor or ganglioneuroma

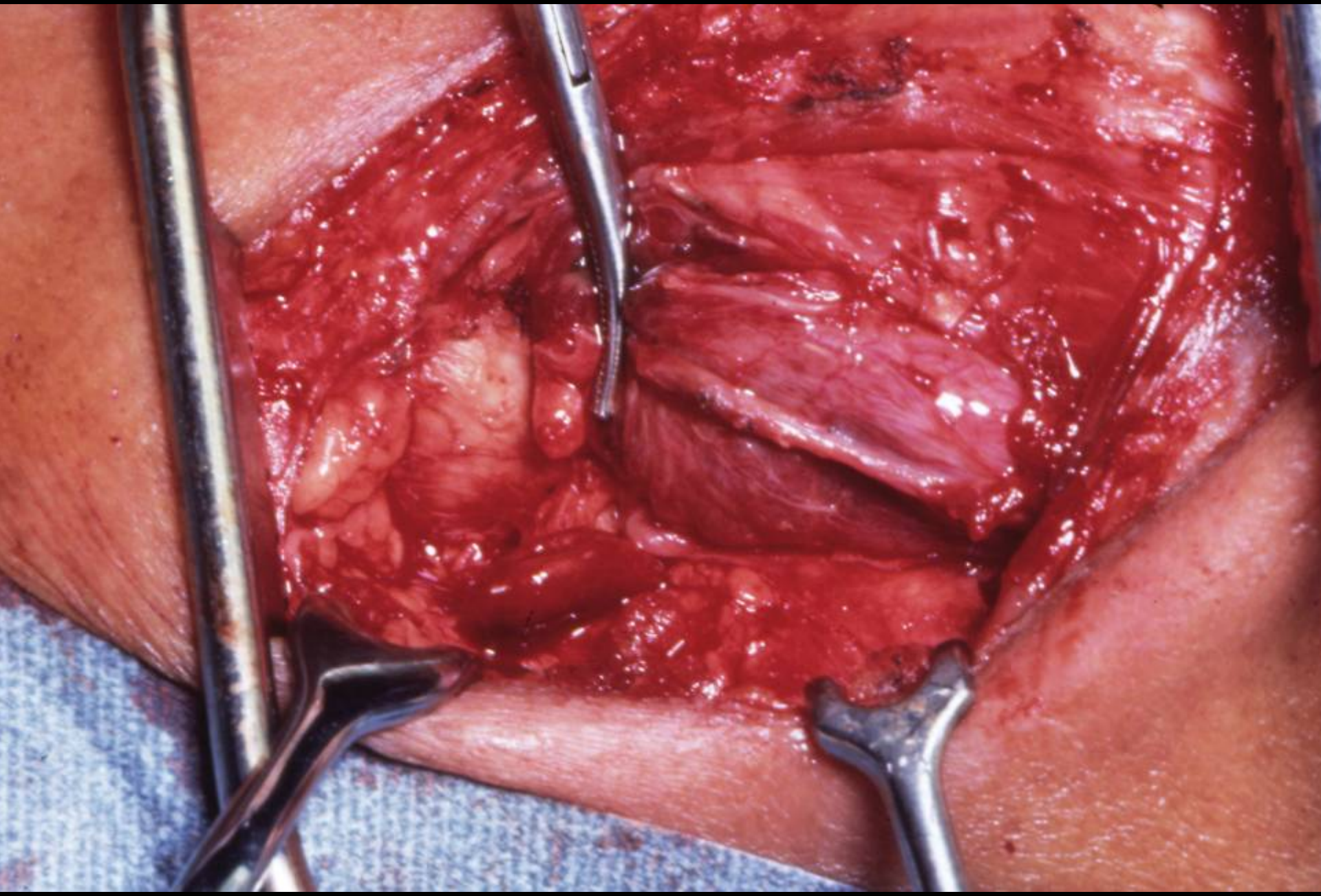
Verner-Morrison Syndrome (VIPoma)

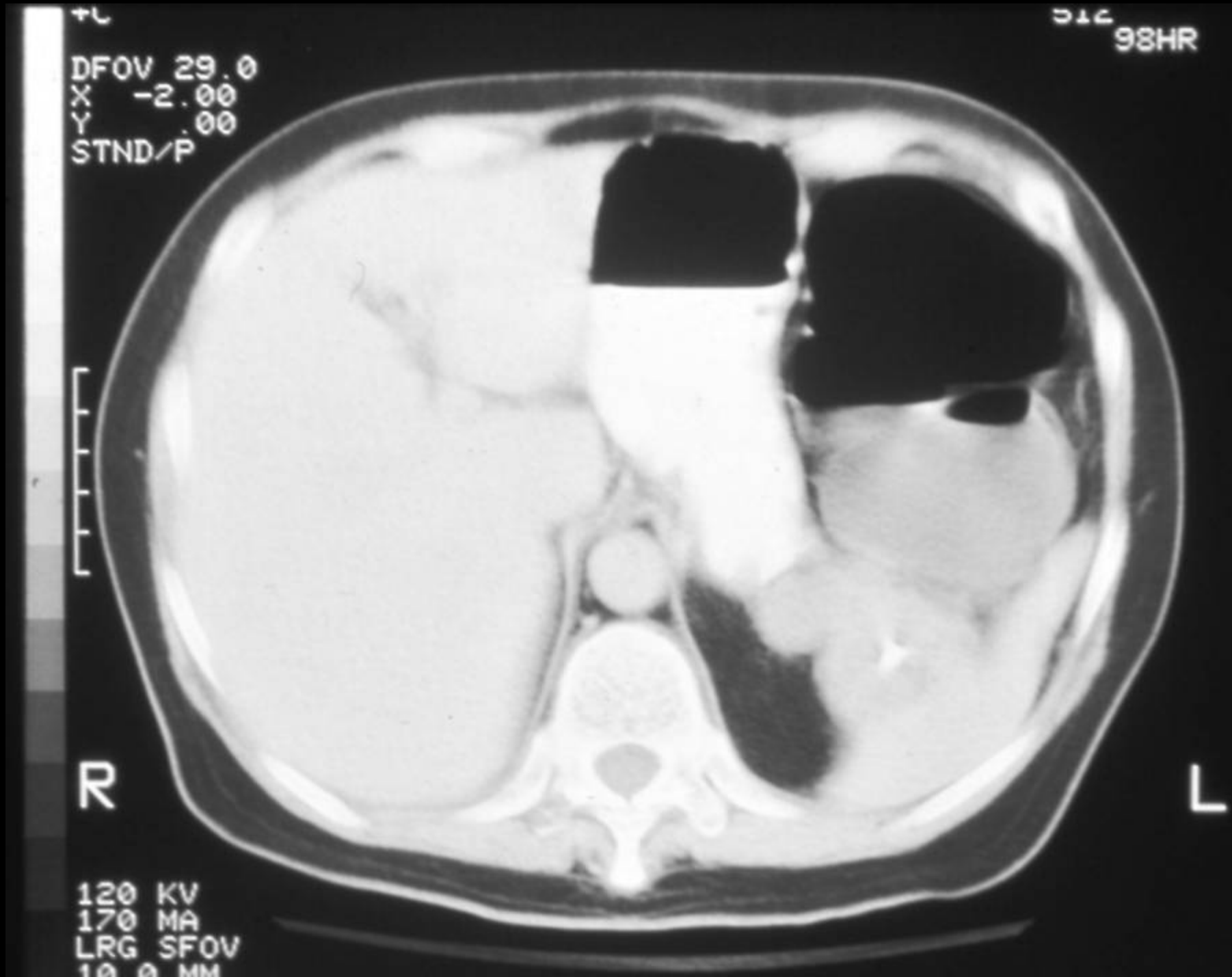
Diagnostic triad:

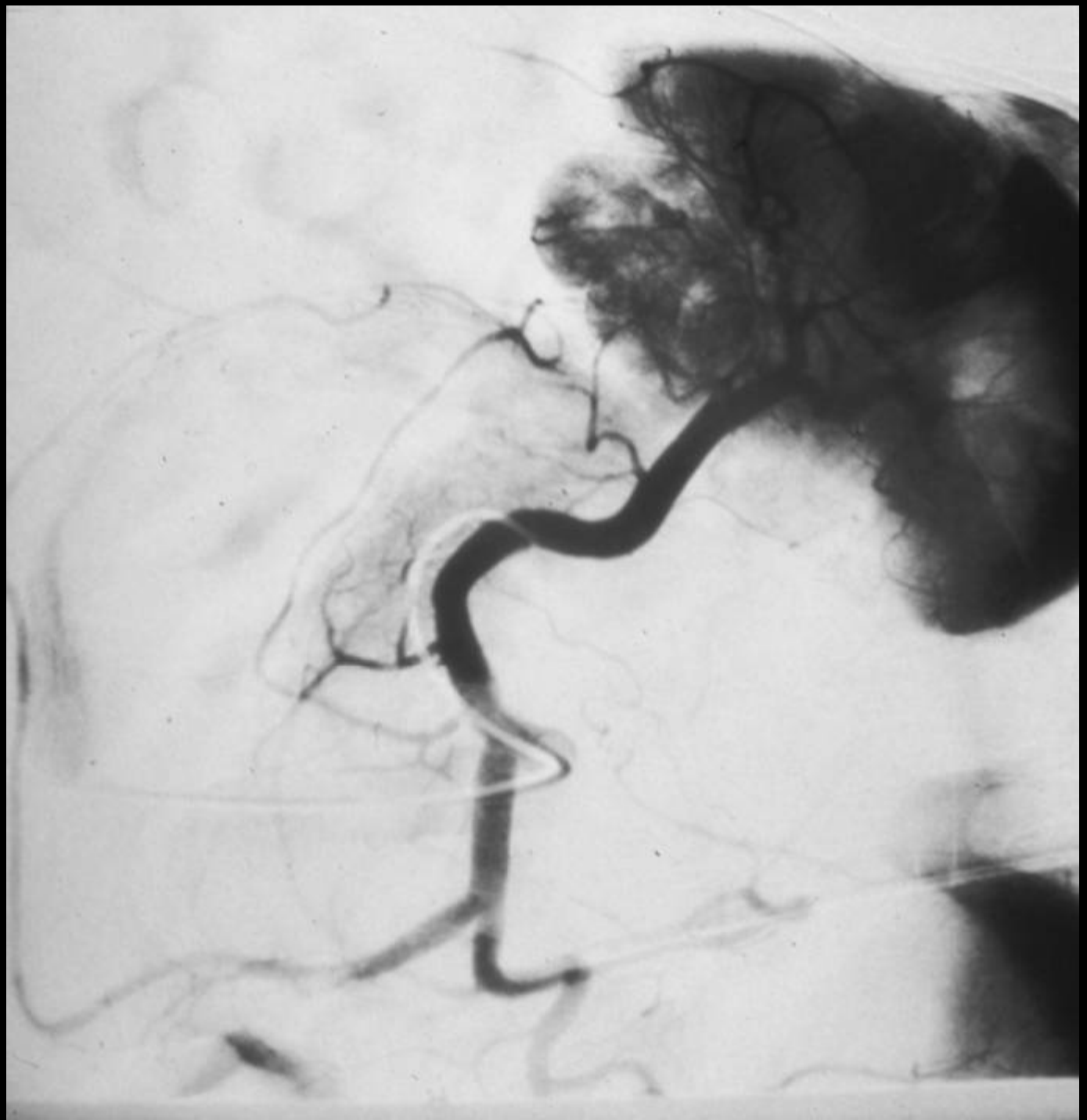
- **secretory diarrhea (3-5 L/day)**
- **elevated VIP level (225-2000 pg/ml)**
- **pancreatic tumor**

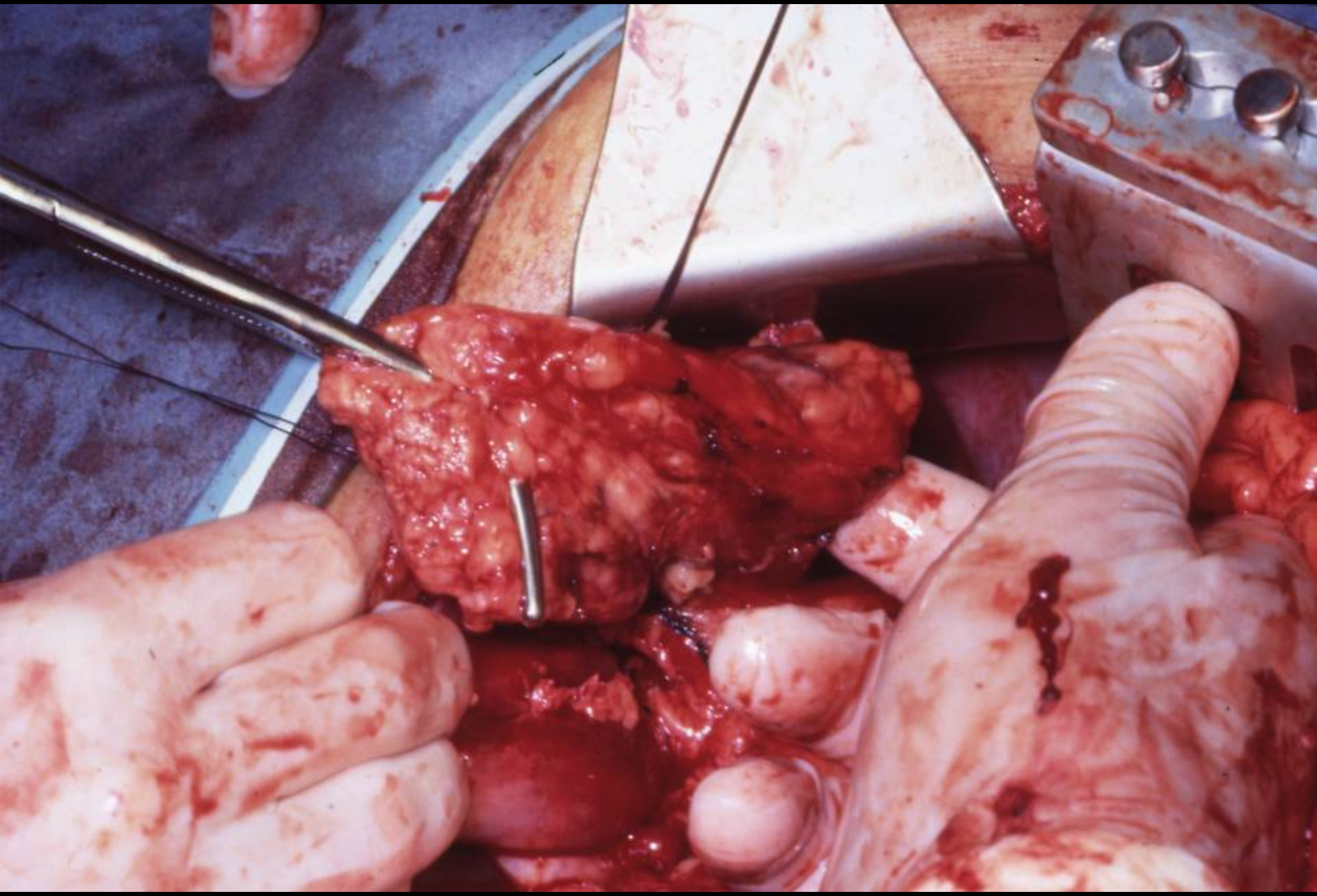
Patient:	**67-year old woman**	
Family History:	**Suggestive for the multiple-endocrine neoplasia syndrome**	
Past History:	**NIDDM, Hyperparathyroidism**	
Chief Complaint:	**Watery diarrhea** **Dehydration** **Hypokalemia** **Hyperglycemia** **Hypercalcemia**	
Hormone Level:	**PTH** **Gastrin** **VIP**	**110 pg/ml** **32 pg/ml** **> 2,000 pg/ml**

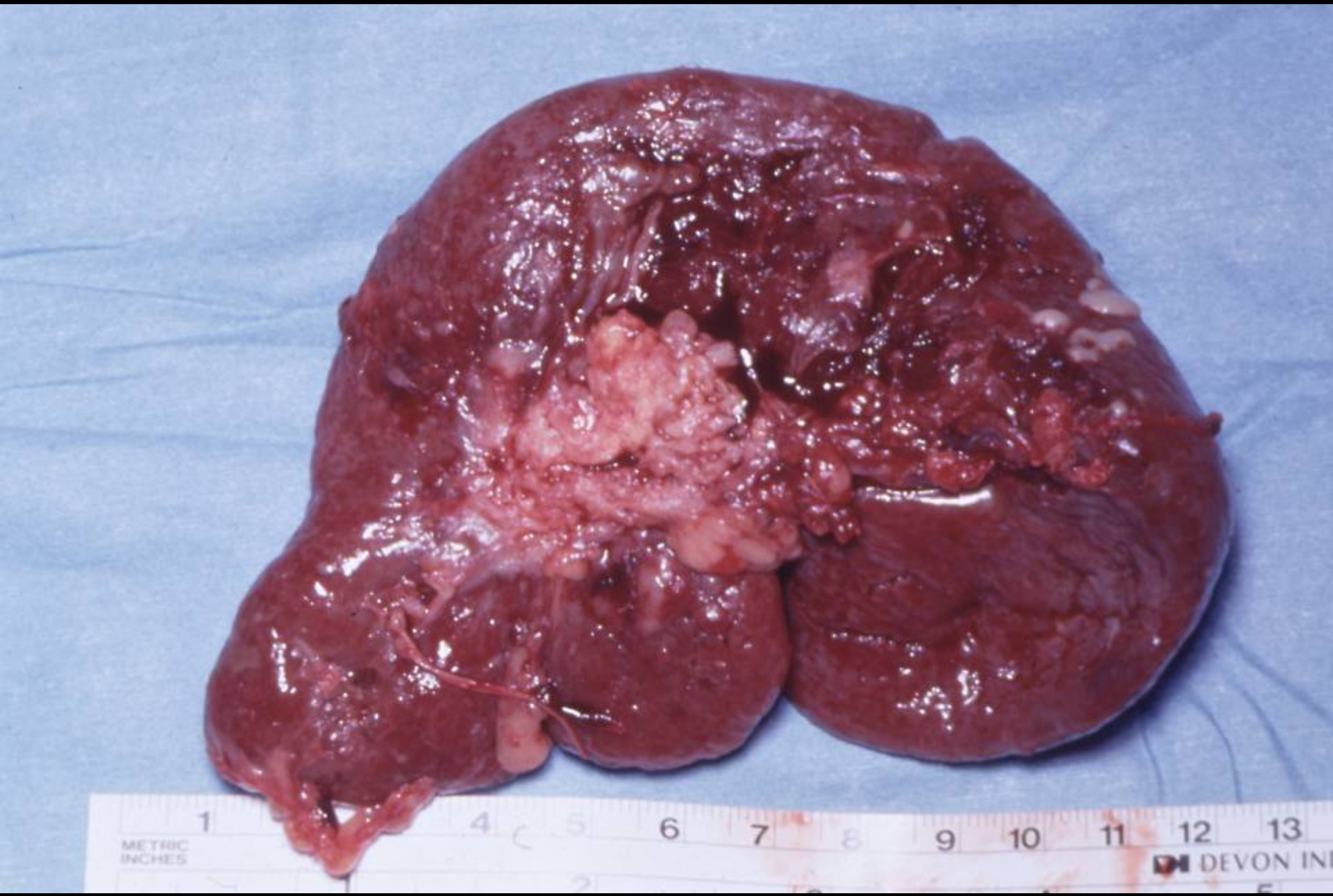

TN
SSN
47
0
4 HR IMAGED BY EGBRISCOE

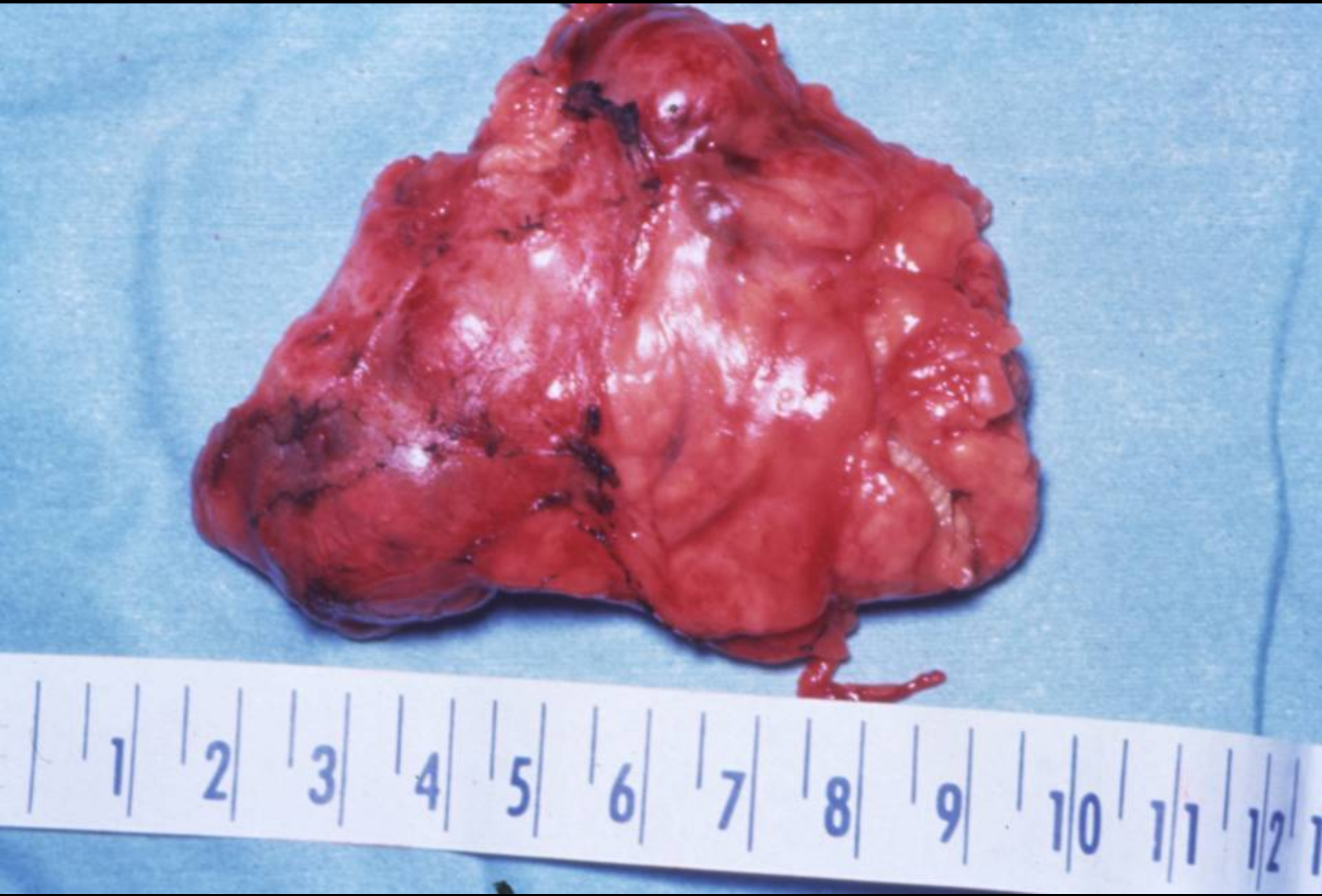



98HR
DFOV 29.0
X -2.00
Y .00
STND/P
R
L
120 KV
170 MA
LRG SFOV






1
6
7
9
10
11
12
13
METRIC
INCHES
DEVON


1
2
3
4
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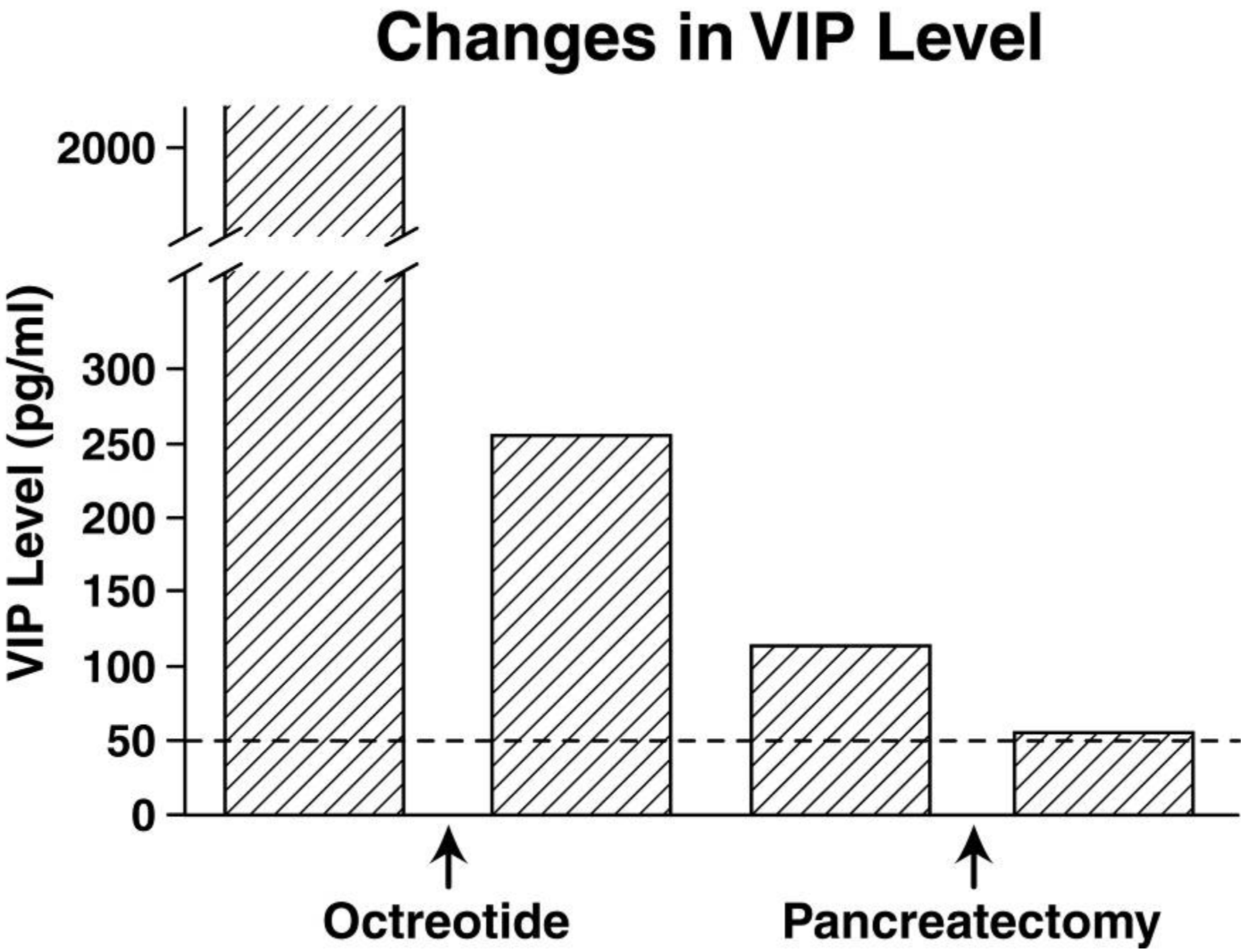
11
12


Changes in VIP Level
2000
300
250
200
150
100
50
0
VIP Level (pg/ml)
Octreotide
Pancreatectomy

History of Glucagonoma

1966 McGavran and colleagues– initial patient skin rash, anemia, diabetes mellitus, and islet-cell carcinoma. Blood and tumor glucagon levels very high.

1974 Mallinson and associates described the characteristic syndrome.

Glucagonoma Syndrome

- skin rash
- diabetes mellitus
- anemia
- weight loss
- elevated glucagon levels

Diagnosis of Glucagonoma

Causes of Hyperglucagonemia

Diabetes

Chronic renal failure

Shock

Acute pancreatitis

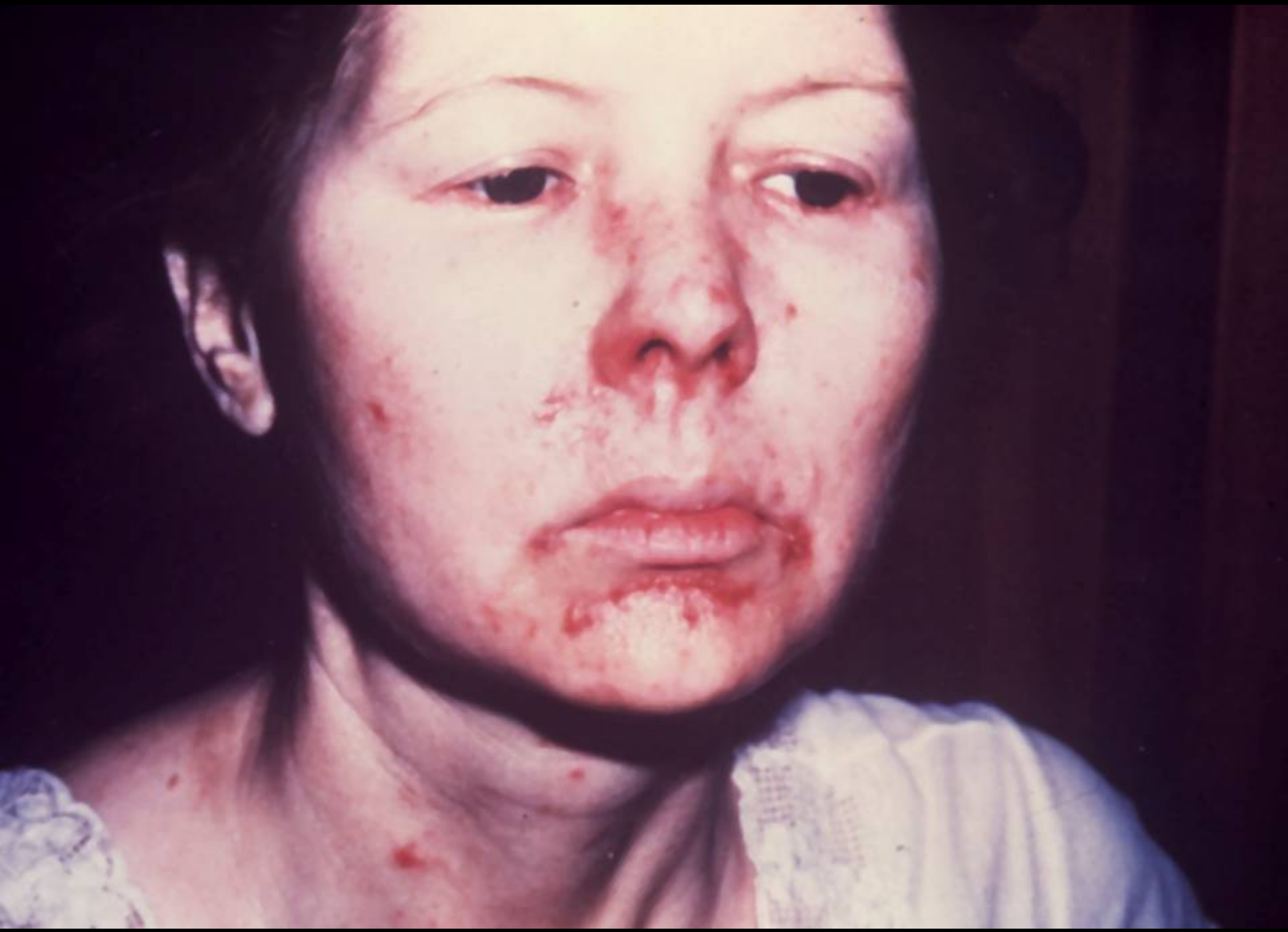
Cirrhosis

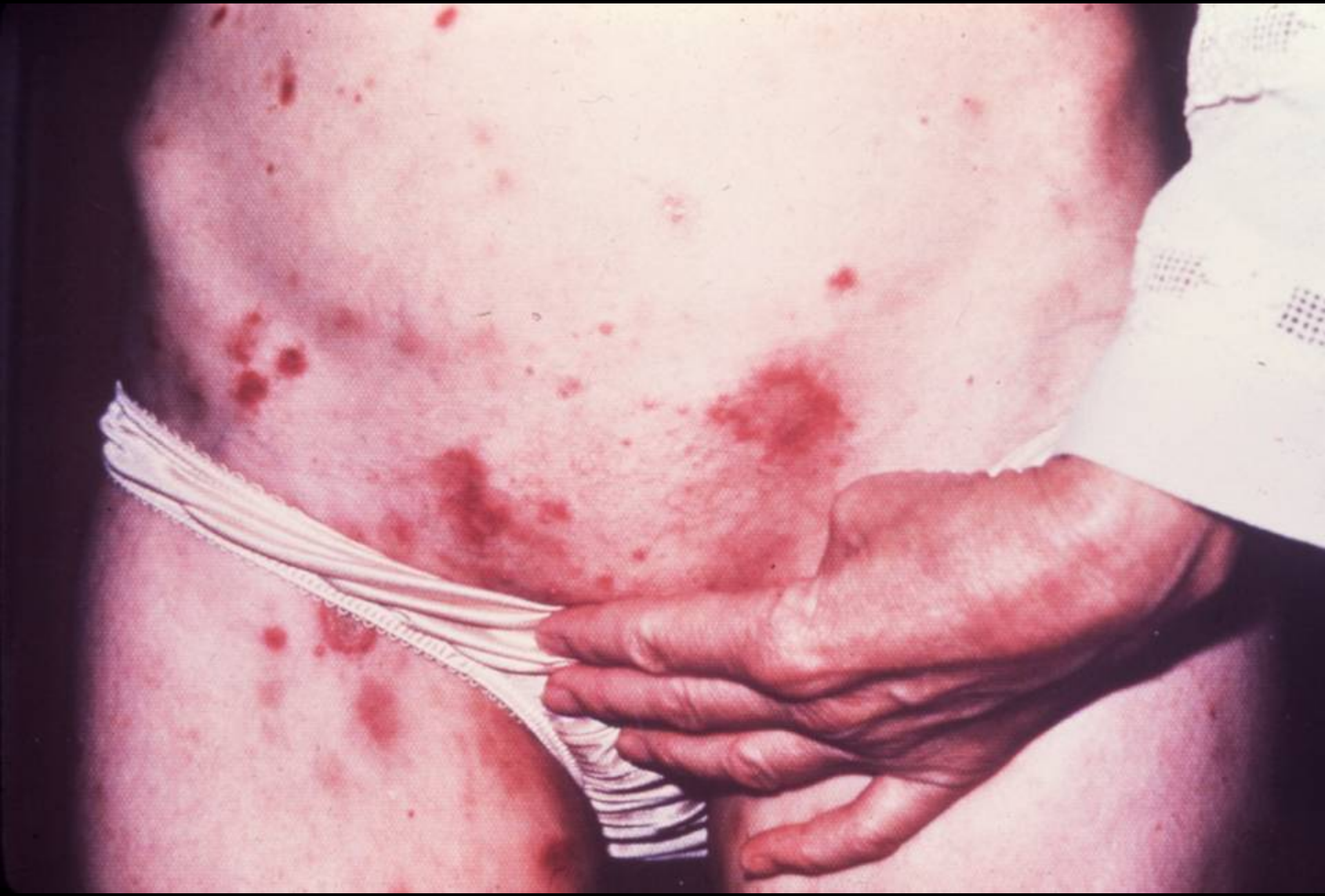
Familial hyperglucagonemia

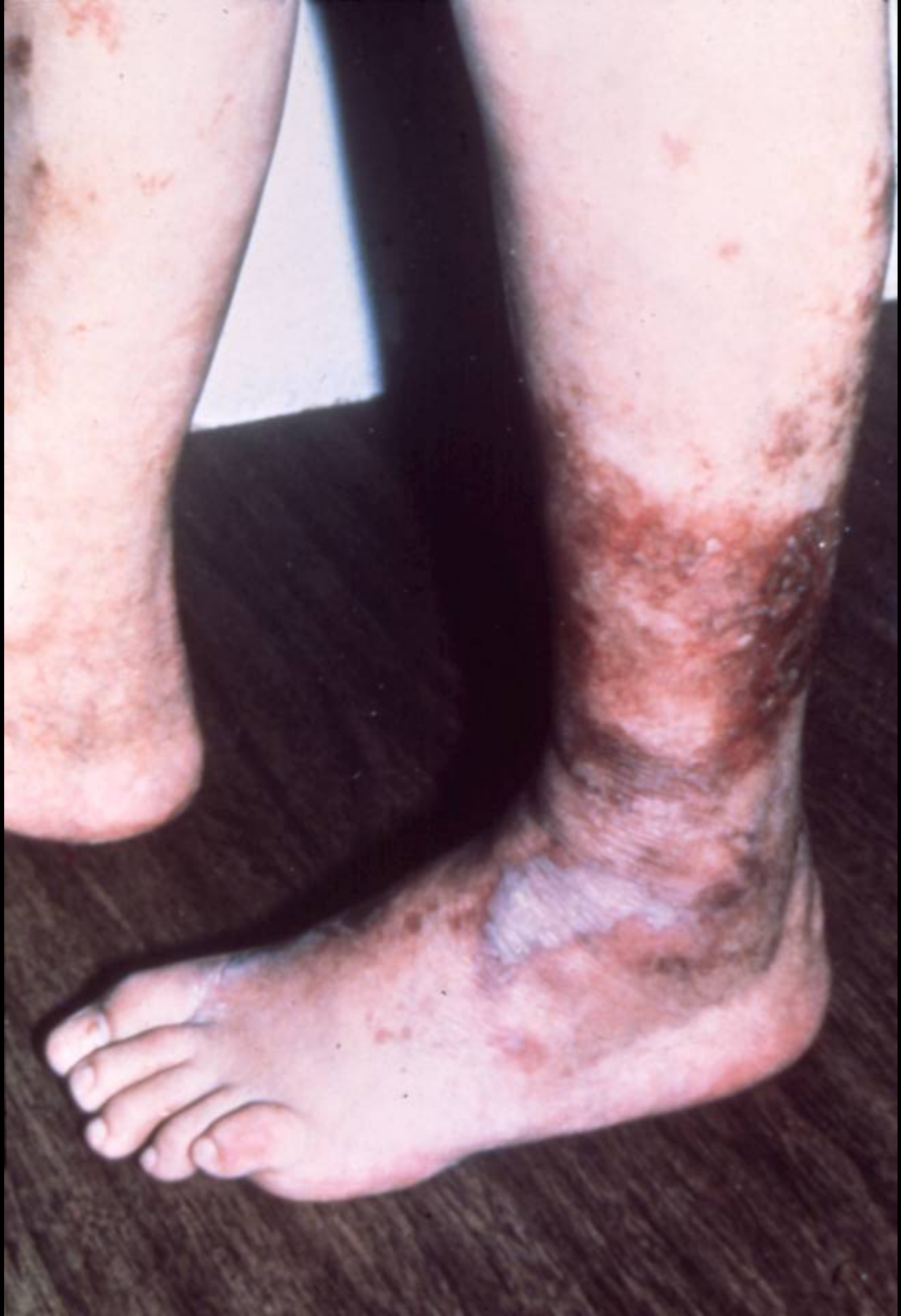
Exercise

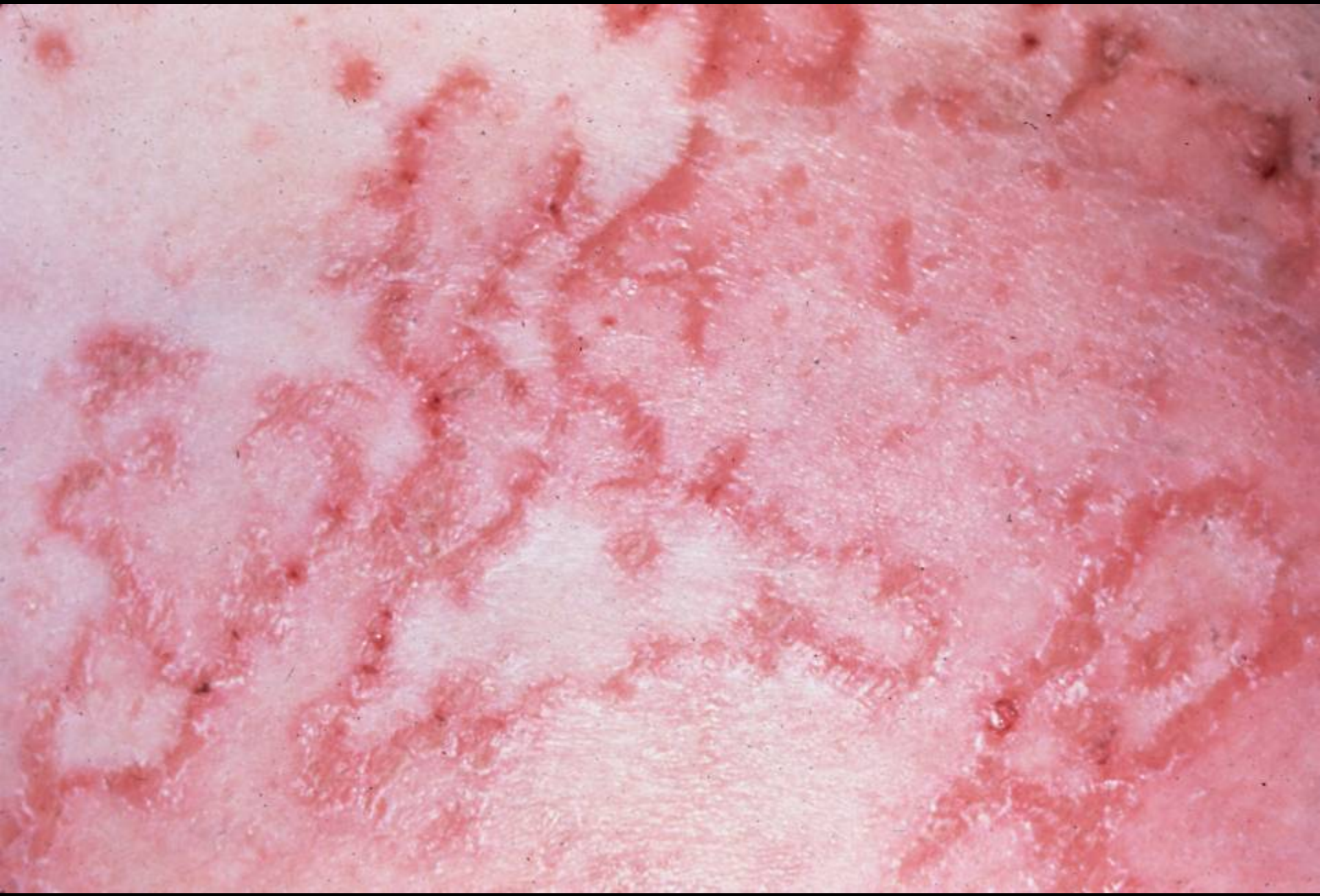
Antiglucagon antibodies

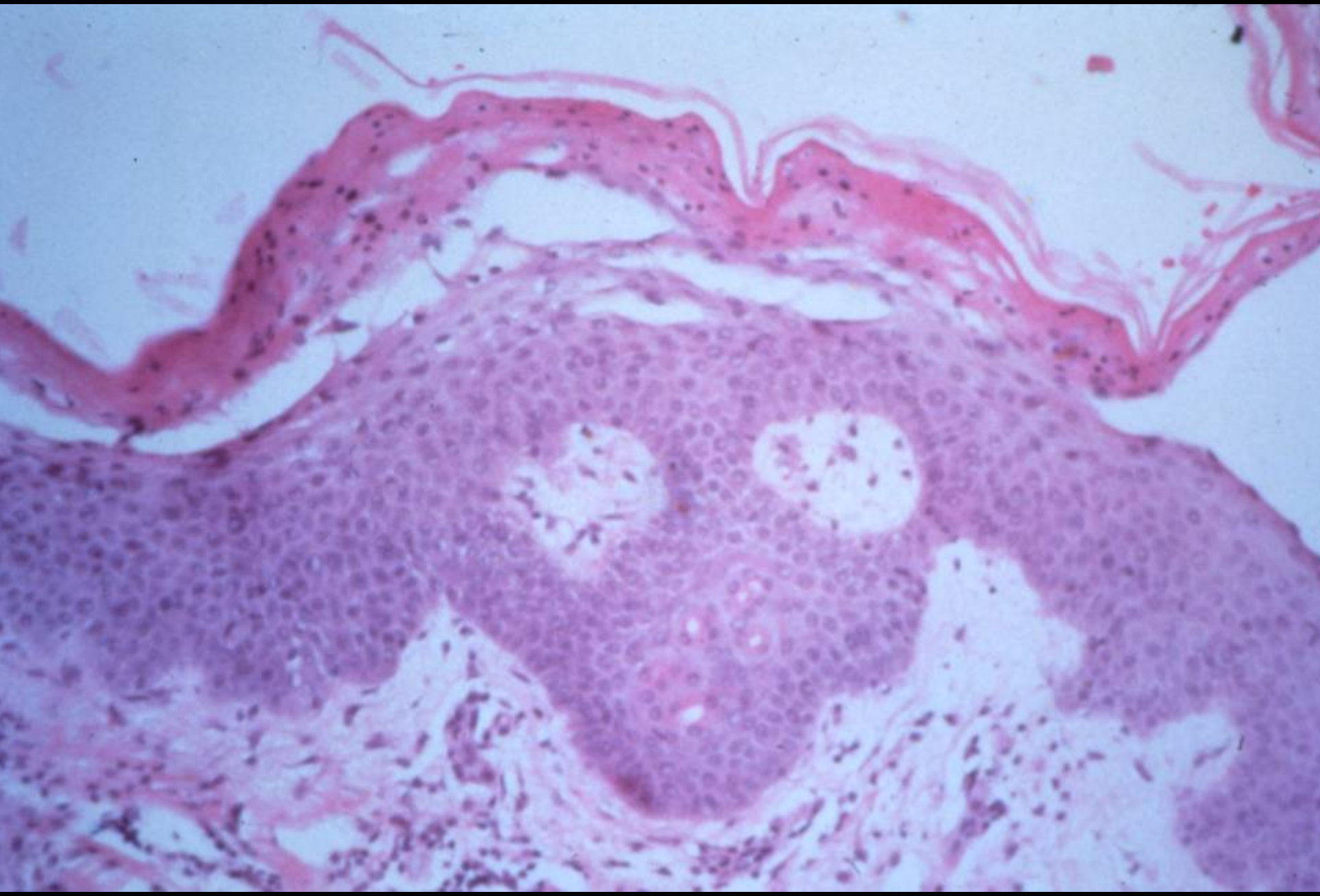
GLUCAGONOMA

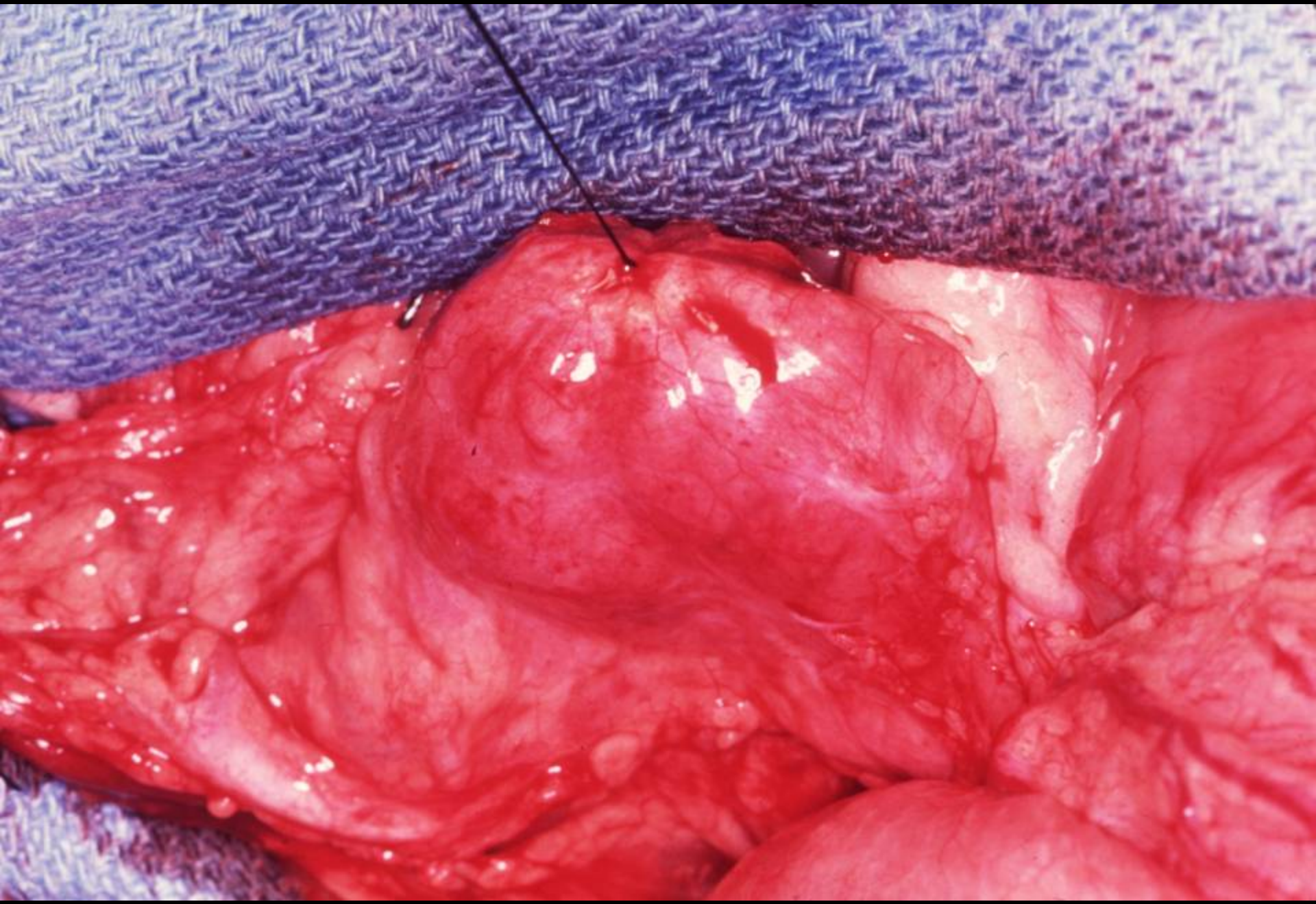


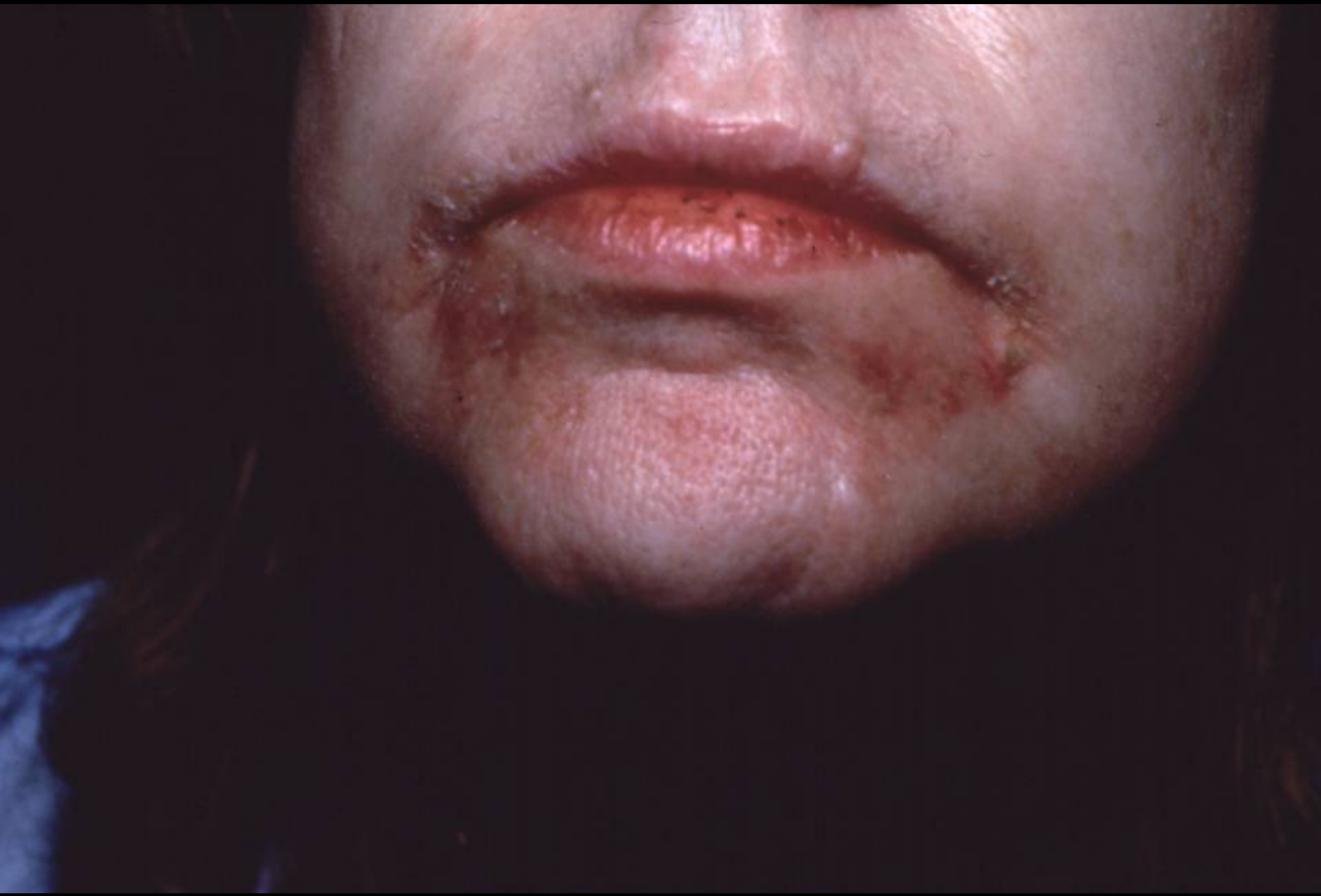


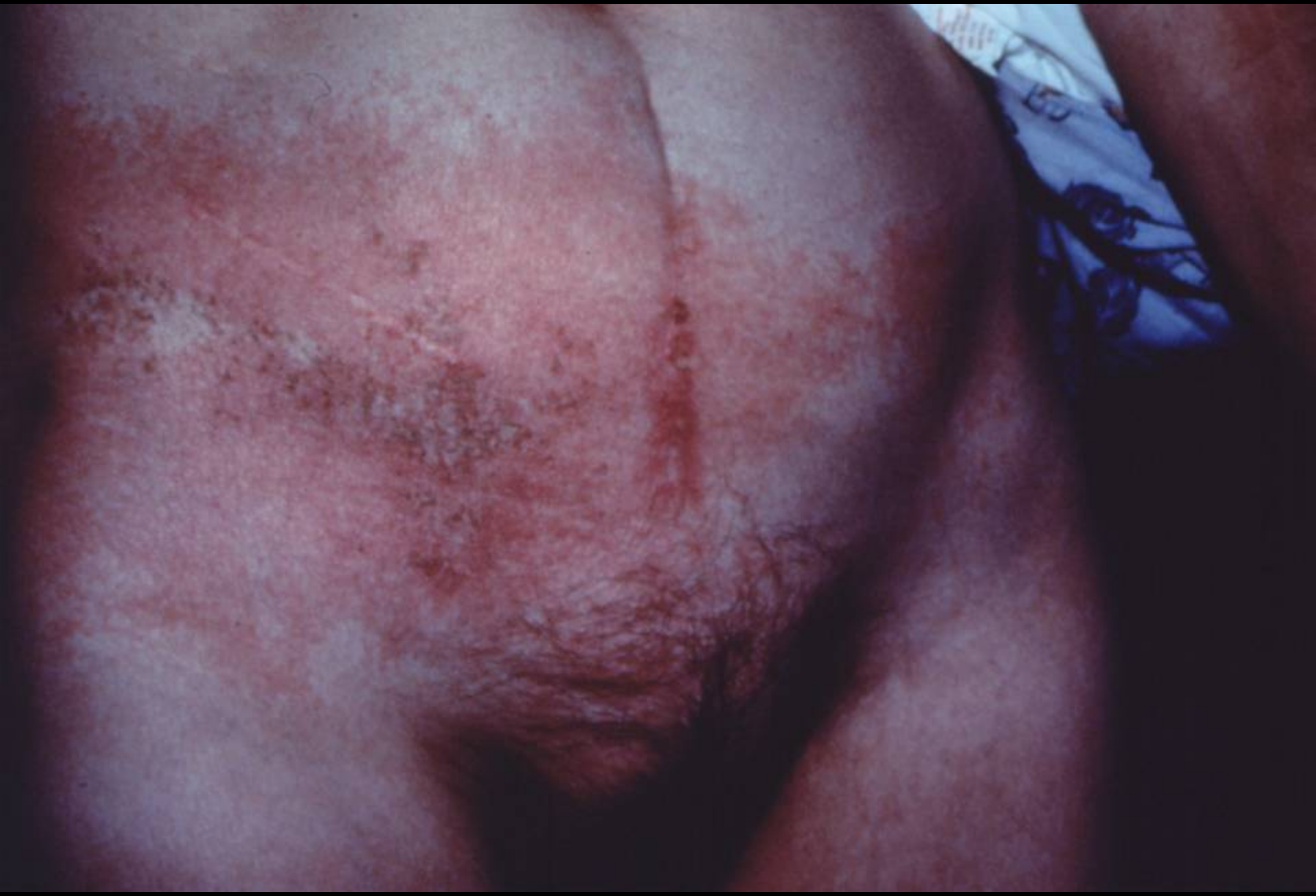


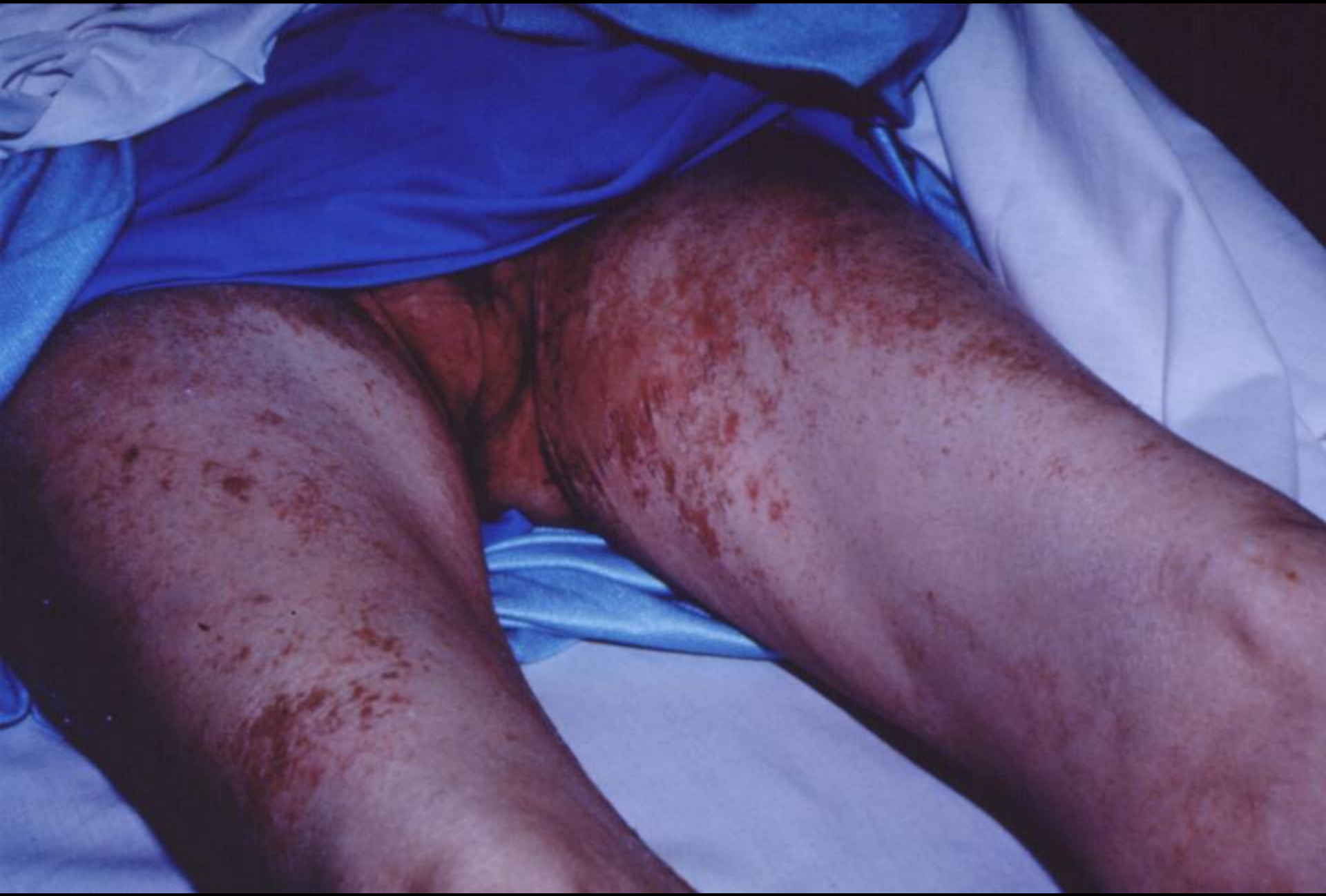












Plasma Amino Acid Concentrations (μmol/L) in a Patient With Glucagonoma and in Normal Volunteers (cont'd)

	Patient With Glucagonoma	Normal Volunteers*
Glucogenic and ketogenic amino acids		
Isoleucine	40†	59 ± 3
Lysine	34†	167 ± 9
Phenylalanine	36†	50 ± 2
Tyrosine	34†	50 ± 4
Ketogenic amino acid		
Leucine	27†	113 ± 10

*Data (mean ± SE) from normal volunteers studied in our laboratory.
†Value less than 2 SD below mean value for normal volunteers.

Klein et al, *Metabolism* 41:1171-1175, 1992

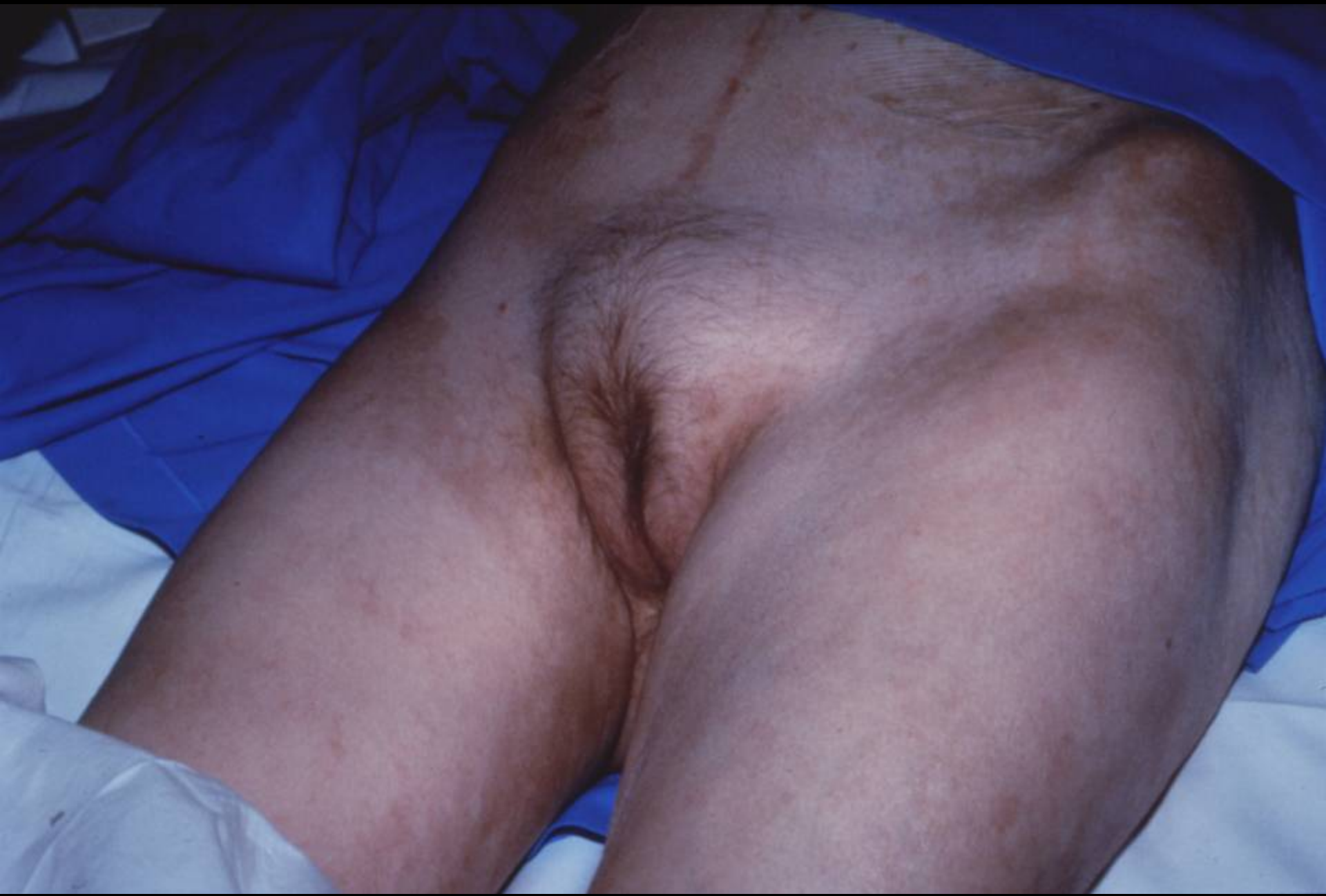
Plasma Amino Acid Concentrations (mmol/L) in a Patient With Glucagonoma and in Normal Volunteers

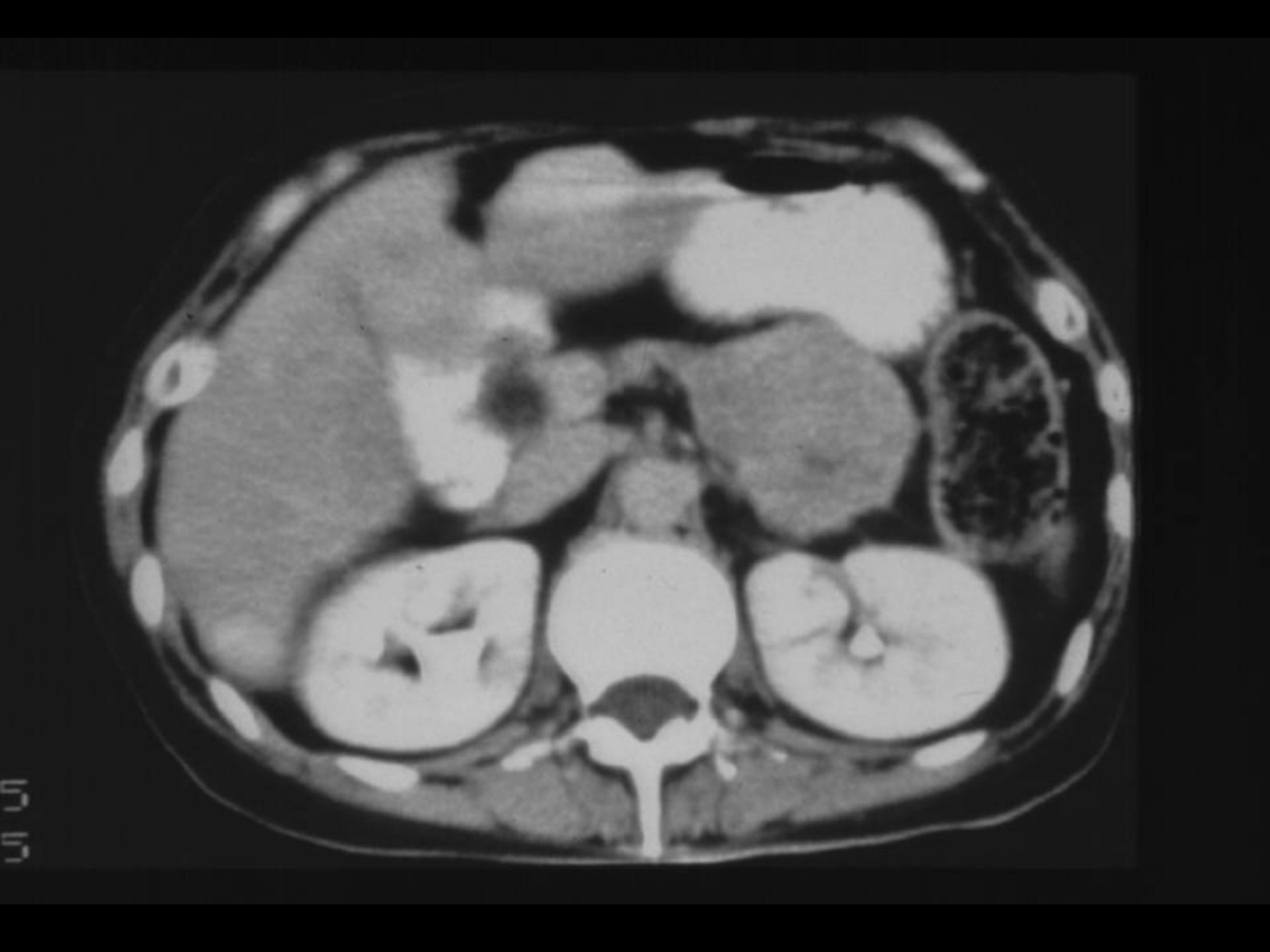
	Patient With Glucagonoma	Normal Volunteers*
Glucogenic amino acids		
Alanine	34†	255 ± 13
Arginine19†	110 ± 7	
Aspartate	2†	10 ± 1
Glutamate/glutamine	63†	546 ± 56
Glycine	73†	226 ± 32
Histidine	38†	80 ± 3
Methionine	16	18 ± 4
Proline	2†	213 ± 16
Serine	29†	119 ± 14
Threonine	17†	127 ± 14
Valine	32†	220 ± 9

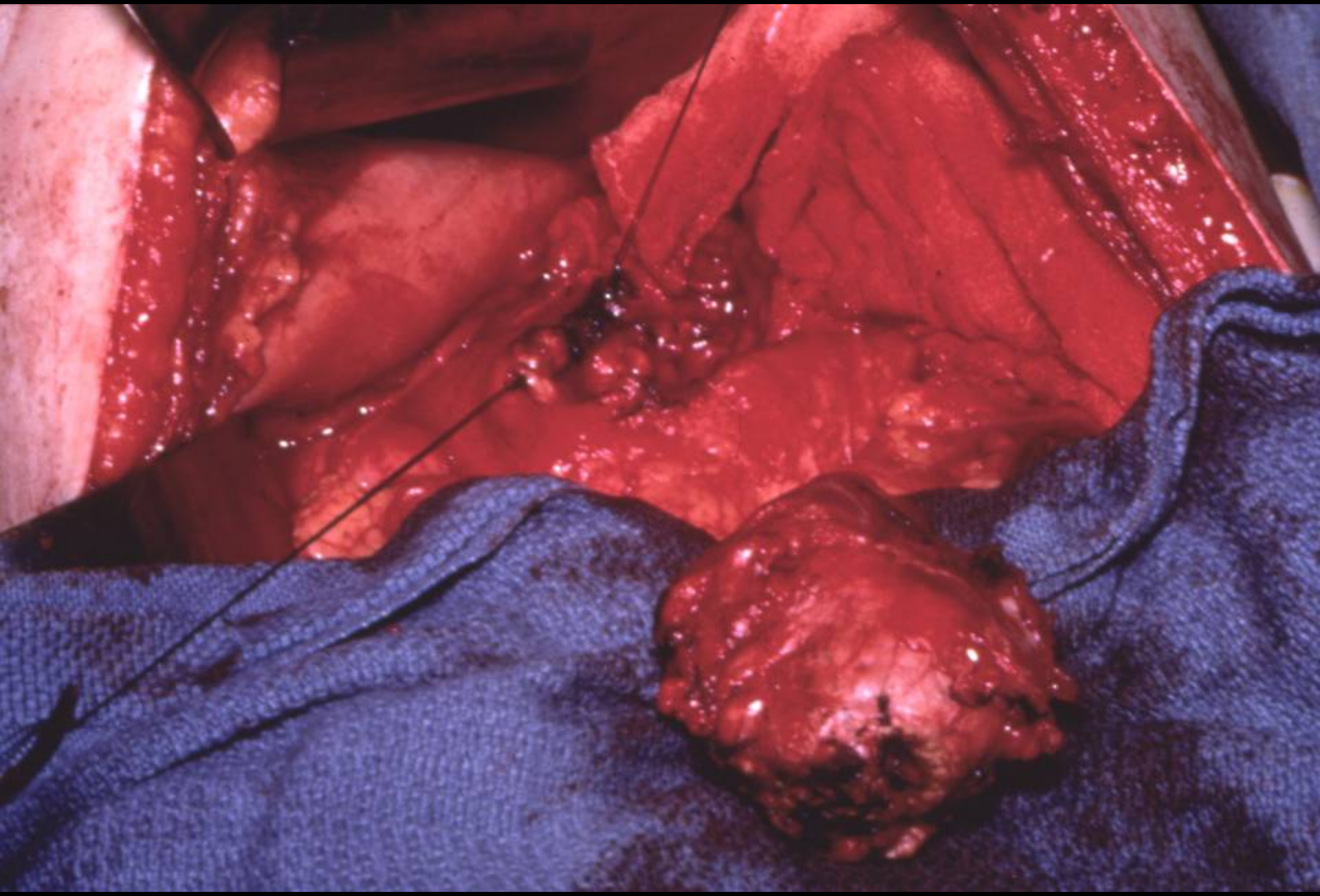
*Data (mean ± SE) from normal volunteers studied in our laboratory.

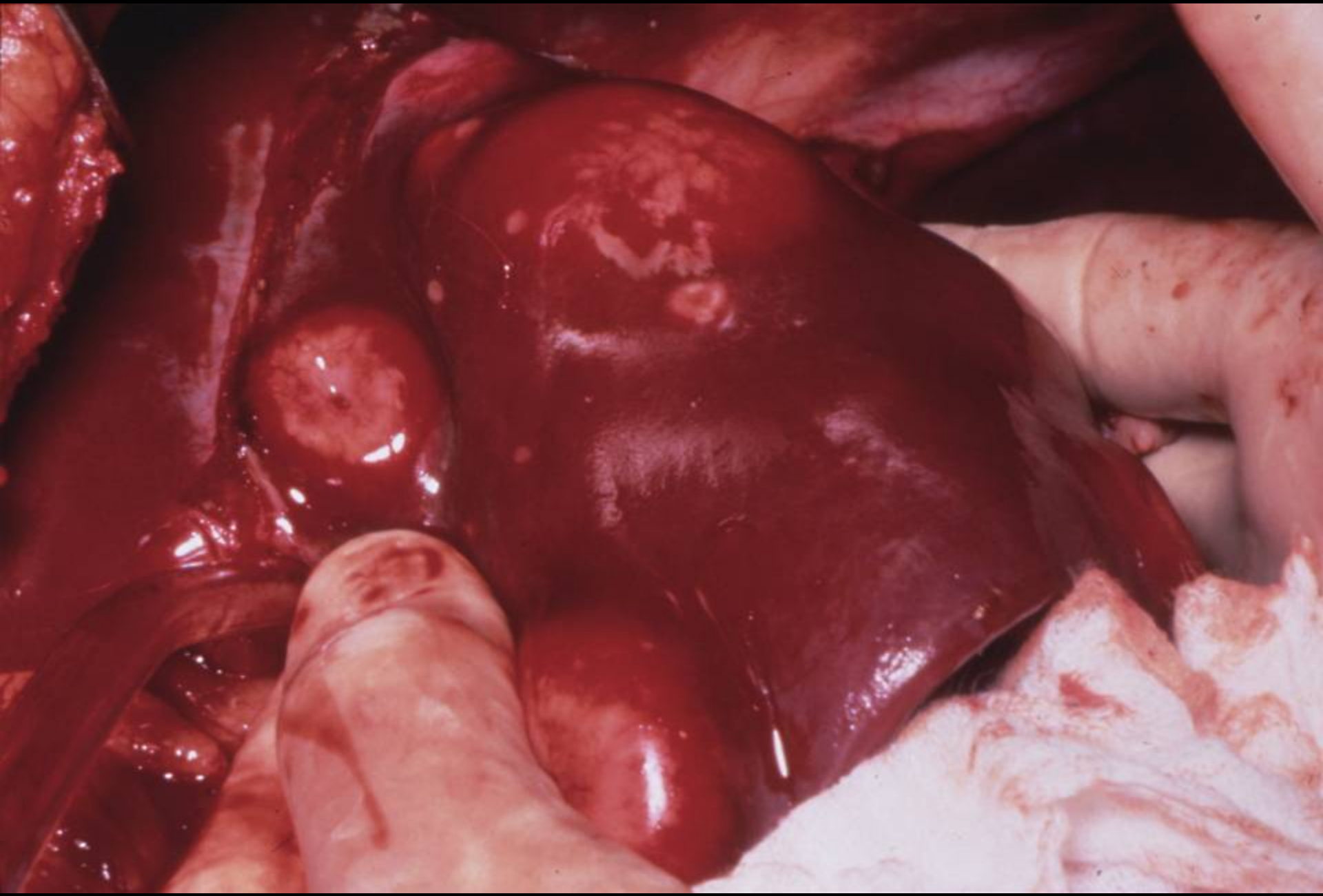
†Value less than 2 SD below mean value for normal volunteers.

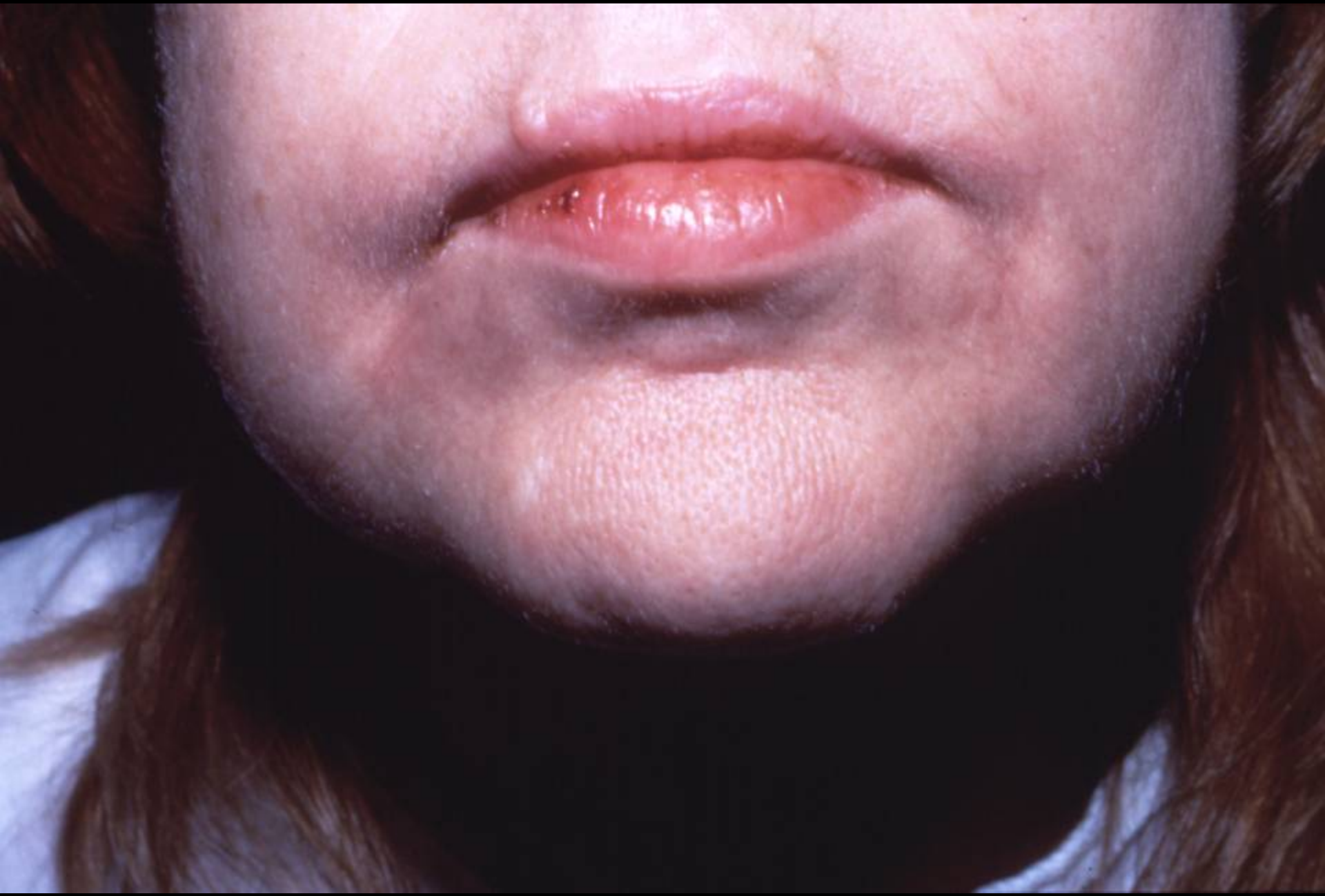
Klein et al, *Metabolism* 41:1171-1175, 1992

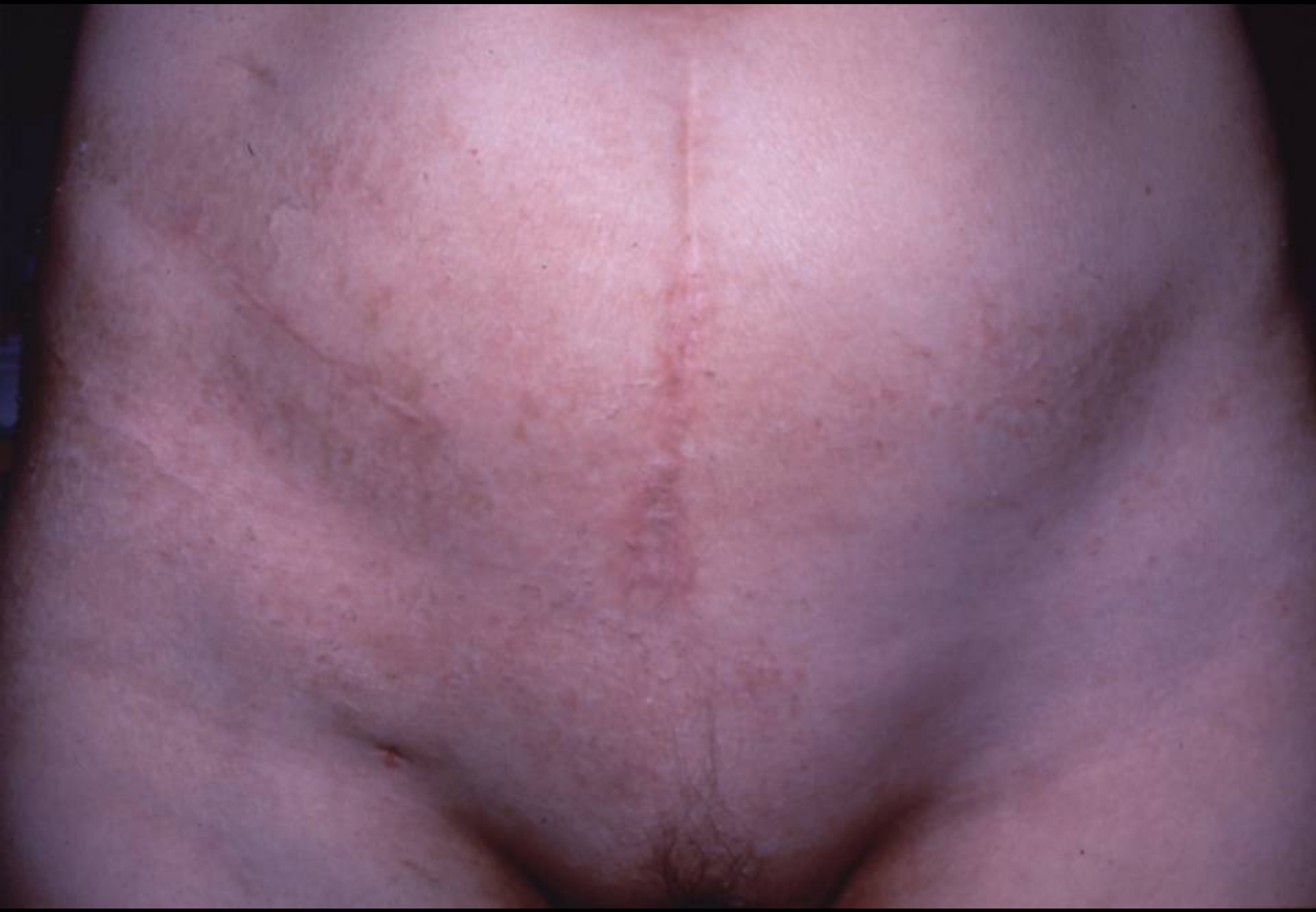












Somatostatinoma

1977 Ganda et al.
Larsson et al.

2 patients with somatostatin producing islet cell tumors

- Nonspecific sx; usually cholelithiasis diabetes, steatorrhea and hyperchlorhydria
- Von Recklinghausen's disease

Somatostatinoma

Diagnostic criteria:

- **steatorrhea**
- **diabetes**
- **hypochlorhydria**
- **gallstones**
- **increased levels of serum STS**
- **pancreatic tumor**

70-90% malignant

At operation for tumor, do cholecystectomy

Cancer of the Endocrine Pancreas

- surgery only curative modality
- effective palliation
  - slow-growing nature
  - pharmacologic therapy
  - combination chemotherapy

AJCC

Stage	T	N	M
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1-3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Luo et al, *J Clin Oncol* 35:274-280, 2017