
CONNECTING THE DOTS: MAKING SENSE OF PARANEOPLASTIC SYNDROMES

JP MCGHIE, MEDICAL ONCOLOGIST; BC CANCER, VICTORIA

For the FPON series
20 Sept 2018



DISCLOSURES

- I have received speakers honoraria from the following companies: Amgen, Astra-Zeneca, Celgene, Eisai, Ipsen, Roche
- I have requested funds from several companies to support continuing medical education on Vancouver Island (as the chair of the Van Isle Oncology Conference, VIONC)
- I participate in clinical trials and some of those trials are sponsored by private companies: Amgen, Celldex

OBJECTIVES

By the end of this presentation, you should be able to...

- 1) Describe the key features of Paraneoplastic Syndromes (PNS).
- 2) Explain how PNS arise (mechanism).
- 3) Discuss the collection of symptoms seen in relation to a primary tumour.
- 4) Manage the symptoms of PNS in a multidisciplinary team.

PLAN FOR TODAY

- Introduction: define paraneoplastic syndrome (PNS)
- Mechanisms: the two main mechanisms of PNS demonstrated in two case reports
- Cases: discuss common scenarios, what we might see and do
- Conclusions: summarize the take home messages



QUESTION 1

- In a word (or two or three), what do you think of when you hear “paraneoplastic syndrome”?

INTRODUCTION



INTRODUCTION

- Full disclosure: I am not a PNS expert



INTRODUCTION

As a medical oncologist in Victoria I treat ...

- Breast Cancer
- Brain Cancer
- Bowel Cancer (and other GI malignancies)

(My cases come, largely, from this cohort)



Direct vs Indirect Effects of Cancer



Organ failure
Effects of therapy

Mass Effect



Hormone/cytokine secretion

Immune responses

INTRODUCTION

Paraneoplastic Syndrome (PNS) defined:

Paraneoplastic syndromes are

- symptoms that occur at sites distant from a tumor or its metastasis.
- clinical syndromes involving nonmetastatic systemic effects that accompany malignant disease.
- syndromes that occur when a cancer causes unusual symptoms due to substances (ie hormones, antibodies) that circulate in the bloodstream.



INTRODUCTION



Armand Trousseau (1801 – 1867)

- Astute observer
- Celebrated instructor
- Has his own syndrome!
- Public health expert
- Designed surgical instruments
- Politician (post French Revolution)
- Spawned a long line of famous physicians

INTRODUCTION



Armand Trousseau (1801 – 1867)

- Clots and cancer seem to co-exist
- Trousseau's Syndrome is the existence of multiple superficial clots in various parts of the body over time
- These clots are sometimes found at multiple locations and can occur in uncommon sites
- Most commonly associated cancers were gastric, lung and pancreas

So great, in my opinion, is the semiotic value of phlegmasia in the cancerous cachexia, that I regard this phlegmasia as a sign of the cancerous diathesis as certain as sanguinolent effusion into the serous cavities

INTRODUCTION



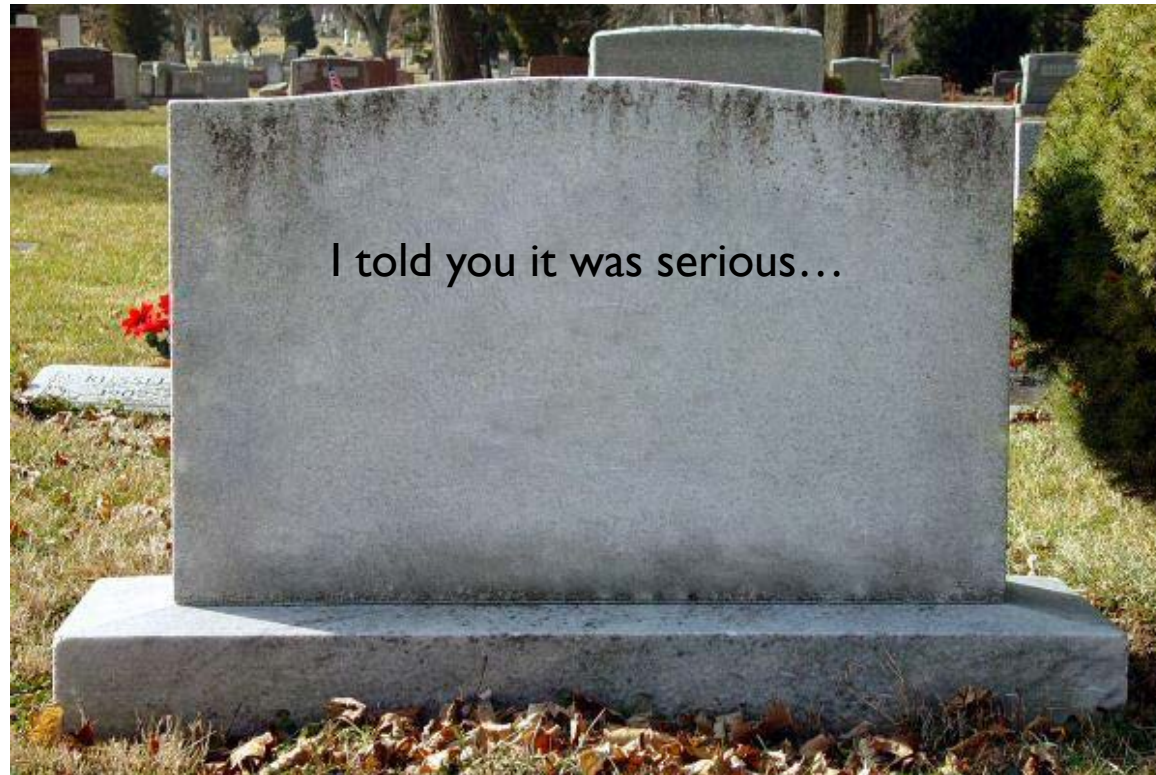
Armand Trousseau (1801 – 1867)

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“If I see clots in a patient who is cachectic, they very likely have cancer”

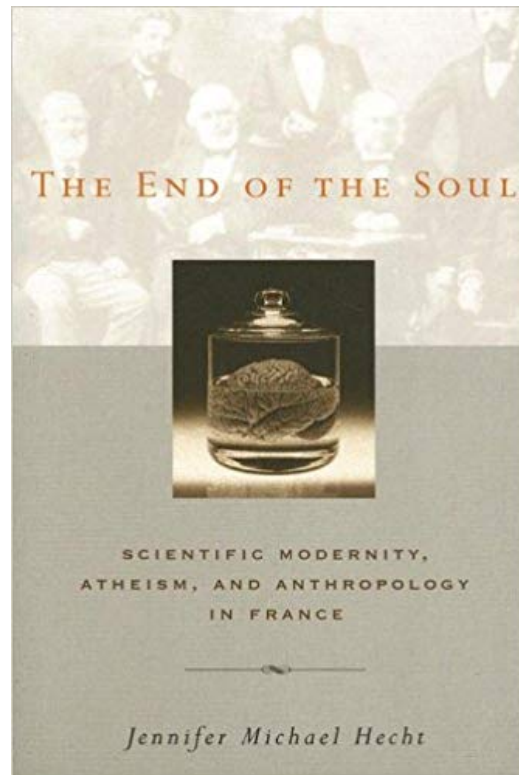
INTRODUCTION

Trousseau developed
Trousseau's Syndrome and
diagnosed himself with
gastric cancer in 1867



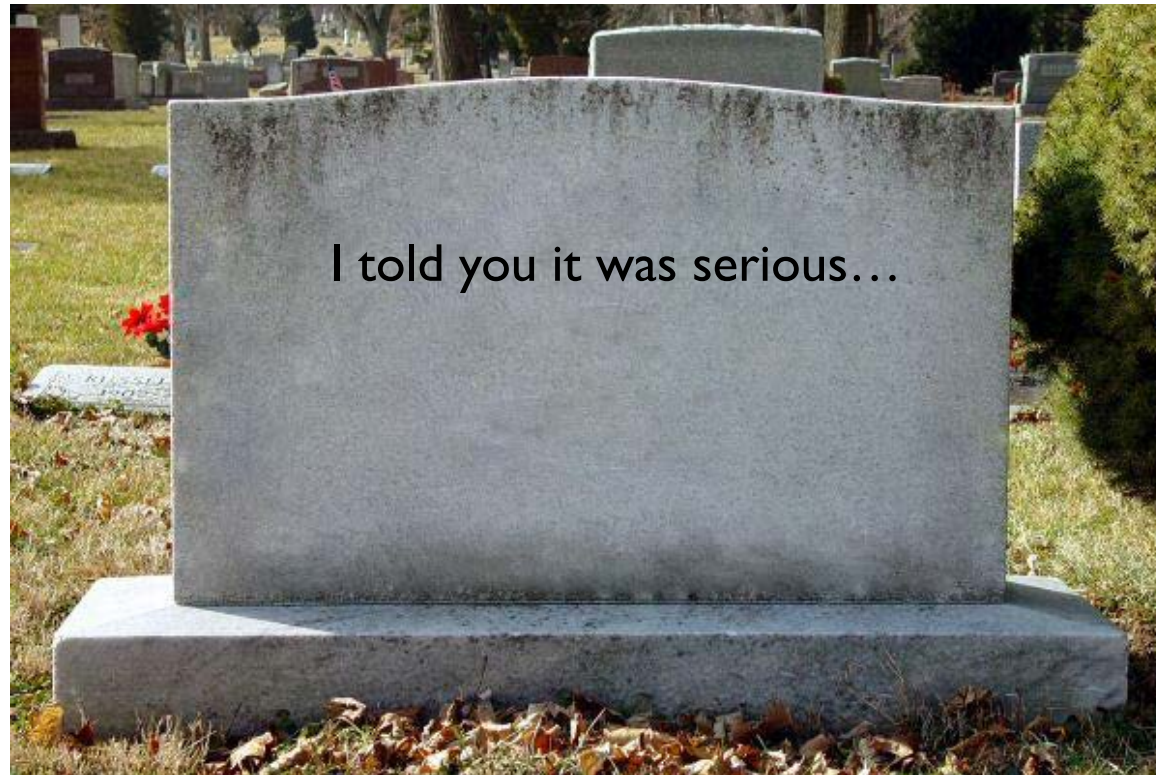
INTRODUCTION

If you were a member of the “Society of Mutual Autopsy” you could perform autopsies. However, when you passed away, it was then your turn to educate the group.



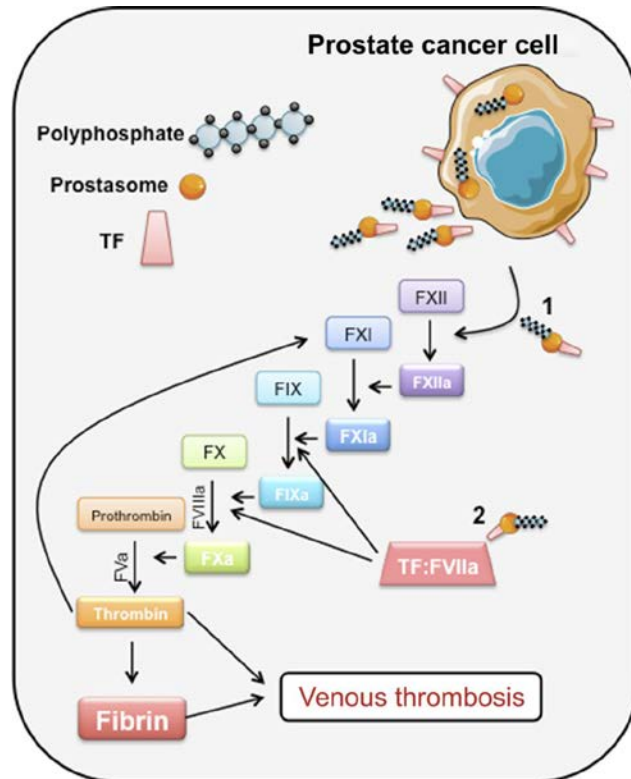
INTRODUCTION

Following autopsy,
Trousseau was diagnosed
with pancreatic cancer
(not gastric cancer)



INTRODUCTION

Understanding Trousseau's Syndrome: in prostate cancer



- Prostate cancer cells secrete microvesicles with long chain polyphosphates on their surface
- These microvesicles activate Factor XII
- Activation of Factor XII leads to thrombosis

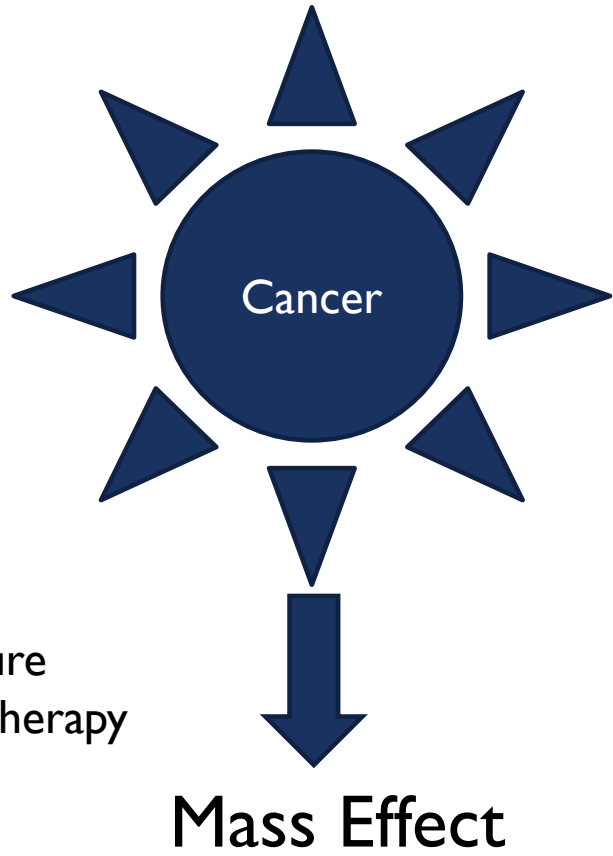
Local cells → Systemic effect

Blood 2015; 126: 1270-1272.

MECHANISMS



Direct vs Indirect Effects of Cancer



Hormone/cytokine secretion

Immune responses

MY FIRST ONCOLOGY CONSULTATION

- “This is Dr. xxxxx of Neurology...”
- “We’d like you to see this 63 year old female...”
- “She presented a week ago with ‘opsoclonus-myoclonus syndrome’... opsoclonus-myoclonus... ‘Dancing Eye Syndrome’...hello?”
- “Our workup revealed a lung lesion and the biopsy was positive for **small cell lung cancer**”



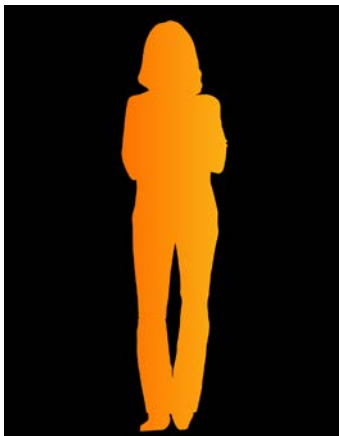
CASE REPORT



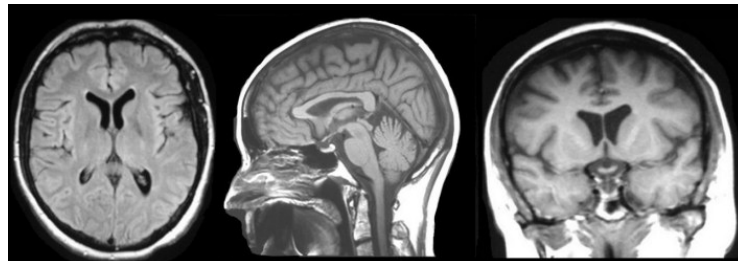
León Ruiz M, Benito-León J, García-Soldevilla MA, Rubio-Pérez L, Parra Santiago A, Lozano García-Caro LA, et al. Biterapia inmunosupresora efectiva e innovadora en un síndrome opsoclono-mioclono-ataxia paraneoplásico e inusual del adulto. *Neurología*. 2017;32:122–125.

MY FIRST ONCOLOGY CONSULTATION

How neurology approached this case...



Unwell
Not herself
Doing strange
things



Rapid eye
movements
Ataxia
MRI normal



Opsoclonus
Myoclonus
Syndrome

Malignancy found
in 60% of cases
In adults, SCLC is
#1 cause

Rule out
infections, toxins,
sarcoid...

MY FIRST ONCOLOGY CONSULTATION

How neurology approached this case...



Search for
antibodies...



Give steroids a
try...



Work up for
malignancy

A SIMILAR CASE IN THE LITERATURE...

- This 62 year old male had a 94 pack-year history of smoking
- The metastatic work up was clear (no lung cancer)



León Ruiz M, Benito-León J, García-Soldevilla MA, Rubio-Pérez L, Parra Santiago A, Lozano García-Caro LA, et al. Biterapia inmunosupresora efectiva e innovadora en un síndrome opsoclono-mioclono-ataxia paraneoplásico e inusual del adulto. *Neurología*. 2017;32:122–125.

A SIMILAR CASE IN THE LITERATURE...

Antibodies Against	Sample	Results
HU	Serum	Negative
CV2	Serum	Positive
Ma I, Ma2	Serum	Negative
amphiphysin	Serum	Negative
GAD	Serum	Negative
LGII	Serum	Negative
CASPAR2	Serum	Negative
NMDAR	CSF	Negative
CAMPAR	CSF	Negative
GABABR	CSF	Negative

León Ruiz M, Benito-León J, García-Soldevilla MA, Rubio-Pérez L, Parra Santiago A, Lozano García-Caro LA, et al. Biterapia inmunosupresora efectiva e innovadora en un síndrome opsoclono-mioclono-ataxia paraneoplásico e inusual del adulto. *Neurología*. 2017;32:122–125.

- CV2 is an antigen on oligodendrocytes...

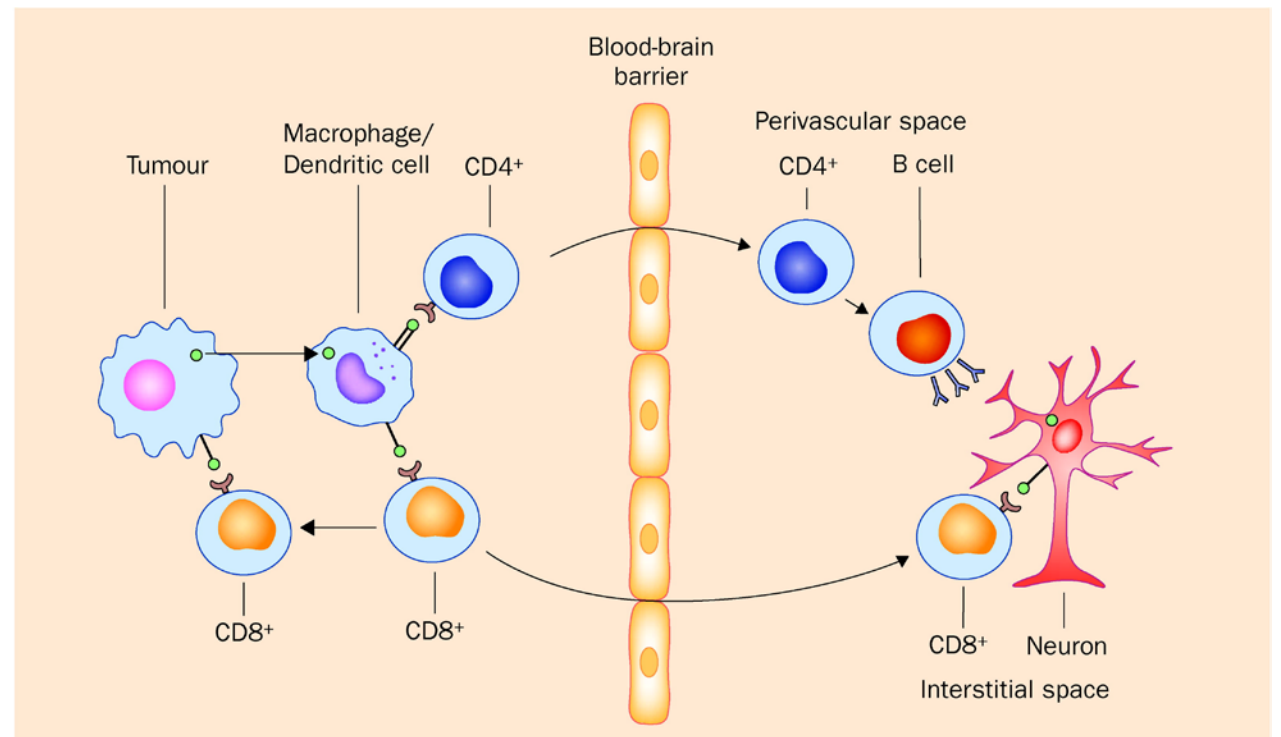
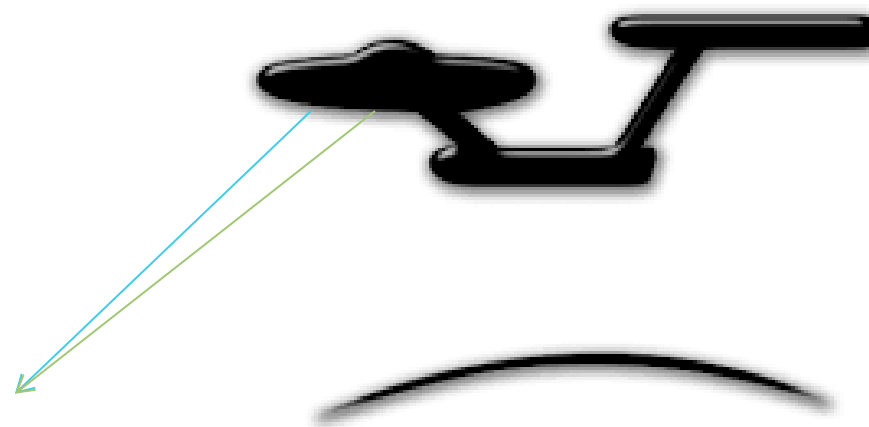


Diagram from Lancet Neurology VOLUME 1, ISSUE 5, P294-305, SEPTEMBER 01, 2002

A SIMILAR CASE IN THE LITERATURE...

- He didn't respond to a pulse of steroids or to intravenous immunoglobulins (IVIg)
- They decide to give him methylprednisolone and cyclophosphamide...full phasers!



León Ruiz M, Benito-León J, García-Soldevilla MA, Rubio-Pérez L, Parra Santiago A, Lozano García-Caro LA, et al. Biterapia inmunosupresora efectiva e innovadora en un síndrome opsoclono-mioclono-ataxia paraneoplásico e inusual del adulto. *Neurología*. 2017;32:122–125.

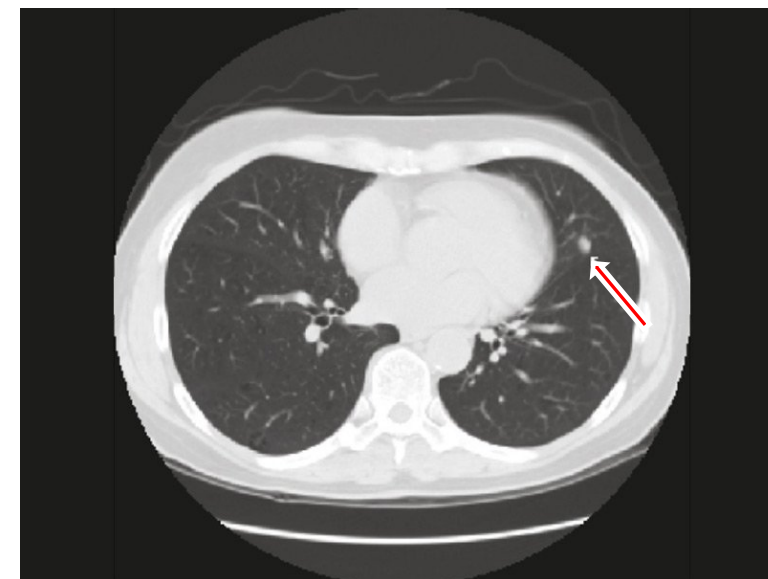
A SIMILAR CASE IN THE LITERATURE...

DAYS					Monthly dose (every 28 days)
1	2	3	4	5	
↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	Methylprednisolone (1 g/24 h) IV
	↓ ↓ ↓ ↓		↓ ↓ ↓ ↓		Cyclophosphamide (50 mg/kg/h) IV
↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	Pantoprazole (1 vial) (40 mg/24 h) IV
→					Fluid therapy, 0.9% saline solution (2000 cc/24 h): 15 mEq KCl/500 cc saline solution
→					Clinical and haemodynamic monitoring
→					Complementary tests to complete aetiological study

León Ruiz M, Benito-León J, García-Soldevilla MA, Rubio-Pérez L, Parra Santiago A, Lozano García-Caro LA, et al. Biterapia inmunosupresora efectiva e innovadora en un síndrome opsoclono-mioclono-ataxia paraneoplásico e inusual del adulto. *Neurología*. 2017;32:122–125.

A SIMILAR CASE IN THE LITERATURE...

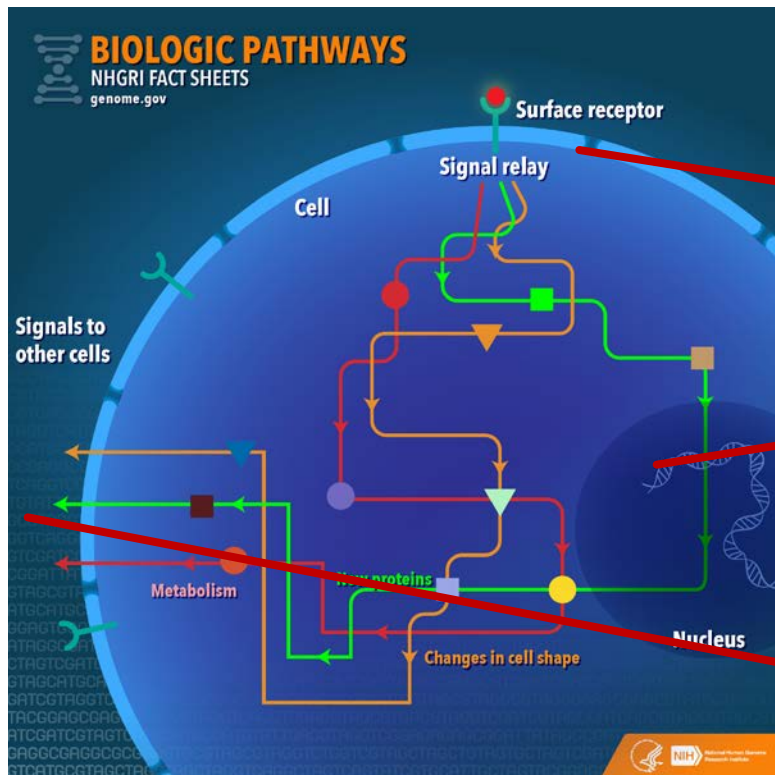
- His symptoms immediately resolved!
- When they tried to reduce the doses one year into therapy his symptoms recurred, and small cell lung cancer was detected
- Unfortunately he passed away 7 months later



León Ruiz M, Benito-León J, García-Soldevilla MA, Rubio-Pérez L, Parra Santiago A, Lozano García-Caro LA, et al. Biterapia inmunosupresora efectiva e innovadora en un síndrome opsoclono-mioclono-ataxia paraneoplásico e inusual del adulto. *Neurología*. 2017;32:122–125.

WHAT HAPPENED HERE?

The Normal Cell

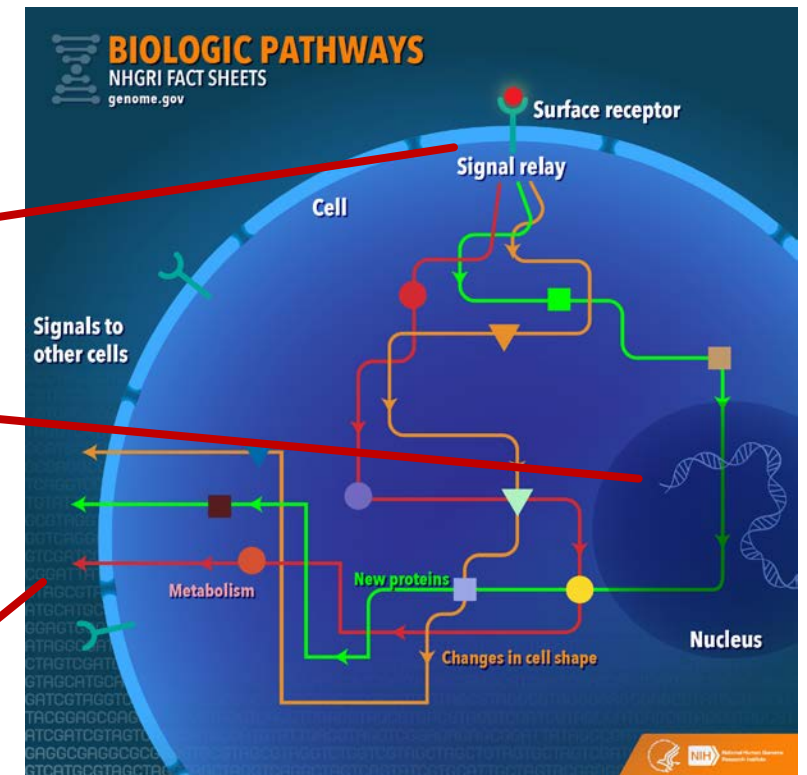


Cell switched on at appropriate times

Limited access to genome

Only appropriate proteins are made

The Cancer Cell



Cell switched on inappropriately

Cell starts to read from "forbidden" parts of genome

The wrong proteins are made

THE IMMUNE SYSTEM ATTACKS THE NORMAL PROTEIN, ON NORMAL CELLS

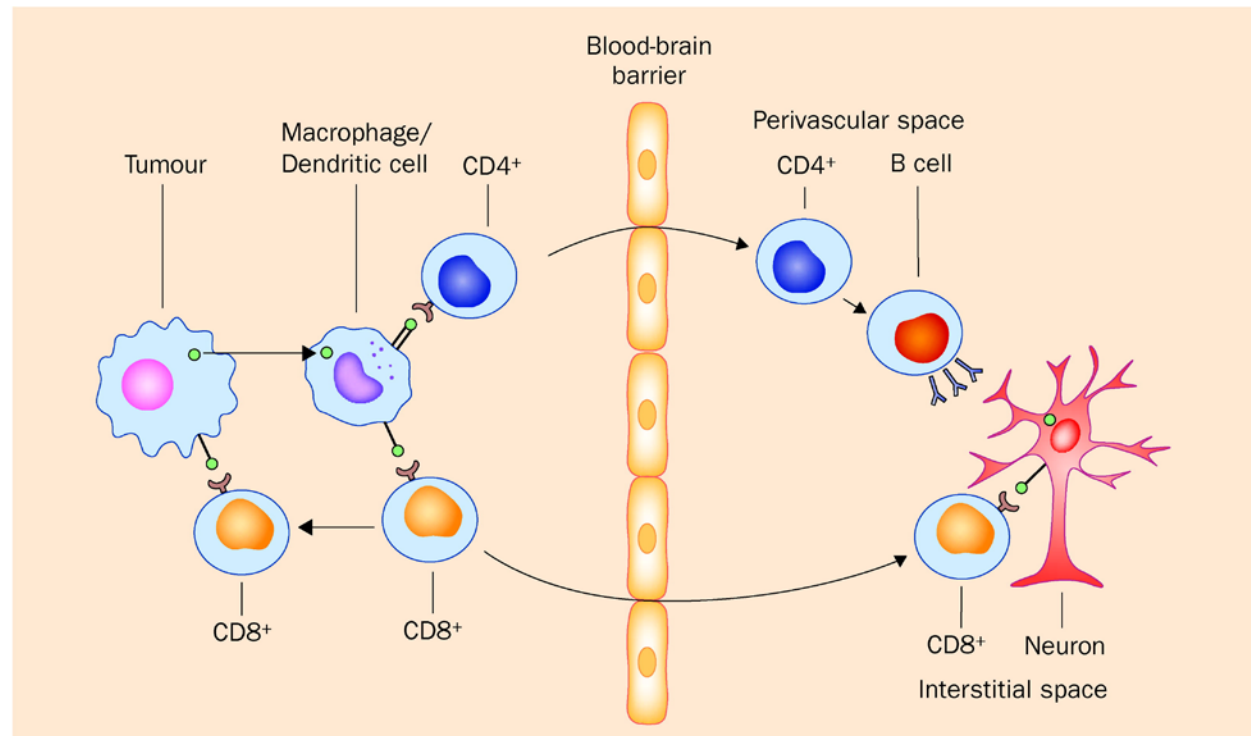
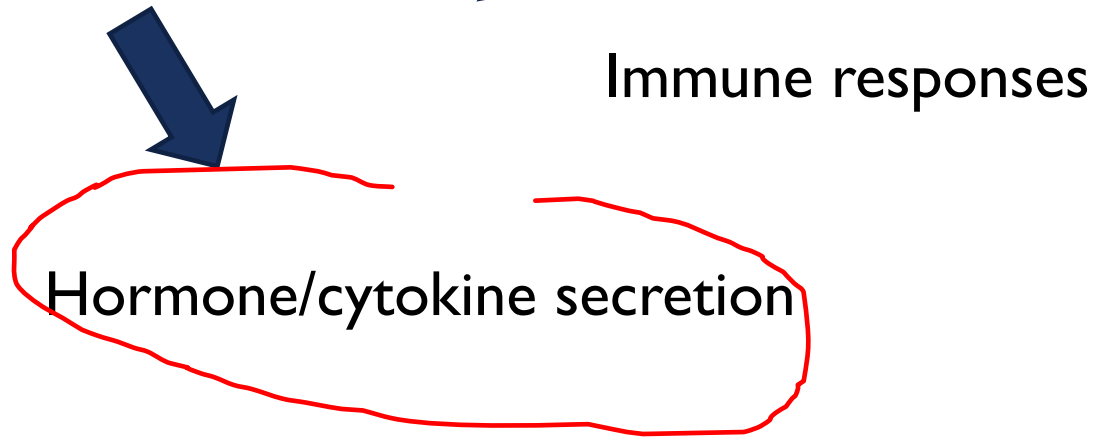
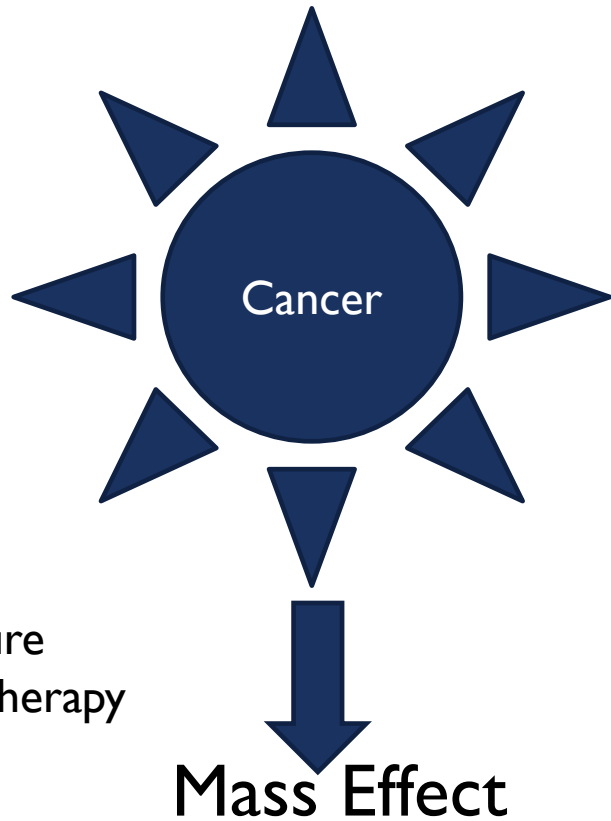
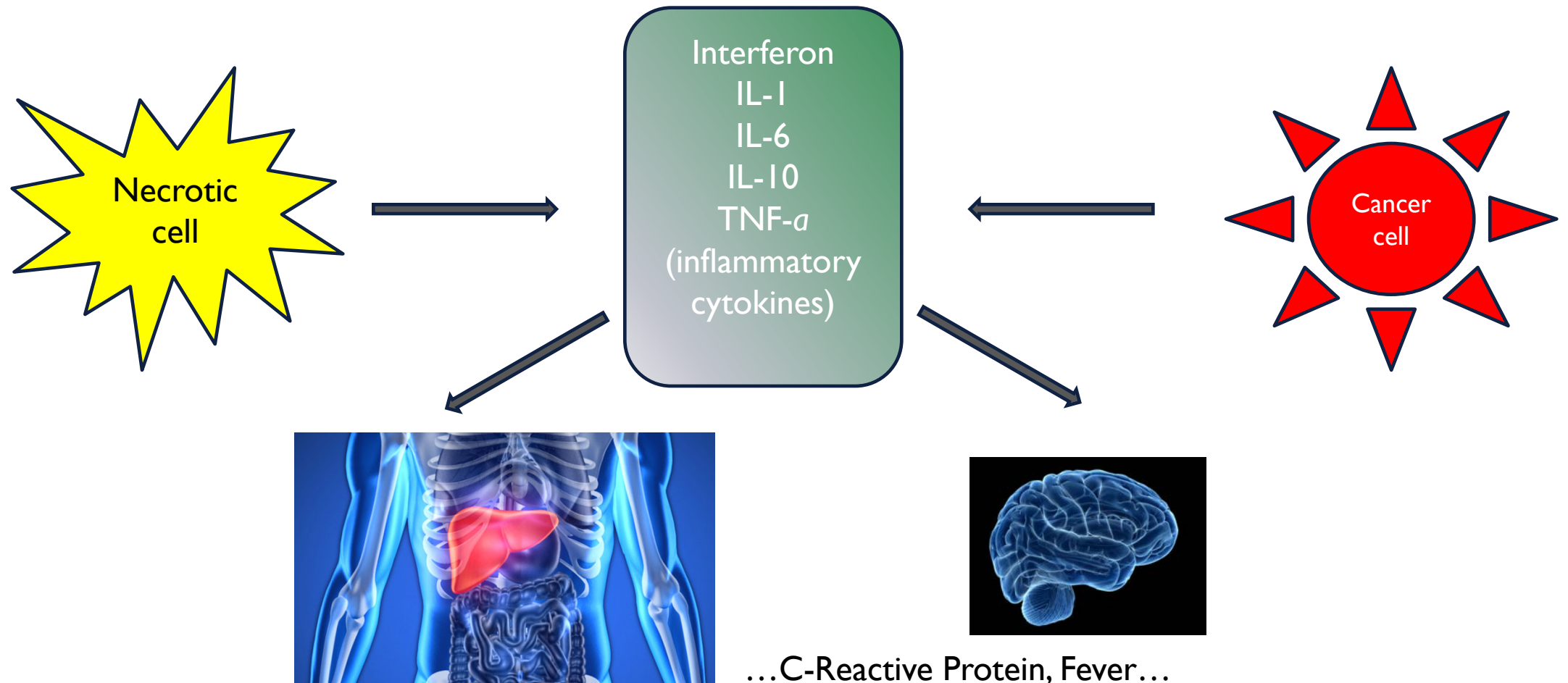


Diagram from Lancet Neurology VOLUME 1, ISSUE 5, P294-305, SEPTEMBER 01, 2002

Direct vs Indirect Effects of Cancer



TUMOUR FEVER



CASE REPORT



35 year old male
with giant cell
tumour of left
femur



Presents 40 years
later with left leg
pain, swelling, fever
of unknown origin

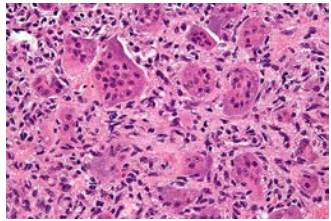


Arthrocentesis,
plain film, CT all
clear



Operating table
Surgical debridement
(presumed osteomyelitis)

CASE REPORT



Found tumour cells in sample, plus TNF- α



Gave naproxen and fever resolved



Amputated femur



Fever resolved; no recurrence of fever or tumour

TWO MAIN MECHANISMS

Immune Mediated

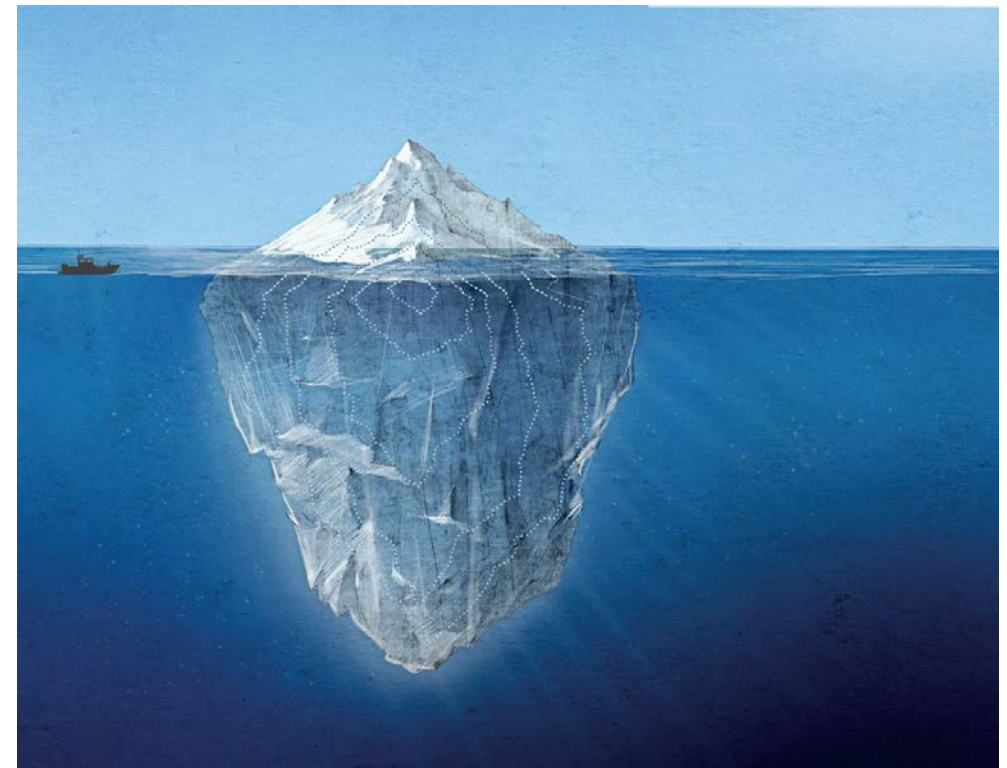
- A cancer cell expresses proteins inappropriately
- The immune system identifies the proteins and creates antibodies, etc
- The immune system attacks any cell that expresses that protein, even if they are normal cells

Hormones / Cytokines

- A cancer cell secretes hormones and/or cytokines inappropriately
- These hormones and/or cytokines create a cascade of effects within the body

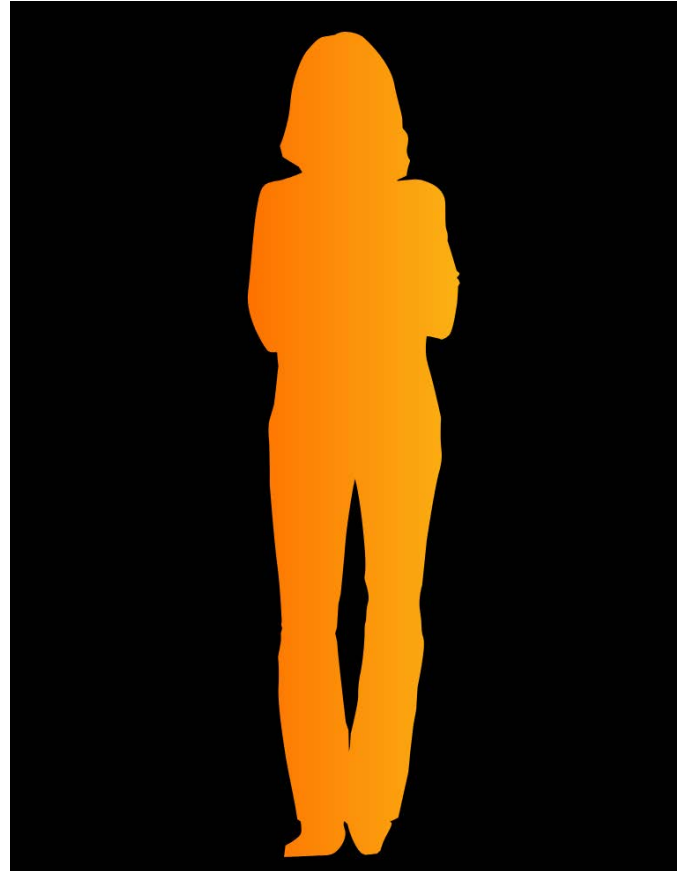
TIP OF THE ICEBERG

- A small number of cancer cells can start this process
- The associated process might be “visible” before the cancer itself is detectable
- The PNS might just be the tip of the iceberg



Created by Shizuka Aoki; published in Canadian Geographic | 1 April 2017

CASES



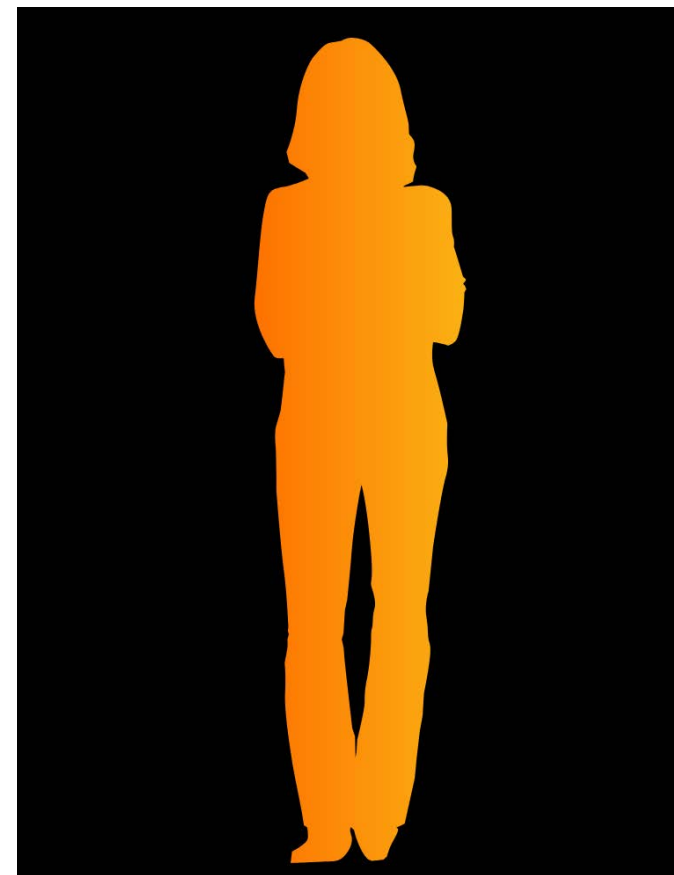


CASE I: SALTY SAM



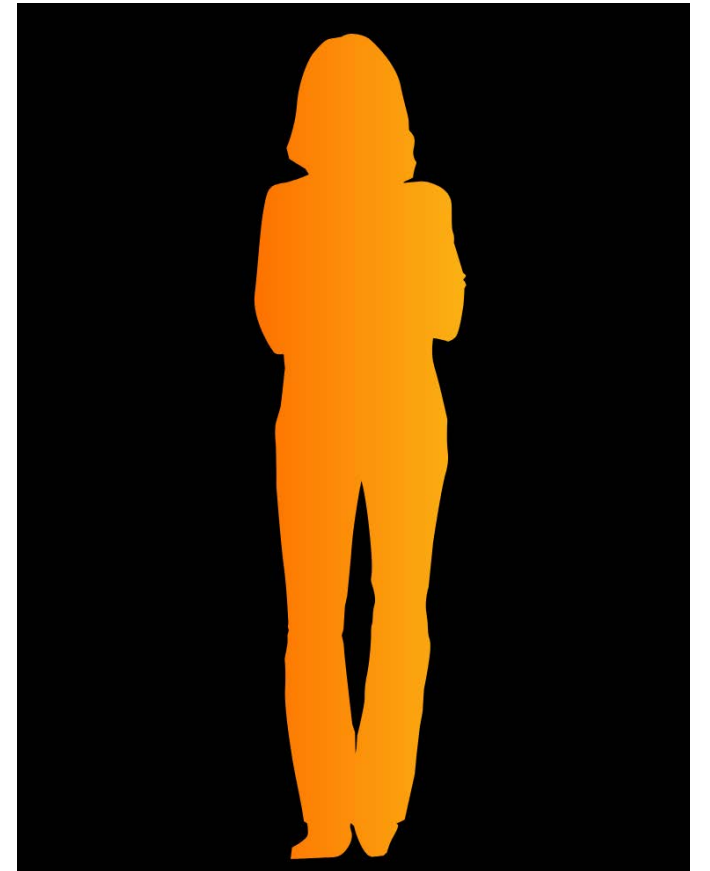
SALTY SAM

- Samantha is a 61 year old female
- She was diagnosed with “curative” breast cancer four years ago and metastatic disease just one year ago (recurrence in bone only)
- Doing well on letrozole (endocrine therapy) and pamidronate (bisphosphonate)
- On 3 month follow up...



SALTY SAM

- Sam was very unwell and her GP, Dr Smarts, brought her in for a full assessment
- The only abnormality found was low sodium at 129.



QUESTION 2

- What is the cause of her low sodium?

Dehydration

SIADH due
to drugs

SIADH
due to
cancer

SIADH due to
stroke



CASE 2: Ms. DIAGNOSIS



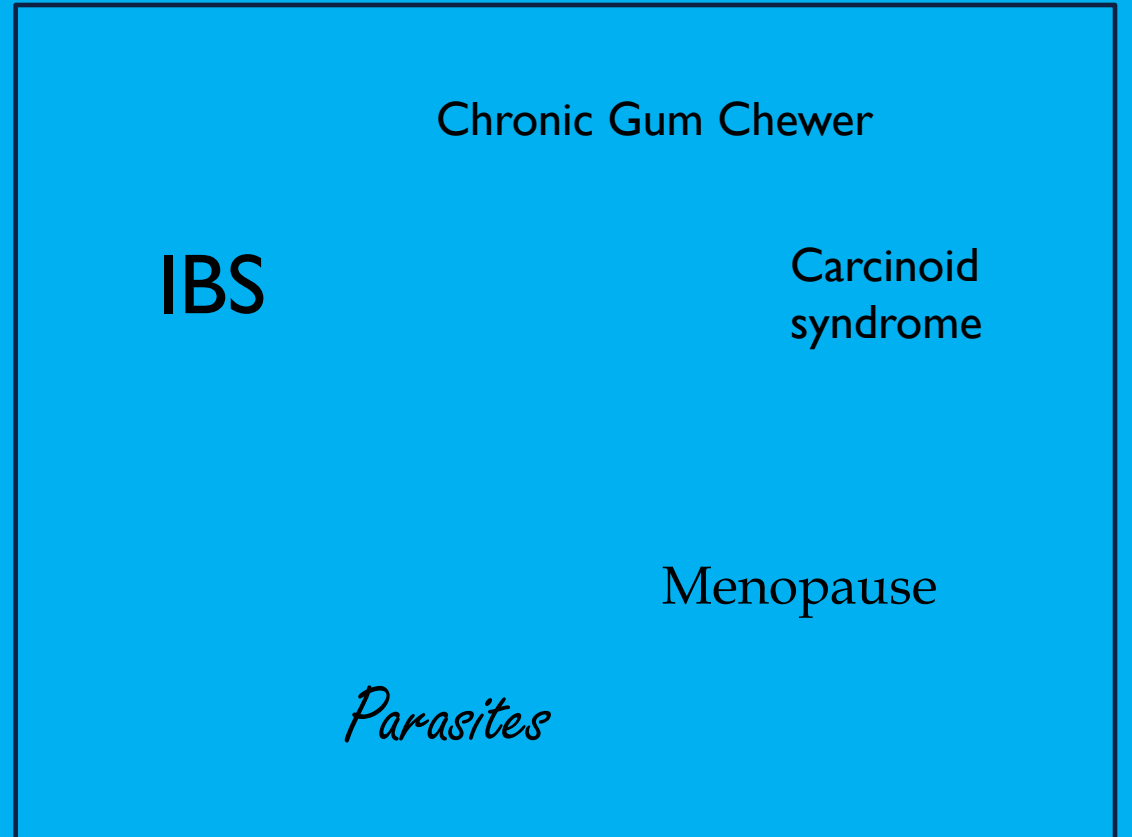
Ms. DIAGNOSIS

- Miss Diagnosis is a very busy 54 year old professional female with virtually no medical history.
- She is also a patient of Dr Smarts.
- Suffers from intermittent diarrhea, bloating, dyspepsia, and flushing.
- She has a supportive partner, no kids, and she remains productive despite her complaints.



QUESTION 2:

- What do you think is the cause of these complaints?





SALTY SAM

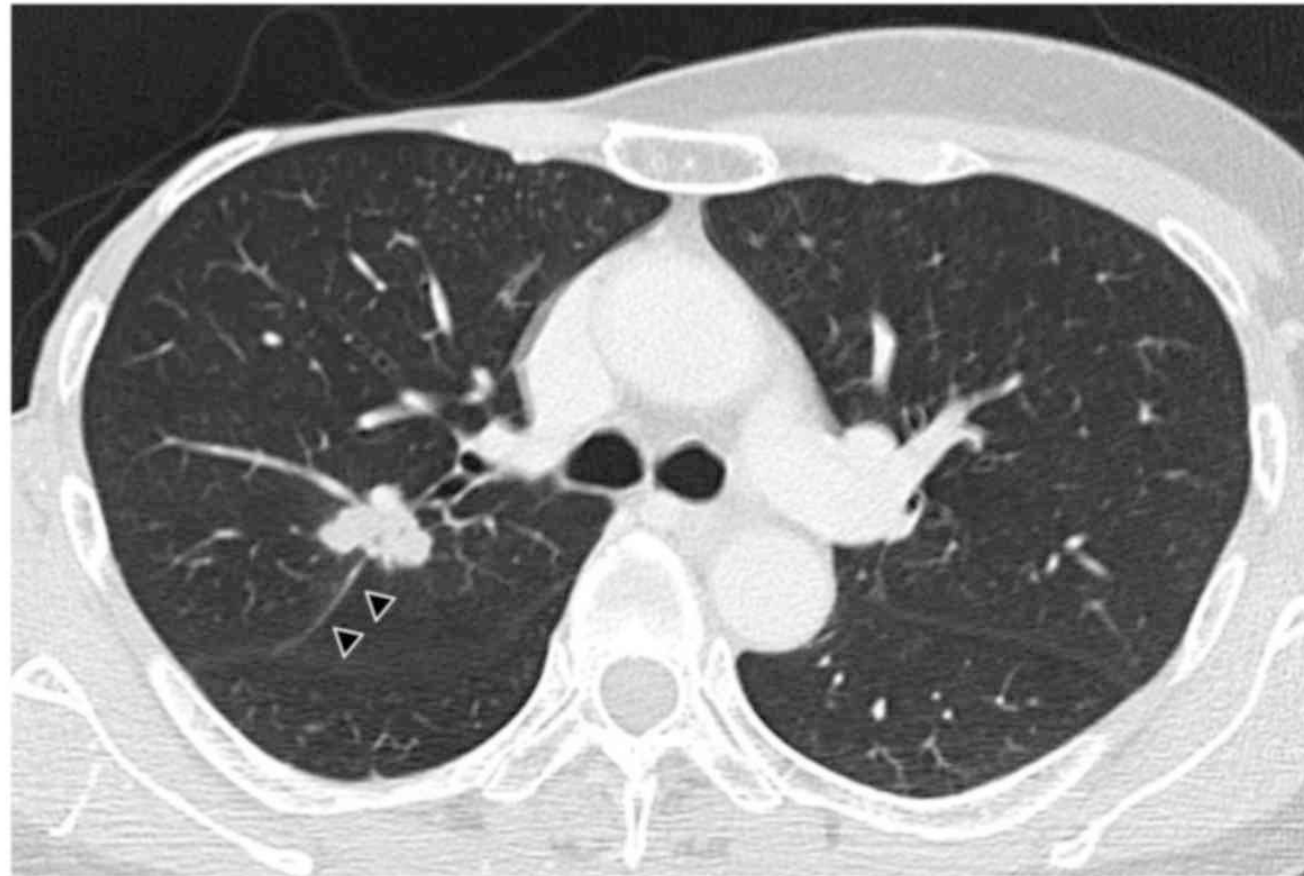
(BACK TO CASE I)



SALTY SAM

- Dr. Smarts was concerned about a low sodium measurement of 129 mmol/L.
- Dr. Smarts wondered about the etiology of low sodium; was this SIADH?
- Dr. Smarts knew that breast cancer with metastases to bone was not likely to cause SIADH; were there metastases in the lungs or brain?
- Dr. Smarts began fluid restriction but wanted to hear my thoughts on a metastatic work up.

WE FOUND THE LIKELY CAUSE OF SIADH...



SALTY SAM

- Fluid restriction didn't work...
- Did not feel we needed hypertonic saline
- Gave “salt” a try...



SYNDROME OF INAPPROPRIATE ANTI-DIURETIC HORMONE SECRETION

A Syndrome of Renal Sodium Loss and Hyponatremia Probably Resulting from Inappropriate Secretion of Antidiuretic Hormone*

WILLIAM B. SCHWARTZ, M.D.,† WARREN BENNETT, M.D.,‡ SIDNEY CURELOP, M.D.§
Boston, Massachusetts

and FREDERIC C. BARTTER, M.D.
Bethesda, Maryland

THIS paper is a report of studies of two patients with bronchogenic carcinoma in whom hyponatremia developed as the result of unexplained failure of renal sodium conservation. The data indicate that sustained inappropriate secretion of antidiuretic hormone was probably responsible for the disorder of sodium metabolism. The physiologic abnormality appears to be analogous to that which can be produced by the continuous administration of pitressin® and water to normal subjects.

CASE REPORTS

CASE 1. W. A., a sixty-year old hat cleaner, complained of coughing up bright red blood for the previous six weeks, and loss of 15 pounds of weight. On physical examination, he was well nourished. The blood pressure was 120/70 mm. Hg. There was marked clubbing of the fingers and toes which the patient said had been present all his life. Physical and neurologic examination was otherwise within normal limits.

Initial routine laboratory studies revealed no abnormalities in the hemogram. Urine examination was negative. Intravenous pyelogram revealed normal structure and excellent dye concentration in both kidneys.

X-ray revealed a 4 by 5 cm. ill-defined mass in the

region of the right pulmonary artery. A biopsy by bronchoscope demonstrated anaplastic carcinoma of the right main stem bronchus, and an exploratory thoracotomy revealed an inoperable tumor at the right hilum infiltrating the esophagus and aorta. In the postoperative period empyema developed, which was satisfactorily controlled with antibiotics and saline solution irrigations. Two weeks after operation serum electrolytes and protein concentrations were measured as a routine procedure. The following values were obtained: sodium, 121 mEq./L.; potassium, 4.6 mEq./L.; chloride, 88 mEq./L.; carbon dioxide content, 24 mEq./L.; calcium, 10.0 mg. per cent; inorganic phosphate, 4.0 mg. per cent; albumin, 2.1 gm. per cent; globulin, 3.7 gm. per cent. The hemoglobin was 9.8 gm. per cent. The patient was given small amounts of normal saline solution and on the following day his serum sodium was 114 mEq./L. and his blood urea nitrogen was 9 mg. per cent. The urine sodium concentration was 70 mEq./L. At this time the physical examination was within normal limits. The blood pressure was 124/68 mm. Hg. Skin turgor and hydration were good. There was no abnormal pigmentation and axillary and pubic hair were normal. During the next two days he was given hypertonic sodium chloride, despite which his serum sodium concentration fell to 103 mEq./L. During this time the patient was asymptomatic. He was then given small doses of DOCA® and very large amounts of supplementary salt. Three days later metabolic studies were begun,

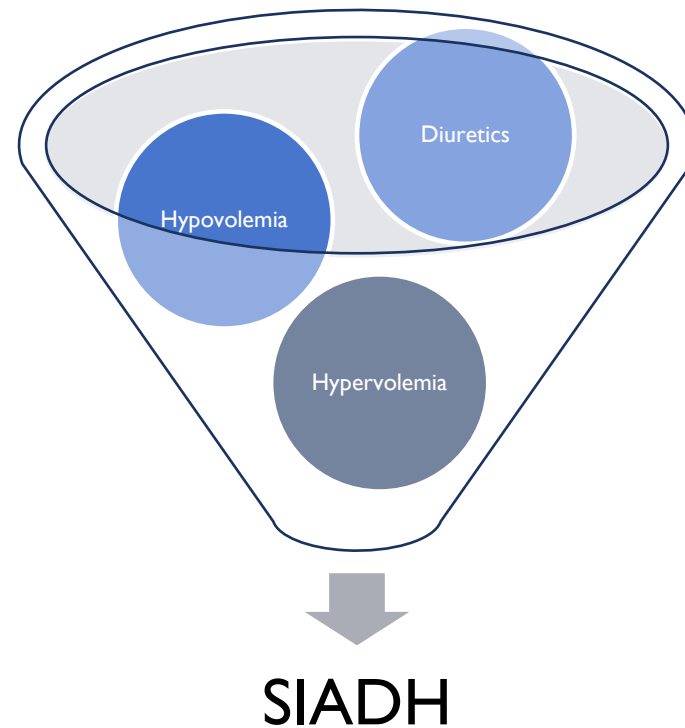
* From the Department of Medicine, Tufts University School of Medicine, and the New England Center Hospital, Boston, Massachusetts and the Section of Clinical Endocrinology, National Heart Institute, National Institutes of Health, Bethesda, Maryland. Supported in part by grants-in-aid from the National Heart Institute, National Institutes of Health, U. S. Public Health Service and the American Heart Association. Presented in abstract, April 30, 1956, American Society for Clinical Investigation [7].

† Established Investigator of the American Heart Association.

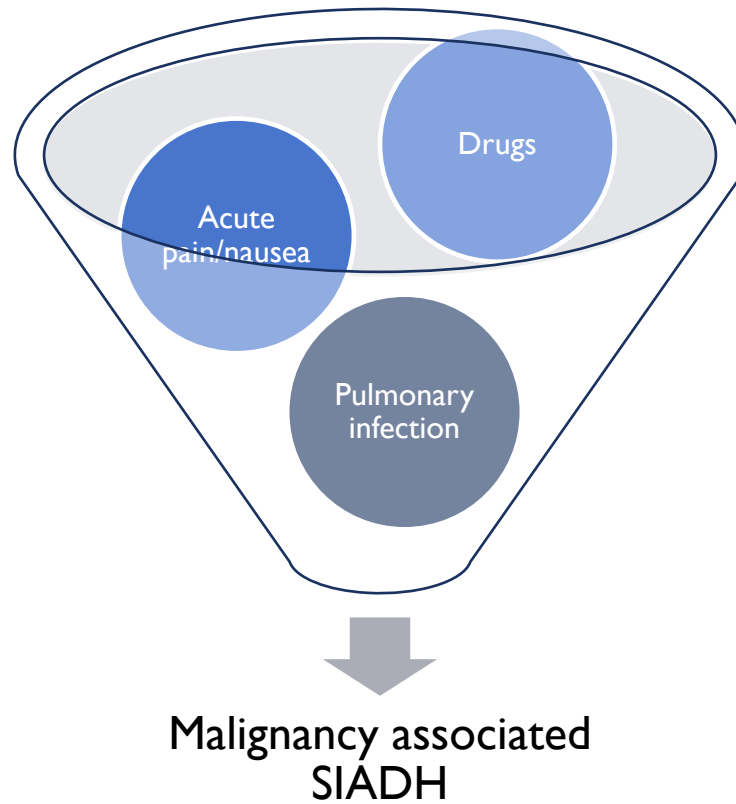
‡ Research Fellow, National Institutes of Health, U. S. Public Health Service.

§ Charlton Fellow, Tufts University School of Medicine, Boston, Massachusetts.

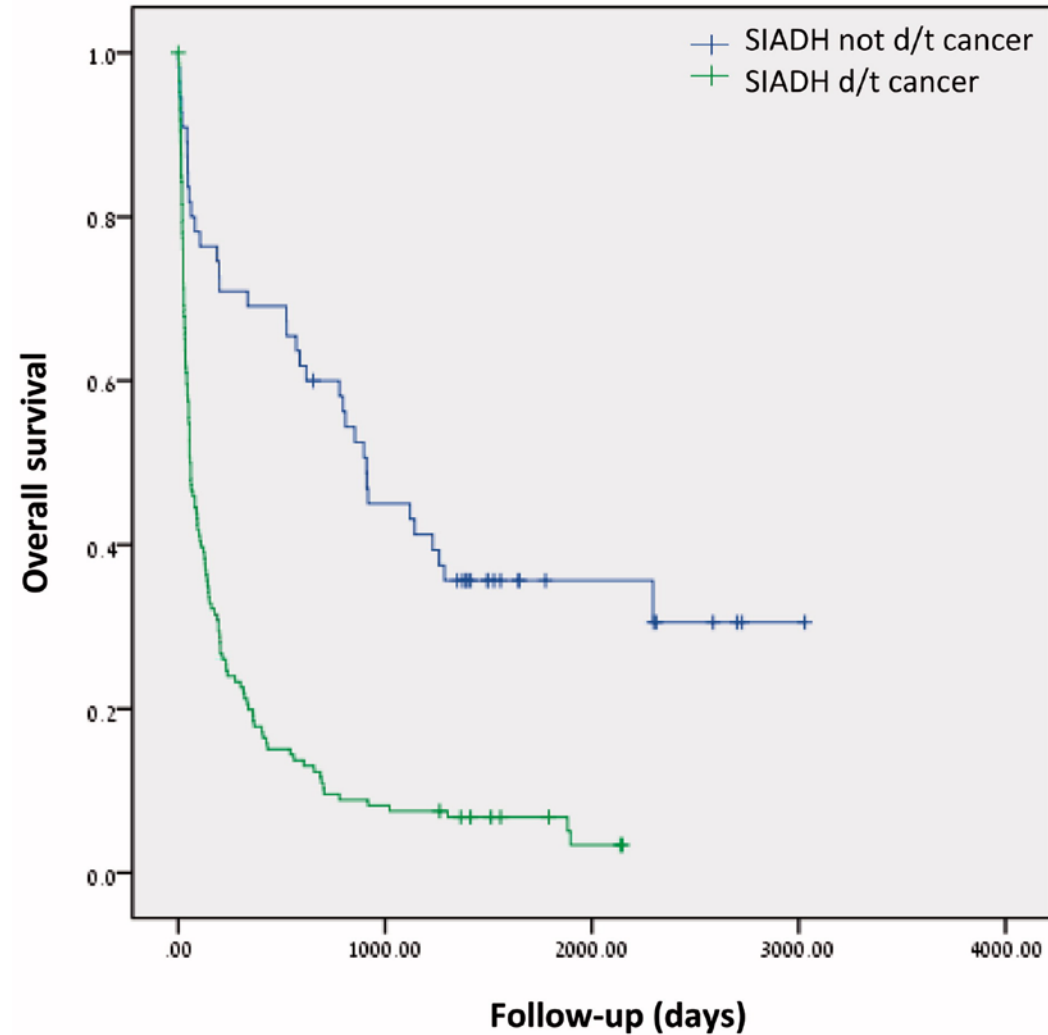
LOTS OF REASONS TO HAVE HYPONATREMIA....



LOTS OF REASONS TO HAVE SIADH....

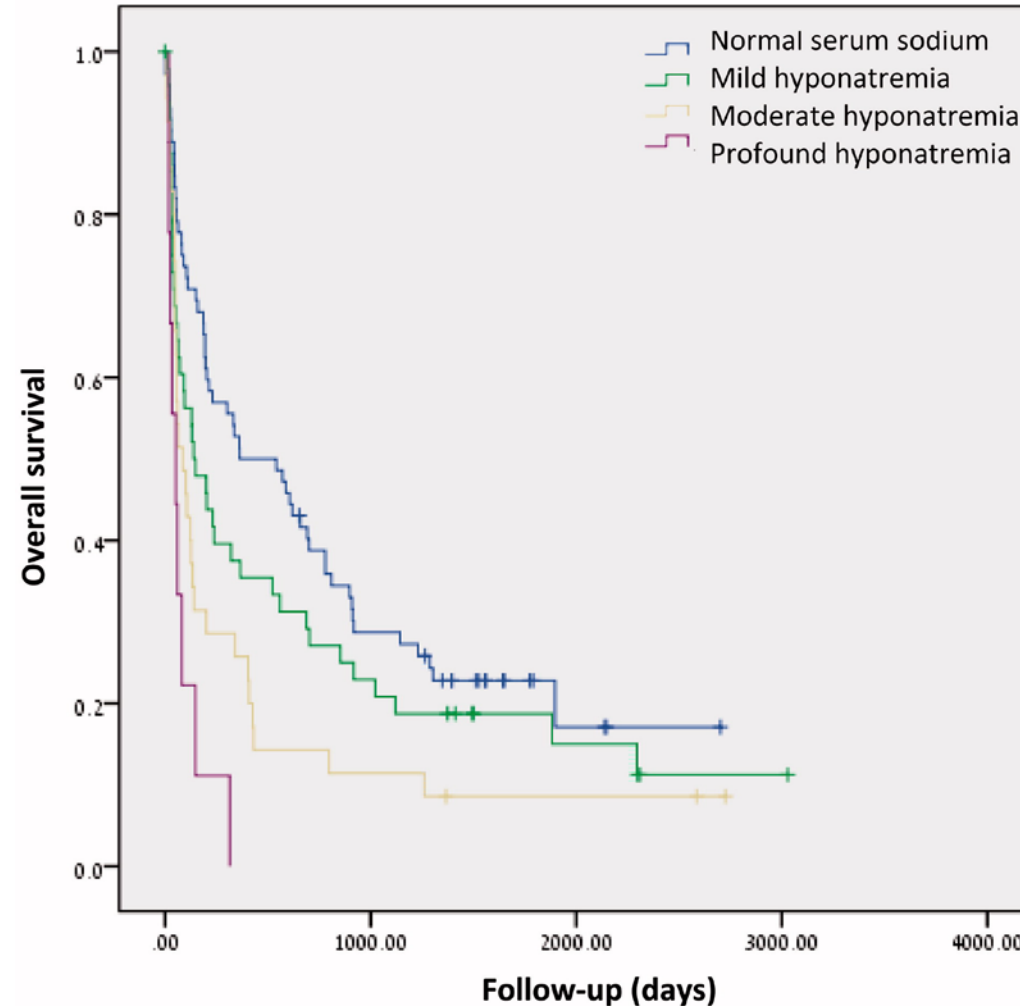


AMONG CANCER PATIENTS, MALIGNANCY ASSOCIATED SIADH IS WORSE...



H. Goldvaser, B. Rozen-Zvi, R. Yerushalmi, A. Gafter-Gvili, M. Lahav & D. Shepshelovich (2016), *Acta Oncologica*, 55:9-10, 1190-1195

AMONG CANCER ASSOCIATED SIADH PATIENTS, THE LOWER THE SODIUM THE WORSE THE PROGNOSIS...



H. Goldvaser, B. Rozen-Zvi, R. Yerushalmi, A. Gafer-Gvili, M. Lahav & D. Shepshelovich (2016), *Acta Oncologica*, 55:9-10, 1190-1195

SALTY SAM

- SIADH is underdiagnosed, and poorly understood
- Recall your differential diagnoses for hyponatremia, and for SIADH
- Find the cause: prognosticate
- Correct it, and improve morbidity, and perhaps mortality





CASE 2:Ms. DIAGNOSIS

(BACK TO CASE 2)



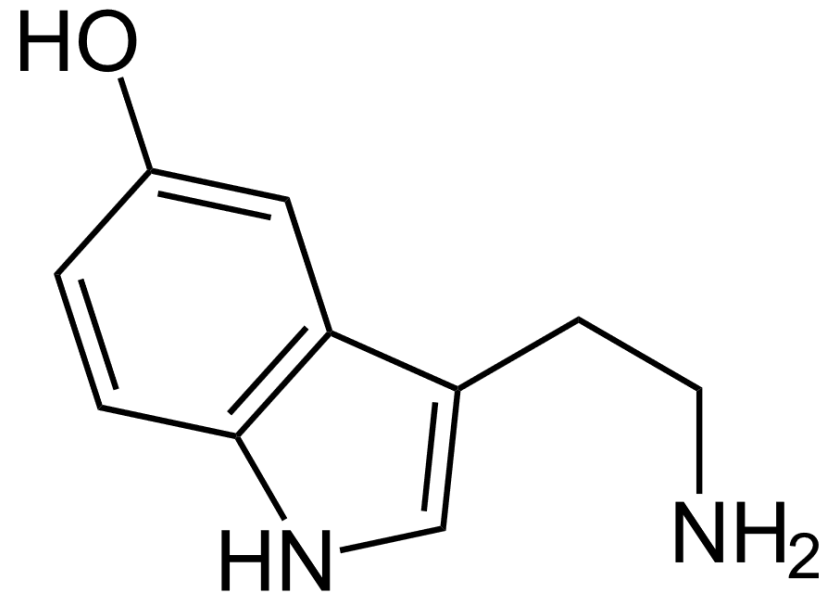
Ms. DIAGNOSIS

- Eventually presents to ER with nausea, vomiting, abdominal pain
- CT imaging reveals source of obstruction in small bowel and multiple liver lesions
- Immediately proceeds to surgery for resection of primary tumour in small bowel
- Surgeon says it “looks like a carcinoid”



Ms. DIAGNOSIS

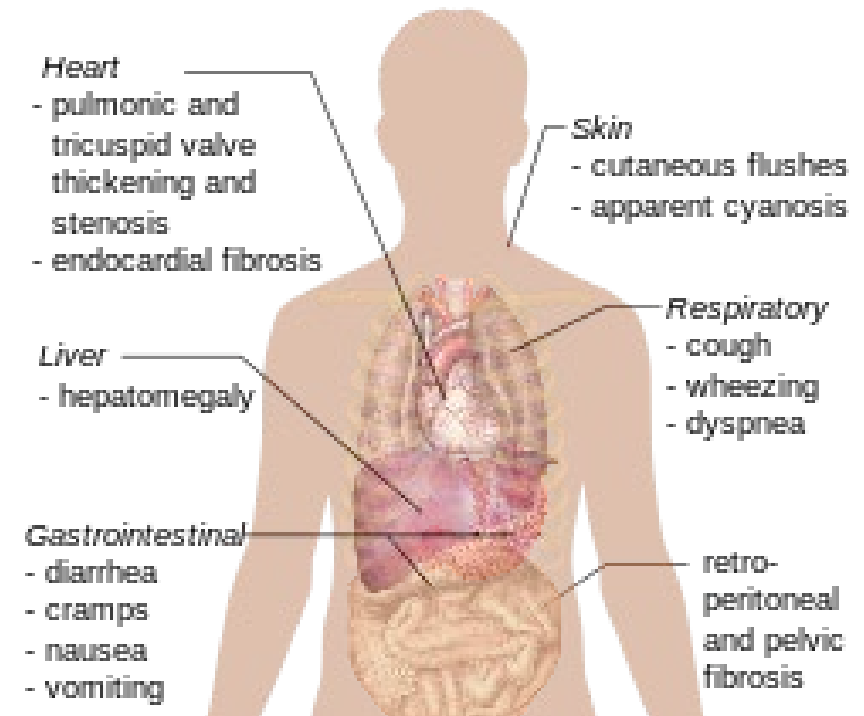
- Carcinoid means “cancer-like”
- Neuroendocrine tumours are real cancers
- 30-40% of these tumours secrete serotonin and create a PNS
- The accompanying PNS is still called “carcinoid syndrome”



Ms. DIAGNOSIS

- The carcinoid syndrome continued after the resection of the primary tumour
- Somatostatin analogs gave Ms. Diagnosis her life back

Carcinoid syndrome



From Wikipedia, carcinoid syndrome

Ms. DIAGNOSIS

- At follow up appointments we see the symptoms re-appear when her monthly injections approach
- At annual imaging we see a little bit of growth each year
- Life expectancy is ~15 years...



Ms. DIAGNOSIS

- Recall the nature of this disease
- Delay in diagnosis is common
- Somatostatin analog therapy helps
- When you hear hoofbeats...

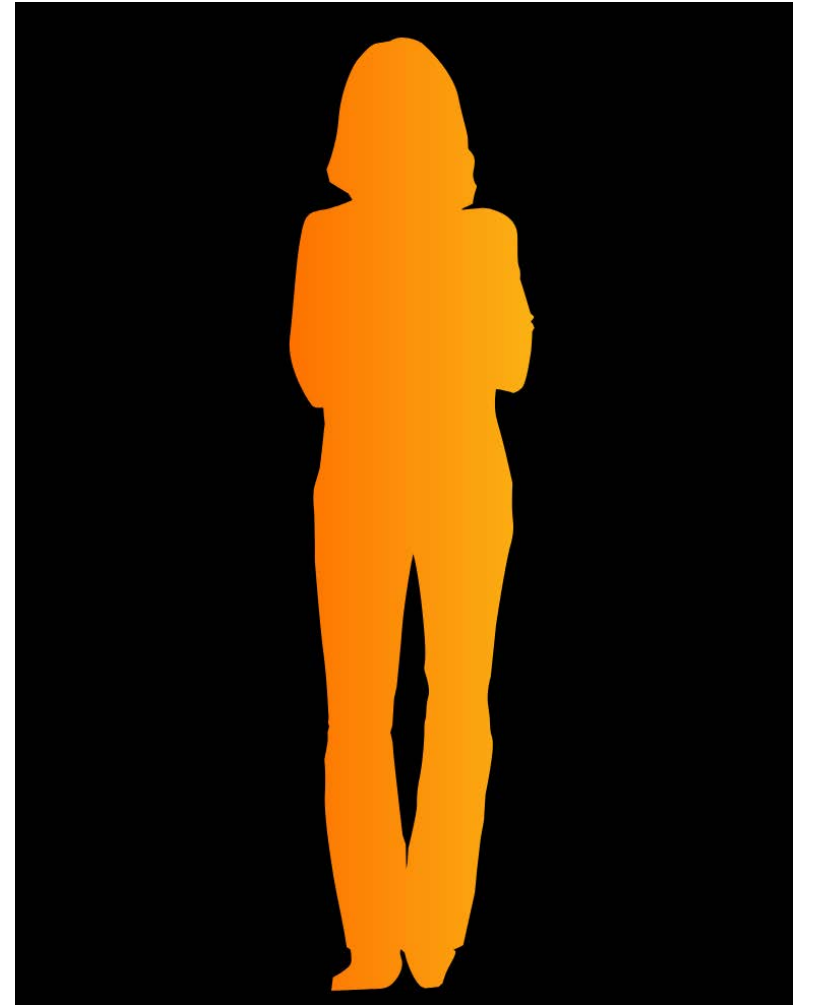


Carcinoid-NeuroEndocrine
TUMOUR SOCIETY CANADA

CONCLUSIONS

A word from the oncology trenches...

- We see the cancer first, and then see the PNS
- Having a PNS is a worrisome sign
- We usually treat the underlying cancer to treat the PNS



CONCLUSIONS

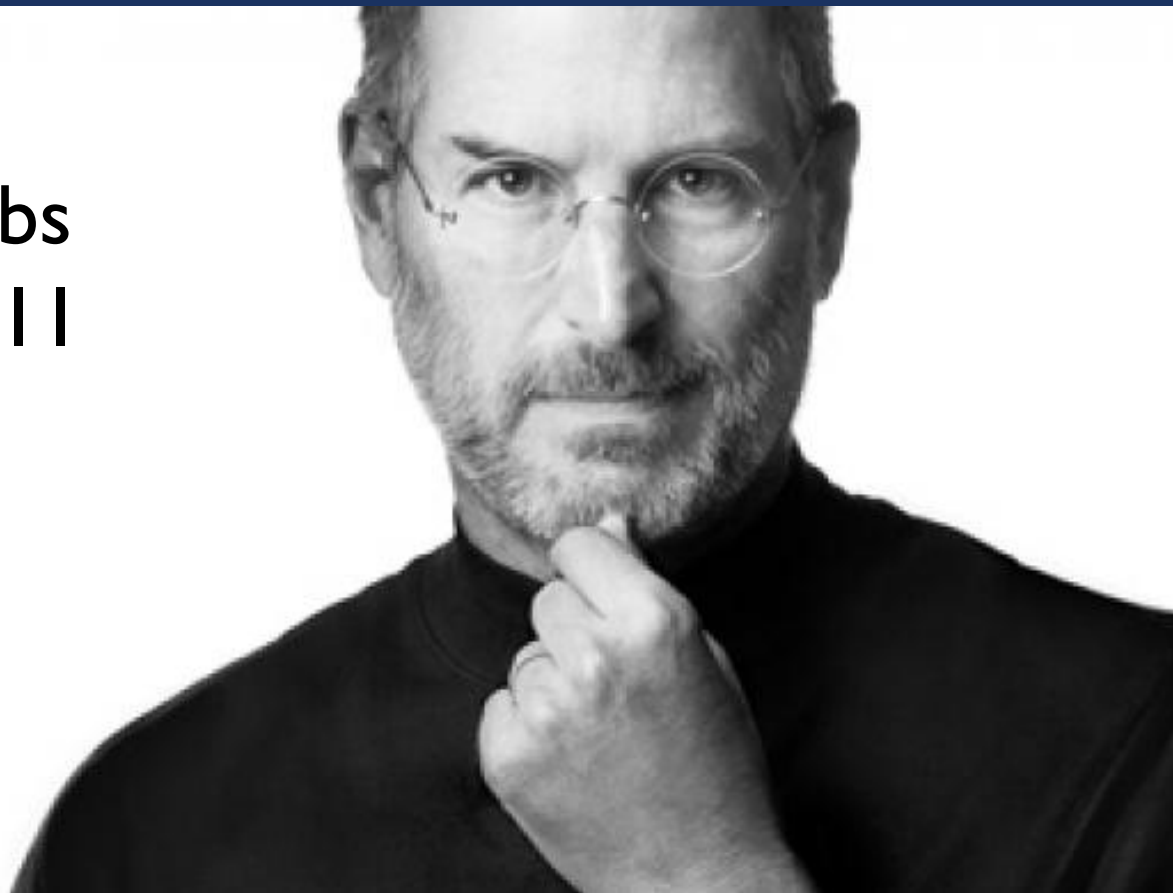
Key Points

- Fascinating syndromes, limitless variability
- Our understanding is limited by the “unknown unknowns”

INTRODUCTION

- PNS are all around us
- You and I see them
- Is this the cancer or a PNS?
(what's the difference?)

Steve Jobs
1955-2011



CONCLUSION

- Thanks so much!

