PROBLEM SOLVING

Here are some human immunology problems which will allow us to review many basic principles.

PROBLEM 1: In September two business rivals from New England, in town for a meeting, have lunch at a downtown Denver restaurant. Halfway through the main course, Jones looks flushed, feels faint, and vomits in the men's room. They take him to Denver Health Medical Center. Smith stays and eats his delicious Rocky Ford Colorado cantaloupe. But he soon develops similar flushing, with skin itch, wheezing, and severe tightness in his chest. Another ambulance takes *him* to Denver Health.

Physical exam on admission to the ER:

	Jones	**Smith**
BP	80/50	110/65
heart rate	155	135
temperature	37.3	37.0
physical exam	slight expiratory râles	coarse râles
	urticaria on chest and abdomen dehydration headache	urticaria on chest and face

History: Both men ordered salad, white wine, and mixed vegetables. Jones had grilled mahi-mahi (a tuna-like fish from Hawaii), Smith had the lasagna. Jones got sick before desert, Smith had the cantaloupe. Jones is allergic to penicillin; Smith has seasonal rhinitis due to ragweed.

Treatment?

Anything further you'd like to know?
Any diagnostic procedures you'd like to do?

Further information: All left over mahi-mahi is taken from the restaurant by State Department of Health, and cultured for bacterial contamination. A rather high number of bacteria are found, but no endo- or exotoxin producers. They say this isn't food poisoning as they know it.
Mahi-mahi extract is obtained; both victims are tested by intradermal injection; neither is positive for immediate wheal-and-flare reaction. Smith is positive to ragweed extract. Sera from both are tested by mahi-mahi, ragweed and penicillin CAP-FEIA; what is CAP-FEIA, and what result do you anticipate?

So what's this all about? A clue to Jones' problem is contained in this ruling by a branch of the Federal Government. To annoy you, I've blanked out a key word.

"The article is subject to refusal of admission pursuant to Section 801(a)(3) in that it appears to bear or contain +++++++++, a poisonous and deleterious substance in such quantity as ordinarily renders it injurious to health [Adulteration, Section 402(a)(1)] and/or it appears to consist in whole or in part, of a filthy, putrid, or decomposed substance, or is otherwise unfit for food, in that it appears to be decomposed [Adulteration, Section 402(a)(3)]."

A (not very helpful, I admit) clue to Smith's problem is: what immunologic principal did Dr. Jenner discover in 1796?

PROBLEM 2: On 8 June 1988, a 31-year old woman with a 2-year history of recurrent genital herpes received a smallpox vaccination in a misguided attempt to treat her disease.

A persistent ulcer developed at the vaccination site on her left arm. On 5 July she was hospitalized for the treatment of "vaccinia necrosum"; the ulcer measured 5 x 5 cm and yielded vaccinia virus on culture. She had multiple perineal ulcers from which herpes was cultured.

Lab tests:	Red blood cells	3.3×10^{12}/L
	White cells	2.2×10^{9}/L
	Differential	13% lymphocytes
	IgA	10 mg/dL
	IgG	310 mg/dL
	IgM	15 mg/dL

On ward	Skin tests with PPD, histoplasmin, candidin, mumps, tetanus, diphtheria, streptokinase all negative. HIV antibody negative.
Treatment	Acyclovir, thiosemicarbazone, vaccinia immune globulin.
Course	The perineal ulcers cleared almost entirely, but the large ulcer on the left arm persisted and gradually enlarged.
	Readmitted to hospital on 19 August with the arm ulcer now 7 x 8 cm, but no evidence of active genital herpes
Treatment	Thiosemicarbazone, vaccinia immune globulin, interferon.
Course	The ulcer did not continue to enlarge, so the patient was discharged. A small lesion, thought to be a mosquito bite, was present on her left thigh. The patient was treated as an outpatient with 8 million units of interferon IV twice a week. The lesion on her leg grew to about 3 x 3 cm.

She was readmitted in October. Both ulcers were positive for vaccinia; they were cleaned up surgically (debrided). Treatment was with the antiviral drugs, and vaccinia immune globulin. Clinical improvement was gradual, but the blood picture remained essentially unchanged.

A careful history revealed that the patient had worked for three years, ending 6 months previous to her first hospital visit, in her brother's electroplating business, where her job was to clean the parts thoroughly so that the plated metal would adhere tightly. Prior to that she worked at a popcorn factory in California, mixing artificial butter flavor into the product. In college she was an intern at Spor Mountain in Utah, the world's largest active beryllium mine.

Differential diagnosis?

Etiology?

Treatment and Prognosis?

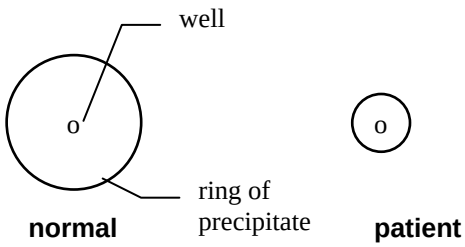
PROBLEM 3: A 16 year old girl was admitted on 23 April 1995 complaining of puffy eyes, shortness of breath, chest pain and nausea for the past two days. Her significant history included a severe sore throat which began 12 days previously, which was treated with a large dose of penicillin intramuscularly.

Physical examination: Facial edema
Blood pressure 190/120
Weight 61 kg (last week: 58)

Urinalysis: Coffee-colored
Red cells and red cell casts
480 mL/first 24 h
4 g protein/24 h

Lab: White count: 12 x 10^9/dL
Total IgE: 40 μg/dL
Penicillin CAP-FEIA: negative

Radial immunodiffusion test: normal or patient's serum in the well, goat antibody to human C3 in the gel.



Kidney biopsy: Thickened basement membrane; microhemorrhages
Many neutrophils in glomerulus

Immunofluorescence tests:

(1). Patient's serum added to a section of normal kidney; washed; fluorescent goat anti-human IgG added; **no fluorescence**.

(2). Patient's kidney stained with goat anti-IgG: **Positive** [what pattern, do you think?]

(3). Patient's kidney stained with goat anti-C3: **Positive** [what pattern, do you think?]

Differential diagnosis?

Etiology?

Prognosis?

PROBLEM 4: A 34-year old medical student, who had a part time job in the immunology department, cut her hand on a rabbit cage. She was taken to the emergency room for stitches, and given a shot of tetanus toxoid subcutaneously in the left upper arm.

By 15 minutes, there was a red, itchy wheal at the injection site. It faded by an hour, and she went home.

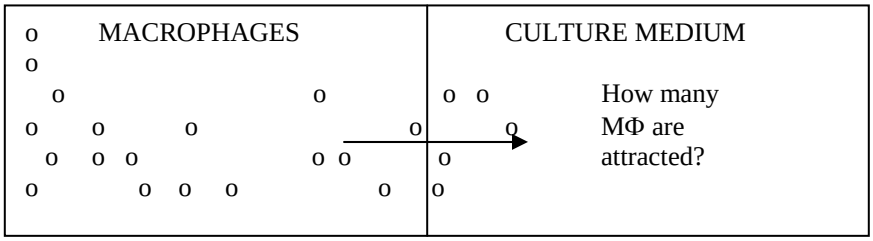
About 6 hours later, the site again became sore, red and hot, although it was not itchy and there was no wheal. She applied a cool compress and took aspirin, and by the next morning the inflammation was nearly gone.

On the second morning, about 38 hours after her accident, the site was again swollen, painful, and red, although not particularly hot. This persisted for another day; as signs of early necrosis were evident at the needle site, she was given a large dose of prednisolone intravenously. The next day the lesion had faded considerably.

Some months later, she consented to have three skin tests with tetanus toxoid. One was biopsied at 15 minutes, one at six hours, and one at 36 hours. **What was seen?**

Serum was obtained, and two immunological tests were performed on it. **Which ones, do you think?**

Her mononuclear cells were put into tissue culture with PHA, tetanus toxoid, or nothing added. After 24 hours, the culture medium was assayed for IL-2 by an ELISA test, and for its ability to attract macrophages from one side of a membrane to the other (a functional test that detects IFNγ and other macrophage chemotactic factors):



Added	IL-2 produced	Mϕ chemotactic activity
nothing	0.3 units	1.2 units
PHA	49 units	78 units
tetanus toxoid	4 units	3 units

So how would you describe her immune response(s) to tetanus toxoid?

PROBLEM 5:

History: A previously healthy 25-year-old woman was seen in the rheumatology clinic with a 4-month history of pain and swelling in the small joints of her hands associated with a blotchy rash over the bridge of her nose and over her knuckles.

Physical exam: Examination revealed mild symmetrical synovitis in the hands and red scaly patches over her knuckles and face consistent with a photosensitive rash. Her blood pressure was normal. Temperature was mildly elevated at 38.3 C.

Lab investigations:

Urine: showed no blood or protein.
CBC and differential: normal.
Erythrocyte sedimentation rate: Elevated at 49 mm/h (an inflammation marker)
Creatinine: normal. (a kidney function marker)

ANA (antinuclear antibodies): Elevated at 1:1280 "homogeneous pattern."
Ab to dsDNA: Negative.
Rheumatoid factor: Negative.
Sun-exposed skin biopsy showed mild vasculitis with neutrophils.

Diagnosis: ?

Treatment: NSAIDs and hydroxychloroquine. Advised to avoid direct UV light.

Course: No improvement over next 6 months. Corticosteroids were offered but the patient refused. Liver function tests were slightly abnormal.

More history:

A thorough family history was positive for a great-aunt with rheumatoid arthritis.

On careful questioning, a resident found that she had forgotten to mention these since she had been taking them for 5 years: low-dose paroxetine (Paxil®) for generalized anxiety disorder, minocycline (Minocin®) for acne, and "Organic Thymus Preparation" "for weak immune systems."

She had been immunized against hepatitis B in college.

Diagnosis: ?
Treatment ?
Outcomes ?