**History and Examination:**
- **Family history** of collagen diseases and cancer
- **Immunization status**
- **Occupational history**? virologist? Sex worker?
- **Travel history** been to African swamps lately?
- **Nutrition** (including consumption of dairy products)
- **Drug history** (over-the-counter medications, prescription medications, illicit substances)
- **Sexual history**
- **Recreational habits**
- **Animal contacts**
- **Surgical history**

*CHECK EVERY LYMPH NODE!* And feel the spleen…

*ASK ABOUT ALL ORGAN SYSTEMS*

**PUOs are caused by**
- infections (30-40%)- mainly kids
- neoplasms (20-30%)- mainly elderly
- collagen vascular diseases (10-20%)
- miscellaneous diseases (15-20%).
- between 5-15% of FUO cases defy diagnosis, despite exhaustive studies.

**SO WHAT COULD BE CAUSING THIS?** massive list of differentials...

### Bacteria
- **ABSCESS:** Previous abdominal operations, trauma, or histories of diverticulosis, peritonitis, endoscopy, or gynecologic procedures. Most common locations are the subphrenic space, liver, RLQ, retroperitoneal space, and the pelvis in women.
- **TUBERCULOSIS:** especially among migrants and the immunocompromised, so do a Chest X-ray
- **URINARY TRACT INFECTION** is easily recognised; so do a Urinalysis
- **ENDOCARDITIS** causing new murmurs, so listen to the heart and take blood cultures
- **CHOLANGITIS** could be clinically silent, so think about doing the LFTs even though they may be normal
- **OSTEOMYELITIS** if there are musculoskeletal symptoms, so do a Tc99 Bone Scan

### Viruses
- **COULD IT SIMPLY BE AN ADVANCED HIV INFECTION?** Typical and atypical mycobacteria and cytomegalovirus (CMV) are opportunistic infections that frequently cause prominent constitutional symptoms, including fever, with few localizing or specific signs, so do HIV and CMV serology
- **HERPESVIRUSES** can reactivate in the immunocompromised and elderly without much external signs; so do EBV Monospot, Herpes serology and Blood film for Atypical Lymphocytes.

Speaking of HIV: could it be CANDIDA or CRYPTOCOCCUS? Could it be TOXOPLASMOSIS?

### Neoplasms
- **Lymphomas and Acute leukaemias** cause fever, night sweats and weight loss.
- **Renal cell carcinoma:** fever being the only presenting symptom in 10% of cases. Hematuria may be absent in approximately 40% of cases, but there will be anaemia and high ESR
- **Adenocarcinomas** of the breast, liver, colon, or pancreas and liver metastases from any site.

### Autoimmune
- Fever may only be the FIRST THING THAT GOES WRONG: watch for arthralgia, rash, nephritis
- **Systemic Lupus:** can get fevery, easily identified with ANA, DsDNA(Ab), etc…
- **Polyarteritis Nodosa:** a systemic necrotising vasculitis; ANCA, high ESR, leucocytosis
- **Rheumatoid Arthritis:** fever can sometimes present without (rather, before) arthralgia. RF.

### Granulomae
- **Sarcoidosis:** look for lymph nodes and granulomae with NON-INVASIVE IMAGING
- **Crohns Disease:** hard one, need Endoscopy and Biopsy

### Medications
- beta-lactam antibiotics, procanamide, isoniazid, alpha-methyldopa, quinidine, and diphenylhydantoin. Just stop the drugs and the patient will cool down within 2 days

### Endocrine
- **HYPERTHYROIDISM:** fever and weight loss often the only signs; run a TSH and T4
- **ADRENAL INSUFFICIENCY:** rare but potentially fatal! Nausea, vomiting, weight loss, skin hyperpigmentation, hypotension, hyponatremia, and hyperkalemia.

### The OTHERS
- **Giant Cell Arteritis** – ESR will be over 100 ask about jaw claudication and visual loss
- **Polymyalgia Rheumatica** -symmetrical pain and stiffness involving the lumbar spine and large proximal muscles.
INVESTIGATIONS:

**FBC:** Anemia, leukaemia, leukocytosis, lymphocytosis? Atypical lymphocytes of EBV or CMV?
- PERIPHERAL BLOOD THICK AND THIN FILMS for malaria

**Urinalysis:** Exclude UTIs and cancers of the urinary tract

**LFT:** mainly to check for viral hepatitis or liver abscess

**Culture EVERYTHING!**

**SEROLOGY—** EBV, CMV, HIV, HEP B and C, toxoplasma, chlamydia

**ESR:** for Giant Cell Arteritis, Polyarteritis Nodosa, etc

**ANTIBODIES:**
- ANA
- Rheumatoid factor
- ANCA
- Double-stranded DNA

IMAGING:

**Chest X ray** - who knows what you may find

**Abdominal Ultrasound** (maybe even in absence of symptoms)

**CT scan of abdomen and pelvis** (if there are vague abdominal symptoms)

**MRI and /or Tc99 Bone Scan** if you suspect osteomyelitis

**ENDOSCOPY** if you suspect Crohns

If all else fails, you may be reduced to doing BIOPSIES.

**For MANAGEMENT, you need an underlying cause.**

No evidence supports prolonged hospitalization in patients who are clinically stable and whose workup is unrevealing.