

## MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

October 25, 1962

### Complications of Antibacterial Therapy

#### Ineffective Drug

- A. Ineffective by virtue of incorrect clinicobacteriological diagnosis (Cases #1 and #2)
- B. Ineffective by virtue of irregular absorption, failure of activation or inactivation
  - 1. Furaltadone - irregular absorption (4-6)
  - 2. Mandelamine - failure of activation (7)
  - 3. Methicillin - inactivation (Table 1)

#### Biological Complications - particularly in association with broad-spectrum antibiotics, steroids and/or antitumor agents

- A. Alterations of bacterial flora
  - 1. Overgrowth of resistant organisms (Case #3) (8-11)
    - a. "Utilization" of vitamins by organisms (12,13)
  - 2. (?) Loss of bacterial function (14-20)
- B. Suppression of antigenic stimulus with susceptibility to reinfection (21)

#### Pharmacological Complications

- A. Principles - idiosyncrasy and/or toxicity to both active drug as well as inactive or trace components
  - 1. Rate and route of metabolism
    - a. Restriction by renal insufficiency (Table 2) (22)
    - b. Restriction by hepatic insufficiency (23-26)
    - c. Restriction by immaturity (renal, hepatic, etc.) (27-34)
  - 2. Detection of hypersensitivity
- B. Clinical applications - all drugs have some toxicity or produce hypersensitivity. Considerations based upon underlying illness and other available drugs.
  - 1. Effective drugs with out reasonable alternative agents
    - a. Amphotericin B - nephrotoxicity, nephrocalcinosis, anemia, hypokalemia, decreased urine 17-OH (?), adrenal insufficiency (35)
    - b. Penicillin G - hypersensitivity,  $\text{Na}^+$  or  $\text{K}^+$  in heart failure or renal insufficiency (36,37)
    - c. Streptomycin - ototoxicity, neuromuscular effects, eosinophilia (38-40)
    - d. Tetracycline - gastrointestinal, provocation of "lupus" (41,42)
    - e. Chloramphenicol - hematologic, "Grey syndrome" (Cases #4, 5) (43-49)
    - f. Colistin - paresthesias, nephrotoxicity (50)
    - g. Kanamycin - ototoxicity, nephrotoxicity, neuromuscular effects (anesthesia, myasthenia gravis) (51-54)
    - h. (?) Novobiocin - skin eruptions, leucopenia, "jaundice" (Cases #1, 6) (55,56)
    - i. Erythromycin - other than propionyl ester lauryl sulfate
    - j. Vancomycin - fever, phlebitis, ototoxicity (57,58)
    - k. Methicillin - fever, eosinophilia, (?) renal, hematologic (Case #6) (59,60)
  - 2. Effective drugs, but other equally effective less toxic agents available
    - a. Erythromycin, propionyl ester lauryl sulfate (Ilosone) - hepatic, eosinophilia (61,62)
    - b. Triacetyloleandomycin (Signemycin, Cyclamycin, TAO) - hepatic, eosinophilia (63)

- c. Demethylchlortetracycline (Declomycin) - photosensitivity (64-66)
- d. Ristocetin (Spontin) - hematologic (67)
- e. (?) Bacitracin - nephrotoxic (68)
- f. Sulfamethoxypyridazine (Kynex, Medice) - erythema multiforme, myocarditis, hematologic (Case #7) (69-71)

	2 mg/ml (1:1000)	10 mg/ml (1:20000)
5% D/W	2	2
5% D/W	2	2
5% Lactate	4	12
Garrow's Solution	5	12
10% D/W	2	4
Normal Saline	5	2
Lactate Ringer's	5	12

#### Antibiotics in patients with renal disease

Antibiotic	% Recovered (mg/day)	Renal Clearance (ml/min)	Half-life (hrs) Normal	Half-life (hrs) Azotemic	Dosage in Azotemia
Penicillin G	50-60	50-100 ml/min	0.5	1-2.5	Aqueous - 10 mg q 4h
Propylpenicillin	50-60	50-100 ml/min	0.5	1-2.5	0.5 gm q 4h
Tetracycline	15	20-30 ml/min	8-12	20-48	0.5 gm q 6h
Chlortetracycline*	18	10-20 ml/min	8-12	8-11.0	normal
Oxytetracycline	10	20-30 ml/min	8-12	8-11.0	normal
Chloramphenicol*					
Active	5-15	20-30 ml/min	3-5	2-4.3	decreased, but
Inactive conjugates	70-80	30-40 ml/min	3-5	61.3-150.3	inactive metabolites
Erythromycin	15	70% excreted	1.5	0.5-5.8	normal
Vancomycin	1.5-3.3	10-20 ml/min	1.5	1.5-2.5	normal
Clindamycin	50-90	50-100 ml/min	2	1.0-2.0	0.5 gm q 6h
Polymyxin B	large	-	6	-	50 mg q 6h
Neomycin	30-40	0-10 ml/min	6	-	decreased

\* Metabolic effect of in vivo inactivated drug is unknown, may be variable as active drug

TABLE I

Maximum Time Period Various Concentrations of Methicillin -  
Intravenous Solution Mixtures Should Be Used or Allowed To  
Stand at 25°C (Loss of potency less than 20%)

	Utility Time (hours)	
	2 mg/ml (1 gm/500 ml)	10 mg/ml (5 gm/500 ml)
5% D/S	2	8
5% D/W	2	8
M/6 Lactate	4	12
Darrow's Solution	4	12
10% D/W	2	4
Normal Saline	4	8
Lactate Ringer's	4	12

TABLE II

Antibiotics in Patients With Renal Disease

Antibiotic	% Recovered in Urine	Renal Clearance	Half-Life (hours)		Dosage in Cases With Azotemia
			Normal	Anuric	
Penicillin G	58-85	560-1080 ml/min	0.5	7.2-10.5	Aqueous - q4-10h
Streptomycin	30-80	30-70 ml/min	2.4-2.7	52-110	1.0 gm, 0.5 gm q2d
Tetracycline	60	62% CCR	8.5	57-108	0.5 gm q2-4d
Chlortetracycline*	18	30-37% CCR	5.6	6.8-11.0	normal
Oxytetracycline	70	85% CCR	9.6	-	
Chloramphenicol*					
active	5-15	24 ml/min	1.6-3.3	3.2-4.3	normal, but
inactive conjugates	70-80	340 ml/min	3.7-4.6	68.5-154.3	inactive retained
Erythromycin	15	76% CCR	1.4	4.8-5.8	normal
Novobiocin	1.5-3.3	low	1.5	-	normal
Kanamycin	52-90	81-156% CCR	3	(?) >72	0.5 gm q2-4d
Polymyxin B	Large	-	6	-	50 mg q8h x3, then 20 mg q8h
Vancomycin	30-40	69% CCR	6	-	decrease

\* Metabolic effect of in vivo inactivated drug is unknown, may be as toxic as active drug

CASE #1: [REDACTED] Post-partum staph pneumonia (inappropriate initial clinicobacteriological correlation)

Present illness: The patient is a 24-year-old [REDACTED] housewife, admitted on [REDACTED]/59 for a seemingly uncomplicated delivery of a full-term child, her fifth. During this period she remained afebrile. At discharge the baby was colonized with 80/81 staphylococci.

On [REDACTED]/59 while in [REDACTED] [REDACTED] the patient had an acute asthmatic attack which was associated with a non-productive cough. On [REDACTED] she developed chills, fever and malaise. The following day ([REDACTED]/59), she came to the emergency room where she was found to have a temperature of 101.8° and rales in the right axilla. Chest x-ray revealed evidence of pneumonitis in the right upper lobe. She was begun on tetracycline 1.0 gm. daily. Two days later, she developed a productive cough and right pleuritic chest pain, still associated with chills and fever.

Past History: The patient had seasonal asthma since the age of 4 years. In addition, she had superimposed pneumonitis age 14 and 22. At age 22 she was hospitalized with bronchopneumonia of undetermined etiology. The patient was allergic to penicillin.

Physical Examination: (She returned to the chest clinic on [REDACTED]/59 and was referred to the hospital.) Temperature 102.2°, blood pressure 110/70, pulse 96, respirations 30. The patient appeared quite toxic but was not cyanotic. Teeth were in very poor repair. Over the right upper lobe there was noted increase in focal fremitus, minimal dullness and inspiratory and expiratory wheezes. There was no clubbing. There were no staphylococcal lesions on the skin.

Accessory Clinical Findings: WBC 14,400 with 83% polys. Hemoglobin 11.6 gm.%. Skin tests including PPD-2, histoplasmin and coccidioidin negative. Sputum smear showed a predominance of gram-positive cocci. Cultures on this showed coagulase-positive staphylococci, phage type 80/81, resistant to penicillin and tetracycline. Sensitive to erythromycin, chloramphenicol, kanamycin, novobiocin, bacitracin, streptomycin and vancomycin. Other blood chemistries included a normal BUN (5 mg.%).

Course in Hospital: The patient was initially placed on chloramphenicol and erythromycin. The following day this was changed to chloramphenicol 1.0 gm. daily and novobiocin 2.0 gm. daily. This was continued for an additional 4 days, during which time her temperature ranged 101° and 104°. On the 4th hospital day ([REDACTED]/59) she was begun on vancomycin in a dose of 2.0 gm. in 1000 cc. 5% dextrose and water, which was administered intravenously over a 16-hour period. With each daily administration of this, the patient had frank shaking chills. The material was discontinued after 6 days ([REDACTED]/59) because of bilateral thrombophlebitis. During the period of vancomycin administration, her temperature varied between 101° and 103°. She became afebrile by [REDACTED]/59 (2 days after vancomycin discontinued). She was then placed on kanamycin 2 gm. daily and chloramphenicol 1 gm. daily, which were continued through the 24th hospital day ([REDACTED]/59). At this time, the kanamycin was discontinued and novobiocin re-instituted. Within 24 hours the patient developed a maculopapular eruption and this was discontinued. She was then maintained on chloramphenicol until her discharge on [REDACTED]/59. At the time of discharge, she was placed on triacetyloleandomycin 1 gm. daily, to be continued for two weeks. Blood cultures obtained during her hospitalization were sterile. The patient was seen in follow-up on [REDACTED]/60, at which time she had no symptoms.



CASE #2: [REDACTED]. Sulfonamide (Gantrisin) hypersensitivity manifest by nephritis, myocarditis and pneumonitis. (Inappropriate initial clinical evaluation)

The patient was a 60-year-old [REDACTED] female admitted on [REDACTED]/57 with the chief complaint of an ulcer on the right leg for one year. Bilateral venous varicosities were noted in 1947. By 1950, she developed bilateral pretibial ulceration and a saphenous ligation was performed. She had had continued difficulty until the present admission.

There was a past history of congestive failure for which she had been digitalized in 1950 and had remained asymptomatic. Also, history of dysuria, frequency and occasional backaches was obtained.

On physical examination cardiac enlargement and bilateral stasic ulceration of the legs were noted. Admission hematologic studies and urinalysis were unremarkable, except for occasional WBC in the urine sediment.

The patient was placed on Gantrisin (4.0 gm. qd) on [REDACTED]/57. On [REDACTED]/57 the patient developed fever which rose step-wise to levels of 101-102° F. and was spiking in course, and noted arthralgias in elbows, wrists and pain on movement of the neck. By 7/26/57, the elbows were warm, swollen and showed evidence of fluid. At this time the Gantrisin was stopped. On the evening of [REDACTED]/57 the patient became hypotensive (BP 95/55), was noted to be oliguric. A blood culture obtained [REDACTED]/57 grew *Klebsiella pneumoniae* from one flask and *Escherichia coli* from the other. During the nine-day period from [REDACTED]/57 to [REDACTED]/57, 4+ albuminuria had appeared and the BUN had risen from 11 to 64 mg.%. Vigorous therapy consisting of neomycin, levophed, oxygen by IPPB, correction of electrolyte imbalance was instituted; however, the patient died on [REDACTED]/57. Pathologic diagnosis: Acute interstitial non-suppurative nephritis and acute interstitial myocarditis.

CASE #3: [REDACTED] Acute lymphocytic leukemia treated with steroids and antibiotics complicated by pseudomonas lung abscess, bacteremia and acute disseminated moni-  
liasis

Present illness: The patient was a 71-year-old [REDACTED] male admitted [REDACTED]/59 with an illness characterized by scattered paresthesias, generalized weakness and easy fatigability for 6 weeks.

Physical Examination: BP 160/80, pulse 96, respirations 18, temperature 99°. The patient was a chronically ill appearing man. The examination revealed no generalized lymphadenopathy and the liver and spleen were not palpable. Neurologic examination was normal except for decreased position sense in the toes.

Accessory Clinical Findings: Hemoglobin 5.1 gm.%, WBC 8,550 with 92% mature lymphocytes and 8% polys. Bone marrow revealed 9.7% blasts, 89% lymphs and 1.3% erythroid elements. Bleeding studies normal except for poor clot retraction.

Course in Hospital: The patient was started on 30-40 mg. of prednisone daily on his 3rd hospital day and received this throughout his 31-day hospital course. From the 21st through the 28th hospital days, he received amethoptine 5 mg. daily. Anemia, leucopenia and thrombocytopenia were progressive. On the 16th hospital day the patient had temperature elevation to 101° associated with a left lower lobe infiltrate and increased sputum production. Therapy was initiated with kanamycin and 10 million units penicillin daily.

On this he became afebrile. With the pulmonary infiltrate, hyperglycemia and glycosuria appeared. On the 28th day, 2 days after antibiotics, temperature recurred and an x-ray revealed right upper lobe infiltrate with probable abscess. Blood culture and sputum culture grew Pseudomonas aeruginosa. The patient was again started on kanamycin and tetracycline without any improvement. Laboratory studies on the 28th hospital day revealed hemoglobin 4.3, white count 1,500, platelets 4,000, fasting blood sugar 400, and BUN 17 gm.%.  
 Postmortem Exam: Acute subleukemic lymphocytic leukemia, extensive bilateral diffuse consolidation with multiple abscesses characterized by large numbers of bacteria but no PMNs. Enterocolitis due to monilia and multiple renal abscesses due to monilia.

CASE #4: [REDACTED]. Sick cell (SS) disease with Salmonella typhosa osteomyelitis complicated by anemia and granulocytopenia

Present Illness: This 4-year-old [REDACTED] boy was admitted on [REDACTED]/61 following an injury to his right knee. A diagnosis of sickle cell crisis was made. Findings included temperature 101° rectally, a swollen, warm and tender right knee. Hemoglobin 9.0 gm.%, WBC 25,600 with 76% polys. The patient left before therapy could be rendered; however, he returned on [REDACTED]. Films of the knee, femur and tibia were taken and revealed no abnormalities.

On the afternoon of [REDACTED]/61, he began complaining of pain in the right elbow. The following day the elbow became hot, swollen and tender. Family presented the child for admission on [REDACTED]/62, at which time he had a temperature of 105.4°. The arm was unchanged on admission and a grade 2-3 systolic precordial murmur was the only other pertinent physical finding.

Accessory Clinical Findings: Hemoglobin 6.0 gm.% with a positive sickle cell prep and subsequently SS hemoglobin. 6 nucleated RBC/100 and 1.6% reticulocytes. WBC 18,400 with 56% segs.

Hospital Course: The x-ray findings of the right humerus and left 8th rib were initially thought most compatible with bone infarction and changes secondary to sickle cell disease. He continued to spike temperatures daily in the range of 102°. On [REDACTED]/62, fluid was aspirated from the periosteal area in the right humerus which grew out a CI salmonella (Salmonella typhosa). At that point, he was begun on chloramphenicol 1 gm. daily (50 mg./kg.). His fever persisted; bone pain did not resolve, and by [REDACTED] his reticulocyte count had dropped from 5.0% to 0.6% associated with a hemoglobin fall to 4.0 gm.%. The chloramphenicol was discontinued and tetracycline begun. Specific laboratory studies are detailed in the table:

Date	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Hgb.	6.0	5.3	6.3	7.1	7.2	7.0	6.4	5.5	5.7	4.0	3.7	8.7
Retics	11.6	8.1	6.5	3.6	—	7.2	9.7	5.0	2.8	0.6	1.1	5.4
WBC	26.9	15.2	13.0	11.8	14.5	17.5	14.7	4.8	10.8	8.1	15.2	15.9
% PMN	77	73	59	56	58	52	49	67	43	19	39	45
Chloramphenicol 50 mg/kg. ————— Discontinued Tx												

Subsequent therapy included colistin and tetracycline and subsequently ampicillin, and final incision and drainage of rib lesions. The patient was discharged on 7/21/62.

CASE #5: [REDACTED]

The patient is a 51-year-old [REDACTED] female who was admitted on [REDACTED]/62 with weakness, scleral icterus and dark urine.

Past History: The patient consumed considerable alcohol in the form of whiskey, vodka and other beverages.

Physical Examination: The patient was rather well-developed and reasonably well-nourished with obvious icterus. The skin showed virtually no spider angiomas. There was no ascites. The liver was down 5 fingerbreadths and was firm and slightly tender. The spleen was not palpable.

Accessory Clinical Findings: Hemoglobin 10.9 gm.%, WBC 23,000 with 86% PMNs. Urinalysis revealed 4+ bilirubin. Serology non-reactive. Total proteins 7.3 gm.% with 2.5 gm.% albumin. SGOT 242, bilirubin 19.4 mg.% total with 10.1 mg.% direct. Ceph flocc 2+/3+, thymol turbidity 8.7, alkalinephosphatase 7.2 and prothrombin concentration 50% of control.

Course in Hospital: Management was directed primarily at her liver disease. During the course of evaluation she was shown to have definite bacterial casts in the urine despite lack of urinary symptoms and negative urinalyses in the routine laboratory. A catheterized urine specimen revealed Proteus mirabilis and Aerobacter aerogenes, 150,000 organisms/ml. The Proteus mirabilis was sensitive to 10 µg/ml. chloramphenicol and 5 µg/ml. kanamycin; the Aerobacter aerogenes was not inhibited by 20 µg/ml. chloramphenicol, but was inhibited by 5 µg/ml. kanamycin. On [REDACTED]/62 she was begun on kanamycin 0.5 gm. daily and chloramphenicol 1.5 gm. daily. Following vitamin K therapy, a liver biopsy was performed which revealed fatty metamorphosis and portal cirrhosis. A progressive decrease in hemoglobin occurred and the chloramphenicol was discontinued on [REDACTED]/62 and the kanamycin on [REDACTED]/62. Bone marrow was performed on [REDACTED]/62 which revealed generalized hypoplasia most severe in the erythroid series. There were scattered basophilic normoblasts, most of which had large cytoplasmic vacuoles. The granulocytic and megakaryocytic series seemed normal. Repeat bone marrow on [REDACTED]/62 revealed marked hypercellularity. No residual vacuolization of erythrocytes was noted. On [REDACTED]/62, serum iron 120 µg.% with total iron-binding capacity 178 µg.%. During the interval of chloramphenicol therapy four stool guaiac determinations were negative and one showed 1+. The course of her hematologic values is recorded in the table:

Date	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Hgb	10.9	7.9	8.7	6.8		6.7		5.1	4.9	8.4	8.1
Retics	5.2								0.3		2.0
WBC	23.0	9.8	14.1	20.7		14.2	10.0	9.1	3.5	3.9	6.0
% PMN	86		81	86		92		85	68	65	46
Platelets	425			162						32.5	480
Stool guaiac				1+	0	0		1+	0		0
Chloramphenicol 1.5 gm. ————— DC I Tx											
Kanamycin 0.5 gm. ————— DC											

The patient was finally discharged on [REDACTED]/62 and has failed to keep her subsequent clinic appointments.

CASE #6: [REDACTED]. Staphylococcal bacteremia treated with multiple drugs including methicillin. Probable leucopenia and neutropenia secondary to methicillin

This 54-year-old [REDACTED] male was admitted for the third time on [REDACTED]/62 with a 4-year history of exfoliative dermatitis, for which he was receiving 20-40 mg. of prednisolone daily. Two weeks prior to admission he developed pustular lesions on the scrotum and lower extremity. These were treated in the emergency room with debridement and soaks; however, he became worse and began to note some orthopnea. On the night of admission he began to talk incoherently and was brought again to the emergency room.

Physical Examination: The patient was a disoriented, acutely ill white male with Cushingoid facies. Blood pressure 140/84, pulse 148, respirations 44, temperature 103°. The chest revealed bilateral rales. The heart was not remarkable. The abdomen was protuberant and a fluid wave was present. There were pustular lesions on the scrotum. The right leg was red, hot and edematous, with pustular lesions on the toe. Neurologic examination was normal except for the gross disorientation.

Accessory Clinical Findings: Hemoglobin 14.6, WBC 15,000 with 94% polys. Urinalysis: 1+ albumin, 9-20 WBC. BUN 39 mg.%, sugar 124 mg.%, CO<sub>2</sub> 24, Cl 80, Na 126, K 3.5. Lumbar puncture revealed 299 WBC with 95% polys. Urine culture grew 300,000 coagulase-positive staphylococci per ml. Spinal fluid culture was positive. Two blood cultures obtained on [REDACTED]/62 revealed > 1000 colonies of staphylococci per ml. Two additional blood cultures on [REDACTED]/62 also contained coagulase-positive staphylococci in large numbers. The organism was resistant in vitro to > 20 µg/ml. penicillin, streptomycin and tetracycline. Sensitive to 1.25 µg/ml. erythromycin, 5 µg/ml. novobiocin, 5 µg/ml. kanamycin, 5 µg/ml. chloramphenicol and 5 µg/ml. vancomycin.

Course in Hospital: On the night of admission the patient was digitalized and a tracheostomy performed. The subcutaneous abscesses in the left thigh were opened, as were those on the right. The patient was started on methicillin and penicillin G. On [REDACTED], he again became restless and disoriented. It was felt that he was having septic pulmonary emboli, so the right common femoral artery was ligated under local anesthesia and an abscess of the right saphenous vein was incised and drained. At this time he was begun on vancomycin. The patient gradually improved. Methicillin was discontinued on [REDACTED]/62 because of apparent development of leucopenia and neutropenia. The patient was subsequently begun on novobiocin and developed a skin eruption. He was discharged on [REDACTED] 62.

Date											
Hgb	14.6	10.6*	9.0	9.8*	8.6	9.5	7.6*	9.3	9.7	9.5	9.2
WBC	15.1	17.4	13.1	7.8	3.7	3.5	2.5	3.7	3.3	5.7	11.3
% PMN	94	91	91	96	81	51	38	53	60	62	62
% Eos		1			1	1		1	2	2	
Fe/TIBC										35/169	
BUN	39	135	50	25		29		30			25
Methicillin 4.0 gm. _____ Pen G 15 million units											



Case #7: [REDACTED] Erythema multiforme exudativum (Stevens-Johnson syndrome)  
 associated with sulfamethoxypyridizine

This 21-year-old [REDACTED] was admitted on [REDACTED] 58 with an acute skin disease of 4 days' duration.

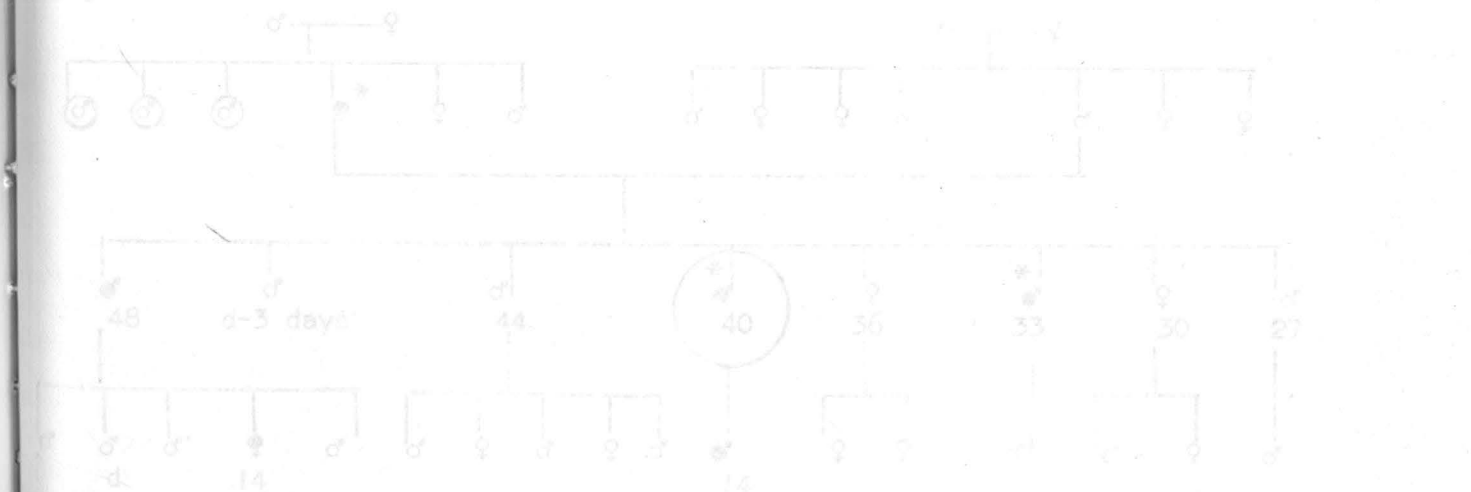
Eleven days prior to admission she sought medical attention because her urine looked "yellow" and there was slight dysuria. She was diagnosed as having a kidney infection and was treated with sulfamethoxypyridizine 0.5 gm. daily for 7 days. Four days ago she noted pruritus and reddish papules over the arms and legs, which rapidly spread to involve the entire body. The papular lesions became vesicular. Three days before admission she noted lesions on the eyelids and mouth.

Physical Examination: The patient was a young white female in acute distress. There was a generalized bullous eruption most marked over the face and upper cheeks. These were universal in distribution, involving the palms and soles. All of the mucous membranes including the conjunctivae, nasal mucosa, tongue, labia and vagina were involved.

Accessory Clinical Findings: Hemoglobin 12.4, WBC 9,700 with 91% polys. Urinalysis revealed 20-25 white cells, though none on cath specimen. Serology npn-reactive. BUN 13 mg.%.  
 Cardiac: The patient was complicated by a low fat diet. Two years ago he began to have attacks of chest pain following exertion. On admission to the hospital he was found to have a low fat diet. Two years ago he began to have attacks of chest pain following exertion. On admission to the hospital he was found to have a low fat diet.

Course in Hospital: The patient was treated with intravenous hydrocortisone and tetracycline. She promptly became afebrile and the skin gradually improved. She was discharged on [REDACTED] 58.

One week at home on tetracycline and rest he had another episode of chest pain following exertion. He was readmitted to the osteopathic hospital, where he was told that he had an extension of the infarct. He was subsequently referred to the Dallas Veterans Administration Hospital. The family history is given below:



KEY: \* = hypercholesterolemia (> 300 in adults, > 250 in children)

\* = xanthomatosis

○ = propositus