[Drug disease]

MEDICAL GRAND ROUNDS
PARKLAND MEMORIAL HOSPITAL
JANUARY 30, 1958

CASE 1 (Thrombocytopenia apparently due to phenacetin) - [redacted]

A 26 year old white female was admitted with a 10 day history of malaise, easy fatigability and feverishness. She had taken APC tablets at home in considerable quantities but the fever and discomfort persisted. Splenomegaly was noted and the patient was admitted. One month before she had delivered a normal infant.

The past history suggested that the patient had rheumatic fever as a child (recurrent sore throat and migratory arthritis). Bed rest and APC's were prescribed during an acute episode one year prior to admission. At this time a diagnosis of aortic stenosis was made.

On examination she was alert and cooperative. A grade II systolic murmur was described in the aortic area. P_2 and M_1 were normal. The liver was felt 5 cm. below the CM in the MCL; it was firm and non-tender. The spleen was firm, tender and 8 cm. below the CM. Discrete, small shotty nodes were palpable in the axillary and inguinal areas.

Course: For 2 days the patient was febrile (temp. 101°F) but thereafter she was asymptomatic. The improvement occurred on bed rest (no specific therapy). An ECG was found to be within normal limits. Two L. E. preparations, 5 blood cultures, 2 sputum cultures and 2 urine cultures were negative. X-rays of hands revealed the changes of osteoarthritis. (Rheumatic valvular disease was considered present by some observers).

Laboratory data (see chart): On the fourth day a platelet count by the direct method was low (54,000/cu mm), a repeat count on the following day was also low (70,000). By the time the patient was discharged the direct platelet count was 134,000/cu mm.

Twenty-eight days following the admission the patient was given an APC tablet. The platelet count two days later was 80,000/cu mm. The myalgia and fever returned. At this time an APC dependent (phenacetin dependent) platelet agglutination was demonstrated. One month later the platelet count was 104,000. Symptoms had subsided.

Hospital Day	1	2	3	4	6	7	18	20	52
Hb gm%	11.0	10.7		8.6					11.8
WBC/cu mm	3,100	4,700	5,850			5,450			
% Segs.	58	60	74			60			
1,000 platelets/cu mm				54	70		134	80	104

Laboratory data (cont'd. Case 1)
Bone marrow smear: M:E Ratio 4:1 (Normal), not remarkable except for eosinophilia 6%.

BSP 15% retention
Cephalin Flocculation 4+
Bilirubin 0.8 mg%
Alkaline phosphatase 7.8 B. U.
Prothrombin 100%

Heterophile antibody - negative
Cold agglutinins - negative
Direct Coombs test RBC - negative
Liver biopsy - normal

Phenacetin dependent platelet agglutination:

1. Pt. serum + donor platelet (28th day) ——→ Negat ve
2. Pt. serum + donor platelets + APC (28th day) ——→ 3+ agg.
3. Pt. serum + donor platelets + APC (33rd day) ——→ 2+ agg.
4. Pt. serum + donor platelets + APC (168th day) ——→ 3+ agg.
5. Proper c ontrols - negative

Summary: This was an apparent example of "drug disease" with the following components: Fever, malaise, hepatosplenomegaly, questionable lymphadenopathy, eosinophilia of bone marrow, anemia, leucopenia and an "allergic" or immune type of drug dependent thrombocytopenia. The history and apparent stigmata of rheumatic fever may be considered to indicate a hypersensitive individual. The thrombocytopenia was only one of several clinical expressions but yielded a positive "objective" test.

CASE 2 (Leucopenia apparently due to sulfadiazine) - [redacted]

A 28 year old colored male was admitted to [redacted] on [redacted]-57 after a chest x-ray examination at [redacted] emergency room. Two weeks prior to admission a profuse watery diarrhea began. His physician prescribed sulfadiazine and during the first 9 days of his illness he took 36 tablets (18 gm) of this drug. Four days before admission the diarrhea subsided. Three days before admission he developed nausea, vomiting, epistaxis and hemoptysis. At the emergency room an x-ray film revealed a diffuse miliary-like infiltration scattered over both lung fields. The latter prompted his transference to [redacted].

The past history was not significant.

Examination indicated a BP of 125/80, pulse rate of 110, respiratory rate of 28/min. There was muscular weakness and poor tissue tungor. Several purpuric foci were scattered over the skin. There was mental confusion. The spleen and liver were not palpable.

Laboratory data:

Laboratory work on admission revealed Hb 14.8 gm, WBC 5,000 (60 segs, 40 lymphs); grossly bloody urine. By the seventh day the Hb had fallen to 6.8 gm% and the WBC count was 1200/cu mm (30% segs, 70% lymphs). On this day the patient's serum plus patient's WBC plus sulfadiazine gave 3+ leukoagglutination (controls negative). The same studies using the patient's serum and the patient's platelets and RBC were negative. The bone marrow smear was interpreted as showing hypocellularity, many degenerated forms, toxic granules in the neutrophils, decreased number of mature neutrophils and megakaryocytes (in keeping with myelotoxic injury).

Course and management: The patient was given INH (1000 mg/day) and pyridoxine (100 mg/day) throughout the hospital stay. Between the 7th and 13th days he was given 2000 cc. of blood. A high spiking fever (103-104°F) remained until the 15th day when he became afebrile.

A liver biopsy (needle puncture) was reported as showing focal granulomata, etiology not apparent. Acid fast stains of the liver were negative. Initially skin tests with histoplasmin, coccidioidin and tuberculin were negative but after 3 months an O. T. 1:100 test was weakly positive. Complement fixation tests for histoplasmosis and coccidoidomycosis were negative. Nine (9) sputum concentrates smeared for AFC were negative. A similar number of sputa were cultured and to date (5 months later) all are negative. A mouse inoculated with sputum on sacrifice showed no acid fast organisms in the testicle, spleen and mesenteric nodes.

A follow-up chest x-ray on [redacted]58 revealed complete clearing of all lung fields except for a small residuum of the infiltrate persisting in the right upper lobe. Today the patient is asymptomatic and working regularly.

Additional laboratory data: (Case 2)

Hosp. Day	1	4	5	7	8	11	13	15	18	20	25	34	42	49	77
Hb gm%	14.8	11.8	9.8	6.8	5.8		6.5	8.7	7.5	8.8	7.8	9.0	11.8	12.3	
Retic. %						2.0	1.8		1.5		11.5	2.4	2.0		
WBC 1000/ cu mm	5.0			1.2			0.75	1.3	3.6	2.4	4.2	10.4	15.6	17.3	9.2
Seg. %	60			30			10	40	60	71	69	85			
Lymph %	40			70			90	60	30	29	31	15			
Platelets 1000/cu mm						34	64			70	100	124			
BUN mg%	36			17											

Eighth day: Na 133, K 4.2, Ca 11.4 mg%, P 3.8 mg%, alkaline phosphatase 3.9 B. U., albumin 4.2, globulin 2.8 gm%, prothrombin 100%.

CASE 2 (cont'd).

Sulfadiazine dependent agglutination:

A. WBC:
1. Pt's. serum + pt's. WBC ——————→ Negative

2. Pt's serum + pt's. WBC + sulfadiazine ——————→ 3+ agg.

B. Platelets

Same scheme as in A tests ——————→ Negative

C. RBC

Same scheme as in A + Coombs test ——————→ Negative

Summary: A likely interpretation of this case considers the entire clinical expression as due to "drug disease". From this view the reaction appeared due to a sulfonamide and to include mental confusion, fever, abdominal discomfort, a diffuse miliary-like pulmonary infiltrate, a hemorrhagic state associated with thrombocytopenia, leucopenia, anemia (pancytopenia), morphologic evidence for myelotoxic injury and evidence for an "allergic" or immune type of drug dependent leucopenia. Again the leucopenia was only one of several clinical expressions but yielded a positive "objective" test. (The anemia and leucopenia may be in part due to a similar mechanism but laboratory confirmation was not forthcoming). The hepatic granuloma may have been due to a reaction to the drug although sarcoidosis was also a possibility. Tuberculosis was considered by some observers.

CASE 3 (Hemolytic anemia apparently due to phenacetin) - [redacted]

A 17 year old negro girl developed an upper respiratory infection and sustained trauma to the jaw 10 days before admission. An injection of penicillin caused urticaria. Relief of this followed a dose of pyribenzamine. For discomfort she was given a prescription containing phenobarbital and phenacetin. During the following three days the urine became dark "like tea" and the sclerae became icteric. Weakness was pronounced and on the day of admission she fainted.

The BP was 120/60, pulse rate 124, resp. 16/min. and temperature 98.4°F. The physical examination, except for icteric sclerae and pallor, was negative.

The patient was in the hospital 7 days during which there was steady improvement. The first day she received 1000 cc. of whole blood. She was given Metacorten 15 mgms. daily. The Hb was 8.7 gms. on the second day and

CASE 3 (Cont'd)

10 gms on the third day. The reticulocyte counts were 4% on the fourth day and 5.7% on the sixth. The WBC dropped to 13,800 on the fourth day, the differential count showed 68 segs, 4 bands, 2 myelocytes, 1 basophile, 15 lymphs and 8 eosinophils. The patient was discharged 7 days later at which time the Hb was 12.4 gms. and the WBC 10,000.

Additional laboratory data on admission:

RBC	1.3 mil/cu mm	Sickle preparation	negative
Hb.	4.0 gm%	Blood culture	sterile
Hemat.	12%	Serum bilirubin	1 mg%
Reticulocytes	0.4%	LE preparation	negative
MCV	91	Urinalysis	normal
MCH	31	Bone marrow:	
MCHC	34%	M:E Ratio 1.8:1	
WBC	36,950/cu mm (left shift)	Normoblastic hyperplasia, adequate megakaryocytes	

Phenacetin dependent RBC agglutination (Coombs test):

1. Pt. serum + RBC (Pt. or donor) + phenacetin ⟶ 1-3+ Coombs test
2. Pt. serum + RBC + phenacetin (inactivated) ⟶ Negative
3. Pt. serum + RBC + phenacetin + fresh serum (inactivated) ⟶ 3+ Coombs test
4. Pt. serum + RBC + phenacetin + fresh serum (inactivated) (inactivated) ⟶ Negative

Summary: This patient received several drugs for a "respiratory infection". One drug (phenacetin), known to give rise to a hemolytic anemia, was implicated in an erythrocytic agglutinative phenomenon. This is an interesting phenomenon since it was apparently dependent on several factors including the patient's RBC or a compatible donor's RBC, a thermostable and storage stable serum factor, a thermolabile and storage labile serum factor and the drug. In accordance with Dacie's terminology for erythrocytic antibodies the patient's serum appeared to contain a drug dependent, cold type of incomplete antibody. Such antibodies are considered to be hemolytic in autoimmune and isoimmune states.

CASE 4 (Pancytopenia apparently due to Chloramphenicol) - [redacted] [redacted]

A 40 months old colored female was admitted on [redacted]-57. Two days before admission she developed abdominal discomfort and diarrhea. One day before

CASE 4 (Cont'd)

admission she complained of pain in the right leg. On the day of admission the right leg became more painful, the patient became feverish and refused food.

The patient had proven sickle cell anemia (SS Hb. pattern) and a brother was similarly affected.

On examination the patient appeared malnourished, poorly developed and in acute distress. The temperature was 102.6°F, pulse 100 and respiration 40/min. The sclerae were not icteric. The lungs were clear. There was evidence for moderate cardiomegaly. A grade III systolic murmur was described at the left costal margin. A soft, tender, hot swelling was present over the anterior surface of the right tibia. A soft swollen area involving the soft tissues was present above the left elbow and movement of the elbow evoked pain. The remainder of the examination was negative.

The initial laboratory work included:

Hb. 7.8 gm%, hematocrit 27%, WBC 29,900 associated with a left shift, serum bilirubin 3 mg% (1.0 mg% direct reading). Febrile agglutinins and 3 blood cultures were negative.

Diagnosis: Acute pyogenic osteomyelitis

Management: Tetracycline (200 mg per day) was started on admission and was continued for 3 days at which time the diagnosis became certain. On this day ([redacted]-57) the patient was started on Chloramphenicol and Erythromycin (1 gm each per day). The temperature curve which had been high and spiking returned to normal by the next (fourth) day. Follow-up x-ray films showed the changes of healing osteomyelitis of the right tibia and left humerus.

Complications: On the 16th day ([redacted]-57) the patient developed bouts of vomiting. The latter continued over several days but did not require parenteral fluid therapy. On the 22nd day ([redacted]-57) the Hb was 2.8 gm%, hematocrit 9.0%. The pulse rate was 120/min and gallop rhythm was described.

Bone marrow aspiration obtained on the 26th day revealed a cellular preparation emphasizing a prominent left shift of the precursors of all formed elements of the peripheral blood. Marked vacuolization of primitive forms was present. (This finding has been considered the result of cellular injury).

Pancytopenia due to myelotoxic injury was considered present and the antibiotics were discontinued (26th day). By the 31st day ([redacted]-57) the Hb. was 3.4 gm%, the reticulocyte count was 7.2% and the child had improved clinically. The peripheral blood continued to improve steadily until the time of discharge on [redacted]-57. The osteomyelitis has apparently healed completely.

Additional Laboratory Data:

Hosp. Day	1	6	12	21	26	29	30	31	32	36	39	42	52	59
Hg gm/100cc	7.8	6.0	5.6	2.8	2.4	3.0	2.4	3.4	3.3	5.2	5.6	7.3	7.6	6.3
Hemat. %	27	20	10	9	9	8	7	11	13	20	22	27	23	20
Retic. %				1.0	1.0	0.6		7.0	24	14		15	10	9
WBC 1000/cu mm(corrected)		29.9	11.6	10.1	4.1	24.0	35.0	88.0	64.3	12.5	8.5	8.0	13.0	
Nucleated RBC 1000/cu mm	0.61		1.97	3.1	2.9	0.72	2.4	79.0	86.0	35.0	6.8	0.56	0.8	
Platelets 1000/cu mm					226					280			332	
MCV cu. mm					89					135			83	

CASE 4 (Cont'd).

Chloramphenicol dependent agglutination
([redacted]-57 serum)

A. Platelets

1. Pt. serum + donor #1 platelet ——————→ Negative
2. Pt. serum + donor #1 platelet + chloramphenicol ——→ ± agg.

3. Pt. serum + donor #2 platelet ——————→ negative
4. Pt. serum + donor #2 platelet + chloramphenicol ——— 2+ agg.

B. WBC:

1. Pt. serum + donor #1 WBC ——————→ 1+ agg.
2. Pt. serum + donor #1 WBC + chloramphenicol ——→ 2+ agg.

3. Pt. serum + donor #2 WBC ——————→ 1+ agg.
4. Pt. serum + donor #2 WBC + chloramphenicol ——→ 3+ agg.

C. RBC (Indirect Coombs test)

1. Pt. serum + pt. RBC ——————→ Negative
2. Pt. serum + pt. RBC + chloramphenicol ——→ negative
3. Pt. serum + pt. RBC + chloramphenicol + fresh serum ——→ 2+

4. Pt. serum + donor #2 RBC ——————→ negative
5. Pt. serum + donor #2 RBC + chloramphenicol ——→ 1+
6. Pt. serum + donor #2 RBC + chloramphenicol + fresh serum ___ 3+

Summary: The acute osteomyelitis apparently responded to a combination of erythromycin and chloramphenicol. The patient already had a hemolytic anemia (sickle cell anemia). The chloramphenicol apparently gave rise to myelotoxic injury and in this case an unusual indication of an "allergic" or immune type of drug dependent anemia and leucopenia. The agglutinative phenomenon was present for the platelets but thrombocytopenia was not demonstrated.

Summary Drug Dependent Agglutination of Formed Elements
(4 year period)

PLATELETS
(direct agglutination)

1. Phenacetin: 6 cases
   4 (1+) 2 (3+)
2. Quinidine: 2 cases
   1 (1+) 1 (3+)
3. Streptomycin: 2 cases
   2 (1+)
4. Ergotrate: 1 case (2+)
5. Penicillin: 1 (3+)
6. Pen-U (Oral): 1 (3+)
7. Phenolphthaline: 1
   (3+)
8. Chloramphenicol: 1
   (2+)
9. Noludar: 1 (2+)
10. Bicillin: 1 (1+)
11. Dexidrine: 1 (1+)

TOTAL 18 positive tests
11 drugs

WBC
(direct agglutination)

1. Sulfadiazine: 1 (3+)
2. Chloramphenicol: 1
   (3+)
3. Penicillin: 1 (3+)
4. Kynex: 1 (3+)

TOTAL 4 positive tests
4 drugs

RBC
(indirect Coombs test)

1. Phenacetin: 1 (3+)
2. Quinine: 1 (2+)
3. Chloramphenicol: 1
   (3+)
4. Dieldrin-Heptochlor:
   1 (3-4+)
5. Penicillin: 1 (1+)

TOTAL 5 positive tests
5 Drugs

GRAND TOTAL 16 drugs
27 positive tests
23 patients

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Concerning References:

1 and 2 ---Describe and discuss original concept of drug dependent platelet antibody (agglutinins and lysin).

3,4,5,6, 7 and 8 --- Consider a thoroughly treated, reasonably common drug dependent platelet antibody, that due to quinidine sensitivity

9 and 10 --- Consider quinine dependent platelet antibodies (agglutinin and lysin)

11 -------- A treatment of Ackroyd's patch test as applied to quinidine sensitivity

12 and 13 -- Consider 2 different expressions of drug dependent leukocytic agglutinins (the short-lived aminopyrine type - first description - and the longer lasting sulfonamide type)

14--------- The first clearcut description of a drug dependent incomplete antibody (determined by the Coombs test) which apparently caused a hemolytic anemia.

15 --------- A description of a special form of a drug dependent antibody associated with hemolytic anemia - what may be termed a drug dependent cold type of incomplete antibody

16 - -----	A general consideration of Chloramphenicol and bone marrow injury with case reports
17,18,19,20	Methods for agglutinative phenomena for platelets, WBC and RBC
21 -------	A description of the cold type of incomplete antibody
22,23,24,25 and 26	Discussion related to hematologic complications of "drug disease".