MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

February 1, 1968

PENICILLIN HYPERSENSITIVITY

Case 1

Erythema Multiforme Associated With Ampicillin Therapy

[redacted], [redacted]

The patient is a 62-year-old [redacted] male who was in excellent health until [redacted]/68, when he developed an illness characterized by fever, myalgias and malaise without localizing features. Because of the persistence of symptoms, he was begun on Ilosone 2 gm daily on [redacted]/68. This drug was continued until [redacted]/68 with no improvement in symptomatology and without development of new features of the illness. At that point, physical examination was unremarkable except for fever. Because of the appearance of pyuria, Ilosone was discontinued and ampicillin 2 gm daily was instituted. On [redacted]/68 he noted pruritic "red blotches" on both elbows. His condition continued otherwise unchanged until the evening of [redacted]/68, when it was noted that the rash was progressing to include most of the body. His temperature at that time was 105° and he was disoriented.

On admission to [redacted] on [redacted]/68, the patient was found to have a temperature of 105.8°, pulse of 100, respirations of 20, and blood pressure of 120/60. The patient was disoriented in all spheres but there was no nuchal rigidity or lateralizing neurological signs. There was present a generalized polymorphous rash with confluent erythema on the face and upper trunk and extensive maculopapular lesions over the back, lower trunk and the extremities. Conjunctivae and sclerae were markedly injected but the oral mucosa was clear. The chest was clear and the heart had normal size and rhythm without murmurs. The liver was down 2-3 fingerbreadths and tender and the spleen was not palpable. Admission laboratory work revealed a hemoglobin of 12, hematocrit of 40, and a white count of 18,000 with a marked left shift. Urinalysis revealed rare red cells and 3-5 white cells per high power field with no albuminuria. The BUN was 19, with creatinine of 1.3. CO_2 and electrolytes were normal. Liver function tests were normal. Lumbar puncture revealed clear spinal fluid with normal opening pressure. There were 9 lymphocytes per mm^3, protein of 73; spinal fluid sugar was 72 with a concomitant blood glucose of 93.

A preumptive diagnosis of erythema multiforme secondary to drug reaction was made and initial therapy consisted of intravenous fluids and efforts to control temperature by aspirin and the hypothermic blanket. Because of the inability to lower temperature by these measures, corticosteroids in large doses were added to the regimen. Temperature remained in the range of 104-105° for the first 48 hours, then very gradually lysed over the next week. During the 2nd hospital day, blood pressure dropped to the range of 90/60 and was accompanied by a diminution in urine output. These features were interpreted as being the consequence of shunting through inflamed skin and the rate of electrolyte infusion was stepped up. Both urine flow and blood pressure responded to this therapy. During the 2nd and 3rd days of hospitalization, myoglobin was demonstrable in the urine. This feature was attributed to the intensive shivering which accompanied efforts at hypothermia. Within the first 3 days there was a modest drop in hemoglobin

to a level of 9.2 with hematocrit of 30.5, at which point it stabilized. He has had trace to 4+ guaiacs throughout his hospital course. Reticulocyte count has remained < 2%. By the 3rd hospital day hematuria and albuminuria had appeared and the BUN had increased to 25 mg.%. SGOT increased to 275 units while other liver function tests remained normal. Skin lesions became bullous in many areas and ultimately sloughed, requiring "burn care".

For the last several days the patient has remained stable in terms of vital signs and urine output. BUN has returned to normal and SGOT remains modestly elevated. He continues to be intermittently disoriented without localizing neurological features. Steroids are gradually being tapered without evidence of flare of his vasculitis.

Case 2

Coombs-Positive Hemolytic Anemia Associated With Penicillin Therapy

[redacted], [redacted]

The patient is a 36-year-old [redacted] woman who was admitted on [redacted]/67 with a history of fever, confusion and tremulousness of approximately one week's duration. The history was obtained from family members that the patient had drunk heavily for many years, but had maintained reasonably good health except for occasional episodes of delirium tremens. On two occasions, in 1958 and 1962, she had been committed to Terrell State Hospital because of alcoholism and irresponsible behavior. When seen in the emergency room she had a temperature of 104°, pulse 128, and blood pressure 118/70. She was disoriented to place and time and was sporadically combative. The neck was supple without adenopathy or venous distention. ENT exam was normal, as was the funduscopic exam. Chest and heart were normal. Abdominal exam revealed a firm liver palpable 3 fingerbreadths below the right costal margin. The spleen was not enlarged. Aside from the mental confusion, the motor neurological exam was normal.

Admission laboratory work revealed a hemoglobin of 11.4 with a hematocrit of 30.7. White count was 10,000 with a left shift. Total bilirubin was 2.2 mg.%, alkaline phosphatase 7.2 Bodansky units, thymol turbidity 8.3, and SGOT 660. Lumbar puncture revealed clear cerebrospinal fluid with an opening pressure of 120 mm. There were 107 WBC per mm^3, 70% of which were mononuclears. The protein was 76 mg.% and the sugar 70 mg.% with concomitant blood sugar of 130. VDRL was negative. Smears for bacteria were negative, as were the cultures.

The patient was put on a program of supportive care and she was essentially unchanged during the first 36 hours of hospitalization, at which time her temperature spiked to 105° and she became semi-stuporous. Marked nuchal rigidity was noted, as was a slight reduction in motor strength of the right extremities. Repeat lumbar puncture revealed spinal fluid having essentially the same characteristics as that seen on admission. Electroencephalogram and brain scan were normal. Carotid angiograms revealed changes suggestive of a left anterior cerebral mass lesion and on the basis of presumptive diagnosis of brain abscess,

therapy was instituted with 20 million units of penicillin and 1 gm of Achromycin IV daily.

The patient's condition worsened steadily over the next several days, with the development of stupor, marked right hemiparesis and disconjugate gaze. Papilledema was not noted on any occasion. On the 5th hospital day she had a generalized seizure and because of pooling secretions, a tracheostomy was done. Repeat carotid arteriograms were unchanged. Lumbar puncture at this time revealed opening pressure of 200 mm of CSF, white count 975 with 90% lymphs, protein 205 mg.%, and sugar 80 with blood sugar 130. Near this point it was recognized that the patient had developed a severe anemia with a hemoglobin of 6 gm.%. Studies were undertaken to characterize the anemia and the patient was transfused with 3 units of blood. This aspect of her course in relation to therapy is shown in the following table:

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hemoglobin	11.4	6.0	7.1	8.3	7.2	8.6	8.8	9.2	10.1
Hematocrit	37	21.0	23	27	23		28		34
Retics		2%	8.2%	10%	10%	8%	3.8%	2.6%	4.0%
WBC (T)	10	16.8	28.1	13.8	21.0	18.0	25.0	18.3	12.0
Coombs direct			Neg	Neg	±	+	+	±	Neg
Indirect Coombs with penicillin					+	++	++		
Guaiac		Neg	Neg	Tr	Neg	Neg			
Bilirubin/direct		2.6/1.4	3.4/1.8	3.6/1.6		1.0/0.6			

G6PD Normal Deficient

Penicillin Rx |——————————————————|

Tetracycline Rx |——————————————————————————|

Cephalothin Rx |————————————|

* Transfusions

After her initial decline, the patient rallied and she ultimately became afebrile without neurological deficit save for continued disorientation and confusion. She was discharged to an extended care facility on [redacted]/67.

Case 3

Nephritis Associated With Methicillin Therapy

[redacted], [redacted]

A 21-year-old male developed a furuncle over his right eye. He was treated initially as an outpatient with incision and drainage and an injection of penicillin G. However, the lesion persisted, and because of the development of chills and fever to 104°, he was seen in the emergency room and admitted.

Physical examination revealed a blood pressure of 120/70 and temperature of 104°. There was a large furuncle on his right forehead surrounded by an intense area of inflammation and edema which involved the forehead, periorbital tissue and eyelids. The right bulbar conjunctiva was injected and edematous. The fundi showed normal appearing discs. Ausculation of the lungs revealed a questionable pleural friction rub but otherwise was unremarkable. Except for tachycardia, the heart was unremarkable. There was no abdominal tenderness or organomegaly. Except for the cellulitis noted above, the skin was clear. The neurological examination was negative. White blood cell count was 11,900 per mm^3, with 47% segmented neutrophiles and 23% band forms. There were no eosinophiles. Urinalysis revealed a trace of albumin, 0-4 white cells and no red blood cells per high power field. No casts were seen. Chest x-ray demonstrated multiple patchy areas of infiltration compatible with septic emboli.

Blood cultures and cultures from the forehead furuncle were obtained and he was started on 8 gm of methicillin IM per day. Subsequently both cultures produced a coagulase-positive Staphylococcus aureus inhibited by penicillin and methicillin at the 1.25 μg per ml level. The methicillin was continued. On his 5th hospital day a left pleural effusion was noted on chest x-ray and a chest tube was inserted. The following day signs of an acute abdomen appeared, laparotomy was performed and the spleen, apparently lacerated inserting the chest tube, was removed. His immediate postoperative course was unremarkable, and he was afebrile and apparently doing well.

Three days following operation and 9 days following the initiation of methicillin, he developed a generalized erythematous maculopapular rash. Diphenhydramine hydrochloride was begun, the pruritis ceased, and the rash faded somewhat but continued to be present. Methicillin was continued following this response to diphenhydramine hydrochloride. Subsequently he seemed to be doing well; he was afebrile and his leucocyte count, probably secondary to splenectomy, varied between 15,000 and 22,000 per mm^3. No eosinophiles were present. BUN and serum creatinine were normal. Twenty-two days after beginning methicillin, the patient developed a temperature elevation to 101°, followed over the next 2 days by bilateral flank pain which was greater on the left. Leucocytosis of 18,000 per mm^3 developed with 35% eosinophiles. Urine revealed RBC too numerous to count, 30-40 WBC per high power field, trace albumin and no casts. BUN rose to 25 mg.% and creatinine to 2.3 mg.%. Creatinine clearance was 27 ml per minute. Urinary output did not fall below 1000 cc per 24 hours.

On physical examination the blood pressure was 140/90, the skin rash was still evident, the abdomen was distended and tender to pressure, and one examiner

felt a left flank mass. There was no lymphadenopathy or arthritis.

Intravenous pyelogram revealed swollen tense renal outlines bilaterally without evidence of a perinephric abscess. Because of the possibility of abdominal abscess, the patient had a laparotomy, which revealed both kidneys to be enlarged, tense and edematous. Biopsy was considered but not done because of fear of bleeding. Careful search revealed no intra-abdominal pus. Postoperatively, methicillin was discontinued, and over the next 2 weeks the hematuria disappeared and the blood pressure returned to normal. During the following 2 months, the BUN and creatinine clearance returned to normal.

The patient was finally discharged, afebrile and with a normal hematologic picture, one month following his second operation. He has appeared entirely well during several outpatient visits since that time.

Case 4

Successful Therapy With Cephalothin Following Penicillin-Associated Anaphylaxis

[redacted]

The patient is a 53-year-old white man who was first admitted to [redacted] on [redacted]/66 shortly after he had sustained a gunshot wound of the head. Evaluation revealed that the bullet had traversed the frontal lobe area and had caused massive destruction of the frontal and ethmoid sinuses. He underwent bifrontal craniotomy with extensive debridement of the destroyed tissue of the frontal lobes. His postoperative course was uneventful and he was discharged some 26 days later with the only apparent residua being scars, a flat affect and blindness. During that admission, the history was obtained that the patient had several years ago developed a pruritic rash 3 or 4 days following a penicillin injection.

The patient was readmitted on [redacted]/66 with the history that he had done well until approximately 1 week earlier, when he developed malaise and mild cough. Some 24 hours before admission he complained of bifrontal headache and was found to have a temperature of 101°. Over the ensuing several hours the headache became quite severe and the temperature increased to 105°. Just before admission the patient became somnolent and difficult to arouse. When seen in the emergency room, the patient was found to have a blood pressure of 150/70, temperature of 104.8°, pulse 120 and respirations 18. He was quite somnolent, but when aroused, responded appropriately. Marked nuchal rigidity was present. Tympanic membranes were normal and there was no tenderness to pressure over the sinuses. The chest was clear and the heart was normal size with a regular tachycardia without murmurs. Abdominal exam was negative. Except for nuchal rigidity, somnolence and blindness, the neurological exam was normal. Admission laboratory work revealed a hemoglobin of 15.4 and a white count of 13,000 with left shift. Urinalysis was normal, as were BUN and electrolytes. Lumbar puncture revealed cloudy cerebrospinal fluid with an opening pressure of 420 mm. There were 2400 polymorphonuclear leucocytes per mm^3. The protein was 287 and the sugar was 25 mg.%, with a concomitant blood sugar of 116 mg.%. Gram stain revealed many gram-positive

diplococci morphologically consistent with pneumococci. Blood and spinal fluid cultures ultimately grew out this organism.

Despite the history of previous reaction to penicillin, it was elected to use this drug in therapy of the patient's pneumococcal meningitis. No skin tests were done. Infusion of 1 million units of penicillin in 500 cc of D5W was started and allowed to go in slowly. During the first 10 minutes of observation, the patient showed no adverse effect and at that point the patient was given an additional 15 million units in an IV push over the next several minutes. Some 30 minutes after the penicillin was instituted, the patient was noted to be in respiratory distress with cyanosis and bronchospasm. There was marked cutaneous flushing and the blood pressure at that time was noted to be 80/40. He was given adrenalin 0.3 cc subcutaneously, Benadryl 50 mg IV push. An intravenous infusion of aminophylline 7.5 grains and hydrocortisone 200 mg was started. A few minutes later the patient vomited and shortly thereafter sustained the first of several grand mal seizures. Endotracheal intubation was effected and the patient was placed on respiratory assistance with IPPB with nebulized bronchodilators. The seizures were controlled with intravenous amytal. At that point the patient's antibiotic program was changed to Keflin 12 gm per day. Within 2 hours after the onset of the anaphylactic state, the patient was postictal with a blood pressure of 160/80, pulse 100, respirations 20 without wheezing or cyanosis. The patient remained stuporous over the ensuing 48 hours, perhaps in part as a consequence of the large doses of barbiturates required to control convulsions. By the 3rd hospital day, the patient was able to respond to questioning and from that point there was progressive clearing of his sensorium. His temperature ranged from 100 to 101° for the first 10 days of hospitalization, when he became afebrile and remained so. Spinal fluid examination on the 4th hospital day revealed 286 leucocytes, 90% of which were polymorphonuclear leucocytes, a protein of 91 and a sugar of 44 mg.% with a concomitant blood sugar of 126. Cultures of this fluid were negative. Spinal fluid on the 16th hospital day, after completion of Keflin therapy, revealed 2 neutrophiles, protein of 76 and a sugar of 52 with blood sugar of 120. There was no rash or other evidence of Keflin toxicity noted during the course of therapy.

Table I

INCIDENCE OF PENICILLIN REACTIONS
IN PATIENTS GIVEN PARENTERAL PENICILLIN

Reference	No. of Patients (Type)	No. of Reactions	Rate/1000
1	19,510 (V.D.)	116	5.9
2	25,550 (V.D.)	249	9.7
3	14,357 (V.D.)	86	6.0
4	979 (Recruits)*	10	11.0
5	16,000 (Recruits)*	16	10.0
6	6,832 (Outpatient)	88	13.0
7	1,303 (Hosp.)	24	18.0
8	408 (Hosp.)	32	78.0

* Prophylactic Bicillin 1.2 mu - was not given to patients with history of previous penicillin reaction

The apparent incidence in the ambulatory V.D. population is probably spuriously low since some minor reactions might not be reported and follow-up was undoubtedly incomplete. The reported incidence in the hospital population (8) is probably spuriously high; all patients were ill, on other drugs (mean 13), and fever which was otherwise unexplained accounted for 40% of the reactions.

Factors found to be directly related to frequency of reactions were total dose, duration of administration, atopic history and previous penicillin reaction. Unrelated factors included age, sex, underlying disease and form of parenteral penicillin used.

Table II

TYPES OF REACTIONS TO PENICILLIN:
RELATIVE FREQUENCY (2)

Reaction	Rate/1000 Patients
Urticaria	5.71
Anaphylaxis	1.05
a. Severe	0.35
b. Mild	0.70
Serum sickness	0.43
Angioneurotic edema	0.23
Dermatitis medicamentosa	0.16
Erythema multiforme	0.04
Other*	1.03
Total	9.70

* Vertigo, nausea, chills, dyspnea, hysteria, dysphagia, Jarisch-Herxheimer

Other reactions attributable to penicillin with unassessed frequency:

Hypersensitivity angiitis
Allergic purpura
Nephritis
Coombs-positive hemolytic anemia

Penicillin as an Antigen

Compounds of low molecular weight (i.e., penicillin) are haptens and are impotent as antigens unless bound irreversibly to a macromolecule such as protein. Penicillin *per se* binds loosely with proteins (e.g., serum albumin), but is incapable of forming the strong covalent bonds essential to construction of an effective haptenic antigen. It follows that penicillin antigens are formed by the finding of protein by the reactive degradation products of penicillin rather than by the parent molecule itself.

In aqueous solution at physiological pH, benzyl penicillin G spontaneously undergoes degradation to a mixture of relatively inactive diastereomers of D-benzylpenicilloic acid and the highly reactive D-benzylpenicillenic acid. The latter substance reacts irreversibly with protein by amino or disulfide linkages (Fig. 1).

It has been established that for a hapten to a) induce the formation of antibody and b) to ultimately undergo reaction with antibody *in vivo* or *in vitro* there must be at least two antigenic determinant combining sites per molecule (bivalent or polyvalent hapten). Moreover, the univalent hapten with only one antigenic site per molecule is capable of blocking an anticipated reaction between a bivalent or polyvalent hapten and its specific antibody. It is this latter feature of the haptenic system which has enabled the incrimination of specific penicillin antigens in various allergic responses.

Example:

$$\underset{\text{Hapten}}{2(H)} + \text{Protein} \longrightarrow \underset{\text{Polyvalent Hapten}}{H\cdot\text{Protein}\cdot H}$$

$$H\cdot\text{Protein}\cdot H \xrightarrow{\text{animal}} \text{anti-}H\cdot\text{Protein}\cdot H$$

$$H\cdot\text{Protein}\cdot H + \text{anti-}H\cdot\text{Protein}\cdot H \xrightarrow[\text{in vitro}]{\text{in vivo}} \text{complex} \begin{cases} \text{Hemagglutination} \\ \text{Hemolysis} \\ \text{Precipitation} \\ \text{Complement-fixation} \\ \text{Anaphylaxis} \\ \text{Etc.} \end{cases}$$

H or H·Protein (Monovalent Hapten) — Blocks reaction

Early hapten inhibition experiments in experimental animals sensitized with penicillin and in patients undergoing hypersensitivity reactions to penicillin suggested that the benzylpenicilloyl (BPO) hapten was responsible for the immune response evoked by exposure to penicillin.

Antibody Classes Involved in Penicillin Responses

Class	Weight	Sedimentation Constant	Mercaptoethanol Stability	Means of Demonstration‡
γM	900,000	19S	Sensitive	HA
γG	160,000	7S	Resistant	HA
γE*	160,000	7S	Resistant	Skin Test

* Whether reaginic activity is mediated by a distinct immunoglobulin (γE) or by subclasses of γG or γA is controversial (20-22). Weight of evidence would tend to favor the former thesis.

‡ γM and γG antibodies are demonstrable through any number of classic antigen-antibody interactions, e.g., precipitation, hemagglutination, complement fixation, etc. Reaginic antibody is demonstrable only through skin test (direct, Prausnitz-Kustner or passive cutaneous anaphylaxis).

Relation of Serum Antibody (RBC Agglutinins) to Penicillin Hypersensitivity

Following Ley's observation that serum from a patient receiving penicillin was capable of agglutinating penicillin-coated red cells (9), several investigators set about evaluating the relationship of these agglutinins to the hypersensitivity state (23-33). By early assay methods it was demonstrated that hemagglutinins appeared in the sera of 5-10% of patients who had ever received penicillin without reaction and up to 80% of patients who had developed a reaction. More recent methods (31,32) have demonstrated the presence of hemagglutinins in greater than 90% of people who have ever received penicillin. The antibodies formed by a given patient are 19S, 7S, or mixed in type with no pattern being distinctive of a previous allergic reaction. The antibody is directed principally, if not entirely, against the benzyl penicilloyl (BPO) determinant. It has been demonstrated that high titers of hemagglutinating antibody do not add significantly to the threat associated with subsequent penicillin therapy. Moreover, it has been observed that patients undergoing anaphylaxis may fail to develop hemagglutinins (33).

Relationship of PPL (Major Determinant) Skin Reactivity to Penicillin Hypersensitivity

Evaluation of skin sensitivity to the benzylpenicilloyl determinant (BPO) (major determinant) was facilitated by the production of benzylpenicilloyl polylysine. Although non-immunogenic, this hapten is capable of eliciting a positive cutaneous response in patients having skin-sensitizing antibody against the BPO determinant.

Representative efforts designed to evaluate PPL sensitivity in penicillin allergy are shown below:

Ref. #35: VD patients screened before therapy

Category	PPL +
1. 1147 with previous penicillin therapy without reaction	4.1%
2. *59 with history of previous reaction	76.0%

Relation of skin test to reaction to subsequent therapy:

	No. of Patients	% Having Allergic Reaction
PPL +	23	39%
PPL -	1147	< 0.1%

* This group was not challenged with therapeutic penicillin

Ref. #36: Recruits screened before Bicillin prophylaxis

Category	PPL +
1. 868 with previous penicillin therapy without reaction	8.4%
2. 125 with no previous penicillin therapy	3.0%
3. *43 with history of previous reaction	35.0%

10 reactions occurred in groups 1 and 2 with subsequent therapy - 3 in PPL +, 7 in PPL -. All reactions were delayed in type.

* This group was not challenged with therapeutic penicillin

Ref. #37: VD patients screened before therapy

Category	PPL +
1. 12,559 with previous penicillin therapy without reaction	8.0%
2. 1,798 with no previous penicillin therapy	4.0%
3. *1,003 with history of previous reaction	40.0%

Relation of skin test to reaction to subsequent therapy:

	No. of Patients	% Having Allergic Reaction
PPL +	418	7.2
PPL -	13,530	0.5

* Despite protocol 33 patients with history of previous allergic reaction and positive PPL skin test received therapeutic penicillin. Reaction rate was 27%; all reactions were delayed in type.

Conclusions:

1. PPL skin sensitivity is useful in documenting past allergic reactions to penicillin.
2. A positive skin reaction is predictive of increased incidence of adverse reaction to therapeutic penicillin.
3. Most patients tolerate penicillin despite a positive PPL skin test; therefore, sensitivity to this hapten would not in itself justify withholding penicillin from the patient having strong indication for its use.
4. These studies, and smaller ones of similar design (38-40), fail to establish the significance of a positive PPL test in the patient with history of previous allergic reaction.

Relationship of Penicillin G (Minor Determinant) Skin Reactivity to Penicillin Hypersensitivity

Strong evidence that the BPO haptenic determinant is not the sole mediator of the allergic response to penicillin in man came from the observations of Siegel (41) who found negative PPL skin tests and positive penicillin skin tests in penicillin sensitive patients and by Perlman (42) who reported life-threatening reactions to a penicillin skin test in 4 patients having negative PPL skin tests. The probable role of minor antigenic determinants in immediate-type penicillin hypersensitivity has been elucidated by Levine, who characterized the immune response in patients who had been observed to undergo adverse reactions to penicillin (43).

Types of reactions evaluated:

1. Immediate: Onset within 1 to 30 minutes. Urticaria, pruritis, asthma, shock
2. Accelerated: Onset within 1 hour to 48 hours. Urticaria and pruritis
3. Late Urticaria: Onset 3 days to 2 weeks after institution of penicillin.
4. Recurrent Urticaria and Arthralgia: Onset 2 to 15 weeks after cessation of therapy
5. Maculopapular Erythema: Onset after 3 days of penicillin therapy

Per Cent of Patients Having Antibody Pattern:

Antibody Pattern	Immediate	Accelerated	Late Urticaria	Recurrent Urticaria	Maculopapular Erythema
(# Pts.)	(12)	(10)	(11)	(16)	(19)
IgM alone	0	0	0	0	90
IgG alone	0	0	0	0	0
*SSA·BPO + IgG and IgM	0	60	91	0	5
SSA·(Minor**) + IgM	42	0	0	56	0
SSA (Minor) + IgG + IgM	16	0	0	25	0
SSA (Minor) + SSA (BPO) + IgG + IgM	42	40	9	19	5

* SSA - skin sensitizing antibody

** Minor determinant mixture. Consists of potassium penicillin G, sodium benzylpenicilloate and benzylpenilloic acid each at 1×10^{-2} molar concentration (41).

Conclusions:

1. Hemagglutinin responses do not clearly distinguish allergic from non-allergic patients.
2. All patients having immediate reactions had skin sensitizing antibody detected by the minor determinant mixture (MDM).
3. All patients having accelerated reactions had skin sensitizing antibody detected either by BPO·PPL or by MDM, suggesting predictive value for these tests. This feature is borne out in a small group of patients (44).
4. SSA·BPO and/or SSA·minor were demonstable in all patients with late urticaria or late urticaria, suggesting value of these tests in retrospective diagnosis of rashes possibly due to penicillin.

Possible Role of a Protein Contaminant in the Allergic Response to Penicillin (45-47)

By separation on a Sephadex column, commercially available benzyl penicillin was shown to contain a protein impurity with penicilloyl groups. This protein was highly immunogenic in experimental animals. In 20 allergic individuals having a positive skin test to regular penicillin G, only 9 showed a positive reaction to penicillin from which the protein impurity had been removed.

The significance of this observation is at present speculative. The regularity with which it is present in commercially available penicillin has not been assessed. The variable presence of such a potent immunogen may account for the discrepancies seen in earlier efforts to correlate penicillin skin test results with the allergic state.

Penicillin-Associated Coombs'-Positive Hemolytic Anemia

1. A hemolytic state most frequently seen in high dose, prolonged therapy
2. May be present without other features of allergic state
3. Usually associated with high titers of γM and γG hemagglutinins
4. Positive Coombs' test may persist for weeks after cessation of therapy
5. Proposed mechanism:
   a) Irreversible binding of hapten (usually BPO) to RBC surface
   b) Subsequent attachment of high avidity γG antibody which is specific for penicillinized cells

Methicillin Nephritis

1. Rare complication of methicillin therapy
2. Manifest by hematuria, albuminuria, occasional oliguria, azotemia, eosinophilia common. Usually has accompanying rash
3. Develops during 2nd to 3rd week of high dose therapy
4. Biopsy reveals glomerulitis
5. Complete recovery after cessation of methicillin

Pseudoanaphylaxis to Penicillin

Syndrome characterized by abrupt onset of paresthesias, extreme anxiety and dizziness occurring at the time of injection. Unaccompanied by hypotension or respiratory distress. Typically occurs after several days of therapy, a fact which would effectively exclude anaphylaxis as considered etiology. Reported cases have been able to continue therapy without subsequent reaction.

Cross Allergenicity Between Penicillins and Cephalosporins

Because of the similarity between the structural configuration of the cephalothins and penicillins (Fig. 2), the possibility of cross allergenicity between the two groups of agents exists.

Studies in experimental animals (63-65) have shown that antibody prepared against penicillin or 6APA would agglutinate cephalothin-coated cells while cephalothin antibody was capable of agglutinating penicillinized cells. Cross reaction by passive cutaneous anaphylaxis, however, was demonstrated in only one study (64).

In initial clinical studies the impression was gained that cephalothin could be used in penicillin-sensitive patients with impunity (66-68). More recently, however, there have been case reports of anaphylaxis in penicillin-sensitive patients receiving initial injections of cephalothin (69-71); moreover, skin sensitizing antibodies to cephalothin have been demonstrated in a penicillin-sensitive patient (72). The potential problem of cross allergenicity cannot be assessed on the basis of data available to date.

Protocol for Skin Testing
(Modified from 74)

Solutions: Benzylpenicillin G 10 units/ml and 10,000 units/ml
*penicilloyl polylysine 1×10^{-5} M and 50×10^{-5} M

Procedure: 1) Inject 0.05 ml of lowest dilution of each i.d.; circle bleb with ink and observe 20 minutes.

2) If negative, increase to highest dilution with the antigen(s) to which response is negative. Read at 20 minutes.

Interpretation: Wheal $\geq$ 10 mm = positive

* Cilligen TM^{-1} and TM^{-50}
Sigma Chemical Company
St. Louis, Missouri

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Coombs' test positive in 8/20 patients without demonstrable hemolytic state.

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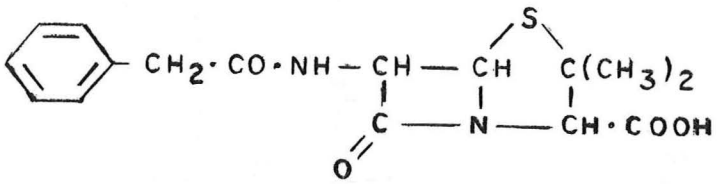
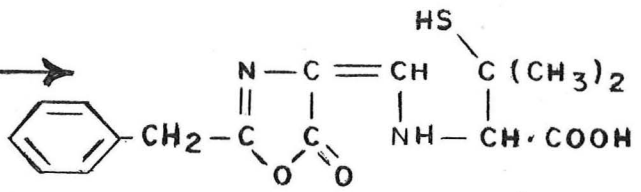
FIGURE 1

POSTULATED ROUTES OF FORMATION OF SEVERAL POSSIBLE PENICILLIN ANTIGENIC DETERMINANT GROUPS

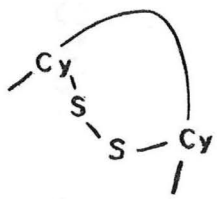


Penicillin (PG)

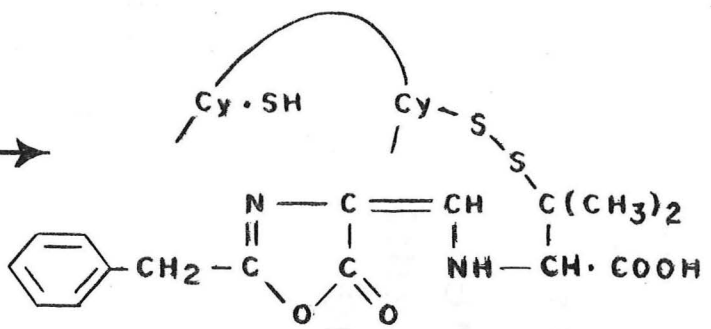


D - Benzylpenicillenic Acid (BPE)

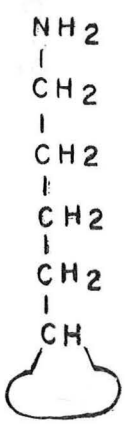
BPE



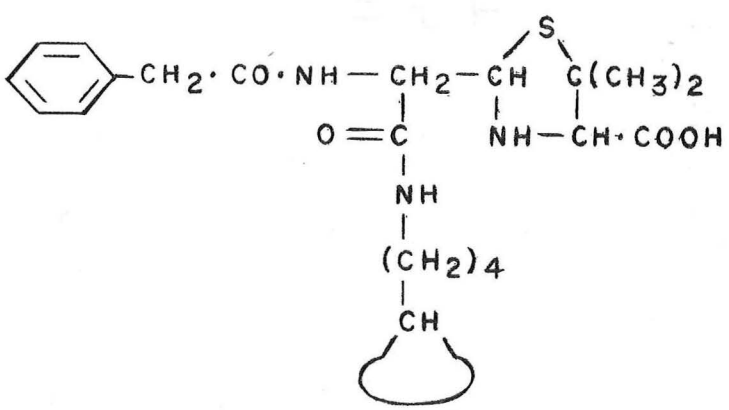
Cystine Disulfide Linkage of Proteins



BPE - Cysteine Mixed - Disulfide Group

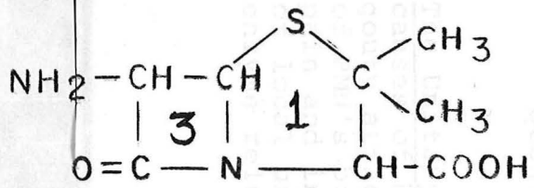


Lysine ϵ - Amino Group of Proteins

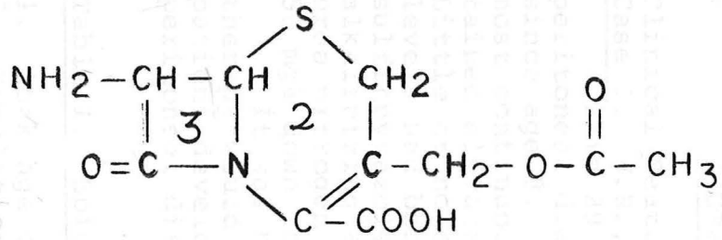


ϵ - N - (D - α - Benzylpenicilloyl) - Lysine Group (BPO)

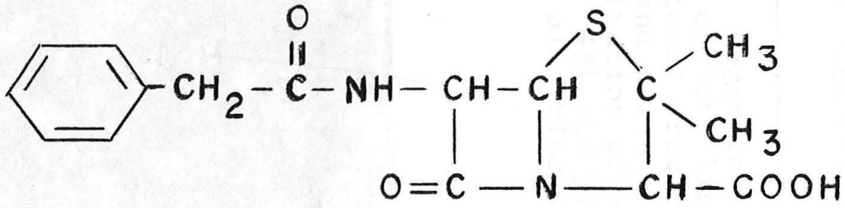
STRUCTURAL FEATURES OF PENICILLINS AND CEPHALOSPORINS



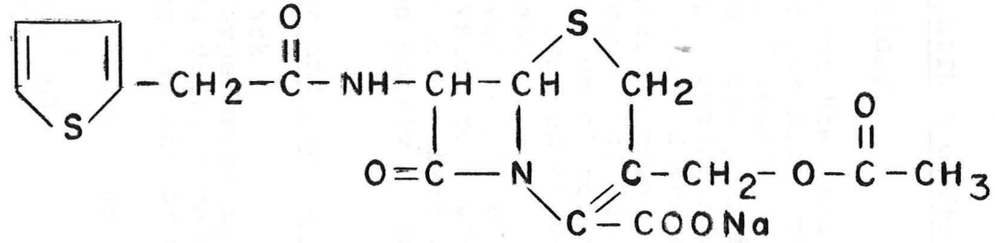
6-AMINOPENICILLANIC ACID (6-APA)



7-AMINOCEPHALOSPORANIC ACID (7-ACA)



PENICILLIN G



CEPHALOTHIN

1- THIAZOLIDINE RING
2- DIHYDROTHIAZINE RING
3- BETA-LACTAM RING

FIGURE 2