of the feet and toes were weak. Good power remained in the lower-limb muscles. Tendon reflexes were absent in the upper and lower limbs, save a much diminished left knee-jerk. Plantar responses were flexor. Abdominal reflexes were present and equal. There was no sensory change in the upper limbs; vibration was absent in the feet. On March 7 moist sounds were still heard at both bases. The physical signs in the central nervous system were unchanged, apart from diminution to pin-prick below the elbows and mid-calf. The patient was given 2 ml. of "hepolon," intramuscularly, daily. There was increased power in the affected muscles on March 23, and considerable improvement in the power of all affected muscle groups on May 2. The knee-jerks were just present.

Discussion

The brain-stem group is remarkably reminiscent of encephalitis lethargica, although it differs greatly from the haemorrhagic influenzal encephalitis first described by Leichtenstern (1890). Drowsiness, with the rapid development of nuclear midbrain lesions, occurred in both cases. The fleeting abnormal plantar responses in one patient and the weakness of proximal muscles groups, with areflexia and peripheral sensory change, in the other indicate a more widespread attack on the neuraxis. Complete recovery ensued within three weeks in Case 1; and equally striking, although slower, was the improvement in Case 2, following a total ophthalmoplegia interna and externa. Unfortunately, it is a matter for speculation whether the condition can be identified with encephalitis lethargica. Von Economo (1931) considers that the somnolent-ophthalmoplegic type is the true basic form of this disease, and is the type that occurs sporadically. Certainly Case 1 might be regarded as a classical example of this variety.

Signs of a transverse or patchy myelitis affecting the lower thoracic cord occurred in two patients after an influenza-like illness. Recovery was slow, and, again, in the absence of pathological material, it can only be suggested that this group corresponds to the two patients described by Greenfield (1930), in whom histological examination disclosed evidence of an acute disseminated encephalomyelitis.

Of the polyneuritic group, Case 5 conforms to the classical type of acute toxic polyneuritis of Guillain, Barré, and Strohl (1916)—a febrile illness for three weeks being followed by facial diplegia, with an increase in the protein content of the cerebrospinal fluid. In Case 6 the patient, after an attack of diarrhoea, became drowsy and confused, with rapid visual failure of a cerebral type. All tendon reflexes disappeared, and the C.S.F. contained 288 mg. of protein per 100 ml., with no increase in cells. During recovery, which occurred rapidly and completely, a homonymous quadrantic field defect was observed. The tendon reflexes in her lower limbs were still absent three and a half months after the onset of symptoms. Case 7 developed a subacute weakness of the dorsiflexors of the wrists and ankles, without sensory change and with a normal C.S.F., three weeks after the onset of symptoms. Case 8 was in every way atypical, a slowly progressive weakness of hip- and shoulder-girdle muscles developing over six weeks and then becoming stationary, with no sensory change and a normal C.S.F., two months after the onset of symptoms. In Case 9 weakness of hip- and shoulder-girdle muscles developed following a 23-day pyrexia, associated with a basal bronchopneumonia. Recovery occurred slowly over the two months she was observed.

This small epidemic of nervous diseases, while of such varied types, appears to be related to some common factor. Whether the prodromal illness was in fact an attack of influenza B is unknown, but the incidence of the cases is related to the peak period of this 1946 epidemic. Certainly, too, it seems that the type of case described above has been unusual during the past few years, as have epidemics of influenza B, sporadic cases of which appeared in England for the first time in 1939. In 1943 only a minor outbreak occurred, but in 1946 the death rate from influenza rose to a higher level than for the two previous years.

Whatever the relationship, however, the three groups seem to be the result of a virus attack on the nervous system, producing either polioclasis or myelinoclasia. It would appear likely from the known characteristics of the viruses which attack the nervous system that two separate viruses are thus concerned.

Summary

A small epidemic of nervous diseases coinciding with an epidemic of influenza B is described.

It is suggested that a myelinoclastic virus and a polioclastic virus are concerned.

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ALLERGIC REACTIONS TO PENICILLIN

BY

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Reports on allergic reactions to penicillin are increasing in number. This is becoming an important problem as more and more patients are receiving penicillin therapy. Evidence is accumulating that the offending agent is the active principle of penicillin. Theoretically, therefore—and actual practice has shown this to be true—reactions may arise with any commercial preparation of the drug. The route of administration has in the majority of cases a bearing on the clinical features and site of the allergic reaction. Local use of penicillin will give rise predominantly to contact or sensitization dermatitis, while parenteral administration is more likely to produce immediate or delayed reactions resembling anaphylaxis.

Review of the Literature

Pyle and Rattner (1944) and Kolodny and Denhoff (1946) reported cases with skin lesions due to penicillin sensitivity. The latter found among dermatological patients treated with parenteral and local penicillin a 25% rate of skin complications as compared with 6% among non-dermatological patients. Especially in cases of fungous infection was contact dermatitis liable to develop, and skin tests were positive to penicillin and to trichophytin. From the study of their cases they concluded that there is no clear-cut relationship between the antigenic substances common to some of the pathogenic fungi (Hyphomycetes) and antigens of *Penicillium notatum* (Ascomycetes), but clinical observations are suggestive. Goldman *et al.* (1946) found 16 instances of contact dermatitis among 350 cases treated with penicillin locally. Vickers (1946) described a case of penicillin sensitization dermatitis; a patch test with penicillin solution was strongly positive. Hellier (1946) stressed the rarity of contact dermatitis due to penicillin as compared with that due to sulphonamides.

More characteristic are the manifestations described since 1943; they are practically always due to intramuscular penicillin and resemble severe urticaria or serum sickness. Lyons (1943), when reporting on penicillin therapy of surgical infections in the U.S. Army, found that there were urticarial reactions not attributable to particular batches of the drug. Of 209 cases 12 (5.7%) had an urticarial reaction, of which he described three types: (a) without fever; (b) with fever to 101° F. (38.3° C.); (c) with fever to 103° F. (39.4° C.) and abdominal cramps. The urticaria appeared as early as the first day or as late as the fourth week. Fever was present only if urticaria was severe, and normally did not exceed 101° F. Skin tests were negative. No precipitins were found in the serum of patients tested during the phase of urticaria, and heterophil agglutinins were not significantly and constantly increased. Criepp (1944) reported a case in which a massive generalized urticaria appeared on resumption of a second parenteral course of penicillin. This persisted for six days. He made special laboratory investigations which showed the presence of some immune substances (reagins and precipitins) in the patient's serum. According to Criepp the following takes place: First penicillin administration—drug discontinued—second penicillin administration → allergic reaction.

Strazza (1946) had a case of a man aged 23 who six days after a course of parenteral penicillin became very ill, with urticaria, pruritus, restlessness, insomnia, pain in the hands and feet, breathlessness, and oedema of pharynx with dysphagia. He recovered after eight days. Calcium gluconate intravenously was ineffective, and a scratch test was negative. The paper on penicillin allergy by Kolodny and Denhoff (1946) gives, among others, data concerning six cases with urticaria and five cases with a serum-sickness type of reaction. This classification is arbitrary, but clinically useful as it permits the separation of mild from severer reactions. In seven patients the reaction started fourteen days after beginning penicillin therapy; in another it began twenty-three days after. Five patients had swelling of small joints of the extremities, oedema of face, moderate lymphadenopathy, generalized arthralgia, myalgia, and malaise. Recovery was complete in four or five days. Adrenaline gave prompt but transient relief. Haswell and Wilkinson (1946) have written an interesting account of four cases presenting a reaction similar to serum sickness; all the patients gave a history of previous treatment with local penicillin. The reaction occurred from six to twelve days after starting intramuscular injections of penicillin. Skin tests were negative.

Gordon (1946) reviewed the literature on the problem of allergy due to penicillin and added three of his own cases. According to this author the incidence of allergic reaction during the course of treatment is not frequent. A delayed serum-sickness type of reaction occurs even more uncommonly—possibly once in 1,500 or 2,000 cases. Gordon's personal cases developed the reaction from two to seven days after cessation of penicillin therapy. The first manifestation in each was an intense urticaria with severe pruritus. Weal formation spread all over the body, and in two out of three oedema of the eyelids occurred. Pain in the joints was noticed; malaise, mild fever, and tachycardia were also present. Both palms presented an exfoliative dermatitis in the later stages of the reaction. Treatment with adrenaline gave satisfactory results, but its effect was transitory. The patients recovered in seven to ten days.

Below are given a list of authors and the number of their published cases. The list includes Barker, Morris and Downing, Sullens, and Macey and Hays, as quoted in Gordon's paper. With my own nine cases the total of collected case histories amounts to forty seven.

	No. of Cases
Lyons (1943)	12
Criep (1944)	1
Barker (1945)	1
Morris and Downing (1945)	1
Sullens (1945)	1
Macey and Hays (1945)	3
Haswell and Wilkinson (1946)	4
Gordon (1946)	3
Strazza (1946)	1
Kolodny and Denhoff (1946)	11
Total	38

They can be classed as (a) allergic hydrarthrosis; (b) urticaria; (c) simulating serum sickness; (d) anaphylactic-shock-like syndrome. Cases of sensitization dermatitis are included. A summary of the clinical features, with a few illustrative cases, follows.

Allergic Hydrarthrosis

I could find no similar published cases. As already noted, swelling of the small joints with arthralgia is a common finding, but isolated articular involvement of a large joint is rare. Four such cases have been seen. They were all similar in their onset, duration, symptomatology, and benign character, and none of the patients had a history of previous penicillin therapy. Three had been treated for syphilis (two with primary syphilis and one with syphilitic arteritis) and one for multiple lung abscesses. The joint swelling occurred two to five days after starting penicillin; the joint involved in all cases was the right knee. Undoubtedly this was pure coincidence, and I am expecting in the future to find other large joints affected. The knee became swollen and slightly tender, and gradually a large effusion developed. There were no signs of inflammation and the general condition remained unaffected; the temperature was not raised, and the small joints were not involved. No

skin eruption was noticed. Penicillin injections were not discontinued on account of this complication, as it was felt that this was not serious enough to warrant such a drastic step. The effusion gradually lessened, and the joint became normal in eight to ten days. Only symptomatic treatment was given.

Illustrative Case

Case 1.—Male aged 42 years. He had never had penicillin before. He was admitted to St. Charles' Hospital on Aug. 26, 1946, suffering from cerebral thrombosis of syphilitic origin. On the 31st penicillin was started in doses of 50,000 units intramuscularly every three hours. The drug used was a commercial batch of the sodium salt in aqueous solution. On Sept. 5 it was noticed that the right knee was oedematous. It was tender to palpation and fluid was present, but the skin was not hot, shiny, or red. An x-ray photograph taken on the same day showed no bone injury. The hydrarthrosis remained for about ten days and then slowly subsided. Eventually the joint returned to its former healthy state. Penicillin therapy was not stopped till the full dosage was given (5,000,000 units). Treatment was symptomatic and there was no recurrence.

Urticaria

This is a mild form of reaction, also called "immediate" by some authors to differentiate it from the delayed reaction of serum-sickness type. In reality the time of occurrence of both is extremely variable. In one case that I studied the onset of a mild urticaria was delayed for several days after cessation of penicillin, while in another a severe serum-sickness-like reaction made its appearance very early during treatment. The only basis for differentiation lies in the clinical features. Urticaria is mild, transient, and often overlooked, while the severe form of serum sickness has a dramatic onset with constitutional disturbance, often pyrexia, and occasionally collapse. This form needs prompt recognition and appropriate treatment.

The urticaria appears most commonly during penicillin treatment, as does the previously described knee effusion. Only the skin is involved, and the principal lesion consists of a blotchy rash against an erythematous background. The small weals are distributed on the trunk—usually the front of the chest and upper abdomen. Limbs, neck, and scalp may also be affected. Pruritus is always present, and this is the first thing the patient notices. The temperature remains normal and there is no tachycardia. In one only of my cases was there a history of previous penicillin administration.

Illustrative Cases

Case 2.—Soldier aged 28, with a diagnosis of post-basal empyema following pneumonia. He had been treated in December, 1945, with intramuscular injections of penicillin. Admitted to St. Charles' Hospital on March 25, 1946. Penicillin in three-hourly doses of 30,000 units was given from April 2 to 16. On the third day after starting injections the patient complained of itching on the chest and abdomen. A mild urticarial eruption was noted and calamine lotion applied locally. Penicillin was continued and no more notice was taken of the urticaria, which faded out after four to five days. I cannot find in the records any mention of a reaction during the first course of penicillin.

Case 3.—A young doctor aged 30, admitted to St. Charles' Hospital for recurrent boils of neck. He had never had penicillin previously. In July, 1946, was started a course of three-hourly intramuscular injections of sodium penicillin for five days; each injection consisted of 30,000 units. Three days after completion of treatment a mild urticarial rash appeared on scalp, neck, and legs. Intense irritation of the skin and moderate nocturnal dyspnoea were present. Intravenous calcium gluconate 10% solution gave no relief. Recovery took place in five to seven days.

Reaction Simulating Serum Sickness

This reaction is not confined only to the skin, but produces in addition an oedema which at times is considerable, arthralgia, bronchospasm, and a severe general reaction. It may occur during penicillin treatment or several days after cessation. On the average the onset is from five to thirteen days after the first injection. In two of my cases penicillin has been given before, and in both a penicillin patch test was positive.

The onset is rather abrupt, with at times fever of 102° F. (38.9° C.). Giant urticaria affects the skin all over the body. Within twenty-four hours the weal formation is completed; even the face is not spared. The skin irritation is intense, and the patient becomes restless and cannot sleep. Angioneurotic oedema is always present in these cases. Particularly noticeable

is the oedema of face, lips, and eyelids. The hands, feet, and forearms are swollen and painful. The oedema is intense, and is a classic example of pitting oedema. One has only to consider this aspect of the reaction to realize how widespread and intense is the damage to the capillaries; fortunately it is transient and recovery is complete. The urine is clear and contains no albumin. Blood pressure remains within normal limits. In one subject only have I noticed subcutaneous bruising of the palms of both hands, and he complained of tenseness and aching in the affected palms. No exfoliative dermatitis was noted in any of my cases. Arthralgia is not the rule. Usually the small joints of hands and feet are involved.

Illustrative Cases

Case 4.—Male aged 27 years, with no personal history of asthma, urticarial rashes, or migraine. He was treated at St. Charles' Hospital for a septic right index finger, and had 700,000 units of sodium penicillin between Sept. 4 and 8, 1946. At that time no complications had been noted and the patient was discharged. On Sept. 17—i.e., nine days after completing the course of penicillin—he became ill with a temperature of 102° F. (38.9° C.) and generalized urticaria. He was admitted again on the 20th. On examination giant weals were seen on neck, chest, abdomen, and thighs. The areas of skin between the weals were erythematous and slightly raised. The palms showed diffused ecchymotic subcutaneous patches. Severe angioneurotic oedema of feet, legs, dorsum of hands, wrists, face, lips, and left upper eyelid was present, and pitting oedema round ankles and dorsum of feet. The patient complained of intense irritation of the skin and tenseness in both hands. His general condition was poor and he was restless. The heart and lungs were normal, as were also the blood pressure and urine. He was put on strict bed rest, hypodermic injections of adrenaline, ephedrine, and phenobarbitone, with calamine lotion locally. The urticaria cleared after three days. The oedema persisted for a few more days and he was allowed up on Sept. 27. He went home on Oct. 1.

Case 5.—Male aged 23 years. This patient had gonorrhoea in May, 1946, and was treated with 150,000 units of penicillin. He contracted syphilis in the following August. He attended a V.D. clinic for treatment and was put on two daily injections of 120,000 units of penicillin in ethyl oleate. After the tenth injection he developed a giant urticaria, and was admitted to St. Charles' Hospital, complaining of severe pruritus, oedema of lips, and malaise. In view of the seriousness of the general reaction penicillin had to be discontinued. The reaction gradually subsided on adrenaline and phenobarbitone. A penicillin patch test was strongly positive. Calcium gluconate 10% solution given intravenously for four days brought no improvement. He was discharged on Sept. 14.

Case 6.—Male aged 26 years, suffering from a discharging sinus of the left shoulder following gunshot wounds. He gave the following history of previous penicillin treatment and allergic reactions: (1) July, 1944, given nearly 2,000,000 units (make unknown) by intramuscular injections. Developed an urticarial rash during treatment; no details supplied. (2) August, 1945, received intramuscular injections of sodium penicillin for 48 hours (total of 270,000 units). Three days later, while at home, urticaria developed. The patient could give no details of its duration or severity.

On July 25, 1946, this patient underwent an operation for chip-grafting of the humerus at St. Charles' Hospital. On the same day three-hourly parenteral penicillin was started, and this was discontinued on Aug. 1, the total dosage amounting to 1,140,000 units. At 11 p.m. on Aug. 3—i.e., nine days after beginning treatment—large urticarial weals suddenly appeared. The arms and legs were covered with them, and the patient complained of pain in the small joints. The temperature and pulse rate were not raised. There was a distressing skin irritation. Adrenaline hypodermically was given at once. His condition gradually improved after a few days, and he was discharged on the 8th.

The patient was readmitted the next day for a repeat of the penicillin course. This was started at once and three days later a mild urticarial reaction appeared. The penicillin was stopped after 1,620,000 units had been given.

Anaphylactic-shock-like Syndrome

Theoretically this may arise in certain subjects, previously sensitized to penicillin, who receive after an interval multiple parenteral injections, or even a single injection, of the drug. I have personally not seen such an occurrence. The case reported by Strazza (1946) presented what appeared to be anaphylactic shock, but skin lesions were also very prominent. O'Donovan and Klorfajn (1946) produced an anaphylactic-shock-like reaction in a previously penicillin-sensitized patient by giving him a single intramuscular injection of 15,000 units of sodium penicillin. Fifteen to twenty minutes after the

injection the pulse became quick and thready, and a throbbing sensation in the face, breathlessness, restlessness, pallor, cold sweats, and mild rigor occurred. Six hours later an oozing dermatitis of the face appeared. He slowly recovered in two days; a patch test became strongly positive on the third day.

Discussion

The frequency of these reactions to parenteral penicillin has been put at varying figures between 0.56% and 5.7%. The former is probably nearer the truth.

The aetiology is still a debatable subject. Some observers believe the reaction to be due to impurities. Others—and these form a majority—incriminate the active principle of penicillin. Commercial penicillins are doubtless increasingly more refined, but reactions are reported in ever larger numbers. The purest form yet known—the crystalline penicillin—gave in the hands of some workers positive skin tests in sensitized subjects. So long as penicillin remains unsynthesized a categorical answer is impossible. The search for specific serum antibodies has so far given no convincing results. All that is known is that a small number of people are susceptible to penicillin sensitization, and that this susceptibility is greatly enhanced in the presence of skin infections, especially those due to a fungus. Previous penicillin treatment, parenteral or local, can predispose to allergic reactions. We have seen that some of these may be very severe and call for cessation of treatment; attempts at desensitization have been made by some workers. O'Donovan and Klorfajn successfully desensitized one of their patients by repeated oral doses of penicillin.

Skin tests have given variable results; the patch test is easy to perform and is frequently positive. Dr. P. Headon suggested dry powdered penicillin on a square of gauze applied to the skin of the chest or arms. In Case 5 a positive result was obtained two hours after application, the patient complaining of itching in the right hand and swelling of the lips. The test was also positive in Case 4, in which it was performed at the time of recovery; the same patient had a negative intradermal test. Adrenaline hydrochloride hypodermically and ephedrine orally give rapid relief. These drugs should be repeated at frequent intervals in conjunction with small doses of phenobarbitone. "Benadryl," the new anti-histamine drug, may be found useful in the treatment of manifestations of penicillin hypersensitivity, especially in cases with marked urticaria.

What should be done if penicillin is again indicated in a case with a history of extensive urticaria following previous penicillin treatment, with subsequent recovery? Most observers are of the opinion that the drug should not be withheld if it is considered important to the treatment. The patient should be watched, and if an unusually severe reaction occurs cessation of penicillin will have to be considered. No useful purpose is served by changing to another commercial batch. Dr. A. E. Shaw suggested the use of skin tests to discover susceptible individuals, especially among those who have had (a) penicillin once or more previously; (b) a history of allergy, such as asthma, migraine, hay-fever; (c) fungus infection; (d) sensitization eczemas. Unfortunately skin tests are often negative in obviously allergic patients, and I wonder whether a preliminary injection of, say, 15,000 units would produce a clear-cut and mild enough reaction to indicate a penicillin reactor.

Summary

Thirty-eight cases of allergic reactions to penicillin have been collected from the literature and reviewed. Emphasis is laid on the manifestations due to parenteral administration.

Nine personal cases are added, of which 4 presented hydrarthrosis, 2 urticaria, and 3 serum-sickness-like reaction.

A clinical description of various types of reaction is given.

Susceptibility to reactions and the use of skin tests are dealt with; frequency, aetiology, and treatment are also discussed.

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