per c.mm. in sicklers and 1,000 per c.mm. in non-sicklers. Perhaps these findings, obtained in hyperendemic areas, are due to local conditions—that is, to mass infection, diminution of the resistance of the body for different reasons, etc.

Investigation in Greece

We had an opportunity of investigating this subject in Chalkidiki, where malaria is endemic and the population shows the highest rate of sickling known in Greece.

Making use of lists supplied by the Department of Malaria in Northern Greece, we examined 136 out of 174 cases of malaria confirmed by microscopical examination and reported during the three years (1952–4). These patients came from four villages with the highest rate of sickling known in Greece (32%, 24%, 19%, 18%). The mean rate of sickling in persons suffering from malaria in this area was only 5.8%. On the other hand, the mean sickling rate in 500 unselected individuals examined in this area was 23.6%. It is noteworthy that the number of sicklers with malaria is extremely low, whereas one would expect it to be similar to that of non-sicklers, because the existing conditions of infection and sensitiveness are the same (Table I).

TABLE I.—*Percentage of Sickling and Malaria in Examined Cases*

Villages	Unselected Sickling			Malaria		
	No. Exam.	Positive	%	No. Exam.	Sickling Positive	%
Parthenon ..	153	49	32	28	1	3·6
St. Nicholas ..	101	24	24	40	2	5·0
Nikiti	143	27	19	31	3	9·6
Ormylia	103	18	18	37	2	5·4
Total ..	500	118	23·6	136	8	5·8

Blood investigations for sickling were made on siblings of families affected by malaria. This was done in order to secure, so far as possible, the same conditions of living and sensitivity to malaria infection. Only the siblings of the children infected by malaria were examined. It seemed to us that the results could give us a better picture of the relationship between malaria and sickling as well as the frequency of the former in persons with or without the latter condition. In fact, we noted that, in the families of sicklers, the members who were not infected by malaria parasites were mostly positive for sickling, whereas those who were negative for sickling were infected more often by malaria (Table II).

TABLE II.—*Families with Positive Sickling and Malaria*

Name	Age (Yrs.)	Malaria	Sickling	Name	Age (Yrs.)	Malaria	Sickling
St. Nicholas				Parthenon			
K. N. S.	9	+	−	E. Th. K.	7	+	−
V. N. S.	7	−	+	D. Th. K.	1	−	Micro-cyt.
A. N. S.	6	−	+				
H. N. S.	10	−	+	M. Th. K.	12	−	−
M. N. S.	3	−	+	A. Th. K.	5	−	−
S. N. S.	30	−	+	T. Th. K.	38	−	+
A. D. P.	15	+	−	A. N. P.	29	+	−
A. D. P.	4	−	+	E. N. P.	2	+	−
G. D. P.	8	−	+	E. N. P.	6	−	+
				N. E. P.	35	−	+
D. A. S.	7	+	−				
M. A. S.	10	−	+	B. I. E.	9	+	−
				I. I. E.	7	−	+
A. Th. D.	11	+	−				
D. Th. D.	8	−	+	A. D. H.	18	+	−
				A. D. H.	8	−	+
A. Th. S.	6	+	−				
G. Th. S.	1	−	+	B. K. K.	8	+	−
				T. K. K.	4	−	+
				N. K. K.	7	−	−
Ormylia				Nikiti			
I. H. M.	12	+	−	G. I. M.	14	+	−
M. H. M.	38	+	−	A. I. M.	11	−	+
A. H. M.	11	−	−	N. I. M.	8	−	−
G. H. M.	7	−	−				
H. I. M.	46	−	+	G. A. K.	8	+	−
				N. A. K.	7	−	−
G. H. E.	8	+	+	M. A. K.	13	−	+
A. H. E.	10	−	−				
L. H. E.	5	−	+	K. M. A.	19	+	−
H. I. E.	47	−	+	G. M. A.	7	−	+

We must admit, with Allison,[4] Brain,[5] and Mackey and Vivarelli[8] that the coexistence of malaria and sickling is of a low order. Sicklers show a stronger resistance against the infection. Their red cells are less susceptible to malarial parasitism, and this may be due to unsuitable environment because of the presence of the abnormal S-haemoglobin.

We also observed that in sicklers infected by malaria the test for sickling, using the sodium bisulphite method, was not always complete for all their red blood cells, in contrast to the cases in which only the sickle-cell trait was present.

Paper electrophoresis revealed an abnormal haemoglobin following the normal haemoglobin, like the haemoglobin of the trait.[11] Unfortunately it is not possible to separate the abnormal haemoglobin quantitatively by paper electrophoresis.

The infestation of some red cells with parasites in the case of sicklers could be explained by the possibly smaller amount of S-haemoglobin present in these cells, unless some special condition of the stroma favours the entrance of the parasite.

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PENICILLIN ANAPHYLACTOID SHOCK

BY

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The clinical advent of penicillin in 1943 opened the antibiotic era. Within a decade, however, the threat of anaphylactoid reactions from this drug gradually emerged[1-23] and is now a grave concern.[24-59] Indeed, penicillin is the prime cause of drug-induced anaphylactoid reactions. It is convenient here to refer to anaphylactoid rather than anaphylactic shock, bearing in mind that some of the reported cases are hardly true examples of the latter.

Casuistic reports continue to appear, and the cautionary remark of Gilman,[60] ". . . One must conclude the guilt of usage rather than of the substance," merits consideration. Smith and Walker[61] emphasized that the ability of penicillin " to sensitize and to cause serious and even fatal accidents should not be minimized." The continued extensive use of this valuable drug means that many patients are becoming sensitized to an anaphylactic degree. Under these circumstances the precept of Hippocrates, " Primum non nocere," is apt.

This review, while not intended as a detailed analysis of universal literature, provides a practical discussion of the extent of the problem and of suitable prophylaxis. This subject is not the sole concern of the pharmacologist or allergist, as there must be few doctors, irrespective of specialty, who are not frequent prescribers of this drug. Hence it may fall within the purview of

any doctor to recognize and treat this emergency. Severe anaphylactoid reactions to penicillin have been fairly adequately described but inadequately discussed. The accompanying illustrative case report is sufficiently instructive to record.

Case Report

On March 4, 1953, a robust Army officer aged 47 walked into the casualty department of Whipps Cross Hospital at 9.30 p.m. for treatment of a cellulitis of the right leg. The duty house-physician ordered one mega unit of crystalline penicillin intramuscularly and a kaolin poultice locally. At 10.15 p.m. a staff-nurse gave the injection into the patient's right arm. Although the vague possibility of accidental venepuncture exists, there was no reason to suspect this.

Ten minutes after the injection, which had caused no discomfort, the patient calmly stated, "Penicillin made me feel dreadful the last time I had it." At precisely 10.30 p.m. the patient, now seated in the treatment room, began to groan. The staff-nurse rushed to investigate. She found the patient still seated, but with bulbar conjunctival congestion and a heliotrope facies. The nurse immediately called out for assistance. The patient's respirations had now ceased, and apnoea lasting two minutes ensued. However, spontaneous respiration resumed without resort to artificial respiration or analeptics. During the apnoea the patient became pulseless, with widely dilated pupils, profuse perspiration, cold and clammy extremities, and urinary incontinence. No epileptiform movements were observed. He had now been placed supine on a mattress, where he lay unconscious for the next fifteen minutes. The only immediate treatment given was forward traction of the tongue, the application of warmth—his temperature was then 97° F. (36.1° C.)—and continuous oxygen administration.

At 10.45 p.m. he was first seen by one of us (R. J. C.). Moderate shock persisted, but there was now no respiratory embarrassment. He lay still with mild cyanosis, pin-point pupils, an impalpable pulse, and a low blood pressure (60/40 mm. Hg). No other abnormal signs were elicited. Consciousness was now returning sufficiently for him to mutter a few words. He complained only of transient epigastric pain. Mercifully, recovery now seemed assured, and in the hope of hastening this he was given 3 ml. (0.75 g.) of nikethamide intramuscularly, as there were no accessible veins for more direct administration. He was then transported to the ward, where a heat-cage was fitted over his bed. Two hours later his temperature had risen to 100.4° F. (38° C.), his blood pressure to 100/70 mm. Hg, and he stated that he was perfectly well. An electrocardiogram taken immediately on his arrival in the ward showed sinus tachycardia (120 a minute) and a reduced amplitude as the only abnormalities. With bed rest and a course of chlortetracycline ("aureomycin") his cellulitis cleared within a week.

His history was non-contributory apart from recent events, which were highly significant. He had a mild attack of nephritis in 1918, pleurisy in 1926, and infective hepatitis in 1945, and had since remained fit until about two weeks before the present admission.

One evening at that time, while visiting friends, he complained of a sore throat, for which one of them gave him two penicillin lozenges. He immediately sucked one of these lozenges, but became alarmed five minutes later by "a tingling sensation creeping up his neck and an almost simultaneous burning feeling as if his face was on fire." Within a few minutes he felt "as if he was being gently but surely choked." He then dashed outside for fresh air, but promptly decided to return hastily to his residence, some 400 yards away. After walking about 100 yards in a dazed state a peculiar visual upset appeared. He could see "about ten of everything coming towards him." On arrival at his door he was "unable to identify the correct one out of some apparent ten doors" in front of him. His left shoulder struck something solid and he gyrated and was pitched to the ground. He could only vaguely recall being assisted inside, laid on a settee, and covered with blankets. His teeth now began to chatter uncontrollably, and he fell into a deep sleep. One hour later he awoke suddenly on the arrival of his doctor, and he stated that he felt quite well again. He was then informed by his doctor that he must have been allergic to penicillin. The patient had since maintained the pious hope that he would be less allergic to penicillin.

Later exhaustive inquiry revealed no other history of allergic disease, no syncope, epilepsy, or earlier administration of penicillin. There had been no known epidermophytosis. Neither subsequent skin-testing nor desensitization to penicillin was seriously considered in view of these clear-cut hyperallergic reactions to this drug. Instead, he was instructed to carry a card under the "cellophane"-covered compartment of his wallet, indicating boldly that he reacted violently to penicillin.

Discussion

Although the fact that many clinicians and practitioners have not encountered this catastrophe is evidence of its rarity, relevant comprehensive publications refute this view. A few selected illustrations will suffice. Bateman *et al.*[22] referred to three anaphylactoid reactions with two fatalities from this drug. Siegal *et al.*[25] also reported three such reactions with one death. Mayer *et al.*[26] added six cases, including one fatality. They described a near-fatality from an intradermal test with only 10 units of penicillin G. Curphey[30] reported two more fatalities. Both Feinberg *et al.*[31] and Sterling[38] recorded a series of nine cases. Five of those recorded by Feinberg *et al.* died. During a panel discussion[39] on this subject nine more cases were cited. Welch *et al.*[41] provided the first systematic study of this phenomenon. Briefly, their survey of the records of 95 hospitals totalling 51,000 beds disclosed 59 anaphylactoid reactions from penicillin with 19 deaths. It is noteworthy that one of these fatalities followed the ingestion of one tablet of dibenzylethylenediamine dipenicillin G (either 100,000 or 200,000 units). They also referred to a report[23] of 25 further severe reactions, involving five fatalities, from the use of penethamate hydriodide ("neo-penil"; "estopen") submitted voluntarily by the manufacturers, Smith, Kline, and French. Indeed, this firm (personal communication) discerningly discontinued the supply of this drug early in 1954. More recently Rosenthal[53] described no fewer than eight fatal penicillin reactions, while Swift[58] added ten cases with one death. This expanding subject was reviewed earlier by Kern and Wimberley,[44] and more recently by Garat and Landa.[52] Certain details of the earlier literature, mentioned by them, have been conveniently omitted here.

Examination of the events in our patient provides grounds for a reassertion of the following points.

(1) Oral medication with penicillin is not devoid of risk. This contention, however, does not invalidate the view of Kern and Wimberley[44] that this route provides a greater measure of safety than the parenteral routes. Nevertheless, our patient sustained a moderate constitutional reaction five minutes after sucking a penicillin lozenge containing only 1,000 units of penicillin. This, our patient averred, was his first administration of this drug. One hesitates to predict the outcome if he had ventured to suck the second lozenge. The reaction described is, however, not unique, for Madalin[60] reported a similar but more profound response. His patient had cacogeusia within two minutes of commencing to suck a lozenge containing 20,000 units of crystalline penicillin. The lozenge was promptly expectorated, and the actual anaphylactoid dose was gauged as being less than 2.000 units. His patient had previously had penicillin, to which he was later shown to be extremely sensitive.

(2) A negative history of penicillin administration is not foolproof against a moderately severe reaction, as evidenced by our patient's response to the penicillin lozenge. Contrary to the experience of Mayer *et al.*,[26] severe anaphylactoid reactions have occurred in patients who had no

knowledge of previous penicillin medication.[53 54] Admittedly, an absence of previous contact with this drug does not harmonize with the theoretical concept of true anaphylaxis.

In these patients, Cormia *et al.*[1] considered, there was usually a history of epidermophytosis linked with their sensitization to penicillin. A further simple explanation is that there are many modes of administration of penicillin—for example, eye, ear, and nasal drops; inhalations; medicated tulle gras; intrapleural and intrathecal instillation, etc. A patient may have received the drug under these circumstances and yet be unaware of this fact in a subsequent interrogation. It is apt to note here that even the topical application of this drug[11 40 55 56] may provoke an anaphylactic response. In Ruskin's patient[55] the route was percutaneous, while in the case described by Carter and Cope[56] an oculentum was responsible.

Moreover, although penicillin has been given without previous adverse reaction, this fact constitutes no guarantee against an anaphylactoid reaction.[54] Frank danger lies in resuming penicillin treatment and not during a course of injections.[31 44] It is essential to be alert to this group because of the apparent safety implied by the history.

(3) It seems improbable in our patient that a fortuitous intravenous escape of part of the intramuscularly administered penicillin was responsible for the major reaction. Surely, the time-lag of fifteen minutes from the injection to the dramatic onset of the event offsets this possibility. Moreover, whereas a lozenge with only 1,000 units of penicillin produced a moderate constitutional reaction in five minutes, he remained symptomless for at least ten minutes after the intramuscular injection of 1,000,000 units.

Instantaneous severe reactions from intramuscular injections of penicillin have often been recorded. One explanation advanced is that the accidental intravenous penetration or permeation of the drug could accentuate or even cause these reactions. Bell *et al.*[59] discussed this possibility, which may apply to some patients in whom there is evidence neither of previous sensitization nor of subsequent incident in relation to a severe reaction to this drug.

Occasional reports mention cacogeusia as an early symptom of a severe reaction to penicillin. Whereas Waldbott[5] regarded this symptom as indicative of a direct intravenous mishap, there is evidence against this assertion. For instance, this symptom can be a feature in the similar misadventures from the oral[50] and percutaneous[55] and ocular[56] routes, unrelated to acupuncture.

Lack of space precludes a description of the assorted patterns of severe penicillin reactions. It is, however, worth recalling that Batchelor *et al.*[62] reported a bizarre immediate reaction to intramuscular injections of procaine penicillin. Six of their eight patients experienced angor animi without any sign of syncope. It is also impossible to discuss here the modes and risks of testing for sensitization* and of desensitization, the severe delayed "serum-sickness-like" reaction, and the hazards of intrathecal administration of penicillin.

Instead, it will be more rewarding to summarize a schematic approach designed to minimize the incidence and degree of these anaphylactoid shocks. For this purpose a cumulative review is presented below. Only certain broad principles with a keynote of caution can be suggested. As Boger *et al.*[39] remarked, "there are no infallible rules covering the phenomena of hypersensitivity to penicillin."

Suggested Prophylaxis

(1) *Reduction of Increased Sensitization.*—The elimination of the indiscriminate use of penicillin, regardless of route or preparation, will minimize a needless increased sensitization of the population. The extreme price of using penicillin when it is not indicated was manifest in a report[53] of eight such anaphylactoid deaths, two of which followed the use of this drug for the treatment of the common cold.

*A term preferred to sensitivity, which is best reserved for the bacteriological aspects of antibiotic activity.

(2) *Precise Anamnesis.*—Routine interrogation concerning previous penicillin therapy with particular attention to reactions (an unfortunate oversight prior to our patient's intramuscular injection) will reveal the need for caution. This inquiry should include pruritus, as pointed out by Swift,[58] since among ten of his patients showing anaphylactoid reactions eight were aware of this symptom following a previous injection of penicillin. A similar inquiry concerning an allergic diathesis is expedient, since many of the reported major reactions have been in asthmatic subjects.

(3) *Decision in Doubtful Cases.*—Where penicillin is specifically indicated but could reasonably be expected to be hazardous, the decision clearly lies between the selection of one of the many other antibiotics (chlortetracycline, oxytetracycline, tetracycline, erythromycin, etc.), and extremely cautious and thorough testing for hypersensitization[26 31 39 44 58] if penicillin is still preferred and time avails. As alternatives, the concurrent administration of antihistamines and the substitution of penicillin O require further investigation before a dogmatic answer on their value is possible. Their value may well be limited to dermal sensitization reactions to penicillin G, as their use otherwise might engender a false sense of security. There is no persuasive evidence that one particular penicillin preparation is safer than another or that oral therapy is very much safer than systemic. The use of greatly retarded repository penicillin products is a potential hazard to be evaluated.

(4) *Cautious Technique of Injection.*—The injection technique should include: (*a*) Use of a fine-bore needle for crystalline penicillin solutions; but, conversely, a wide-bore needle for procaine penicillin suspensions to obviate its occlusion by the crystals. (*b*) Routine preliminary aspiration for blood while the needle is *in situ* for a subcutaneous or intramuscular injection of the drug. Alternatively, the procedure cited by Bell *et al.*[59] appears commendable. Here a separate insertion of the needle and a careful watch that no blood escapes precede the attachment of the loaded syringe. (*c*) Waldbott's recommendation[5c] of a preliminary injection of one or two drops of the penicillin preparation, followed by a safety pause of 45 seconds before delivering the main injection. This is of course equivalent to a test dose. (*d*) Choice of the subcutaneous rather than the intramuscular route in doubtful cases. (*e*) The selection of the upper arm as the site of injection so that in emergency a tourniquet can be readily applied.

There is no commercially available preparation of an anti-hyaluronidase type nor a penicillin neutralizer such as penicillinase for dire emergency.

(5) *Exemplary Surveillance and Preparedness.*—This includes a willingness of both the administrator and the patient to remain at hand for twenty minutes after the injection, thus providing a relatively safe period of vigilance for the severe immediate anaphylactoid reactions. Conversely, Kern and Wimberley[44] stressed the rapidity of onset of symptoms in some of the reported cases in which fatality supervened before any full-scale attempt at resuscitation could be instituted. In many other cases, however, there has been a longer latent period of five to ten minutes. The supervisor should be alert for the warning sign of congestion of the bulbar conjunctivae[54] and for the first complaint of tingling, difficulty in breathing, giddiness, or faintness indicative of impending anaphylactoid shock. It is suggested that, where possible, a "penicillin-resuscitation tray" be immediately available and stocked with liquor adrenalinae, and ampoules for the intravenous use of an antihistamine, a vasopressor amine, nikethamide, and aminophylline. As Hoagland[63] has pointed out, the first essential is preparedness to meet the emergency.

(6) *Adequate Documentation and Publicity.*—Cards boldly indicating hypersensitization to penicillin should be retained in the wallet or handbag by the patients concerned. Alternatively, a small disk conveying the same information could be attached from the neck and concealed under the clothing in case the patient should be brought in an unconscious

state for treatment, which might include penicillin. Above all, patients who have been given penicillin in any form should, for their own safety, be told even though no adverse reaction ensued. Swift[58] has shown the value of careful documentation in a clinic where penicillin is widely used.

For the benefit of all concerned, publicity from manufacturers could be increased by the adoption of "manufacturers' slips of caution"[58] displayed on the bottles or included in the packages of all penicillin preparations. Further publication of case reports and/or their submission to a central agency collating such data would permit a true assessment of the frequency of these reactions. Since most injections of penicillin are given by nurses they should be informed that these anaphylactoid reactions require prompt recognition and treatment. As an additional safeguard they should re-question the patients about previous courses or applications of penicillin and ascertain if any apparently related adverse effects had occurred. Here needless confusion is avoided by speaking the simple language of the patient and inquiring if anything went wrong previously rather than using the terms "sensitivity" or "allergic reactions."

Summary

The literature on anaphylactoid reactions from penicillin is briefly reviewed. A further case is reported to emphasize that moderately severe reactions can follow the use of penicillin lozenges and that there are occasional instances of severe reactions even when no history of previous administration of the drug can be elicited. A detailed description of a subsequent profound anaphylactoid shock in this patient is presented. A scheme for reducing the frequency and degree of these catastrophes is outlined.

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Medical Memorandum

Reactions to Intramuscular Iron

A new iron-dextran complex ("imferon") has recently been described (Baird and Podmore, 1954; Cappell *et al.*, 1954; Scott and Govan, 1954). It is reputed to be less toxic and more stable than saccharated iron oxide ("ferrivenin"). The dosage administered is 2 to 5 ml. (100 to 250 mg. of iron) as compared with the usual maximum dose of 5 ml. (100 mg. of iron) of intravenous saccharated iron oxide. Adequate serum concentrations have been obtained after the administration of the iron-dextran complex, the maximum absorption occurring in the first one to two days and the serum iron level falling to normal about the seventh day. Toxic reactions were not observed, but discomfort at the site of injection lasting up to twelve hours and staining of the skin were noted.

Dempster *et al.* (1954) obtained satisfactory results, but encountered local reactions in several patients and had to stop treatment in 2 of their 16 patients. Callender and Smith (1954) encountered four severe reactions in a limited period; two of these occurred soon after injection and two showed a delayed reaction of an allergic character. They gave the patients iron and dextran separately without producing any reaction, and suggest that the combination of iron and dextran may result in a sensitizing compound. Jennison and Ellis (1954) state that all their patients attained a satisfactory haemoglobin concentration. They report a few cases of local reaction; but mild general reactions, including nausea, vomiting, depression, fainting, and skin rash, occurred in 20% of their patients. Ross (1955) reports a delayed allergic reaction in a man of 55 and an early reaction after 1.5 ml. given intravenously to a youth of 17.

Reactions due to intravenous saccharated iron oxide fall into two main groups, early and late. The early consist mainly of cardiovascular collapse and of pain in the chest, back, and limbs possibly due to ischaemia. These occur even after doses of 100 mg. or less. The late (delayed) reactions are uncommon and occur after larger doses, usually 300 mg. or more. Nissim (1954) found only 13 cases of late reaction in the literature, of which only two had suffered an early reaction.

Librach (1953) considers allergy to be an important factor, especially in the production of early reactions, and believes they may be due to a natural hypersensitivity.

It seems as though the new iron-dextran complex may present us with combined early and late (delayed) reactions, the main symptoms of which have been observed previously. The accent is, however, upon symptoms hitherto uncommon. This is to be expected, as the mechanism of toxicity varies with the other properties of the whole molecule injected (Nissim, 1954).

CASE REPORT

On September 22, 1954, a married woman aged 46 was admitted to hospital for total hysterectomy. She had suffered from menorrhagia for two years, and on examination the uterus was enlarged by fibroids to the size of a