QUININE SENSITIVITY

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Cinchonism, which is the name given to the symptom-complex of nausea, vomiting, disturbance of vision, tinnitus, and nerve deafness, may occur in any patient taking large doses of quinine (Goodman and Gilman, 1956). It is probably a physiological result of the high quinine content in the blood. When a patient who is taking only small doses of the drug develops the symptoms of cinchonism he is said to have an intolerance, or idiosyncrasy; there is no evidence that this is dependent upon an immunological mechanism (Pillsbury *et al.*, 1956).

A wide variety of dermatoses have been described in patients taking quinine systemically, and contact dermatitis may follow the topical application of quinine. These eruptions are thought to be based on an allergic process. Quinine, even in high concentration, has no irritant or direct toxic action on the skin. Although a large number of people have quinine-containing preparations applied to their skin as medications, scalp lotions, chemical contraceptives, or for other purposes, only a small number will develop an eruption: those who do so will nearly always show thereafter a positive patch test to dilute solutions of a quinine salt.

Eruptions ascribed to systemic administration of quinine are thought to be examples of allergic hypersensitivity because: (1) they are dissimilar to the effects of overdosage (cinchonism), (2) they may be provoked by extremely small doses of the drug, and (3) they occur only, and always, on re-exposure to the drug. In common with most instances of supposedly allergic drug reaction, skin tests by prick, scratch, intradermal, or patch technique are usually negative, unless the patient has been additionally sensitized by cutaneous contact.

We report here the details of five patients who developed a rash attributable to quinine, each of whom was positive to the patch test. Some of them also experienced systemic reactions.

Case Reports

Case 1.—A man aged 40 presented in 1955 with a rash of 10 weeks' duration on his arms, legs, and genitalia which was diagnosed clinically as lichen planus. He gave a previous history of a contact dermatitis of the penis after his wife's use of a contraceptive pessary containing quinine. Some time later he suffered an episode of an eruption on the genitalia, palms, and soles after the ingestion of quinine. His general practitioner suspected that the presenting rash was also due to quinine sensitivity, since it seemed to have begun after the patient's wife had again used a quinine-containing contraceptive pessary. A patch test to a 2% solution of quinine sulphate was positive after 48 hours.

Case 2.—A 25-year-old man presented in 1956 with an eczematous eruption of his perineum and genitalia which had been present for two months; it started after his wife had begun using a proprietary brand of a quinine-

containing contraceptive pessary. Patch tests to the pessary and to a 2% solution of quinine sulphate were positive. Tests with 0.1% mercuric chloride and ammoniated mercury ointment were negative.

Case 3.—A man aged 31 was referred in 1957 by his general practitioner as a case of balanitis, possibly due to contact dermatitis. He had been using a rubber condom, and his wife may have been using chemical contraceptive pessaries. Positive patch tests were obtained with a piece of rubber from the condom, a quinine-containing pessary, and a 2% solution of quinine sulphate.

Case 4.—A man aged 36, whose occupation was a ladies' hairdresser, was first seen in May, 1953, with an acute dermatitis of the scalp, face, neck, and left hand of two weeks' duration. This had started on his bald scalp the day after he had used a proprietary brand of quinine-containing hair-restoring lotion; it resolved after one week's treatment in hospital. In the next few years he had several mild recurrences of dermatitis of the face and hands, and in 1957 he had a further acute attack necessitating admission to hospital. On this occasion a patch test with 2% quinine sulphate was positive, and the past history was obtained that at the age of 22 he had had an eruption on the genitalia after his wife's use of a chemical contraceptive containing quinine. In 1958 he again developed an acute dermatitis of the face and hands. This had begun on the day after he had had a tooth extracted, and, although none of the materials used by his dentist contained quinine, it is possible that the patient had taken a quinine-containing analgesic tablet.

Case 5.—A man aged 40 was seen in March, 1961, with a generalized itching, macular, erythematous eruption which was not scarlatiniform. He had recently had an entirely similar episode. Both attacks cleared up in three or four days. His previous history was that in childhood he had developed a scarlet-fever-like rash after taking a "tonic"; he was subsequently told that he was sensitive to quinine. When aged 34 he had an acute dermatitis of the scalp after using a proprietary hair lotion (presumed to have contained quinine). Further inquiry then revealed that both episodes of the erythematous rash this year started on the day after he had drunk gin and "bitter lemon." A proprietary brand of the latter contains 3 mg. of quinine per 100 ml. Skin tests were done with 1% quinine sulphate in normal saline. The scratch and intradermal tests gave negative immediate-type reactions, but the patch test was strongly positive after 72 hours.

Discussion

The most common eruption caused by quinine is a generalized scarlatiniform rash, and Osler (1901) includes quinine rash in the differential diagnosis of scarlet fever. Although skin tests are not usually helpful in the diagnosis of drug allergy, there are isolated reports of positive skin reactions with quinine sensitivity. Boerner (1917), Dawson and Garbade (1930), Settle (1936), and Orr (1945) each described finding a positive immediate wheal response to a scratch test with quinine in subjects sensitive to oral quinine. Settle's patient had a fixed drug eruption with bullae on the palms, and the scratch test itself provoked a focal flare.

In cases reported with a positive patch test to quinine a previous cutaneous contact with the drug had usually occurred (Kissmeyer, 1938; Bonnevie, 1939; Dold, quoted by Bonnevie, 1939). However, in 3 of the 20 patients described by Bonnevie no previous quinine contact was discovered. Bloch (1924) reported the case of a boy of 14 with atopic eczema who had a positive patch test to quinine, who had had no previous contact with quinine. A small dose (10 mg.) of quinine by

mouth produced an acute facial eruption, swelling of the fingers, and an attack of asthma 10 hours later.

Novy and Lamb (1957) described the case of a patient who presented at the age of 36 with a generalized dermatitis 24 hours after drinking a "few gin and tonics." He had had repeated eruptions since childhood, each caused either by the ingestion or application of quinine, and the whole pattern of his illness was very similar to that of one of our patients (Case 5).

Contact dermatitis from quinine is mentioned by Sulzberger (1940), by Becker and Obermayer (1947), and by Urbach and Gottlieb (1946). The last-mentioned authors published the photograph of a patient with an acute dermatitis of the face after using a hair lotion containing quinine.

Since 1938 quinine has been included in the standard series of patch tests applied to all patients with eczema at the Finsen Institute in Copenhagen. The incidence of positive reactions to quinine has steadily declined and are now distinctly rare (Hjorth, personal communication, 1961).

All of our five patients had positive patch tests and all gave a clinical history of a reaction after cutaneous contact with quinine. It is difficult to estimate whether quinine is a potent contact sensitizer or not, unless one can relate the incidence of reactions to the number of persons exposed to it. One would not regard it as a strong sensitizer when compared with penicillin, sulphonamides, or paraphenylenediamine; it is interesting to note, however, that contact sensitivity has been experimentally produced in guinea-pigs (an animal less prone to contact sensitivity than man) by the repeated topical application of quinine (Landsteiner and Chase, 1941).

More serious forms of adverse reaction to quinine are acute intravascular haemolysis and purpura. In the latter the platelet count may be low, and may be associated with a circulating antibody to the quinine-platelet complex (Ackroyd, 1958). This antibody can be demonstrated by an *in vitro* test similar to that used for detecting allergic thrombocytopenia from use of "sedormid."

Discombe (1958) states: "Quinine has long been notorious as a determinant of blackwater fever in patients with malignant tertian malaria . . . and in occasional patients who have never been exposed to malarial infection. Of these the most important group is pregnant women." This special susceptibility in pregnancy probably relates to the large single dose that may be taken for a reputed abortifacient effect, as in the fatal case reported by Vartan and Discombe (1940). Although the mechanism of this acute haemolysis is not known, observations made by Brost (1956) on two sisters with quinine purpura, one of whom had also had quinine-induced haemolysis, suggests that there may be a genetic factor which makes the patient's erythrocytes susceptible to destruction by quinine (Discombe, 1958). This may be of a similar nature to the glucose-6-phosphate dehydrogenase defect which is responsible for the lysis of ageing red cells by pamaquin and other drugs (*Brit. med. J.*, 1961).

Sources

Cinchona, the dried bark of the cinchona tree, contains a mixture of more than 20 alkaloids, the most important being two pairs of optical isomers: (1) L-quinine and

D-quinidine, and (2) L-cinchonidine and D-cinchonine. The structural formula of quinine is:

the four asymmetric carbon atoms being marked in bold letters.

Quinine has now been largely replaced as a prophylactic against malaria, and is less popular as a constituent of "tonics" and simple analgesic and antipyretic mixtures—probably because it has been established to have only a weak antipyretic action, and to be no more effective than aspirin as an analgesic (Goodman and Gilman, 1956). Of the common proprietary analgesics only "anadin" contains quinine to the extent of 5 mg. in each tablet. The *Dental Formulary* contains an equivalent quinine-containing analgesic tablet, which is apparently widely prescribed by dentists (Hadgraft, personal communication, 1961). Quinine is still given orally to patients with myotonic conditions and non-specific night cramps.

Quinine is used in combination with an ion-exchange resin as quinine carbacrylic resin ("diagnex") as an oral tubeless test for gastric acid secretion. One of its soluble salts (0.003% w/v of quinine) is the "bitter" in "bitter lemon" and "tonic water." It may be encountered topically in proprietary hair lotions. Harry (1955) gives the prescription of a typical scalp lotion as 0.2% quinine in an alcoholic solution. It is employed in some chemical contraceptives for its spermicidal effect—for example, Rendall's contraceptive pessary contains 3.5% of quinine.

Summary and Conclusions

Five cases are described of patients who were proved by patch tests to have allergic contact sensitivity to quinine. Three of them presented with a contact dermatitis from quinine, and the others had had such episodes in the past. Three of the patients had experienced eruptions from systemic administration of quinine, and one reacted after drinking a proprietary brand of "bitter lemon." None of them gave positive scratch or intradermal tests to the drug.

The literature on quinine-induced skin eruptions, the toxic effects of quinine, and the role of skin tests in quinine sensitivity are briefly reviewed, and reference is made to the more common ways in which patients may encounter quinine.

REFERENCES

- Ackroyd, J. F. (1958). In *Sensitivity Reactions to Drugs*, edited by M. L. Rosenheim and R. Moulton, p. 28. Blackwell, Oxford.
- Becker, S. W., and Obermayer, M. E. (1947). *Modern Dermatology and Syphilology*, 2nd ed., p. 172. Lippincott, New York.
- Bloch, B. (1924). *Arch. Derm. Syph. (Berl.)*, **145**, 34.
- Boerner, F. (1917). *J. Amer. med. Ass.*, **68**, 907.
- Bonnevie, P. (1939). *Aetiologie und Pathogenese der Ekzemplkrankheiten*. Nyt Nordisk Forlag, Copenhagen.
- Brit. med. J.*, 1961, **1**, 1377.
- Brost, U. (1956). *Geburtsh. u. Frauenheilk.*, **16**, 698.
- Dawson, W. T., and Garbade, F. A. (1930). *J. Amer. med. Ass.*, **94**, 704.
- Discombe, G. (1958). In *Sensitivity Reactions to Drugs*, edited by M. L. Rosenheim and R. Moulton, p. 6. Blackwell, Oxford.
- Goodman, L. S., and Gilman, A. (1956). *The Pharmacological Basis of Therapeutics*. Macmillan, New York.

- Harry, R. G. (1955). *The Principles and Practice of Modern Cosmetics*, vol. I, *Modern Cosmeticology*, 4th ed. Hill, London.
- Kissmeyer, A. (1938). *Acta derm.-venereol. (Stockh.)*, **19**, 153.
- Landsteiner, K., and Chase, M. W. (1941). *Proc. Soc. exp. Biol. (N.Y.)*, **46**, 223.
- Novy, F. G., and Lamb, G. R. (1957). *J. Amer. med. Ass.*, **164**, 91.
- Orr, J. (1945). *Brit. med. J.*, **2**, 604.
- Osler, W. (1901). *Principles and Practice of Medicine*, 4th ed. Pentland, Edinburgh.
- Pillsbury, D. M., Shelley, W. B., and Kligman, A. M. (1956). *Dermatology*. Saunders, London.
- Settle, R. O. (1936). *J. Amer. med. Ass.*, **106**, 1801.
- Sulzberger, M. B. (1940). *Dermatologic Allergy*. Thomas, Springfield, Ill.
- Urbach, E., and Gottlieb, P. M. (1946). *Allergy*, 2nd ed., p. 701. Heinemann, London.
- Vartan, C. K., and Discombe, G. (1940). *Brit. med. J.*, **1**, 525.

MENSTRUATION AND CRIME

BY

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It has been shown that during menstruation a deterioration occurs both in a schoolgirl's work and in her behaviour (Dalton, 1960a, 1960c), and it is also at this time that women are most liable to be involved in accidents (Dalton, 1960b) or to be admitted to hospital with an acute psychiatric illness (Dalton, 1959). This gradual recognition of the social significance of menstruation in the various aspects of a woman's life has led to an investigation of the importance of the menstrual factor in crime.

Over a period of six months in one of H.M. Prisons I interviewed all newly convicted women below the age of 55 on the first weekday after their sentence. The prisoners were asked their age, parity, duration of menstruation, length of cycle, date of last menstruation, and whether they observed any symptoms before or during menstruation. A similar interview was arranged for all prisoners who had been reported to the governor for bad behaviour while serving their sentence.

Results

Of the 386 newly convicted prisoners, 284 (74%) were menstruating regularly and 156 (41%) had committed their offence during the previous 28 days. Table I shows the distribution of the menstrual history of the newly convicted prisoners.

TABLE I.—Menstrual History of 386 Criminal Women

Regular menstruation	284
Offence committed within 28 days ..	156
More than 28 days since offence ..	102
Unable to recall date of last menses ..	26
Amenorrhoea	38
Probably pubertal	6
pregnant	28
Puerperal	4
Menopause	64
Natural	48
Artificial	16

In analysing the results, the method used was that described in previous surveys into the relationship of menstruation to acute psychiatric illness (Dalton, 1959)

and accidents (Dalton, 1960b). The menstrual cycle was divided into seven four-day periods, in which Days 1–4 represented menstruation and Days 25–28 the premenstruum. The relationship of the date of offence to menstrual cycle in the 156 women who committed their offences during the previous 28 days is shown in Table II.

Nearly half of all crimes (49%) were committed by women during menstruation or in the premenstruum. On a normal distribution, only two-sevenths (29%) of all crimes would be expected during this period of eight days. The probability of a distribution, such as has been found, occurring by chance is less than one in a thousand ($\chi^2=12.7$ on 1 d.f.) and therefore suggests that the association between menstruation and crime is highly significant.

TABLE II.—Time of Crime of 156 Regularly Menstruating Women

Day of Cycle	No.	%
1–4	41	26.3
5–8	13	8.3
9–12	20	12.8
13–16	21	13.5
17–20	19	12.2
21–24	7	4.5
25–28	35	22.4
Total	156	100

Menstruation seems of greater importance in crimes of theft: 56% of such crimes occurred during menstruation and the premenstruum, whereas for prostitution the figure was 44% (Table III). Seven of the

TABLE III.—Crimes Committed During Menstruation and Premenstruum

Type	Crimes during Menstruation and Premenstruum		Total Crimes	χ^2 on 1 D.F.	Probability
	No.	%			
All crimes	76	48.7	156	30.9	<0.001
Theft	36	56.3	64	18.5	<0.001
Prostitution	34	43.6	78	8.6	<0.01
Alcoholism	7	53.8	13	*	*
First offence	21	51.2	41	10.3	<0.001
2nd and 3rd offences ..	25	49	51	10.4	<0.001
4 or more offences ..	19	47.5	40	7.0	<0.05

* Too few to determine probability.

13 (54%) alcoholics were sentenced at this time. "Theft" is used here to include all offences against another's property—for example, shoplifting, burglary, embezzlement, forgery. "Prostitution" covers those convicted under the Street Offences Act, 1959. "Alcoholism" covers those found drunk and disorderly in public places and refusing, or unable, to pay the fine. Menstruation is also of greater importance among first offenders than among those with more than three previous convictions. It was noted that nulliparous women were most liable to commit their offences during the premenstruum and the parous women during menstruation; this is similar to the difference in accident proneness among nulliparous and parous women (Dalton, 1960b).

The dates of conviction of those 102 women who menstruated regularly and whose crime had been committed more than 28 days previously were evenly distributed throughout the menstrual cycle. It would appear, therefore, that menstruation had no prejudicial effect on those women during their appearance in court.

"Premenstrual tension" was defined as mood changes, headaches, tiredness, bloatedness, or mastitis during the