bilirubin excretion. The decreases in serum bilirubin concentrations during treatment in Case 9 cannot be attributed to this, and delay in red cell or haemoglobin breakdown due to steroids (Katz *et al.*, 1957) seems unlikely to explain such great reductions. Alternatively, deviation of haemoglobin metabolism to compounds which do not react with the diazo reagent, or increased storage of bilirubin in the reticulo-endothelial system and other tissues, might be responsible, but the coincident decreases in this study in serum levels of alkaline phosphatase, which is thought to be eliminated mainly in the bile, are more compatible with increased excretory activity.

The usefulness of corticotrophin and steroids in distinguishing between intrahepatic and extrahepatic jaundice has encouraged us to incorporate the test in the routine investigation of obstructive jaundice of uncertain cause. After two weeks, in which time standard investigations (stool occult blood, haematology, barium meal, liver-function tests) have been done, a five-day trial of corticotrophin or steroids on the serum bilirubin level is performed if the diagnosis remains in doubt. Oral prednisone (20 mg. t.d.s.) may be the drug of choice. It reaches the liver direct in portal blood, and corticotrophin has the disadvantage of variable potency due to batch differences. An apparent response to this measure is followed by continued treatment. In patients who fail to respond and in whom there is no haematological contraindication, liver biopsy can be performed with less hazard than laparotomy in the jaundiced patient, and its interpretation in obstructive jaundice was well reviewed by Johnson and Doenges (1956).

Unfortunately, cases which are equivocal from clinical and biochemical standpoints often have non-specific histological findings. However, dilatation of large intrahepatic bile ducts and bile extravasation suggest extrahepatic obstruction, while, as in Case 2, evidence of liver-cell damage and cellular infiltration indicates hepatitis. In addition, cirrhosis or another unsuspected lesion may be demonstrated, as in Case 12. If the diagnosis is still in doubt, laparotomy with arrangements for cholangiography must be considered to resolve the doubts of both doctor and patient. Obstructive jaundice is not harmful (Atkinson *et al.*, 1956), and it is reasonable to wait eight weeks for possible improvement, as operation is poorly tolerated by patients with hepatitis (Sherlock *et al.*, 1954). Sometimes, as in Case 1 (who was jaundiced for nine months), laparotomy appears inevitable in a patient subsequently shown to have hepatitis, but the relative absence of liver-cell damage on clinical, biochemical, and histological investigation probably allows these patients to withstand operation better than others with hepatitis.

Summary

In 12 patients with obstructive jaundice of uncertain cause, the effect of a five-day trial of steroid or corticotrophin therapy was of great value in reducing serum bilirubin levels and in differentiating between intrahepatic obstruction due to hepatitis and extrahepatic obstruction. Serum alkaline phosphatase concentrations also fell during treatment, although to a less extent, thus suggesting that the reduction of jaundice caused by corticotrophin or steroid drugs was due to increased bile excretion. The drugs acted immediately and no difference was apparent between corticotrophin and steroids.

The place of these drugs and other measures in the diagnosis and management of obstructive jaundice is discussed.

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THROMBOCYTOPENIC PURPURA DUE TO QUINIDINE

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The fundamental observations on drug-induced thrombocytopenia were made by Ackroyd (1949a, 1949b, 1951, 1954) in his classical work on "sedormid" purpura. He showed that the drug caused agglutination and lysis of the patient's platelets *in vitro*, and that the addition of the drug to the patient's blood *in vitro* inhibited clot retraction.

We describe below a simple method for showing platelet agglutination. This method enables the investigator to obtain suspensions of platelets which have no tendency to spontaneous clumping. Stress is laid on the clinical features of quinidine purpura and the practical conclusions to be drawn from them.

Case Report

On December 31, 1957, a man aged 50 was admitted to Hadassah Hospital because of haematuria and purpura. He looked seriously ill. There were widespread petechiae, and blood-filled blisters were seen in the mouth and on the tongue. The urine had the appearance of blood. The blood pressure was 170/100. The blood count showed haemoglobin, 69%; erythrocytes, 3,500,000; leucocytes, 10,000 (neutrophils 59%, eosinophils 2%, monocytes 2%, lymphocytes, 37%). No platelets were seen; bleeding-time was 2 minutes; coagulation time 2 minutes, and prothrombin 58%. The urine showed many red cells. The tourniquet test was strongly positive. Prednisone, 60 mg. a day, was given. By his fourth day in hospital the urine was clear, the platelet count had risen to 25,000, and he was feeling much better. By the seventh day the platelets had risen to 100,000; two days later they numbered 240,000.

A detailed history revealed that the patient had had a myocardial infarction two years previously. In July, 1957, he was given quinidine because of palpitations; he took four 0.2 g. tablets. A month later he took another tablet. Two days before admission he felt palpitations and took two tablets, one at midday and one in the evening (0.4 g.). That night he had a severe rigor and his temperature rose to 39° C. (102.2° F.). Next day he felt weak and noticed a rash on his hands. On the following day blood appeared in his urine and he was sent to hospital. He had taken 1.4 g. of quinidine at intervals, over a period of six months.

In the third hospital week—that is, when the patient's blood picture had become entirely normal and the prednisone treatment had been stopped—the following tests were carried out:

Clot Retraction Test, Qualitative Method

This test was done in the ward as follows: solutions (in normal saline) of quinidine sulphate 1:2,000 and quinine hydrochloride 1:2,000 were procured. Three standard laboratory test-tubes were taken; to the first was added 0.2 ml. of the quinine solution, to the second 0.2 ml.

FIG. 1.—The clot-retraction test (qualitative method) as performed in the ward. The two outside tubes (quinine and saline) show negative results; the centre tube (quinidine) shows a positive result. In this photograph the test was done with Linzenmeier blood sedimentation tubes.

FIG. 2.—The thrombocyte-rich plasma of the patient after incubation with quinidine solution at 37° C. for one hour, showing agglutination of platelets (+++).

FIG. 3.—The thrombocyte-rich plasma of the patient with saline (control), showing complete absence of agglutination. Photographs of Figs. 2 and 3 were taken with the phase contrast microscope. ($\times 400$.)

of the quinidine solution, and to the third 0.2 ml. of normal saline. Blood was taken from the patient by venepuncture, using a ward syringe. To each tube was added 2 ml. of blood. The tubes were inverted four times. They were kept at room temperature and examined after 4 and 24 hours. If free serum was seen the test was taken as negative; if no free serum could be seen it was regarded as positive. In this way quinidine repeatedly gave positive reactions, while quinine and saline always gave negative reactions (Fig. 1). Quinidine gave negative results when tested similarly with the blood of 10 other patients.

The reliability of this simple procedure is stressed, since it enables the clinician to make the diagnosis in the ward. This test, as performed above, was still positive 10 weeks after the patient's admission; a further test four weeks later was negative. These results were confirmed in the laboratory, using the quantitative method.

Patch Test.

This was carried out according to the method of Freedman, Brody, and Barr (1956). The results were negative.

Thrombocyte Agglutination Test

The anticoagulant was Na_2 "sequestrene" 5% at pH 7.2 (corrected with NaOH). Glassware was siliconized with "siliclad." Drug solutions were made up as follows in normal saline: quinidine sulphate, 2 and 20 mg., quinine hydrochloride 2 and 20 mg., phenobarbitone 2 and 20 mg. per 100 ml. A siliconized bacteriological test-tube (5 cm. long with outside diameter 9 mm.) was marked with wax pencil at the 1-ml. level; 0.1 ml. of anticoagulant was added. After warming the hand a deep finger puncture was made. When the blood was flowing freely it was collected straight into the tube up to the mark and well mixed with the anticoagulant; 1 ml. of blood was usually enough. The tube was then centrifuged at room temperature at 800–1,000 r.p.m. for three to five minutes. The upper layer of thrombocyte-rich plasma was removed with a siliconized pipette and transferred to a small siliconized test-tube, which was tapped gently to secure even spread of the platelets. This thrombocyte-rich plasma was distributed into small siliconized test-tubes, two drops in each tube. To each tube was added one drop (of the same size) of one of the drug solutions under test. The mixtures were incubated for one hour in a water-bath at 37° C. The tubes were removed and, using a siliconized pipette, a small drop was placed on a siliconized slide, covered with a siliconized coverglass, and examined microscopically. Incubation for a further hour caused the agglutination to be even more marked; platelet flocculation could then be seen with the naked eye.

Results.—This test, and the clot-retraction test, were performed on the patient's blood in the third hospital week, and repeated once a week for eight weeks. Tests with the controls were done twice. The results were graded as follows:

+++ , Complete agglutination into large clumps with no free platelets (as in Fig. 2).

++ , Agglutination into smaller groups with free platelets to be seen.

+ , Agglutination into very small groups; from 2 to 3 agglutinates visible in every field.

— , No tendency to agglutinate whatsoever. (As in Fig. 3.)

	Quinidine		Quinine		Phenobarb.		Saline
	2 Mg./100 ml.	20 Mg./100 ml.	2 Mg./100 ml.	20 Mg./100 ml.	2 Mg./100 ml.	20 Mg./100 ml.	
Patient	+++	+++	—	—	—	—	—
20 controls .. .	—	—	—	—	—	—	—
6 patients on quinidine	—	—	—	—	—	—	—
Patient's daughter ..	—	—	—	—	—	—	—

Follow-up: fourteen weeks after admission the patient's platelet-rich plasma was examined again with quinidine; result was ++. At examination seven months after admission the result was +.

Clot Retraction Test, Quantitative Method

In this test the drugs and glassware were as above. 0.1 ml. of the drug solution was mixed with 0.9 ml. of the patient's blood, taken as above. The test-tubes were incubated for three hours at 37° C. Readings were made according to the formula:

$$\frac{\text{serum expressed, in ml.}}{\text{whole blood in ml.}} \times 100$$

Results are shown in the following Table.

	Quinidine 20 Mg./ 100 ml.	Quinine 20 Mg./ 100 ml.	Phenobarb. 20 Mg./ 100 ml.	Saline
Patient	0	52–56	52–56	52–56
20 controls .. .	48–60	48–60	48–60	48–60
6 patients on quinidine	52–58	52–58	52–58	52–58
Patient's daughter ..	51	53	53	51

Follow-up: The test was repeated on the patient's blood 14 weeks and seven months after admission; clot retraction

in the presence of quinidine showed no difference from the saline control on both occasions.

Controls.—The controls for both tests were 20 patients and medical personnel of both sexes and various age groups who had never received quinidine. We also tested six patients who had regularly been receiving quinidine for periods varying from a month to a year. The blood of the patient's daughter was also examined.

Other Laboratory Procedures

In order to eliminate the possibility of idiopathic thrombocytopenic purpura due to a platelet panagglutinin in the patient's serum, the following procedure was carried out.

Samples of platelet-rich plasma from two normal persons, of the same blood group as the patient, were prepared as above. Two drops of the patient's serum (after inactivation for 30 minutes at 56° C.) were added to one drop of normal platelet-rich plasma, mixed and incubated for one hour, one sample at 4° C. and another at 37° C. Controls were: physiological saline and serum from two blood-compatible normal persons in place of the patient's serum. Thus, samples of platelet-rich plasma from two normal persons were tested with the patient's serum, the serum of two normal persons, and with saline. No agglutination was observed.

In order to find evidence of a factor in the patient's serum capable of agglutinating normal platelets in the presence of quinidine, the above procedure was repeated with the addition of one drop of quinidine solution (2 mg. per 100 ml.) to each mixture. Control tests were done simultaneously without quinidine. No agglutination was observed. This finding is commented upon below.

(These procedures were carried out in the third and fourth weeks following admission.)

Discussion

Dose of Quinidine

Purpura may appear at any time in any patient taking quinidine. Thus a patient may take quinidine for years, either continuously or intermittently, when suddenly purpura appears (Freedman *et al.*, 1956; Bigelow and Desforges, 1952). Sensitization may develop during a patient's first course of quinidine; in such cases there is a "lag" period before the onset of purpura; this period may be as short as five days (Collins, 1950). Some of the reported cases resemble our case, in which there is a definite history of a sensitizing dose, followed after an interval by the precipitating dose.

Patients suffering from quinidine purpura vary considerably in their sensitivity to the drug. This is readily seen in the summary compiled by Bolton and Dameshek (1956), in which are tabulated the results of the test doses given in the reported cases. Thus as little as 15 mg. caused the platelet count to drop to 5,000 with bleeding in one case, whilst in another case 0.2 g. caused the platelets to fall to 90,000, no bleeding taking place. The sensitivity of the individual patient also does not remain constant. This is exemplified in the case of Moodie (1950): here a test dose of 0.2 g. a day led to purpura after four days, but later on purpura appeared after a total of only 64 mg. had been administered during four days.

Since the sensitivity varies from patient to patient, and since the sensitivity varies in the same patient from time to time, it is impossible to fix an "optimal" test dose in any given case; by "optimal" is meant a dose which causes a drop in the platelet count large enough to be convincing but which does not cause bleeding. We believe that it is ethically wrong to give a test dose, because its outcome can never be predicted.

Although there is no definite correlation between the amount of quinidine ingested and the extent of the bleeding which it provokes, we stress that in the fatal case reported by Bourne and O'Sullivan (1957) the patient went on taking 0.96 g. of quinidine daily for four days after the onset

of purpura. Death was due to cerebral haemorrhage. It follows that a patient should stop taking the drug at the very first signs of thrombocytopenia; it is of practical importance to know what these signs are.

Prodromal Symptoms

In our case there appeared to be a definite prodromal stage; after having taken two tablets of quinidine, the patient had a severe rigor during the night and his temperature rose to 39° C. Several authors describe similar features. Siegal and Horn (1950) reported fever after a test dose. Hirsch and Dameshek (1950) described a case in which gum bleeding and purpura were preceded by a chill and a feverish sensation. In Case 2 of Bolton and Dameshek (1956) the bleeding episode was preceded by a period of a week marked by chills, fever, and fatigue followed by nausea, abdominal pain, and diarrhoea.

Other symptoms are described. Nussbaum and Shulman (1952) described lethargy and somnolence. In the case of Collins (1950) lethargy followed a test dose. In Case 4 of Bolton and Dameshek (1956) weakness, nausea, and tiredness are mentioned. In the case of Norcross (1950) the illness began with coma and convulsions. Larson (1953) mentioned headache after a test dose. In the case of Breu and Zollner (1940), which terminated fatally, the illness started with anaphylactic shock and urticaria. Other symptoms mentioned in the case reports are itching, feeling uncomfortable, and pains in the limbs.

It is impossible to assess in what proportion of cases the purpura is preceded by prodromal symptoms, since some authors omit to state how the patient felt before the bleeding started. Barkham and Tocantins (1954) described a case without such symptoms.

It may be concluded that in an appreciable proportion of cases the bleeding episode is preceded by various symptoms, the main ones being fever, chills, weakness, lethargy, nausea, and headache. It may be noted that the prodromal symptoms of quinidine purpura share certain features with "cinchonism" (as described by Goodman and Gilman (1955)), such as nausea, headache, and fever.

The Haemorrhagic Episode

The bleeding may start in an atypical fashion. Our patient noticed black spots on his tongue, but their importance was understood only next day. In the case of Nussbaum and Shulman (1952) there occurred gum bleeding, which at the time was attributed to local causes. Local causes could easily be blamed for epistaxis or for uterine bleeding. Bleeding of all kinds and in all grades of severity have been described, including melaena, cerebral haemorrhage, haemoptysis, and haematuria. In the great majority of cases a purpuric skin rash is present.

It is worth noting that the best-known complication of quinidine treatment—embolism after reversion from atrial fibrillation to sinus rhythm—might be confused with the results of haemorrhage due to thrombocytopenia. For example, either of these complications might be the cause of haemoptysis during quinidine treatment. Should haematuria or hemiplegia appear the same differential diagnosis must be considered.

Duration of the Haemorrhagic Episode

Our patient was seriously ill on admission. His condition rapidly improved: seven days after his taking the quinidine the haematuria had ceased and the purpura was beginning to fade; return of the platelet count to normal levels took another four days. All the case reports of quinidine purpura show the same picture—that is, a haemorrhagic state which lasts from one to seven days after stopping the drug, full haematological remission usually coming some days later. Likewise, this same pattern is reported to be usually seen in cases of sedormid purpura. This "seven-day pattern" of thrombocytopenic purpura, characterized by cessation of bleeding within a week of stopping the drug, seems to be the typical result of the action of a rapidly eliminated factor whose primary effect is the destruction of

thrombocytes in the peripheral blood. Many reports of drug purpura in the literature conform to this "seven-day pattern." As examples may be cited the following cases: butobarbitone (Young, 1957), quinine (Steinkamp *et al.*, 1955), digitoxin (Berger, 1952), "mapharsen" ("mapharside," oxophenarsine hydrochloride) (Schwartz and VonderHeide, 1945). However, the clinical pattern cannot be taken as the only criterion in classifying the drug purpuras; it is merely suggestive. It may be postulated that the purpuras due to quinidine, quinine, and sedormid form a clinico-pathological entity.

To this group may be added other drugs if they conform to the following criteria: (a) The clinical picture should be typical, with cessation of bleeding within a week of stopping the drug, full haematological remission coming some days afterwards. (b) The primary action of the drug is platelet destruction in the peripheral blood. This may be assumed when thrombocytopenia follows within a few hours of giving the drug; absence of megakaryocyte aplasia in the bone marrow tends to confirm this. (c) Thrombocyte agglutination should be demonstrable in the presence of the drug *in vitro*. This should be confirmed by the inhibition of clot retraction in the presence of the drug.

Practical Considerations

The physician using quinidine will wish to know how common quinidine purpura is, and what should be done about it. In 1941 Broch described the first undoubted case: by 1956 Bolton and Dameshek were able to list 28 cases. If we add our case, the fatal case of Bourne and O'Sullivan (1957), and the four cases of Freedman *et al.* (1956), at least 34 cases are on record. The last-mentioned authors comment on the fact that they diagnosed their four cases during a period of seven months at one hospital. The condition is not common, but it is not merely of academic interest.

It is pointless to do daily platelet counts during the administration of quinidine, since the drop can occur suddenly at any time. It is the usual practice to give a test dose of one tablet before starting a course of quinidine; two to three hours later the treatment is begun if there are no untoward effects. We make the suggestion that if any suspicious symptoms arise a tourniquet test should be performed and, if possible, a platelet count done before proceeding. The physician prescribing quinidine should be alert for the prodromal symptoms of thrombocytopenia, described previously; the similarity of these symptoms to those of cinchonism must not be ignored. The appearance of constitutional symptoms calls for the immediate cessation of the drug, which must not be resumed until a platelet count is done. As many of the recorded cases of quinidine purpura were in patients who had been taking the drug at home with little or no supervision, it is important to impress on domiciliary patients to stop the drug and seek medical advice on the appearance of constitutional symptoms, a rash, or bleeding.

Serological Findings

The addition of quinidine to the patient's platelet-rich plasma caused the platelets to clump into large discrete masses. No lysis of platelets occurred; this agrees with Ackroyd's (1951) observation that lysis appears only in the presence of complement. We used sequestrene as anticoagulant, making use of its anticomplementary effect (Bolton, 1956), so as to prevent platelet lysis and thus simplifying the reading of the results.

In his studies on sedormid purpura, Ackroyd (1949a, 1949b) showed that there is a factor in the serum of sensitized patients, which, when added to the platelets of normal persons, causes agglutination in the presence of the drug. He concluded (Ackroyd, 1954) that sedormid unites with platelets to form an antigen which reacts with the factor in the serum. A similar factor in the serum of patients with quinidine purpura has been demonstrated by Bolton and Young (1953), Weisfuse, Spear and Sass (1954), and Bolton and Dameshek (1956); they were able to obtain

agglutination of normal platelets on the addition of the patient's serum and quinidine. Bigelow and Desforzes (1952) had inconsistent results, as they found the factor in plasma but not in serum. However, Barkham and Tocantins (1954) were unable to find such a factor in the serum of their patient. We, too, were not successful in demonstrating the presence of a serum factor. Apparently these inconsistencies are due to variations in technique, such as the choice of anticoagulant and the period and temperature of incubation.

However, we wish to put forward for consideration the following theoretical possibility: that the serological process is a direct antigen-antibody reaction between quinidine and sensitized platelets. It might then be postulated that changes in the platelets *in vitro* due to blood coagulation or to centrifugation could detach the factor from the platelets, and this could account for its presence in the serum. The extraordinary rapidity of action of quinidine in cases of sensitivity seems to support the idea of a direct reaction.

Summary

A case of quinidine purpura is described. It is shown that the diagnosis can be made in the ward by a simplified version of the clot-retraction test.

A simplified method for demonstrating platelet agglutination is described.

The prodromal symptoms of quinidine purpura are described and their importance is stressed.

It is shown that many of the drug-induced thrombocytopenias conform to a definite clinical pattern, and certain criteria are proposed for classification.

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A memorandum on the care of epileptics has been prepared for the Central Health Services Council by the Standing Medical Advisory Committee and is to be sent to all general practitioners in the National Health Service. Concentrating on the medical and social aspects of epilepsy, the memorandum offers advice on the "management" of epileptics, and on their training and employment. There are paragraphs about the welfare services available to them, about epileptic colonies, and about the problems of marriage and having children. The memorandum states that there are about 180,000 epileptics in England and Wales: probably about 70% of cases occur before the age of 20 and 85% before the age of 25.