ASSESSMENT OF DRUG THERAPY IN PARKINSONISM

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Until about 1946 the treatment of choice in Parkinsonism included the use of preparations of belladonna or stramonium. For a long period the "Bulgarian treatment" (including the use of *Atropa belladonna* harvested in Bulgaria), introduced by Ivan Reaff in 1926, was in vogue, and there has been considerable controversy over the relative merits of this method of treatment and analogous methods, which included the use of English belladonna (Neuwahl and Fenwick, 1937; Alcock and Carmichael, 1938; Hill, 1938). Vollmer (1940), however, showed that the effect of the Bulgarian treatment was due to the alkaloids in the belladonna and not to the dietetic regimen in this form of treatment.

In post-encephalitic Parkinsonism large doses of atropine are often required (Hall, 1937). Even in moderate doses side-effects are common and include excessive dryness of the mouth, loss of power of accommodation for near vision, intractable constipation, delirium, hallucinations, and hyperthermia. In order to minimize these side-effects there was a quest for new drugs which possess the central anticholinergic effect of atropine but minimal atropine-like effect on post-ganglionic fibres of the parasympathetic system.

Perhaps the most familiar synthetic drug is benzhexol ("artane"). Critchley (1958) reviewed the anti-Parkinson drugs, and these include ethopropazine ("lysivane"), bethtropine methanesulphonate ("cogentin"), caramiphen hydrochloride ("parpanit"), and orphenadrine hydrochloride ("disipal"). The clinical usefulness of orphenadrine has been reported by Gillhespy and Ratcliffe (1955), and from their experience they rate orphenadrine as the most effective drug, followed by ethopropazine and benzhexol (Gillhespy, 1956). A new drug was recently prepared by Sandoz Products Limited for use in Parkinsonism (designated "UK.738"). An attempt has been made to assess its value by comparing its effects with those of orphenadrine; a placebo was also used during this clinical trial.

Pharmacology

Orphenadrine.—This drug differs in chemical structure from diphenhydramine ("benadryl") solely by the possession of an ortho-methyl substituent on one of the benzene rings (see Fig. 1). This slight modification of the diphenhydramine molecule has reduced its antihistaminic activity and increased its atropine-like effect. The toxicity of orphenadrine is about the same as that of diphenhydramine; the LD_{50} in mice is approximately 25 mg./kg. intravenously. Orphenadrine is put up in yellowish tablets containing 50 mg. of the drug.

UK.738.—This is a synthetic tropine derivative—N-ethyl-nortropine benzhydryl ether hydrobromide (see Fig. 1). In experimental animals the peripheral anti-

cholinergic potency of UK.738 is only 7 to 20% that of atropine. UK.738 has also a marked antihistaminic activity. It prevents catalepsy produced in cats by the injection of chlorpromazine. Acute toxicity tests show that it is very safe; the LD_{50} in rats is 18.5 mg./kg. body weight by the intravenous route. UK.738 is available in the form of colourless tablets containing 2 mg. of the drug.

FIG. 1.—Chemical structure of (A) orphenadrine and (B) UK.738.

Method and Material

The subjects for these studies were among 67 patients in the two wards in Stobhill General Hospital, Glasgow, reserved for the care of patients suffering from post-encephalitic Parkinsonism. Most of them had been in hospital for over 10 years. Their ages ranged from 42 to 62 years.

In selecting patients for inclusion in groups for study the following circumstances were taken into account. A relatively small number (by comparison with the total number of patients available) could be studied in detail by a single observer at one time. Patients suffering from gross deformities of the hands were excluded because the ability to use at least one hand was necessary to allow measurement of the strength of the grip. Only those suffering from Parkinsonism of moderate severity were normally used; in none of the subjects was the disability rated as mild. One of the objectives was to determine the effect of drug therapy on the prevention of Parkinsonian crises—both oculogyric and sweating crises—and therefore 10 patients known to have suffered from such crises were purposely included in the series.

Two types of studies were carried out. The first was a double-blind trial to evaluate the effectiveness of UK.738 and orphenadrine. The second was an "acute" study designed to discover the length of time between taking the drug and the onset of therapeutic effects, and the timing of "peak" activity in the pharmacological effects produced.

Double-blind Trial

The patients were studied in two groups of 12 (six men and six women in each group). The number was kept small in order that the patients might be observed in greater detail. As orphenadrine and UK.738 tablets were of different colours, two placebos had to be used in order to eliminate the psychological effect known to be associated with the mere colour of a tablet.

Each drug (including the placebos) was given in a dosage of two tablets three times daily for three weeks.

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A master chart was prepared so that the drugs were given in a randomized fashion. This chart was given to the pharmacist, and he allocated at random various letters of the alphabet to each of the four types of tablet. Only the pharmacist had access to the key to the identity of the tablets. Every Saturday he sent to the wards individual packets of tablets for the patients. The label on each packet showed the patient's name, the date, and the direction to take two tablets three times daily. No other information was given.

In order to minimize the risks of precipitating withdrawal syndromes (when changing from an active substance to a placebo), a scheme was devised to effect overlapping of treatments at the week-end (Table I). Thus patients received on Saturday afternoon two tablets of the new set and on Sunday two tablets of the new set in the morning and evening, the set of tablets in current use being given only in the afternoon.

TABLE I.—Scheme Devised for Overlapping Treatment at the Week-end

Day	Tablet		
Friday	A	A	A
Saturday	A	B	A
Sunday	B	A	B
Monday	B	B	B

A=Tablet in use in the current week. B=Tablet for the next week. One week=Monday to Sunday inclusive.

From Monday to Friday the new set of tablets was given as usual (two tablets thrice daily). When, over a period of some days, a patient appeared to be lapsing into a state of serious disability while taking a particular type of tablet, the treatment was stopped and the pharmacist was asked to supply to the patient the next type of tablet on the chart. The tablets were given at definite times—namely, 8.45 a.m., 1 p.m., and 6 p.m.

The following simple quantitative measurements were made on Thursdays in the women's ward and on Fridays in the men's ward: these observations always began at 2.30 p.m.

1. *Measurement of Strength of Grip, Using a Mercury Column Dynamometer.*—A modified sphygmomanometer bag was connected to a mercury manometer and the bag was pumped up to a pressure of 60 mm. Hg. The patient was then instructed to squeeze the bag as forcibly as possible. The rise in the mercury column was noted, and this was taken as a measure of the strength of the grip. Three attempts were made by the patient, and the highest reading was recorded.

2. *Amount of Active and Passive Movement of Neck (full flexion: full extension).*—This was measured by asking the patient to perform full flexion and full extension of the cervical spine. When these movements were made the distance between the external occipital protuberance and the tip of the seventh cervical spine was measured. The difference between the two readings was regarded as the total flexion-extension movement of the neck.

3. *Ability to Write.*—This was tested by asking the patient to write his name (and in some cases the date) and finally to draw a circle and a spiral.

In some patients the time taken to walk a given distance was noted; and in a few others cinematographic records were made of their attempts at feeding, or while they tried to rise from a chair or tried to walk.

Tremor was observed and assessed visually, as the use of suitable apparatus was impracticable when large numbers of patients were being studied. Rigidity was measured by the observer's performing passive movements of the joints, especially the elbow-joint.

The nursing sister in charge of the patients recorded daily on the form provided the patient's ability to swallow (as good, fair, or poor), the external evidence of sialorrhoea (as +, ++, or +++), ability to dress, ability to walk, the number of falls per day, the number and severity of crises (oculogyric and sweating), the type of sleep (normal, noisy, or disturbed). In addition to the ward sister's records, I observed the patients daily; thus any significant changes were recorded independently. Soon after the trial began it was found that the form was not comprehensive enough: further data were required regarding the patient's ability to rise from a chair, ability to feed himself, and his mental state. I gave special consideration to these points. At the end of each week a summary of the patient's condition was recorded.

Most of the patients on this trial were already receiving benzhexol. Before the trial was begun all were placed on 15 mg. of benzhexol daily, and this was gradually reduced over a few weeks to 5 mg. daily.

Study to Demonstrate Duration and Type of Drug Action

Eleven patients were selected for this study. Later the number was reduced to eight, as two patients suffered from tremor severe enough to prevent their applying sustained pressure to the sphygmomanometer bag, and one patient was withdrawn because there was very little weakness of skeletal muscle.

Three types of active tablets were used: orphenadrine, benzhexol, and UK.738. The patients also received placebo tablets for control purposes.

Method.—This was an "acute" study. On the day before starting the experiment the patient received the last dose of his usual tablets at 12 noon; and at 6 p.m. he received the placebo. At 9.30 a.m. the next morning (the day of the experiment) measurements were made and recorded and the tablets were given with a copious draught of fluid. Measurements were then made hourly. Observations were made on the strength of the grip, the amount of active extension-flexion movement of the neck, the degree of rigidity and tremor (using the plus system), the amount of salivation (by observing the amount of dribbling and the degree of moistness of the mouth, especially the tongue), the heart rate (apex beat), and the size of the pupils. Estimation of the size of the pupils was later abandoned as it proved to be impracticable to standardize the conditions (amount of daylight, etc.) under which the observations were made. During the periods of observation the patients were seated in comfortable chairs and were instructed not to walk about the ward (except to use the lavatory). They were allowed to read and to have lunch at the usual time. They were not told what drugs they were having, but the objectives of the experiment were explained in general terms. In view of the "acute" nature of these experiments the observer was necessarily aware of the nature of the treatment.

Results in Double-blind Trial

In the final assessment the therapeutic value of each drug was graded as satisfactory, fair, or poor. The

results obtained for each type of tablet are shown in Table II: they were regarded as satisfactory in 15 of the patients who received orphenadrine, whereas U.K.738 produced a satisfactory result in only five patients; and none of the patients received any benefit from taking the placebo.

TABLE II.—Results of Double-blind Trial

Drug	Satisfactory	Fair	Poor
Orphenadrine	15	7	2
U.K.738	5	9	10
Placebo	0	0	24

Strength of Grip.—This was significantly increased in 15 patients when they were on active drugs compared with their performance on placebo tablets. Orphenadrine was usually the more effective treatment. The increase for both hands was 50% and 31.7% for orphenadrine and U.K.738 respectively (see Table III). It is of interest to note that the beneficial effect of these drugs on the power of grip was sometimes confined to one hand—usually on the weaker side.

TABLE III.—Strength of Grip and Range of Active Neck Movements in 15 Patients Showing Differences which are Highly Significant; Mean Values

Indices of Measurement	Placebo 1	U.K. 378	Diff. %	Placebo 2	Orphenadrine	Diff. %
Power of grip: Right hand ..	89.9	119	+32	95	137	+44
Left ..	85.1	111.1	+30.5	77.7	121.1	+56
Active neck movements (cm.) ..	3	4	+33	3.2	4.8	+50

Extension-flexion Movement of Neck.—The overall percentage increase in the active extension-flexion movement was 32.5 and 15% for orphenadrine and U.K.738 respectively (Table IV). When the comparison was restricted to the 15 patients who showed significant increase in the strength of the grip, the benefit amounted

to a 50% improvement after orphenadrine and 25% after U.K.738 (see Table III). The range of passive movement showed no significant difference between the

TABLE IV.—Strength of Grip and Range of Active Neck Movements in All Patients Studied; Mean Values

Indices of Measurement	Placebo 1	U.K. 378	Diff. %	Placebo 2	Orphenadrine	Diff. %
Power of grip: Right hand ..	124	144	+16	122	155	+27
Left ..	103.7	124	+20	99	125	+26
Active neck movements (cm.) ..	4	4.6	+15	4	5.3	+32.5

effects of the placebo and active drugs. This result is accounted for partly by the fact that assessments which depend on *passive* movement of the neck turned out to be unreliable under conditions of clinical practice, and this method is not recommended.

Writing.—Before the start of the clinical trial 20 patients were able to write without difficulty. During the investigation, however, it was found that five of them could no longer write because of the onset of the curious phenomenon of akinesia: at some point in the act of writing movement ceases, the pencil point remains in contact with the paper for an indefinite time—two minutes or more. In such circumstances the patient usually abandoned the attempt to continue writing. When the results of the clinical trial were reviewed it was found that this peculiar type of apraxia had occurred in these five patients while they had been receiving placebo tablets (Figs. 2 and 3) and in one patient while receiving U.K.738. Akinesia did not occur in any of the patients while they were under treatment with orphenadrine.

Patient's Ability to Feed Himself.—Sixteen patients were unable to feed themselves while they were taking placebo tablets. The disability was abolished in four of them by giving U.K.738, and in 12 who received orphenadrine.

Rigidity and Tremor.—Only 9 of the 24 patients (37.5%) benefited by an appreciable reduction in the degree of rigidity by giving potent drugs. In 10 (41.6%), however, the administration of placebo tablets resulted in gross aggravation of the tremor. Orphenadrine was more effective than U.K.738 in relieving rigidity and tremor.

Sweating.—There were individual patients for whom both U.K.738 and orphenadrine were effective in preventing excessive sweating. During this trial five patients who had hitherto not complained of excessive sweating were greatly inconvenienced by this disability while receiving only the placebo tablets. The excessive sweating was worse at night-time. Before the clinical trial two patients suffered from recurring and severe sweating

FIG. 2.—Patient's handwriting while on (A) Orphenadrine (100 mg. t.d.s.). (B) U.K.738 (4 mg. t.d.s.). (C) Placebo (2 tabs. t.d.s.).

FIG. 3.—Patient's handwriting while on (A) Orphenadrine (100 mg. t.d.s.). (B) U.K.738 (4 mg. t.d.s.). (C) Placebo (2 tabs. t.d.s.).

crises requiring treatment with intravenous sodium phenobarbitone (Onuaguluchi, 1961). One of them was free from sweating crises while receiving UK.738. Judged by the criteria listed above, UK.738 was the drug of choice for this patient: swallowing was regarded as good during this period, whereas it was graded as fair while he was receiving orphenadrine and poor when given only placebo tablets. This patient has accordingly been treated with UK.738 from the time of the clinical trial—a period of 10 months—and he has continued to do well. On one occasion, however, when UK.738 was temporarily out of stock, he was placed on orphenadrine 100 mg. thrice daily. He was not informed of the change of treatment. Within a few hours he was flushed and began to sweat profusely; and swallowing became much more difficult. In a few days treatment with UK.738 was resumed and there was immediate improvement.

Oculogyric Crisis.—Neither orphenadrine nor UK.738 seems to have any important effect on the frequency and severity of oculogyric crises. Only 2 of the 11 patients who suffer from oculogyric crises experienced a definite reduction in the frequency and perhaps in the severity of the crises when receiving orphenadrine.

Drowsiness.—Seven of the 24 patients were very drowsy while taking placebo tablets (an effect interpreted as the result of withdrawing active therapy) and two of them while taking UK.738. In one patient

receiving placebo tablets deterioration was complicated by catatonic stupor, and he had to be roused by repeated intramuscular injections of UK.738 in doses of 2 mg.

Mental Depression.—Signs of depression were noted in 15 out of 24 patients while they were receiving treatment with placebo tablets, and also in six patients during treatment with UK.738. None of the patients were depressed while under treatment with orphenadrine. On the contrary, orphenadrine often abolished depression rapidly and sometimes produced some degree of euphoria. One patient who liked knitting became tearful and lost interest in her pastime while she was on placebo therapy; but about 24 hours after receiving orphenadrine she said: "I feel like flying"; and this was in spite of the fact that at that time the physical accompaniments of the post-encephalitic syndrome were only slightly relieved.

Side-effects

Orphenadrine.—Two patients (men) complained of difficulty in starting the act of micturition. There was, however, no retention of urine. Three patients had involuntary jerky movements (myoclonus) of the limbs, but in two of them this effect passed off as treatment continued. One patient complained of dizziness about one to one and a half hours after taking the tablets. Another patient complained of nervousness ("jittery") about one hour after taking orphenadrine. Two patients had bleeding episodes during orphenadrine treatment. This

was possibly a coincidence. One of them suffered from a hiatus hernia with oesophageal ulcers. The other had acute erosion of the gastric mucosa with severe melaena; his condition necessitated partial gastrectomy, but the bleeding-point was not found at operation. In this patient haemorrhage began about 15 minutes after dental treatment (scaling and polishing). Five patients complained of a burning sensation in the throat, but this was not unbearable.

UK.738.—No side-effects were noted. The drowsiness seen in two patients might be regarded as a side-effect, but it was more probably a sign of inadequate drug therapy: the occurrence of drowsi-

FIGS. 4, 5, 6, and 7.—Effect of 100 mg. of orphenadrine, 10 mg. of benzhexol, 4 mg. of UK.738, and 2 placebo tablets on the strength of grip in eight patients.

FIG. 8.—Mean dynamometer readings in eight patients after administration of 100 mg. of orphenadrine, 10 mg. of benzhexol, 4 mg. of UK.738, and 2 placebo tablets. Each point represents mean of at least 12 tests.

ness was even greater in patients receiving placebo tablets.

Results in Second Study

Figs. 4, 5, 6, and 7 show that peak action (as judged by the effect on muscle power) occurred about two hours after orphenadrine, and two to three hours after benzhexol. It was comparatively difficult to define the period of maximum activity due to UK.738. Orphenadrine is more rapidly excreted from the body than is benzhexol as judged by the duration of therapeutic effects. Fig. 8 shows the mean dynamometer readings in eight patients after taking orphenadrine, benzhexol, UK.738, and placebo tablets. In the individual patient the effect of orphenadrine may last up to six hours, but the most effective period is from two to four hours after taking the tablet. In this type of acute experiment for the assessment of drug action extension-flexion movements proved to be unsatisfactory.

It appears that, of the three drugs, benzhexol has the greatest antisialogogue activity; orphenadrine is appreciably less active. In making such comparisons, however, it must be emphasized that they refer to quantities of the various drugs which have become standardized as the doses usually employed in clinical practice—namely, benzhexol 10 mg., orphenadrine 100 mg., and UK.738 4 mg.

Discussion

The results of the drug trial show that orphenadrine and UK.738 have useful pharmacodynamic actions in patients suffering from post-encephalitic Parkinsonism, but orphenadrine is much more effective therapeutically than UK.738.

One outstanding effect of orphenadrine is in the relief of depression. This confirms the views of Doshay and Constable (1957) and Robinson and Dick (1960). It is noteworthy that such disabilities as difficulty in swallowing, disturbances of speech, and incontinence of urine—which are regarded as contraindications to surgical operation on the globus pallidus and thalamus (Cooper *et al.*, 1958; Gillingham *et al.*, 1960)—may be greatly alleviated by adequate treatment with the potent drugs now available.

Methods of Assessment of Drug Therapy

The value of objective measurements in the assessment of drug therapy in Parkinsonism has been doubted (Schwab and Leigh, 1949; Gillhespy and Ratcliffe, 1956; Gillhespy, 1960). On the other hand, Berkowitz and

Alvermann (1952) thought that subjective evaluation was unreliable. Further, Eliasson and Tejning (1956) and Agate *et al.* (1956) were able to show that some quantitative measurements were reliable in the assessment of drug therapy.

The character of the patient's handwriting is commonly regarded as indicating the severity of tremor. In this study, however, in a large proportion of patients tremor was diminished or disappeared altogether from the hand in the act of writing, though the other hand continued to shake. Only in a small proportion of patients was it possible to demonstrate the degree of tremor by examining the handwriting (Fig. 9).

Other methods which have been used for the measurement of tremor include: (1) the method of Eliasson and Tejning (1956), and (2) the use of apparatus with electronic devices (Agate *et al.*, 1956; Wachs *et al.*, 1960).

Quantitative measurement of rigidity is still difficult, although the apparatus devised by Agate *et al.* (1956), Webster (1960), and Wachs *et al.* (1960) is said to be reliable. Wachs *et al.* (1960) found, however, that they obtained approximately the same degree of accuracy by clinical assessment (grading as +, ++, etc.).

Although James Parkinson (1817) regarded muscle weakness as one of the cardinal manifestations of "the shaking palsy," few modern writers stress this symptom. In the present series muscle power in the 24 patients studied was less than 50% of that of comparable normal people. These findings suggest that in assessing disability in Parkinsonism measurement of muscle power should be a routine procedure. The mercury dynamometer is preferred to the spring dynamometer as the former is less irksome to the patient. It should be noted that if a patient's muscle power is normal no increase in power can be expected from drug therapy.

The results of "acute" experimental studies serve to emphasize the importance of certain points in the design of clinical trials of drugs used to relieve Parkinsonism. Peak periods of pharmacological activity occur. It follows that in a clinical trial the time of administration of the drug and the period in which observations are made must be adhered to rigidly.

Two other important factors which are apt to affect the results of objective measurements are emotion and lack of familiarity with the procedures involved in the tests.

To eliminate these sources of fallacy, measurements should be made at set times and on specified days. Further, a period of two to three weeks should be devoted to ensuring that the patient fully understands what he has to do and that he performs the test adequately: he is then ready to take part in the clinical trial.

It is likely that the most reliable method for assessing the therapeutic value of a drug is to note the results of objective measurements and also the response of the patient subjectively. Although Schwab and Prichard (1951) and Moore (1951) tried to express their final results quantitatively, in individual patients it is hardly

FIG. 9.—Patient's handwriting while on (A) Orphenadrine (100 mg. t.d.s.). (B) UK.738 (4 mg. t.d.s.). (C) Placebo (2 tabs. t.d.s.).

possible to be more precise than to classify the therapeutic effect of a drug as satisfactory, fair, or poor.

Summary

The relative therapeutic value of orphenadrine and UK.738 was studied by means of a double-blind trial. Orphenadrine 100 mg. thrice daily produced satisfactory results in 15 out of 24 patients, and thus was much more effective than UK.738 4 mg. thrice daily.

Simple quantitative data were collected relating to strength of grip, range of active and passive movement of the neck, and the ability to write. It was shown that such quantitative tests and other objective evidence can be of value in assessing the therapeutic value of drugs used in Parkinsonism.

It was shown that after oral administration of orphenadrine peak activity occurred in about two hours whereas peak activity due to benzhexol occurred in two to three hours. It was not possible to demonstrate clearly a similar peak of activity for UK.738.

It follows that when the relative merits of drugs are being determined by objective testing due regard should be paid to the phase of maximal activity, otherwise the findings will not be comparable.

Fallacious results are also attributable to failure to appreciate the far-reaching effects of emotional upsets in these patients; and their lack of practice in experimental procedures also makes for unreliable data.

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TWO FURTHER CASES OF CURLING'S ULCER IN MAJOR BURNS IN CHILDREN

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The occurrence of ulceration of the intestinal tract as a complication of burns has long been recognized. Although this association had previously been described by Swan (1823), Dupuytren (1832), Cooper (1839), and Long (1840), the description by Curling in 1842 attracted greater attention, and the lesion has since that time usually been referred to as "Curling's ulcer." His comprehensive report of 10 cases concerned solitary ulcers of the duodenum only, but among more than 150 cases reported since that time there have been instances of oesophageal, gastric, duodenal, and ileal ulceration, sometimes multiple.

Case 1

A girl aged 12 was admitted to this hospital on December 31, 1960, with extensive clothing burns involving about 40% of the total body surface, mostly full-thickness loss. The areas affected were the lower part of the face, front of neck, the chest, upper two-thirds of the abdomen extending to the left half of the back, both upper limbs to the tips of the fingers, and half of the left thigh. There was no history of gastro-intestinal symptoms prior to the injury and no organic disease was evident.

The patient was resuscitated adequately by intravenous replacement therapy and given a course of intramuscular penicillin. Local treatment consisted of occlusive absorptive dressing and minimum debridement under an anaesthetic. Because of persistent pyrexia and urinary infection she was later given a course of oral chloramphenicol followed by sulphadimidine. From the beginning she was given a high-calorie, high-protein diet. Although her general condition remained satisfactory it was not possible to undertake grafting because of the presence of fat necrosis.

During the evening of February 9, 1961, she passed altered blood per rectum, followed an hour later by about 3 oz. (85 ml.) of blood clot. For the previous fortnight she had passed loose stools on a number of occasions, but culture failed to isolate any causative organisms. On February 10 she passed fresh blood and clots repeatedly per rectum, and next day haemorrhage became almost continuous. Despite repeated vomiting there was no haematemesis. Blood loss was replaced by continuous transfusion of whole blood amounting to 6 pints (3.4 litres) in 24 hours. Surgical intervention was not undertaken in view of grossly infected abdominal burns and the patient's poor general condition.

Sigmoidoscopy was performed to exclude pathological conditions in the lower large intestine, but it was negative. A blood count on February 11 gave the following results: haemoglobin 55% (8.1 g./100 ml.); total leucocytes 19,800/c.mm., polymorphs 84%, eosinophils 4%, monocytes 8%, metamyelocytes 4%; bleeding-time 80 seconds; clotting-time 1½ minutes; platelets 420,000/c.mm.

During the next two days the patient's condition improved slightly, and by February 13 the bleeding had stopped. Some of the healthy granulating areas were covered with autografts on February 14. Towards that evening the patient again passed fresh blood per rectum. Her condition rapidly deteriorated and she died shortly afterwards. Swabs from the burned areas taken a few days before death yielded