hour; haemoglobin, 12.9 g. per 100 ml.; W.B.C., 6,000 (normal differential); urine normal, no albumin or Bence Jones protein, no L.E. cells; W.R. negative; A.S.T., 75; D.A.T., 1:2; total protein, 7.3 g. % (albumin 4.1 g., globulin 3.2 g.); protein electrophoresis normal; no cryoglobulins or other abnormal protein, apart from fibrinogen, which was 616 mg. per 100 ml.; acid and alkaline phosphatase, normal; blood urea, normal; x-ray film of lumbar spine normal; x-ray film of the sinuses showed some opacity of the right antrum. He has been reviewed by Dr. Edwin Clark, who could find no neurological abnormality, and by Mr. Peter Martin, who could find no abnormality in the peripheral vessels. Over the past two years his symptoms have gradually subsided with reassurance and analgesics. The E.S.R. remains between 60 and 80 mm. in one hour, and he still has a high fibrinogen content of the blood.

Here one of the rarer collagen disorders, such as polyarteritis nodosa, was considered but not established.

Discussion

Although the E.S.R. is higher in women than in men and shows some day-to-day variation, particularly in women (Greisheimer, 1927) and quite apart from menstruation (Benson and Rogers, 1941) and pregnancy (Hamilton, 1953), in normal adults it does not exceed the value of 20 mm. in one hour, which we have taken as our upper limit of normal. As age increases, the sex difference is less obvious and the normal level tends to rise, showing a wider range (Reinbourne, 1952).

In group I 15 of our patients were over 60 years, 10 between 50 and 60, and six under 50. However, of those in whom we were unable to find an adequate explanation for the rise in E.S.R. only three were over 60, five being between 50 and 60, and three under 50. It does not seem likely to us that in the two cases (Nos. 13 and 17) of the oldest age group, who have remained in good health and have now been followed for three and two years respectively with the E.S.R. remaining between 20 and 30 mm. in one hour, the raised value is due solely to their age and random variation, since in a third similar case the E.S.R. settled under observation in five months. That it is important not to accept age as the reason for an E.S.R. between 20 and 30 until full investigations have been carried out is shown by other patients with a similar initial reading who have later developed obvious rheumatoid arthritis or been found to be suffering from such diseases as tuberculosis of the knee.

Out of 31 cases in group I a disease process was diagnosed in 20, although in some it did not become obvious for a period of time. These results are similar to those of Cutler (1932), although the actual final diagnosis differed from his, since his series showed a high incidence of chest diseases. Similarly, our results should not be strictly compared with those of Liljestrand (Liljestrand and Olhagen, 1955; Olhagen and Liljestrand, 1955), since our cases were selected by referral to a rheumatology clinic, whereas his came from a general medical clinic. However, we agree with him that carcinoma as a cause of this high E.S.R. is rare. In his series of 37 cases with a raised E.S.R. of obscure cause, no final explanation could be given in 21 cases, and these were all women. In our similar group of 11 cases, 8 were women, and the prognosis does not seem at this distance to be bad.

The high incidence of rheumatoid arthritis in patients of advancing years and the difficulty in establishing its diagnosis are of particular interest. Clinically, a fairly confident diagnosis was made in 14 of the patients, though only eight fulfilled the criteria described earlier. This problem has been discussed by Bagratuni (1956), who described what he calls "anarthritic rheumatoid disease." The entity, described sometimes as the fibrositic prodromal phase of rheumatoid arthritis, is well known (Ropes and Bauer, 1945); but whereas in his cases there was little evidence to suggest joint involvement, in all except one of ours there was ultimately definite evidence of arthritis. The value of a rise in E.S.R. in differentiating early arthritis from fibrositic pains has also been stressed by Slocumb (1936), and can be confirmed by us in cases not included in this series.

Summary

An unexplained rise of the sedimentation rate above 20 mm. in one hour was found in 51 new patients out of approximately 900 attending a rheumatology clinic over a period of 3½ years.

Thirty-one of these remained high over one month, and eight of them have developed typical rheumatoid arthritis, while six are probably suffering from this disorder. In eleven others no cause for the raised E.S.R. could be found, and their general health has remained good. In five it returned to normal within one year, while in six it has remained high.

The presence of a high E.S.R. should lead to a careful assessment and investigation of the patient, but, particularly in older people, it is not necessarily associated with a bad prognosis.

REFERENCES

- Bagratuni, L. (1956). *Lancet*, 2, 694.
Benson, L., and Rogers, E. J. (1941). *J. Lab. clin. Med.*, 26, 987.
Cutler, J. W. (1932). *Amer. J. med. Sci.*, 183, 643.
Greisheimer, E. M. (1927). *Ibid.*, 174, 338.
Ham, T. H., and Curtis, F. C. (1938). *Medicine (Baltimore)*, 17, 447.
Hamilton, G. M. (1953). *J. Obstet. Gynaec. Brit. Emp.*, 60, 409.
Liljestrand, A., and Olhagen, B. (1955). *Acta med. scand.*, 151, 425.
Olhagen, B., and Liljestrand, A. (1955). *Ibid.*, 151, 441.
Reinbourne, E. T. (1952). *Hum. Biol.*, 24, 57.
Romanus, T. (1944). *Acta med. scand.*, 117, 535.
Ropes, M. W., and Bauer, W. (1945). *New Engl. J. Med.*, 233, 592, 618.
Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Proc. Soc. exp. Biol. (N.Y.)*, 68, 1.
Slocumb, C. H. (1936). *J. Lab. clin. Med.*, 22, 56.
Sykes, W. O. (1948). *Brit. med. J.*, 1, 393.
Westergren, A. (1926). *Amer. Rev. Tuberc.*, 14, 97.

THERAPEUTIC TRIAL OF AZACYCLONOL

BY

S. GRAY, M.B., D.P.M.

AND

A. D. FORREST, M.B., M.R.C.P., D.P.M.

Royal Edinburgh Hospital for Mental and Nervous Disorders

Azacyclonol ("frenquel") has been the subject of pharmacological study in America since 1954. Chemically it is related to pipradol hydrochloride ("meratran"), which is alpha-(2-piperidyl) benzhydrol hydrochloride, while azacyclonol is the gamma isomer, alpha-(4-piperidyl) benzhydrol hydrochloride. Azacyclonol has been shown to protect subjects against the experimental psychosis induced by lysergic acid diethylamide (Fabing, 1955). The central effect appears to differ from that of reserpine and chlorpromazine, which act on the mesodiencephalic activating system. Azacyclonol again differs in its effects from pipradol hydrochloride, which is believed to be a central stimulant without concomitant autonomic effects (Rinaldi, Rudy, and Himwich, 1955). Favourable clinical responses to azacyclonol in various psychotic states have been reported (Fabing and Hawkins, 1955; Cohen and Parlour, 1956; Browne, 1956). The best responses were obtained in toxic hallucinatory states (Proctor and Odland, 1956), whereas the results in schizophrenia have been somewhat variable. This paper presents the results of treatment with azacyclonol in 56 patients with schizophrenia and two patients with alcoholic hallucinatory states.

Controlled Trial

Forty patients (20 female and 20 male) were the subjects of a controlled trial. The mean age of the women was 51, with a range of 28-75 years. The mean age of the men was 38, with a range of 18-63 years. For the whole group the length of stay in hospital ranged from 6 months to 27 years, the mean being 10 years. The diagnosis in each case was schizophrenia (hebephrenia 20, paranoid schizophrenia 19, catatonic schizophrenia 1). The only criteria for admission to the trial were that the diagnosis was schizophrenia and that the patient appeared to be subject to hallucinatory experience. Thirty patients were able to discuss these experiences at interview. We decided that it would be unreasonable to withdraw any drugs the patients were already receiving, provided that there had been no change in their mental condition attributable to these drugs in the four weeks prior to the onset of the trial. In fact, 17 patients were receiving reserpine and 6 were receiving chlorpromazine. These drugs were continued unchanged during the course of the trial. On the other hand, we decided that if a patient's clinical condition indicated E.C.T., then that patient would have to be withdrawn from the trial. One man was withdrawn for this reason after three days. Two women were withdrawn after five days, as they refused to take the tablets. These three patients were replaced, the replacements being "scored" as if they had begun the trial on the proper date.

Allocation to Groups.—With the use of random numbers (taken from Bradford Hill's *Principles of Medical Statistics*) the patients were allocated to four groups of 10. The pharmacist had meanwhile made up the azacyclonol (20 mg.) and placebo tablets into bottles labelled A and B. Group 1 had five weeks on A, then five weeks on B. Group 2 went through the reverse sequence. Group 3 had tablet A and Group 4 had tablet B for the whole period of 10 weeks. The dose was 1 tablet three times a day. The nature of tablets A and B was known only to the pharmacist until the trial was completed.

Method of Assessment.—All the patients were interviewed before the trial. Further interviews were held at 3, 5, 7, and 10 weeks, each observer seeing the same patients throughout. At each interview information regarding hallucinations, delusions, and range of activity was recorded on a prepared card. In addition a clinical rating—that is, improved, no change, or worse—was entered on the card. During the period of the trial (10 weeks) white blood cell counts were made at fortnightly intervals on each patient.

Toxicity Study

Four patients were studied outside the controlled trial. These patients were kept in bed and were given azacyclonol, 60 mg. daily. Temperature, pulse, and blood pressure (supine position, mean of two readings) were recorded twice daily. Liver-function tests, estimation of blood urea nitrogen, and W.B.C. counts were performed on the day before and on the second and ninth days of the trial. Fluid intake and output were measured over 24-hour periods before the trial and during the sixth day and night. The patients were examined for evidence of skin rashes before and on the ninth day of the trial.

Clinical Trial

Apart from the controlled trial, 18 patients have been treated with azacyclonol over periods ranging from four weeks to three months. The dosage has varied from 60 to 180 mg. daily. The mean age of this group is 30, with a range of 18 to 42 years. The diagnoses were schizophrenia (16 patients) and alcoholic hallucinatory states (2 patients). The length of stay in hospital ranged from one day to 10 years, the mean being 18 months.

Results of Controlled Trial

In accordance with the method described above it was possible to compare the changes in clinical rating during 30 "azacyclonol periods" and 30 "placebo periods" in the 40 patients under study. The results are shown in Table I.

TABLE I.—Controlled Trial (40 Patients)

Treatment	No. of Patients	No Change	Improved	Worse	Total
Azacyclonol	30	19 (63.4%)	10 (33.3%)	1 (3.3%)	30
Placebo	30	15 (50%)	14 (47.7%)	1 (3.3%)	30
Total	60	34 (56.7%)	24 (40%)	2 (3.3%)	60

$$\chi^2 = 0.556. P < 0.5 > 0.2.$$

Two points of interest emerge from these rather surprising results. Firstly, a comparison of the results in patients receiving other drugs with those receiving azacyclonol alone. There were 11 patients who received azacyclonol alone, four of these showing improvement. Of the 19 who received other drugs in addition to azacyclonol, six showed improvement. The difference is not significant. Secondly, in the male patients there were some obvious changes in activity during the trial—that is, activity as exemplified in the interview situation; for instance, the patients were more talkative and restless. In fact, one of them was rated as worse on account of more obvious disturbance in thinking and perception. The changes in the 20 male patients are shown in Table II.

TABLE II.—Controlled Trial (20 Male Patients)

Treatment	No. of Patients	Activity Rating		
		More Active	No Change	Total
Azacyclonol	15	5	10	15
Placebo	15	0	15	15
Total	30	5	25	30

$$\chi^2 = 2. P < 0.2 > 0.1$$

As regards alteration in hallucinatory experience, evidence is available about 30 patients (involving 47 periods of observation) who were willing and able to discuss their hallucinatory experiences at interview. Every patient had auditory hallucinations, but three patients had visual hallucinations in addition. The results are shown in Table III. Two patients claimed that their visual hallucinations stopped entirely; as regards the auditory hallucinations, our impression was that, although there was a diminution in intensity and frequency in some patients, in none of the patients did the experience cease entirely.

TABLE III.—Controlled Trial (30 Patients)

Treatment	Changes in Hallucinations		
	No Change	Improved	Total
Azacyclonol	19	5	24
Placebo	20	3	23
Total	39	8	47

Results of Toxicity Studies

The W.B.C. counts made at fortnightly intervals during the controlled trial revealed no significant alteration during either the azacyclonol or the placebo periods. There was no observed alteration in temperature, pulse, blood pressure,

TABLE IV.—Fluid Balance and Blood Urea Nitrogen Before and During Treatment with Azacyclonol

Patient	Pre-trial				Azacyclonol			
	In-take (oz.)	Day Urine (oz.)	Night Urine (oz.)	B.U.N. (mg./100 ml.)	In-take (oz.)	Day Urine	Night Urine	B.U.N. (mg./100 ml.)
M. McC.	44	53 (1012)	22 (1024)	11.6	54	51 (1014)	27 (1022)	16.2
W. S. . .	40	31 (1012)	24 (1014)	24.5	64	46 (—)	59 (1014)	55.0
J. McG.	42	29 (1018)	16 (1022)	16.2	48	54 (—)	14 (1024)	9.3
J. C. . .	52	16 (1022)	16 (1024)	12.9	48	36 (—)	19 (1020)	10.6

The figures in parentheses refer to the specific gravity of the urine samples.

W.B.C. counts, or liver-function tests in the four patients subjected to detailed study. Two patients showed an increase in blood urea nitrogen; in both cases there was an associated alteration in fluid balance with a tendency to an increased volume of night urine (see Table IV). None of these patients showed any abnormal urinary constituents at this time. One patient (W. S.) had previously been suspected of having renal damage, but investigations had been negative. Subsequent to this trial he was found to have evidence of renal changes compatible with a diagnosis of chronic nephritis, although he was at the time symptom-free.

Results of Clinical Trial

These patients were seen by one of us (A. D. F.) before treatment was begun, and thereafter at intervals of three weeks. The changes in "clinical rating" and in hallucinatory experience are shown in Table V.

TABLE V.—*Clinical Trial: Changes in Clinical Rating and Hallucinations (18 Patients)*

	No Change	Improved	Worse	Total
Clinical rating	5	13	—	18
Hallucinations	10	8	—	18
Total	15	21	—	36

It should be emphasized that in four patients the hallucinatory experience stopped completely. Two of these later received E.C.T., but in each case there had been a reduction in hallucinatory experience before the E.C.T. was begun. Three patients were on reserpine and three on chlorpromazine when the azacyclonol was introduced. These drugs were continued as in the controlled trial. These patients did rather worse than the group as a whole—that is, only two out of the six improved. Of the 13 patients who improved on azacyclonol, four have since been discharged and two have left hospital for a period of leave. We are maintaining these patients on smaller doses of azacyclonol (40–60 mg. daily).

Illustrative Cases

Brief case histories of two patients who have left hospital are reported.

*Case 1 (Diagnosis: Alcoholic Hallucinoses).—*A 41-year-old man, who gave a past history of alcoholism, had been admitted to hospital on three previous occasions, but had never before experienced hallucinations. The family history was negative. Three weeks before admission he began drinking heavily, but stopped suddenly after four days. Three days later he began to have auditory and visual hallucinations, and these persisted until his admission. Physical examination on admission revealed no evidence of hepatic enlargement or of peripheral neuritis. Mentally he was tense, suspicious, and intensely hallucinated. The auditory hallucinations were heard as the voices of friends and of the medical staff. He spent most of his time answering these "voices." He also saw, in the garden, visions of St. Francis of Assisi and McDonald of the Isles. There were no animal hallucinations. He was given parenteral vitamin B for one week and was then put on azacyclonol, 60 mg. t.d.s. His hallucinatory experience was greatly reduced by the end of three weeks. The visual hallucinations had stopped and the auditory hallucinations had diminished in intensity so that he now regarded them as "unreal," and was not obliged to answer them. Thereafter he was given E.C.T. (six treatments), and was symptom-free when he left hospital. When seen a month later he was found to be in good health.

*Case 2 (Diagnosis: Schizophrenia).—*A 19-year-old youth had a 10-day history, starting with a "blackout" at work. He then began to express strange ideas—for instance, that his drink at work was being tampered with. He became very argumentative; and on the night before admission he was very disturbed, walking up and down the street in his

pyjamas. The patient's mother suffered from ideas of persecution and one brother was an epileptic. Physical examination on admission revealed no abnormality. An E.E.G. showed nothing conclusive, although there was some slow activity in the right temporal region. Mentally he was perplexed and restless. He was quizzical in manner and uncooperative in a humorous sort of way. He was auditorily hallucinated and felt he was being influenced by some agency outside himself. He was put on azacyclonol, 100 mg. t.d.s., but became very excited, and the drug was stopped after 48 hours. For a week he was treated with chlorpromazine (100 mg. t.d.s.); his behaviour became more controlled, but his hallucinations and feelings of being influenced persisted unchanged. Then the chlorpromazine was stopped and he was given azacyclonol, 60 mg. t.d.s. Three weeks later his hallucinations and feelings of influence had ceased. He was much more alert and no longer perplexed. He gave in his notice a week later and was discharged from hospital.

Discussion

This trial has served to emphasize some important factors involved in the evaluation of new drugs in psychiatry. Firstly, chronic schizophrenics improve as a result of the additional attention involved in any therapeutic trial. Secondly, psychiatric assessment when applied to minor degrees of change in mental state is not very precise, although probably more informative than any other techniques available. Many of the drugs at present used in chronic schizophrenia produce quite clear effects—for instance, the weight and behaviour changes of reserpine—and trials of such drugs are not really "blind." This trial was "blind": the nursing staff were unable to distinguish the active preparation from the placebo. Another point is that improvement in chronic schizophrenics treated with new drugs has usually implied greater conformity with the hospital regime. Such an effect is beneficial from the point of view of the hospital and of the patient, but is of little help in evaluating the effect of the drug on the disease process itself. Azacyclonol seems to have no sedative effect, and any improvement in behaviour appears to be secondary to the effects of the drug on the disturbances of thought and perception as seen in schizophrenia and some acute toxic psychoses. In fact, it is our impression that azacyclonol acts partly as a cerebral stimulant.

Feldman (1957), in a comparative study of various ataractic drugs, noted "turbulence" as a side-effect of treatment with azacyclonol in 10.7% of patients (the comparable figure for reserpine was 6.5%). "Turbulence" is here used, we understand, to describe the restless, active stage first reported by Barsa and Kline (1955) in regard to reserpine. In an attempt to check whether azacyclonol has any effect on normal people we gave 40 mg. (2 tablets) and placebo (2 tablets) on consecutive evenings to six normal volunteers (the drug order was randomized). Three reported no effects, two reported restlessness with azacyclonol, while one reported overactivity on both occasions, although more pronounced on the evening when azacyclonol was taken. These results, although quite inconclusive, are in line with the observations reported in the controlled trial.

Azacyclonol appears to have been the subject of the usual cycle of early enthusiasm and later criticism, although in this case there has been a fair degree of consistency among the reports in the literature. The earlier reports defined schizophrenia as the main indication, and reported good results in chronic as well as acute cases (Fabing and Hawkins, 1955; Rinaldi *et al.*, 1955). Later papers reported good results in acute schizophrenic reactions and in toxic hallucinatory states (Cohen and Parlour, 1956; Proctor and Odland, 1956). The most recent paper (Forster and Henderson, 1957) reports a trial in 18 chronic schizophrenics in which benefit was observed in only one patient. The dosage used in these various trials varied from 60 to 400 mg. daily.

The controlled trial reported here is open to several criticisms. The patients were all chronic and the dosage

was small (60 mg. daily). More important was an intrinsic defect in our method of assessment, which resulted in the apparent superiority of the placebo to the drug. We think that the explanation lies in the stimulant effect of the drug (equivalent to Feldman's observation of "turbulence"), which made the patient's mental disturbance more obvious in the interview situation. That this can also be true of reserpine we can confirm from personal experience. But, even allowing for these criticisms of our method, our results do suggest that azacyclonol is unlikely to be a very useful drug in the treatment of chronic schizophrenia.

The results of our clinical trial seem promising enough to warrant a more extensive trial of the drug in cases of acute schizophrenia and alcoholic hallucinosis. One difficulty in evaluating drug therapy of such acute cases is that a proportion remit spontaneously and no precise criteria are yet available for indicating which patients should have azacyclonol. Some later American papers—for example, Cohen and Parlour (1956)—suggested that azacyclonol had very little anti-hallucinatory effect. Our experience suggests that hallucinatory experience of recent onset, whether schizophrenic or toxic, is an indication for treatment with azacyclonol.

The only report of any toxic side-effect of azacyclonol is contained in the paper by Forster and Henderson (1957). They found elevation of the non-protein nitrogen in 11 out of 18 patients treated with azacyclonol. We have found similar changes in two patients. One of these was later shown to have signs indicative of chronic nephritis. However, the blood urea nitrogen did fall later to near normal levels when the dose of azacyclonol was reduced.

Summary

We have described a controlled trial of azacyclonol in 40 chronic schizophrenic patients. The results suggest that azacyclonol is not going to be of great value in the treatment of this type of patient.

We subsequently treated 18 patients (16 schizophrenics, 2 toxic hallucinatory states) with azacyclonol. The illness was of more recent onset in these patients than in those involved in the controlled trial: 13 patients improved and 6 have since left hospital.

Our clinical impression is that azacyclonol has a central stimulant action and that part of the poor result of the drug in the controlled trial was due to the masking effects of excitement and overactivity.

The only toxic effect observed was a rise of blood urea nitrogen in two patients out of a group of four who were subjected to detailed study. In one patient the elevation was not of significant degree, and in the other patient evidence of chronic nephritis was later established.

We thank Dr. T. A. Munro, physician-superintendent, for his advice and encouragement; Dr. D. Crombie and his staff for laboratory investigations; the nursing and secretarial staff for help in running the trial; and Mr. R. W. Richards, of Riker Laboratories, who kindly supplied us with frenquel and placebo tablets.

REFERENCES

- Barsa, J. A., and Kline, N. S. (1955). *J. Amer. med. Ass.*, **158**, 110.
 Browne, N. L. M. (1956). *J. nerv. ment. Dis.*, **123**, 130.
 Cohen, S., and Parlour, R. R. (1956). *J. Amer. med. Ass.*, **162**, 948.
 Fabing, H. D. (1955). *Science*, **121**, 208.
 — and Hawkins, J. R. (1955). *Dis. nerv. Syst.*, **16**, 329.
 Feldman, P. E. (1957). *Amer. J. Psychiat.*, **113**, 589.
 Forster, W., and Henderson, A. L. (1957). *Canad. med. Ass. J.*, **76**, 97.
 Proctor, R. C., and Odland, T. (1956). *Dis. nerv. Syst.*, **17**, 25.
 Rinaldi, F., Rudy, L. H., and Himwich, H. E. (1955). *Amer. J. Psychiat.*, **112**, 343.

Plans of the new building for the National Library of Medicine, Washington, provide for a five-story building with accommodation for 1,290,000 volumes (a little more than double the present number).

TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH ORAL PHENOXYMETHYLPENICILLIN

BY

GERALD SANDLER, M.B., M.R.C.P.

Medical Registrar, Royal Infirmary, Sheffield

AND

PETER A. PARISH, M.B., Ch.B.

House-Physician, Royal Infirmary, Sheffield

From the Department of Pharmacology and Therapeutics,
University of Sheffield and Royal Infirmary, Sheffield

With the preparation of phenoxymethylpenicillin in 1947 by Behrens and his co-workers an important stable oral form of penicillin was introduced. Effective absorption and therapeutic blood levels have been reported by many observers (Wright *et al.*, 1955; Martin *et al.*, 1955; Rinsler and Cunliffe, 1956; Holborrow *et al.*, 1956). A number of diseases have been successfully treated with the drug, including pulmonary infections (Hart *et al.*, 1956), beta-haemolytic streptococcal infections (Breese and Disney, 1956), dental abscesses (Hermann, 1955), and gonorrhoeal urethritis (Marmell and Prigot, 1956; Love and Weir, 1956). In subacute bacterial endocarditis clinical experience with phenoxymethylpenicillin is more limited. A cautious approach is necessary in treating a condition which a relatively short time ago was associated with such a high mortality, and which responds so favourably in most cases to parenteral penicillin. This disease can be successfully treated by oral phenoxymethylpenicillin, however, as is shown by the two cases described, in one of which it was the sole form of antibiotic therapy.

Case 1

A female domestic worker aged 37 presented with a two-weeks history of headache, malaise, loss of energy, sore throat, joint pains, anorexia, vomiting, and fever. She gave a past history of acute rheumatic fever at the age of 24, when she was confined to bed for four months.

On examination she was pyrexial and had dental caries. Her fingers were clubbed. She had a sinus tachycardia, the characteristic murmurs of mitral stenosis and regurgitation, and moderate cardiomegaly, but no evidence of congestive cardiac failure. Her spleen was not palpable.

Investigations.—Haemoglobin, 8.1 g./100 ml.; leucocyte count, 12,000/c.mm.; E.S.R. (Westergren), 65 mm. in the first hour; microscopy of the urine showed red blood cells; x-ray examination of the chest showed a mitral cardiac configuration with increased pulmonary vascular markings; electrocardiogram showed notched P waves. Six blood cultures were negative, and this may have been due to a three-day course of sulphonamides just before admission to hospital, but the seventh yielded a growth of *Streptococcus viridans*.

Treatment was begun with intramuscular injections of crystalline penicillin, 500,000 units six-hourly, and this dose was gradually increased over two weeks to 3,000,000 units six-hourly in view of the persistence of pyrexia and elevation of the E.S.R.

Soon after parenteral therapy was started local pain and tenderness occurred at the injection sites, and was associated with progressively increasing bruising and oedema. The temperature remained high and a two-weeks course of streptomycin, 1 g. intramuscularly daily, was given, but with no effect on the raised temperature. At this time, because