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MALARIAL THERAPY IN THE NEPHROTIC SYNDROME

BY

A. G. SHAPER, M.B., Ch.B., D.T.M.&H.

From the Tropical Diseases Centre, Sefton General
Hospital, Liverpool

The effect of infection on the nephrotic syndrome has long been known, and massive diuresis with disappearance of oedema and great diminution in proteinuria has been observed to follow a variety of agents, including measles, chicken-pox, pneumonia, infusions of plasma or dextran, large doses of urea, or corticotrophin. The occasional dramatic response elicited by one or other of these agents has led several physicians to the use of malaria, as this was an acute fever that could be easily induced and readily controlled. The reasons for using malaria as a therapeutic agent have varied from that of Gairdner (1952), who considered that there was sufficient clinical evidence for the empirical use of acute febrile infections, to that of Byrne (1952), who holds that the response shown is due to stimulation of the acute defence phase of the adaptation syndrome of Selye. In conditions such as the nephrotic syndrome, where treatment after treatment may follow with no sign of symptomatic relief, "it behoves the physician to attempt in turn those agents which are known to have initiated remissions, as, in the earliest stages at least, this condition may be reversible" (Gairdner, 1952).

There is still much discussion and dispute regarding the nomenclature and classification of renal disease, and for the purpose of this report the term "nephrotic syndrome" is used. This term (Squire, 1953) is applied to those cases with oedema, proteinuria, and hypoalbuminaemia, but without hypertension, nitrogen retention, or electrolyte disorder, and without an appreciable excess of red blood cells in the urine. The majority of cases in this series can be regarded as Ellis Type II nephritis, but as this description implies the presence of particular pathological changes, and as in so many patients with renal disease the essential pathology is not known, it is justifiable to use a wider descriptive term.

Malarial therapy has been used over a period of several years in the Tropical Diseases Centre, using strains of benign tertian malaria, and occasionally *Plasmodium ovale*, in patients with the nephrotic syndrome. In some it was used as a primary procedure, in others as a last resort after many varied and unsuccessful forms of therapy. Brief clinical reports are given of seven patients in whom the infection had been sufficiently severe and long-continued to regard them as having undergone "malarial therapy." The methods of infection and the management of induced malaria are dealt with by Shute (1952).

Method

Selection of Cases.—There are no precise indications for the use of malarial therapy. It is usually reserved for patients with a nephrotic syndrome which has failed to respond to more conservative forms of treatment.

Duration of Treatment.—The patient should be allowed to have as many rigors as he is capable of withstanding. The indications for cutting short the treatment are a marked deterioration in general condition, sustained fever, or severe oliguria.

Interruption of Quotidian Fever.—In most cases the fever initially assumes a quotidian periodicity but then settles down to a tertian periodicity. In some the quotidian fever persists, and in order to procure relief from the daily paroxysm a single dose of bismuth sodium thioglycollate ("thio-bismol"), 0.2 g. intramuscularly, may be given. This will usually cause the fever to become tertian in periodicity. Alternatively, small doses of quinine may be given for one day. This may stop the fever, but it will relapse in a week or two.

Method of Eradication of Malarial Infection.—In all patients the fever can rapidly be terminated by giving full doses of chloroquine, mepacrine, or quinine for a few days. In those infected by blood inoculation from other patients suffering from malaria this will eradicate the infection. In patients infected by parenteral injection of sporozoites, or by feeding infected anopheline mosquitoes, the treatment must be continued with a ten-day course of pamaquin, 10 mg. three times a day (Adams and Macgrath, 1953), to sterilize the exo-erythrocytic cycle of parasite development which results from this mode of infection, or a relapse will occur.

Case 1

The patient, a man aged 29, had a history of oedema of the lower limbs and puffiness of the face, associated with some lumbar backache over a period of six weeks. On admission there was pitting oedema of the lower limbs of moderate severity and the urine contained a moderate amount of protein, granular casts, and a few red blood cells. The blood pressure was 130/80 mm. Hg; the retinal vessels were normal. Other findings were: haemoglobin, 100%; serum proteins, 2.45 g.%, with reversal of the albumin/globulin ratio; blood urea, 28 mg. per 100 ml. and serum cholesterol, 262 mg. per 100 ml. The patient was observed for three months, during which time he was treated with a high-protein salt-free diet; although the serum protein level rose to 5.67 g.% the oedema gradually increased in severity until it was generalized and extreme.

Malarial Therapy.—He was infected with a strain of *P. vivax*, using infected anopheline mosquitoes. After a short initial period of irregular fever the temperature assumed the usual tertian periodicity. After four pyrexial episodes associated with severe rigors, his oedema had further increased, so that even in the sitting position it extended to his cervical region. There was a marked reduction in urinary output, accompanied by gross haematuria. The fever was stopped with chloroquine.

Four days after the subsidence of fever his urinary output increased to 80–100 fl. oz. (2,270–2,840 ml.) daily, on an intake of 40–50 fl. oz. (1,140–1,420 ml.). This diuresis continued for four weeks, leaving only minor residual oedema of the legs and sacrum. The diuresis then ceased, and over the next two weeks there was a slight increase in the oedema. As a relapse had not occurred the patient was reinfected with benign tertian malaria, and developed a gross haematuria, followed after 24 hours by a temperature rise and a rigor. After four pyrexial episodes, the haematuria was still present and the oedema was more marked. The fever was interrupted for one week with bismuth sodium thioglycollate, and its reappearance was again preceded by gross haematuria, followed by increasing oedema. After a further five pyrexial episodes the fever was arrested with chloroquine. During the next eleven days

there was a moderate diuresis, the urinary output exceeding fluid intake by an average of 10 fl. oz. (284 ml.) daily. At this stage the general condition was very good, there was minimal oedema of the ankles on walking, and the urine showed a trace of protein but no blood or casts.

Frequent estimations of the blood urea during the course of the malaria showed fluctuations up to 50 mg. per 100 ml. The serum protein fell to 3.77 g.% in the first week of fever, rising after two weeks to 5.02 g.% and falling to 4.7 g.% at the termination of the infection six weeks after commencement. There was constant reversal of the A/G ratio.

Six months later the patient was readmitted, having suffered a relapse of his initial sporozoite infection. This had again been heralded by haematuria, followed two days later by fever. In the interim he had remained extremely well, with only slight swelling of the ankles on moderate exercise—for example, dancing. On examination he had no oedema, and his blood pressure was 110/65 mm. Hg. The serum proteins were 6.79 g.% (albumin 2.54 g., globulin 4.25 g.), and the blood urea 25 mg. per 100 ml.; the urine contained a moderate amount of protein, a few granular casts, and a small number of red blood cells. During the ten days over which the patient was observed during treatment with quinine and pamaquin his urinary output exceeded his intake by an average of 19 fl. oz. (540 ml.) daily.

Subsequent History.—Eighteen months after the start of malarial treatment the patient remained well and was carrying on his employment as a travelling salesman. He felt tired occasionally, but had no swelling of the legs even on continued exercise. There was no sacral or limb oedema, the fundi were normal, and the blood pressure was 130/90 mm. Hg. The urine contained a small amount of protein, a few granular casts, and some red blood cells. The serum proteins were 7.1 g.% (albumin 4.04 g., globulin 3.06 g.); serum cholesterol, 274 mg. per 100 ml.; and blood urea, 25 mg. per 100 ml.

Case 2

The patient, a man aged 47, had suffered from swelling of the lower limbs, which slowly increased over the 20 months prior to his admission. On admission there was marked pitting oedema of the lower limbs, scrotum, and sacrum, with ascites and oedema of the lower abdominal wall. The blood pressure was 180/95 mm. Hg; blood urea 54 mg. per 100 ml.; and serum cholesterol, 199 mg. per 100 ml.; the urine contained a trace of protein, with granular casts and a few red blood cells. Abdominal paracentesis was done on several occasions.

Malarial Therapy.—The patient was infected intravenously with sporozoites of benign tertian malaria, and became febrile after 12 days; he subsequently had eight severe paroxysms with rigors. During this period his oedema and ascites increased, his haemoglobin level dropped from 85% to 37%, and there was a marked reduction in his urinary output. The blood urea rose to 60 mg. per 100 ml., and on account of his poor general condition the malaria was stopped with chloroquine. The plasma proteins after malaria therapy were 4 g.% (albumin 2.53 g., globulin 1.47 g.). In the next four weeks no diuresis occurred and abdominal paracentesis had to be repeated on several occasions. The patient returned home and remained in bed, taking a self-prescribed remedy of lemon-juice, tartaric acid, and magnesium sulphate. After three weeks at home he noticed an obvious increase in his daily urinary output, and one week later his sporozoite-induced malaria relapsed. He continued to have paroxysms for three weeks before he returned to hospital. He then had no ascites or oedema of the abdominal wall, and there was only minimal pitting oedema of the lower limbs. After two further rigors in hospital the malarial infection was eradicated with a course of quinine and pamaquin. The blood pressure was 130/80 mm. Hg; blood urea, 60 mg. per 100 ml.; and the urine showed a heavy albumin deposit, with granular casts and occasional red blood cells. No estimation of serum proteins was made.

Subsequent History.—One year later he was back at work as a lorry driver. He had had no swelling of his legs, but there was slight breathlessness on exertion. There was no anaemia or oedema of his lower limbs, and his fundi were normal. The blood pressure was 180/100 mm. Hg, and the urine contained a large amount of protein but no casts or blood cells. Serum proteins were 5.4 g.% (albumin 4.2 g., globulin 1.2 g.); serum cholesterol, 187 mg. per 100 ml.; and blood urea, 138 mg. per 100 ml.

Case 3

A man aged 52 complained of increasing swelling of the lower limbs, puffiness of the face, and dyspnoea on exertion over the two months prior to admission. On admission there was moderately severe oedema of the lower limbs and sacrum, the blood pressure was 160/95 mm. Hg and the urine contained protein and hyaline and granular casts. The serum proteins were 4.56 g., with a reversed A/G ratio; blood urea, 32 mg. per 100 ml. and serum cholesterol, 250 mg. per 100 ml.

Malarial Therapy.—The patient was infected with benign tertian malaria by intravenous blood inoculation; after seven days his temperature rose sharply, and he had malarial paroxysms on 14 successive days. A small dose of quinine was given, and this produced an apyrexial period of seven days, which was followed by a further five rigors before the malaria was arrested therapeutically. Over this period the haemoglobin dropped from 85% to 30%, the blood urea rose to 54 mg. per 100 ml., and the serum proteins fell to 4.04 g.% (albumin 1.41 g., globulin 2.63 g.).

During the 24 days of malarial treatment the urinary output varied from 20 to 50 fl. oz. (570 to 1,420 ml.), but at no time did the output exceed the fluid intake. Two days after the malaria had been treated a diuresis began; this persisted for three weeks, during which the patient remained in hospital. The average daily excess of output over intake was 20 fl. oz. (570 ml.), no allowance being made in this calculation for the fluid loss via skin, respiration, and stools. On discharge the patient still had a moderate degree of pitting oedema of the lower limbs, but the diuresis did not seem to be diminishing. The urine still contained protein and casts.

Subsequent History.—For one year after discharge he led a sedentary life and had not returned to work. He remained dyspnoeic on exertion, and noticed slight swelling of his ankles on moderate exercise, but there had been no marked oedema. On examination his general condition was good, but there was a small left pleural effusion. His blood pressure was 200/120 mm. Hg; blood urea, 64 mg. per 100 ml.; serum cholesterol, 350 mg. per 100 ml.; and serum proteins, 5.21 g.% (albumin 2.9 g., globulin 2.31 g.). The urine contained a moderate amount of protein, granular and epithelial casts, and a few red blood cells.

Case 4

This patient, a youth of 18, was admitted three months after the gradual onset of swelling of the legs and face, associated with a feeling of tiredness. He had been treated with antibiotics, mersalyl, ion-exchange resins, and dietary measures, all without success. On admission there was marked ascites with oedema of the lower limbs, sacrum, genitalia, and arms, and in addition there were bilateral pleural effusions. The blood pressure was 135/90 mm. Hg; serum proteins, 4.18 g.% (albumin 1.11 g., globulin 3.07 g.); serum cholesterol, 395 mg. per 100 ml.; and blood urea 68 mg. per 100 ml. The urine contained protein, many granular casts, a few hyaline casts, and a few red blood cells.

Malarial Therapy.—He was infected with *P. vivax* by intravenous blood inoculation, and within a period of four days (April 26) developed gross haematuria, followed by pyrexia, and a sudden increase in the oedema. He then suffered nine malarial paroxysms, and during this period showed no tendency to diuresis. His urinary output fell

gradually to about 15 fl. oz. (420 ml.) daily, his haemoglobin dropped from 80% to 30%, and there was a marked deterioration in his general condition. The malaria was interrupted by subcurative quinine treatment (May 11), and an abdominal paracentesis relieved his distress. Twelve days (May 23) later fever recommenced, and he suffered a further nine paroxysms. There was no diuresis during this time, and further abdominal paracentesis was required. The malarial infection was then eradicated with chloroquine (June 4). During the next three months no diuresis occurred. Details of the blood chemistry are set out in the Table.

Blood Chemistry at Intervals During the Malarial Fever in Case 4

	April 29	May 4	May 9	May 14	May 24	June 1	July 31
Total protein (g.%)	4.91	4.46	3.79	4.30	3.46	3.26	2.96
Albumin (g.%)	1.61	2.24	1.46	1.63	1.45	1.41	1.52
Globulin (g.%)	3.92	2.22	2.46	2.67	2.01	1.85	1.44
Blood urea (mg. per 100 ml.)	80	68	60	61	46	53	51
Cholesterol (mg. per 100 ml.)							543

Subsequent History.—Over a period of four months following malarial therapy he remained on a high-protein diet with gradual decrease in the oedema. He has been discharged from hospital with pitting oedema of a moderate degree.

Case 5

A woman aged 25 had noticed a gradual swelling of the lower limbs, with progressive increase in weight over a period of eight months. On admission she had gross oedema of the lower limbs and thighs. The blood pressure was 140/95 mm. Hg, and the urine contained protein, granular casts, and an occasional red blood corpuscle. The blood urea was 32 mg. per 100 ml.; cholesterol, 696 mg. per 100 ml.; and total serum proteins 5.01 g. %.

Malarial Therapy.—The patient was infected by blood inoculation with benign tertian malaria, and after ten days' incubation had nine paroxysms. There was marked constitutional upset with an increase in the proteinuria and she became very distressed. The malarial infection was stopped. She was observed for a further two months, during which time there was no diuresis or improvement in her clinical condition. At this stage the serum proteins were 4.9 g. %, the blood urea was 27 mg. per 100 ml., and the serum cholesterol had dropped to 350 mg. per 100 ml. Two months later the oedema had increased considerably, and the serum cholesterol had risen to 530 mg. per 100 ml. The patient has been watched for a further two years; although there has been a gradual improvement in her physical condition, she still has protein and casts in the urine. Her blood pressure has remained at normal levels, and she has slight oedema on exercise only.

Case 6

The patient, a woman aged 52, was admitted with oedema of the lower limbs, abdominal wall, and arms, and some puffiness of the face of two weeks' duration. There had been no preceding acute infection, and she was considered to be suffering from an exacerbation of a latent nephritis. On admission she had bilateral pleural effusions, the blood pressure was 180/100 mm. Hg, and the urine contained protein, granular casts, and a few red blood cells. The serum proteins were 4.56 g. %; blood urea, 50 mg. per 100 ml.; and serum cholesterol 127 mg. per 100 ml. There was no response to infusions of dextran or to high-protein salt-free diet.

Malarial Therapy.—The patient was infected with benign tertian malaria by intravenous blood inoculation, and became pyrexial after two weeks; she was allowed to have five paroxysms of fever. She was very exhausted and cyanosed during each attack, so the fever was discontinued by chloroquine treatment. Four days later there was a slight increase in the urinary output, but this moderate diuresis

was sustained for only 48 hours, and it made no clinical difference to her oedema. Her condition one month after malarial therapy was slightly worse than initially, her protein level was 5.46 g. %, and her blood urea was 52 mg. per 100 ml. Two months later she died from pulmonary oedema and generalized oedema due to chronic nephritis.

Case 7

A woman aged 22 had suffered a gradual onset of generalized oedema, thought to be due to Ellis Type II nephritis, for which she had been treated for nine months. On admission she had marked oedema of the lower limbs, gross ascites and oedema of the abdominal wall, and a large right pleural effusion. The blood pressure was 120/90 mm. Hg, the urine contained protein, granular and epithelial casts, and red blood cells. The blood urea was 34 mg. per 100 ml. and the serum cholesterol 214 mg. per 100 ml. She was observed for a further four months on various treatments, during which time there was a gradual deterioration in her condition, with increase in the oedema.

Malarial Therapy.—The patient was infected by blood inoculation with *P. ovale*, and after eight days she became pyrexial. There was a sudden and marked increase in the amount of oedema and ascites, and she thereafter suffered seven very mild paroxysms, with only minor fever, and at times no rigors. At no period did she show any clinical signs of improvement in her renal condition, and there was no diuresis. Her haemoglobin fell from 80% to 50%, her blood urea rose to 52 mg. per 100 ml., and repeated abdominal paracenteses were necessary. The malaria remitted spontaneously at this stage, and she remained afebrile for two weeks. She then relapsed, but, apart from two or three minor pyrexial episodes, the presence of malaria parasites in the blood was not associated with any marked constitutional effects. The infection was eradicated with proguanil. One month later her condition was still unchanged, so she was reinfected, this time with benign tertian malaria by intravenous blood inoculation. After two minor pyrexial episodes her physical condition began to deteriorate rapidly, so the infection was stopped. Two weeks later she died.

Comment

Of these seven nephrotic patients treated by malarial infection three have had a marked remission of symptoms. Case 1 showed a most dramatic response, which has been well sustained. Cases 2 and 3 have been free of symptoms for a year, and the former, despite a high blood urea level, is working full time and feels well. The improvement shown in Case 4 cannot be closely associated with the malarial therapy—it is probably due to the high-protein diet—while the improvement in Case 5 cannot be associated with malarial therapy. The last two patients (Cases 6 and 7) died of their basic condition, but as they were both severely ill and the malarial paroxysms were poor or curtailed in number it would be unfair to say that malarial therapy had failed. Since the aetiology of the renal condition in these seven patients is not known, one can but speculate on the mechanisms by which the improvement has been initiated in Cases 1, 2, and 3. These cases do, however, encourage the continued trial of malarial therapy in this type of renal disease.

In Cases 1 and 4 the onset of malarial fever was preceded by macroscopic haematuria; this may have been an indication of increased damage to the renal tissues. In malaria the serum proteins, particularly the serum albumin, are usually reduced and there may be considerable increase in the serum globulin. Blood urea levels were not raised to any significant extent, despite pre-existing renal damage. The behaviour of serum cholesterol is extremely important, as it has been postulated by Gairdner that the beneficial effects of malarial therapy may be due to reduction in the serum cholesterol level. Most workers have reported a reduction in the cholesterol concentration at some time during the course of the malarial attack. Crespin and Zaky (1919) showed that the level fell to below normal values

just before the onset of a paroxysm, became normal or slightly raised in the pyrexial period, and fell to normal in the latent periods between attacks. Fairley and Bromfield (1933) in cases of induced malaria, showed that although hypocholesterolaemia occurred in some cases of well-established malaria, the levels rose to normal upon the termination of the attack.

A point in assessing the effects of malarial therapy is to preclude any diuretic action on the part of the drugs used to terminate or eradicate the infection. To this end fluid-balance charts were examined from 20 National Service men admitted to the Tropical Diseases Centre suffering from acute benign tertian malaria. They were all treated with chloroquine, quinine, and pamaquin; in none of them was any significant or prolonged diuresis noted as a consequence. It was therefore concluded that if a diuresis did occur following the use of antimalarial drugs in patients with the nephrotic syndrome it was in no way related to the action of these drugs.

Summary

Seven cases of the "nephrotic syndrome" have been treated by malarial therapy.

Three cases have had marked remission of symptoms lasting over one year.

It is considered that there is an indication for the continued use of malarial treatment in nephrotic patients who do not respond to more conservative treatment.

I wish to thank Dr. A. R. D. Adams, Professor B. G. Macgregor, and Dr. C. S. McKendrick, under whose care these patients were admitted. I am grateful to Dr. A. R. D. Adams for his advice and assistance in preparing this paper.

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Medical Memoranda

A Fatal Case of Pernicious Anaemia Associated with Chloramphenicol Treatment

An increasing number of deaths from aplastic anaemia after treatment with chloramphenicol are being reported. A case of pernicious anaemia is described below which, on account of numerous intercurrent infections, was treated with two courses of chloramphenicol. Subsequently the patient developed an aplastic anaemia and died five months after the second course.

CASE HISTORY

A married woman aged 65 was admitted to hospital on August 1, 1952, with a six-months history of dyspnoea on exertion, swelling of the ankles, and increasing pallor.

On examination there was extreme pallor with a lemon-yellow tint. The tongue was smooth and she had a pyrexia of 99 to 100° F. (37.2 to 37.8° C.). There were signs of congestive cardiac failure, with normal heart sounds, and a blood pressure of 130/50 mm. Hg. No abnormalities were found in the chest, abdomen, or central nervous system. A catheter specimen of urine showed a heavy pyuria with a growth of *Bact. coli* organisms. A blood count gave: Hb, 2.5 g.% (14.8 g.=100%); red cells, 570,000 per c.mm.; C.I., 1.5; M.C.V., 123 cubic μ ; M.C.H.C., 35.7%; white cells, 4,950 per c.mm. (polymorphs 57%, lymphocytes 43%). Nucleated red cells were seen in the peripheral blood films.

The serum bilirubin was 0.9 mg. per 100 ml. Histamine-fast achlorhydria was present. Iliac bone puncture revealed a megaloblastic marrow. A diagnosis of pernicious anaemia was made on the above findings.

After an initial transfusion of $\frac{1}{2}$ pint (280 ml.) of packed red cells, treatment with vitamin B₁₂ was begun on August 5. For the first fortnight she was given 100 μ g. weekly, and thereafter until she left hospital on September 10 she had 100 μ g. fortnightly. A maximum reticulocyte response of 11% occurred five days after the onset of specific treatment. Although the response seemed a low one in view of the initial red cell count, it is known that intercurrent infections will considerably modify the reticulocyte peak, and at this stage the patient had a heavy urinary infection. Furthermore, a reticulocyte crisis may be reduced if specific treatment is preceded, as in this case, by a blood transfusion. The blood count on August 23 was: Hb, 6.5 g.%; red cells, 2,220,000 per c.mm.; C.I., 1. On August 25 it was: Hb, 10.7 g.%; red cells, 3,820,000 per c.mm.; C.I., 0.9; white cells, 22,400 per c.mm. (polymorphs 82%). By September 16, when she left hospital, the blood count was: Hb, 11.7 g.%; red cells, 4,100,000 per c.mm.; C.I., 0.96.

In the meantime, starting on August 3, a five-day course of "sulphatriad" (8 g.) was given for the urinary infection. By August 9 the urine was sterile. On the 10th a ten-day course of 19 g. of chloramphenicol was started on account of a left basal pneumonia. By the end of August frequency and dysuria had returned, and a further catheter specimen on September 8 showed a heavy growth of *Bact. coli*, which *in vitro* tests showed to be sensitive only to chloramphenicol. A further course of 9 g. of this drug was therefore given between September 10 and 15. The urine again became sterile, but before leaving hospital a further reinfection with *Bact. coli* was treated with 12 g. of chlor-tetracycline. During all this time the blood urea was never higher than 50 mg. per 100 ml.

On September 16 the patient left hospital symptom-free on a maintenance dose of 100 μ g. of vitamin B₁₂ fortnightly. She was next seen on November 28, when the blood count was: Hb, 6.5 g.%; red cells, 2,360,000 per c.mm.; C.I., 0.90. At this stage the amount of vitamin B₁₂ was increased to 100 μ g. twice weekly. A fortnight later the blood count was approximately unchanged, but by December 19 it had fallen to: Hb, 5.6 g.%; red cells, 2,100,000 per c.mm.; platelets, 62,000 per c.mm. She had had numerous epistaxes during the previous three weeks.

She was readmitted on December 20 and given a small blood transfusion. Also liver treatment consisting of "hepastab," 2 ml. on alternate days, was started. On January 2, 1953, a blood count showed Hb, 6.8 g.%; red cells, 2,350,000 per c.mm.; C.I., 1; white cells, 2,600 per c.mm. (polymorphs 37%, lymphocytes 63%). On the same day an iliac puncture suggested an aplastic anaemia. The total nucleated count was 7,600 per c.mm. and myeloid hypoplasia together with a relative erythroid hyperplasia was present, giving a total myeloid-erythroid ratio of 2:1 respectively. Ten days later, in spite of a further transfusion, the blood count was Hb, 7.04 g.%; red cells, 2,270,000 per c.mm.; C.I., 1; platelets, 41,000 per c.mm. Thereafter she developed numerous petechial haemorrhages and died on February 19.

Necropsy.—The body was that of a thin woman with numerous petechial haemorrhages in the skin and subcutaneous tissue. The lungs were pale but otherwise normal. The myocardium showed fatty degeneration and numerous haemorrhages. The gastro-intestinal mucous membrane was congested and haemorrhagic, the stomach otherwise appearing normal. The liver showed fatty degeneration, and the spleen numerous old infarctions. The kidneys showed bilateral arteriosclerosis with disruption of the renal pattern. The ureters and bladder were normal. The bone marrow of the sternum and iliac bones and femur were pale and fatty. The pancreas and adrenals appeared normal.

Histology.—There was fatty degeneration of the liver, and the splenic pulp showed poorly defined Malpighian