

Observations on the polyneuropathy and the disordered pyruvate metabolism induced by nitrofurazone in cases of sleeping sickness due to "Trypanosoma rhodesiense"

Autor(en): **Robertson, D.H.H. / Knight, R.H.**

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Observations on the polyneuropathy and the disordered pyruvate metabolism induced by nitrofurazone in cases of sleeping sickness due to *Trypanosoma rhodesiense*.

By D. H. H. ROBERTSON and R. H. KNIGHT.

Reference has already been made in the literature to trials with nitrofurazone (5-nitro-2-furfuraldehyde semicarbazone) in sleeping sickness (EVENS et al., 1957; APTED, 1960) and to the need for an effective therapeutic agent in the treatment of subjects with infections refractory to melarsoprol. The ultimate results of nitrofurazone in the treatment of advanced late-stage sleeping sickness due to *Trypanosoma rhodesiense* are irregular and unpredictable (APTED, 1960; ROBERTSON, 1961 a) but because good results may be sometimes obtained in patients with an otherwise hopeless prognosis, nitrofurazone merits further investigation. FIERLAFYN (1960) has reported favourably on the initial results of nitrofurazone treatment in *T. gambiense* infections but long term results have not yet been obtained.

Nitrofurazone has, however, serious disadvantages: it has a generally reversible degenerative effect on the seminiferous tubules (WILDERMUTH, 1955; HALTIWANGER, 1961) and causes haemolytic anaemia in persons with a deficiency of erythrocyte glucose-6-phosphate dehydrogenase (ROBERTSON, 1961 a, 1961 b).

A further disadvantage is the occurrence of a polyneuropathy (WILDERMUTH, 1955; EVENS et al., 1957; ROBERTSON, 1959; APTED, 1960). The experimental work showing that nitrofurazone causes a disorder of pyruvate metabolism (PAUL et al., 1952; PAUL et al., 1954; PAUL et al., 1956) and the clinical features of the induced polyneuropathy (ROBERTSON, 1959) suggested that nitrofurazone causes an ultimate biochemical and neurological lesion similar to that found in beriberi. The investigations of JOINER et al. (1950), the discussion by THOMPSON and CUMINGS (1957) on the aetiology of polyneuropathy, and the observations already mentioned led us to make a study of the nitrofurazone-induced polyneuropathy in cases of sleeping sickness, the results of which are presented here.

Materials and Methods.

Smith, Kline and French Laboratories Ltd. kindly supplied nitrofurazone as uncoated tablets which were stored in the dark (see SPROSS, 1953). The oral dose of nitrofurazone was 0.5 g given thrice daily at 8.00, 12.00 and 16.00 hrs.

Thiamine when given specifically was given as Benerva (Roche). Vitamin B group therapy was given as Becosym (Roche) which contained thiamine, riboflavin, nicotinamide and pyridoxine.

Calcium pantothenate (D-pantothenic acid, calcium salt, Laboratory Reagent of the British Drug Houses Ltd.) when given orally was dissolved in water immediately before administration. Injection of calcium pantothenate (Adelaide Child/Hosp. The Extra Pharmacopoeia [1958], 1, 159) contained 50 mg per ml.

Suramin was given as Antrypol (Imperial Chemical Industries Ltd.); melarsoprol as Melarsen Oxide/BAL (May and Baker Ltd.) was given intravenously (IV) as a 3.6 per cent (w/v) solution in propylene glycol.

Cerebrospinal fluid (C.S.F.) examinations are abbreviated thus: C.S.F.: leucocytes per cmm; mg protein per 100 ml (SICARD and CANTALOUBE method, 1916); trypanosomes per cmm, or if found only in the centrifuged deposit +, and if not found 0.

If trypanosomes were not found during the leucocyte count, using a Fuchs Rosenthal cytometer, 8-10 ml of C.S.F. were centrifuged for 10 minutes at 2,500-3,000 r.p.m. (750-1000 g) and the deposit was examined for trypanosomes. The degree of abundance of trypanosomes in thick blood films is assessed arbitrarily (0, +, ++, +++).

Pyruvate was estimated by a modification of the method of FRIEDEMANN and HAUGEN (1943). Solutions were filtered by passing them through a Pasteur pipette containing a loosely-fitting cotton wool plug. Duplicate determinations were carried out on the protein-free filtrate of the blood and each day on which estimations were made duplicate determinations were also carried out on solutions of lithium pyruvate containing the equivalent of 1 mg and 2 mg pyruvic acid per 100 ml solution.

Blood, taken into a 5 ml syringe previously wetted with a heparin solution, was ejected into a test tube. Two millilitres of blood were measured by pipette and blown into a screw-cap bottle containing 10 ml 10 per cent (w/v) trichloroacetic acid. The pipette was allowed to drain and touched on the side of the bottle. The mixture was then shaken vigorously and centrifuged and the supernatant filtered. Four millilitres of the filtrate were pipetted into a boiling tube and warmed in a water bath at 25°C for 10 minutes after which 1 ml of a freshly prepared solution of 2,4-dinitrophenylhydrazine (100 mg in 100 ml 2 N-HCl) was added. The mixture was allowed to react for 5 minutes after which time 4 ml of toluene were added and the tube and contents shaken mechanically for 2 minutes. The toluene layer was removed and filtered and 3 ml were transferred to a boiling tube containing 6 ml of 10 per cent (w/v) Na₂CO₃. The mixture was shaken for 2 minutes after which the aqueous layer was removed and filtered. Five millilitres of the filtrate were mixed with 5 ml of 1.5 N-NaOH and after ten minutes the optical density of the solution was measured at 520 mμ against water in a Unicam SP 1400 absorptiometer.

Pyruvate metabolism tests were carried out in most cases in a manner similar to that used by JOINER et al. (1950). After the patient had fasted overnight, 50 g of glucose were given orally in about 200 ml of water at 0 min. and again at 30 min., while venous blood was taken with minimal constriction for pyruvate determinations at 0, 60, 90, 120 and 150 min. A modified pyruvate metabolism test was carried out on one of the patients (Case No. 6) and is described later.

Patients Treated.

Brief case histories only are given as the important features of the clinical reactions are illustrated in the Figures and described under the heading *Clinical and Laboratory Findings*.

No. 1. Male fisherman aged about 35 years with intermediate-stage trypanosomiasis. Presenting features: weakness; apyrexial (after previous suramin treatment); pains in the limbs for 3 weeks.

Thick blood film, trypanosomes +++.
Gland-juice, not examined.
C.S.F.: 46; 25; 0.

No. 2. Male fisherman aged about 30 years with early-stage trypanosomiasis. Presenting features: trypanosome chancre on the face; hyperalgesia of the muscles; tachycardia.

Thick blood film, trypanosomes +++.
Gland-juice, trypanosomes +++.
C.S.F.: 1; 18; 0.

No. 3. Male cultivator aged about 25 years with early-stage trypanosomiasis. Presenting features: trypanosome chancre on the right calf; fever.

Thick blood film, trypanosomes ++.
Gland-juice, trypanosomes ++.
C.S.F.: 3; 20; 0.

No. 4. Male fisherman aged about 30 years with early-stage trypanosomiasis. Presenting features: pyrexia; aching pains; malaise. While awaiting transfer to hospital suramin 1.0 g IV had been given and as this was not known at the time a lumbar puncture was carried out on reaching hospital; soon after he became collapsed.

Thick blood film, trypanosomes +++.
Gland-juice, trypanosomes +++.
C.S.F.: less than 1; 22; 0.

Legend for Figures 1 a, 2 a, 3 a, 4 a, 5 a, 6 a, 7 a.

The clinical course of the syndrome observed during and after nitrofurazone treatment. *F*: fasting concentration, *M*: maximum concentration of pyruvic acid in the blood during the course of the metabolism tests.

The severity of the peripheral limb pain of polyneuropathy is represented in the diagrams in the following grades:

- 0 = no pain while in hospital. Most subjects had some pain when walking barefoot on stony ground but this was discounted in the assessment shown in the figures.
- 1 = complaint of some pain.
- 2 = pain causing continual discomfort.
- 3 = pain causing continual severe discomfort, especially if causing insomnia.

No qualitative differentiation of type of pain has been made in the numerical grading, but this has been attempted in the text. The absence, or degree of severity of other signs and symptoms are assessed in degrees from 0 to 5 in the figures. A qualitative definition of paraesthesiae has not been attempted.

Cerebrospinal fluid (C.S.F.) examinations are abbreviated thus: C.S.F.: leucocytes per cmm, mg protein per 100 ml (SICARD & CANTALOUPE, 1916); trypanosomes per cmm, or if found only in the centrifuged deposit +, and if not found 0.

Legend for figures 1 b, 2 b, 3 b, 4 b, 5 b, 6 b, 7 b.

The pyruvate metabolism tests. At time 0 min, 50 g of glucose was given by mouth.

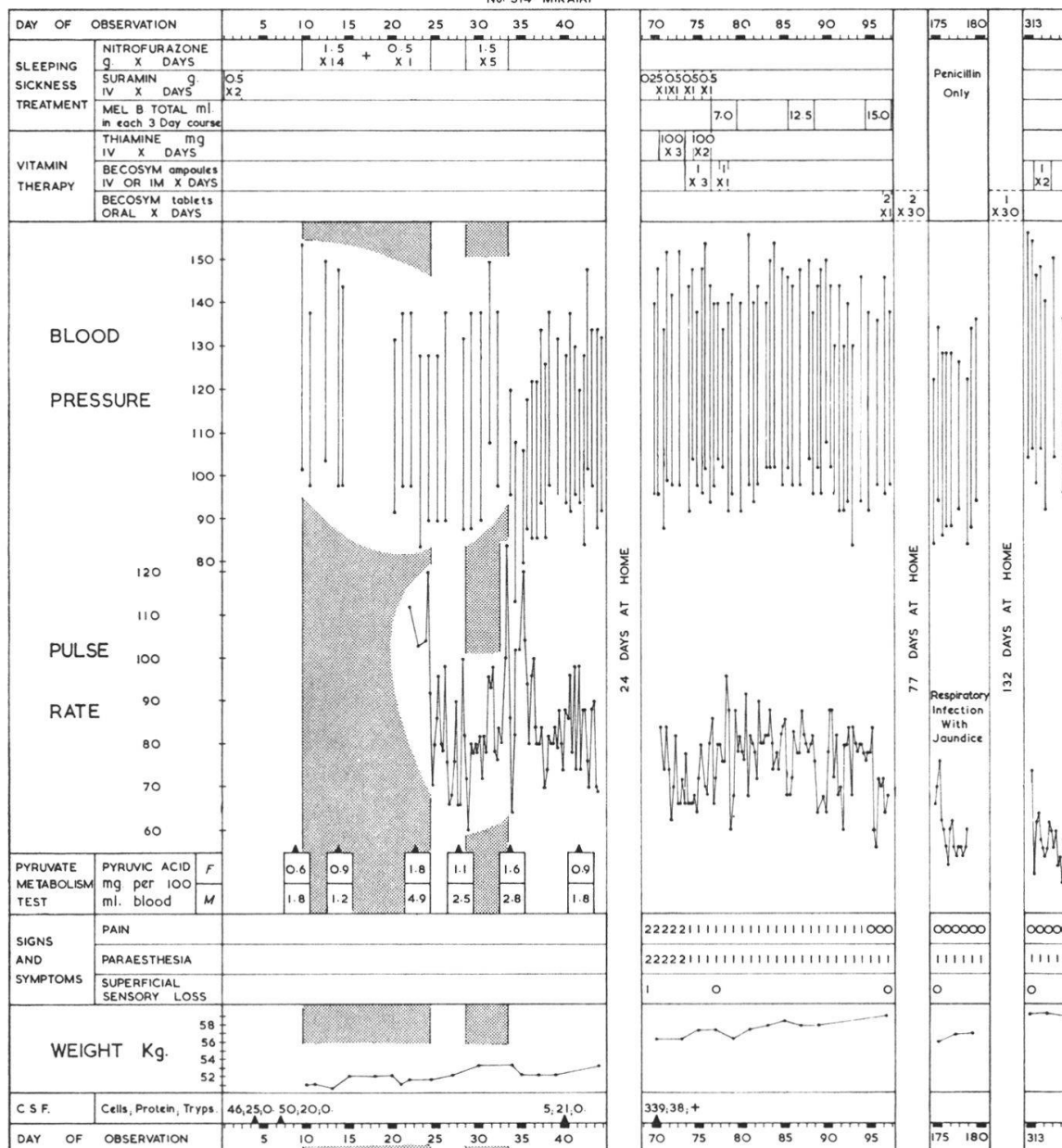


Fig. 1 a. Case No. 1.

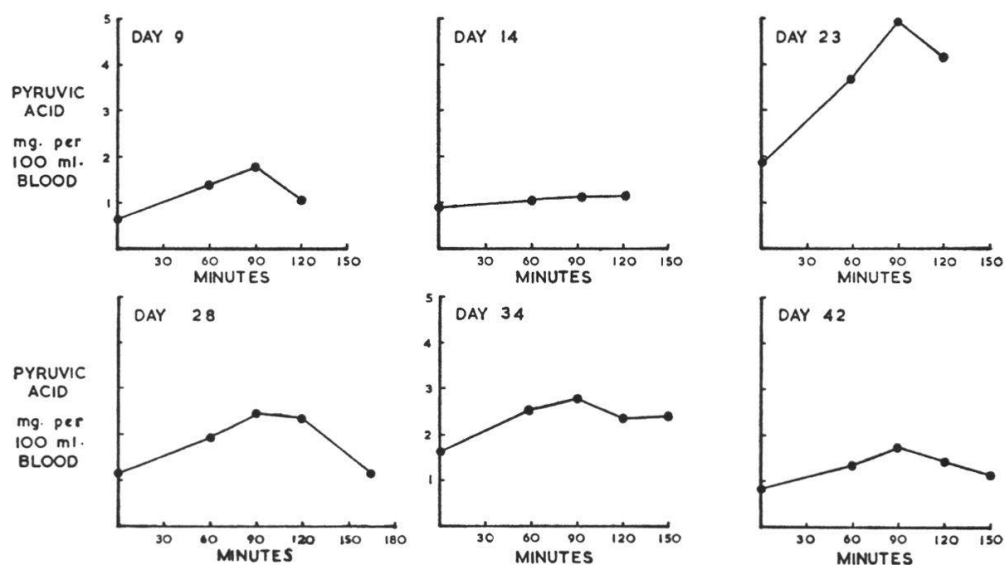


Fig. 1 b. Case No. 1.

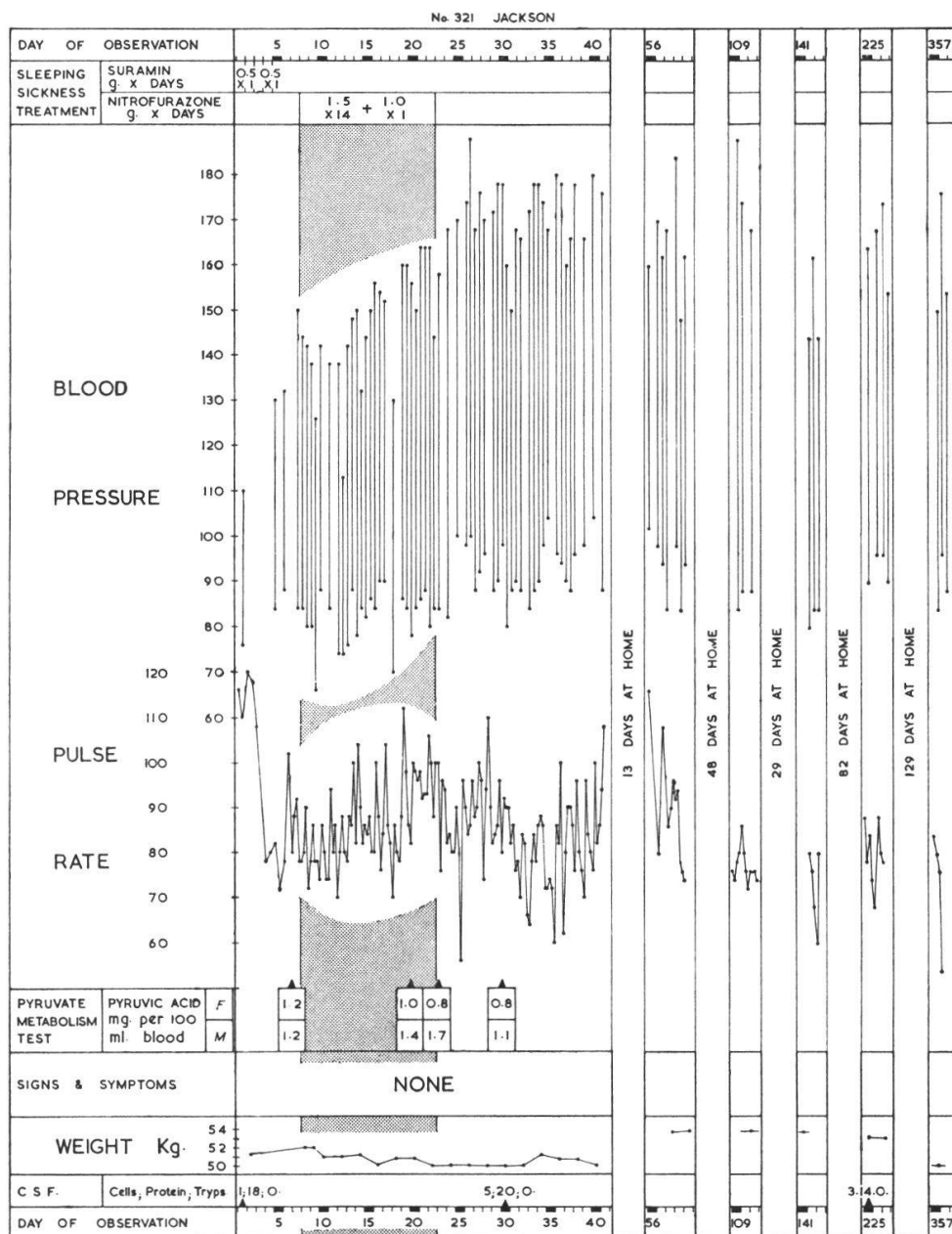


Fig. 2 a. Case No. 2.

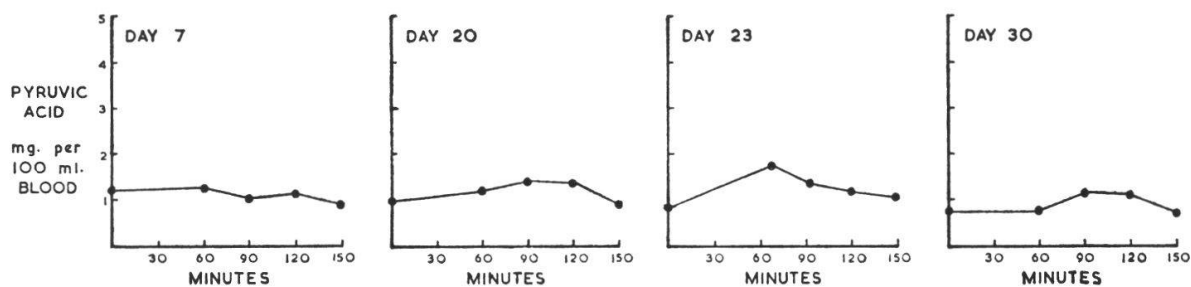


Fig. 2 b. Case No. 2.

DAY OF OBSERVATION		5 10 15 20 25 30 35								65 70 75 80 85 90 95 100 105								140		225 230 235 240																
SLEEPING SICKNESS TREATMENT	NITROFURAZONE g. X DAYS	1-5 X 3		1-5 X 10																																
VITAMIN	THIAMINE mg. IV X DAYS											25 X 5																								
	BECOSYM ampoules IV OR IM											50 X 1																								
	BECOSYM tablets ORAL X DAYS											X 5									X 1 X 1 X 1 X 1 X 1 X 1 X 1 X 1															
THERAPY	calcium pantothenate ORAL mg X DAYS											4 X 5 4 X 2 4 X 2									MARMITE DAILY															
	calcium pantothenate IM mg X DAYS											50 X 5									3 X 20 2 X 30															
																					50 X 10															
BLOOD PRESSURE																																				
PULSE RATE																																				
PYRUVATE METABOLISM TEST	PYRUVIC ACID mg. per 100 ml. blood	F	I-1 I-1	I-4 I-0	M	1-8 1-5	2-3 1-8																													
SIGNS AND SYMPTOMS	PAIN	2 3 3 3 3 3 3 3 3 3 3 2																																		
	OTHER	MOTOR WEAKNESS AND ATAXIA																																		
		ANDROSIS OF HANDS & FEET FIRST SIGN OF RETURN OF SWEATING.																																		
WEIGHT Kg																																				
C S F	Cells; Protein; Tryps	3,20,0 2,25,0 1,17,0 1,14,0																																		
DAY OF OBSERVATION		5 10 15 20 25 30 35 65 70 75 80 85 90 95 100 105 140 225 230 235 240																																		
		EXACERBATION WITH SLOW IMPROVEMENT EXACERBATION NORMAL SWEATING																																		

Fig. 3 a. Case No. 3.

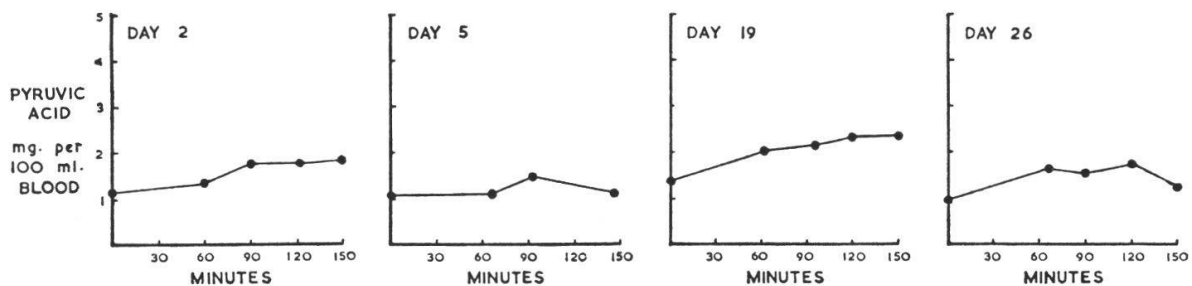
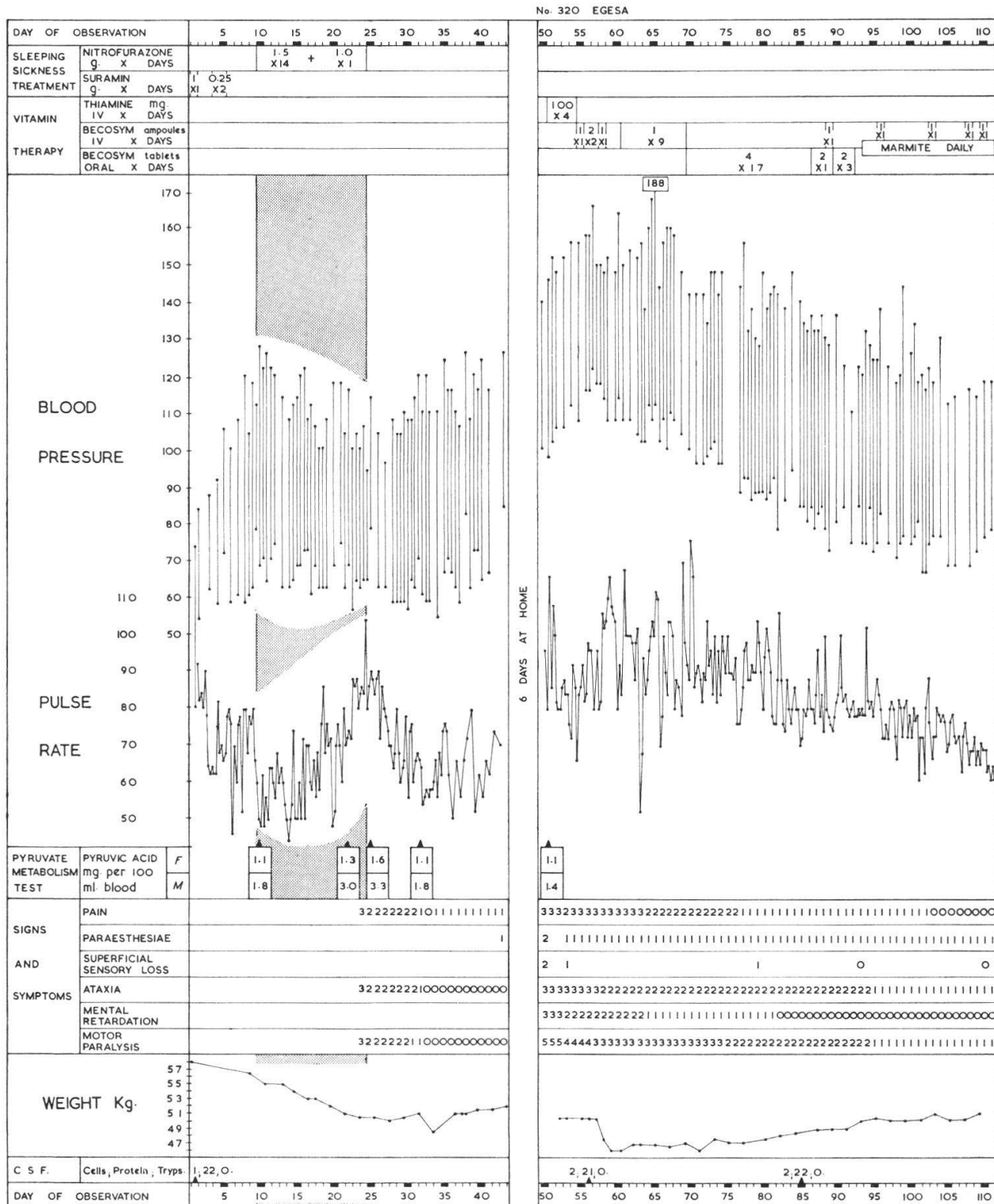


Fig. 3 b. Case No. 3.



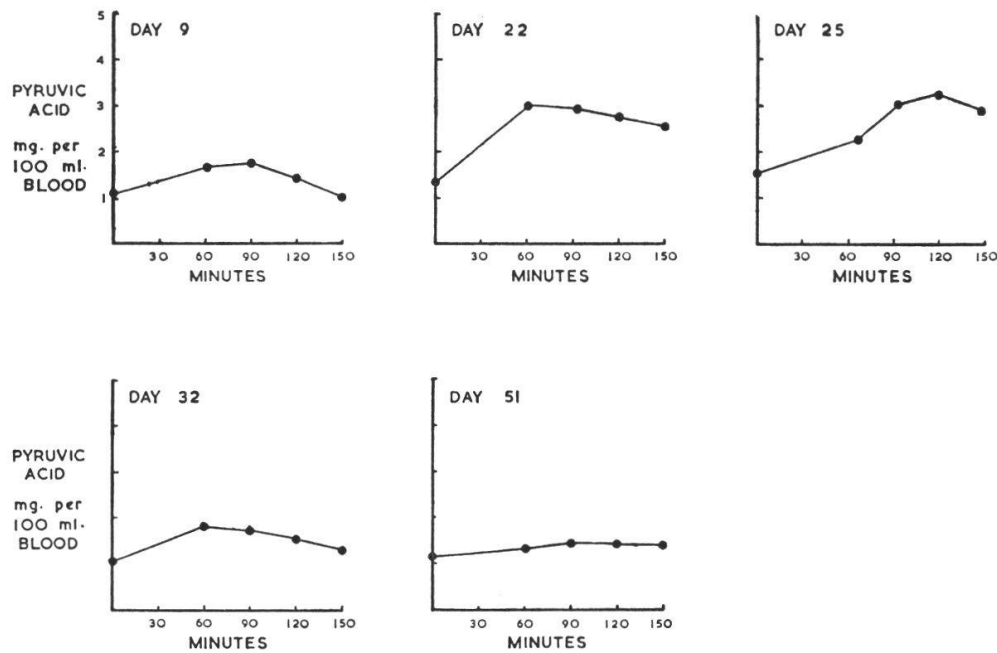


Fig. 4 b. Case No. 4.

No. 5. Male cultivator aged about 25 years with early-stage trypanosomiasis. Presenting features: pyrexia, tachycardia.

Thick blood film, trypanosomes +.

Gland-juice, trypanosomes +++.

C.S.F.: 1; 20; 0.

No. 6. Female cultivator aged about 35 years with late-stage trypanosomiasis who had relapsed 9 months after melarsoprol treatment. Presenting features: marked spasticity of all limbs, the upper being adducted at the shoulders and flexed at the elbows, the lower being maintained in rigid extension; tremors; incoherence; mental retardation; somnolence; incontinence.

Thick blood film, trypanosomes 0.

Gland-juice, trypanosomes 0.

C.S.F.: 42; 37; +.

In addition to the usual pyruvate metabolism tests a modified test (Fig. 6 c) was carried out on this patient with the object of observing any immediate effect of thiamine on an abnormally high blood pyruvate concentration. It was considered that if effects were to be attributed unequivocally to thiamine then the vitamin should be administered after a high and constant concentration of pyruvate in the blood had been reached. Accordingly, the patient was fasted overnight and after an initial dose of 50 g of glucose, further doses of 15 g of glucose dissolved in water flavoured with orange juice were given at 30-minute intervals over a period of 450 min. At 302 min. 50 mg of thiamine chloride hydrochloride were given by subcutaneous injection and at 306 min. a further 50 mg of the vitamin were given by intravenous injection. Blood was taken for the estimation of pyruvate at 0, 120, 180, 240, 299, 360, 420 and 492 min. Values of 3.3, 3.7, 3.6 and 3.5 mg pyruvic acid per 100 ml of blood were found at 120, 180, 240 and 299 min., respectively, indicating the suitability of this regime of glucose administration for producing a relatively constant

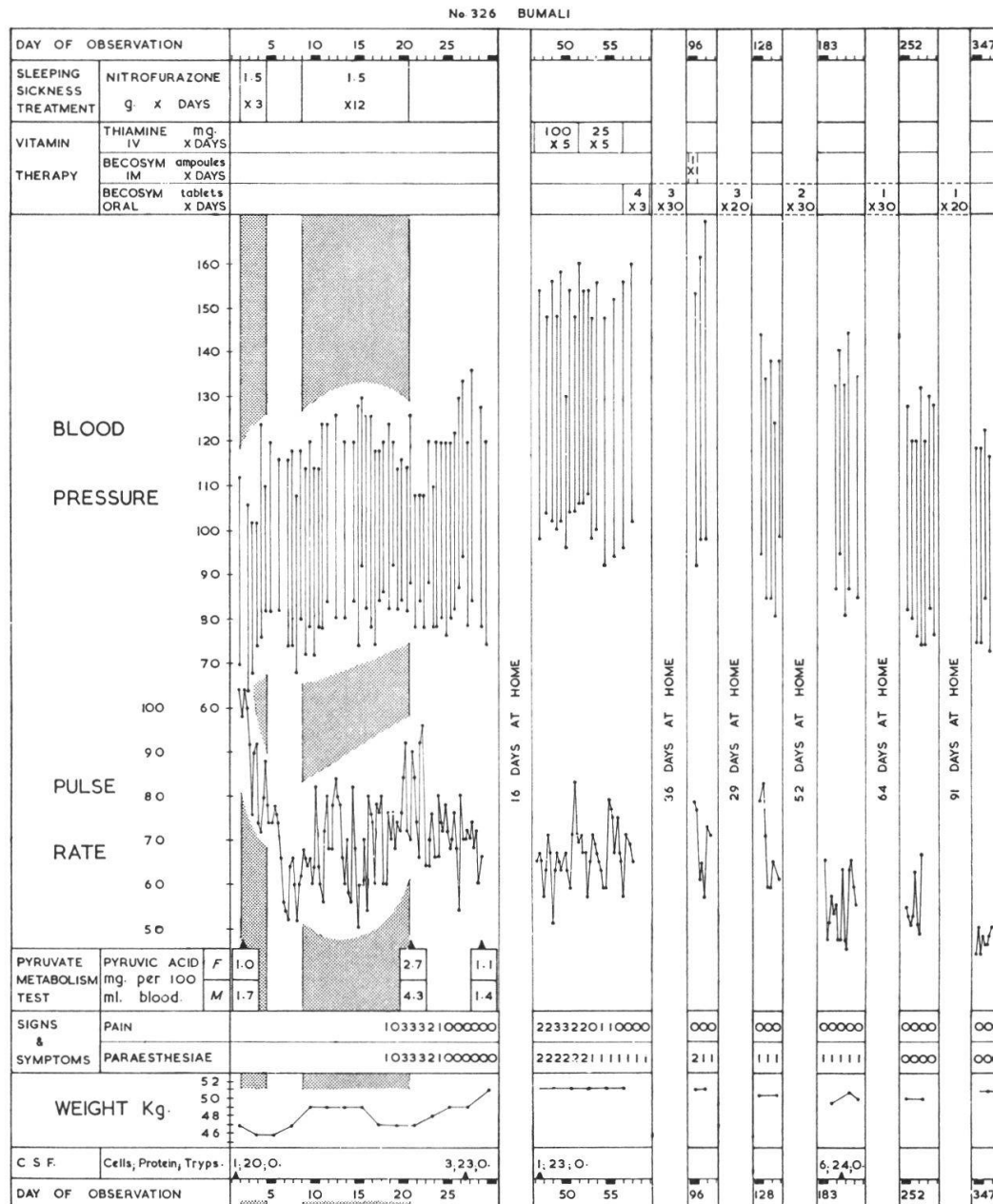


Fig. 5 a. Case No. 5.

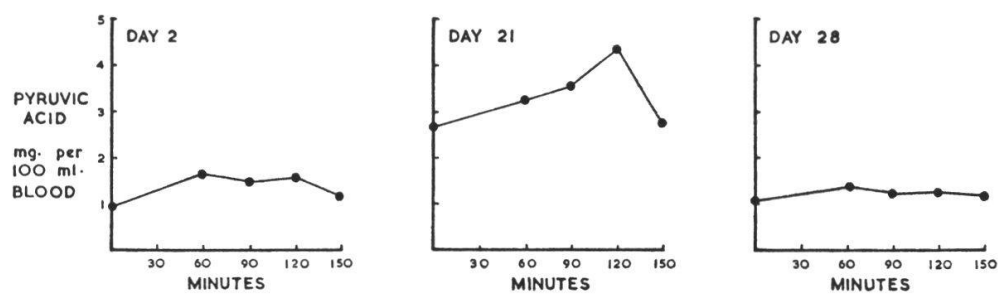


Fig. 5 b. Case No. 5.



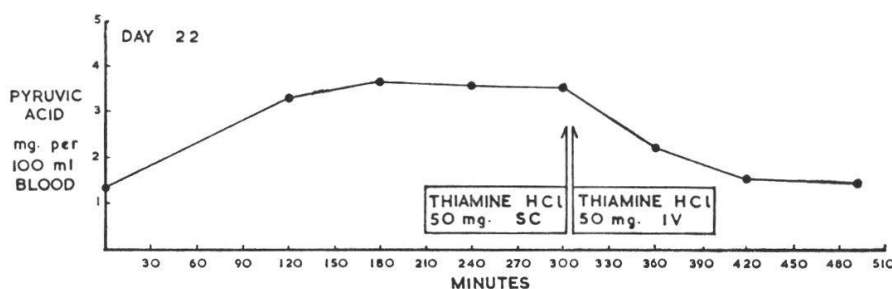


Fig. 6 c. Case No. 6. The modified pyruvate metabolism test. At time 0 min. 50 g of glucose was given; 15 g of glucose was then given every 30 min. up to 450 min.

concentration of pyruvate. It is reasonable to conclude that the decrease to 2.2 mg pyruvic acid per 100 ml blood which occurred in the hour following the administration of thiamine was due to the vitamin.

No. 7. Female cultivator aged about 30 years with late-stage trypanosomiasis. Presenting features: somnolence; mental retardation.

Thick blood film, trypanosomes 0.

Gland-juice, trypanosomes +.

C.S.F.: 195; 55; +.

Tracings of electrocardiograms, taken on days 60, 80 and after retreatment with melarsoprol on day 138 are reproduced in Fig. 7 c. The standardization (19 mm \equiv 1 millivolt) used in the first record (day 60) was retained for the others illustrated; voltage changes described below have been corrected (10 mm \equiv 1 millivolt) and are given in millimetres in the customary way.

Sinus rhythm was maintained and the tachycardia ultimately improved. Rates of 111, 109 and 55 per minute were obtained on days 60, 80 and 138 respectively. The P-R interval showed little change (0.16, 0.12 and 0.16 seconds respectively). There was pronounced elevation of the RS-T junction (J) which decreased gradually (4.7, 1.6 and 1.3 mm respectively in V2 for example). ST elevation decreased also. T wave inversion was pronounced on day 60 especially in V4 but became less. Voltage decreases were noted (R + S in V2 = 11.1, 11.1 and 4.7 mm on days 60, 80 and 138 respectively).

When examined again on day 261 ST segments were normal. Though the electrocardiogram was substantially normal, T waves, normal in V1-V4, gave way to shallow (1.5-2.0 mm) T wave inversion in V5-V6. This inversion was altered to an elevation (0.5 mm) after exercise. There was no clinical evidence of myocardial damage at this time.

The earlier electrocardiogram changes are consistent with the clinical diagnosis of myocardial involvement. During and following nitrofurazone treatment she developed tachycardia which was exacerbated by exercise: an electrocardiograph was not available at this stage.

Clinical and Laboratory Findings.

Related to the trypanosomiasis. Nitrofurazone without preliminary suramin cured two patients (Nos. 3 and 5), both in the early stage of *T. rhodesiense* trypanosomiasis. These patients had

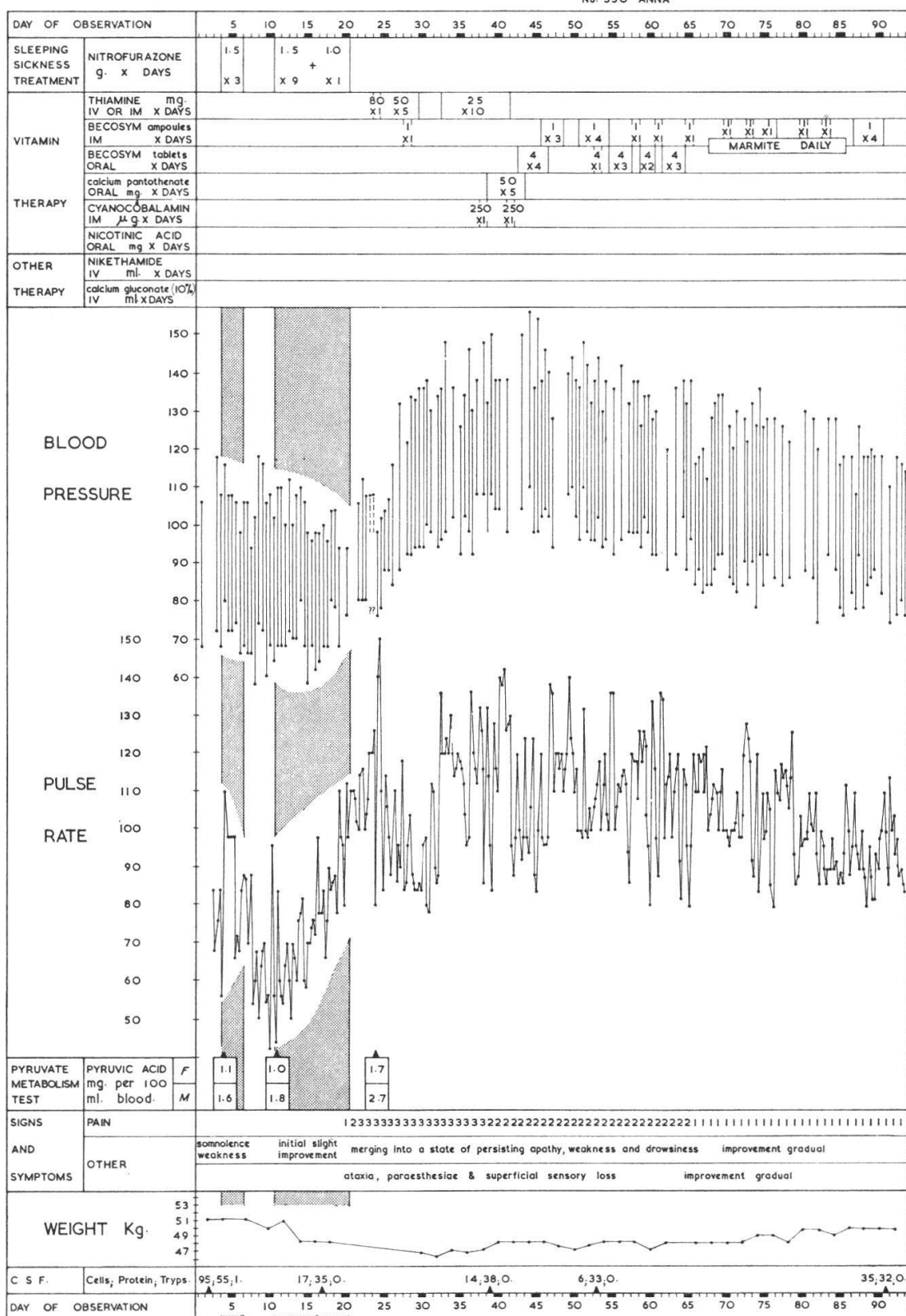


Fig. 7 a. Case No. 7.

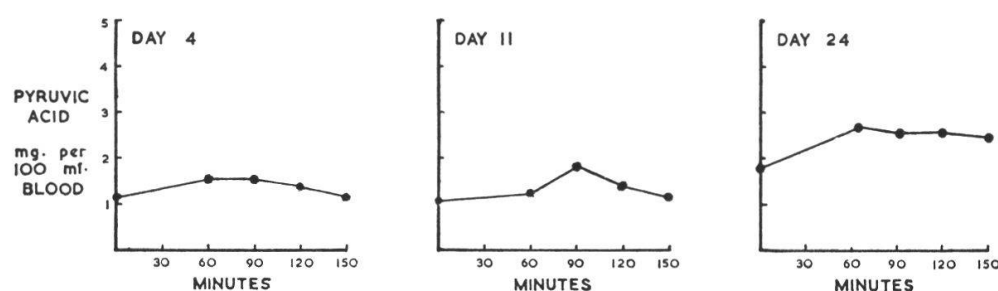


Fig. 7 b. Case No. 7.

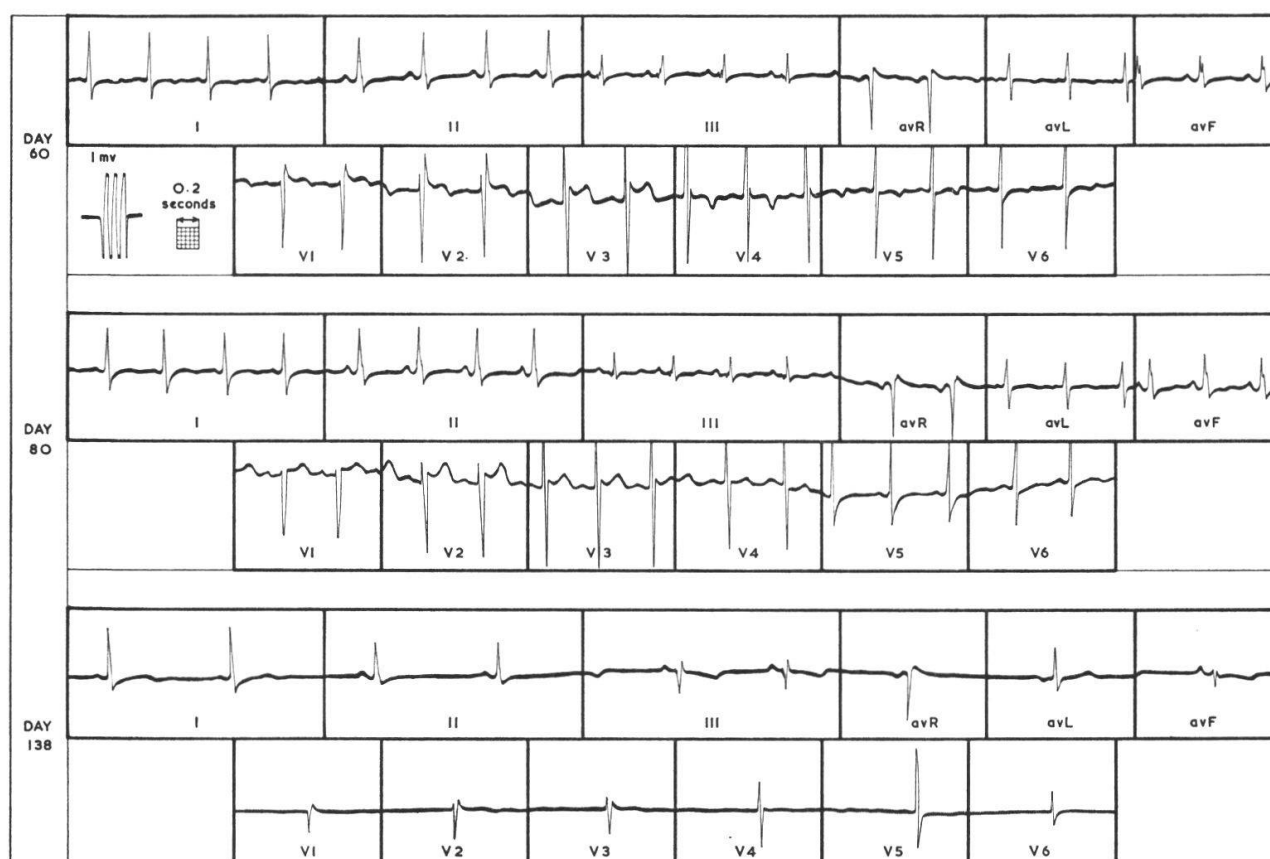


Fig. 7 c. Case No. 7.

Electrocardiograms taken on days 60, 80 and 138.

normal cerebrospinal fluids six months or more after treatment and did not relapse during a follow-up period of 3 years.

Two others in the advanced stage (Nos. 6 and 7), one a relapse after a previous melarsoprol treatment, showed a remission after nitrofurazone alone, but relapsed ultimately. A subject (No. 1) in the intermediate stage with a C.S.F. pleocytosis also showed a remission but relapsed rapidly after a course of nitrofurazone with preliminary suramin. Two patients (Nos. 2 and 4), given preliminary suramin before the nitrofurazone course, were cured.

Related to the toxicity of nitrofurazone. A rapid deterioration in the condition of patient No. 3 (hypotension, weakness, anorexia and weight loss) took place when nitrofurazone was given in the febrile stage without preliminary suramin and this made us reluctant to give the drug to febrile patients. This reluctance was also based on the fact that nitrofurazone interfered with pyruvate metabolism, which is also disordered during hypermetabolic states (WILLIAMS et al., 1943) and there was a fear that fever might exaggerate or precipitate the nitrofurazone polyneuropathy. High pyrexia itself is associated with a high blood pyruvate concentration and fever may exaggerate or precipitate polyneuropathy in beriberi (PLATT, 1958).

Though the first appearance of a definite mild sign or symptom of peripheral nerve involvement was taken as a reason for immediate withdrawal of nitrofurazone, this criterion was insufficient to avoid the very serious sequelae. The first clinical indication of toxicity in most cases was a gradual increase in the resting pulse rate and a deterioration in the exercise tolerance test.

The total dosage given in these cases was lower than that given by WILDERMUTH (1955) who was able to give a patient with testicular cancer 1.5 g. daily for 2 weeks followed by 2.0 g. for 2 weeks (total 49.0 g) before severe polyneuropathy necessitated termination of treatment. None of our patients received a total of more than 24.0 g. or a daily dose of more than 1.5 g. for more than 15 consecutive days, yet severe disabilities occurred even with a lesser dosage.

In early-stage trypanosomiasis the peripheral nerves and myocardium are unlikely to show changes though pathological involvement of the former has been demonstrated in fatal cases of *T. gambiense* meningoencephalitis (JANSSEN et al., 1956): in late-stage *T. rhodesiense* infections the myocardium may be involved (HAWKING & GREENFIELD, 1941). Clinical manifestations of such lesions may be absent and are seldom clear-cut and do not resemble the syndromes described here as resulting from nitrofurazone poisoning. The polyneuropathy and cardiopathy induced by nitrofurazone has striking clinical and biochemical similarities to beriberi and the burning-feet syndrome.

Paraesthesiae. A precise description of the differing forms of paraesthesiae was not possible but local language sufficiently distinguished these symptoms from actual pain. In one case (No. 1) paraesthesiae in the periphery of the limbs did not appear until about 30 days after withdrawal of nitrofurazone, during which time relapse occurred with a return of trypanosomes in the C.S.F. In all cases except one (No. 2) paraesthesiae occurred and

were subject to remissions and exacerbations. The paraesthesiae diminished centrifugally and were among the most persistent symptoms.

Pain. At the onset of the polyneuropathy pain extended peripherally from the knees and elbows. Though subject to severe exacerbations and remissions, the pain tended ultimately to become localized to the fingers and balls of the feet. In the upper limbs, pain was always less severe and disappeared much earlier than in the lower, where it eventually became persistent in the soles of the feet and predominated in the balls of the feet. This pain was very refractory to treatment and persisted for months, and was especially troublesome when the patient walked barefoot on rough ground. In some cases it was necessary for patients to be given shoes for as long as eighteen months.

Two main types of pain could be differentiated clinically during the course of the nitrofurazone-induced polyneuropathy. The first form was a burning pain in the feet, predominantly a metatarsalgia, exacerbated characteristically at night and causing insomnia. The patient sought relief by putting the feet outside the bed-clothes, in water, or by grasping the feet firmly. This type of pain was experienced by three patients (Nos. 3, 4 and 5). One patient (No. 4) used to lie in a semi-squatting position grasping his feet in an attitude identical to that described by CRUICKSHANK (1946) in his account of the painful feet syndrome in prisoners-of-war in the Far East. In one patient (No. 3) the characteristic burning-feet syndrome arose during the protracted course of his polyneuropathy 29 weeks after withdrawal of nitrofurazone. In this case an indication of its nature and of an effective form of treatment was obtained. Immediate but temporary relief was achieved by the inhalation of amyl nitrite and a permanent remission was obtained by intramuscular calcium pantothenate (50 mg. daily for ten days). The relief obtained with parenteral calcium pantothenate emphasizes the similarity of this burning-feet syndrome induced by nitrofurazone with that described by GOPALAN (1946), which occurred as a clinical entity, separate from beriberi, among impoverished people in South India. Gopalan's syndrome involved the balls of the feet, was subject to paroxysmal exacerbations of excruciating pain and was associated also with paraesthesiae and hyperidrosis. Two of our subjects with the burning-feet syndrome had hyperidrosis (Nos. 4 and 5) and one (No. 3) anidrosis. In Japanese prisoner-of-war camps nicotinic acid by injection was used with some success in the treatment of the burning-feet syndrome: SMITH & WOODRUFF (1951) attributed this effect to its vasodilator action. The relief of this particular pain in

case No. 3 with amyl nitrite and in two other similar cases (unpublished) is in line with this observation. HARRISON (1946) had some success with amyl nitrite in the burning-feet syndrome. Though BIBILE et al. (1957) failed to obtain significant results with pantothenyl alcohol in the treatment of their patients, it is possible that if patients were selected with the specific type of pain described above then better results might be obtained.

The second type of pain, involving the hands, legs and feet and eventually persisting as a chronic ache was clinically distinct from the first variety. It was gradually relieved by rest and was subject to remissions and exacerbations. The pain was unaffected by vitamin B group therapy and parenteral calcium pantothenate, specifically, did not relieve one patient (No. 7) with this chronic residual pain. The pain diminished ultimately to become a chronic metatarsalgia especially experienced when walking barefoot on stony ground.

Disorders in sensation to light touch. Hypoaesthesia or anaesthesia to light touch was observed in four cases (Nos. 1, 3, 4 and 7). Sense of the direction of passive movements of the thumb or big toe was temporarily disordered in one case. Vibration sense, though unfortunately not tested early in the course of this syndrome, was not involved in the later stage.

Ataxia. Ataxia of the gait was noted in two cases (Nos. 3 and 7) and ataxia of the fine movements of the hands in three (Nos. 3, 4 and 7). The gait ataxy was probably due partly to pain and partly to sole anaesthesia.

Disorders of sweating. Hyperidrosis of the hands was noted in two cases (Nos. 4 and 5); the feet were also hyperidrotic in one (No. 4). Anidrosis of the hands and feet was noted in one patient (No. 3).

Disorders of the reflexes. Abdominal reflexes were lost in two cases (Nos. 4 and 7) and loss of tendon reflexes including the triceps and supinator was noted in one patient who developed very severe polyneuropathy (No. 4).

Motor defects. In all patients, except the subject developing hypertension only (No. 2), there was evidence of motor nerve involvement. At the onset of the polyneuropathy motor weakness was generalised and mainly peripheral; it was especially severe in one patient (No. 4). During the period of established polyneuropathy, after withdrawal of nitrofurazone, muscular weakness and wasting in the periphery of the limbs was severe in two patients (Nos. 3 and 4).

Clinical course of the polyneuropathy. In one patient (No. 1) who developed polyneuropathy after a latent period following

withdrawal of nitrofurazone there was no neurological sign or symptom during the course of nitrofurazone treatment. A relapse of trypanosomiasis occurred during this latent period and this probably precipitated the polyneuropathy. One patient (No. 2) did not develop a polyneuropathy even though he received a 15-day course (22.0 g.). In one (No. 3), mild, sensory symptoms developed insidiously during treatment; in another (No. 4), the onset of pain and other symptoms was very abrupt and severe while in another (No. 5) paraesthesiae preceded the sudden onset of severe peripheral limb pain. In the cases with trypanosomal meningoencephalitis (Nos. 6 and 7) the onset of pain was also abrupt.

Though most patients improved rapidly after withdrawal of nitrofurazone, deterioration occurred on their return home. The subsequent remissions and exacerbations are illustrated in the figures; signs and symptoms persisted for many months.

Skin changes other than disorders of sweating. Minor skin changes were observed in three cases during the course of the nitrofurazone polyneuropathy. One patient (No. 5) developed a slight superficial desquamation in the legs and in two others (Nos. 3 and 4) there was hyperkeratosis and hyperpigmentation of the umbilicus. None developed hyperpigmentation such as that described in a patient who was given melarsoprol and nitrofurazone concurrently (ROBERTSON, 1959). This patient developed a severe polyneuropathy and also became hyperpigmented especially in the face and areola of the nipples. Melanosis is a feature of chronic arsenical poisoning (GOODMAN & GILLMAN, 1956) but it seems likely that nitrofurazone played some part in its production as such a melanosis has not been observed in 150 patients personally treated by one of us (D. H. H. ROBERTSON) with melarsoprol alone.

Cardiovascular disorders. A defervescence in the febrile cases (Nos. 3, 5 and 7) and an initial decline in the rapid pulse rate was observed in all subjects treated with nitrofurazone alone. In all cases, however, a gradual increase in the resting pulse rate was observed during nitrofurazone treatment and the increase generally preceded any significant fall in blood pressure. In two cases, in which a simple exercise tolerance test was done (Nos. 5 and 7) a deterioration was apparent before resting pulse rates became abnormal.

Decline in the systolic blood pressure and a narrowing of the pulse pressure were observed (Nos. 1, 4, 5, 6 and 7) towards the end of the nitrofurazone courses. In one patient (No. 3) hypotension occurred during initial treatment: because of this, in subsequent

treatments, a three-day preliminary course of nitrofurazone was followed by a rest of four days. One patient (No. 2) showed an apparent gradual increase in systolic blood pressure during treatment and nitrofurazone was withdrawn because of this sign. This hypertension persisted with little change during a follow-up period of about a year and was not associated with any sign of polyneuropathy. It may have been a case of essential hypertension with a fall in blood pressure associated with sleeping sickness.

On withdrawal of nitrofurazone the resting pulse rates and systolic and pulse pressures improved. In three cases (Nos. 4, 5 and 7) an initial improvement in the BP and pulse rate was followed by a prolonged hypertensive episode with tachycardia. The tachycardia recurred in a severe form in two of these (Nos. 4 and 7) and settled very slowly in parallel with the decrease in hypertension. The hypertension reached a maximum at 25-30 days after withdrawal of nitrofurazone and a gradual decline of the blood pressure to limits acceptable as normal took about 40 days in the two patients confined to bed (Nos. 4 and 7). In the other, an ambulant patient (No. 5) with mild symptoms, the decline occurred between 5 and 8 months after cessation of treatment. It should be noted that in two cases (Nos. 4 and 5) hypertension developed before any vitamin B group therapy was given. In the other case (No. 7), with an alarming tachycardia, hypotension and low pulse pressure, thiamine was given parenterally on the fourth day after the course. Though there was no immediate change—within 200 minutes—in blood pressure or pulse rate after injection, a general widening of the pulse pressure occurred and an increasing systolic and diastolic hypertension developed within three days. In one patient (No. 4) there was clinical evidence of cardiac enlargement—displacement of the apex beat—during the hypertensive phase of the illness; the apex beat gradually returned to within the mid-clavicular line.

Discussion

The clinical evidence indicates that the cardiovascular disorder occurring during nitrofurazone treatment was due to the toxic effect of nitrofurazone upon the myocardium. The syndrome has close similarities to beriberi both clinically and biochemically. It has been shown that monkeys fed on polished rice develop myocardial necrosis (FOLLIS, 1958) and the data discussed by OLSON (1958) support the view that the heart participates in the general metabolic defect which characterizes thiamine deficient tissue. The possibility that a paralysis of the vagus nerve contributes signi-

ificantly to the tachycardia seems unlikely as in the most severely affected patient (No. 7) digital compression of the carotid sinus halved the heart rate. Furthermore the possible role of the vagus paralysis as a cause of tachycardia in beriberi has been discounted for the reasons enumerated by SPILLANE (1947).

The initial hypotension probably was due to a myocardial defect similar to that of beriberi though peripheral vasodilatation may have played a part, by analogy with beriberi (FOLLIS, 1958). The ultimate hypertension in three cases shows a very striking similarity to that described by WALTERS (1953) in his patients suffering from beriberi. Some of his patients showed arterial hypertension on admission and in others it followed the institution of thiamine therapy. In one of Walters's patients, hypertension led to death from left ventricular failure; this suggests that the similar hypertension produced as a sequel to nitrofurazone therapy may be dangerous. Our cases were remarkably similar to those of Walters except that oedema was never present. Walters's patients, however, before the onset of beriberi, were pearl-divers who consumed large quantities of rice while our subjects were inactive, at rest and generally anorexic while on nitrofurazone. The occurrence of hypertension in dietary polyneuropathies is also described by CRUICKSHANK (1952), who discusses possible mechanisms; he considers the relationship of pain to hypertension but it should be noted that in one of our cases (No. 5) with hypertension, the pain, which was of the burning-feet variety, had disappeared long before a decline in hypertension was observed.

Clinical aspects of the pyruvate metabolism tests. It appears from the evidence of the long pyruvate metabolism test in one of our cases (No. 6) that at least the greater part of the impairment in pyruvate metabolism is readily reversible by thiamine. A similar rapid improvement in pyruvate metabolism is also seen in beriberi treated with thiamine (PLATT, 1958). Though in this case (No. 6) rapid improvement of signs and symptoms of polyneuropathy took place when thiamine was given two days after completion of nitrofurazone administration, in another (No. 7) treated with an almost identical course of nitrofurazone, clinical deterioration occurred with development of hypertension, protracted polyneuropathy, apathy and other signs. This evidence suggests that though this impairment in metabolism of pyruvate is corrected by thiamine, organic damage has already been sustained and is not readily reversible. From the other evidence, especially that in Case No. 4, it is apparent that a return of the pyruvate metabolism towards normal can be accompanied by deteriorating cardiovascular and peripheral nerve lesions. It is reasonable to conclude

that the degenerative processes responsible for the clinical manifestations of polyneuropathy are initiated by the biochemical lesions produced by nitrofurazone and that the correction by thiamine of that part of the disorder which is measured by a pyruvate metabolism test may not prevent further deterioration of the induced pathological lesion. It is possible, therefore, that patients with polyneuritis such as those investigated by JOINER et al. (1950), who show no abnormality in pyruvate metabolism may have had such an abnormality at the onset of the disease.

The pathogenesis of the manifestations of thiamine deficiency disease is not fully understood (HANDLER, 1958) and it follows that the reasons for the variability of syndromes in polyneuropathy either due to nitrofurazone or to lack of dietary thiamine are also not clear.

Precautions in the therapeutic use of nitrofurazone. The dangers of the haemolytic effect of nitrofurazone in patients with the erythrocyte glucose-6-phosphate dehydrogenase deficiency has been emphasized and attention has been drawn to the frequency of this trait among Africans (KNIGHT & ROBERTSON, 1963). A practical method which has been devised for giving nitrofurazone to subjects with this haemolytic trait (ROBERTSON, 1961a, 1961b) is based on the principle that drug-induced haemolysis is self-limiting and self-correcting in spite of continued administration of the drug (BEUTLER, 1959). A test such as that of Motulsky and Campbell with the precautions described by KNIGHT & ROBERTSON (1963) is convenient for recognizing the presence of the haemolytic trait before treatment is commenced. If this is not possible, then very cautious dosage with nitrofurazone (or any drug liable to produce a similar haemolytic effect) should be given and the haematocrit value should be determined daily before dosage.

It is clear that, because of the danger of haemolysis and polyneuropathy, nitrofurazone should be reserved for cases which are proved to be resistant to melarsoprol and the drug must be used with extreme care. Subjects with *T. rhodesiense* sleeping sickness in the advanced stage who relapse after one course of melarsoprol may be cured by a second course. However, if a second relapse occurs melarsoprol is unlikely to cure the infection. It is for such relapses that trial with nitrofurazone should be reserved because it is toxic as well as uncertain in its action and may not cure the disease. Apted's experience with nitrofurazone emphasizes this (APTED, 1960).

Clearly it would be unwise for reasons already discussed to give nitrofurazone to acutely febrile patients. Such patients, even relapses, may be rendered afebrile, aparasitaemic and fitter in the

general sense by a preliminary course of suramin. A dosage of suramin 0.25-0.5 g. given intravenously on alternate days for 2-4 doses is suggested after which nitrofurazone, 1.5-2.0 g. daily, could be given in divided doses for a period of 5 to 7 consecutive days. A period of rest is obviously necessary and the courses could be repeated. A careful clinical assessment should be made daily and the occurrence of a gradual increase in pulse rate should be taken as a warning that the drug should be temporarily withdrawn. Serial electrocardiograms should also be carried out as another of our relapsing patients (unpublished) given 0.5 g. nitrofurazone thrice on one day while in a febrile state, showed a reduction in the voltage of T waves in all precordial leads with inversion in V1 and V2. This change was transient and the T waves reverted to normal within 48 hours.

From the work discussed in this paper it seemed reasonable that concurrent parenteral thiamine during treatment might prevent the polyneuropathy syndrome. That this is not the case is shown by the following example. The patient whose treatment is shown below developed polyneuropathy (burning-feet and hypertension) of a severity slightly less than that in Case No. 5 reported above.

Days 1-3, 8-14, 21-27, 34-40, nitrofurazone, 3×0.5 g. daily; Becosym, 3×1 ampoule IV daily. Days 4-7, 15-20, 28-33, 41-46, Becosym, 1 ampoule IV daily.

Whether or not concurrent thiamine therapy influences the therapeutic activity of nitrofurazone is not known.

Other rational precautions include the maintenance of the patient at rest during treatment and the diet offered should presumably be high in protein rather than carbohydrate. Anorexia and vomiting might be diminished by the use of coated tablets; however, it should be recognized that anorexia, which is a first sign of beriberi, may be partly due to an action other than the local one.

Apart from the value of rest little can be said of the efficacy of therapeutic procedures other than that of giving amyl nitrite and calcium pantothenate for the relief of the specific pain in the burning-feet syndrome induced by nitrofurazone. Experience of others suggested the use of nikethamide (CRUICKSHANK, 1946), calcium gluconate or nicotinic acid (HARRISON, 1946) but these were used only in one patient (No. 7) when she had a chronic metatarsalgia, which was distinct from the classical "burning-feet syndrome" described.

Mild polyneuropathy has been described with nitrofurantoin, *N*-(5-nitro-2-furfurylidene)-1-aminohydantoin, therapy (HANSEN

& MOORE, 1954). Involvement of predominantly cranial nerves has occurred with prolonged (7-14 weeks) furaltadone, *N*-(5-nitro-2-furfurylidene)-3-amino-5-(*N'*-morpholinylmethyl)-2-oxazolidone, treatment (LEE, 1960), though peripheral nerves were involved also in one case described by HUSSAIN & KOILPILLAI (1960). Comment on the disorder of pyruvate metabolism is made below, but it is clear from the clinical aspect that the neurological syndromes arising from nitrofurazone therapy bear a close similarity to those in the dietary neuropathies.

We have demonstrated three main features in the clinical pathology of patients intoxicated with nitrofurazone. Firstly, there was an accumulation of pyruvate in the blood of patients given a loading dose of glucose. Secondly, the raised and sustained level of pyruvate, induced in a patient given frequently repeated doses of glucose, was rapidly reduced by parenteral thiamine (Fig. 6c). Thirdly, the intravenous administration of thiamine with each dose of nitrofurazone may fail to prevent the appearance of polyneuropathy.

It is known that nitrofurazone interferes with the overall metabolic processes of living organisms as well as with the activity of isolated enzyme systems. PAUL et al. (1956) showed that nitrofurazone inhibits the formation of acetyl coenzyme A from pyruvate and they concluded that it did not react directly on thiamine. GREEN (1948), however, demonstrated that the inhibiting effect of nitrofurazone on the growth of *Escherichia coli* in culture is reversed by either thiamine or pantothenate. FRIEDGOOD & GREEN (1950) stated that rats dosed with nitrofurazone developed unspecified signs of multiple vitamin deficiencies and recovered after withdrawal of the drug.

Our demonstration that parenteral thiamine rapidly reduced a previously stable high concentration of pyruvate in the blood, appears to be at variance with the conclusions of PAUL et al. (1956). A possible explanation of this discrepancy is that certain of the effects seen after the administration of the drug are due to metabolites of the drug which are known to vary between man and other animals (KNIGHT, 1960; PAUL et al., 1960) and which may have an antithiamine activity. Though one metabolite isolated by PAUL et al. (1960) from the urine of rabbits dosed with nitrofurazone was inactive towards bacteria, its *in vitro* activity against enzyme systems was not investigated.

Nitrofurazone must be added to the list of substances (PASSMORE & MEIKLEJOHN, 1957; SARETT & MORRISON, 1958) which produce signs resembling those of thiamine deficiency in man or animals.

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Zusammenfassung

2 Patienten in einem frühen Stadium von *T. rhodesiense*-Infektion konnten mit Nitrofurazone geheilt werden. 2 andere ähnliche Frühstadien erhielten vor der Nitrofurazone-Behandlung Suramin und wurden ebenfalls geheilt. Ein Pa-

tient, welcher sich in einem Intermediärstadium befand, zeigte einen Rückfall kurz nach der Suramin- und Nitrofurazone-Behandlung. 2 Patienten in vorgerückten Stadien zeigten Besserung nach reiner Nitrofurazone-Behandlung, wurden aber später rückfällig.

In 6 von 7 Fällen produzierte Nitrofurazone eine Polyneuropathie ähnlich Beriberi und ein Burning-feet Syndrom. Die damit verbundene Störung des Pyruvat-Metabolismus konnte mit Thiamin korrigiert werden, jedoch sprach die Polyneuropathie auf die Behandlung mit der Vitamin B-Gruppe nicht an. Die nächtlichen Schmerzen, welche durch das Burning-feet-Syndrom erzeugt wurden, konnten rasch, aber nur vorübergehend durch Inhalationen mit Amylnitrit behoben werden, und diese Schmerzen verschwanden vollständig nach parenteraler Applikation von Calciumpantothenat. Andere sekundäre Schmerzen konnten nur langsam und unvollständig durch Bettruhe und verschiedene Behandlungsmethoden behoben werden.

Résumé

Deux cas d'infection par *T. rhodesiense*, au stade du début, ont été guéris par le Nitrofurazone. Deux autres malades traités préalablement par la Suramine, ont également été guéris par le Nitrofurazone. Un patient au stade intermédiaire de la maladie fit une rechute peu après un traitement comprenant successivement la Suramine puis le Nitrofurazone. Enfin, deux patients au dernier stade de la maladie ont présenté une amélioration lors du traitement par le Nitrofurazone seul, mais ce n'était qu'une rémission passagère.

Sur sept cas traités au Nitrofurazone, six ont développé un syndrome poly-névritique rappelant le bérubéri et le burning-feet. Le désordre métabolique de l'acide pyruvique a pu être corrigé par la thiamine, tandis que la polyneuropathie ne répondait pas à un traitement par les vitamines du groupe B. De leur côté, les douleurs nocturnes du syndrome burning-feet cédaient immédiatement, mais de façon passagère, à l'inhalation de Nitrite d'amyle. Un traitement parentéral de Pantothénate de calcium les écartait définitivement, alors que d'autres effets secondaires ne régressaient que lentement grâce au repos et à d'autres traitements.