

Severe Staphylococcal Infection with Pneumonia Treated by Plasmapheresis and Plasma Exchange

A Preliminary Report

J. B. KING, J. B. DE VAAL

SUMMARY

Three cases of extremely severe staphylococcal infection are reported. All 3 patients were treated by plasmapheresis and fresh plasma or fresh-frozen plasma replacement, and all made a steady recovery. In all 3 cases blood culture for *Staphylococcus aureus* was positive, 1 patient had osteitis, and 1 signs of spinal cord compression by an infectious process (an abscess). It is thought that the abovementioned procedures may offer a useful additional line of therapy for desperately ill patients with staphylococcus infections.

S. Afr. med. J., 58, 849 (1980).

During recent years the death rate from severe staphylococcal disease has fallen. Death rates as high as 75% were quoted 20 years ago,¹ but recently overall death rates of 20-30%^{2,3} have been reported. These figures are still high, even though many of the deaths occur in persons concomitantly suffering from another disease (e.g. immunosuppression in malignancy, diabetes mellitus). There are, however, recurrent reports of the development of a severe staphylococcal infection in someone apparently previously well and progressing to a fatal outcome, despite full intensive care and antibiotic therapy. These patients with severe staphylococcal disease are usually young and often males.³ The relationship between the toxicity of the organism and host resistance has not been fully explored for this or any other potentially lethal infection. However, there is a resemblance to the fulminating infection which may develop in the immunosuppressed patient and progress to rapid death, despite full therapy with appropriate antibiotics. Using this untested analogy the use of plasma exchange seemed rational; perhaps these patients had suffered a temporary immune deficit in the face of overwhelming infection?

This preliminary report covers 3 such patients, all of whom were adjudged to have an exceedingly poor prognosis but who have recovered fully.

Department of Haematology and Respiratory Intensive Care Unit, Tygerberg Hospital and University of Stellenbosch, Parowvallei, CP

J. B. KING, M.B. CH.B., M.MED. (MED.), L.M.C.C.
J. B. DE VAAL, M.B. CH.B., M.MED. (INT.)

Date received: 3 September 1980.

PATIENTS AND METHODS

Three unselected patients were referred to the Respiratory Intensive Care Unit, Tygerberg Hospital, Parowvallei, CP, and were proved to have *Staphylococcus aureus* infection (1 had a *Proteus* in the sputum as well). They were treated with the full intensive care regimen, tracheostomy, and daily plasma exchange on a Hemonetics machine (Hemonetics Corporation, Braintree, Mass, USA) for as long as necessary. The machine was brought to the patient's bedside, and from 2-2.5 l of plasma were withdrawn at a time. It was replaced with: (i) obligatory citrate solution, approximately 25% of the total; and (ii) fresh-frozen plasma (FFP) or fresh liquid plasma (FLP). At least 1.5 l of FFP or FLP were transfused each time. FLP was used because it has been reported to contain at least as much fibronectin as does FFP (R. Stead — personal communication). Blood was taken before and after plasmapheresis for the following investigations: full blood count, including platelet, reticulocyte and differential counts; coagulation screen, including fibrinogen, fibrinogen split products (latex agglutination method), fibrinogen 'monomer' (ethanol gelation), activated partial thromboplastin time, prothrombin time ratio, and thrombin time; complement (C3, C4); estimation of blood urea and electrolytes (Na, K, Cl, Ca, P), uric acid, creatinine, bilirubin, serum albumin and globulin (electrophoresis and immunoelectrophoresis), SGOT, SGPT, LDH, and alkaline phosphatase. The blood gases were closely monitored (P_{O_2} , P_{CO_2} , pH).

Case 1

This 15-year-old youth was previously well, but developed an influenza-like illness and his condition rapidly deteriorated. He was admitted to the Respiratory Intensive Care Unit at Tygerberg Hospital on the 5th day of the illness, when he was extremely ill. His respiratory rate was over 60/min, his arterial P_{O_2} 5.5 kPa when given 40% oxygen and 8.5 kPa when given 100% oxygen after a tracheostomy (Fig. 1). At bronchoscopy the tracheal mucosa had the appearance of haemorrhagic necrosis. *Staph. aureus* and *Proteus vulgaris* were grown from the sticky sputum, and *Staph. aureus* was isolated on blood culture. Chest radiographs showed extensive bronchopneumonia (Fig. 2, top). A tracheostomy was immediately performed and he was given antibiotic therapy with penicillin, cloxacillin, gentamicin and fucidin, the *Staphylococcus* being sensitive to all. Plasmapheresis was commenced on the day of admission to the Unit and

continued for 5 days. He improved rapidly and plasmapheresis was then discontinued. However, a late recrudescence of fever and constitutional symptoms led to a brief course of plasmapheresis together with antibiotics as above (Fig. 2, bottom). Improvement was again rapid and this time sustained. Blood gas values were not affected, and there were no late complications.

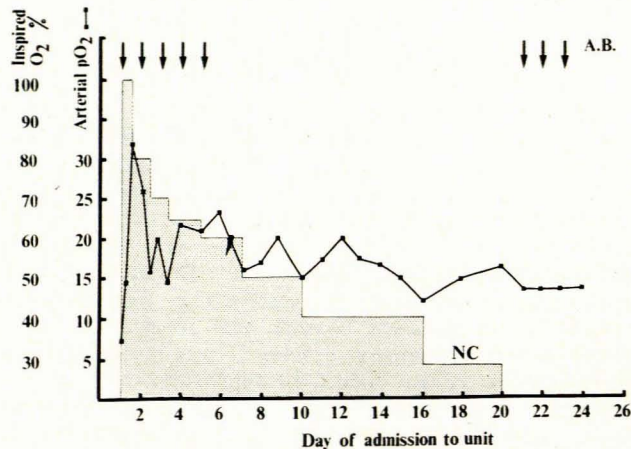


Fig. 1. Case 1. The hatched area depicts the percentage of oxygen administered (NC = nasal catheter).

Case 2

This 15-year-old boy, previously well, developed spontaneous pain in the right shoulder with pyrexia and severe constitutional disturbance 3 days before admission to the Orthopaedic Wards at Tygerberg Hospital. Osteitis of the right humerus was diagnosed and an osteotomy was performed. Pus containing *Staph. aureus* was cultured from a bone specimen and a blood sample which was sensitive to all major antibiotics. A full course of therapy with cloxacillin, penicillin and fucidin was begun but his condition deteriorated very rapidly. Lung changes were observed clinically and radiographically (Fig. 3, top), together with evidence of disseminated intravascular coagulation (Table I). On the 8th day of the illness he was transferred, desperately ill, to the Respiratory Intensive Care Unit at Tygerberg Hospital. Tracheostomy and treatment with 100% oxygen gave an arterial Po₂ of 8.0 kPa. Plasmapheresis was commenced the same day and he rapidly improved, although he remained ill and pyrexial (Fig. 4). A gallium scan suggested 10 or 11 foci of bone infection throughout the body. However, after plasmapheresis had been performed 10 times he was judged well enough for the procedure to be discontinued. He showed immediate evidence of deterioration in terms of blood gas values and chest radiographs, and plasmapheresis was recommenced on alternate days. After a further 4 procedures his lungs appeared practically normal, with one small pneumatocele at the right lung base. The osteitis of the right humerus was also clearing up, and he was discharged back to the Orthopaedic Wards (Fig. 3, bottom).

Case 3

This 30-year-old woman had had several skin furuncles over the past 2 months, but remained otherwise well.

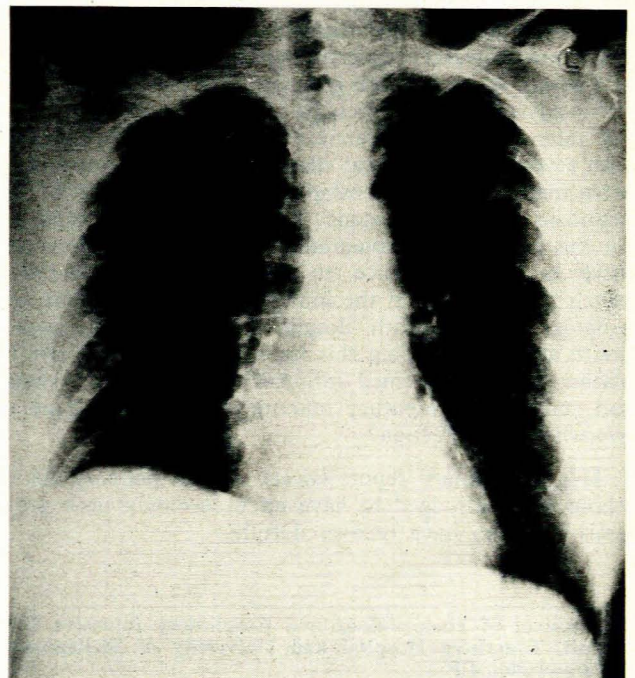
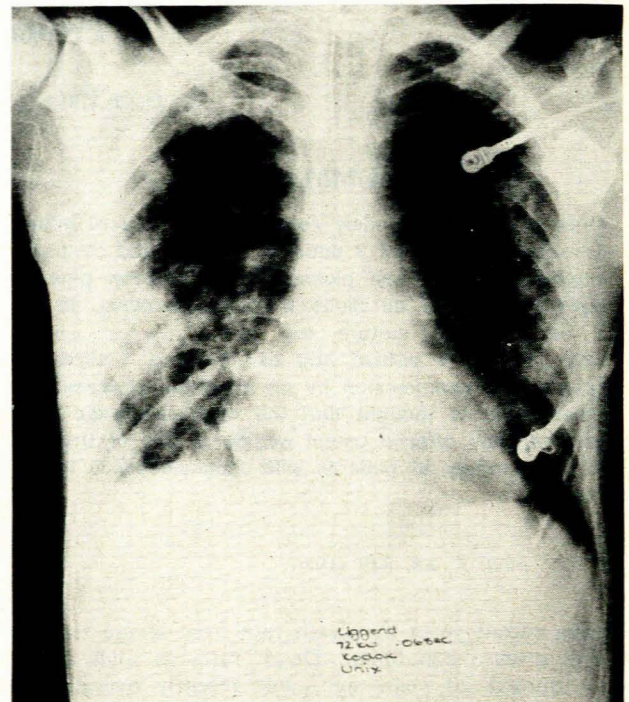


Fig. 2. Case 1. Chest radiographs on admission (top) and discharge (bottom).

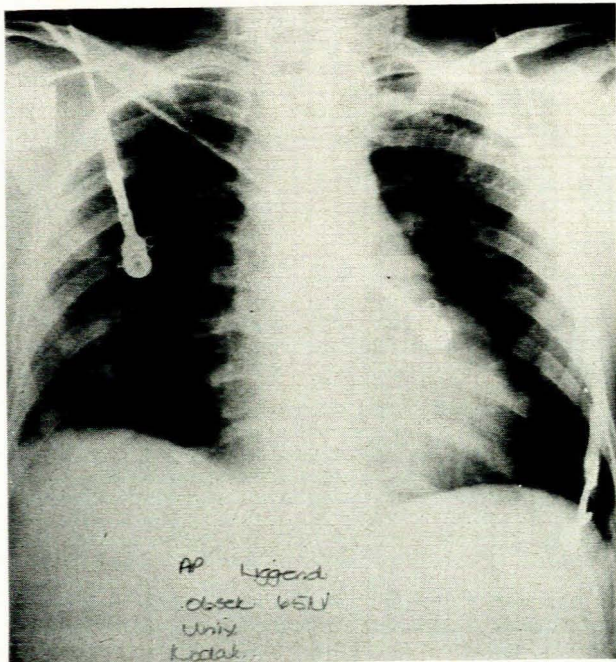
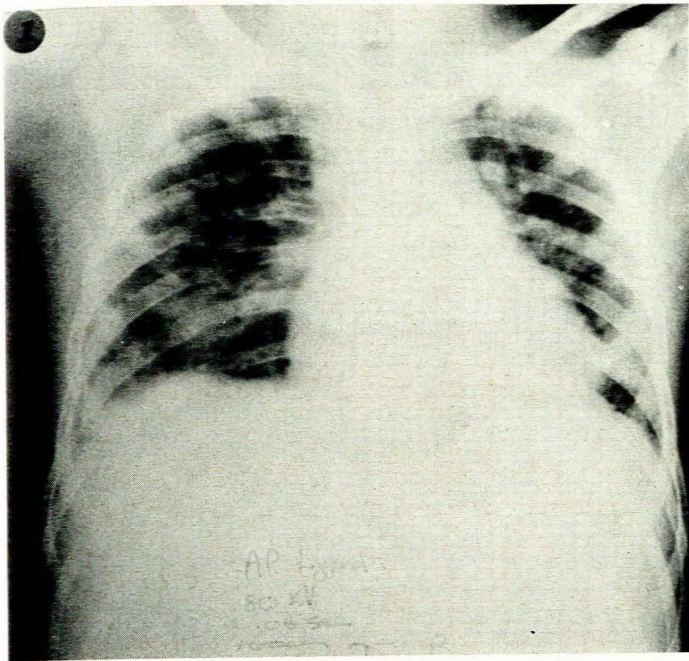


Fig. 3. Case 2. Radiographs on admission (top) and discharge (bottom) from Unit. Pneumatocele visible in right lower lobe on discharge.

There was a family history of diabetes mellitus, but a glucose tolerance test was negative. She developed low backache, thought to be due to a fractured coccyx, and a coccygectomy was performed. The next day she became pyrexial and generally ill. There was radiographic evidence

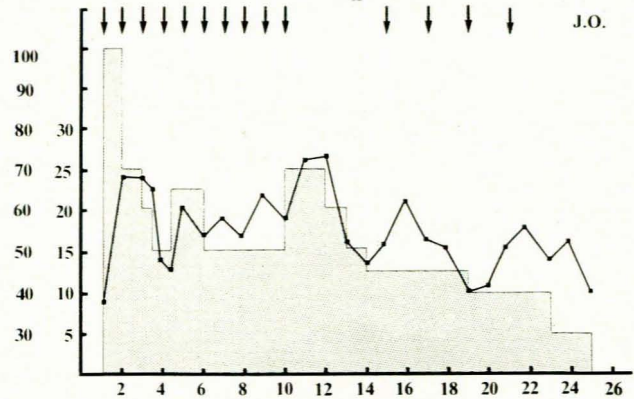


Fig. 4. Case 2. The hatched area depicts the percentage of oxygen administered.

of bronchopneumonia, with a falling arterial Po₂. The backache became worse. Lumbar puncture failed, but pus containing Gram-positive cocci was aspirated in relation to the vertebral column, cultured, and proved to contain *Staph. aureus* sensitive to the full range of antibiotics. Blood and sputum cultures were also positive for *Staph. aureus*. She was judged to have a very poor prognosis, and was flown 1 600 km to the Respiratory Intensive Care Unit at Tygerberg Hospital. On arrival she was deeply cyanosed with a respiration rate of 55/min. In addition to the bronchopneumonia (Fig. 5, top), she had evidence of paraparesis at T10 (hypo-algesia, extensor plantar reflexes, motor weakness). A tracheostomy was done and the full intensive care regimen begun, with plasmapheresis three times during the first 24 hours. The neurosurgical diagnosis was of spinal cord compression possibly due to an epidural abscess; laminectomy was advised as soon as the patient was judged fit enough for major surgery. The arterial Po₂ improved rapidly (Fig. 6), together with a striking improvement in her general condition; this was commented on after plasmapheresis had been performed the first time. The evidence of spinal cord compression disappeared over the first 4 days, and by the time she was well enough for laminectomy the indication for the operation no longer existed. Ileus complicated the picture for several days. She then developed a *Pseudomonas* empyema with pneumonia, and this responded slowly to carbenicillin (Fig. 5, bottom). Plasmapheresis was performed twice more because of general concern for her well-being, but this was probably unnecessary. She is now out of the Respiratory Intensive Care Unit.

COMMENT

As the present death rate of severe staphylococcal infection is 20 - 30%, the recovery of 3 patients could statistically have occurred by chance. The reason for reporting such a small series is the strong impression made on all observers that these patients were in a terminal stage, and the equally strong impression that plasma exchange led to profound improvement in their overall condition.

A pneumatocele developed in the right lower lobe in

TABLE I. PARAMETERS OF INTEREST IN CASES 1, 2 AND 3

	Day of admission to Unit	Hb (g/dl)	WBC ($\times 10^9/l$)	Platelets ($\times 10^9/l$)	Blood transfusion (units packed cells)	Fibrinogen (mg/dl)		Monomer	FDP	Total plasmapheresis	
						Before	After			Withdrawal	Transfusion
Case 1	1	14,4	6,8	193		1 000	820	-	-		
	2	13,5	5,8	237		1 000	650	-	10		
	3	12,9	10,1	310		670	545	-	-		
	4	12,5	13,1	358		770	565	+	10		
	5	11,7	21,2	577		650	460	-	-		
	6	11,2	29,0	684		590					
	7	10,1	25,5	756	2	540					
	8	11,7	23,2	812		495					
	10	11,2	18,2	901		550					
	11	11,9	16,6	1 082	2	530					
	20	13,4	11,2	629		430				15,2	11,25
Case 2	1	9,7	48,4	177	2	245	230	+	10		
	2	10,5	28,2	100		220	252		40		
	3	9,9	26,6	125		215	222		-		
	4	8,6	13,3	136	1	215	185		-		
	5	8,8	14,9	222		225	245	+	-		
	6	8,6	13,7	283	3	150	182	-	-		
	7	11,6	13,7	254		165	175	-	-		
	9	11,4	9,9	329		177	206	-	-		
	10	10,4	21,4	203		203	210	-	-		
	12	10,4	20,2	321		238	250	+	-		
	14	10,0	18,6	432	2	370					
	16	11,0	16,2	366		300				31,4	23,0
Case 3	1	9,1	13,1	78	3	850	650	-	40		
	2	11,3	8,5	76		480	380	-	10		
	3	10,1	5,4	84		530	425	-	-		
	4	9,8	5,3	88		380	265	-	-		
	5	9,8	5,5	107		250	238	-	-		
	6	9,8	5,8	85		225	185				
	7	9,6	7,4	74	2	245	288				
	8	10,9	9,2	55		298	220				
	10	10,3	8,4	32		450	335				
	12	10,3	15,7	169	2	209	220				30,2
	20	11,7	17,9	377							

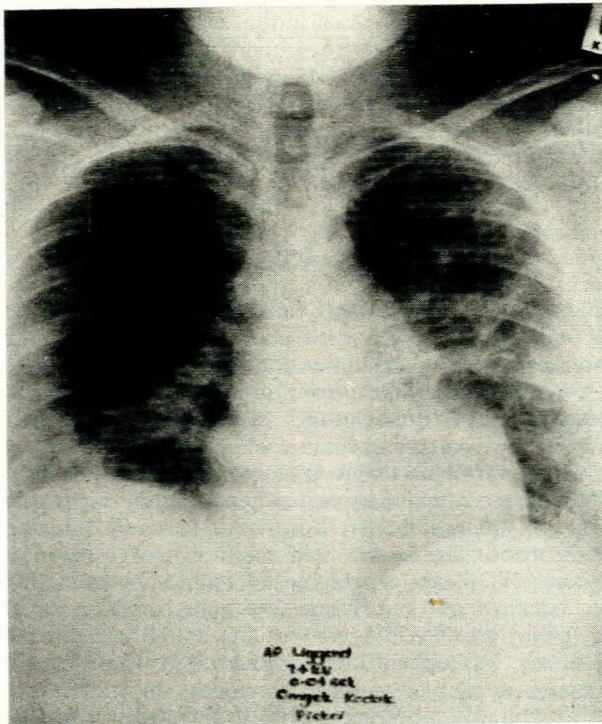
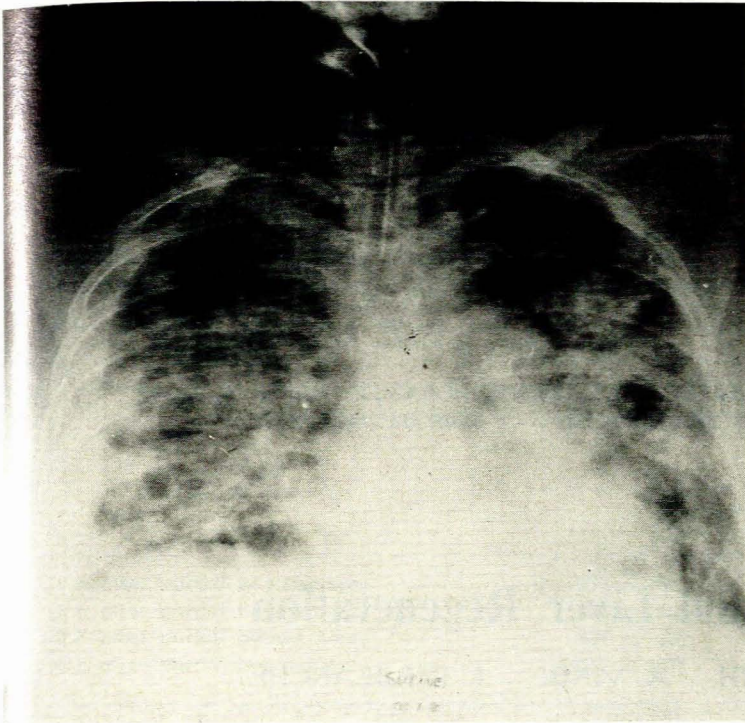


Fig. 5. Case 3. Radiographs on admission (top) and discharge (bottom) from Unit. Resolving *Pseudomonas* empyema visible on right side on discharge.

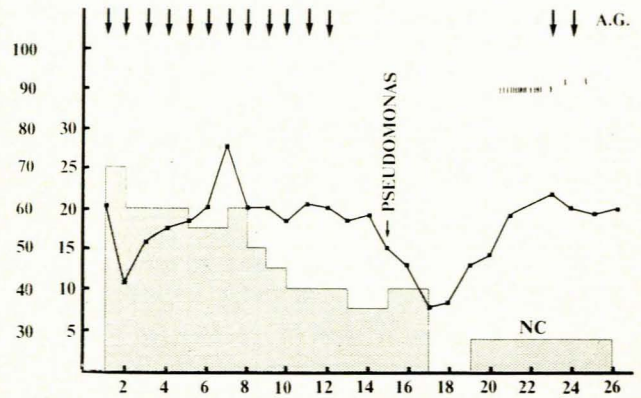


Fig. 6. Case 3. The hatched area depicts the percentage of oxygen administered (NC = nasal catheter).

patient 2 and progressed to a late abscess. Apart from this, the course in all 3 patients was characterized by absence of 'shock lung', pneumatocele or lung abscess.

Investigations so far carried out do not reveal the reason for the effectiveness of this form of treatment. The routine investigations show no deviations beyond those expected in severe infection. Some of these investigations are reported in Table I. We are awaiting assays for fibronectin and C1q. There may well be several reasons for the improvement, such as removal of the toxic products of inflammation and of particulate matter (immune complexes, thromboplastin, fibrin) as well as the administration of inhibitors (e.g. antithrombin III, C1 esterase inhibitor), fibronectin,⁴ and immune globulins.

In this situation, the patient was too ill to be moved to the machine, and therefore a mobile plasmapheresis machine was essential. The Hemonetics machine processes batches of blood; this involves the withdrawal of between 450 and 750 ml of blood, depending on the size of the bowl used. When used on healthy donors, withdrawal of the appropriate amount of blood is well tolerated, but this is not the case with seriously ill patients. Therefore, careful attention was given to fluid balance; plasma replacement was begun simultaneously with plasmapheresis, and the blood pressure and pulse rate were monitored every 10 minutes. In patient 2, venous pressure was so low that blood would not flow at first, and 1 litre of FFP had to be given before the flow rate to the machine was adequate. Thereafter there were no complications. No histamine release reactions were seen, but in patient 2 profound shock and cyanosis developed transiently during the 6th procedure. There was difficulty in obtaining sufficient group-specific plasma for this patient (group AB) and low-titre group A plasma was used. No subsequent evidence for blood group incompatibility was found, however, and the origin of this reaction remains obscure. The procedure was discontinued, and he made a rapid recovery.

There was a slow fall in haemoglobin levels with time in all 3 patients, but not to a degree greater than could be expected on general grounds in patients with very severe infection. The direct and indirect antiglobulin tests were negative at all times.

In conclusion, it is suggested that this procedure should be considered in the therapy of life-threatening staphylococcal infections. It is simple to use, relatively inexpensive, and may offer a new approach to this serious problem.

We wish to thank the staff of the Respiratory Intensive Care Unit for their skilled assistance, in particular Dr H. van Straaten, Dr James Joubert for reading and commenting on

the manuscript, and the Western Province Blood Transfusion Service for assisting in staffing the machine after hours.

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Insulin, Glucagon and Liver Regeneration

R. E. KIRSCH, L. O'C. FRITH, A. VINIK, J. TERBLANCHE

SUMMARY

Partially hepatectomized rats receiving intragastric amino acids synthesize less DNA than similar rats receiving intragastric water alone. In the present study insulin and glucagon levels were measured in rats receiving amino acids or water alone. In both groups of rats insulin levels were depressed and glucagon levels elevated. These findings suggest that insulin and glucagon do not play a major role in the regulation of liver regeneration after partial hepatectomy in the rat.

S. Afr. med. J., **58**, 854 (1980).

The role of insulin and glucagon as initiating and/or potentiating factors in liver regeneration (compensatory hyperplasia) after partial hepatectomy remains controversial; the discussion is based: (i) on the known stimulating effect of these hormones in tissue culture; (ii) on changes in insulin and glucagon levels after partial hepatectomy; and (iii) on the results of ablation/repletion experiments.¹⁻⁷ Using incorporation of ¹⁴C-thymidine into DNA as an index of regeneration, we have previously found that partially hepatectomized rats fed pharmacological amounts of amino acids via an intragastric catheter synthesized

significantly less DNA than partially hepatectomized rats receiving intragastric water alone.⁸ In order to determine whether amino acids depressed regeneration by changing insulin and glucagon levels we have measured the concentration of these hormones in portal and systemic blood at intervals varying from 0 to 4 hours after partial hepatectomy in groups of rats fed amino acids or water. The possible role of glucagon as a hepatotropic factor was further examined by measuring DNA synthesis in a group of rats pretreated with a specific antiserum to glucagon before partial hepatectomy.

MATERIALS AND METHODS

Male black-hooded Long-Evans rats weighing between 170 and 190 g were housed under controlled conditions of temperature and humidity and allowed water and food *ad lib.* throughout the period of study. Partial hepatectomies were performed under diethyl ether anaesthesia, with removal of the median and left lateral lobes.⁹ All partial hepatectomies were performed between 08h00 and 09h30. Immediately after partial hepatectomy rats received 2 ml of water alone or 2 ml of a solution containing amino acids. The amino acid mixture used consisted of arginine 19,30 mg, asparagine 14,40 mg, isoleucine 6,68 mg, leucine 12,91 mg, lysine 29,21 mg, methionine 5,17 mg, phenylalanine 7,75 mg, proline 31,61 mg, threonine 16,52 mg, tryptophan 3,99 mg and valine 13,07 mg. The amounts are similar to those previously shown to depress DNA synthesis following partial hepatectomy in the rat.⁸ Half an hour, 1 hour, 2 hours and 4 hours after partial hepatectomy, groups of rats were anaesthetized with diethyl ether, the abdomen was opened, and blood was

MRC Liver and Endocrine Research Groups, Department of Medicine, University of Cape Town

R. E. KIRSCH, M.B. CH.B., M.D., F.C.P. (S.A.)

L. O'C. FRITH, B.SC.

A. VINIK, M.D., F.C.P. (S.A.)

J. TERBLANCHE, CH.M., F.C.S. (S.A.) F.R.C.S.

Date received: 27 August 1980.