

Mitochondrial Function and Free Fatty Acid Levels in Rats after Portacaval Shunt

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SUMMARY

The effects of portacaval shunting on the oxidative phosphorylation process of mitochondria isolated from rat liver and skeletal muscle were evaluated and correlated with mitochondrial free fatty acid (FFA) contents. ADP/O ratios, respiratory control index and QO_2 values were significantly depressed in liver mitochondria from portacaval-shunted rats; these changes were associated with decreased mitochondrial FFA contents. The mitochondrial function of skeletal muscle was unaltered.

S. Afr. med. J., 56, 181 (1979).

Portacaval shunting has been reported to have certain beneficial effects on two inherited diseases, viz. glycogen storage disease and familial hypercholesterolaemia.¹⁻⁶ However, the exact mechanism whereby this procedure achieves these effects has not yet been established. Recent work on animals has shown that the metabolic consequences of portal diversion are more complex as well as more profound than has been realized.^{7,8}

Relatively little is known about subcellular changes occurring in liver tissue after portacaval shunting. In rats, the significant loss of liver glycogen content has been shown to be related to the decreased food intake, whereas hepatic atrophy after portacaval shunting appears to be directly related to the shunting of portal blood away from the liver.⁹ This phenomenon could be due to the lowered insulin supply, which has been shown to be a major portal factor responsible for maintaining cell size and number.¹⁰ Synthesis of cholesterol and of total fatty acids was found to be similar in portacaval-shunted and control rats.⁹

Ischaemia of the liver, produced by clamping either the portal venous blood flow or the hepatic artery blood supply, resulted in a significant depression of mitochondrial function,¹¹⁻¹³ which was attributed to increased mitochondrial free fatty acid (FFA) contents.¹² Since shunting of the

portal blood away from the liver could possibly induce chronic ischaemic conditions within the cells, this study was undertaken to evaluate the effects of portacaval shunting on the mitochondrial oxidative phosphorylation process as well as on the mitochondrial FFA content of liver and muscle. The role of dietary intake in portacaval-shunted rats was also evaluated by studying mitochondrial function in appropriate pair-fed and *ad libitum*-fed control animals.

MATERIALS AND METHODS

Animals

Male BD 9 rats (230 - 280 g) were used. The animals were housed individually in metabolic cages fitted with wide wire-mesh bottoms. The animals were allowed to adapt for a period of 1 week before experimentation. A reversed light-darkness cycle was adopted and the rats were sacrificed in the mid-dark phase.

Four series of rats were studied: (i) portacaval-shunted rats (PCS); (ii) sham-operated rats, pair-fed to PCS rats (S); (iii) normal control rats, pair-fed to PCS rats (PFC); and (iv) normal control rats, fed *ad libitum* (ALC).

The portacaval shunt operation was performed as described by Lee *et al.*¹⁴ The sham operation was performed under similar conditions and the sham-operated controls were individually matched in terms of ischaemic time and weight to PCS animals. The mean ischaemic time was $13,1 \pm 0,3$ min.

All animals were observed for 42 days from the day of operation, fed once per day, and the food intake and body weight recorded. On the 42nd day, 24 hours after their last feed, the rats were sacrificed.

Mitochondrial Studies

Mitochondria were prepared from liver and skeletal muscle (quadriceps) tissue for the study of oxidative phosphorylation. Two mitochondrial isolation media were used: (i) sucrose (0,25M), tris-HCl (1 mM), EDTA (1 mM) (pH 7,4) was used for liver tissue; (ii) KCl (0,18M), EDTA (10 mM) (pH adjusted to 7,4 with tris base) was used for muscle tissue. All available liver tissue and the quadriceps muscles from both legs were placed directly into ice-cold isolation medium and minced finely with scissors. After washing the tissue 3-4 times to remove all traces of blood, fresh isolation medium was added before homogenization (>12 volumes per g tissue). The liver was homogenized at maximum speed with a Polytron PT 10 homogenizer (± 3 seconds), whereas the muscle tissue was homogenized for longer periods (4×5

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Date received: 12 December 1978.

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seconds) or until no whole particles of tissue were seen. Liver mitochondria were prepared as described by Sordahl *et al.*¹⁵ The final pellet was suspended in sucrose-tris-EDTA medium at a concentration of 30-40 mg mitochondrial protein per ml. Skeletal muscle mitochondria were isolated according to the method of Molé *et al.*¹⁶ and finally suspended in KCl-EDTA, yielding a suspension medium containing 10-15 mg mitochondrial protein per ml.

The oxidative phosphorylation process of liver and muscle mitochondria was studied polarographically as described by Sordahl *et al.*¹⁵ The incubation medium for liver mitochondria contained KCl (75 mM), tris-HCl (50 mM), K_2HPO_4 (12.5 mM), $MgCl_2$ (5 mM) and EDTA (1 mM). Glutamate (5 mM, tris salt, pH 7.4) and succinate (5 mM, tris salt, pH 7.4) were used as substrates. The incubation medium for muscle mitochondria consisted of sucrose (0.25M), tris-HCl (10 mM, pH 7.4) and K_2HPO_4 (8.5 mM), using glutamate (5 mM) as substrate. To produce state 3 respiration, a 0.1-ml aliquot of ADP (containing 400-450 nmol ADP) was added. The exact amount of ADP added (which is equal to the amount of ATP formed) was determined spectrophotometrically, using a millimolar extinction coefficient of 15.4.¹⁵ The incubation temperature for these studies was 25°C. Mitochondrial protein content was measured by the method of Lowry *et al.*¹⁷

The following indices of mitochondrial function were measured: ADP/O ratios (nmol ATP produced per atom oxygen consumed); mitochondrial oxygen uptake (QO_2) (state 3: natoms oxygen uptake in the presence of ADP/mg protein/min; state 4: natoms oxygen uptake after phosphorylation of ADP/mg protein/min); respiratory control index (RCI) (ratio of oxygen consumed in the presence of ADP to that after phosphorylation of ADP).

FFA Determination

On the 42nd day blood was drawn under ether anaesthesia from the abdominal aorta in all rats and collected in EDTA. FFAs were extracted from plasma and mitochondria according to the method of Dole and Meinertz¹⁸ and analysed by a Beckman model GC4 gas chromatograph as described.¹⁹ The total FFA content of each sample was calculated as the sum of the individual FFA measured.

Preparation of Specimens for Electron Microscopy

Blocks obtained from the liver immediately after the rats had been killed were diced in precooled (4°C) 3% glutaraldehyde in 0.1M phosphate buffer (pH 7.2) into 1-mm³ blocks. These were fixed in 3% glutaraldehyde for 24 hours and postfixed in 1% OsO_4 in Millonig's buffer (pH 7.3)²⁰ at 4°C for 2 hours. The blocks were then dehydrated in a graded series of ethanol solutions and in propylene oxide, embedded in Epon 812, sectioned at 100 nm, and stained with uranyl acetate²¹ and lead citrate.²² The sections were examined with a Philips EM 300 electron microscope at 60 kV.

Morphometry

Five blocks from each animal were taken at random and electron micrographs taken at an initial magnification of 6 840 and printed at a magnification of 17 100. The surface area of the mitochondrial outer membrane as well as the surface area of the mitochondrial cristae was determined by the use of square lattices.²³

RESULTS

Mitochondrial Oxidative Phosphorylation (Table I)

Liver: Mitochondria, isolated from the livers of ALC rats, using sucrose-tris-EDTA as isolation medium, with glutamate and succinate as substrates, yielded ADP/O ratios, RCI and QO_2 values similar to those reported by other workers.^{11,15}

Mitochondria isolated from livers of PCS animals exhibited significantly depressed ADP/O ratios as well as RCI and QO_2 values, compared with the other 3 groups. This significant depression was evident with both glutamate and succinate as substrates. Compared with ALC mitochondria, the percentage depression in ADP/O, RCI and QO_2 of PCS mitochondria averaged 26%, 45% and 34% respectively, with glutamate as substrate. Figs 1 and 2 show oxygraph tracings obtained from liver mitochondria of PFC and PCS rats, which clearly illustrate the marked differences observed in the parameters of mitochondrial function.

TABLE I. LIVER AND SKELETAL MUSCLE MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION OF CONTROL AND PORTACAVAL-SHUNTED RATS*

Liver	ADP/O	RCI	QO_2
Substrate:			
glutamate			
ALC (6)	2,79 ± 0,08	6,29 ± 0,41	72,63 ± 2,46
PFC (8)	2,42 ± 0,08	5,89 ± 0,54	72,92 ± 4,64
P	<0,01	NS	NS
S (8)	2,41 ± 0,06	5,25 ± 0,36	87,10 ± 2,45
P	<0,005	NS	<0,005
PCS (9)	2,07 ± 0,19	3,45 ± 0,62	48,18 ± 6,92
P	<0,005	<0,005	<0,01
Substrate:			
succinate			
ALC (6)	1,87 ± 0,06	6,53 ± 0,40	141,06 ± 3,90
PFC (8)	1,62 ± 0,06	7,05 ± 0,52	147,13 ± 13,04
P	<0,02	NS	NS
S (8)	1,68 ± 0,05	5,93 ± 0,45	178,32 ± 5,44
P	<0,05	NS	<0,001
PCS (9)	1,43 ± 0,11	3,99 ± 0,61	114,78 ± 10,87
P	<0,005	<0,01	<0,05
Skeletal muscle			
Substrate:			
glutamate			
PFC (6)	3,41 ± 0,13	9,65 ± 1,31	71,49 ± 8,63
S (8)	3,31 ± 0,07	10,68 ± 1,63	93,24 ± 13,47
PCS (9)	3,36 ± 0,15	8,70 ± 0,99	77,96 ± 6,75

* Results expressed as mean ± SEM. P values indicate significance of difference from ALC. Numbers in parentheses indicate number of animals.

TABLE II. MITOCHONDRIAL FFA CONTENTS IN LIVER AND SKELETAL MUSCLE

	14:1	16:0	16:1	18:0	18:1	18:2	20:4	Total
Liver								
ALC (5)		22,94 ± 3,02	3,89 ± 0,30	12,60 ± 1,03	13,96 ± 1,29	34,91 ± 1,71	16,49 ± 1,23	108,2 ± 6,72
PFC (8)	0,45 ± 0,23	10,39 ± 3,09	2,80 ± 0,47	7,80 ± 1,41	8,83 ± 2,05	21,57 ± 4,2	7,98 ± 2,74	63,6 ± 12,63
<i>P</i>		<0,02	NS	<0,02	NS	<0,02	<0,02	<0,01
S (8)	1,02 ± 0,21	6,25 ± 0,62	3,16 ± 0,38	7,95 ± 0,49	5,56 ± 0,54	14,25 ± 0,84	3,96 ± 0,73	47,4 ± 2,77
<i>P</i>		<0,001	NS	<0,005	<0,001	<0,001	<0,001	<0,001
PCS (8)	0,95 ± 0,25	11,74 ± 2,60	3,32 ± 1,23	7,15 ± 0,77	12,49 ± 2,63	15,51 ± 2,28	5,17 ± 1,24	61,9 ± 8,56
<i>P</i>		<0,02	NS	<0,005	NS	<0,001	<0,001	<0,005
Skeletal muscle								
ALC (5)		22,90 ± 3,02	5,67 ± 0,96	16,88 ± 2,04	11,58 ± 1,26	44,00 ± 2,12	32,30 ± 15,44	110,74 ± 7,41
PFC (8)	3,39 ± 0,19	14,12 ± 2,31	5,44 ± 1,36	15,04 ± 4,21	10,58 ± 1,93	35,52 ± 4,71	5,94 ± 2,88	82,80 ± 6,20
<i>P</i>		<0,02	NS	NS	NS	NS	NS	<0,02
S (8)	2,43 ± 0,46	13,58 ± 2,25	5,38 ± 0,93	13,76 ± 2,08	7,35 ± 1,11	23,80 ± 3,05	—	70,90 ± 5,75
<i>P</i>		<0,05	NS	NS	<0,05	<0,001	—	<0,005
PCS (8)	4,89 ± 1,40	15,61 ± 1,39	4,32 ± 0,62	18,58 ± 3,06	8,12 ± 0,78	21,57 ± 1,77	3,83 ± 1,70	93,70 ± 8,62
<i>P</i>		<0,05	NS	NS	<0,05	<0,001	NS	NS

* Results expressed as nmol/mg mitochondrial protein (mean ± SEM).
P values indicate significance of difference from ALC. Numbers in parentheses indicate number of animals.

PAIR-FED CONTROL RATS

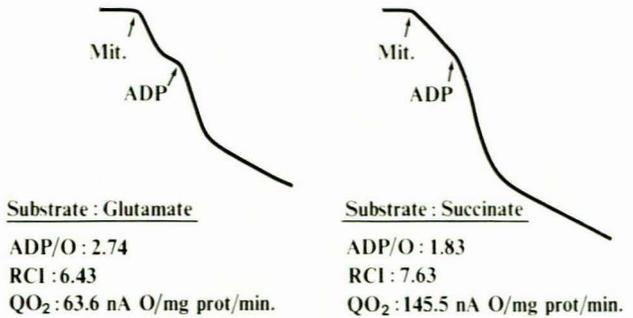


Fig. 1. Oxygraph tracings of liver mitochondria from PFC rats. (Substrates: glutamate (5 mM); succinate (5 mM); amount of ADP added: 438 nmol.)

PORTACAVAL SHUNTED RATS

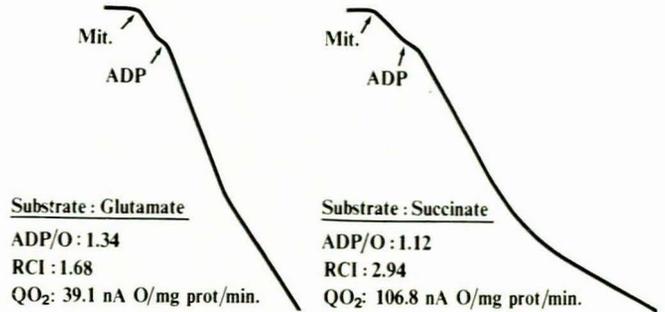


Fig. 2. Oxygraph tracings of liver mitochondria from PCS rats. (Substrates: glutamate (5 mM); succinate (5 mM); amount of ADP added: 446 nmol.)

The reduced food intake in S and PFC rats affected mitochondrial function: mitochondria isolated from PFC rat livers had a significantly lower ADP/O ratio ($P < 0,01$) than mitochondria from ALC rats, while the RCI and QO_2 values were unchanged. Mitochondria isolated from livers of S rats had significantly lower ADP/O ratios compared with liver mitochondria from ALC rats, whereas the QO_2 values were increased. These phenomena were observed with both glutamate and succinate as substrates.

Skeletal muscle: Mitochondria isolated from the quadriceps muscle of S, PFC as well as PCS rats exhibited no changes with regard to ADP/O, QO_2 and RCI values.

Liver and Skeletal Muscle Mitochondrial FFA Contents (Table II)

The total FFA content of mitochondria isolated from PFC, S and PCS rat livers was significantly lower than that of ALC rat livers ($P < 0,01$, $P < 0,001$ and $P < 0,005$ respectively). Analysis of the individual FFA fractions showed a tendency of all FFA (except C14:1) to be decreased in mitochondria from PFC, S and PCS rat livers. In these 3 groups the mitochondrial C16:0, C18:0 and C20:4 contents were significantly lowered compared with those of ALC rats.

The total FFA content of skeletal muscle mitochondria of PFC and S rats was significantly lowered ($P < 0,02$ and $P < 0,005$ respectively). However, the total FFA content of PCS rat skeletal muscle mitochondria was unchanged. Skeletal muscle mitochondrial C16:0 content was significantly lowered in all 3 experimental groups.

Electron Microscopic Findings

Ultrastructural morphometric analysis of the hepatocytes of the 4 different groups showed that the only relevant change present was the significant reduction (30%) in the surface area of the mitochondrial cristae membranes in PCS rats compared with those of ALC rats. No statistically significant differences were observed in the number or size of the mitochondria of liver tissue of PCS and ALC rats (Figs 3 - 6).

DISCUSSION

This paper is the first to describe marked alterations in mitochondrial structure and function occurring in rat liver tissue after portacaval shunting. Whether these mitochondrial changes are due to events occurring in the liver immediately after portacaval shunting, or to events occurring during the 42-day period after the operation, has not yet been established.

Portacaval shunting induced lasting liver mitochondrial functional changes which persisted when the mitochondria were incubated in a suitable medium under favourable



Fig. 4. Electron micrograph of PCS rat liver ($\times 10\,500$).



Fig. 3. Electron micrograph of ALC rat liver ($\times 10\,500$).

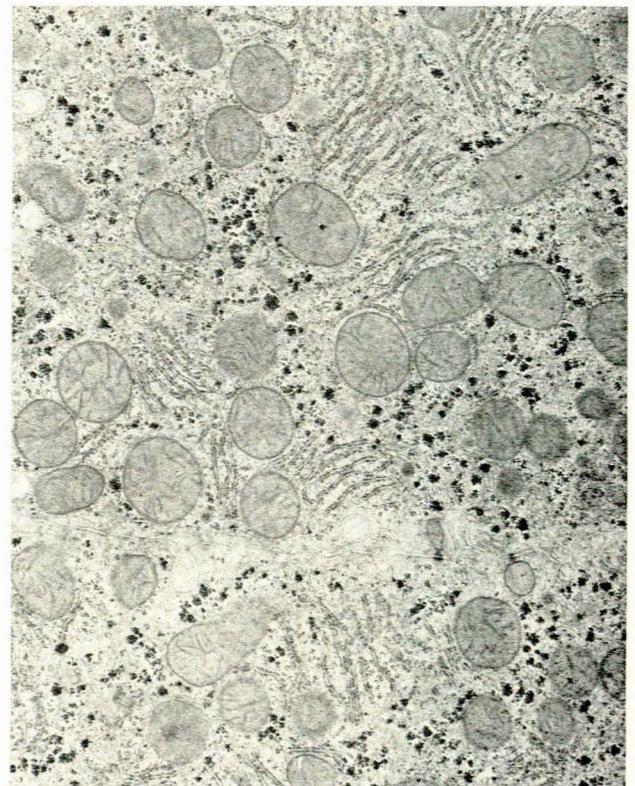


Fig. 5. Electron micrograph of ALC rat liver ($\times 26\,000$).

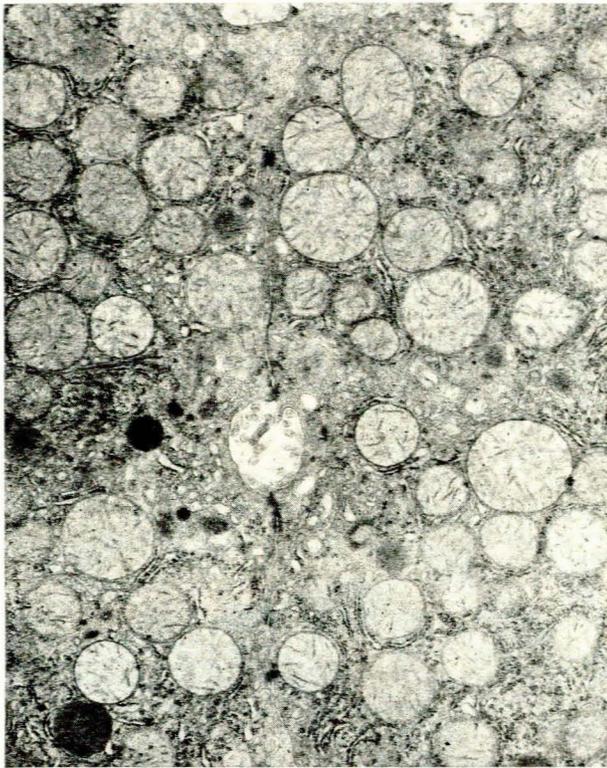


Fig. 6. Electron micrograph of PCS rat liver ($\times 26\,000$).

conditions. Oxidative phosphorylation of mitochondria isolated from the liver of PCS rats was significantly depressed with both substrates studied: mitochondrial ADP/O ratios as well as RCI and Q_{O_2} values were significantly lowered (Figs 1 and 2, Table I). The percentage depression was greatest for the respiratory control index (glutamate: 45%; succinate: 39%) which is considered to be the most sensitive index of mitochondrial function.²⁴ This was due to a decrease in the rate of state 3 respiration, as well as to an increase in state 4 respiration rate.

It is also of interest that glutamate oxidation is more sensitive to injury than succinate oxidation. The depression in RCI and Q_{O_2} averaged 45% and 34% respectively with glutamate as substrate, compared with 39% and 19% with succinate. These findings suggest that oxidation of NAD-linked substrates may be more susceptible to injury induced by portacaval shunting.

These significant changes in the oxidative phosphorylation capacity of mitochondria isolated from livers of PCS rats were substantiated by the finding of a reduced surface area of the mitochondrial cristae membranes which are intimately associated with the processes of electron transport and oxidative phosphorylation.²⁵

The exact mechanism by which portacaval shunting affects mitochondrial function of the liver is not yet known. However, it appears to be a specific effect on liver tissue, since mitochondria isolated from skeletal muscle of PCS rats functioned normally (Table I). The reduction in food intake by PCS rats could play a role

in the above observations, since mitochondria isolated from the livers of both PFC and S rats had lower ADP/O ratios when compared with ALC rats. However, portacaval shunting also caused an additional reduction in RCI and Q_{O_2} values.

A similar depression in mitochondrial function has also been observed in ischaemia of the liver. Production of ischaemia by either vascular occlusion of the median or left lobe²³ or by incubation of excised liver tissue in a moist chamber at 37°C^{11,22} resulted in reduction of mitochondrial ADP/O, RCI and Q_{O_2} values. Although the hepatic blood supply following portacaval shunting in rats has not yet been determined, the shunting away of portacaval blood could induce an ischaemic situation in the liver and thereby affect mitochondrial function.

Elevated mitochondrial FFA levels have been suggested as the cause for the reduction in mitochondrial oxidative phosphorylation observed in hepatic ischaemia.²⁶ A 6-7-fold increase in mitochondrial FFA levels was found after 2 hours of ischaemia at 38°C.²⁶ However, the results obtained in the present study are not in line with the above theory, since the FFA levels were significantly lowered in liver mitochondria from all 3 experimental groups. The effects of lowered mitochondrial FFA levels on mitochondrial function have not yet been established. Since these levels were observed in both liver and skeletal muscle of all 3 pair-fed groups, this could possibly be related to reduced food intake.

The depressed mitochondrial oxidative phosphorylation process in myocardial ischaemia has been shown to be associated with increased levels of tissue FFA, while mitochondrial FFA levels remained unaltered.¹⁹ The possibility therefore exists that mitochondrial function in PCS animals may be associated with increased tissue levels of FFA. However, this remains to be determined. It has been shown that the FFA-synthesizing capacity of the liver is not affected by portacaval shunting, since the incorporation of 1-¹⁴C-acetate into FFA is similar in all groups.⁸

Another factor to be considered is the depression in plasma glucose and insulin levels observed in PCS rats.⁷ Addition of glucose and insulin to the perfusate of hypoxic perfused hearts caused a significant improvement in mitochondrial oxidative phosphorylation.²⁷ However, it is clear that further work is necessary to elucidate the exact mechanism whereby portacaval shunting affects subcellular changes in liver tissue.

In summary, the results obtained clearly showed a significant depression in mitochondrial function of liver tissue occurring after end-to-side portacaval shunting, which is an indication of the significance of maintained portal circulation in hepatic function.

This reduction in mitochondrial oxidative phosphorylation capacity could contribute to the impairment of liver function often associated with this procedure.²⁸ The reduction in food uptake observed in these animals also appears to be of significance in the interpretation of the results.

The authors wish to thank the South African Medical Research Council and the University of Stellenbosch for financial support.

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Pain

H. W. SNYMAN

On the letterhead for this conference appears an apt quotation from Keats:

'Pleasure is oft a visitant
but pain clings cruelly to us'

Allow me to say:

'From different times
and mental climes
came Milton and Keats
but sensitive each
to the deep barb of pain.'

in order to quote the earlier Milton:

'A sense of pleasure
we may well spare of life perhaps
and not repine
but live with content
which is the calmest life.
But pain is perfect misery
the worst of evils,
and excessive
overturms all patience.'

The medical profession has always been under pressure to supply public explanations of the diseases with which it deals. On the other hand, it is an old characteristic of the profession to devise comprehensive and unifying theories on all sorts of medical problems. Both these statements apply to pain — one of the most important and clinically striking phenomena and expressions of man since his origin in the mists of time.

Need I emphasize the obvious that pain as such cannot be directly observed; what we do observe are persons claiming that, and/or behaving as though, they are in pain. What then is this pain? The definition I submit follows that of Engel¹ and that of Fabrega and Tyma:² Pain is an unpleasant perception which the individual explicitly refers to his body and which can represent a form of suffering. The emphasis is thus on perception, unpleasantness, and the link with the body or physical apparatus in order to distinguish pain from other unpleasant perceptions such as guilt, sadness, 'mental pain' and even nausea. Furthermore, the affective properties of pain in this instance feature more than the purely sensory properties.

Within the great diversity of human types, the way in which people will react, what they will say and how they will behave when experiencing this unpleasant sensation called pain will vary considerably. What they say and how they behave are observable as the external accompaniments of the presumed internal state of pain; these are grouped and referred to as pain behaviour. There may be movement, involuntary and voluntary, and changes in demeanour and in facial expression. More important and helpful to us is what they say in attempting to describe and to qualify the pain experience. This is the linguistic dimension of pain, the pain language within the language usage of that person and the people to whom he belongs.

The response to and avoidance of noxious stimulation is an elemental factor in the adaptation of all living systems and thus also of man. We see pain as a warning and thus as a protective mechanism. Man's capacity for symbolization, however, introduces a different dimension to the problem. It is not only a central nervous system but

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Inaugural address at the Pain Conference, Cape Town, 23 February 1979.