MEDICAL GRAND ROUNDS

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THE ASYMPTOMATIC HYPOGLYCEMIC STATES:

THE ROLE OF NON-GLUCOSE SUBSTRATES IN MAINTAINING NORMAL CEREBRAL METABOLISM AND FUNCTION DURING CERTAIN HYPOGLYCEMIC STATES

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I. THE OCCURRENCE OF ASYMPTOMATIC HYPOGLYCEMIA IN CONDITIONS SUGGESTING CEREBRAL UTILIZATION OF NON-GLUCOSE SUBSTRATES (LACTATE, ACETATE, KETONES)

A. Glycogen Storage Diseases - Type I (Von Gierke's) and Type III (Cori's)
B. Neonatal Period
C. Fasting provoked episodes of hypoglycemia associated with profound lactic acidosis in some subjects with chronic renal failure.
D. Diabetic patients with chronic renal failure during dialysis with glucose-free solutions containing 33 mM of acetate.
E. During insulin-induced hypoglycemia after prolonged starvation.
F. Prolonged heavy muscular exercise

II. POSSIBLE MECHANISMS FOR PROFOUND HYPOGLYCLEMIA WITHOUT SYMPTOMS OF NEUROGLUCOPENIA

A. ADEQUATE CEREBRAL DELIVERY OF GLUCOSE DESPITE LOW BLOOD GLUCOSE LEVELS.

Cerebral delivery of glucose CD gl is the product of cerebral blood flow (CBF) and arterial glucose concentration. Since there is large biologic variation in CBF, the CD gl also varies widely. As a consequence the ability to tolerate reductions in arterial glucose levels without decreasing CD gl below a critical level may be important in some cases of asymptomatic hypoglycemia.

TABLE 1

ASYMPTOMATIC HYPOGLYCEMIA SECONDARY TO ADEQUATE CEREBRAL DELIVERY OF GLUCOSE DESPITE HYPOGLYCEMIA

Subject	CBF ml/100gm/min	Art.GLucose mg/dl	C D glucose mg/100gm/min	Symptoms of Neuroglucopenia
A	40	80	32	No
	40	70	28	No
	40	40	16	Yes
B	70	80	56	No
	70	40	28	No

B. SUBSTITUTION OF CERTAIN ORGANIC ACIDS FOR GLUCOSE IN THE MAINTENANCE OF NORMAL CEREBRAL OXYGEN UTILIZATION AND CEREBRAL FUNCTION AND STRUCTURE.

III. BRIEF REVIEW OF CEREBRAL METABOLISM

It is evident from the fact that the adult brain which weighs only 2% of body weight but utilizes 20% of the basal oxygen consumption is one of the most metabolically active organs.

The general consensus is that under ordinary circumstances glucose is the obligatory and almost exclusive substrate for cerebral energy production. That the brain's energy under usual ordinary circumstances derives from glucose oxidation is supported by the stoichiometric relationship between cerebral oxygen uptake and glucose utilization and by the cerebral respiratory quotient of unity.

When glucose is deprived acutely, cerebral oxygen consumption falls and neuroglucopenic symptoms appear.

On the average the adult brain utilizes about 100-150 gms of glucose per day or 70-105 mg/min. (Gottstein et al, 1972) The mean value is about 90 mg/min. In the post-absorptive state, the hepatic ouput of glucose is about 150-180 mg/min. Fifty percent of this is used by the brain. Of the large amount of glucose required almost all (>93%) is oxidized to CO_2 and H_2O. Under normal conditions glycolytic breakdown is less than 7%.

The aerobic metabolism of this large amount of glucose requires the utilization of about 50 cc of O_2 per min., an amount equal to 20% of the basal oxygen consumption. These enormous needs for glucose and oxygen of the adult brain are met by a very high cerebral blood flow (CBF) which averages 800-950 ml/min or 15-20% of the cardiac output. At 800 cc/min the CDgl and CDO_2 are 640 mg/min and 160 ml/min respectively, significantly in excess of the 90 mg/min and 50 ml/min utilized.

These large requirements of the adult are dwarfed by the requirements of the growing infant and child. By 6 years of age CBF has attained high levels and declines later to the level of normal young adults. In the 6 year old the $CMRO_2$ is 5.2 ml/100 gm brain/min or a total O_2 consumption of 60 ml/min. This is more than 50% of the total basal body O_2 consumption of the child.

TABLE 2

CEREBRAL FLOOD FLOW AND OXYGEN CONSUMPTION IN MAN FROM CHILDHOOD TO OLD AGE

Life Period	Age	Cerebral Blood Flow (ml/100 g/min)	Cerebral O_2 Consumption (ml/100g/min)
Childhood	6	106	5.2
Normal Young Adulthood	21	62	3.5
Normal Elderly	71	58	3.3

(from Sokoloff, 1972)

IV. CEREBRAL UTILIZATION OF NON-GLUCOSE SUBSTRATES

Recent recent data suggest that the brain in vivo may be more flexible in its use of substrate than was previously believed to be the case. These newer data indicate that a variety of organic acids present in the blood under physiologic and pathophysiologic conditions can be oxidized by the brain of man.

In 1967 in the classic studies on brain metabolism in human subjects during prolonged fasting, Owen et al, identified ketones as the substrate capable of substituting in large part for glucose in cerebral metabolism.

TABLE 3

CHANGES IN CEREBRAL UTILIZATION OF SUBSTRATE
DURING A 38-41 DAY FAST IN 3 HUMAN SUBJECTS

Brain oxygen substrate equivalents in mmols/liter of blood

Substrate	A-V Difference	Calc.O_2 Equivalent
Glucose	0.26	
Lactate	-0.20	
Pyruvate	-0.03	
Glucose + (L+P)/2	0.145	0.87
β-Hydroxybutyrate	0.34	1.53
Acetoacetate	0.06	0.24
∝-Amino Nitrogen	0.09	0.42
Total Substrate Equivalent		3.06
Measured oxygen consumption		2.96

(from Owen et al, 1967)

After 5-6 weeks of starvation when plasma ketone levels averaged 7.8 mmol/l glucose oxidation accounted for only 30% of the oxygen consumption of the human brain whereas ketone uptake could account for 60% of the oxygen consumed (β-OHB 52% and AcAC 8%).

Today I wish to review the data which suggest that certain organic acids i.e., acetoacetate, β-hydroxybutyrate, lactate, and acetate can significantly replace glucose in the maintenance of normal cerebral function when blood glucose falls to hypoglycemic levels. In addition, we will review data which helps define the conditions prerequisite for such adequate substitution.

V. THE ABILITY OF LACTATE TO SUBSTITUTE FOR GLUCOSE AS A SUBSTRATE FOR CEREBRAL OXYGEN METABOLISM

In 1941 Wortis, Bowman, Goldfarb, Fazekas and Himwich studied the ability of lactate to substitute for glucose during prolonged insulin induced hypoglycemic coma in schizophrenic subjects. The utilization of lactate during hypoglycemia was evidenced by an increased utilization of oxygen by the brain. However, the magnitude of this utilization apparently was not great enough to produce clinical recovery from coma.

TABLE 4

EFFECT OF INTRAVENOUS SODIUM LACTATE ON CEREBRAL METABOLISM OF SCHIZOPHRENIC PATIENTS (14) IN INSULIN COMA

	ART. GLUCOSE mg/dl	ART.-JV O_2 ml/dl	ART.-JV LACTATE mg/dl	STATE OF CONSCIOUSNESS
Before Lactate	43	2.7	7.0	Comatose
After Lactate	39	4.0	14.0	Comatose
Change		+48%	+100%	

(Wortis et al 1941)

Arterial-jugular vein oxygen difference and lactate difference increased from 2.7 ml/dl and 7 mg/dl during the comatose state to 4 mg/dl and 14 mg/dl after the intravenous administration of 20 grams of sodium lactate. Despite this 48% increase in cerebral O_2 utilization (CBF did not change) and doubling of lactate uptake by the brain, only 2 of the 14 subjects showed some clinical improvement as evidenced by a decrease in the depth of coma. However, none recovered completely from coma.

These data indicate that the brain in vivo can oxidize lactic acid but not at a rate sufficient to sustain cerebral function. This limited rate could be secondary to insufficient enzymatic activity for oxidizing lactate or more likely by a limited diffusion rate of lactate across the blood-brain barrier.

In 1974 Nemoto, Hoff, and Severinghaus utilizing more elegant techniques restudied the magnitude that lactate could substitute for glucose in 8 dogs rendered hypoglycemic by insulin and hyperlactatemic (8 mmol/l) by lactate infusion. Cerebral blood flow (CBF), A-V for lactate, glucose and O_2 were determined permitting measurement of CMR-La, CMR-glu and $CMRO_2$.

As plasma lactate stablized around 7-8 mM brain A-V lactate difference increased significantly and CSF lactate rose to about 5 mM.

TABLE 5

LACTATE UPTAKE AND METABOLISM BY BRAIN

Mean Brain-Blood Flow, Oxygen, Glucose and Lactate Metabolism During Insulin-Induced Hypoglycemia in Eight Dogs

	CBF	A-V, mM		CMR, μO_2eq per gm min		
	ml/100 gm min	La	Gluc.	La	Gluc.	O_2
Control	44.5	-0.01	0.52	-0.01	1.49	1.52
Hypoglycemia	37.7					1.26
La Loading	47.8	0.27	0.45	0.45	1.18	1.64

(Nemoto et al, 1974)

During hypoglycemia $CMRO_2$ fell 17% from 1.52 to 1.26. Following lactate loading $CMRO_2$ returned to normal levels i.e., 1.64 µmol/min/gr/brain.

The metabolism of glucose accounted for 1.18 μO_2 eq/min/gm or 75% of the $CMRO_2$. The lactate utilized by the brain accounted for 28% of the $CMRO_2$ (0.45 μO_2 eq/min/gm.)

These data indicate that lactate can stoichiometrically replace about 25% of the glucose used by the dog's brain as substrate during hypoglycemia. The data suggest that uptake may well be transport limited by saturation of carriers facilitating passage of lactate across the blood-brain barrier and into brain cells, since plasma lactate was raised to about 7-8 mM in these studies and cerebral extration of lactate from arterial blood averaged only around 3 to 5% (Nemoto et al, 1974). Fractional extraction was not increased by hypoglycemia.

THERE ARE HOWEVER CLINICAL DATA WHICH SUGGEST THAT UNDER CERTAIN CIRCUMSTANCES THE CAPACITY OF THE LACTATE CARRIERS MAY BE INCREASED TO A DEGREE SUFFICIENT TO MAINTAIN NORMAL MENTATION AND CEREBRAL FUNCTION IN THE PRESENCE OF PROFOUND HYPOGLYCEMIA WITH PLASMA GLUCOSE LEVELS AS LOW AS 9 mg/dl. (Rutsky et al 1978; Maguire et al, 1978, Mataverde et al, 1974)

During chronic renal failure a syndrome of recurrent hypoglycemia associated with severe lactate acidosis has been reported. There are at least three characteristics features of this syndrome.

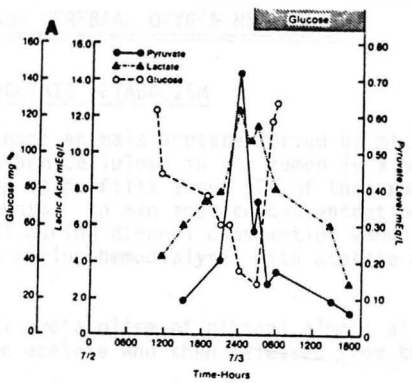
1. It occurs spontaneously during fasting in patients with chronic renal failure.

2. The severe lactic acidosis is stopped by the administration of glucose.

3. DESPITE PROFOUND HYPOGLYCEMIA SOME PATIENTS ARE FULLY ORIENTED AND UNAWARE OF THE LOW LEVELS OF BLOOD SUGARS.

FIGURE 1

ASYMPTOMATIC HYPOGLYCEMIA WITH LACTIC ACIDOSIS



(Maguire et al, 1978)

This subject was alert the day prior to the test when his blood glucose was 23 mg/dl. During the test his blood glucose fell to 29 mg/dl and although the concommitant lactic acidosis (12 mmol/l) produced marked hyperventilation he did not develop symptoms of neuroglucopenia.

This apparent increase in transport of lactate across the blood-brain barrier may be related to the increased permeability of the blood-brain barrier in uremia reported in the studies of Freeman et al (1962), of Fishman (1967 and 1970) and of Glazer (1974).

That the increased permeability of the blood-brain barrier in these subjects is related to changes accompanying chronic renal failure is supported by two other observations.

1. In alcoholic ketoacidosis with high lactate levels the hypoglycemia is symptomatic.

2. In the syndrome of recurrent hypoglyclemia and lactic acidosis occurring in congestive heart failure, the hypoglycemia has been reported to be symptomatic. (Medalle et al, 1971)

VI. THE ABILITY OF ACETATE TO SUBSTITUTE FOR GLUCOSE AS A SUBSTRATE FOR CEREBRAL OXYGEN METABOLISM

A. REVIEW OF ACETATE METABOLISM

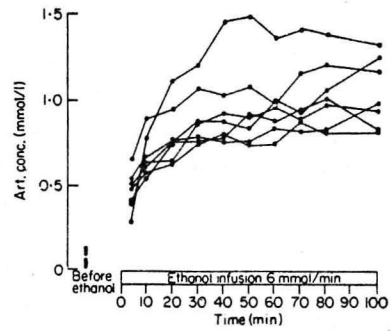
In fed ruminant animals acetate formed by microbial fermentation of cellulose and hemicellulose in the rumen is a major source of energy. In sheep it fulfills about 50% of that ruminant's daily caloric requirements. In man acetate concentrations normally are less than 0.2mM except during ethanol consumption when plasma acetate rises to 1 to 2 mM and during hemodialysis with acetate containing dialysate.

During hepatic metabolism of ethanol almost all of the ethanol is converted to free acetate and then released from the liver. (Lundquist et al, 1962)

This results in a steady state concentration of acetate between 1-2 mmol/l. The failure of acetate concentration to continue to rise is evidence that it is used in preference to other substrates by the extrahepatic tissues of man and animals (Lundquist, 1962).

Figure 2

ARTERIAL ACETATE CONCENTRATION FOR THE DIFFERENT SUBJECTS BEFORE AND AFTER ETHANOL TREATMENT



(from Juhlin-Dannfelt, 1977)

Studies from our laboratory in dogs have indicated that during ethanol metabolism acetate produces a significant 35% impairment of peripheral glucose utilization. Jorfeldt and Juhlin-Dannfelt in 1978 also reported an inhibition of glucose utilization across the legs of human subjects in association with an increase in acetate utilization.

TABLE 6

MEAN LEG UPTAKE (mmol/min) IN 5 HUMAN SUBJECTS

	Control	After Ethanol
Acetate	---	0.25
Glucose	0.12	0.06
Lactate	-0.11	-0.05
Oxygen	1.99	1.96

(from Jorfeldt & Juhlin-Dannfelt, 1978)

Plasma acetate turnover rate in young adults at the normal fasting plasma acetate level of only 0.174 mM averaged 8.3 µmol/min·kg or 835 mmol/70 kg/day and accounted for 13% of total oxygen consumption (Skutches et al, 1979).

TABLE 7

PLASMA ACETATE CONCENTRATION, TURNOVER, AND OXIDATION IN YOUNG ADULT

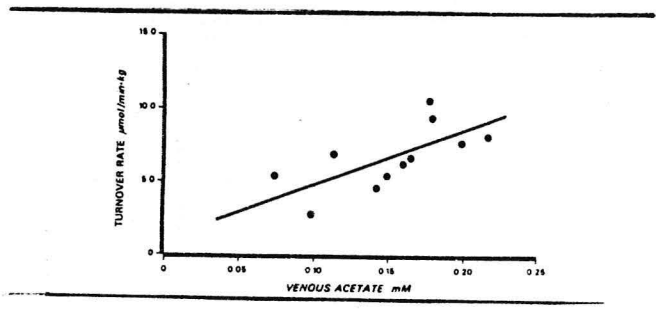
Plasma Acetate Concentration	Plasma Acetate Turnover	CO_2 Output from Acetate Oxidation
mM	µmol/min·kg	%
0.174	8.23	13.2

(Skutches et al, 1979)

Skutches et al (1979) also have shown that the total body rate of acetate utilization correlates directly with the plasma acetate level.

Figure 3

EFFECT OF INCREASE IN PLASMA ACETATE ON ACETATE TURNOVER RATE IN MAN



(from Skutches et al, 1979)

In 1962 Lundquist's data indicated that at a plasma acetate level of 1.5 mM, the rate of acetate oxidation could reach 300 mmol/hr and thereby account for furnishing about 1500 cal/day. During the metabolism of alcohol, about 50% of the acetate released from the liver is utilized by the muscle mass (Jorfeldt and Juhlin-Dannfelt, 1978); 10% by the brain (Juhlin-Dannfelt, 1977) and 10% by the heart (Lindeneg et al, 1964).

In 1977 Juhlin-Dannfelt studied cerebral metabolic rates of glucose, acetate, and oxygen in 7 healthy males during ethanol infusions which resulted in a blood alcohol level of 12 mmol/l and a plasma acetate level of about 1 mmol/l.

TABLE 8

ARTERIAL-JUGULAR VENOUS DIFFERENCES OF OXYGEN, ACETATE, GLUCOSE, LACTATE, BEFORE AND AFTER ETHANOL IN 7 MEN

	Before	Ethanol Administration 6 mmol/min			
mmol/l	Ethanol	40 min	60 min	80 min	100 min
Oxygen	3.71	3.42	3.39	3.40	3.36
Acetate		0.11*	0.10*	0.12*	0.12*
Glucose	0.70	0.56*	0.47*	0.48*	0.46*
Lactate	-0.06	-0.03	-0.01*	-0.02*	-0.03*

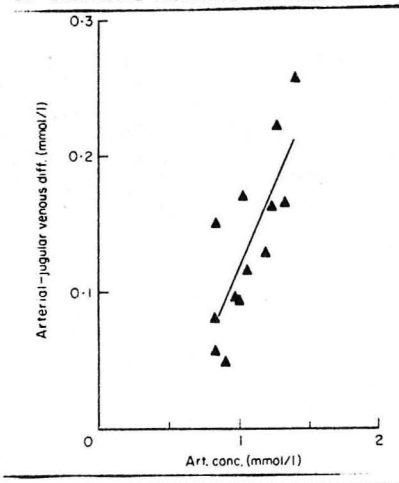
*Asteriks indicate significantaly different from the value before ethanol.(Juhlin-Dannfelt, 1977)

Prior to ethanol administration, glucose uptake by the brain accounted for 100% of the oxygen utilized. As acetate uptake by the brain increased, glucose uptake by the brain decreased and accounted for only 86% of the oxygen used.

The data also indicated that acetate utilization by the brain was directly related to the arterial acetate concentration.

Figure 4

EFFECT OF INCREASE IN ARTERIAL ACETATE LEVELS ON CEREBRAL ACETATE UPTAKE IN MAN



(from Juhlin-Dannfelt, 1977)

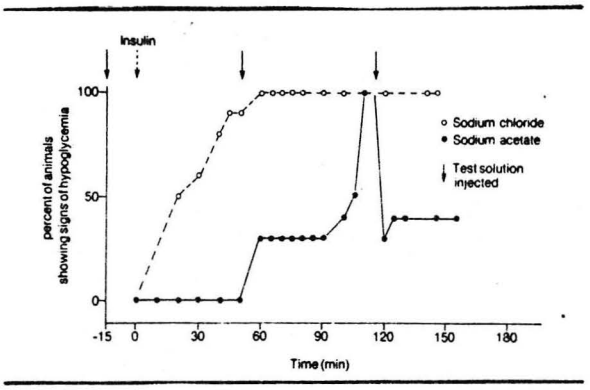
These data indicate a significant uptake of acetate by the human brain but in normoglycemic man with plasma acetate levels between 1 to 2 mmol/l acetate could account for only 6% of the oxygen used by the brain. (Juhlin-Dannfelt, 1977).

B. ACETATE AS A SUBSTITUTE FOR GLUCOSE IN CEREBRAL METABOLISM DURING HYPOGLYCEMIA

The studies of Urion et al (1979) in mice suggest that acetate can substitute for glucose in cerebral metabolism when profound hypoglycemia is present. In those studies they showed that the intraperitoneal administration of acetate not only prevented the central nervous system manifestations of insulin-induced hypoglycemia but also reversed them when they were present.

Figure 5

EFFECTS OF SODIUM ACETATE ON THE CENTRAL NERVOUS SYSTEM SIGNS OF INSULIN-INDUCED HYPOGLYCEMIA

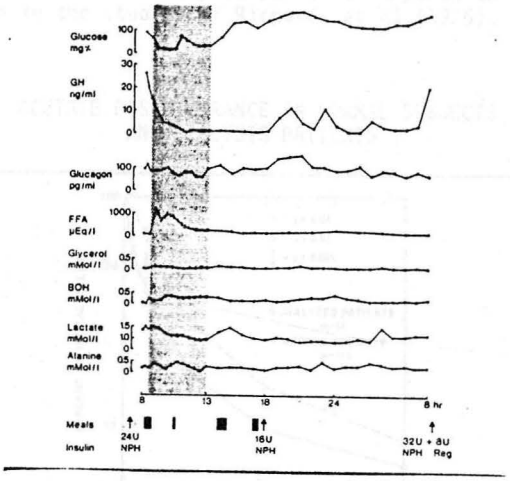


The percent of mice showing signs of hypoglycemia is shown as a function of time. (from Urion et al, 1979)

THERE ALSO ARE SUBSTANTIAL CLINICAL DATA WHICH INDICATE THAT UNDER CERTAIN CIRCUMSTANCES ACETATE METABOLISM BY THE HUMAN BRAIN CAN OCCUR AT A MAGNITUDE SIGNIFICANT TO SUSTAIN NORMAL CEREBRAL FUNCTION DESPITE PROFOUND HYPOGLYCEMIA. UREMIC DIABETIC PATIENTS DIALYSED WITH GLUCOSE-FREE DIALYSATE CONTAINING 33 mM ACETATE WHO DEVELOP VERY LOW PLASMA GLUCOSE LEVELS (20 mg/dl) MAY NOT MANIFEST ANY SUBJECTIVE OR OBJECTIVE EVIDENCE OF NEUROGLUCOPENIA (Hansen et al 1979, Orskov et al 1980).

Figure 6

ASYMPTOMATIC HYPOGLYCEMIA DURING DIALYSIS



(From Hansen et al, 1979)

Despite breakfast, during dialysis this patient's plasma glucose fell to 20 mg/dl where it remained for over 1½ hours until 20 grams of IV glucose were administered. Shortly thereafter it decreased again to hypoglycemic levels. The patient was totally unaware of the two prolonged hypoglycemic episodes.

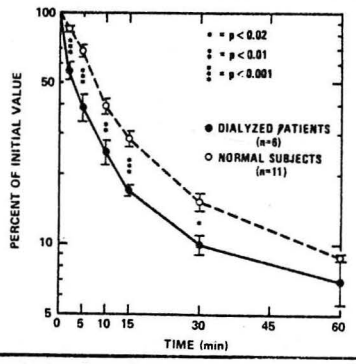
These investigators point out that diabetic uremic patients undergoing dialysis with glucose-free dialysate containing 33-35 mM acetate not uncommonly develop quite severe hypoglycemic levels lasting prolonged periods and AS A RULE DO NOT EXHIBIT ANY SIGNS OR SYMPTOMS OF HYPOGLYCEMIA. The absence of symptoms or signs of hypoglycemia cannot be ascribed to either diabetic or uremic neuroencephalopathy since insulin-induced hypoglycemia outside the dialysis periods were readily perceived by the identical subjects.

In these subjects plasma acetate reaches levels as high as 2 to 5 mmol/l. In view of the steep linear relationship between arterial plasma acetate concentration and cerebral uptake of acetate, the A-JV acetate difference would be expected to increase to 0.90 mmol/l at an arterial level of 4 mmol/l, i.e. 7.5 fold increase in A-JV acetate difference as plasma acetate increases from 1 to 4 mmol/l. With plasma acetate levels at least between 2 to 5 mmol/l the magnitude of the cerebral uptake of acetate apparently is sufficient to maintain cerebral metabolism and function in the presence of profound hypoglycemia.

Another factor which may be important in the ability of uremic patients undergoing dialysis with glucose-free acetate containing dialysate to develop asymptomatic hypoglycemia is the more rapid rate of acetate utilization of dialysis patients compared to normal subjects as shown in the studies of Richards et al (1976).

Figure 7

ACETATE DISAPPEARANCE IN NORMAL SUBJECTS AND DIALYSIS PATIENTS



Plasma acetate levels are expressed as a percent of the value at termination of dialysis or of the acetate infusions (Richards et al, 1976)

In summary, the ability of uremic subjects to substitute the metabolism of acetate for glucose in sufficient quantities to maintain normal cerebral oxidative metabolism and function during profound hypoglycemia may be related to the following:

1. Possible increased acetate transport across the blood-brain barrier in the presence of hypoglycemia and/or uremia.

2. High levels of plasma acetate (2 to 5 mM) which occur during dialysis especially in view of the linear relationship between arterial acetate concentrations and cerebral uptake of acetate.

3. Ability of the uremic dialysis patients to more rapidly metabolize acetate.

4. Finally, the rapid metabolism of sodium acetate to sodium bicarbonate would raise pCO_2 and thereby very likely increase cerebral blood flow and the cerebral delivery of acetate.

VII. THE ABILITY OF KETONES TO SUBSTITUTE FOR GLUCOSE AS A SUBSTRATE FOR CEREBRAL OXYGEN METABOLISM

A. EFFECTS OF FASTING

The classical studies of Owen et al in 1967 examining the substances utilized by the human brain as substrate for oxygen utilization during prolonged starvation revealed that β-OHB (52%) and AcAc (8%) together accounted for 60% of the total cerebral O_2 consumption. Cerebral glucose consumption fell and accounted for only 30% of the O_2 consumed.

Shortly thereafter Smith and colleaques (1969) reported induction of brain β-OHB dehydrogenase by fasting in rats as an explanation for Owen's findings. This could not be confirmed even in the laboratory of origin. (Sokoloff, 1973).

According to Krebs and many other investigators brain ketone body utilization is a function of transport across the blood-brain barrier and not a function of oxidative enzymatic adaptation. Rates of ketone transport increase as blood ketone concentration rises. Numerous studies revealed the uptake of ketones by the brain varies directly with arterial concentration. The studies of Gottstein et al (1971,1972) in adults and of Persson et al (1972) in infants and children on the cerebral uptake of ketones revealed a significant direct relationship between arterial ketone concentration and cerebral uptake (A-JV difference).

In 1974 Ruderman et al studied the regulation of cerebral ketone-body and glucose metabolism in vivo in the rat. Their data showed three important physiologic facts:

1. The rates of cerebral utilization of AcAc and β-OHB are governed by their concentrations in plasma. The uptake of ketone bodies by the rat brain is linearly related to the arterial ketone body concentration.

2. The transport of ketones across the blood-brain barrier most likely is the rate limiting step in the cerebral metabolism of ketones since the concentrations of acetoacetate and β-hydroxybutyrate in brain cells were very low compared to plasma levels.

3. As ketone utilization by the brain increased there was a simultaneous decrease in glucose uptake.

TABLE 9

EFFECT OF CHANGES IN KETONE CONCENTRATION ON GLUCOSE UTILIZATION BY THE BRAIN

State of Animal	Calculated O_2 Consumption (mM)			% of O_2 Used Due to Ketones
	Glucose	Ketone Bodies	Total	
Fed	2.78	0.02	2.80	0.6
Starved 24 h	2.19	0.61*	2.81	22
Starved 48 h	1.85	0.64*	2.55	25
Streptozotocin-diabetes	1.15*	1.24*	2.39	52
Phlorrhizin-diabetes	1.32*	1.02*	2.32	44
Starved 24 h, then infused with 3-hydroxy-butyrate	1.19*	1.79*	2.99	60

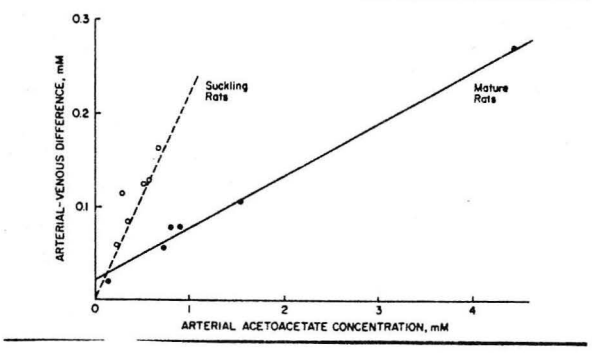
*Values significantly different from those of the fed group.
(Ruderman et al, 1974)

B. EFFECTS OF AGE ON CEREBRAL KETONE TRANSPORT AND UTILIZATION

Krebs (1971) and associates (Hawkins et al, 1971) reported that cerebral uptake of ketone bodies of suckling rats is three to four fold greater than adult rats. Both are linearly related to arterial ketone body levels but for any given arterial ketone level, arterial-jugular venous ketone difference is significantly greater in suckling rats.

FIGURE 8

RATES OF TRANSFER OF ACETOACETATE INTO THE BRAINS OF SUCKLING RATS COMPARED TO ADULT RATS



(from Krebs, 1971 and Hawkins et al, 1971)

The studies of Gottstein et al (1971 and 1972) in adults, and of Persson et al (1972) in infants and children on the cerebral uptake of ketone bodies revealed the following relevant facts.

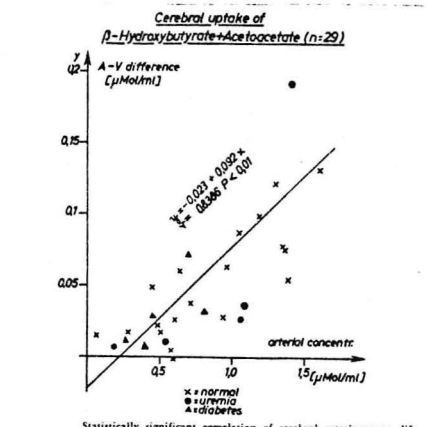
1. In human subjects the uptake of ketones by the brain varies directly with their plasma concentrations.

2. Even after just an overnight fast a measurable A-JV difference for ketones across the brain is present. Ahlborg and Wahren (1972) and Juhlin-Dannfelt (1977) also found A-JV ketone differences after an overnight fast. However, under these circumstances the rate of ketone utilization accounted for only 3 to 4% of the oxygen used by the brain. (Juhlin-Dannfelt, 1977).

3. For any given arterial plasma concentration of ketone bodies, infants and children increase the cerebral uptake of ketone to a significantly greater degree than do adults. The twofold greater Art-JV ketone difference in infants and children compared to adults suggests increased permeability and transport capability across the blood-brain barrier of infants and children. (Robinson and Williamson, 1980)

This coupled with the almost twofold greater cerebral blood flow per gram of tissue in infants and children results in an almost four-fold greater cerebral utilization of ketones. (Robinson and Williamson, 1980)

FIGURE 9

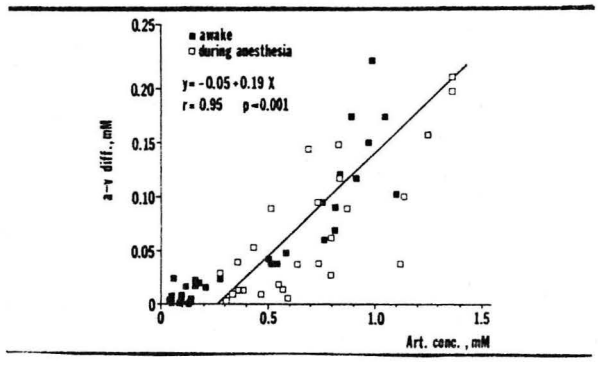


Statistically significant correlation of cerebral arteriovenous differences of total ketone bodies and arterial concentrations.

(from Gottstein et al, 1971)

FIGURE 10

EFFECT OF INCREASING ARTERIAL LEVELS OF KETONES ON CEREBRAL KETONE UPTAKE IN INFANTS AND CHILDREN



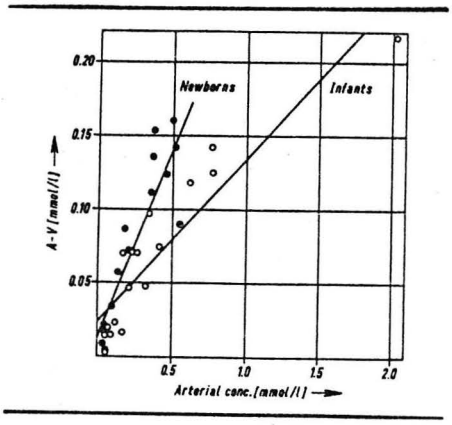
(From Persson et al, 1972)

At the arterial ketone concentrations present after an overnight fast, the utilization of ketones by the adult brain accounts for only 3 to 4% of the total cerebral oxygen utilization (Juhlin-Dannfelt). By contrast, the utilization of ketones by the brain of infants and children after an overnight fast accounts for 13% of total cerebral oxygen utilization (Settergren, Lindblad and Persson, 1976).

THE ASYMPTOMATIC HYPOGLYCEMIA WHICH CAN OCCUR IN HUMAN NEONATES RATIONALLY CAN BE ASCRIBED NOT ONLY TO AN EVEN GREATER PERMEABILITY THE NEONATAL BLOOD-BRAIN BARRIER TO KETONES AND THE SUBSEQUENT GREATER UPTAKE OF KETONES BY THE BRAINS OF NEONATES COMPARED TO INFANTS, BUT, ALSO TO THE EASE OF DEVELOPMENT OF HYPERKETONEMIA IN HUMAN NEONATES (Kraus et al, 1974; Persson and Gentz, 1976).

FIGURE 11

COMPARISON OF THE CEREBRAL UPTAKE OF KETONES
IN HUMAN NEWBORN BABIES AND INFANTS



(from Kraus et al, 1974)

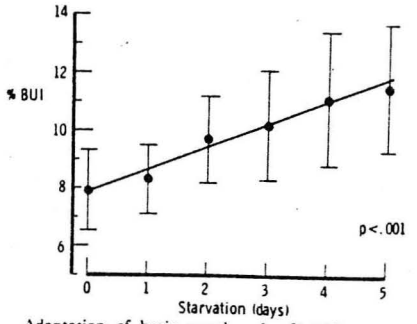
C. EVIDENCE FOR INDUCTION OF THE TRANSPORT MECHANISM OF KETONES ACROSS THE BLOOD-BRAIN BARRIER

In the adult human the increased ketone body utilization by the brain during starvation which accounts for 60% of the total cerebral oxygen utilization cannot be ascribed to increases in the activities of the ketone body metabolizing enzymes and had been linked solely to the increased plasma levels of ketones characteristic of prolonged starvation.

However, the studies of Gjedde and Crone (1975), of Moore et al (1976), and Spitzer (1973), indicate that INDUCTION OF THE TRANSPORT MECHANISM FOR KETONE BODIES ACROSS THE BLOOD-BRAIN BARRIER OCCURS DURING STARVATION AND FAT FEEDING.

FIGURE 12

ADAPTATION OF CEREBRAL KETONE TRANSPORT DURING STARVATION



Adaptation of brain uptake of D-[3-^{14}C]hydroxybutyrate during starvation.

(From Gjedde and Crone, 1975)

The Brain Uptake Index (BUI) increased significantly with the duration of starvation indicating adaptation of the transport mechanism.

At the usual level of β-OHB seen in rats after 5 days starvation, the transport of β-OHB from blood to brain was twice as great as would be expected if no induction of transport took place. At higher levels of ketonemia, transport rates are four-fold greater in starved rats than the capacity of the non-induced transport mechanism at the same level of ketonemia in fed rats. (Gjedde and Crone, 1975)

The data from Spitzer, 1973 also reveals that in dogs starved 8 days facilitated transport of β-OHB is induced and results in a 2.4 fold greater A-JV ketone difference across the brain at similar arterial ketone concentrations compared to dogs fasted only 1 day.

TABLE 10

CHANGES IN CEREBRAL UPTAKE OF KETONES (mmol/l) DURING β-OHB INFUSION (5 mg/kg/min) AFTER PROLONGED FASTING IN DOGS

	After 1 Days' Fasting (N=5)	After 8 Days' Fasting (N=7)
Arterial AcAc	0.470	0.511
A-V AcAc	0.055	0.072
E% AcAC	11.7%	14.1%
Arterial β-OHB	1.515	1.329
A-V β-OHB	0.069	0.164
E% β-OHB	4.5%	12.3%

(From Spitzer 1973)

There is incontrovertable evidence that ketones bodies can substitute for glucose as the major cerebral metabolic substrate during prolonged starvation in man. Moreover, there are data which show that this process is aided by induction of the transport system for ketones across the blood-brain barrier during prolonged starvation and by the elevated plasma ketone levels characteristic (7 to 8 mM) of prolonged starvation.

D. CAN KETONES SUBSTITUTE FOR GLUCOSE DURING ACUTE HYPOGLYCEMIA?

A major problem is whether or not ketones can substitute for glucose in sufficient quantities to maintain normal cerebral metabolism and function DURING ACUTELY INDUCED HYPOGLYCEMIA.

1. INSIGHTS FROM THE SYNDROME OF ALCOHOLIC KETOACIDOSIS

Alcohol-induced ketoacidosis is uniquely suited to examining some of the problems of substrate substitution for glucose in the maintenance of cerebral metabolism, since this condition is associated not only with hypoglycemia in about 23% of the cases but also with significant elevations of three organic acids (acetate, ketones, and lactate) capable of oxidation by cerebral tissue.

MEAN β-OHB - 7.8 mmol/l (2.4-22.4)
MEAN LACTATE - 5.4 mmol/l (0.7-20.6)
MEAN ACETATE - 1-2 mmol/l (if alcohol still present in blood)

The studies of Platia and Hsu in 1979 in patients with alcohol-induced hypoglycemia and ketoacidosis suggest that this is not necessarily the case and other changes are required to induce the transport process and increase the transport of ketone bodies across the blood-brain barrier. Despite high levels of ketones and elevated lactate levels these subjects were comatose secondary to hypoglycemia.

TABLE 11

LABORATORY SUMMARY OF NONDIABETIC ALCOHOLIC PATIENTS WITH HYPOGLYCEMIC KETOACIDOTIC COMA

Case	Art. pH	Serum Acetest	Urine Acetest	Serum Glucose (mg/dl)	Serum Bicarb. (mEq/L)	Lactic Acid (mEq/L)	Serum β-OHB (mEq/L)	Anion Gap
1	7.16	+	+	25	14	2.6	9.8	27
2	7.18	+	+	21	15	2.3	---	21
3	7.23	-	-	27	17	---	7.3	22
4	7.19	-	-	21	13	2.2	8.5	29
5	7.18	+	+	19	15	2.4	5.9	24
Mean	7.19	---	---	23	15	2.4	7.9	25

Platia & Hsu 1979

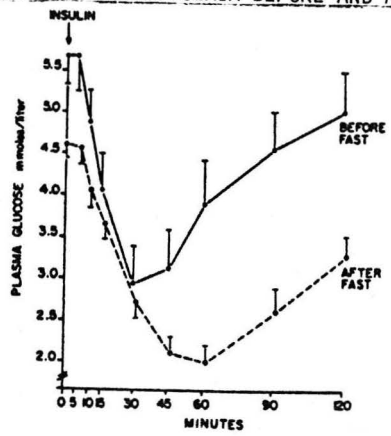
Evidence that the comatose state in these subjects indeed was secondary to insufficient cerebral delivery of glucose and insufficient magnitude of utilization of ketone bodies is seen from the prompt clinical response of these subjects to IV glucose administration.

However, the studies of Drenick and associates (1972) in human subjects indicate that WHEN AN ACUTE FALL IN BLOOD GLUCOSE TO HYPOGLYCEMIC LEVELS IS PRECEDED BY A PROLONGED FAST, KETONE BODIES CAN THEN SUBSTITUTE FOR GLUCOSE AND BE METABOLIZED AT A RATE OF SUFFICIENT MAGNITUDE TO MAINTAIN NORMAL CEREBRAL FUNCTION FREE OF ANY OBJECTIVE OR SUBJECTIVE EVIDENCE OF NEUROGLUCOPENIA. This suggests that when there is enough time to allow adaptation of the ketone transport process across the blood-brain barrier, hyperketonemia will result in sufficient cerebral ketone utilization to maintain normal cerebral function.

In 9 obese subjects symptomatic insulin-induced hypoglcyemia was produced prior to fasting. After 2 months of complete fasting, insulin-induced hypoglycemia to levels lower than the prefast control studies did not produce any clinical or biochemical evidence of neuroglucopenia.

Figure 13

INSULIN-INDUCED HYPOGLYCEMIA BEFORE AND AFTER FASTING



Plasma glucose concentrations and per cent changes from base line after insulin; before and after prolonged fasting ($N = 9$, means $\pm$SEM).

(From Drenick et al, 1972)

TABLE 12

MEAN CHANGES IN A-V SUBSTRATE DIFFERENCES ACROSS THE BRAIN IN 5 FASTING OBESE MEN DURING INSULIN INDUCED ASYMPTOMATIC HYPOGLYCEMIA

mmol/L	Minutes After Insulin					Mean
	0	30	45	60	120	30-120 min.
ß-OHB	0.21	0.68	0.70	0.54	0.86	0.70
Glucose	0.24	0.10	0.07	0.20	0.11	0.12

(Drenick et al, 1972)

During the post-fast insulin tolerance test plasma ß-OHB fell from 8.0 to 6.7 mmol/l. Despite the fall in plasma ketone, the extraction of ketones by the brain increased as the A-JV ketone difference rose from 0.21 to 0.70 mmol/l during the 30-120 minute post-insulin period. Simultaneously with the three-fold increased uptake of ketones was a 50% fall in glucose uptake as evidenced by a decrease in A-JV glucose difference from 0.24 to 0.12 during this same period of time.

It therefore appears likely that there are two necessary preconditions to assure adequate cerebral utilization of ketones in the presence of an acute fall in blood glucose concentration. Both of these preconditions appear to occur with prolonged starvation (greater than 2 days in man):

1. Elevation of plasma concentrations of ketone bodies

2. Induction of the transport carrier for ketones across the blood-brain barrier. (This in turn may be related to the duration of hyperketonemia)

2. INSIGHTS FROM THE GLYCOGEN STORAGE DISEASES (TYPE I & III)

These preconditions assuring adequate cerebral substitution of ketones for glucose are apparently met in some (Types I & III) of the GLYCOGEN STORAGE DISEASE since many investigators have reported that frequently these children may be completely asymptomatic with blood glucose levels less that 10 mg/dl (Levine et al, 1954, Howell, R.R., 1972, Van Crevald, 1961, and Zuppinger 1975).

FIGURE 14

Clinical Conference on Metabolic Problems

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Glycogen Storage Disease

This is a recording of a weekly conference held at Michael Reese Hospital, conducted and edited by Dr. Rachmiel Levine and Dr. Matthew Taubenhaus. Participants include members of the various clinical and research departments of the Hospital, and of the intern and resident staff.

QUESTION: Why do not some of these patients have symptoms associated with the hypoglycemia?

DR. LEVINE: This is a very difficult question to answer properly. On the basis of all the evidence available, we usually state that the neurones utilize only glucose for energy. All the oxygen consumption of the brain is accounted for by the glucose uptake in vivo or in vitro. Only glucose or an immediate glucose precursor is useful in the relief of hypoglycemic coma. Yet, many patients with glycogen storage disease may not show any central nervous system symptoms even at levels of blood glucose ranging from 0 to 20 mg. %. What fuel is the brain using in such instances? No definite answer is at present possible.

(from Levine and Taubenhaus, 1954)

This ability to have unimpaired CNS function in the presence of profound hypoglycemia is very likely the consequence of the following:

1. The increased permeability of the blood-brain barrier to ketones and increase rate of ketone transport in infants and young children compared to young adults.

2. The increased cerebral blood flow in children (106 ml/100gm brain/min) compared to adults (60 ml/100 gm/min).

3. The increase cerebral delivery of ketones as a consequence of (2) and of the elevated levels of plasma ketones (and lactate) in these children.

TABLE 13

THE CHARACTERISTICS OF GLYCOGEN STORAGE DISEASES

Functional tests in hepatic glycogenoses[1]

Type	Blood parameters	Functional tests: Fasting	Glucagon (fasting)	Glucagon (post-prandial)	Glucose	Galactose or Fructose	Glycerol	Ethanol
I	glucose lactate ketones	very low very high high	no rise strong rise	no rise	n/diabetic fall fall	no rise rise	low rise unaltered	no fall fall rise
III	glucose lactate ketones	low/n n/high very high	no rise mild rise	n	n/diabetic strong rise fall	n strong rise	strong rise rise	strong fall rise strong rise
VI	glucose lactate ketones	low/n n/high very high	n		n n/rise fall	n rise	strong rise mild rise	mild fall rise rise

[1] Compiled results from STEINITZ (1967), SENIOR and LORIDAN (1968b), FERNANDES *et al.*, [1969], SPENCER-PEET *et al.* [1971] and the present study.

(from Zuppinger, 1975)

3. THE ENIGMA OF ASYMPTOMATIC HYPOGLYCEMIA DURING PROLONGED HEAVY MUSCULAR EXERCISE

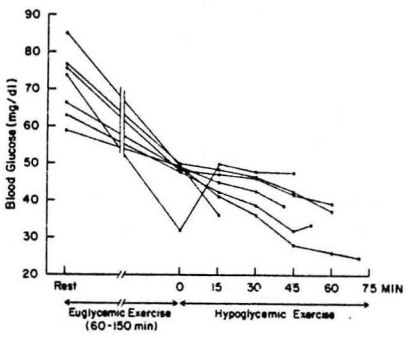
In 1982 Ahlborg and Felig reported the occurrence of asymptomatic frank hypoglycemia (blood glucose ⩽45 mg/dl) in 50 percent of healthy subjects who exercised on a bicycle ergometer at 58% of their maximal oxygen uptake from 3-5 hours. Blood glucose first started to fall after 40 minutes, the most marked rate of fall occurred in the third hour and by 3.5 hours blood glucose was below 45 mg/dl in half the subjects.

In another study Felig and associates (1982) reported the occurrence of asymptomatic hypoglycemia in 37% of healthy men who exercised to exhaustion on a cycle ergometer at 60 to 65 percent of their maximal aerobic power.

Despite hypoglycemic levels between 25 and 48 mg/dl the subjects continued to exercise for an additional 15 to 70 minutes. Their exhaustion time was no different than the euglycemic subjects and they did not show signs of neuroglucopenia.

FIGURE 15

ASYMPTOMATIC HYPOGLYCEMIA DURING PROLONGED HEAVY EXERCISE IN HEALTHY MEN



(From Felig et al, 1982)

Previous studies on brain substrate utilization during exercise (Ahlborg and Wahren, 1972) failed to show significant utilization of any substrate other than glucose at a work load of 55 to 70 per cent of the subjects physical working capacity for one hour.

The data indicate that the glucose requirement of the brain persists unchanged during exercise of this type and duration. All of the oxygen utilized could be accounted for by the oxidation of glucose.

These studies however, shed no light on the substrate utilization of the brain in subjects who remained asymptomatic despite significant hypoglycemia during prolonged heavy exercise since none of these subjects developed hypoglycemia.

The prolonged heavy exercise that produced asymptomatic hypoglycemia was not associated with hyperketonemia and lactate levels rose only about 1 mmol/l from 0.5 to 1.5 mmol/l. (Ahlborg et al, 1982) There is no immediate explanation for the absence of signs or symptoms of neuroglucopenia in these subjects.

Future studies on cerebral blood flow, extraction of organic acids and the cerebral delivery of glucose during exercise induced hypoglycemia should help elucidate this problem.

VIII. SUMMARY

1. The enzymatic activity of the brain is great enough to utilize β-OHB, acetoacetate and lactate in amounts of sufficient magnitude to substitute as substrate for glucose during hypoglycemia provided these organic acids are transported across the blood-brain barrier in large enough quantities.

2. There is no evidence for cerebral adaptation of ketone metabolizing enzymes during conditions which produce high rates of ketone utilization.

3. The rates of cerebral utilization of acetate, lactate, and ketones are related directly to their arterial concentration.

4. Substrates which can substitute for glucose in maintaining cerebral energy production and normal cerebral function during profound hypoglycemia are capable of doing this only under restricted conditions.

a) appropriate magnitude of ketone utilization requires not only elevation of plasma ketone levels but also the adaptation of the transport mechanism of ketones across the blood-brain barrier. This in turn requires a prior period of starvation and/or a prior period of hyperketonemia. The total amount of ketones transported in neonates, infants, and children is augmented by a high cerebral blood flow and a transport rate for ketones greater than that present in adults.

b) substitution of acetate or lactate for glucose during profound hypoglycemia has been reported only during chronic renal failure when the plasma levels of these substrates were elevated for other reasons. This suggests that chronic renal failure in some way leads to an increase in the transport mechanism for these substances across the blood-brain barrier. This supposition is supported by the increased permeability of blood-brain barrier said to occur during chronic renal failure.

5. No adequate pathophysiologic explanation for the fact that the hypoglycemia of prolonged muscular exercise can be asymptomatic is forthcoming from available published data. Areas for future study have been outlined.

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