

Table1:- Affect of increased ratios of Acetyl CoA/CoA and NADH/NAD.

Randle cycle	Proposed hypothesis						
PYRUVATE-→P.D.H → Acetyl CoA (glycolysis) ↑ (Acetyl CoA/CoA) ↑NADH/NAD) In MM ← β- oxidation (of fats) T.C.A. cycle NB: - When Acetyl-CoA, the end products of both glycolysis and B-Oxidation, there is competition for the substrate, Oxalo- acetate. According to Randle only PDH is inhibited by the increased ratios of Acetyl-CoA/CoA& NADH/NAD, blocking the entry of glycolytic products in to Kerb's cycle.	↑ Acetyl CoA/CoA ↑NADH/NAD P.D.H T.C.A. cycle blocked for glycolysis products Both major energy metabolisms are inhibited A.M.P.K β-oxidation of fats is inhibited CITRATE SYNTHASE Conversion of iso-citrate to α-ketoglutarate blocked. T.C.A cycle blocked for both metabolisms ISOCITRATE DEHYDROGENASE T.C.A cycle blocked for both metabolisms CITRATE LYASE Cytoplasmic level of Acetyl CoA is low. ↓β-oxidation ↑Lipogenesis Condensation of Acetyl CoA with O.A is inhibited. T.C.A cycle blocked for both metabolisms NB :- The same increased ratios in fact inhibit multiple enzymes whose consequences are depicted above. <table border="1"> <thead> <tr> <th colspan="2">Fate of Acetyl CoA already Accumulated in mitochondrial matrix.</th></tr> <tr> <th>From glycolysis</th><th>From β-oxidation</th></tr> </thead> <tbody> <tr> <td> ↓P.D.H ↑P.C G.N Started </td><td> ↓A.M.P.K • G.N • Lipogenesis and • Ketogenesis Are started </td></tr> </tbody> </table>	Fate of Acetyl CoA already Accumulated in mitochondrial matrix.		From glycolysis	From β-oxidation	↓P.D.H ↑P.C G.N Started	↓A.M.P.K • G.N • Lipogenesis and • Ketogenesis Are started
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NBRed line/arrow- indicates inhibition/decreased concentration Green line/arrow- indicates stimulation/increased concentration							

Table-2:- Post PDH inhibition events- Preferential initiation, perpetuation and access to T.C.A cycle of β -oxidation products over glycolytic products.

Case 1:- $\uparrow$ Pyruvate $\uparrow$ Citrate (current view)	Case 2:- $\downarrow$ Pyruvate $\downarrow$ Citrate (proposed hypothesis)
$\uparrow$ Acetyl CoA/CoA $\uparrow$ NADH/NAD <pre> graph TD A["$\uparrow$ Acetyl CoA/CoA $\uparrow$ NADH/NAD"] -- red T-bar --> B["$\downarrow$ P.D.H"] B --> C["$\uparrow$ Pyruvate"] C --> D["$\uparrow$ P.C"] D --> E["$\uparrow$ Citrate"] E -- green arrow --> F["$\uparrow$ ACC"] F --> G["$\uparrow$ Acetyl"] G --> H["$\downarrow$ A.C."] H --> I["$\downarrow$ Acetyl CoA"] I -- green arrow --> J["$\uparrow$ β-oxidation of fats"] I -- green arrow --> K["Allosteric Stimulation"] K --> J J -- green arrow --> L["Net Effect – NIL (B-oxidation remains inhibited)"] </pre> Net Effect – NIL (B-oxidation remains inhibited)	$\uparrow$ Acetyl CoA/CoA * $\uparrow$ NADH/NAD <pre> graph TD A["$\uparrow$ Acetyl CoA/CoA * $\uparrow$ NADH/NAD"] -- red T-bar --> B["$\downarrow$ P.D.H"] B --> C["$\downarrow$ Pyruvate"] C --> D["$\downarrow$ P.C"] D --> E["$\downarrow$ Citrate"] E -- green arrow --> F["$\downarrow$ ACC"] F --> G["$\downarrow$ Acetyl"] G --> H["$\downarrow$ A.C."] H --> I["$\downarrow$ Acetyl CoA"] I -- green arrow --> J["$\uparrow$ β-oxidation of fats"] I -- green arrow --> K["Allosteric Stimulation"] K --> J J -- green arrow --> L["Stimulation"] </pre> Stimulation
If pyruvate is increased consequent to PDH inhibition, the end result should have been stimulated B-Oxidation as contended by Randle, but actually the B-Oxidation is inhibited. Contention of Randle cyclethus not fulfilled, if pyruvate is actually increased initially.	Contention of Randle cycle fulfilled If initial pyruvate level is low. * The inhibitory effect lasts only until the ratios are reversed. ** The inhibitory effect is constant and continues in starvation/DM2.

Table 3:- Blockages of Glycolytic pathway in starvation/DM2

Randle cycle	Proposed hypothesis
Glucose 1st block FBP PEP Pyruvate 2nd block ↓PDH ↓Acetyl CoA ↑Pyruvate** ↑ G.6P*	Glucose 1st block FBP PEP 2nd block** Pyruvate 3rd block Acetyl CoA ↓P.K ↓PDH ↑Glucagon ↓insulin ↓FBS ↑ATP ChERBP ↑G.N? ↓PKM2 ↑G.6P* ↑G.6P H.M.P stunt Glycogenesis G.N Glycolysis cycle GA3P Esterification Glycerol T.G (exogenous) T.G (endogenous) DE NOVO FAT SYNTHESIS ↑NADPH ↑T.G pool*** Lipolysis ↑F.A ↑MCD ↑AMPK ↑ACC 2 β-oxidation ↑PPAR α ↑F.A
Only two blocks are suggested by Randle as seen above. * Experimentally disproved subsequently. ** Pyruvate accumulates consequent to failure to enter TCA cycle due to inhibition of PDH.	An additional 3rd block at the level of PK is suggested by this hypothesis. * Re-routing of increased G.6 P into glycogenesis pathway and HMP stunt explains the experimental observations of non – increased of G.6P. ** Proposed additional block. -causing low Pyruvate level. *** Replenishes TG pool to allow perpetuation of β-oxidation indefinitely in untreated DM type 2.