b.clarke@ucl.ac.uk

"McArdle's Disease" or, "Causation without Statistics?"

Brendan Clarke

Department of Science and Technology Studies, UCL

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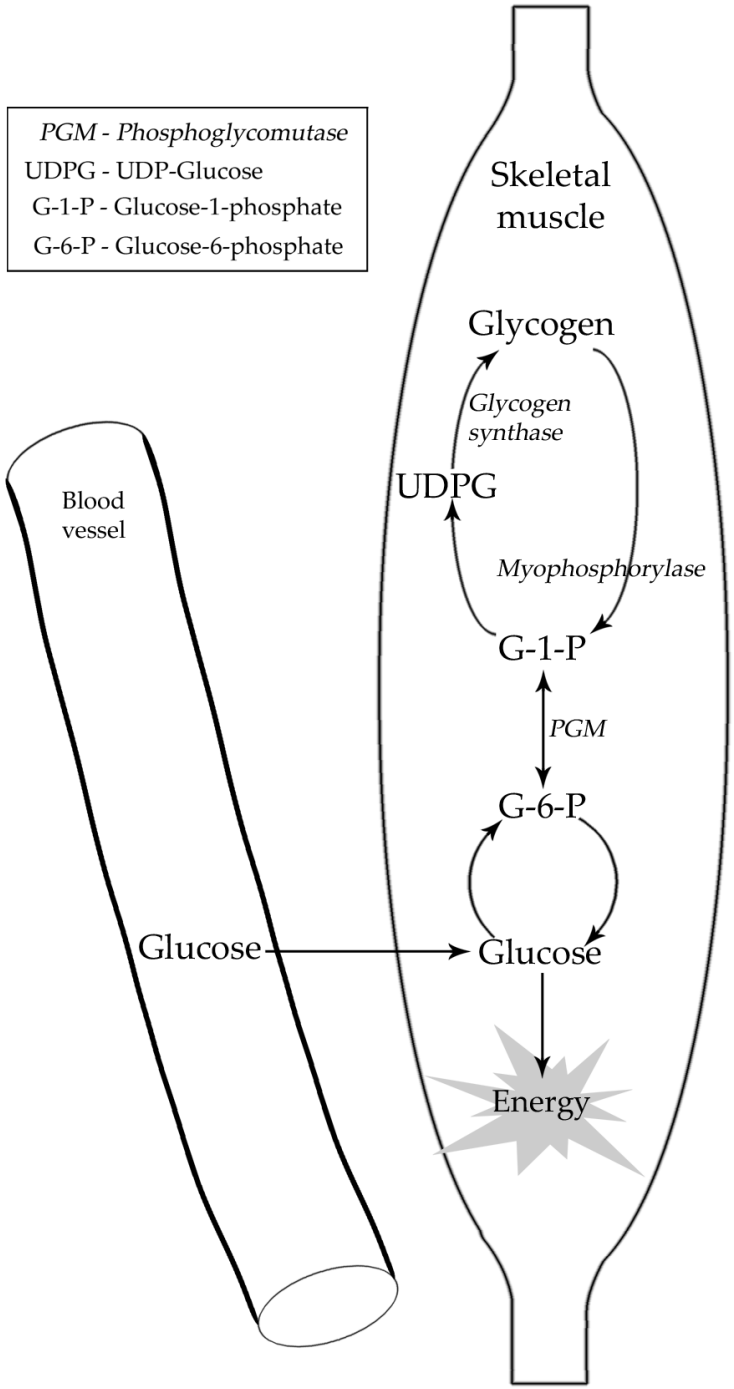
Introducing McArdle's Disease

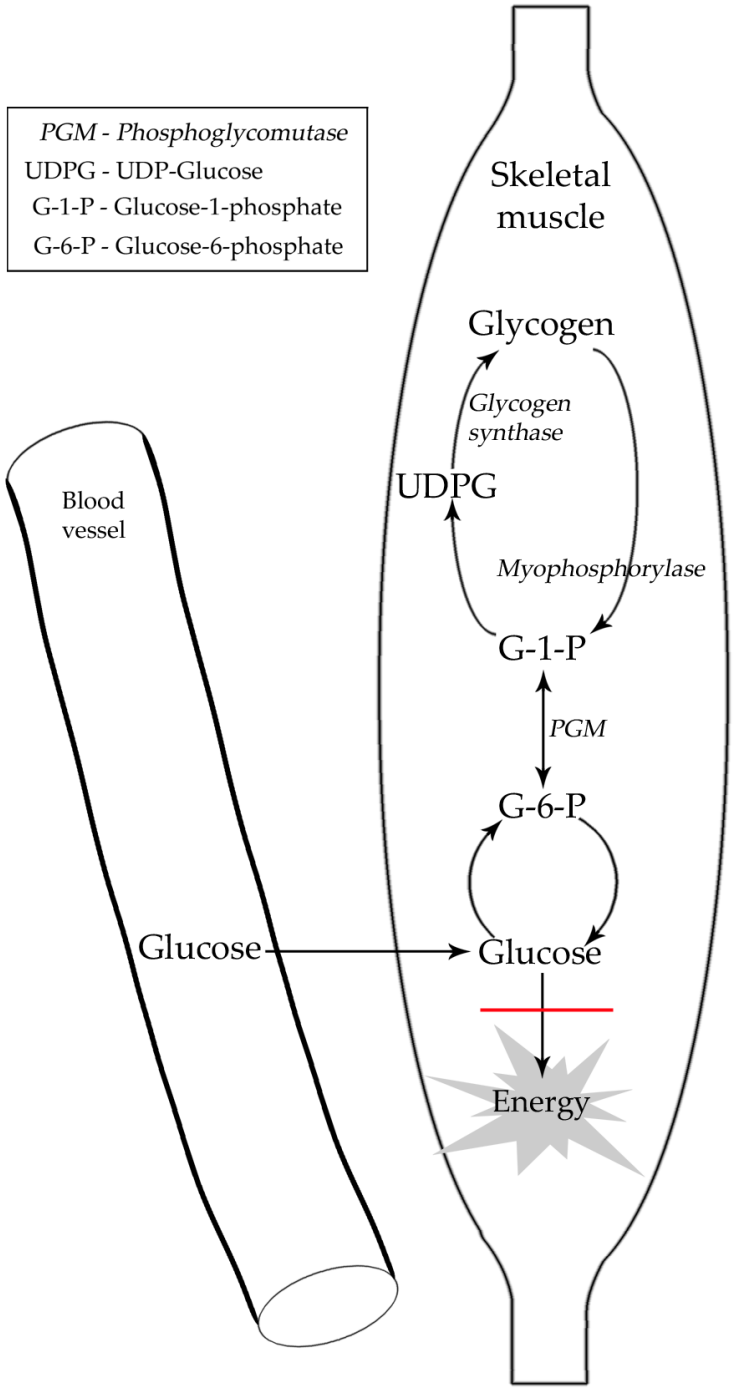
- Rare genetic disorder
- Tiredness and pain on exertion
- Functional absence of myophosophylase
  - Normal anabolic pathway (glucose to glycogen)
  - Abnormal catabolic pathway (glycogen to glucose)
- Many (20+) mutations; one disease


PGM - Phosphoglycomutase
UDPG - UDP-Glucose
G-1-P - Glucose-1-phosphate
G-6-P - Glucose-6-phosphate
Skeletal muscle
Glycogen
Glycogen synthase
UDPG
Myophosphorylase
G-1-P
PGM
G-6-P
Blood vessel
Glucose
Glucose
Energy

The Discovery of McArdle's Disease–I

(McArdle, 1951)

- 1947–1951, Brian McArdle
- 30 year old man, George W.
- Pain and fatigue on exertion
- Physical illness
  - Low lactate, electrically silent muscle cramps
  - Possibly due to abnormal glycogen metabolism
  - ?glyceraldehyde phosphate dehydrogenase deficiency (converts glyceraldehyde 3-phosphate to 1,3-bisphosphoglycerate)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The Discovery of McArdle's Disease–II

(Mommaerts et al., 1959; Pearson et al., 1961)

- Mommaerts group, Los Angeles, 1959–1961
- 19 year old man, D.G.
- Clinical similarities to George W.
- Identified myophosphorylase as causative entity
  - Large quantities of normal glycogen in muscle
  - Absence of myophosphorylase activity in muscle samples
  - Normal glycolytic function restored if:
    - Myophosphorylase added
    - glucose-1-phosphate or glucose-6-phosphate added

The Discovery of McArdle's Disease–III

(Larner and Villar-Palasi, 1959; Schmid and Mahler, 1959; Schmid et al., 1959; Schmid and Hammaker, 1961)

- Schmid group, Boston. 1959–1961
- 54 year old man, A.D.
- Clinical developments:
  - deterioration with time (clinical course)
  - second wind phenomena
- Lack, rather than inhibition, of myophosphorylase
- Heritable, in an autosomally recessive fashion
- Possible treatment approaches investigated

Causation without Statistics?

- So by the end of 1961, the clinical features of the disease are well described.
- The disease is caused by myophosphorylase deficiency.
- We have excellent mechanistic evidence for this
- But, we have no statistical evidence apparent in the formulation of this causal claim

1. McArdle's disease is defined in terms of its pathological abnormality. Non-functional myophosphorylase in an individual means that, by definition, they have McArdle's disease
2. This aetiological standpoint-type definition renders the functional absence of myophosphorylase as a universal, necessary and sufficient cause of the disease
3. The causes of the absence of this enzyme (for instance, a new or inherited mutation) are more-or-less irrelevant to the diagnosis
4. Importantly, these causes are non-modifiable at the time of presentation
5. The behaviour that is required for the disease to become clinically apparent (exertion) is common to the point of ubiquity
6. There are multiple mutations that cause myophosphorylase defects, which complicates DNA analysis. Diagnostic tests rely on demonstrating an absence of myophosphorylase (Hilton-Jones, 2001, 122, 124–5)

The Aetiological Standpoint

- So, because of the link between link between myophosphorylase deficiency (pathology) and McArdle's disease (clinicopathological), the presence of myophosporylase deficiency makes a difference to the effect
- This difference-making is very strong, happening in a relatively deterministic fashion
- Even if we were to 'accidentally' find myophosphorylase deficiency in an asymptomatic person, we would (probably) say they had asymptomatic McArdle's disease
- As an aside, this is a very similar position to early germ-theory causation, before developments in the importance of host factors in disease

Conclusions

I think it's reasonable to take this case as a very minor exception. Myophosphorylase is an unusual causal factor, in that its influence on the effect is so strong. There are few others like it–generally genetic (single gene mutations, aneuploidy), but we might also include trauma or toxic injury.
But it still doesn't quite fit in with epistemic causation in medicine, supported by mechanistic and probabilistic evidence.

Options...

Option 1: Regard claims of causation in this case as faulty, requiring statistical investigation (but pragmatic problems...)

Option 2: Treat these sorts of causal factors as *de facto* exceptions? to epistemic cause

Option 3: Interpreting the 'deterministic' definition of the disease as probabilistic (P(McArdle's|Myophosphorylase deficiency) = 1)

Option 4: Abandon the requirement for statistical evidence

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