Making Mechanisms: McArdle's syndrome

Progress in Medicine Conference

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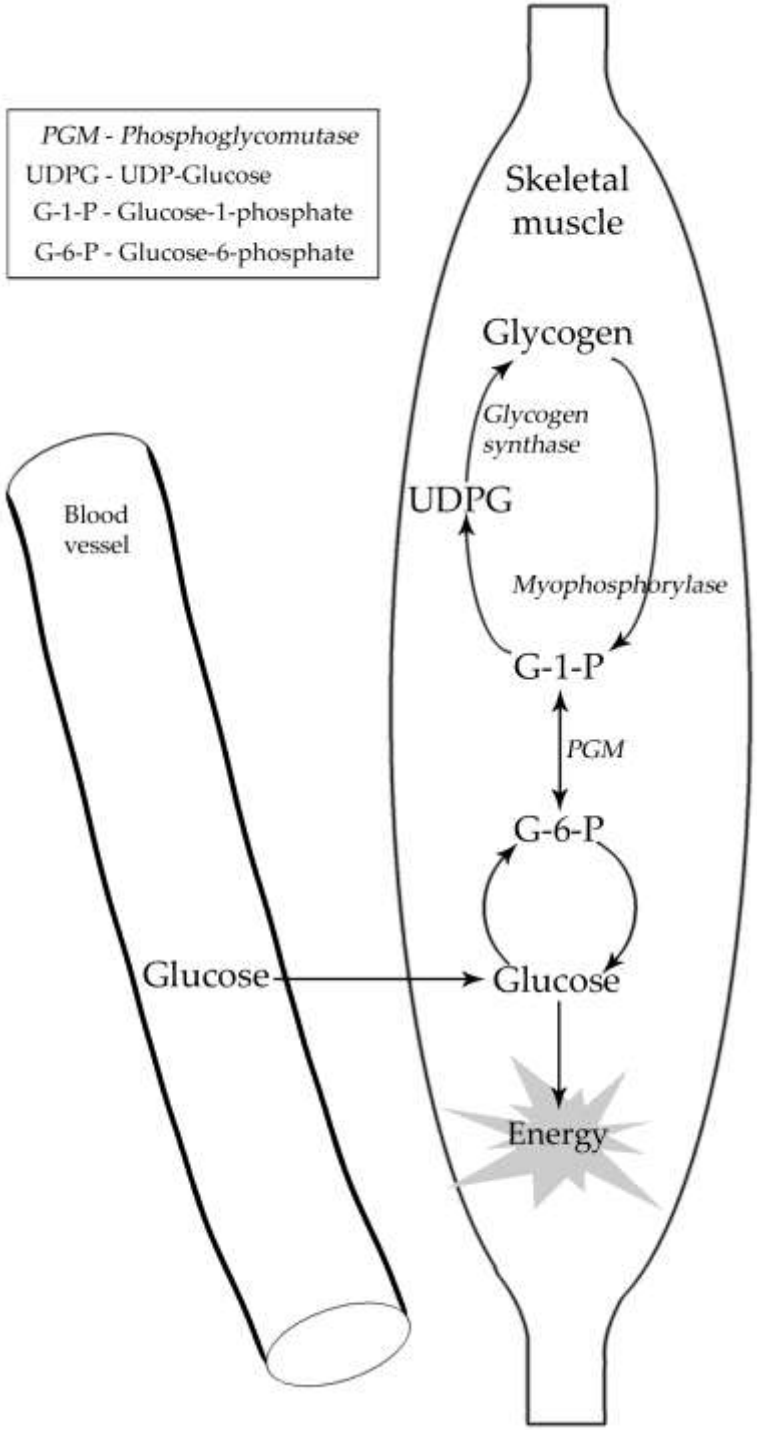
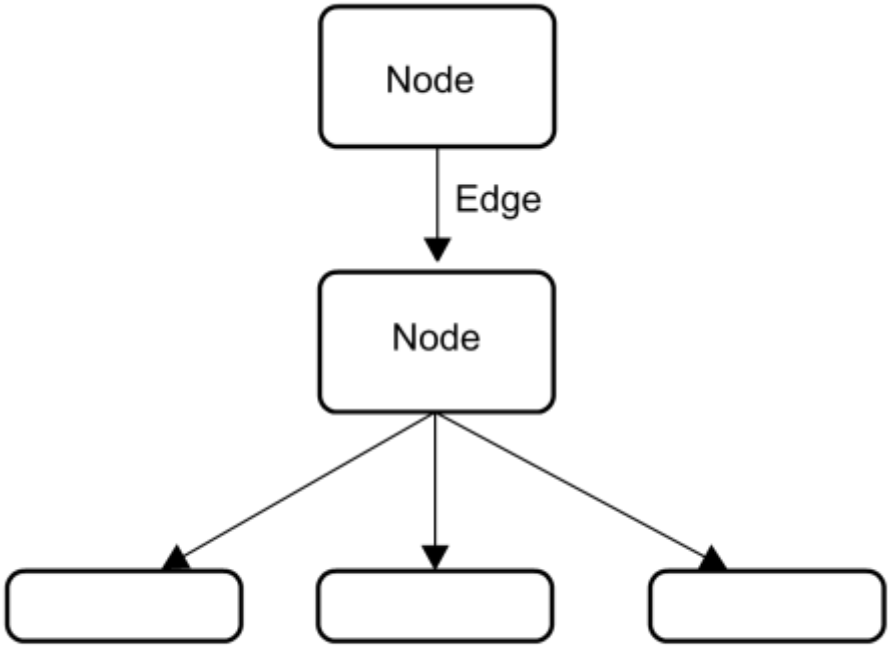
McArdle's syndrome

- Rare genetic disturbance in carbohydrate metabolism
- First described by McArdle [1951]
- Caused by myophosphorylase deficiency


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

Mechanisms

- Nodes are the entities
- Edges are the causal activities of their nodes
- Nodes and edges are interlevel
- Nodes and edges are organized together in some way to do something



Philosophical accounts of mechanism

- Machamer, Darden and Craver, 2000
- Craver, 2007
- Glennan, 2002
- Bechtel and Abrahamsen, 2005
- Woodward, 2002

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- All, to some degree, have normative aspirations

Why make mechanisms?

- Understand complex causal relationships
- Track changes in causal understanding
- Identification of interesting features
- Teaching and learning

Complexity and mechanism

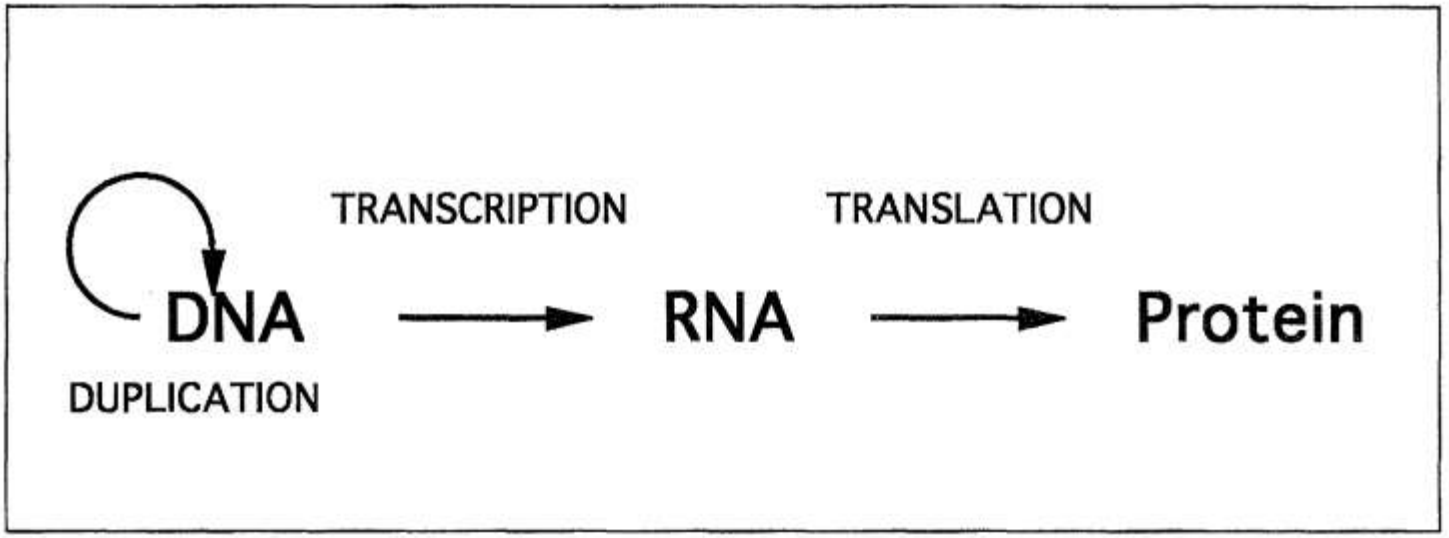
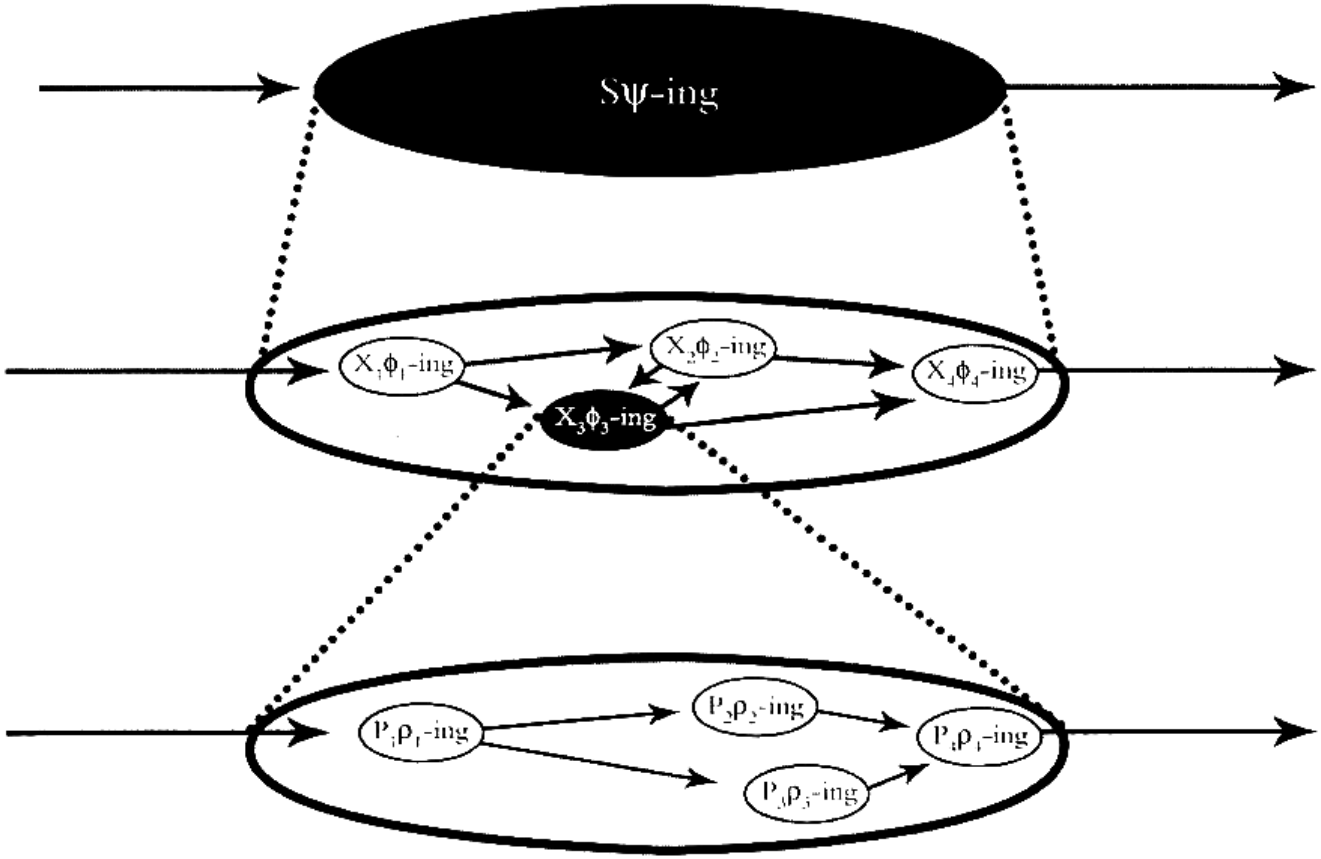


Figure 3. Watson's central dogma diagram (redrawn, based on Watson 1965).

Reproduced without permission from Machamer, Darden and Craver, 2000: 16

Complexity and mechanism



Reproduced without permission from Craver, 2007: 189

Complexity and mechanism

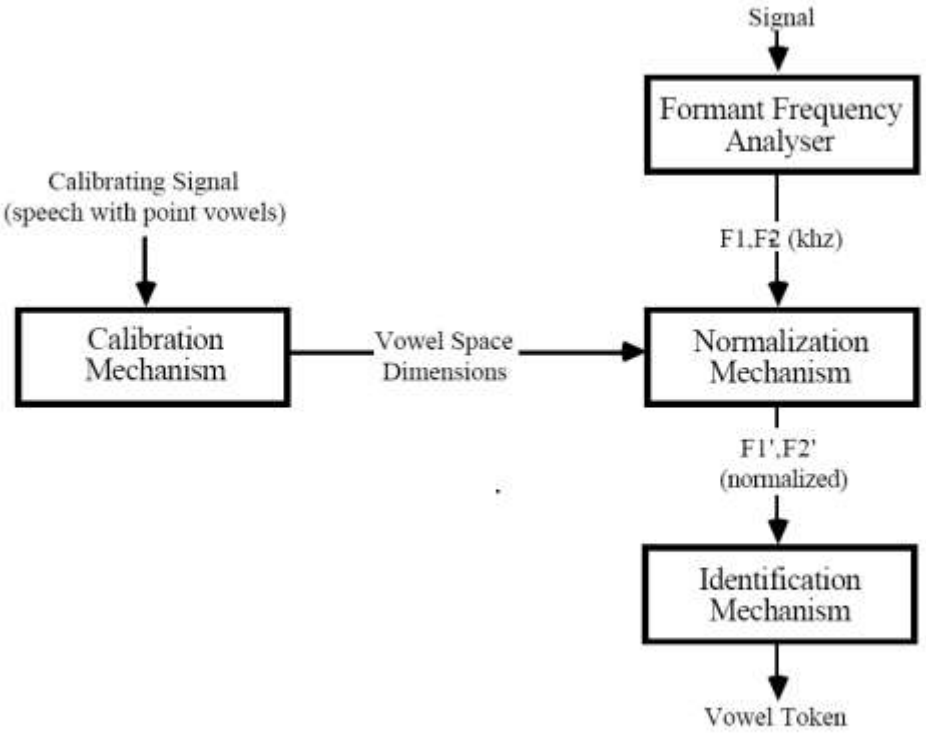


Fig. 3: The Gerstman Vowel Normalization Model

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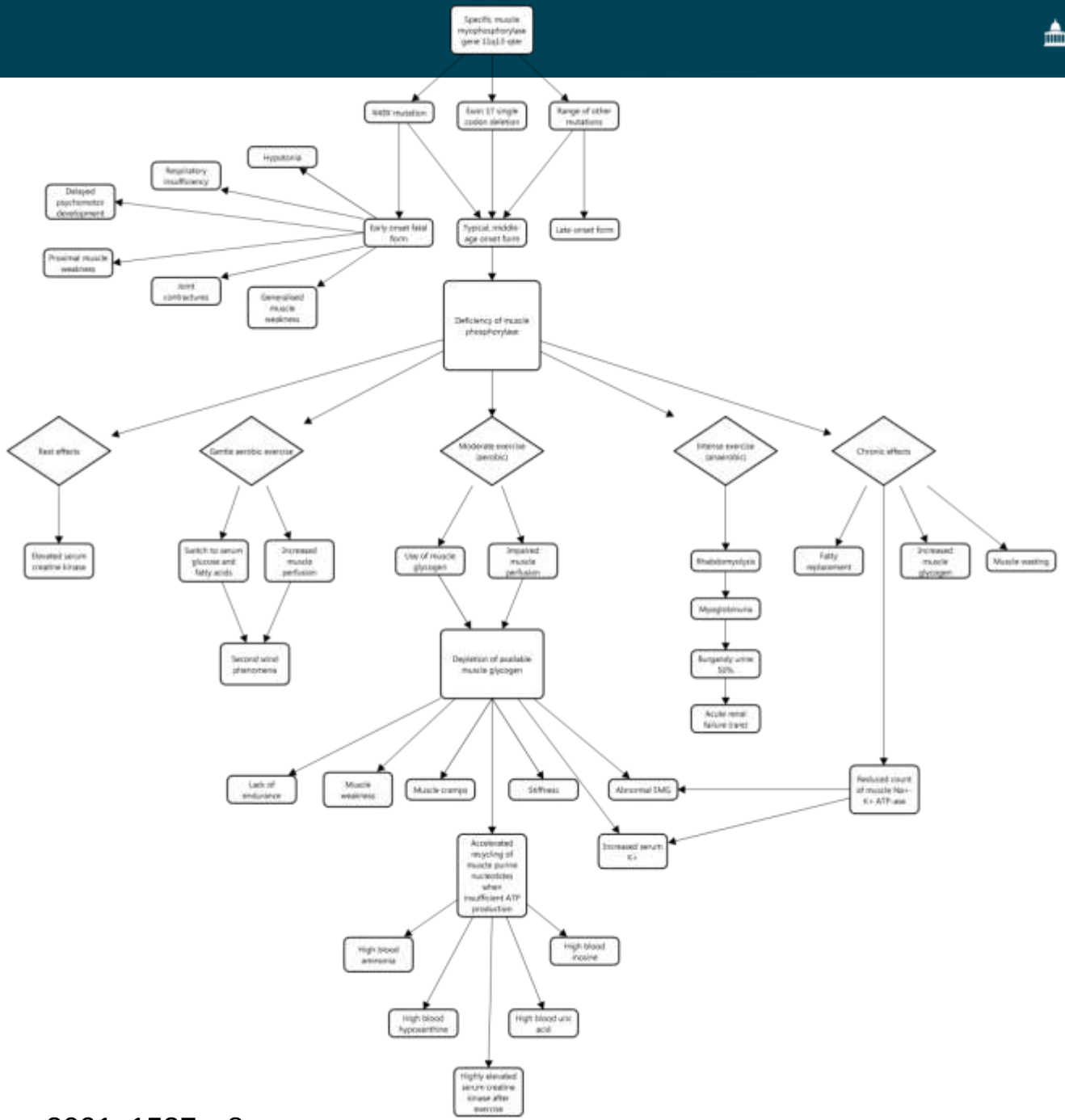


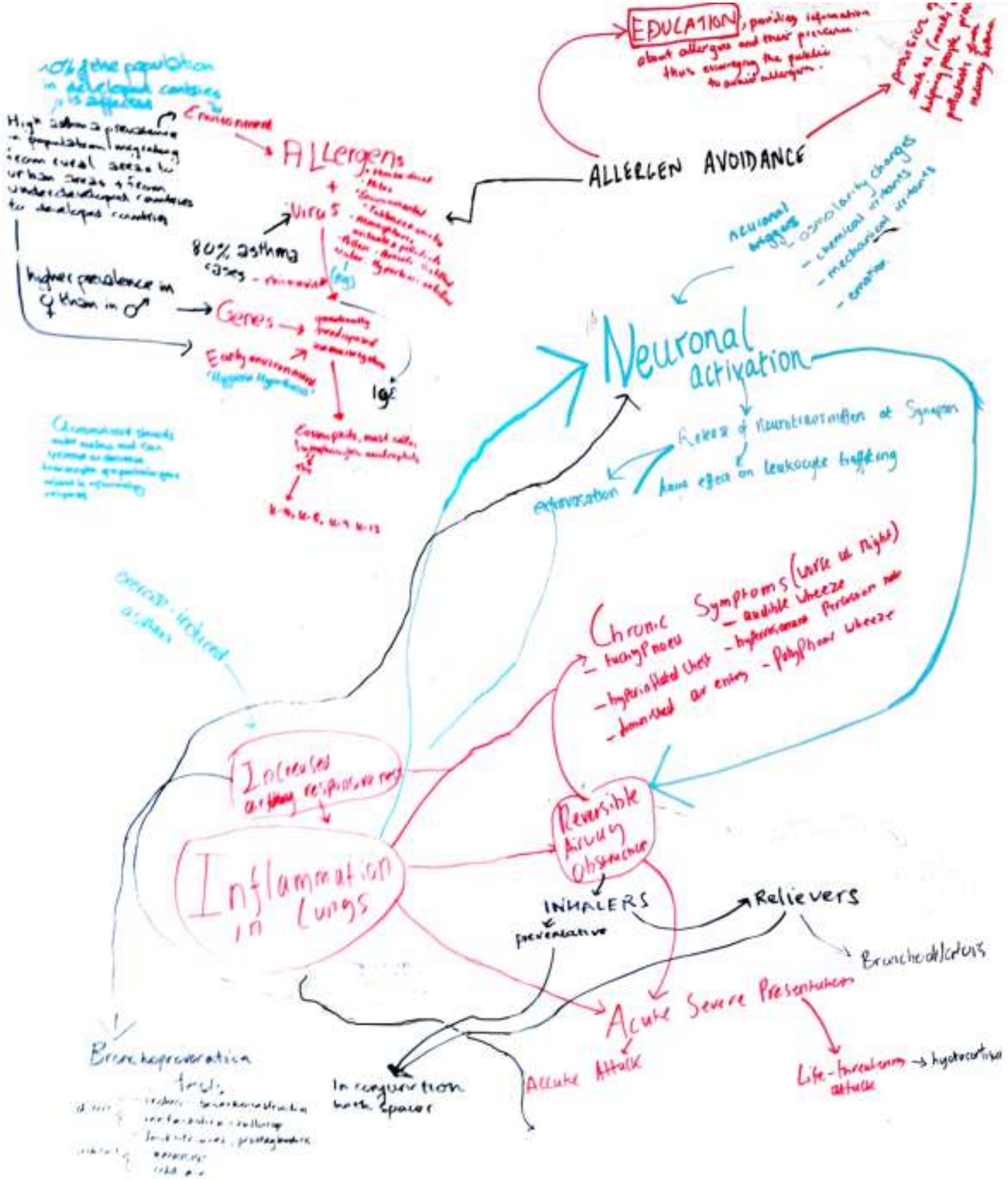
Derived from Chen, 2001: 1537—8

Complexity?

- Large numbers of activities and entities
- Levels
- Generic versus single-case causes
- Background conditions
- Pathology versus physiology
- Changing knowledge
- Incomplete knowledge
- Stochastic relationships
- Planning and mortal limitations...

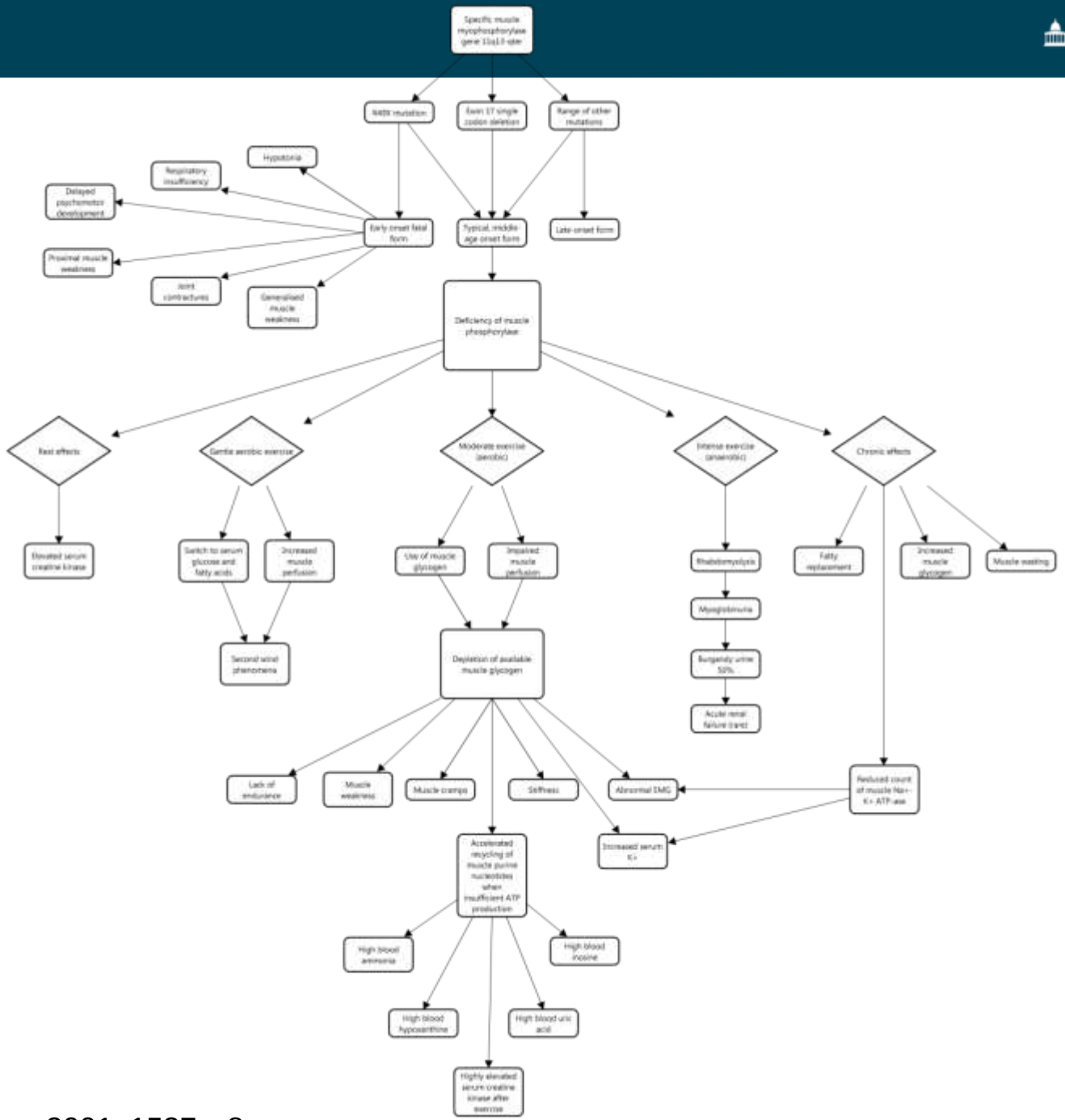
Making mechanisms

- Pen and paper


EDUCATION
ALLERGEN AVOIDANCE
Environment
Allergens
Virus
80% asthma cases
Genes
higher prevalence in ♀ than in ♂
Early environment
'Hygiene Hypothesis'
IgE
neuronal triggers
- osmolarity changes
- chemical irritants
- mechanical irritants
- emotion
Neuronal activation
Release of Neurotransmitters at Synapses
extravasation
Chronic Symptoms (worse at Night)
- audible wheeze
- diminished air entry
- polyphonic wheeze
exercise-induced asthma
Increased airway responsiveness
Inflammation in Lungs
Reversible Airway Obstruction
INHALERS
preventative
Relievers
Bronchodilators
Acute Severe Presentation
Acute Attack
Life-threatening attack
In conjunction with spacer
Bronchoprovocation tests

Making mechanisms

- By hand
- Using design software (Visio, lovelycharts.com)



Derived from Chen, 2001: 1537—8

Making mechanisms

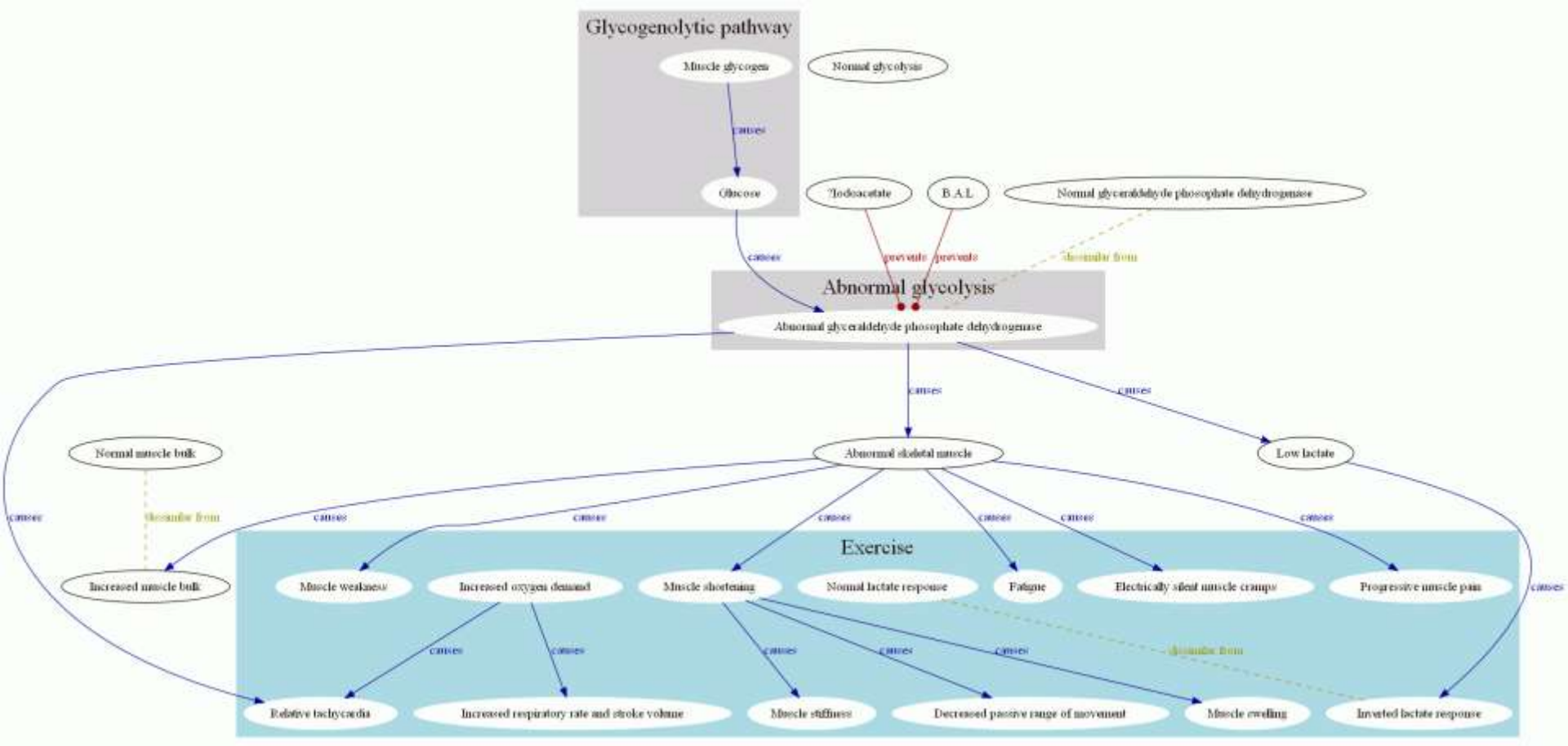
- By hand
- Using design software (Visio, lovelycharts.com)
- A third way...

The Complex Mechanism Browser

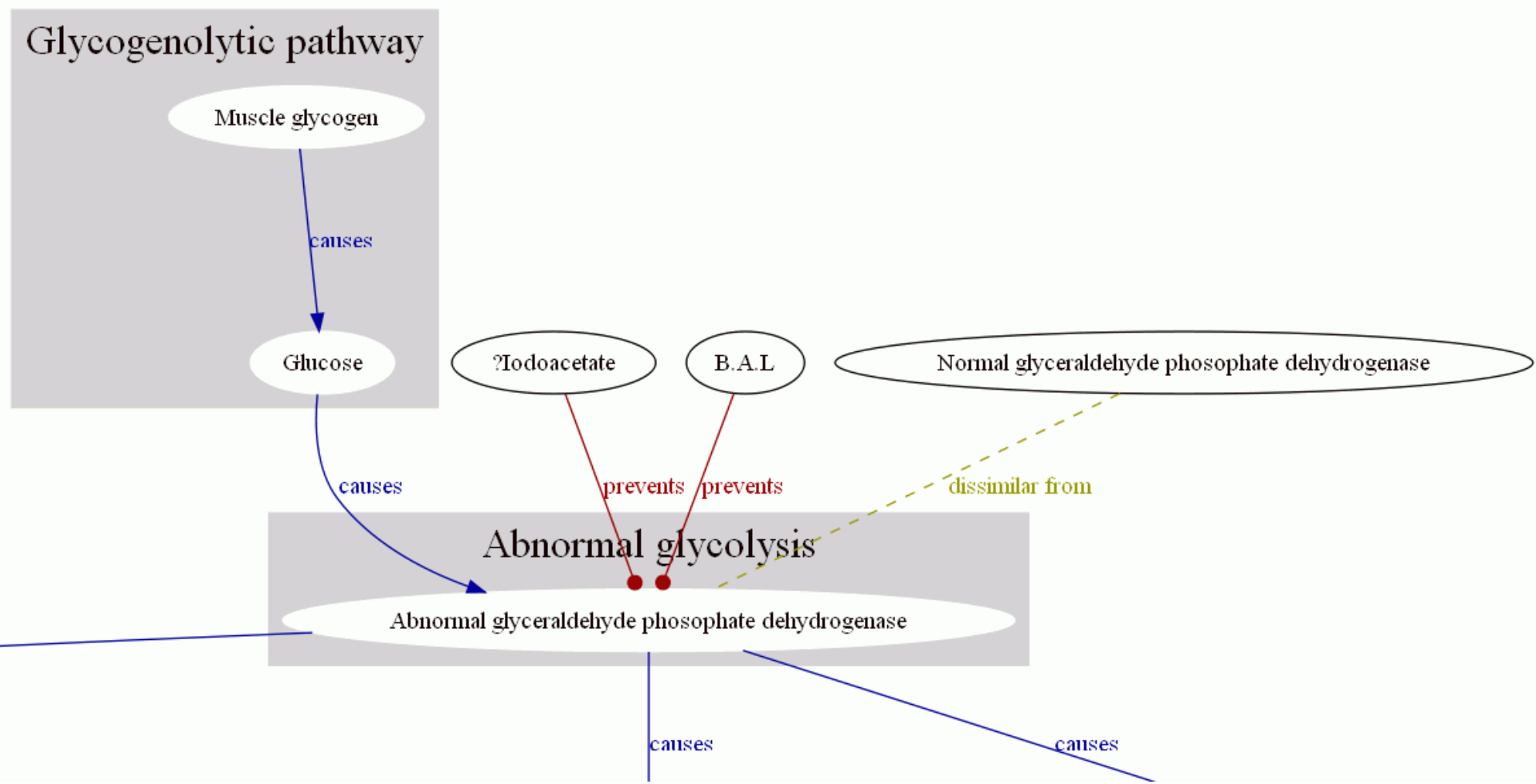
- Text input of causal claims
- Routing etc automated
- Ability to re-use sections of mechanism
- Clear visual differentiation between different relationships
  - *Causes* - *Prevents*
  - *Similar* - *Dissimilar*
  - *Background condition* - *Component*

Example

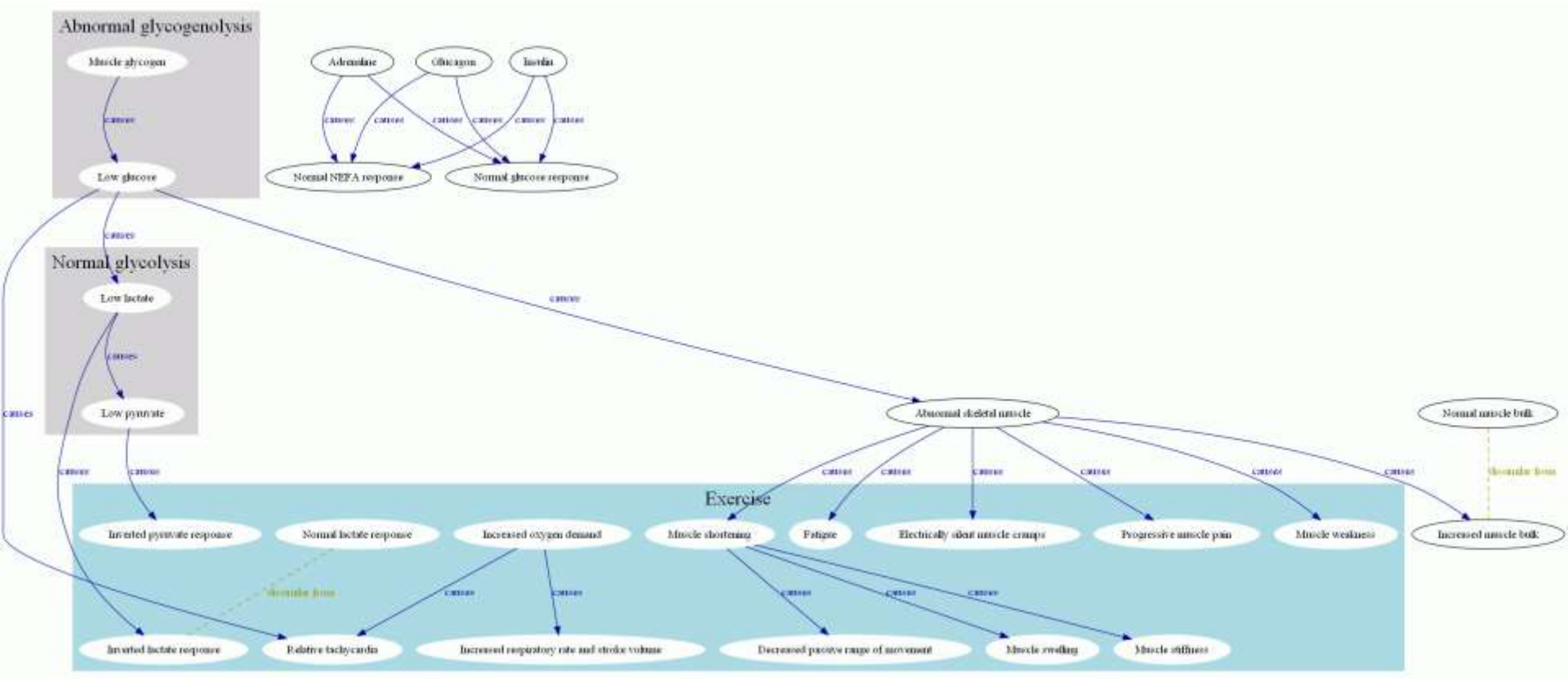
- Based on McArdle's syndrome
  - Manageable literature
  - Philosophically, historically and medically interesting
- Constructed from first 8 publications (1951—1961)
- Aim: to explore the chronological development of causal arguments and their evidence



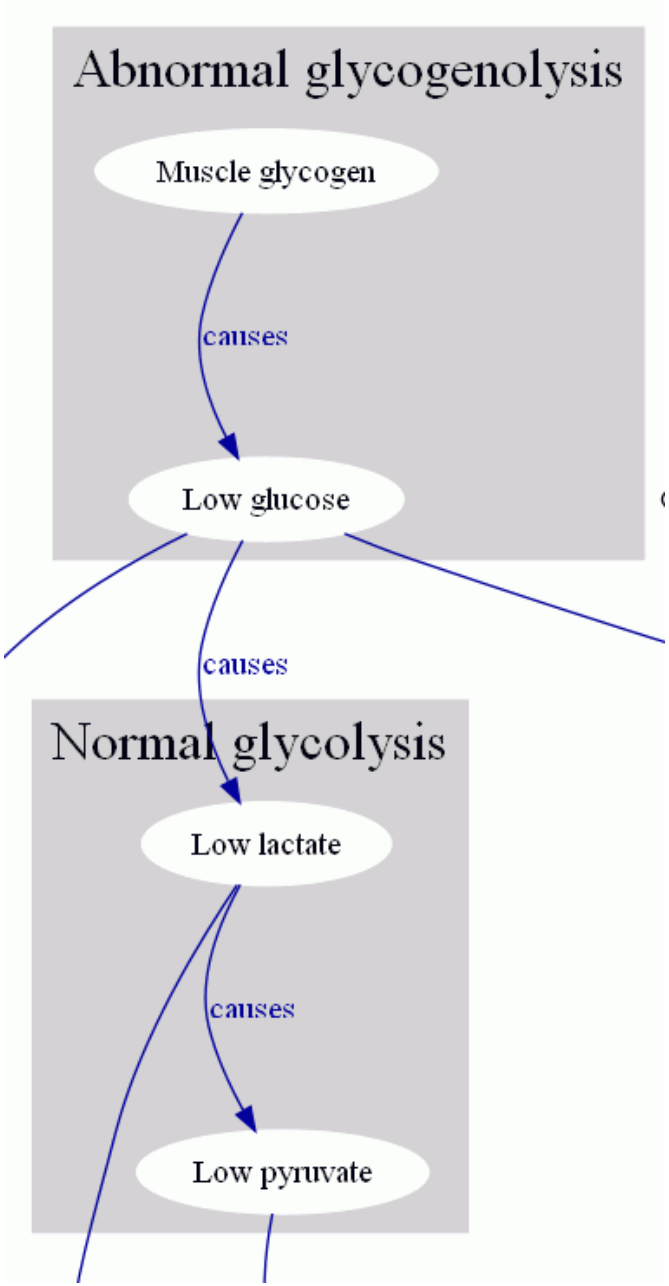
McArdle, 1951



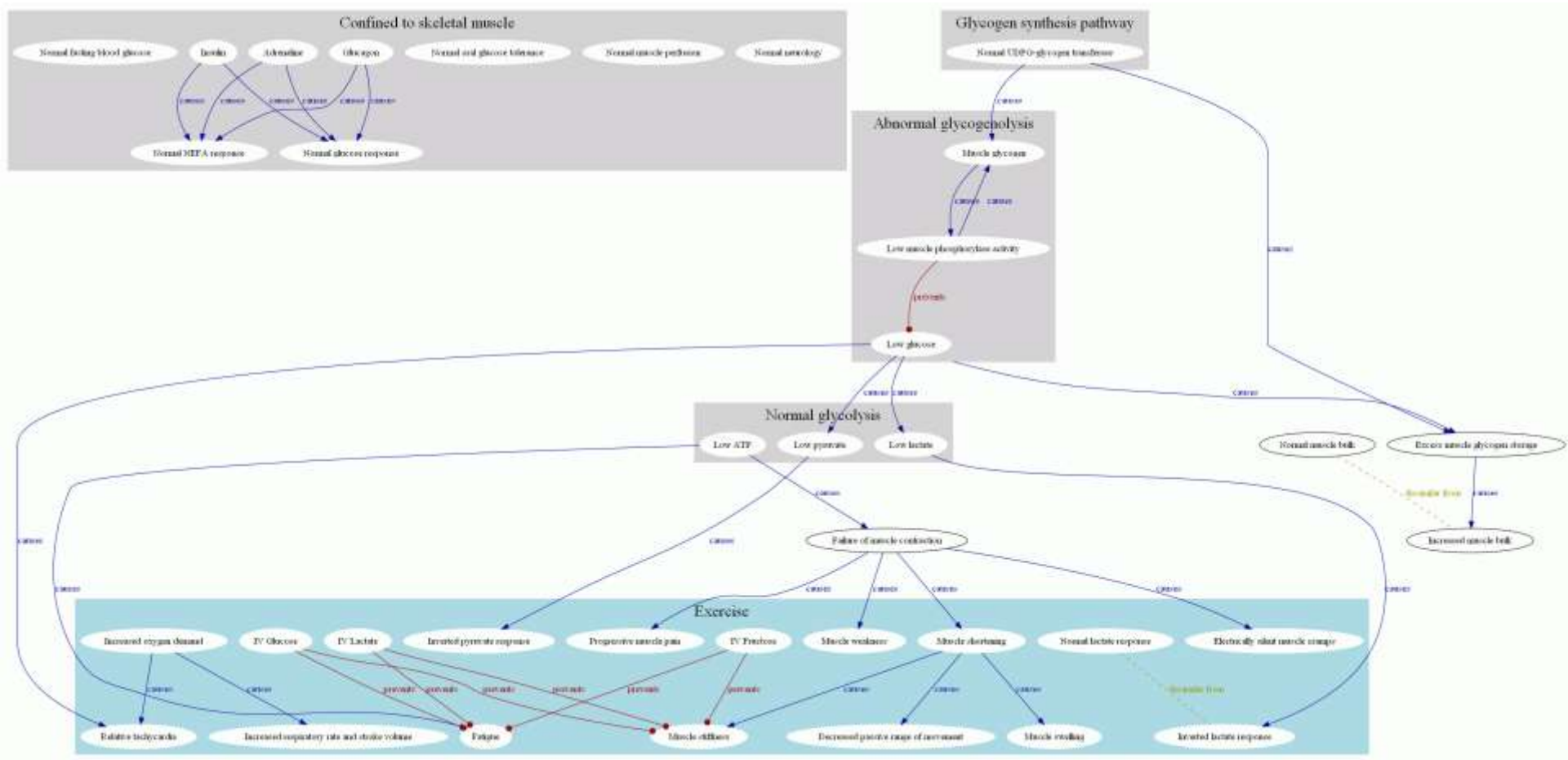
McArdle, 1951



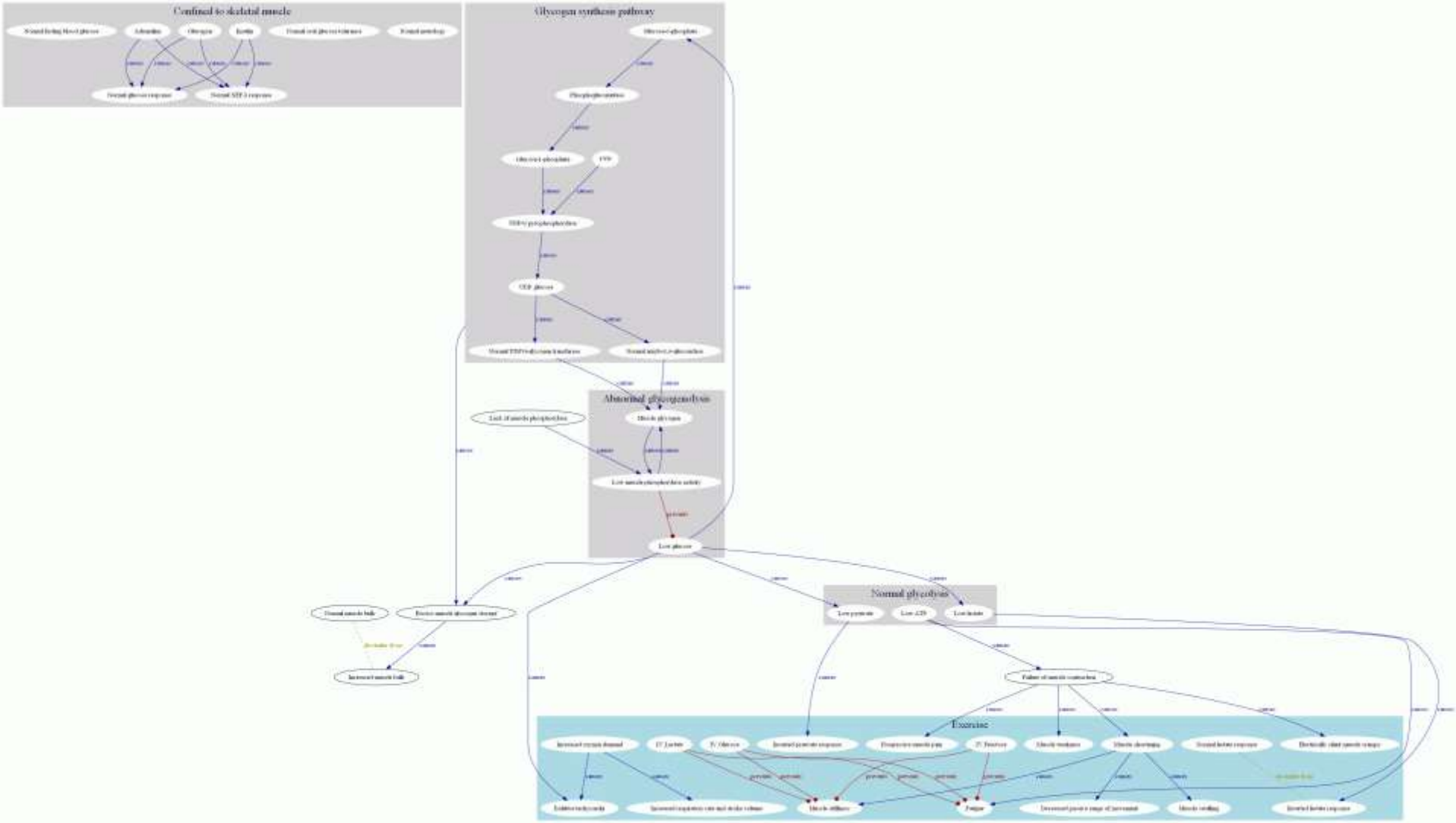
Schmid and Mahler, 1959a



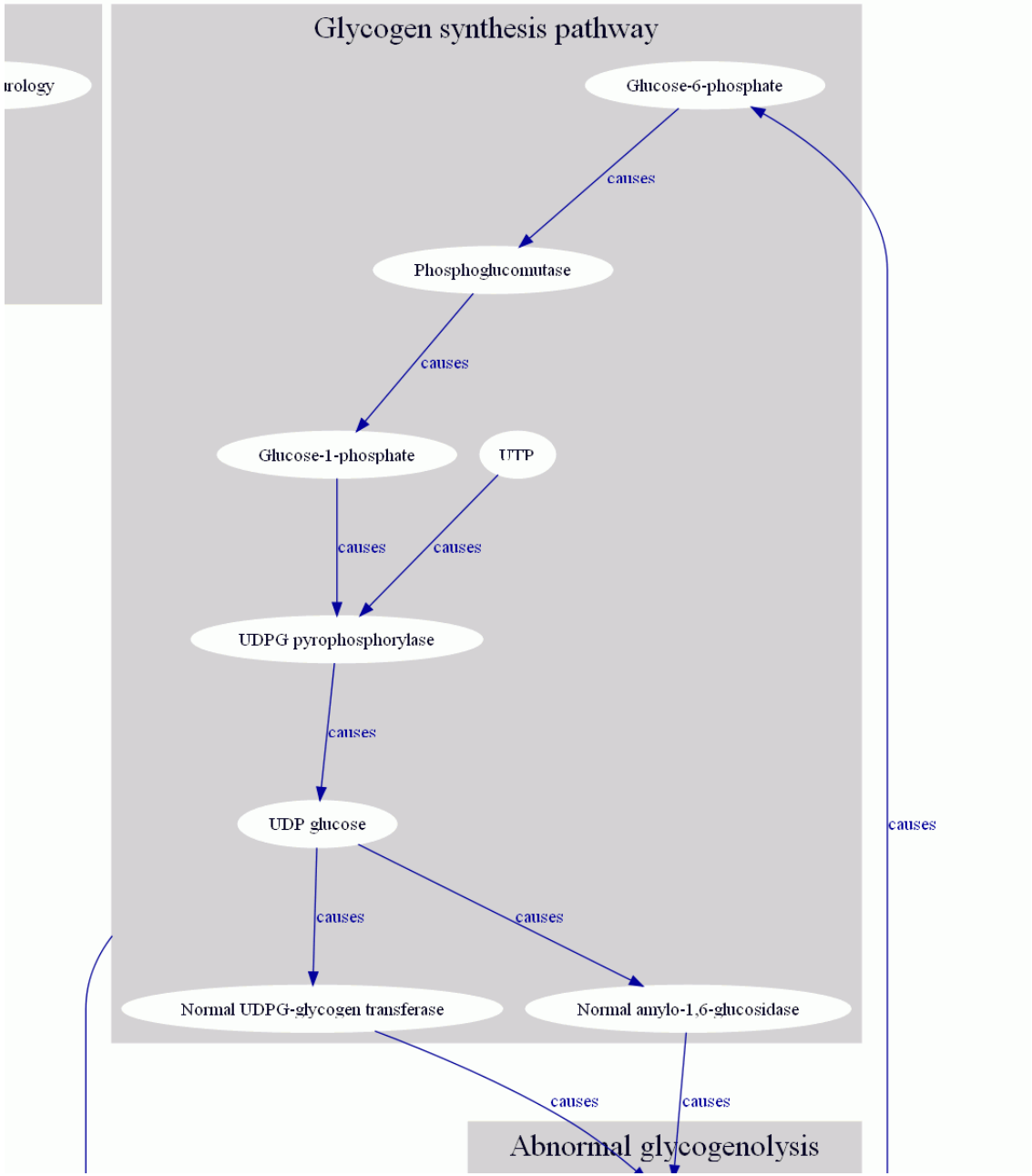
Schmid and Mahler, 1959a



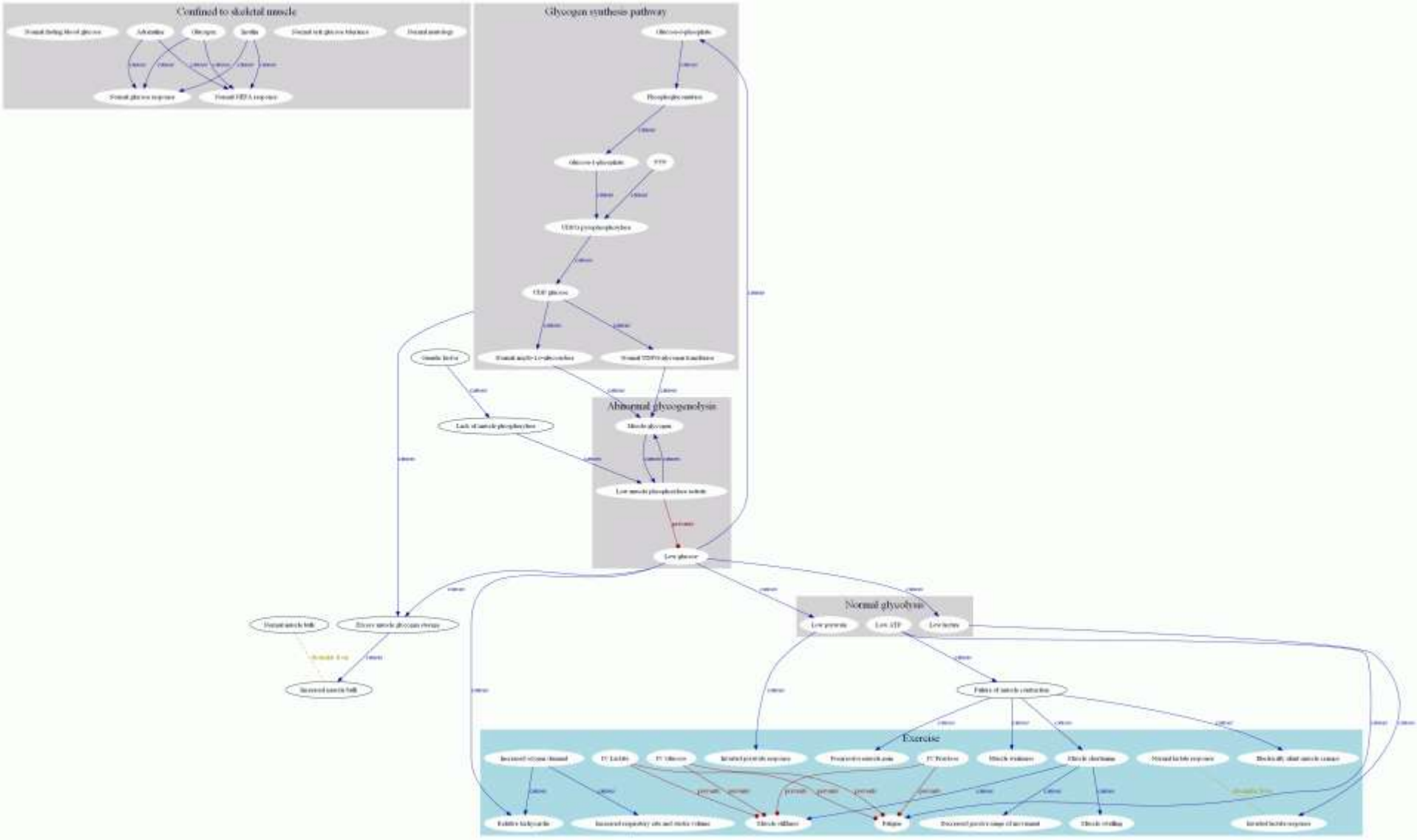
Mommaerts et al, 1959



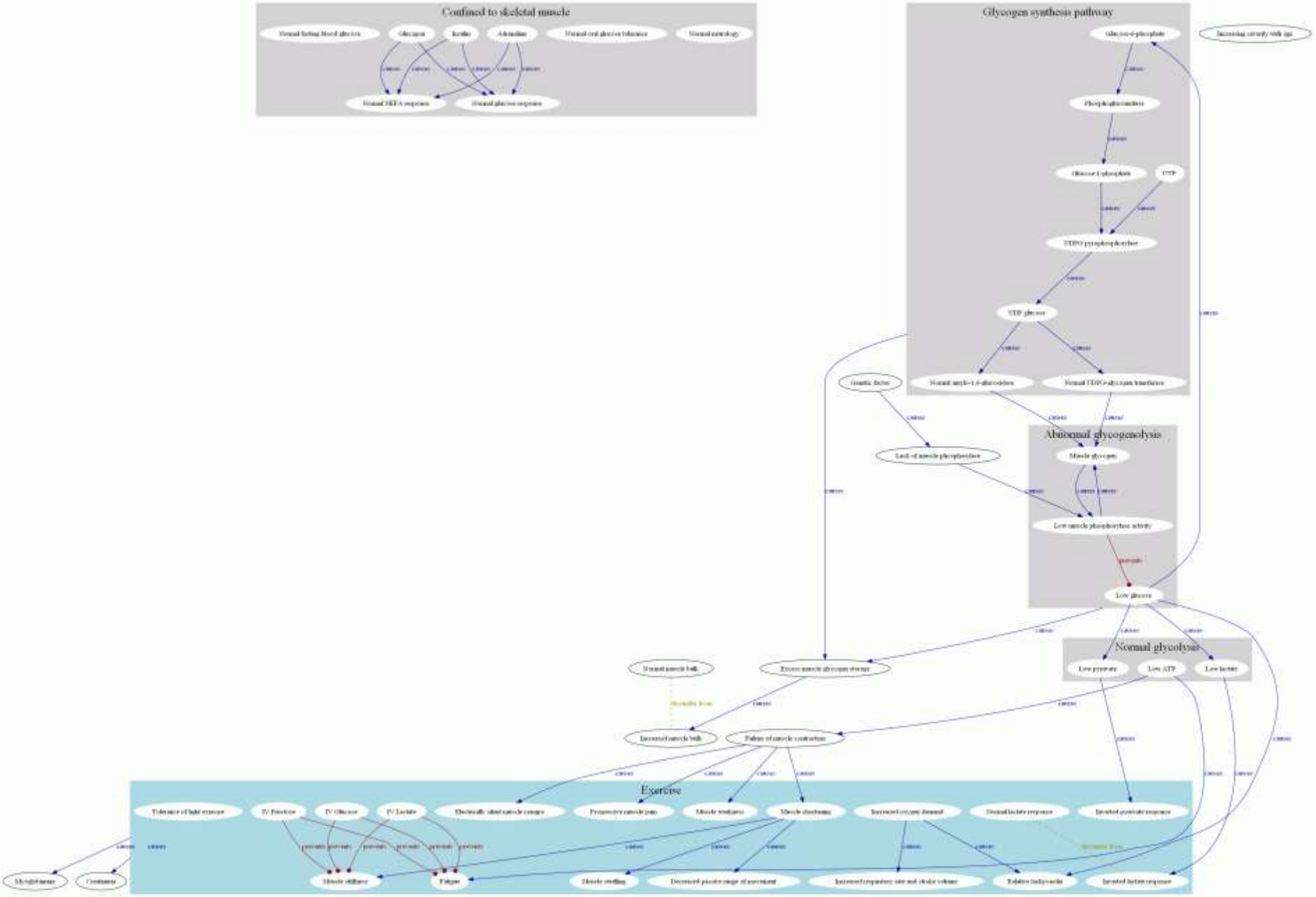
Larner and Villar-Palasi, 1959



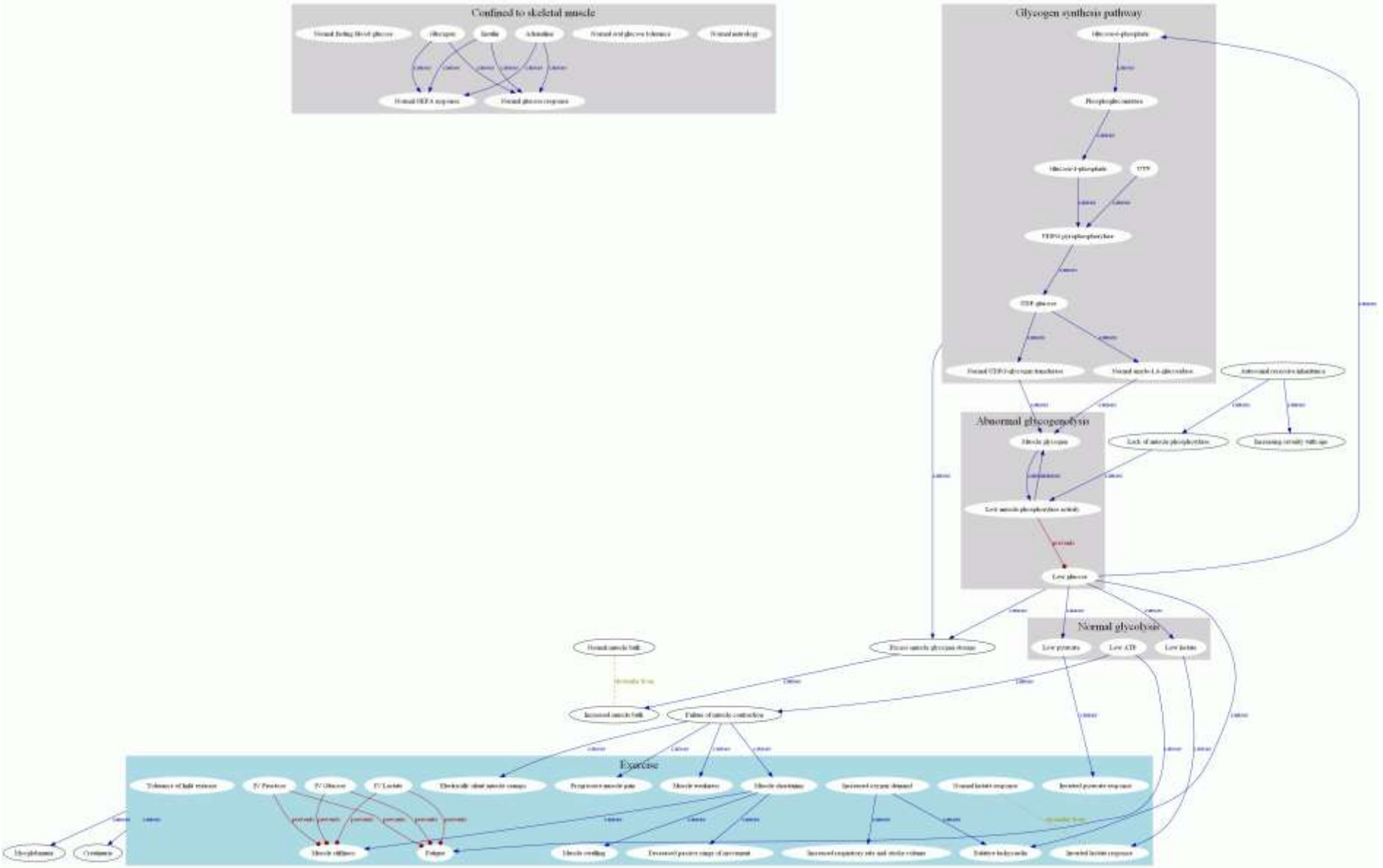
Larner and Villar-Palasi, 1959



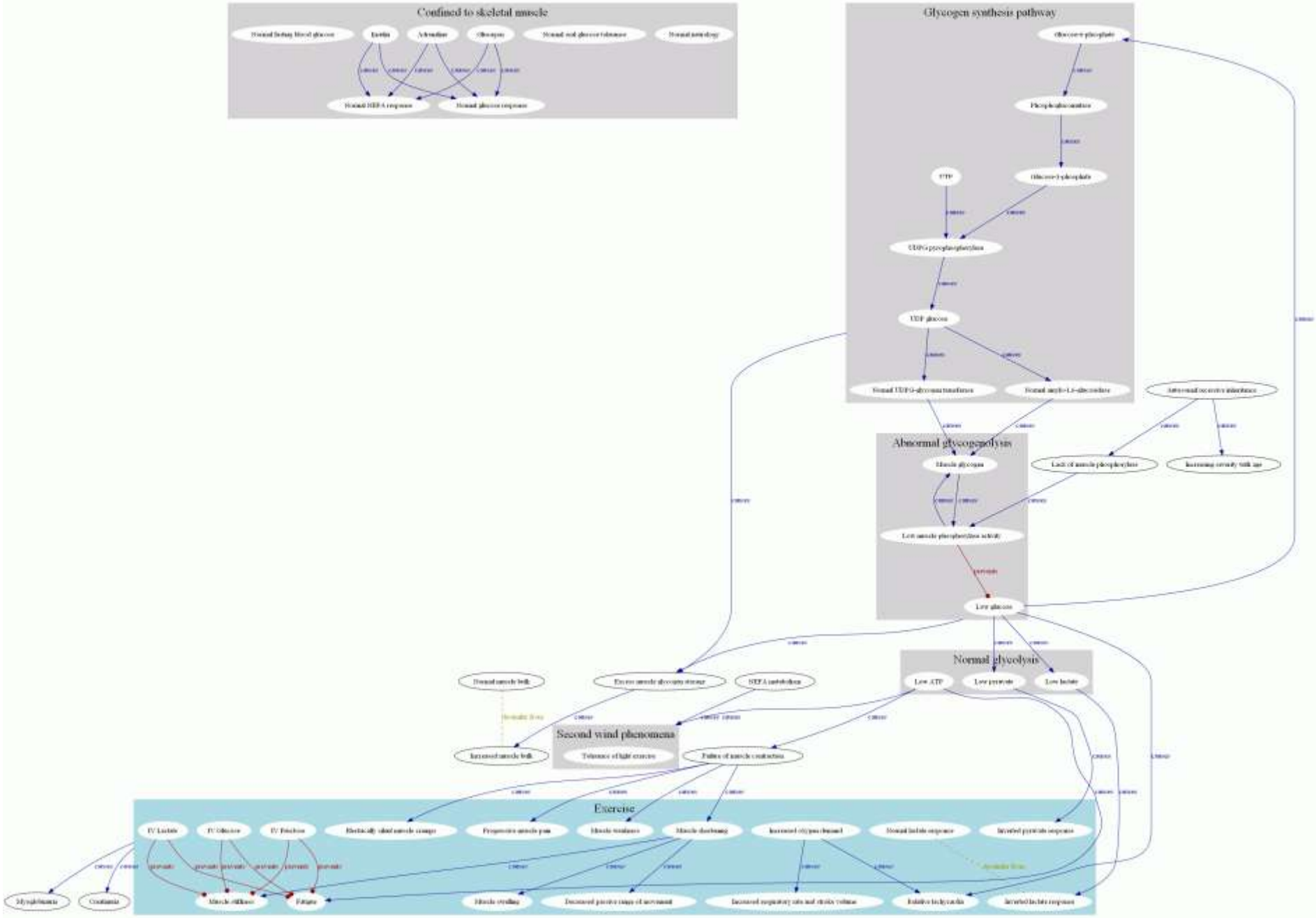
Schmid, Robbins and Traut, 1959



Schmid and Mahler, 1959b



Schmid and Hammaker, 1961



Pearson, Rimer and Mommaerts, 1961

Technology

- Graphviz takes care of aesthetics
- CMB rationalises the data management
- Abstraction is King

Technology

- Text only appears once
- SQL assigns ID numbers automatically

id	text	level
1	Increased muscle bulk	9
2	Abnormal skeletal muscle	8
3	Progressive muscle pain	9
4	Increased respiratory rate and stroke vo	8
5	Relative tachycardia	8
6	Normal neurology	9
7	Muscle weakness	9
8	Muscle stiffness	9
9	Decreased passive range of movement	9
10	Muscle shortening	8
11	Muscle swelling	9
12	Increased oxygen demand	7
13	Normal muscle perfusion	8
14	Electrically silent muscle cramps	7
15	Inverted lactate response	6
16	Abnormal glyceraldehyde phosophate dehyd	5
17	Muscle glycogen	4
18	Normal glycolysis	5

Technology

- Tables of numbers link concepts

id	from	type_id	to
1	2	1	1
2	22	4	1
3	2	1	3
4	2	1	7
6	10	1	8
7	10	1	9
8	10	1	11
9	12	1	4
10	12	1	5
19	24	4	15
20	23	5	3
21	23	5	4
22	23	5	5
23	23	5	7
24	23	5	8
25	23	5	9
26	23	5	10
27	23	5	11

Technology

id	from	type	to
1	Abnormal skeletal muscle	causes	Increased muscle bulk
2	Normal muscle bulk	dissimilar from	Increased muscle bulk
3	Abnormal skeletal muscle	causes	Progressive muscle pain
4	Abnormal skeletal muscle	causes	Muscle weakness
6	Muscle shortening	causes	Muscle stiffness
7	Muscle shortening	causes	Decreased passive range c
8	Muscle shortening	causes	Muscle swelling
9	Increased oxygen demand	causes	Increased respiratory rat
10	Increased oxygen demand	causes	Relative tachycardia
19	Normal lactate response	dissimilar from	Inverted lactate response
20	Aerobic exercise	background to	Progressive muscle pain
21	Aerobic exercise	background to	Increased respiratory rat
22	Aerobic exercise	background to	Relative tachycardia
23	Aerobic exercise	background to	Muscle weakness
24	Aerobic exercise	background to	Muscle stiffness
25	Aerobic exercise	background to	Decreased passive range c
26	Aerobic exercise	background to	Muscle shortening
27	Aerobic exercise	background to	Muscle swelling

Technology

from	type	to	paper_year	paper_title
Abnormal skeletal muscle	causes	Increased muscle bulk	1951	Myopathy Due to a Defect in Muscle Glycogen Breakdown.
Abnormal skeletal muscle	causes	Increased muscle bulk	1959	Glycogen Synthesis in Muscle Lacking Phosphorylase.
Abnormal skeletal muscle	causes	Increased muscle bulk	1959	A Functional Disorder of Muscle Associated with the Absence of
Abnormal skeletal muscle	causes	Increased muscle bulk	1959	Syndrome of Muscular Dystrophy with Myoglobinuria: Demonstratio
Abnormal skeletal muscle	causes	Increased muscle bulk	1959	Enzymes in a Glycogen Storage Myopathy.
Normal muscle bulk	dissimilar from	Increased muscle bulk	1951	Myopathy Due to a Defect in Muscle Glycogen Breakdown.
Normal muscle bulk	dissimilar from	Increased muscle bulk	1959	Glycogen Synthesis in Muscle Lacking Phosphorylase.
Normal muscle bulk	dissimilar from	Increased muscle bulk	1959	A Functional Disorder of Muscle Associated with the Absence of
Normal muscle bulk	dissimilar from	Increased muscle bulk	1959	Syndrome of Muscular Dystrophy with Myoglobinuria: Demonstratio
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Abnormal skeletal muscle	causes	Progressive muscle pain	1959	Glycogen Synthesis in Muscle Lacking Phosphorylase.
Abnormal skeletal muscle	causes	Progressive muscle pain	1959	A Functional Disorder of Muscle Associated with the Absence of
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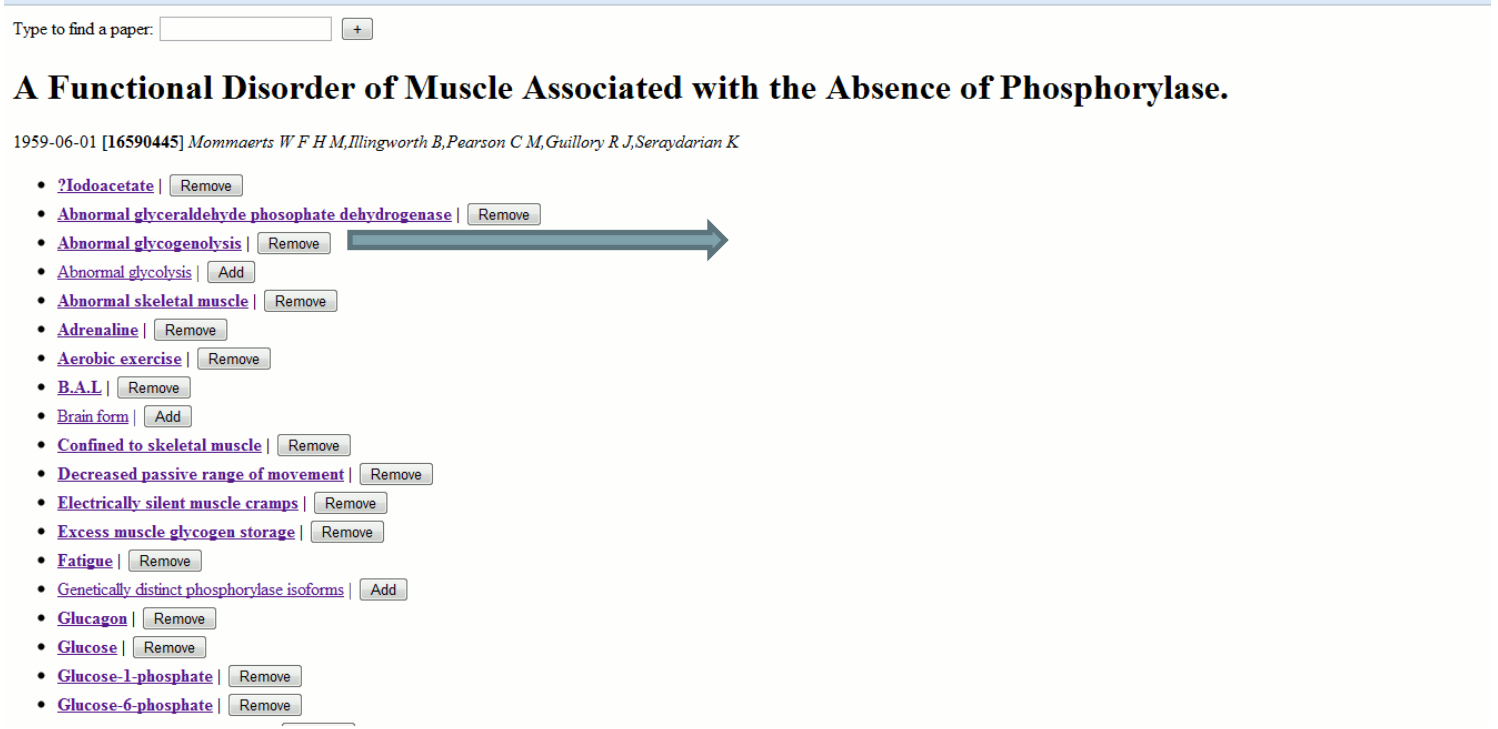
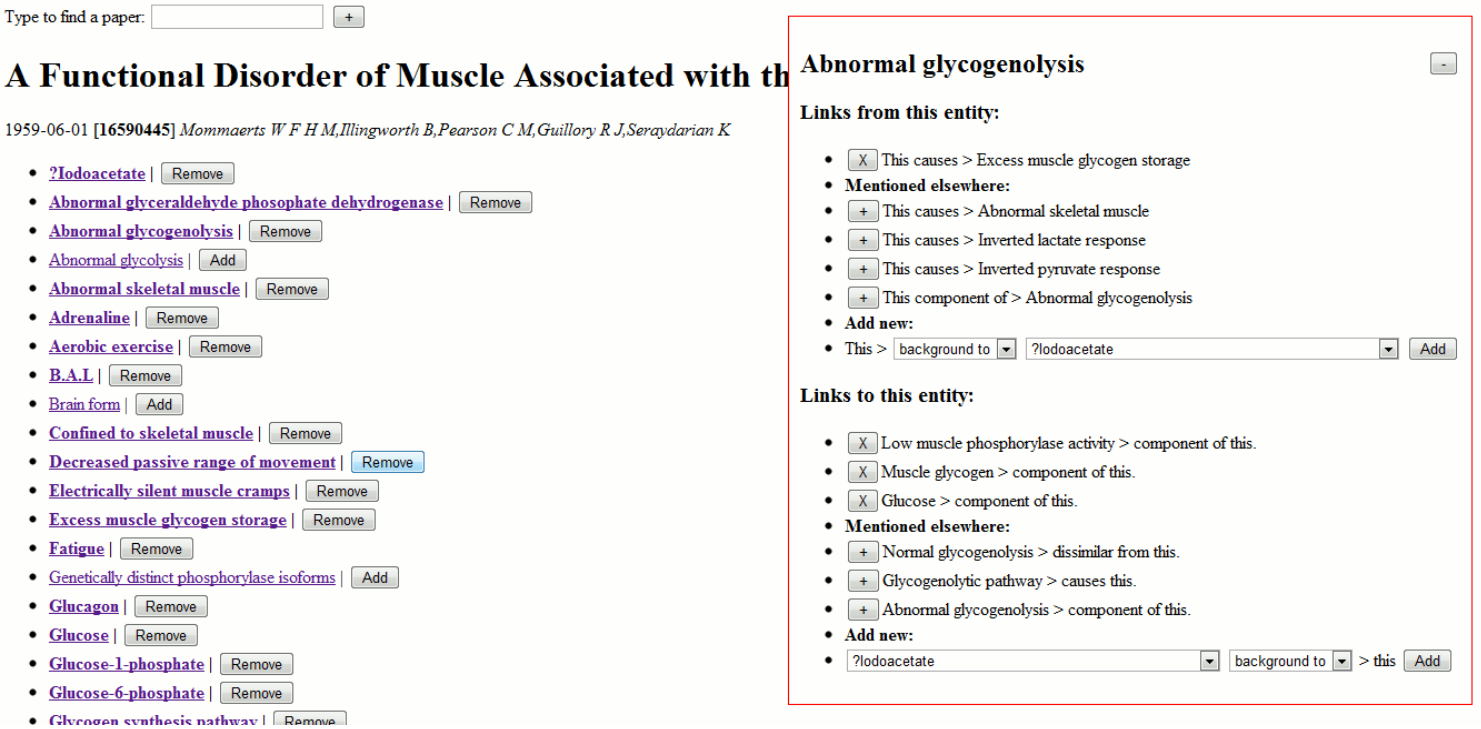
Technology


Type to find a paper:
+
A Functional Disorder of Muscle Associated with the Absence of Phosphorylase.
1959-06-01 [16590445] Mommaerts W F H M,Illingworth B,Pearson C M,Guillory R J,Seraydarian K
?Iodoacetate | Remove
Abnormal glyceraldehyde phosophate dehydrogenase | Remove
Abnormal glycogenolysis | Remove
Abnormal glycolysis | Add
Abnormal skeletal muscle | Remove
Adrenaline | Remove
Aerobic exercise | Remove
B.A.L | Remove
Brain form | Add
Confined to skeletal muscle | Remove
Decreased passive range of movement | Remove
Electrically silent muscle cramps | Remove
Excess muscle glycogen storage | Remove
Fatigue | Remove
Genetically distinct phosphorylase isoforms | Add
Glucagon | Remove
Glucose | Remove
Glucose-1-phosphate | Remove
Glucose-6-phosphate | Remove

Technology


Type to find a paper:
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A Functional Disorder of Muscle Associated with th
1959-06-01 [16590445] Mommaerts W F H M,Illingworth B,Pearson C M,Guillory R J,Seraydarian K
?Iodoacetate | Remove
Abnormal glyceraldehyde phosophate dehydrogenase | Remove
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Abnormal glycolysis | Add
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Brain form | Add
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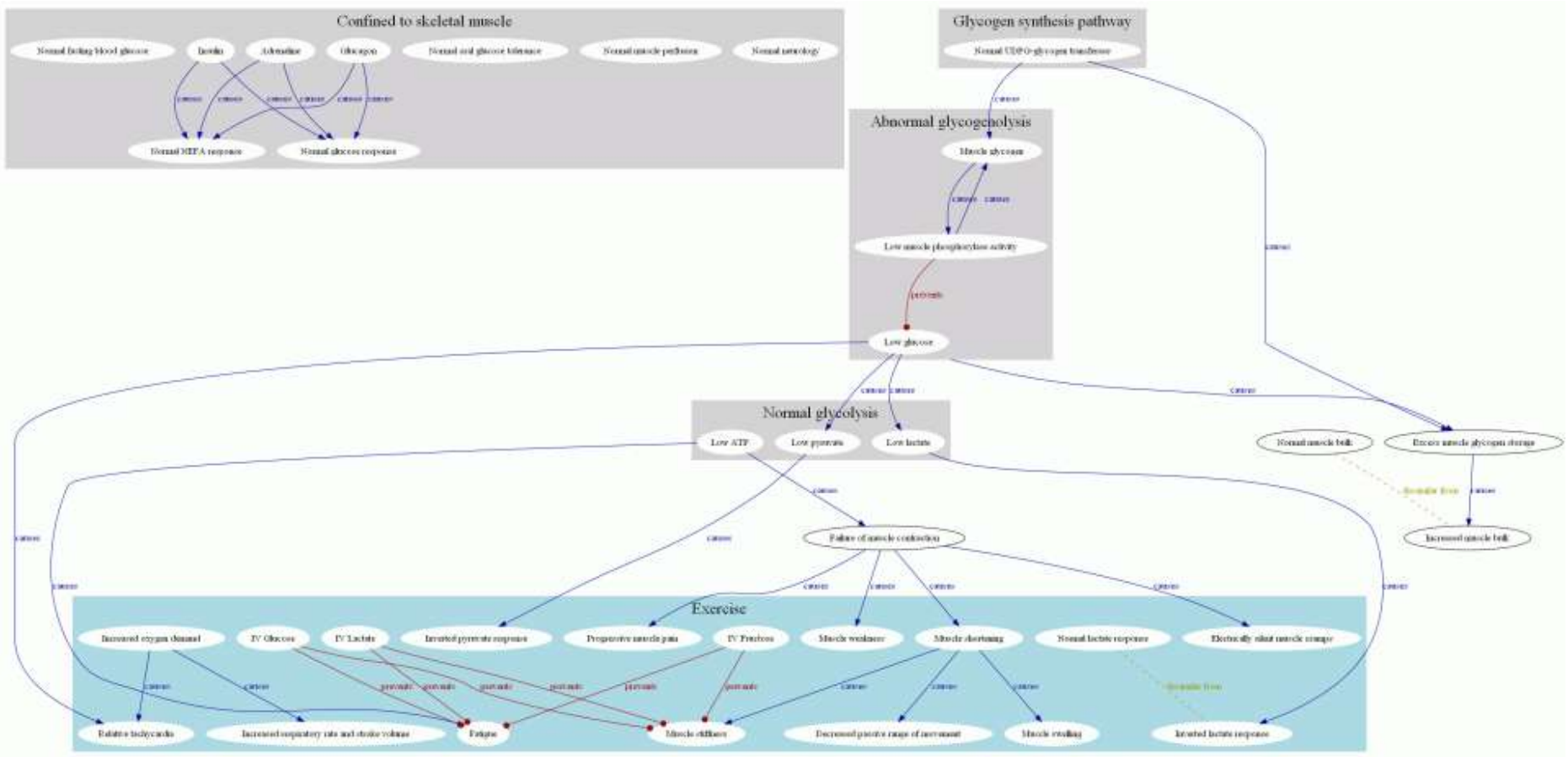
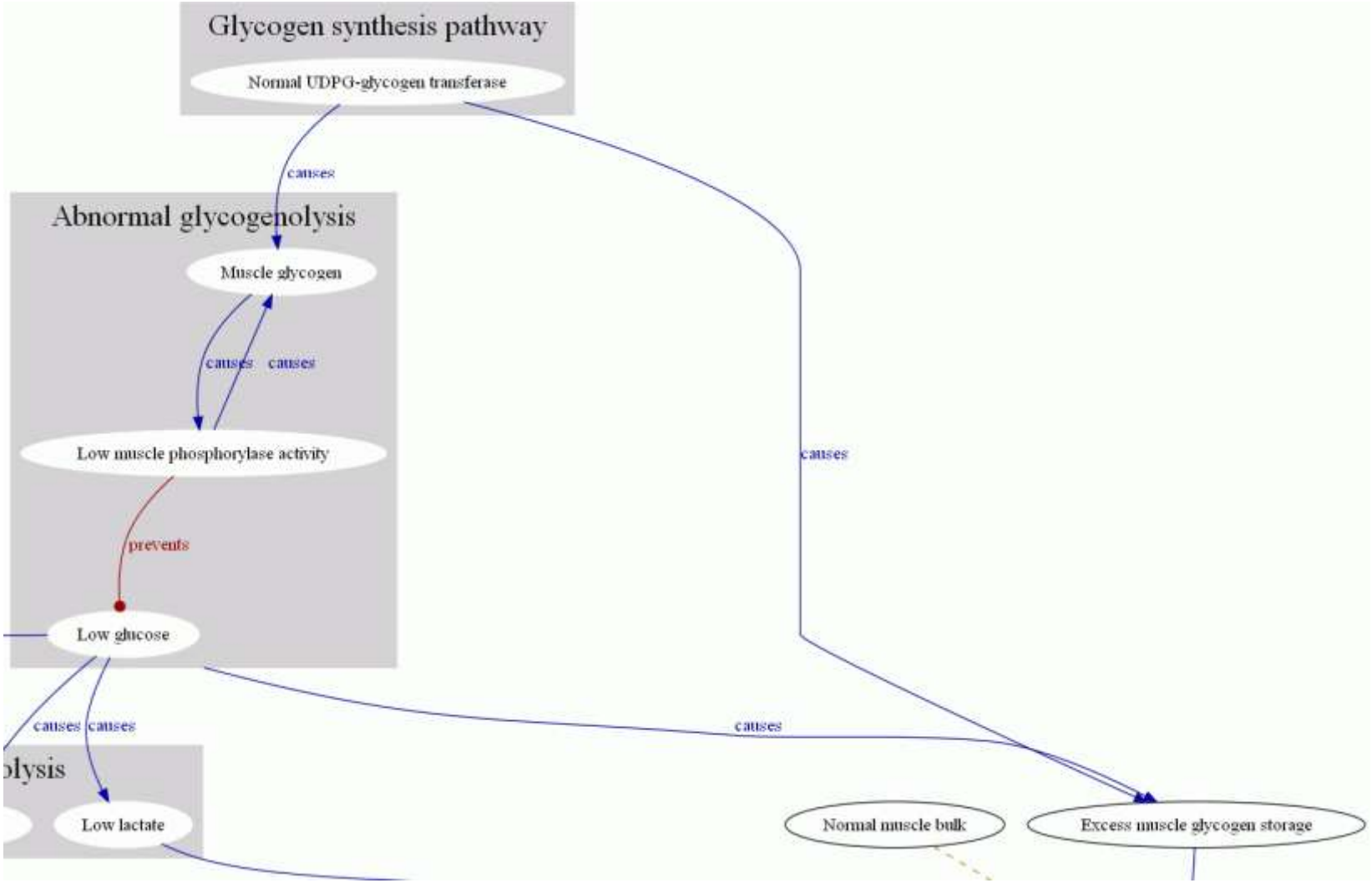
Decreased passive range of movement | Remove
Electrically silent muscle cramps | Remove
Excess muscle glycogen storage | Remove
Fatigue | Remove
Genetically distinct phosphorylase isoforms | Add
Glucagon | Remove
Glucose | Remove
Glucose-1-phosphate | Remove
Glucose-6-phosphate | Remove
Abnormal glycogenolysis
-
Links from this entity:
X This causes > Excess muscle glycogen storage
Mentioned elsewhere:
+ This causes > Abnormal skeletal muscle
+ This causes > Inverted lactate response
+ This causes > Inverted pyruvate response
+ This component of > Abnormal glycogenolysis
Add new:
This > background to ?Iodoacetate Add
Links to this entity:
X Low muscle phosphorylase activity > component of this.
X Muscle glycogen > component of this.
X Glucose > component of this.
Mentioned elsewhere:
+ Normal glycogenolysis > dissimilar from this.
+ Glycogenolytic pathway > causes this.
+ Abnormal glycogenolysis > component of this.
Add new:
?Iodoacetate background to > this Add

Technology


Confined to skeletal muscle
Glycogen synthesis pathway
Abnormal glycogenolysis
Low glucose
Normal glycolysis
Low ATP
Low pyruvate
Low lactate
Failure of muscle contraction
Exercise
Muscle weakness
Muscle shortening
Fatigue
Muscle stiffness
Muscle swelling

Technology


Glycogen synthesis pathway
Normal UDPG-glycogen transferase
causes
Abnormal glycogenolysis
Muscle glycogen
causes
causes
Low muscle phosphorylase activity
prevents
Low glucose
causes
causes
causes
causes
olysis
Low lactate
Normal muscle bulk
Excess muscle glycogen storage

Conclusions

- Normative accounts of mechanism must accommodate complex mechanisms
  - Complex mechanisms feature in scientific and medical practice
  - Complex mechanisms reveal conceptual difficulties in a way that simple mechanisms do not
- CMB is presented as a means of producing and exploring such mechanisms
  - To explore philosophical issues
  - As an historical tool
  - For use in scientific practice

Acknowledgements

- Graphviz - http://www.graphviz.org

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