The Newcastle upon Tyne Hospitals
NHS Foundation Trust

Patient with black renal stones

MetBioNet BMS Group
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Healthcare at its best
with people at our heart

Male, early 40s*

- Long-standing history of back and hip pain
- Previous hip replacement
- Two recent episodes of passing renal stones
- Investigations
  - Renal stones analysis
  - X-ray

**presentation comprises details from several cases to protect patient identity*

Stones analysis

- 76% calcium phosphate
- 20% calcium oxalate

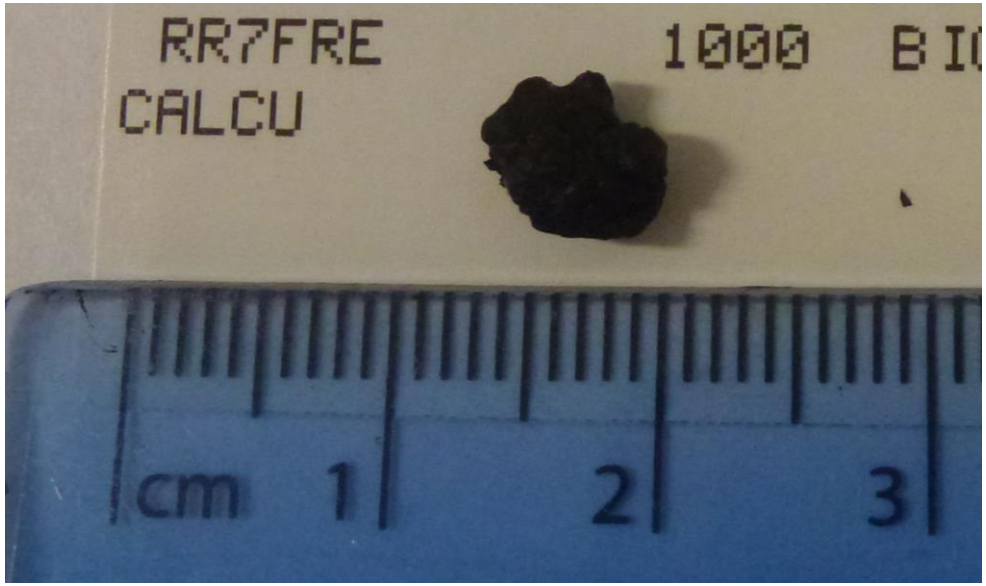


Photo provided by Laura Corbiere Senior BMS, QEH Gateshead

X-ray

- Intradiscal calcification
- Causes include:
  - Degenerative
  - Ochronosis
- Ochronosis
  - Accumulation of homogentisic acid in connective tissues
  - Dense spinal disc calcification

- Measurement of urine homogentisic acid

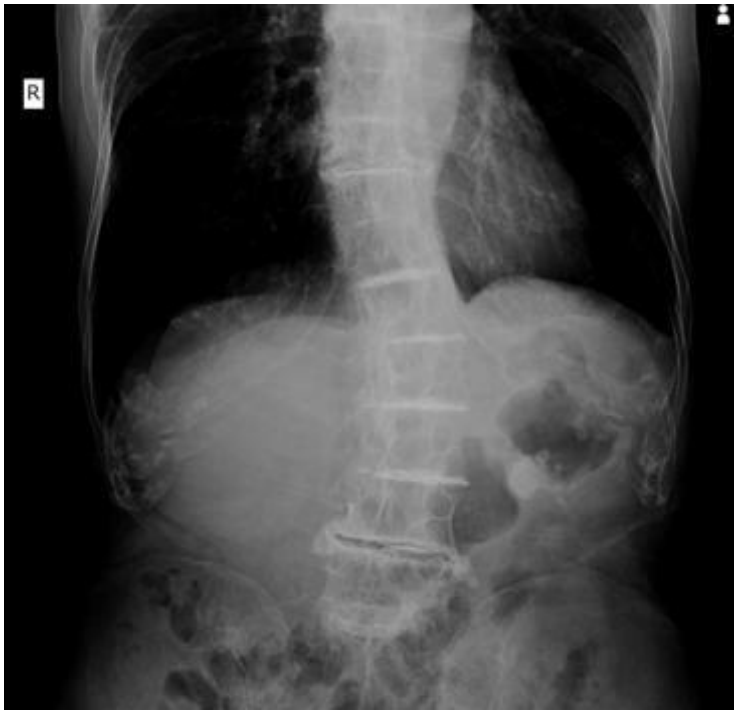
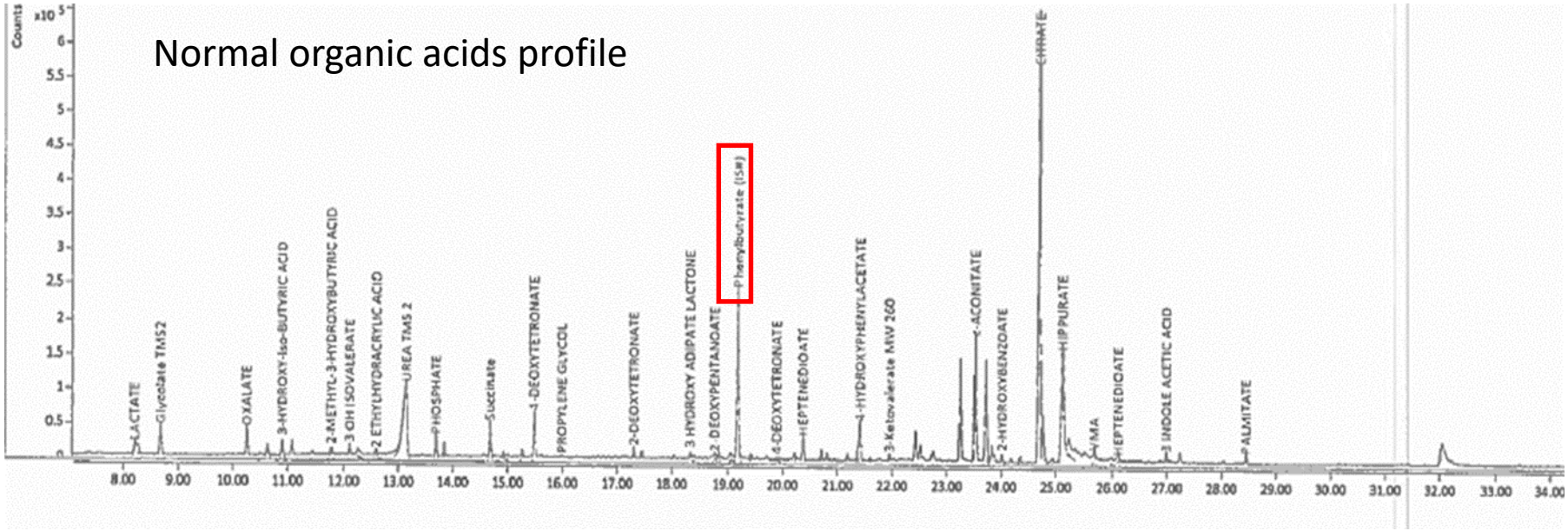
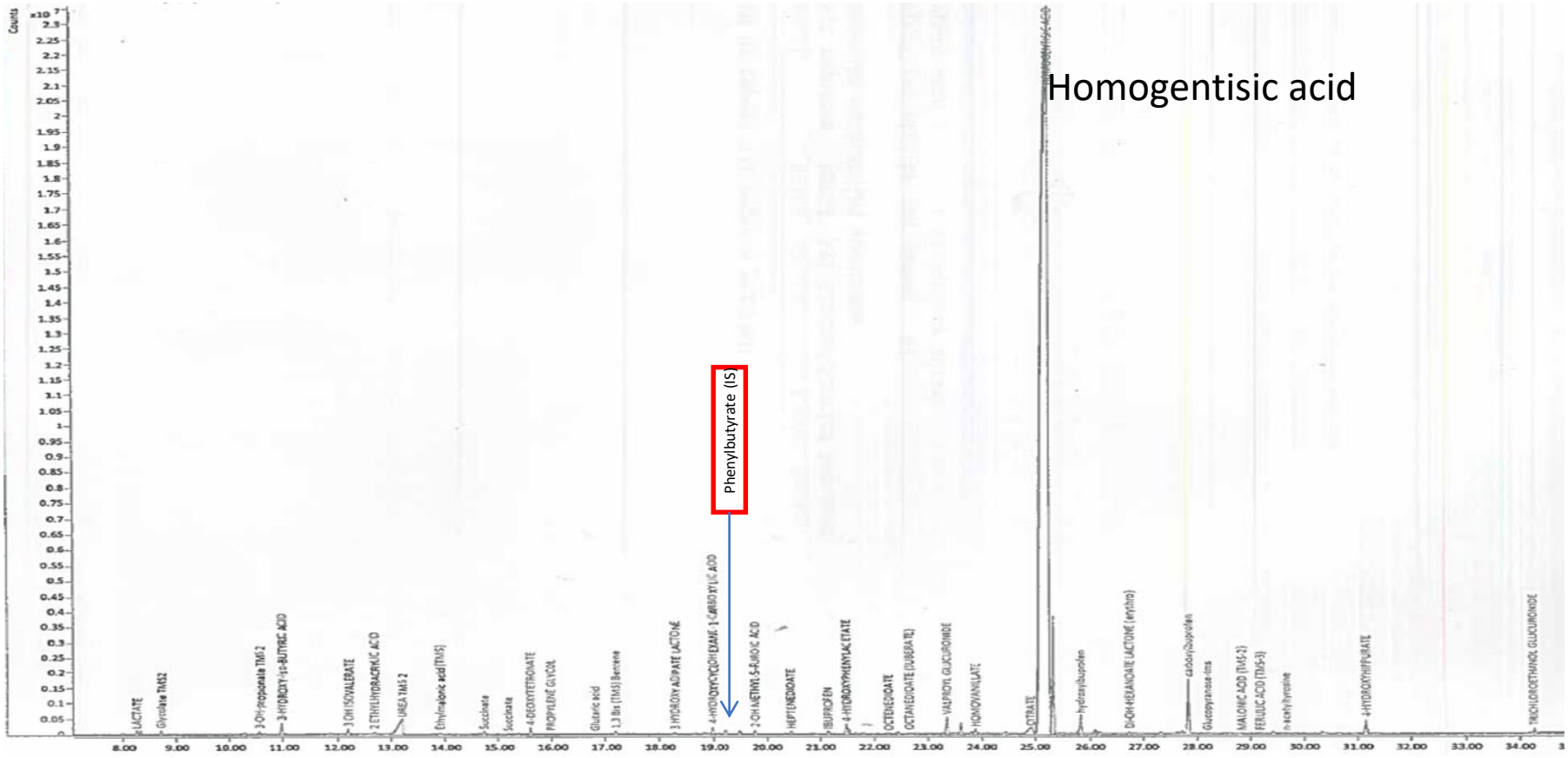


Image from https://radiopaedia.org

Homogentisic acid

- Detected on urine organic acids analysis





Grossly elevated homogentisic acid, consistent with alkaptonuria (homogentisate dioxygenase deficiency)

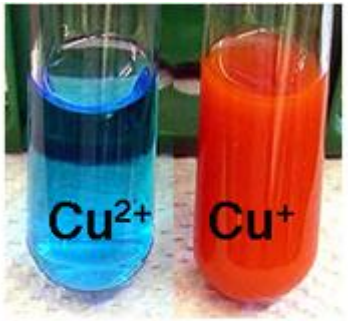
Suggest repeat to confirm and referral to national alkaptonuria service.

Alkaptonuria

- X-rays of an Egyptian mummy from 1500 BC showed extensive intervertebral disc calcification
- Bone biopsy showed black zones
- Black pigment extracted, identified as homogentisic acid
- Earliest reports of alkaptonuria

Böedeker, 1859

- 44-yr old man with lumbar spine pain
- Urine reduced alkaline copper solutions
- No evidence of diabetes
- Urine darkened when left to stand, from the surface of the tube
- Oxidation accelerated when alkali added to the sample
- New substance called ‘Alkapton’
- Alkaptonuria

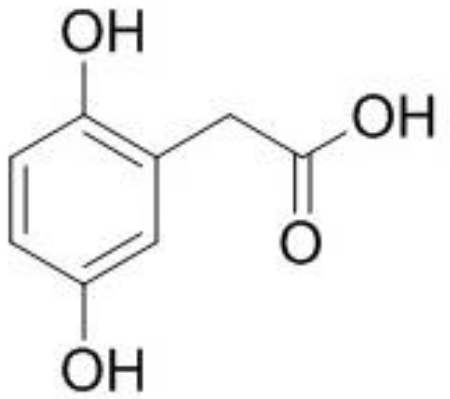


Control (blue) Positive test (red)

Virchow 1866

- Patients with AKU have tissues with ochre pigmentation under microscopy
- ‘Ochronosis’
- Black pigmentation observed in intervertebral discs, tracheal cartilage and ligaments

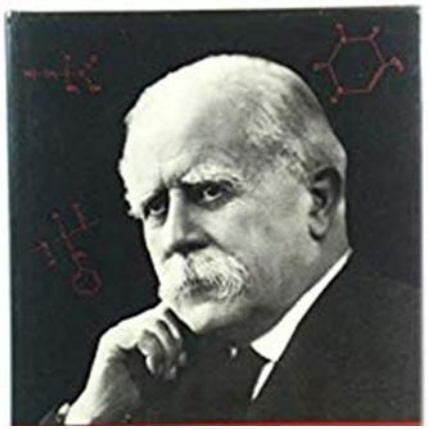
- Chemical structure of ‘Alkon’ identified in 1891
- Homogentisic acid



Archibald Garrod

Incidence of alkpatonuria: A study in chemical individuality

Lancet, December 1902



Full text reproduced in
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PMID: 12784973 PMCID: PMC2588790

current in this manner but I have seen steady improvement take place under its continued use.

In many cases no special diet is necessary. When there is any emaciation a liberal diet is required which may be supplemented by two extra pints of milk in the day. If there is great emaciation forced feeding may be necessary.

In a large number of cases, and especially in those which are seen in hospital out-patient practice, we can unfortunately carry out little more than medicinal treatment and often in circumstances which are not at all favourable to recovery. Belladonna was frequently prescribed and was useful in some cases but I have often been disappointed in the results of its use. To be of service in exophthalmic goitre any line of treatment should be steadily maintained for some weeks or even months and patients often dislike to continue taking belladonna in sufficient doses to produce physiological effects. Convallaria has proved useful in cases in which the frequency of the pulse has been very high and is more effectual in lowering the pulse-rate than other cardiac tonics. Bromides are useful in cases in which there are marked nervousness and tremors. Arsenic is useful in nearly all cases and may be combined with other drugs with advantage. The best results are obtained by giving small doses of three or four minims of Fowler's solution three times a day for a month or two or for the first three weeks of each month for five or six months. Of the animal extracts thymus and suprarenal tablets have both been of service. Thyroid extract is harmful, as it often exaggerates the symptoms, and should not be given in exophthalmic goitre. Special measures are frequently required for the treatment of urgent symptoms. The sudden attacks of diarrhœa were readily controlled by laudanum and dilute sulphuric acid. Severe attacks of palpitation with very rapid pulse yielded to the application of an ice-bag to the præcordial area. Persistent vomiting in acute cases is difficult to treat. On the whole rectal feeding and the administration of morphia, either subcutaneously or by the rectum, gave better results than other lines of treatment.

Newcastle-on-Tyne.

THE INCIDENCE OF ALKAPTONURIA: A STUDY IN CHEMICAL INDIVIDUALITY.

BY ARCHIBALD E. GARROD, M.A., M.D. OXON., F.R.C.P. LOND.

PHYSICIAN TO THE HOSPITAL FOR SICK CHILDREN, GREAT ORMOND-STREET; DEMONSTRATOR OF CHEMICAL PATHOLOGY AT ST. BARTHOLOMEW'S HOSPITAL.

ALL the more recent work on alkaptonuria has tended to show that the constant feature of that condition is the excretion of homogentisic acid, to the presence of which substance the special properties of alkapton urine, the darkening with alkalies and on exposure to air, the power of staining fabrics deeply, and that of reducing metallic obtained had the melting-point of ethyl homogentisate (120° C.). Further observations, and especially those of Mittelbach,[4] have also strengthened the belief that the homogentisic acid excreted is derived from tyrosin, but why alkaptonuric individuals pass the benzene ring of their tyrosin unbroken and how and where the peculiar chemical change from tyrosin to homogentisic acid is brought about, remain unsolved problems.

There are good reasons for thinking that alkaptonuria is not the manifestation of a disease but is rather of the nature of an alternative course of metabolism, harmless and usually congenital and lifelong. Witness is borne to its harmlessness by those who have manifested the peculiarity without any apparent detriment to health from infancy on into adult and even advanced life, as also by the observations of Erich Meyer who has shown that in the quantities ordinarily excreted by such persons homogentisic acid neither acts as an aromatic poison nor causes acid intoxication, for it is not excreted as an aromatic sulphate as aromatic poisons are, nor is its presence in the urine attended by any excessive output of ammonia. However, regarded as an alternative course of metabolism the alkaptonuric must be looked upon as somewhat inferior to the ordinary plan, inasmuch as the excretion of homogentisic acid in place of the ordinary end products involves a certain slight waste of potential energy. In this connexion it is also interesting to note that, as far as our knowledge goes, an individual is either frankly alkaptonuric or conforms to the normal type, that is to say, excretes several grammes of homogentisic acid per diem or none at all. Its appearance in traces, or in gradually increasing or diminishing quantities, has never yet been observed, even in the few recorded temporary or intermittent cases. In cases in which estimations have been carried out the daily output has been found to lie within limits which, considering the great influence of proteid food upon the excretion of homogentisic acid and allowing for differences of sex and age, may be described as narrow. This is well illustrated by Table I., in which the cases are arranged in order of age:—

TABLE I.—*Showing the Average Excretion of Homogentisic Acid.*

No.	Sex.	Age.	Average excretion of homogentisic acid per 24 hours on ordinary mixed diet.	Names of observers.
1	M.	2½ years.	3·2 grammes.	Erich Meyer.
2	M.	3½ ,,	2·6 ,,	A. E. Garrod.
3	M.	8 ,,	2·7 ,,	Ewald Stier.
4	M.	18 ,,	5·9 ,,	P. Stange.
5	M.	44 ,,	4·6 ,,	Mittelbach.
6	M.	45 ,,	4·7 ,,	H. Ogden.
7	M.	60 ,,	5·3 ,,	Hammarsten.
8	F.	60 ,,	3·2 ,,	H. Embden.
9	M.	68 ,,	4·8 ,,	Wolkow and Baumann.

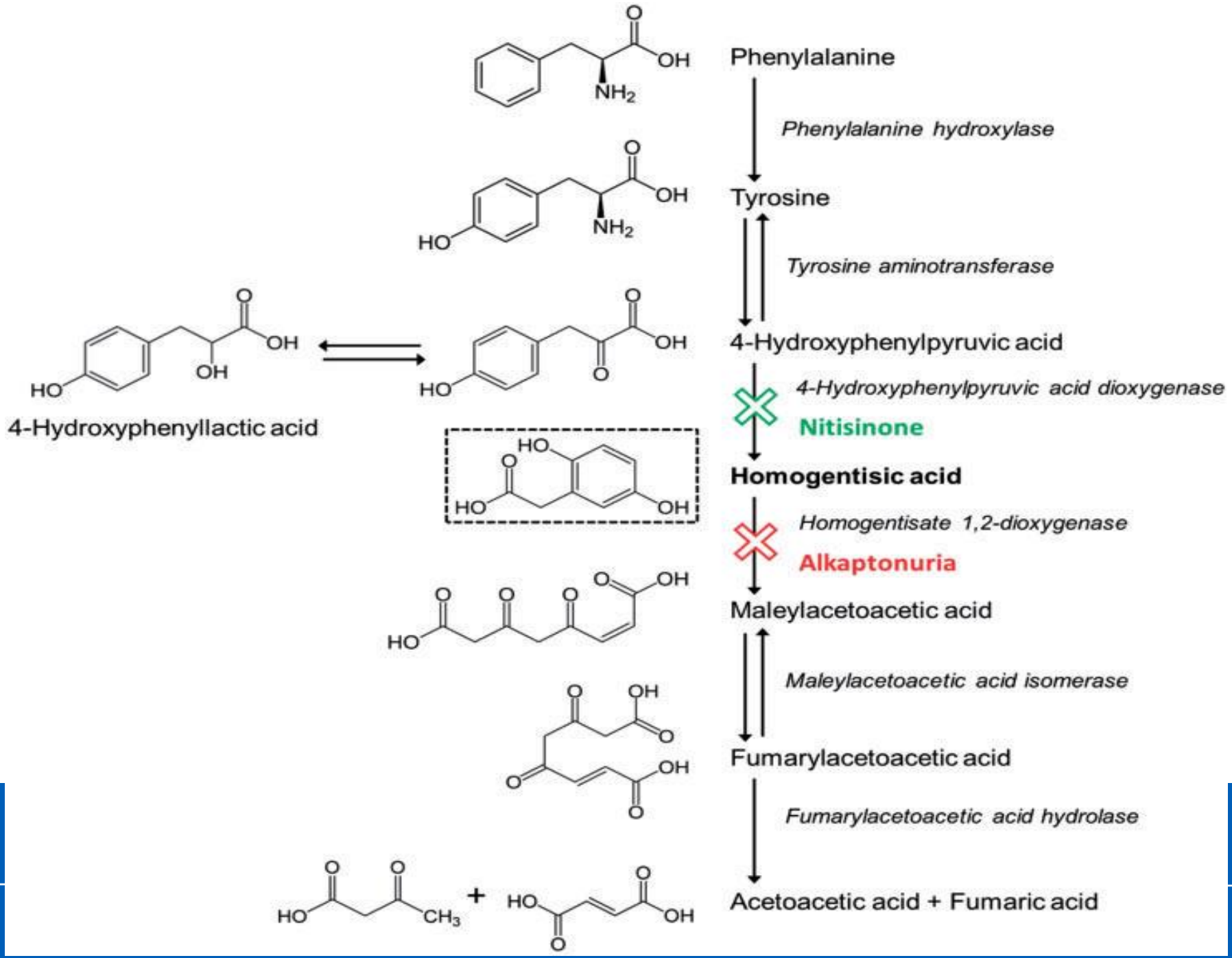
Archibald Garrod 1902

- Patients with alkaptonuria excrete homogentisic acid
- Urine darkens on alkalinisation or exposure to air
- Alkaptonuria is the nature of an alternative course of metabolism ‘somewhat inferior to the ordinary plan’
- Individuals are either alkaptonuric or conform to normal type
- Congenital and life-long
- Apt to make its appearance in siblings whose parents are normal
- Many are offspring of marriages of first cousins who do not exhibit this anomaly

- First use of the term ‘Inborn Error of Metabolism’

Alkaptonuria

- Autosomal recessive
- Prevalence is 1 in 250,000 – 1,000,000
- No approved disease-modifying therapy
- Low protein diet – ineffective


Phenylalanine
Phenylalanine hydroxylase
Tyrosine
Tyrosine aminotransferase
4-Hydroxyphenylpyruvic acid
4-Hydroxyphenylpyruvic acid dioxygenase
Nitisinone
Homogentisic acid
Homogentisate 1,2-dioxygenase
Alkaptonuria
Maleylacetoacetic acid
Maleylacetoacetic acid isomerase
Fumarylacetoacetic acid
Fumarylacetoacetic acid hydrolase
Acetoacetic acid + Fumaric acid
4-Hydroxyphenyllactic acid

Patient follow-up

- Referred to AKU clinic in Liverpool
- Gene mutation analysis
  - Homozygous mutation in *HGD* gene
- On nitisinone trial
- Increased plasma tyrosine (levels up to 800 µmol/L)
- Controlled with reduced protein in diet
- Some improvement of symptoms

Alkaptonuria

- Rare, iconic, inherited metabolic disorder
- Accumulation of homogentisic acid resulting in debilitating joint pain
- Homogentisic acid measured by urine organic acids analysis
- First reported disorder to follow Mendelian inheritance
- National service has enabled clinical trials of disease modifying therapy with positive outcomes

AKU
Alkaptonuria Society

https://akusociety.org