

## HISTORY OF MEDICINE ΙΣΤΟΡΙΑ ΤΗΣ ΙΑΤΡΙΚΗΣ

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### Favism

### A brief history from the “*abstain from beans*” of Pythagoras to the present

Favism is a form of hemolytic anemia and jaundice following the intake of fava beans and other legumes and various drugs. It is caused by a hereditary abnormality of the red cell enzyme glucose-6-phosphate dehydrogenase (G6PD). The condition is common in the Mediterranean basin. Various disturbances caused by fava beans, and especially toxic hemolytic anemia, have been recognized even from the period of Pythagoras, and the adage “be far from the consumption of fava beans” constitutes part of his consultations.

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Κυαμισμός – βραχεία ιστορική αναδρομή από το «*κυάμων απέχεσθαι*» του Πυθαγόρα έως σήμερα

*Περίληψη στο τέλος του άρθρου*

#### Key words

Favism  
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«...*κυάμων απέχεσθαι*...», “...*kyamon apechehesthe*...”  
“...*be far from the consumption of fava beans*...”

(part of Pythagorean consultations)

Favism (favisme, fabismus, favismo, fabism) is a reaction to the ingestion of the fava plant, its beans, pods and, most likely, foliage, or to inhalation of fava pollen. It is due to a hereditary abnormality of the red cell enzyme glucose-6-phosphate dehydrogenase (G6PD), which can cause sudden destruction of the red cell with hemolytic anemia and jaundice following the intake of fava beans, other legumes or various drugs. Favism is common in the Mediterranean area, Africa and southern Asia. More than 400 genetic variants have now been recognized.

The consumption of fava beans originated in the Near East in late Neolithic times and later they were cultivated in ancient Egypt, Greece and Rome. Fava beans are mentioned several times in the Iliad of Homer (8th to 9th century BC).<sup>1,2</sup> The ancient Greeks apparently associated the little black spot on the hilum of the bean with death and, although the beans were sometimes offered in sacrifices to Apollo, the priests were strictly forbidden to eat the fava bean or

even to mention its name. Unlike the Egyptians and Greeks, the Romans held the fava beans in high esteem among legumes. The beans referred to by Pythagoras (c. 570 to c. 495 BC) are fava beans (*vicia fava*, *vica faba vulgaris*), which botanically are classified as a large seeded vetch. The plant is well adapted to the Mediterranean region because it is very hardy to the cold and grows vigorously during the cool wet months of winter. There is evidence that it has for centuries been a unique and invaluable part of the diet of the people living in the Mediterranean basin. Its history is redolent with superstition, prohibition, magic and fear.<sup>3–18</sup>

It is well known that for some people fresh fava beans can be poisonous. Although common and known of for centuries, favism as a genetically transmitted disease was recognized only at the beginning of the 20th century and its mechanism was fully explained only in the last decades.

In Classical Greece doctors had seen the importance

of the environment, natural elements and “aliments” for maintaining the right balance of the organism. The occurrence of hemolytic anemia in individuals due to lack of the enzyme G6PD was known about for many years. It was called “favism”, relating its occurrence to the consumption of fava beans (the corresponding Greek words are «κύαμοι», (“kyamoi”), «κυαμισμός» (“kyamismos”, i.e., favismus). The observation that the consumption of fava beans causes various disturbances was the first instance of recognition of toxic hemolytic anemia and the rule «κυάμων απέχεσθαι» (“kyamon apechesthe”), “be far from the consumption of fava beans”, constitutes part of Pythagorean consultations.<sup>10,19–28</sup> This rule restricted the consumption of a legume that is named the Greek fava bean (*kyamos Hellenikos*, *Vicia faba*, *Vicia faba*) that had already been cultivated and used in the Mediterranean since the Prehistoric era. Theophrastus (372 to c. 285 BC)<sup>29</sup> used the word *kyamos* (*vicia faba*) to characterize the plant as well its kernel. Pliny (23 to 79 AD)<sup>30,31</sup> and Dioscorides (40 to 90 AD)<sup>32</sup> separated the Greek fava bean from the *fava Aegyptia*, pointing out that the Pythagorean rule concerns only the Greek fava bean. Empedocles (495 to 435 BC)<sup>33–36</sup> during the 5th century BC continued the Pythagorean teaching declaring that «δειλοί, πάνδειλοι, κυάμων από χείρας έχεσθαι», “deiloi, pandeilo, kyamon apo cheiras echesthe” – “unhappy, lot of miserables, not touched by fava beans”. Kallimachos (310 to 240 BC) during the 3rd century BC wrote «και κυάμων από χείρας έχεις, ανιόντος εδεστού, καγώ Πυθαγόρας ως εκέλευε» “kai kyamon apo cheiras echeis, aniontos edestou, kago Pythagoras os ekeleve” – “I say also, as said Pythagoras, you do not touch upon fava beans, that is corroded food”.<sup>37</sup> Pythagoras refused to walk through fields of fava beans and forbade his disciples to eat them. He is said to have met his death at the hands of the people of Crotonia in Ancient Italy.<sup>38,39</sup> Pursued by them, Pythagoras died at the hands of his enemies because he would not flee across a bean field, he came to the edge of a bean field and, rather than set foot in it, was caught and killed as reported by Artemidoros (1st century BC), Cicero (106 to 43 BC), Iamblichus (c. 245 to c. 325 AD), Diogenes Laertios (c. 3rd century AD), Pausanias (2nd century AD), Porphyry (234 to early 4th century AD) and Grigorios Nanzyanzynos (329 to 390 AD).<sup>20,40–45</sup> Iamblichus tells of the time when some Pythagoreans were being pursued by their enemies and they came across a field of fava bean plants in bloom. Rather than disobey their master’s dictates and flee through the field, they were slaughtered, and when two who were captured were questioned about their beliefs, they refused to answer. The husband chose death and the wife, a Spartan, bit off her tongue and spit it at her captors to avoid “spilling the beans”.<sup>22</sup>

The rejection of fava beans is also reported by philosophers of India constituting very probably prevention lauded by the Greeks. Whether or not poisoning was the basis of Pythagoras’ pronouncement, for many this argument is not certain. This debate is well summed up by Aristotle (384 to 322 BC) and Aulus Gellius (c. 125 to c. 180 AD), who say that Pythagoras proscribed fava beans either because they look like genitals (testicles), or because they resemble the gate of Hades, for they alone have no joints, since these two correlate well with traits connecting beans with human life and generation referred to by other ancient writers. Alternative interpretations are that they spoil, or that they resemble the base of the universe, or that it was believed that beans really mean eggs and the eating of an egg is similar to eating the animal that comes from it, or because of oligarchy, as the beans were used or drawing lots.<sup>19,23</sup>

Aristotle and Diogenes Laertios proposed that the Pythagoreans rejected fava beans because they are possibly poisonous and they provoke flatulence, which can destroy one’s mental peace by keeping one awake with a rumbling stomach.<sup>20</sup>

The later sect known as the Orphics believed that Pythagoras had forbidden the eating of fava beans because they contain the souls of the dead. “Eating fava beans and gnawing on the heads of one’s parents are one and the same,” went one of their sayings.

Herodotus (485 to 421 BC) reports that Egyptian priest considered beans to be unclean, while Pausanias and Porphyry note that they were forbidden for Orphics and the initiates at Eleusis, and they were items not to be touched, including them in a list along with pomegranates, recently delivered women and dead bodies, showing a possible relationship with religious dogmas.<sup>34,43,44</sup>

All the above testimonies emanate from members of the population that were not doctors. Although the Hippocratic doctors could not ignore the Pythagorean dietetics, the prohibition of fava beans is not reported in their treatises.<sup>19</sup>

Around the turn of the 20th century, physicians began to recognize the occurrence of favism after eating fresh fava beans and began to notice that some people suffer a sudden illness that, in some cases, led rapidly to death. The cause seems obvious today, but it was not until 1904 when Clemens von Pirquet came up with the medical definition for allergies. Before this time, it was difficult for doctors to comprehend the concept that what might be fine for one person might be poison for another. The first modern report of favism (favismus, kyamismos) is found in

a Lisbon magazine where in 1843 Manuel Pereira de Mira Franco reported the case of individual who presented with jaundice each time where he ingested fava beans.<sup>46</sup> From 1856 the Sicilian Antonio Mina La Grua,<sup>47</sup> but also other doctors, such as Di Pietra-Leone, Rizzo-Matera and Pietro Messina pointed out cases of jaundice from inhalation of products, possibly ethereal oils, of the fava bean flowers. They identified the hereditary nature of this illness, and distinguished this form of icterus from the jaundice of malaria, and confirmed the main role of fava beans. Giovanni Mule Bertolo (1900) observed the appearance of hemoglobinuria and proposed the term "favismus". The Sicilian patient Salvare Greco (his surname points to his Greek origin but also to his "stigma" of favism) suffered from favismus as did his maternal grandfather and commented that based on his experience and his inheritance this corresponded with the instruction of Pythagoras for the non consumption of fava beans.

On the threshold of the 20th century doctors hypothesized that the pathophysiology of favismus was hemolysis (destruction of red corpuscles) and at a congress in Rome in 1894 G. Montano reported hemoglobinuria (and no hematuria as was previously believed) as the main symptom of the disease, and distinguished the "decisive" reason for the disease, namely fava beans' and the "predisposed" reason, idiosyncrasy.<sup>48</sup> Cases were also reported in Italy by Girotti (1899), Camillis (1901), and in Sardinia by Went (1899), and Steani (1904). In Greece between 1895 and 1905 Doukas, Skavetzos, Kavvadias, Vellopoulos, Kontogeorgis, Tselios and others recognized the illness in various regions of Greece, both mainland and island regions. The epidemiological studies of Gasparrini in 1905 clarified the clinical picture, the familial character and the eclectic presentation in young persons, particularly males.<sup>17,49,50</sup>

The possible explanation of favism began to appear in the 1920s, when scientists found that G6PD deficiency actually provides a defence against malaria, which was the main health problem in Greece and Southern Italy at that time. It was not until the 1940s that W. Boyd from Boston noted that the British, in contrast to Mediterranean people, never developed favism after ingestion of fava beans, suggesting a genetic difference as the possible explanation. This information became more relevant during World War II, when treating malaria with quinine-based drugs resulted in a reaction to the medicine in the same people who presented hemolysis after eating fava beans.<sup>51-55</sup>

Subsequently, the complex explanation for the illness became evident from the experience of American doctors using antimalarial drugs on African Americans observed

the "favismus of blacks" and related it with the favismus of the Mediterranean origin. Later, lack of the enzyme G6PD was clarified as the cause of hemolysis. For years various constituents of the fava beans were incriminated, but also rarely other flowering plants, in the challenge of hemolysis. It was observed that the syndrome was released mainly after consumption of fresh fava beans and, to a lesser extent, dry or boiled fava beans, and after simple contact with the fava bean fruits or flowers, even at a distance, and that the substance may be transported via breast feeding. The Greek work of Choremis, Doxiadis, Kattamis, Stamatoyannopoulos, Fessas, Zannos-Mariolea and others provided new information on the subject of favism and its extent in Greece, with the discovery of "hot spots" in various specific regions, and on elements of the nature and the inheritance of illness.<sup>56-70</sup> Later the physiological polymorphism of the enzyme G6PD was recognized, together with the existence of irregular molecules of the enzyme, and details of the hereditary transfer. Greek pediatricians realized the relationship of G6PD deficiency with neonatal jaundice, its correlation with bone damage as in thalassemia, the co-incidence of the illness in the regions with malaria and also with other thalassemic syndromes, and the selection advantage offered by lack of the enzyme in malaria infection in the heterozygous women but not in the hemizygous men. The "Mediterranean phenotype" of the illness was recognized, and also variants of the enzyme, which were named after Greek regions or cities (e.g., Athens, Corinthus, Orchomenos, Levadeia, Karditsa, Attica, Thessaly, etc.) became known. It became apparent that the condition is most common in males, only women who carry the gene from both sides of the family are sufferers, and the condition is most severe among infants and children and that the "poison" can be passed to the nursing infant in the mother's milk.<sup>64-70</sup>

From all these publications it is apparent that even today it may be acceptable that the Pythagorean prohibition of the consumption of fava beans is valid.

It has been found that fava beans contain several chemical compounds that resemble those found in quinine. They are rich in two glycosidic compounds, vicine and convicine, which constitute about 2% of the dry weight. Upon ingestion, these glycosides are hydrolysed enzymatically to form pyrimidine aglycones, divicine and isouramil, respectively. The proposed mechanism for favism is that these new compounds consequently undergo redox cycling and the process depletes reduced glutathione, leading to the formation of free radicals and hydrogen peroxide.

After decades of research it was demonstrated that fava

beans themselves also fight malaria in the same way as G6PD deficiency (reducing the amount of oxygen in the blood). Theoretically, when fava beans are consumed by people with G6PD deficiency who don't suffer from favism (the vast majority), the resistance to malaria is raised. On a theoretical basis, even if fava beans are dangerous to a percentage of people, their benefits for the remainder of the

population far outweigh their shortcomings. Additionally during recent years there is documentation that fava beans (*Vicia faba*) have lipid-lowering effects and may also be a good source of antioxidants and chemopreventive factors.<sup>71–94</sup>

Is this the secret behind Pythagoras' puzzle? It remains hard to say, 26 centuries later. One thing is for certain: Pythagoras himself is not talking.

## ΠΕΡΙΛΗΨΗ

### Κυαμισμός – βραχεία ιστορική αναδρομή από το «κυάμων απέχεσθαι» του Πυθαγόρα έως σήμερα

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Κυαμισμός είναι η εμφάνιση αιμολυτικής αναιμίας και ίκτερου μετά τη βρώση κυάμων ή και διαφόρων φαρμακευτικών ουσιών, που οφείλεται σε μια κληρονομική ανεπάρκεια της αφυδρογονάσης της 6-φωσφορικής γλυκόζης. Η κλινική αυτή συνδρομή είναι αρκετά συχνή στους κατοίκους της λεκάνης της Μεσογείου και είναι γνωστή από την αρχαιότητα, αφού ο Πυθαγόρας ήδη από εκείνη την εποχή, ανάμεσα στις άλλες προτροπές, καθιέρωσε τη συμβουλή της μη κατανάλωσης κυάμων με το γνωστό αφορισμό του «κυάμων απέχεσθαι».

**Λέξεις ευρητηρίου:** Ανεπάρκεια αφυδρογονάσης της 6-φωσφορικής γλυκόζης, Κυαμισμός, Πυθαγόρας

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