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Urine: The Divine Fluid and Its Diagnostic Values

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ABSTRACT

Until the 17th century, uroscopy was the prime diagnostic tool used in laboratory medicine. Urine is the first body fluid which studied scientifically. Even now a day's urine examination is still the common diagnostic laboratory test for a range of diseases with comparatively more reliability and concise efficacy in addition to its cost-effectivity and simple procedure. It is a non-invasive test, so it was always accepted by both physicians and patients easily. During the journey of uroscopy to urinalysis, a series of inventions and innovations were adopted by the physician to improve the technique and technology in urine examination; which are being systematically summaries in this paper. Authors will try their best to synchronize all those efforts, valuable inputs, and instruments & techniques used down through medical history.

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INTRODUCTION

Urine examination is of paramount importance in diagnosis since the beginning of organized medicine. It was not only performed for the diagnosis of diseases rather for confirmation of pregnancy and sex determination of the fetus too.[1] *Hippocrates* (ancient father of clinical nephrology)[2] is credited as the original uroscopist but it is believed that it was practiced since the pre-Hippocratic era.[3,4,5] A paragraph on uroscopy has been written in the Hippocratic treatise '*Book of Prognostics*.'[1] Due to its diagnostic and prognostic value, urine was called as "*Divine fluid*" and "*a liquid window to the body and soul.*"[3,4,5] Middle ages (650 AD marks for the emergence of 'Islamic medicine')[6] physicians like *Avicena, Ismail Jorjani*, *Razi*, etc. used the term *boul*, *dalil* (sign), and *aab* (water) for urine and *tafsira* (commentator on body condition) for uroscopy.[4,7] Historically *uroscopy* is referred as the first documented laboratory test.[4,8] The term uroscopy is derived from the Greek word "*uroscopia*" which means a scientific examination of urine.[3] This is the visual examination of urine for the diagnosis and prognosis of the disease.[9,10] As advancement in chemistry and physics, uroscopy become urinalysis in the late 18th and early 19th centuries.[5] Urinalysis is a more comprehensive term used now a day for physical, chemical, and microscopic examination of urine. The term analysis was introduced by *Robert Boyle* (1627-1691) for precise and exact investigation.[11] *Hippocrates* (460-377BC), described the uroscopy scientifically.[8,12] According to him urine is a filtrate of four humours that is *Blood, Phlegm Yellow Bile*, and *Black Bile*.[3,12] *Erasistratus* (3rd century BC), described that urine is formed in the kidney. The filtration of urine first described by *Lycus*.[6] *Galen* (129 – 200AD- The Father of Experimental Medicine), redefined the Hippocratic hypothesis that urine is not a filtrate of humours, rather it is a filtrate of blood.[3] He described that the kidneys clear the blood. *Oribasius* (326-403), Physician to Emperor Julian the Apostate, coined the term "ureter" and conclude that kidneys absorb urine from the blood circulation.[2,13] According to *Avicenna* normal urine is lemon-yellow (*utruji*) in color which settles well and has a mild odor. He describes eight diagnostic parameters of urine i.e., volume, color, density, transparency, sediments, odor, froth, and taste and their clinical significances.[7] *Avicenna* has mentioned the difference between humans and animals urine. The difference between man and woman urine has also been described by him. He used to warn his students that sometimes patients brought other liquids or animal urine to test the skill of the physician. [1,7,8] By the valuable contribution of various scholars uroscopy becomes urinalysis. For higher and better specificity of urinalysis, physicians were always using the best equipment and technique

available in that era. A lot of scientific techniques and equipment had been used in this journey of urine examination; some of them will be discussed in this article.

MATERIAL AND METHODS

The relevant information about uroscopy and urinalysis is collected from classical Unani (Greece-Arabic-Indian) text, books of history of medicine, periodicals, journals & research articles available on the internet. Search engine Google, Google Scholar, Google pdf has also been used to extract the relevant references. The collected data has been analyzed and arranged in a systematized manner as they were tested with time.

EQUIPMENT AND TECHNIQUE

Quaroorah

Figure No. 1: Medieval period physician examining Quaroorah

https://www.granger.com/results.asp?image=0609555&screenwidth=1024

Quaroorah is an Arabic word that means flask. It was a container for the collection and examination of the urine sample. It was made up of glass or Blur or Crystal (Blur is flint glass).[4,7,14,15] *Avicenna* (980 – 1037AD) in his famous medical treaties *'Al-Qanoon Fit Tib'* (Cannon of Medicine) describes the method of collection of a urine sample for uroscopy and also describe the factors which alter the character of the urine sample. He refers urine sample taken in the morning is the best one for analysis.[7] Persian physician, *Ibn Abbas Majooshi* (930-994 AD) hypothesized that the yellow sediment found in urine is due to *yellow bile* from the hepatobiliary system.[8,14] *Ismail Jurjani* (1040 -1136AD), another Persian physician, adamant that collecting the full amount of 24-hour urine sample should be stored in a bladder shaped vessel and keeping it out of sunlight and heat to prevent possible change in color of sample.[8]

Matula

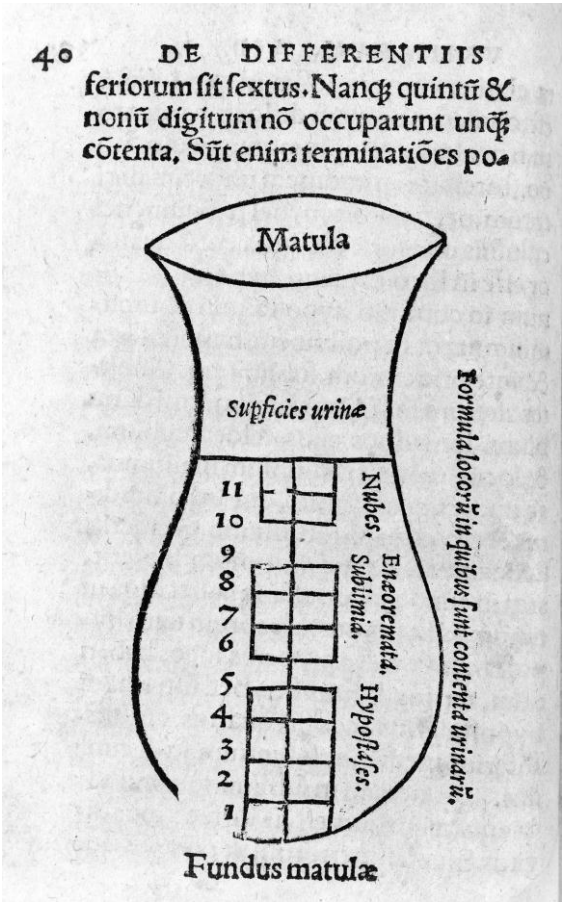

Figure No. 2: graduated Matula

https://commons.wikimedia.org/wiki/File:Woodcut_of_urine_flask._Wellcome_L0012935.jpg

Gilles de Corbeil (1165–1213) introduced *Matula* (*Jorden*) and wrote a poem on uroscopy.[16,17] It was the modified version of *Quaroorah*, used for uroscopy. *Matula* was also a bladder shaped urine container made up of clear and thin glass.[3,18] It was vertically divided into 4 levels, where the uppermost denotes illness of the head, second levels for heart and lungs, third level for the abdomen, and urogenital organs respectively.[1] These divisions were further subdivided into 11 and 24 boxes to denote the involved organ in each of the body cavities more precisely.[19] *Joannes Actuarius* (1275–1328) believed that out of four digestion in the body, urine is the filtrate of third digestion. He described urine sediment on four elements (fire, air, water, and earth) theory, fire and air are light elements that rose on the top whereas the heaviest element earth sinks in the bottom. He also modified his *Matula*, which was graduated into eleven segments,[8] he explains the bubble on the surface of urine represents abnormality of the head whereas sediment in the bottom represents ailments of the lower extremity. *Matula* was to be held only in the right hand and it was the badge of honor for physicians like the white apron and stethoscope does today.[3] Physicians began carrying a *Matula* on horsebacks as a professional trademark.[17]

Color of Urine

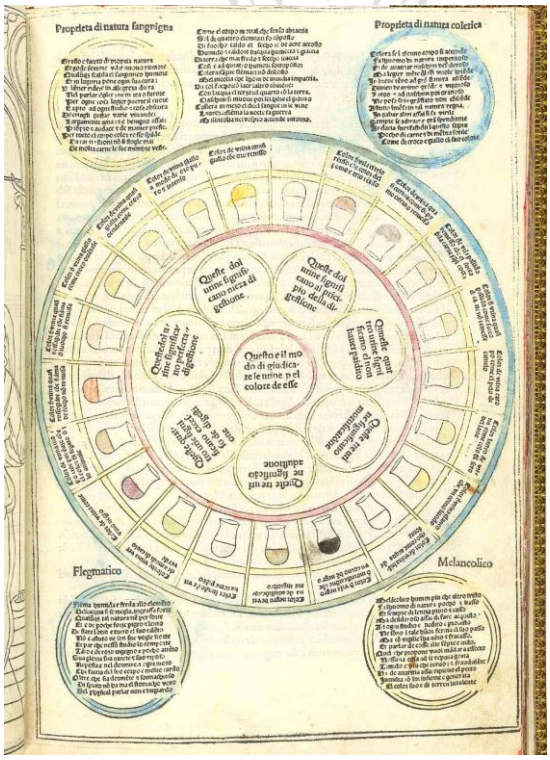

Figure No. 3: Johannes de Ketham's self-diagnostic color wheel

https://twitter.com/storiamedicina/status/1039140450718892032

The color of urine was always the vital criteria for urine examination. In ancient *Babylon*, urine color was compared with other fluid-like paint, wine dregs, beer, or beet juice by physiocrats for diagnostic purposes.[13] *Theophilos* (7th century AD) wrote the book '*De urinis*', the first known and exclusive book published on the subject of urine. He defines urine as *colamentum sanguinis.* In this book, he describes 20 color shades of urine: albus, lacteus, glaucus, charopos, subpallidiu, pallidus, subcitrinus, citrinus, subrufus, rufus, subrubeus, rubeus, subrubicundus, rubicundus, inopos, kyanos, viridis, lividus niger, adustus, and niger mortificatus.[18] Each color was interpreted for different pathological conditions. An Arab physician *Isaac Israeli* (832-932) authored the book '*Kitab al-Baul'* on the subject of urine. He developed a portable chart of humoural and urine assessment and claimed it could determine every known disease of that time.[5] *Avicenn*a describes different shades of five colors (yellow, red, green, black, and white) of urine and their clinical significances. He also describes the diet, drugs, regimen, and physiological conditions that mask the original color of urine.[7] In the late middle ages, physicians often carried a folded calendar that contains a urine color chart along with necessary astrological information and other medical references.[20] The oldest urine glass disc reported dates back from 1400 AD. In 1491, the book '*Fasciculus Medicinae'* published by *Johannes de Ketham*, mentioned a self-diagnostic color wheel. This urine color wheel was large, circular, surrounded by 21 different colored urine-filled *Matula*. The color and consistency of the test urine sample could be matched with the color of *Matula* for diagnosis. Four small circles, one at each corner of the wheel contain a description of the four-body temperament.[21] This urine color wheel was based upon humoral theory of diseases. The Color of urine is the reflection of an imbalance in the various humors in the body. Urine color denotes the body temperament; hence the four temperaments (choleric, melancholic, sanguineous, and phlegmatic) can easily be assessed by urine examination.[17]

Using this urine color wheel patients could self-diagnose their disease. As a result of this in the 16th-century urine, examination become the most precise and final tool of diagnosis among most of the physicians. It was so popular and rational that physicians start diagnosing the disease only from the urine, without clinical examination. Urine becomes the dumb messenger of the patient. However, *Joannes Actuarius* warned of the dangers of diagnosis made through only urine examination.[3] *Thomas Brian* strongly condemned the dumb messenger technique of uroscopy. He declared urine is a *harlot, or a liar* and states "it was fare better for the Physician to see his patient once than to view his urine twenty times".[8]

Al-chemical (chemical) method of urine examination

It was *Theophilus Protospatharius* (7th century) who first tries to analyze urine by heating it and found proteinuria by a manifestation of cloudiness, it was claimed as the first documented laboratory technique.[8],[3]

Anatomical furnace: It was human body shaped equipment, scaled on 24 levels.[19] It was designed by *Leonhardt Thurneiser* (1530-1595) for boiling the urine. By this technique, the location of the patient's ailment was assumed based on fumes and spattering. [20,22] He also tries to compare urine to a stream rushing down a mountain. He hypothesized that as the stream picks up sand and dust particle and carries along with them, similarly urine caries information from different parts of the body during its journey.[20]

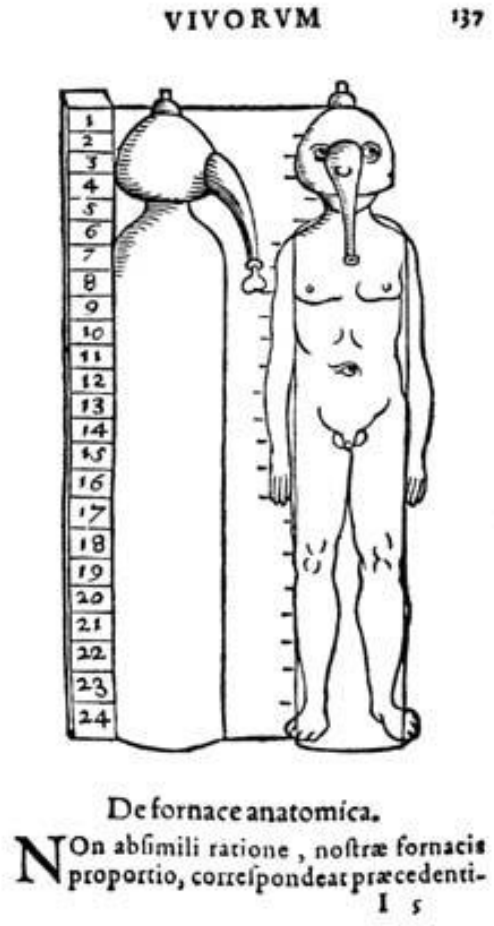

Figure No. 4: Anatomical furnace (human body shaped)

https://longstreet.typepad.com/thesciencebookstore/2013/02/finding-scientific-method-in-uroscopy-1577.html

Paracelsus (1493-1541) used vinegar to precipitate protein from urine,[13] but he was unable to interpret the finding with a disease condition. In 1694, *Frederick Dekkers* clarify this laboratory finding with proteinuria.[3,20,22] Actually this condition was explained by *Hippocrates* dates back as the presence of a bubble on the surface of urine is a sign of kidney disease and long illness. [2,20]

Albuminuria in eclampsia of pregnancy was reported by *John Lever* in 1843. In 1815, *Michel Chevreul* detects the presence of sugar (glucose) in diabetic urine.[11] The study of urea and the procedure for its isolation was developed by *Antoine Francois Fourcroy* (1755-1809) and *Nicholas Vauquelin* (1763-1829), and in 1817 *William Prout* isolated pure urea from urine. *Prout* also listed apparatus (a specific gravity bottle, litmus papers, turmeric paper, a blow-pipe, and forceps together with two discs of glass plate) required for performing laboratory tests on urine in the second edition of his book entitled '*An Inquiry into the Nature and Treatment of Diabetes, Calculus and the Affections of the Urinary Organs'* published in 1825.[23,24]

Later in 1882, *Woldemar Von Schoeder* devised a test for urea using bromine in chloroform. In 1847, the presence of an unusual protein was described by *Henry Bence Jones* in a patient with a fractured rib.[11] In 1857, *Wilhelm Petters* and *Adolf Kussmual* noted acetone in urine.[25] Reducing substances in some urine samples was quantitatively determined *Hermann Christian von Fehling* (1812-1885). *Max von Pettenkofer* (1818-1901) detected bile salts in urine. In 1831, *Heinrich Rose* developed the biuret test for albumin. *Johann Jacob Bezelius* (1779-1848) described that normal urine is acidic with a specific gravity of 1.025 and contains urea, phosphate, sodium chloride, and ammonium chloride. He also discovered few elements such as cerium, selenium, thorium, and others. He described that albumin, fibrin, blood, urates, oxalates, xanthine, cystine, sugar, bile and pus might be present in urine during the disease condition.[1] In the 19th century, several other chemical substances like creatinine, indicant, melanin, homogentisic acid, bilirubin, urobilin, urobilinogen, bile salt, etc. were also detected in urine. *Adolf Reinsch* (1862-1916) devised a test for the detection of metal in the urine. *The spectroscopic* analysis technique was developed by *Gustav Kirchoff* and *Robert Wilhelm Von Bunsen* in 1859.[11]

PH of urine: The term titratable acidity was coined by *Otto Folin* in 1904 [26] and the titrimetric method to measure net excretion of acid/base was devised by *K Jorgensen* in 1957.[27] *Lovibond comparator* was used for measurement of urine PH in the early 20th

century. The color comparison method to measure urine PH was developed by *AB Hasting* in 1925. Later on, an improved PH meter was developed by *Arnold Beckman* in 1934. *Handerson* and *Palmer* describe the colorimetric method for urine PH determination. The first colorimeter was probably designed by *Houtou Labillardiere*. In 1854, *Joles Duboscq* devised an early colorimeter. The qualitative colorimetric method was devised by *John Thudichum* in 1865, he also studies about urine pigment and haematin.[11]

1. **Urinacidimeter:** It was invented in 1933 by *Enrico Cauchi* for the evaluation of acidity in urine. This urinacidimeter consists of a 30cm long and 1cm wide tube, which was closed at one end and opened at another. It was divided into three sections, the first section for the solution of water lime, the second one for phenolphthalein, and third for pure urine. This was used to measure the acidity of urine expressed in grams of oxalic acid per liter.[28]

2. **Down Brother's test:** This was also an instrument for the evaluation of urine acidity. This instrument was provided by *Down Brother's*, London; consist of a 30cm long and 1cm wide vertical tube, which was closed at the bottom, and upper end with a glass cap. It was divided into two parts, one 10cm for urine and the other for sodium hydroxide. *Cauchi* reports that reading of this instrument was not accurate.[28]

3. **Ruhemann's Uricometer:** *Cauchi* described *Ruhemann's Uricometer* as best to measure the acidity of urine. It was consisting of a graduated test tube opened at one end and closed at another. The lower end was indicated with "S" while the upper end with "Y". The space between S and Y was divided into two halves .[28]

The reaction of Moritz Weisz: This reaction was used as a diagnostic and prognostic value for tuberculosis (TB).[28]

Urine specific gravity test: The density of urine was one of the important parameters in uroscopy. *Avicenna* pointed out the possible diagnostic value of urine density in the early days. In the early 17th century, *Cardinal Nicolaus Cusanus* (1401-1464) suggested the idea of the clinical significance of the weighing of urine. He compares the weight of urine with the weight of rainwater. However, some historian believes *Jon Baptista Van Helmont* (1579-1644) relate the weight of urine to an equal amount of rain water's weight. The specific gravity of normal urine is 1.025 described by *Johann Jacob Bezelius.*[1] The urinometer was introduced by Johann *Florian Heller* (1813-1871) in 1849. It was a thermometer shaped mercury-based floating urinometer for ascertaining the specific gravity of urine. [19,24]

Urine Test strips: The foundation stone of the strip test was led down by *Avicenna*, in the case of jaundice he noted that urine stained the linen cloths.[7,20] In 1914, *J Cruikshank* and *J Moyes* applied nitrite test strip (Griess) to urine, this nitrite test strip was developed by *Johann Griess*. *Jules Maumene* (1818 – 1898) impregnated a strip of merino wool with the "tin protochloride" (stannous chlore) in 1850 to detect urine sugar. Nowadays "test strips" are a widely used method. It is commercially available since 1950. A unique nylon mesh layer technology was developed by *Roches*.[11,27]

Uromancy: Urine is the probably first and most scientifically examined body fluid and most abused too.[1] The study of urine for divination (fortune telling) was called *uromancy*,[3,] and practitioners were called as uromancers. In ancient Rome, urine drifted into the pot of uromancers. Like physicians, they were also studied, swirled, and even tested urine to peek into the future.[5] After *Johannes de Ketham's* self-diagnostic urine color wheel uroscopy becomes easy. *Leaches* (unqualified medical practitioners) take the role of healers. There is an interesting story that "to mask pregnancy, a woman mixed her urine with cow urine, unfortunately, the Leche diagnosed that both she and her cow were pregnant".[3] In the 16th and 17th centuries, Uromancy flourish more. Every uromancers have their way of explanation of results and relate them with destiny. A stylish physician depicted in *Chaucer's Canterbury Tales* traveling to town for on pony with his urine basket.[8,16] Abuse of uroscopy was also reflected in Shakespeare's play, Henry IV.[1] Urine was also examined by to identify pure evil.[5] The physician who falsely pronounced results of urine examination was named as *lying oracle or piss prophets or pisse-mongers or water-caters or pisse-procrastinators*.[29] Thomas Brian strongly opposed the witchcraft of uroscopy. He published *The Pisse-Prophet or Certaine Pisse Pot Lectures*, in 1637.[16]

In the Roman period, the proverb "*Pecunia non olet*" (money does not smell) was popular, because of the monetary value of urine as gold. At that time urine collecting jars were placed at public places for pedestrians to urinate, which was used in soap making due to detergent property of ammonia in urine.[30] In the Renaissance periods, Al-chemists tried to extract gold from urine.[8]

Urine microscopy

The first sophisticated instrument used in urinalysis was a microscope. It is believed that *Pierre Borel* (1620-1689) is the first user of microscopy in medicine. Collected evidence by

him in 1655 indicates that the compound microscope had been invented in 1590 by *Zaccharias Janssen*.[24] The microscope brings revolutionary improvement in medical science. In 1666, uriniferous tubules were identified by *Marcello Malpighi* (1628-1694-father of microscopic anatomy)[2] by using a microscope. In 1840, RBC, Pus cells, a variety of crystals were recognized- this was the early use of the microscope in clinical practice. Urine cytology becomes a method of identification of malignant cells in various body fluids in 1853 when *F. Donald* published *The practical application of microscope in cancer*. Cells of different parts of the urinary tract were illustrated by *Beale* in 1854 and probably *Lambl* illustrates malignant cells from carcinoma of the bladder in 1856.[11] *James Ewing* identified malignant cells coming from a carcinoma of the bladder in his urine.[25] Leucocyte counting technique by microscope was developed by *J D Rant* and *W Shepherd*. In 1881, rod-shaped bacteria in urine were observed by *William Roberts* and [the] first paper on observation of bacteria in fresh urine was published by him.[20] In 1840, bacteria were observed in urinary deposits but at that time their clinical significance was unknown.[11] In urinalysis usually, microscopic examination is done to detect microorganisms and cytological findings.

Mass spectrometry

In 1859, *Gustav Kirchoff* and *Robert Wilhelm Von Bunsen* developed a spectroscopic analysis technique. The instrument for mass spectroscopy was first developed by *Joseph John Thomson* (1856-1940) and *Francis Aston* (1877-1945) in early 1900s.[11]

A paragraph on uroscopy has been written in Hippocratic treaties- '*Book of Prognostics*.[1] Out of 423, 37 Hippocrates aphorisms dealt with the renal problem.[6] After a journey of rising and fall for thousands of years, nephrology emerged in 1961.[19] Today's scholar who deals with the subject of urine is called as urologist or nephrologist.

CONCLUSION

From the above discussion, it can be concluded that urine was always the vital subject of interest for physicians due to its therapeutic importance. In every era, scientists were trying to do more accurate and valuable urine examinations to diagnose the disease. The technique used in the contemporary era is a result of the rigorous work of physicians for thousands of years. Even now a day's urine examination and their diagnostic accuracy for various diseases are in fashion because of its specificity and sensitivity in addition to its cost-effectivity and easiest procedure. Basic information on urine examination, various tools, techniques, and

equipment used as a diagnostic tool all through medical history have been mentioned in this article. But the extensive description of ancient theory (regarding urines diagnostic value) on the latest scientific parameters is need of the time to cut the accelerating cost of diagnosis.

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