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Urological Research

Stone analysis*

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In this paper on the state of the art of stone analysis, the following aspects are treated: the kinds of stones to be analyzed; the epidemiology of gallstones (in brief); the compounds found in stones; the reliability of different analytical methods; the use and advantage of stone analysis; and last but most important: what should be done concerning stone analysis?

Kinds of stones

Figure 1 illustrates many different stones formed in the body, including such types as sialiths, broncholiths, coproliths and phleboliths. The most important in terms of incidence and therapeutic consequences are urinary stones and gallstones. Artificial stones, created by the human mind, are a special analytical challenge.

Epidemiology

The epidemiology of urinary stones has been treated by W. G. Robertson (this issue); therefore the present paper includes only a few remarks on the epidemiology of gallstones. A previous largescale study [9] used multiple regression analysis to evaluate the epidemiological data. These figures show that cholesterol and bilirubin stones are influenced by different factors (Table 1).

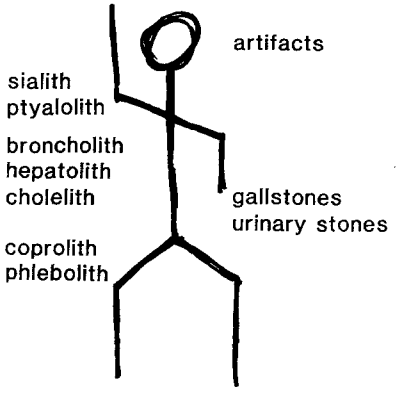

Fig. 1. Different kinds of stones formed in the body. The most frequent stones are mentioned on the *right*

Table 1. Factors causing gallstones

Epidemiology of gallstones	
Cholesterol stones:	Sex (f), fertility, obesity, age Oral contraceptives, clofibrate therapy Industrialized countries
Bilirubin stones:	Chronic hemolysis Chronic infections Parasite infections Developing countries

For cholesterol stones, the "four-f rule" – „female, fertile, fat, forty" – still holds true. Their increasing prevalence with age, especially in women [8] is well known. The ratio of women to men changes, from 4:1 for young people to 2:1 for the elderly [2]. Moreover, the incidence of cholesterol stones in women increases with the number of children [6].

The biochemical mechanisms of cholesterol and bilirubin supersaturation are entirely different; therefore, the prevalence of bilirubin stones is influenced by other factors [7]. Sex, fertility and obesity have no influence on their occurrences. However, some diseases known to result in the formation of bilirubin stones typically occur in developing countries [1]. According to Kanada [5], the ratio of cholesterol to bilirubin stones in Japan ranges from 3:1 in industrialized centers to 1:3 in rural areas. The overall prevalence of cholesterol stones is about 10%, and the overall incidence in 1 year is about 1% [10]; these figures are about the same as those observed for urinary stones.

* Revised version of the oral presentation

Table 2. Compounds occurring in gallstones

Main compounds:	Cholesterol hydrate	85%
	Calcium bilirubinate	15%
Impurities:	Polymerized bilirubin	
	Calcite, Aragonite, Vaterite	
	Calcium palmitate	

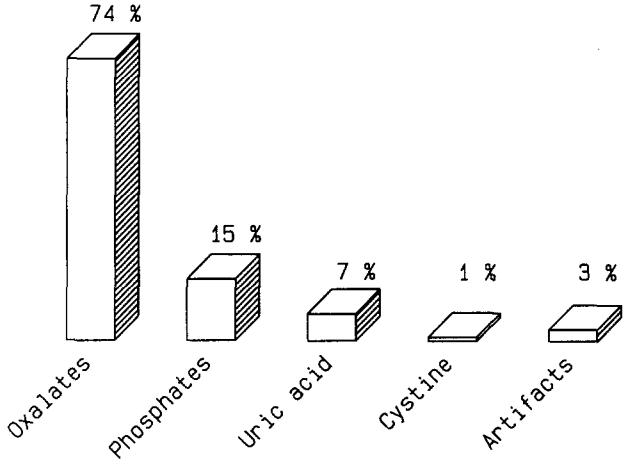

Fig. 2. Compounds occurring in urinary stones (University Hospital Zürich; $n = 28{,}000$; March 1, 1990)

Table 3. Analytical methods used in stone analysis

Common methods:	Chemical reactions in solution
	Infrared spectroscopy
	X-ray diffraction
Special methods:	Polarized light microscopy
	Thermo analysis
	Solid state chemical reactions

Compounds

Only a few compounds are found in gallstones (Table 2) including cholesterol monohydrate and the bilirubinates or calcium and magnesium. Minor compounds such as polymerized or unconjugated bilirubin are important for the solubility of gallstones [11]. In contrast to those in gallstones, the compounds in urinary stones show much more variability. Special and very rare compounds are not mentioned in this report, but they must also be properly detected in before the correct therapy can be chosen for these special patients (Fig. 2).

Analytical methods

Most of the compounds to be detected in stones are crystalline in form; thus, analytical methods commonly used in clinical chemistry, are not suitable for their evaluation. Methods for the analysis of crystalline compounds are well known in crystallography and mineralogy. Table 3 shows the methods used for stone analysis.

In chemical tests to analyze urinary calculi, the stone is dissolved and the ions in the dissolved compound are identified; these tests are specific for ions. The principle of infrared spectroscopy is measurement the wavelength of electromagnetic energy absorbed by the vibration of atoms in ions or molecules; this procedure is specific for atom groups. The purpose of X-ray diffraction is to measure the angle and intensity of electromagnetic radiation diffracted by crystal lattices. This technique is specific for crystal lattices, which are specific for each compound.

The three methods that are seldom applied can be characterised as follows. Microscopy by polarized light is typically used in mineralogy; tiny crystals can be identified, but some experience is required for rapid analysis of mixed substances. Thermo-analysis is applied in industry for purity control; however, since one important thermo-analytical signal is sensitive to impurities, this method is not suitable for urinary stones, which are normally not very pure substances. Chemical reactions with the undissolved stone material furnishes more information than the reaction of ions in solution. The experience in international quality control using this kind of solid-state chemistry has been quite good, but the application of this method to mixed substrates such as urinary stones is not that simple.

International quality controls

How reliable are these analytical methods? In carrying out international quality control [4], we take care to test only samples with one pure compound. The result is judged to be wrong if a compound is reported that would lead to incorrect therapy. Differences that do not influence the therapy and metaphylaxis are not considered to be important. The following compounds are regarded to be equal: calcium oxalate, mono- and dihydrate; uric acid and uric acid monohydrate; and sodium and ammonium hydrogen urate.

The first sets of data shown in Table 4 concern 20 quality-control series involving 43 substances and 4,104 results. Of the latter, 2,664 of were obtained by chemical test; 1,032 by infrared spectroscopy; and 408, by X-ray diffraction. Over a 10-year period, true-positive results were achieved in 65%, 94% and 95% of the tests performed by chemical analysis, infrared spectroscopy and X-ray diffraction, respectively. Agains, these tests involved only pure substances that were sent to the laboratories.

Was there an increase in quality from one 5-year period to the next? Not at all; all methods showed a decrease in quality between 1980–1984 ($n = 995/252/141$ for chemistry, infrared spectroscop and X-ray diffraction, respectively) and 1985–1989 ($n = 1{,}669/780/267$): chemistry, from 77% to 58%; infrared spectroscopy, from 96% to 93%; and X-ray diffraction, from 99% to 93%. The main reason for the decreasing quality of these analyses was that during the second period, more rare and difficult

Table 4. Results of International quality controls

Substance	Period	Chem		IR		XD	
		t+	f+	t+	f+	t+	f+
All	1980–1989	65	26	94	5	95	5
All	1980–1984	77	19	96	3	99	1
	1985–1989	58	30	93	6	93	7
Oxalate }	1980–1984	84	15	96	4	100	0
Uric acid }	1985–1989	81	6	97	2	98	2
Xanth + 2,8 DHA	1980–1989	22	63	90	9	88	11
SiO_2 $CaCO_3$	1980–1989	52	25	94	5	96	4

t+ = True-positive results (%); f+ = false-positive results (%); chem = chemical tests; IR = infrared spectroscopy, XD = X-ray diffraction, Xanth = xanthine; 2,8-DHA = 2,8-dihydroxyadenine

compounds were sent to the laboratories. Therefore, it is better to look at the test quality of definite compounds.

However, even for the most common substances, such as calcium oxalates or uric acid, the percentage of correct results was only about 80% for chemical analysis as compared with 96% for infrared spectroscopy and X-ray diffraction. The quality did not change much between 1980 are 1989 (1980–1984, $n = 285/74/40$; 1985–1989, $n = 726/325/109$).

Rare compounds such as xanthine and 2,8-dihydroxyadenine are evidently more difficult to identified ($n = 248/125/45$): 22% true-positive results were obtained using chemistry as compared with about 90% for infrared spectroscopy and X-ray diffraction. Although a true-positive rate of 22% is bad enough, the false-positive rate of 63% is worse; the latter result means that in 63% of tests a compound was reported to be present that did not occur in the sample.

Similar results were obtained for the most common artifacts quartz and calcite (calcium carbonate) ($n = 419/201/65$): only 52% of the tests were true-positive for chemistry as compared with about 95% for infrared spectroscopy and X-ray diffraction. Agains the failure to find a compound that is present in the sample is bad, but it is worse to find compounds that do not occur in the sample (25% of all artifacts). In these cases, the medical doctor informs the patient about the specific findings (e.g., calcium oxalate) and recommends special diets that should be followed, whereas the patient knows that he gave the doctor a small stone that he just picked up from the street!

In every respect, infrared spectroscopy and X-ray diffraction analysis of stones (gallstones or urinary stones) show much higher reliability than either the old-fashioned or the most modern chemistry test kits.

Therapeutic importance

What is the importance of stone analysis? For urinary stones, the advantage of a correct stone analysis is quite clear. Using proper metaphylaxis, the recidivistic quota can be drastically reduced. I would like to mention a bad experience reported by Albrecht Hesse (Bonn). Due to incorrect analysis, a cystine-former was treated as a calcium phosphate-builder and underwent 13 surgical interventions. Correct stone analysis would have reduced the number of operations to one-third or even less.

For gallstones, the advantage of a correct stone analysis is not so obvious. In Zürich we get 4,000 stones/year for analysis, but only 1% of these are gallstones; this is curious, since the prevalence of urinary stones and gallstones is about the same. As knowledge and experience with cholelithiasis increases, the chemical composition of gallstones becomes more important, since cholesterol and bilirubin stones require different treatment [3, 11].

Conclusion

A politician's closing remarks should be effective, but those of a scientist should be honest as well. What is the state of the art of stone analysis? Considering the results of 10 years of international quality control, instead of using the term "state of the art" in stone analysis, I prefer to discuss the "state of misuse" of analytical tools.

A scientist would never accept a method for determining potassium, glucose or pregnancy that proved to be entirely wrong in $> 20\%$ of all cases. What is the reason for continuing to use the suspicious chemical method? One answer could be: we have always done it that way. However for the removal of urinary stones, the methods been universally adopted is now lithotripsy. The correct answer to the above question, which would enable the use of the chemical method, might involve the following. Chemical analysis costs less than infrared spectroscopy or X-ray diffraction but involves the same reimbursement, resulting in higher earrings; moreover there is no control. If a doctor were to use a pregnancy test that was as faults as chemical stone analysis, nature would inform him and the patient about the quality of the test in a short time. Thus, one is forced to apply a reliable test. In stone analysis, we are free to choose a reliable test; hopefully, we will make use of this freedom.

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