

The urinary drop spectrometer

Information from the external urine stream permits early, painless diagnosis of obstructions with an optical instrument developed by an interdisciplinary group.

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A new diagnostic instrument that can potentially affect the lives of hundreds of thousands of people has resulted from a collaboration among physicians, physicists, engineers and mathematicians. This article is the case history of the interdisciplinary study which culminated in the development of the urinary drop spectrometer, a painless instrument, now in clinical use, for the early detection of lower-urinary-tract abnormalities. As the name implies, this instrument analyzes the spectrum of drops into which the urinary stream breaks up. As the drop spectra carry a "memory" of the passage the fluid has traversed, their statistics may be used to map the delicate tubes of the urinary system. Figure 1 shows how the output of the spectrometer clearly distinguished output from patients suffering from two different disease conditions from each other and from that of a normal individual. We will see how these clearly distinguishable differences arise, and how they form the basis for medical diagnosis.

The medical problem

About 10% of hospital admissions involve urological difficulties,¹ of which probably a majority² originate with obstructions or infections, or both, many due to anomalies in the outlet tract from the bladder to the exit opening

known as the meatus (see figure 2). The serious consequences occur when these troubles migrate up to the kidneys, which are a fine, complex pollution-control system necessary in all higher vertebrates.³ Even our personalities are believed to depend greatly on the operation of this system.⁴

The hydrodynamic inference is simple. The normally sterile urine is an extremely vulnerable culture for bacterial growth. These bacteria attempt to invade from outside, and the periodic emptying of the bladder "holding tank" washes them out.

Anomalies in the lower system give the invaders a potential foothold. A one-way valve, the uretero-vesical junction (see figure 2), normally isolates the lower tract from the critical upper tract (ureters and kidneys). When lower-tract resistance grows, the bladder compensates⁵ by strengthening its muscles so that it can raise the pressure. The pressure increase, from the normal 40 mm Hg to as much as 120 mm Hg, is well documented, but the sensing mechanism (a flow sensor?) that stimulates the squeezing is not understood.

The higher bladder pressure during voiding (resting pressure is 10–20 mm Hg) causes a backward leakage called reflux through the uretero-vesical junctions. The last protection has been breached, and the vulnerable kidneys are attacked.

In females the incidence of bladder infection is high, probably because the urethra is so short (4 cm). These infections lead to hardening and permanent change of the tissue underlying the lining of the urethra, which makes the pro-

cess of periodic reinfection more rapid. The delicate interplay of very soft, sealing mucous membranes and sphincter muscles, controlled both by active squeezing and by passive relaxation, is strained in such circumstances and results in incontinence and other manifestations that occupy a large part of the effort of urologists.

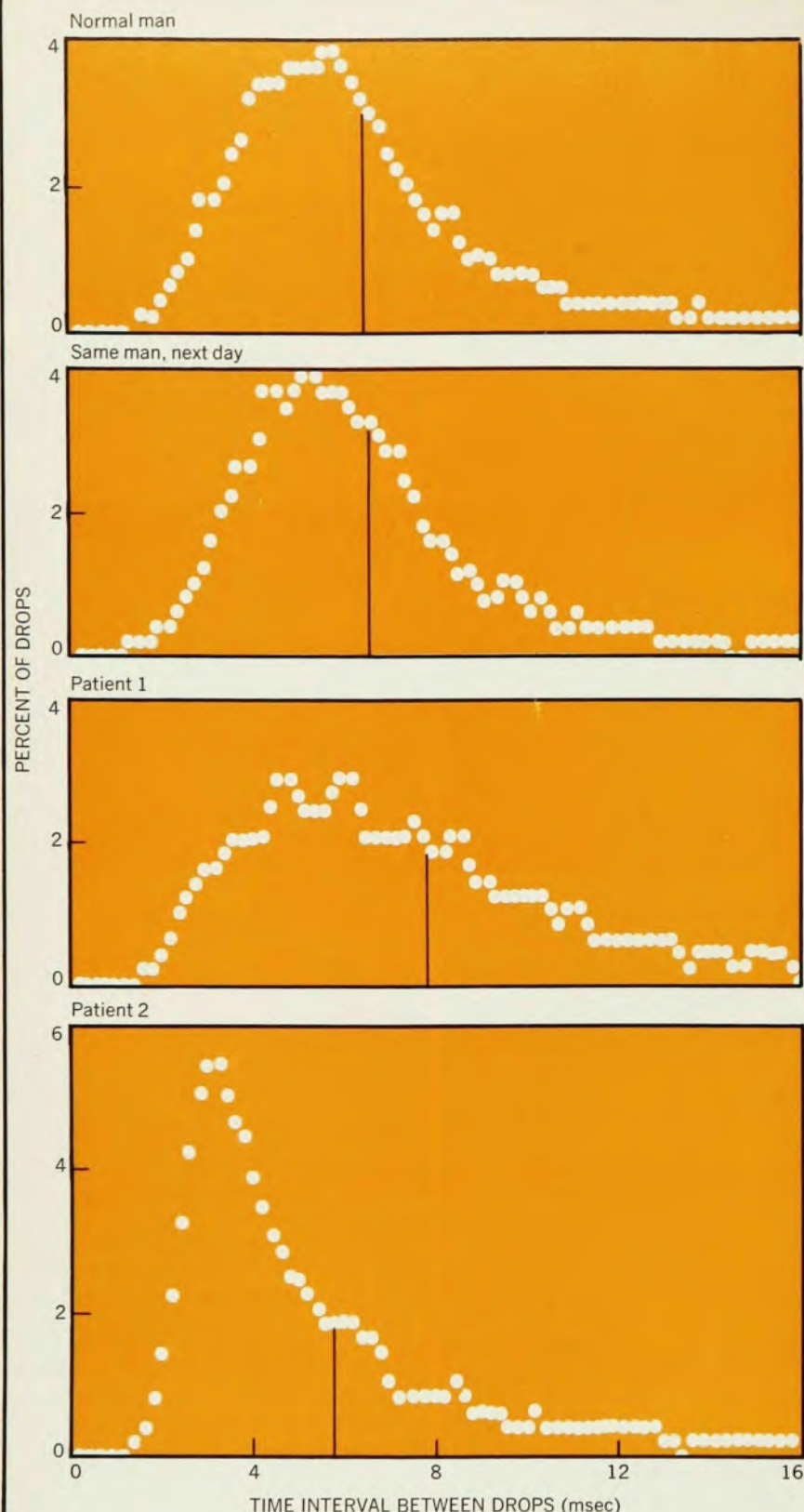
In males a different and even more common problem exists. According to Rubin H. Flocks,⁶ 25–50% of males over 50 will have prostate difficulties. In its commonest form, benign prostatic hypertrophy, this gland enlarges and, as it is something of a "doughnut" around the urethra, partially (sometimes totally) obstructs the flow of urine during voiding. In about half of these cases surgical procedures should be performed to preclude more serious consequences. The tissue changes in prostatic hypertrophy are thought to be⁷ hormonally connected and to begin at a much younger age. Conventional diagnostic tools of urology cannot detect such slight changes.

Unless the physician can be sure that his patient is starting to develop benign prostatic hypertrophy, it would be irresponsible to start drug treatments, since such treatments commonly lead to other complications unrelated to urology.⁷ What is needed, then, is a diagnostic technique that can be used repeatedly on patients who exhibit no advanced urinary-tract difficulties.

An interdisciplinary project

In 1962 one of the authors (Ritter) met Norman Zinner, then a resident in urology at the University of Virginia, at

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Time-interval histograms obtained with the urinary drop spectrometer. The vertical black line marks the centroid of the distribution, indicating the average time interval between successive drops. The top two graphs, taken of the same person on successive days, illustrates the repeatability of the measurements. For patient 1, suffering from benign prostatic hypertrophy, the distribution is flattened, with the average shifted to the right. Patient 2, with meatal stenosis, has a more peaked distribution with a shorter average time interval between drops. Figure 1

a cocktail party. Zinner was interested in problems connected with measurements of the pressure-flow relations in the voiding of young women. The generally accepted notion⁸ then was that the female urethra (the tube connecting the bladder to the outside, normally about 4 cm long) was at least 6 mm across at the narrowest point during urination. This belief was grounded on the insertion of metal probes known as sounds into the urethra.

Since interdisciplinary projects have never been a reliable way for young physicists to gain tenure, the work on some simple calculations of pressures and flow rates in the lower urinary tract proceeded on something like alternate Sunday mornings. It quickly became apparent from the calculations that the width of the urethra was unlikely to exceed 3 mm, and that the mechanical forces exerted by probes during urination are several orders of magnitude larger than the natural hydrodynamic forces in the body.⁹ Urologists were understandably reluctant to accept such a remarkable statement on the basis of calculations alone, but were finally convinced when a large model was constructed, involving a pitcher of saline solution, at 98.6°F and 40 mm Hg pressure, connected to a 4-cm long stainless-steel pipe whose diameter could be varied. With a 6-mm diameter tube, the "bladder" emptied in a few seconds (compared to 15 sec in a normal voiding). The visual impact was particularly vivid for one prominent urologist, who commented that it "looked like a horse."

Winning this battle generated enthusiasm, and the collaboration received a much-needed impetus. The medical and physiological problems were discussed, and it soon became clear that this important "lower urinary tract" was an interesting and complex physical system with strange, little-understood methods of control. It also became clear that the study of it, extremely limited in normal humans, was fraught with huge experimental difficulties of a kind entirely different from those of conventional physics.

The next step in the development of the instrument was a colloquium at the University of Washington. About 20 men, including four urologists, two psychiatrists, five engineers, two lawyers and a physicist, discussed ways of defining and measuring "normal" urination. Since there is a large psychological component to urination (a stressful psychiatric interview can lead to much higher bladder pressures than normal coughs and strains), it was felt that a method had to be found that would not interfere either physically or psychologically with the subject.

We first thought of "bugging" the men's dormitories, hoping to perform

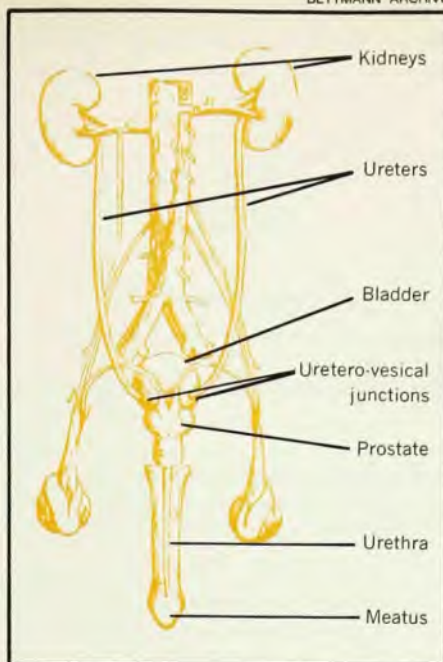
some hidden measurement, possibly of flow, at various urinals, and to tape the information for analysis. Secret pictures, probably with infrared light, would be taken for identification.

The lawyers objected to doing it that way. Instead we evolved a compromise in which students would agree in advance to the possibility of such measurements in certain dormitories, but would never know whether a particular urinal were so connected. Of course we expected to get occasional pictures of a dog, or to find gallons of water poured down at one "urination," but after a few months such tricks would surely die down.

With the legal problems disposed of, the problem of finding a suitable flow-meter came up. What was needed was an instrument that could measure the flow rate as a function of time with a resolution of less than 0.1 or 0.2 sec, this being a time characteristic of physiological changes such as sphincter openings. Therefore, no meter requiring collection of urine could be used. A system of baffles was tried, with the idea of measuring momentum transfers from the urine stream, but the evaporation of fluid from the surfaces caused baseline shifts in the instrument comparable to the signals themselves.

Drops and their statistics

These studies made it clear that no instruments then in existence could be used to make the desired measurements of the urine stream.¹⁰ The next possibility was high-speed movies, which would allow at least a visual inspection of the urine stream. A description of the technical difficulties involved in such a venture is probably out of place here. In spite of these, after a number of tries, a movie was made; it showed clearly that drops form in the breakup of the external urine jet.¹¹ They were vibrating and rotating. They had a variety of sizes, shapes, spacings and velocities and appeared to have a wavelike envelope. The suggestion was inescapable that they contained a huge amount of information—but was it usable?



Male urinary system seen from behind, as drawn by Italian anatomist Andreas Vesalius (1514–1564), showing passageways through which urine flows. Figure 2

The realization that the external urine stream might contain information about the urethra through which the stream had passed formed the basis for the development of the urinary drop spectrometer. It is clear that, if you believe that there is information in the external urine stream, you are immediately faced with two problems. First, you have to find clinically acceptable ways to extract that information and, second, you have to be able to interpret the information once you have it.

Although high-speed photography is clearly not a technique that can be used in a clinical setting, the problem of sequences of "particles" is quite familiar to the nuclear physicist. If you want information about a stream of drops, do time-of-flight analysis! It is simple to imagine how an instrument such as this could be put together.

Such a system was built and tested¹² using thin-sheet light fields formed and

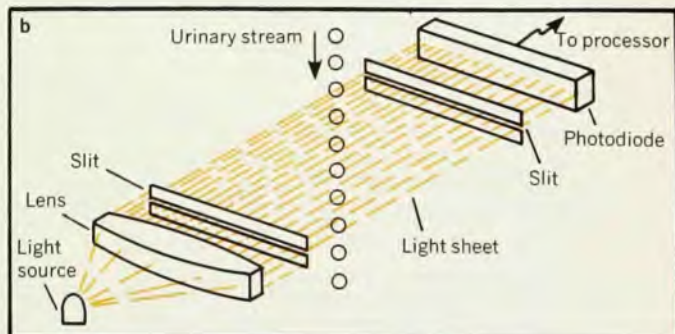
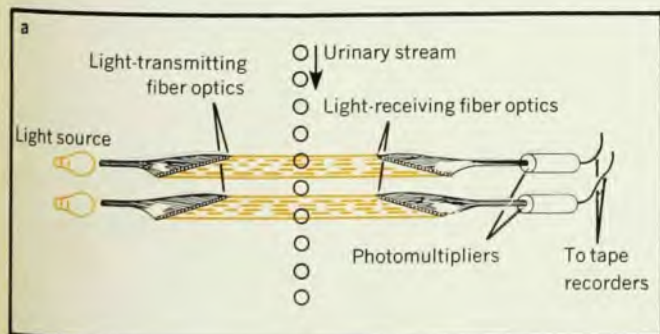
sensed with fiber-optics circle-to-slit converters (figure 3a). In a later version of the urinary drop spectrometer, the beam is collimated by a lens and defined by slits while a solid-state photodetector replaces the photomultiplier tube of the first model (figure 3b).

The electrical pulse trains formed by drops passing through the light sheets were tape-recorded. Even visual observation of these recordings on the oscilloscope showed the difference among male patients with varying types of obstruction. Table 1 lists the main features of a normal urination.

Once this instrument had been developed and its potential conceived, the need for large-scale clinical testing became crucial. The earlier flowmeter experiments were set aside, and two more men now joined the research effort: Arthur Sterling, who was about to receive his PhD in chemical engineering for work on the breakup of liquid jets, and John Van Ness, a mathematician involved in problems of discriminant analysis.

Lacking any deep understanding either of the process by which the urine jet breaks up or the manner in which information is carried by the drops, we did a number of empirical studies using time-interval analysis, both on metal tubes containing known obstructions and on patients. A commercially available electronic device sufficed for these first analyses. Even though such an analysis involved leading-edge triggering on each drop, and therefore folded in the drop size and rotational and vibrational motions with the actual spatial separation between the drops, we obtained significant results.

As expected, we observed large differences between the patterns due to proximal obstructions (near the bladder) and those due to distal obstructions (near the meatus). Histograms like those in figure 1 have now been made for about 4500 voidings by about 1600 individuals, and there have been no counterexamples to these characteristic patterns for any case in which the obstruction or nonobstruction was known.



Two versions of the urinary drop spectrometer. In the original version (a), the light field was produced and detected with fiber optics. In the newer model (b), the light is collimated by a lens, and a solid-state

photodetector replaces the photomultiplier tubes used before. The output is processed to obtain time-interval, drop-frequency or other distributions. Figure 3

Table 1. Typical voiding parameters for a normal adult male

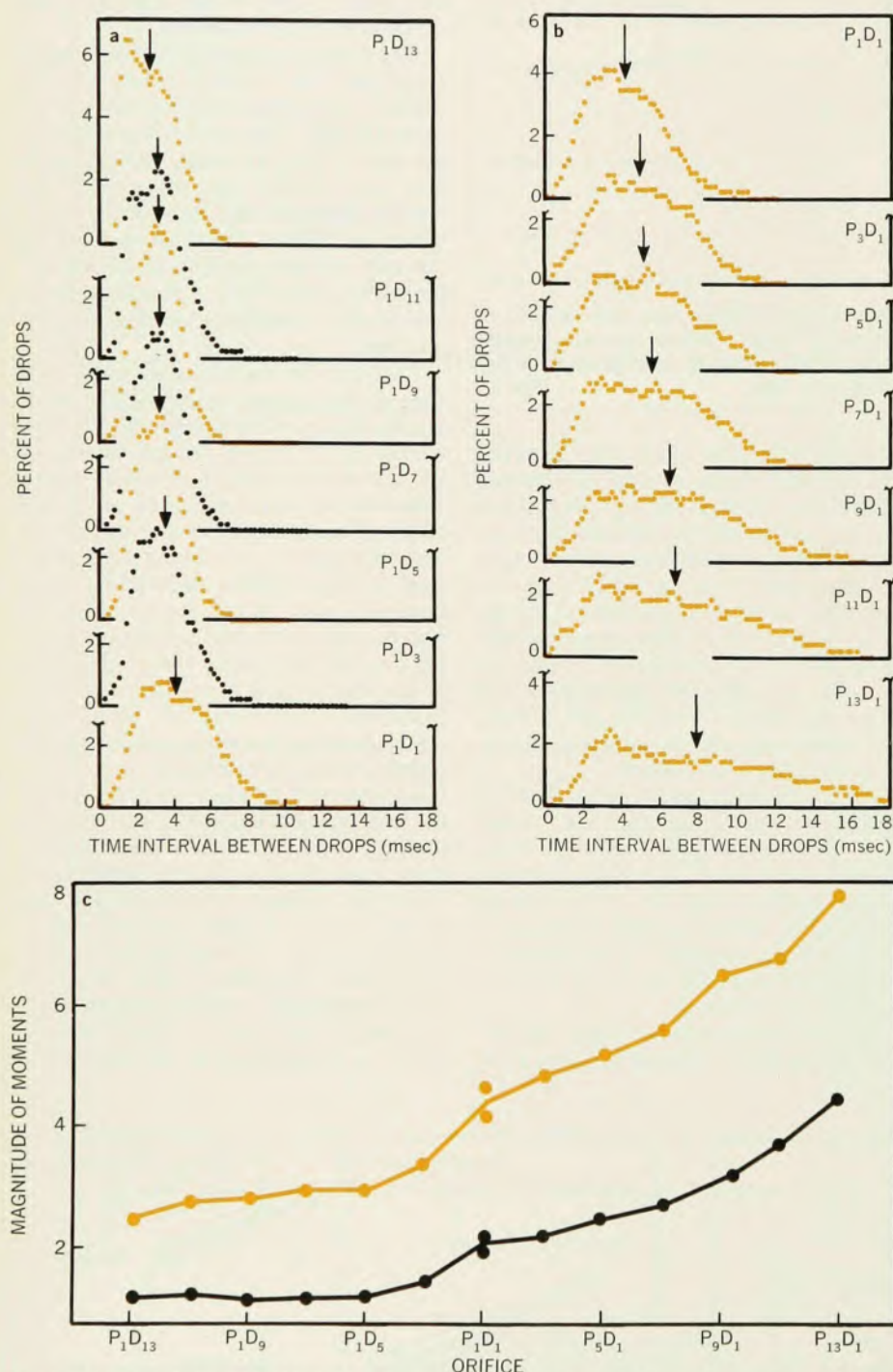
Volume	270 cc
Duration	~13 sec
Mean flow rate	21 cc/sec
Mean drop volume*	0.12 cc
Number of drops*	2250
Mean drop velocity**	~200 cm/sec
Mean drop frequency*	170 drops/sec

* Excludes "satellites" of volume below 0.017 cc.

** Referred to height at meatus.

Table 2. Model orifice sizes

Orifice subscript	Diameter (mm)
1	3.25
3	2.92
5	2.64
7	2.36
9	2.11
11	1.88
13	1.57



Time-interval distributions obtained with the apparatus shown in figure 6. In the symbols, P and D refer to proximal (upper) and distal (lower) orifices; the diameters corresponding to the subscripts are given in Table 2. P₁D₁ is equivalent to a straight tube. Spectra for distal obstructions as diameter is increased are shown in (a), while (b) shows spectra for proximal obstructions of decreasing diameter. The arrows show the increasing first moment (centroid). The first moment (in color) and the second moment (skewness, black) are graphed in (c) as functions of the tube configuration.

Figure 4

To test the sensitivity of the method, we made a simplified brass model having flow properties similar to those of the outlet tract. It had a straight tube for the urethra, with annular obstructions insertable at various locations. The time-interval histograms, as in figures 4 a and b, clearly and repeatedly revealed differences of 0.25 mm in orifice diameter at any location tested, as long as the pressure was not varied radically (more than $\pm 40\%$). The differences, which could be observed visually by overlays, were recorded by taking moments. Figure 4c shows the responses of the first (centroid) and second moments to, first, the stepwise opening of the distal orifice and, then, secondly, the closing of the proximal orifice.

Pulse-height distributions are also highly informative: Two major groups, the main drops and the satellites, characterize a normal urination. The pulse height is proportional to the amount of light occluded, hence the drop "diameter." Another useful measure is the power spectrum, which is the squared modulus of the Fourier transform of the pulse train.

Closely related to the time-interval histogram is the drop-frequency curve, merely a time plot, during the urination, of the number of drops per second that pass the light field. Such a plot, figure 5, illustrates the several epochs in a urination. Spastic sphincters and other pathological conditions can be diagnosed on such plots.

Clinical tests

In 1972, Zinner was appointed Boerhav Professor at the Akademisch Ziekenhuis (University Hospital) in Leiden, and undertook a program of extensive testing in the Poliklinik Urologie of Professor Peter Donker. A drop spectrometer was set up in the clinic to gather data on a large number of patients. It quickly became apparent that the most difficult problem was that of classifying the patients.

If the most important use of the method was to make sensitive, early diagnoses, and there were no existing methods for such diagnoses, the spectrometer was, in a sense, on its own. We could follow large numbers of nor-

mal young men until some of them had developed each of the various categories of disease. Another possibility would be to extrapolate results from patients with well-developed problems. We have actually taken both of these courses.

In recent years a mathematical method for treating such data, called "cluster" or "discriminant" analysis, has been developed. In cluster analysis, the data form an n -dimensional vector space in a computer memory. Each dimension corresponds to one measurement. For example, if we took 20 points in the power spectrum of each patient, coupled with 5 pieces of data such as height, weight, age and sex, there would be a 25-dimensional vector for each patient. The points formed by the set of all patients would be the data. The appearance of mathematically-defined clusters that correlated with various types of disease would indicate success. The degree of success would depend on how tightly the clusters grouped and how separated they were.

After a "learning" period the computer would have sufficient data to classify the clusters. Hypersurfaces of given probability density would be generated, and new, unknown patients could then be classified from their location in the vector space, a value being assigned to the probability of their belonging to each class of disease and to the normal group.

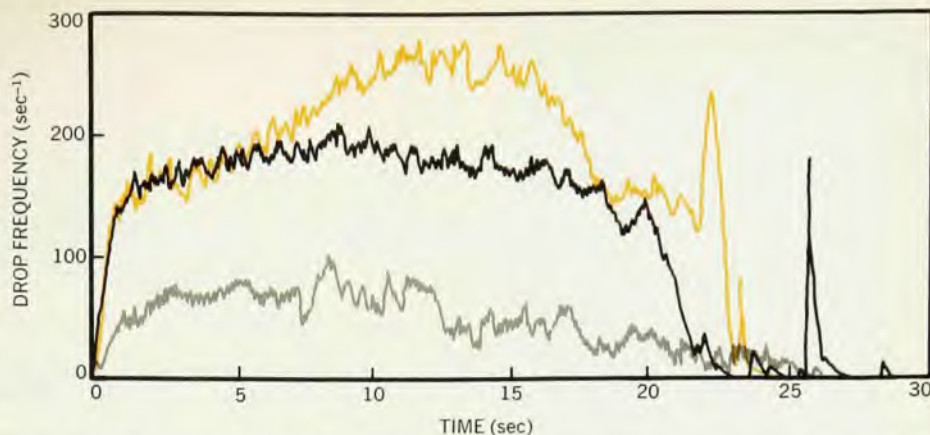
The use of this method depends entirely on the relevance of the measurements used as components of the vectors. There are ways to assess the value of each measurement entered, but choosing a poor method of analysis will lead to the rejection of most of the variables. The study is time-consuming and difficult for each chosen method; it would take years to treat data from large numbers of patients by all of the proposed methods.

Clinical work now being carried on by Zinner in Los Angeles (where he is Chief of Urology at the Charles R. Drew Postgraduate Medical School) is aimed at solving a variety of specific problems. For example, the use of flowmeters, with all their limitations, is still well known and accepted in urology. A series of experiments relating the urinary drop spectrometer results to those from a well-known flowmeter are being carried out for several disease conditions.

Now the physics

A quantity of clinical data already subjected to time-interval analysis is now being scrutinized further by means of pulse-height distributions. We hope that the combined analysis will allow us to make more specific diagnoses of patients so far only classified into broad categories.

Although we know that the urinary



Clinical data showing the time variation of the drop frequency obtained with the urinary drop spectrometer in a normal person (black line), a patient with a proximal (upper) obstruction (gray) and a patient with a distal (lower) obstruction (color). Figure 5

drop spectrometer can be used to provide information about the condition of the lower urinary tract, we have little understanding of the means by which this information is transferred from the urethra to the urine drops. Such physical understanding is not, of course, essential to the development of the instrument as a clinical tool. Nonetheless, some understanding of the hydrodynamics of the lower urinary tract and of the breakup of liquid jets would greatly facilitate the development of reliable information-processing systems for the instrument. Consequently we are making, in parallel with the clinical work, an effort to understand the basic hydrodynamic processes in the lower urinary tract. We are working on the theory of flow in constricted tubes and of jet breakup and checking the theory on our own instrument (see figure 6), as well as trying to resolve puzzling points that come up in connection with the clinical work.

While the problem of flow in constricted tubes with deformable walls is beyond the scope of present theoretical techniques, a wide literature does exist on laminar flow in rigid constricted tubes,¹³⁻¹⁵ mostly in connection with blood flow in constricted arteries (arteriosclerosis). Since flow in the urethra is probably turbulent,⁹ the way the fluid carries information about obstructions to the mouth of the tube is far from being understood. For the simpler problem of laminar flow, one can trace the relaxation of the velocity profile downstream from an obstruction^{16,17}; the profile retains this information for about 1000 diameters downstream. Thus, at least for laminar flow, the information-transfer process in the tube can be understood.

The theory of the breakup of the capillary jet is in relatively better shape, having been pioneered in 1879 by Lord Rayleigh.¹⁸ Given a cylinder of inviscid liquid of radius a , he imposed a propagated disturbance upon the surface with

an amplitude r assumed to vary with distance x and time t as

$$r = a + \xi(k)e^{i(kx \pm \omega t)}$$

where k is the wavenumber of the disturbance and $\beta = \beta(k)$ is its complex angular frequency. If β has an imaginary part, β_i , the jet will be unstable and β_i represents the growth rate of a disturbance with wavenumber k . Disturbances of this form were applied to velocities v and pressures P in Euler's equation

$$\frac{\partial v}{\partial t} + (v \cdot \nabla)v = -\frac{1}{\rho} \nabla P$$

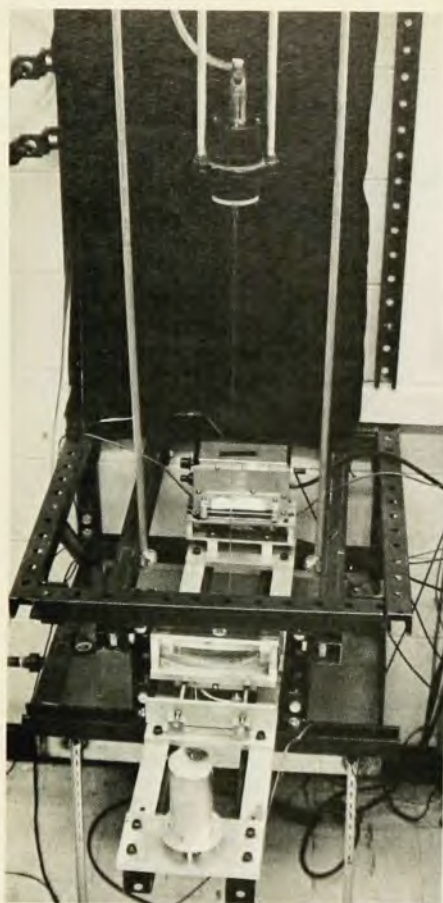
where ρ is the density of the liquid. The jet can be stable only as long as the liquid pressure is balanced by surface tension. Assuming the jet to be moving at a constant uniform velocity, Rayleigh arrived at the following stability criterion for $\beta_i(k)$:

$$\beta_i^2(k) = \left(\frac{\sigma}{\rho a^3} \right) (k^2 a^2 - 1) (ka) \frac{I_1(ka)}{I_0(ka)}$$

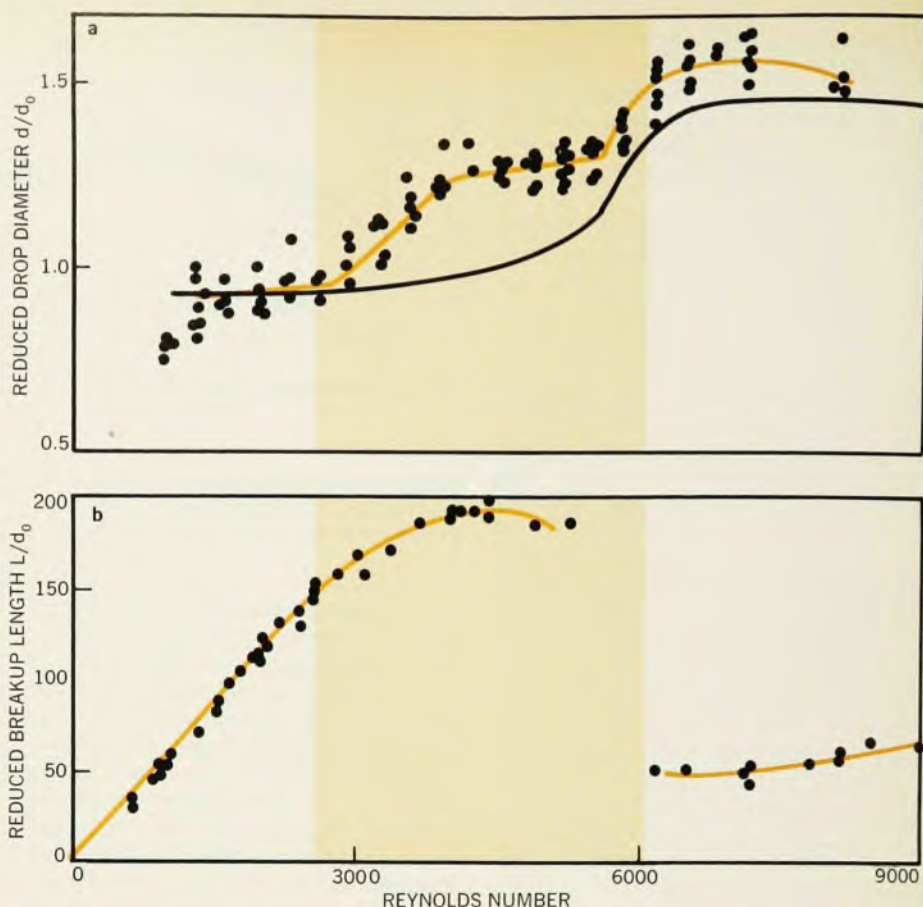
where σ is the surface-tension coefficient.

A graph of this function shows β_i to rise almost linearly from zero at $ka = 0$, curve to a maximum at $ka = 0.698$ and drop sharply back to zero at $ka = 1$. Rayleigh deduced that the jet would be dominated by disturbances of the corresponding wavelength if the initial disturbance level were uniform. He predicted that the jet would break up into drops of more or less uniform diameter of about 1.9 times the jet diameter. Subsequent investigators who have concerned themselves with this problem have taken into account such effects as viscosity,¹⁹ ambient atmospheric pressure^{20,21} and velocity profile relaxation.²²

This work has been almost exclusively concerned with the breakup length of the jet (the length of the fluid jet before it breaks into drops). This problem has obvious practical significance in carburation and injection processes, but is of



Experimental installation, consisting of jet-producing apparatus with interchangeable orifice constrictions, modeling lower urinary tract (above), and urinary drop spectrometer (below). Figure 6



Diameter d of the largest drops (a) and breakup length L (b), in units of the minimum stream diameter d_0 , as functions of the Reynolds number. The black line in (a) is a fit to the data, while the colored line represents the prediction of Rayleigh's theory with jet contraction taken into account. L rises linearly in the (left-hand) laminar region; the transition region is shown in color, the turbulent region in white. Figure 7

little use to us. Only recently²³ have studies of the time evolution of a laminar jet into a sequence of different-sized drops been undertaken. No theory for drops from turbulent jets exists.

The theoretical understanding of the physical processes taking place in the lower urinary tract thus leaves a lot to be desired and a great deal of theoretical work will have to be done to improve the situation.

The experimental program

At the University of Virginia we constructed an experimental facility that consists of a drop spectrometer and an apparatus that allows us to form vertical jets to be analyzed. As we have mentioned, the major problems to be resolved are to find ways to extract useful information about the jet from the spectrometer output.

Initially we centered our attention on jets formed by circular hard-walled tubes. By connecting the output of the spectrometer to standard pulse-height analyzers, we have been able to carry out the first investigations of the distributions of drop sizes in jets.

This can be done only approximately, because the pulse height represents the maximum width of the drop as it passes

the light field. The vibrations and rotations mentioned above make it impossible to make an exact deduction about the drop size (and hence the flow rate) from the pulse height. According to Van Ness, however, the average of the cross section is greater than the diameter of a sphere of the same volume. Since this is the only way in which non-interfering time-dependent flow rates can be obtained, measurements of this type, even at the level of 25% accuracy, are of great interest to clinicians.

We took readings of pulse heights in jets, calculated the flow rates on the assumption that all of the drops are spherical and compared the results to the amount of fluid collected. The results of the measurements with circular orifices, some of which are still in progress, are encouraging. This work will be extended with elliptical orifices (where an obviously large quadrupole deformation of the drops will exist at jet breakup).

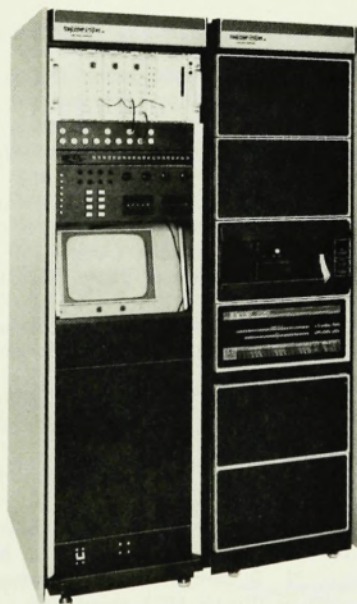
The general result of pulse-height analysis for Reynolds numbers ranging from 1000 to 8000, after corrections for jet contraction and gravity, is that the drop distribution exhibits two or more peaks, corresponding to clustering of drops in one large and one or more

small sizes. In the laminar-flow regime, the distributions have an interesting, rather complex structure which is repeatable, but not yet fully understood. Some important trends begin to emerge, however, when one considers the main (largest) drop sizes.²⁶ Using the Rayleigh theory and taking jet contraction into account, we can predict drop diameters that agree very closely with experimental data in the laminar range, and qualitatively in the turbulent range; see figure 7.

In medical situations, the height of the patient above the light sheet will vary, making it necessary to study the variation in the drop statistics as a function of distance along the jet. The time-interval distributions, under Reynolds numbers approximating human voidings (about 7000) vary appreciably as the height varies from 25 cm to 70 cm. Putting it another way, there is about a 15% reduction in the numbers of drops of volume above 0.017 cc as we move from 25 to 70 cm along the stream. Whether this is a coalescence of drops or a sequential breakup to smaller ones is not yet clear.

Other plans include studies with flexible tubes, which will approximate physiological conditions more closely.

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It is clear that there are enough problems to be tackled to keep any experimental program busy for a long time.

Other problems in urology

After five years of effort, the urinary drop spectrometer has now shown itself to be useful in the hands of a skilled clinician. If it is to find broad application, many of the problems we have mentioned must be solved, and it must become simple enough to be used without special skill. As alternative diagnostic techniques are not in sight, the need for the method makes it worth the effort.

In the course of this work, a huge variety of physical problems in the urinary tract have become known to us. Although clinicians have a tremendous skill in evaluating and treating urological problems, and although urologists are doing extremely clever and useful research, they are well aware that many problems fall directly into the categories that are best studied by physical scientists.

For example, the basic understanding of the wavelike motion of the ureters is just beginning to emerge.²⁷ From the considerable amount of information available, an overall model should be possible. Another problem is the measurement of the mechanical nature of the soft urethral lining. One physicist has proposed, and shown good evidence for, a mechanism of supersonic-flow limitations, due to the yielding of the urethral wall,²⁸ as a major factor in flow

control during urination, and as a potential explanation for many puzzling clinical observations. Pulse properties and digital methods, an old field in physics, form the heart of data-handling in the urinary drop spectrometer method. Perhaps similarly radical approaches will solve more of these problems.

We hear more and more often these days that physicists ought to become involved with problems that have some direct impact on society. Perhaps it would be more correct to say "become involved once again," since it has been the traditional role of the physicist to be the generalist of the sciences. This is certainly true in the applications of physics to medicine, where such eminent researchers as Hermann von Helmholtz, Ernst Mach, Lord Rayleigh, J. J. Thomson, John Henry Poynting, Albert Einstein and Dennis Gabor have made important contributions. Although present-day physics activity in medicine is largely centered around the fields of radiology and molecular biophysics, there are many other areas of medicine in which a physicist can work. One such field, as we have seen, is urology. The contributions of biomedical engineers to medicine are indisputable but, because of their unique background and insights into basic phenomena, there is a need that only physicists can fill.

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