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The Probability of a Probability

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A 67-year-old man presented to the emergency room with diffuse, burning abdominal pain. During his evaluation he was found to be in atrial fibrillation; serum sodium was 124 mEq.

Some intra-abdominal process is presumably going on to explain the burning pain. I would like to know how long he has had this complaint and how long he has had the atrial fibrillation. I don't know why his serum sodium is low. It could be caused by sodium depletion, water intoxication, adrenal insufficiency, the syndrome of inappropriate antidiuretic hormone, or a variety of other causes. I am not sure I can tie these findings together.

The patient had had diffuse, burning abdominal pain for three weeks. He reported no nausea, vomiting, weight loss, hematemesis, melena, or change in bowel habits. He had a remote history of peptic ulcer disease. He denied recent alcohol use but had smoked one to two packs of cigarettes a day for several years. His only medication was an occasional aspirin.

On physical examination he was not in distress. His blood pressure was 150/88, and his pulse rate was 130 and irregularly irregular. The lungs were clear. No murmurs were heard. The abdomen was benign. Stool was trace guaiac-positive. The rest of the examination was normal.

In view of the seemingly benign history and findings, I don't know why he came to the emergency room at this time complaining of pain, unless an acute onset of atrial fibrillation caused some new, unexplained symptoms. I still don't know how that would relate to the finding of the low serum sodium.

Laboratory data were as follows: WBC 15,200, hemoglobin 15.5, hematocrit 42, glucose 128 mg/dl, sodium 124 mEq/L, potassium 3.7 mEq/L, chloride 91 mEq/L, carbon dioxide 20 mEq/L, BUN 6 mg/dl, and creatinine 0.9 mg/dl. Urinalysis showed specific gravity 1.020 and pH 7. Dipstick and sediment examination were unremarkable. ECG showed atrial fibrillation with frequent PVCs. Chest x-ray was compatible with chronic obstructive pulmonary disease. A retrocardiac hiatal hernia was present.

The high white cell count suggests the possibility of an infection, but the differential isn't given, and it could be helpful. The high specific gravity

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of the urine is inappropriate for the hyponatremia. Since the patient was a smoker and lung cancer is a frequent cause of SIADH, I thought he might end up having a lung nodule. Apparently, one was not seen on the chest x-ray.

The patient was admitted for evaluation of atrial fibrillation and abdominal pain. The atrial fibrillation reverted to sinus rhythm spontaneously, and the patient was treated with digoxin. Myocardial enzymes were not elevated. Thyroid function tests were normal. An echocardiogram showed normal valves and ejection fraction and a left atrial size of 3.7 cm. The gastrointestinal symptoms resolved, and his stool became guaiac-negative.

The pain is gone without treatment. These findings are compatible with many things, but I would be interested in knowing what gastrointestinal workup he had. The atrial fibrillation appears to have been adequately evaluated, but the low serum sodium appears to have been lost.

One month later, the patient returned with recurrent atrial fibrillation and abdominal pain. Once again the stool was guaiac-positive. Serum sodium was 128, and serum osmolality was 268, with a simultaneous urine osmolality of 384.

His arrhythmia reverted to sinus rhythm with quinidine therapy after initial heparinization. The stool remained guaiac-positive. The possibility of an occult gastrointestinal lesion was suggested as the cause of the apparent SIADH.

The osmolality studies are certainly compatible with SIADH. I am not sure about an association with gastrointestinal lesions. I am much more familiar with the association with pulmonary lesions.

Colonoscopy revealed multiple adenomatous polyps with no evidence of malignancy. A barium swallow revealed right upper quadrant calcification and a large hiatal hernia with gastrointestinal reflux. Follow-up serum sodium was 132.

I suppose his abdominal burning could be related to the hiatal hernia with reflux, but I do not see an explanation for his low serum sodium and apparent SIADH. If there was no evidence of malignancy (and I assume all the polyps were removed and examined microscopically), I would not do any further gastrointestinal workup. I would consider getting a CT scan of his chest to make sure he does not have an occult neoplasm in his lung.

The patient was seen at follow-up four months later. He complained of poor appetite and a 12-pound weight loss. Chest x-ray revealed a 2-cm mass in the right hilum with collapse of the right lower lobe. Serum sodium was 122. Biopsy of the lesion on bronchoscopy showed a poorly differentiated squamous cell cancer. Hyponatremia was treated successfully with demeclocycline, and a workup for metastatic disease was negative. A right pneumonectomy was performed; two of 13 carinal nodes were positive for tumor. The patient was given radiation therapy.

I wonder if the mass could have been hidden on the chest x-ray by the hiatal hernia. I would be interested in reviewing that with a radiologist.

In retrospect, should SIADH have been worked up more aggressively earlier? I might have gotten the chest CT earlier, because I am not familiar with gastrointestinal lesions causing SIADH. The colonic polyps just did not make sense to me as the cause of the hyponatremia.

Editors' Comments: In the patient presented here, the correct diagnosis was missed for five months, and a "far-out" erroneous diagnosis was made instead. In retrospect, the physicians responsible for the patient's care seem foolish. The patient was a heavy smoker, his chest x-ray showed evidence of chronic lung disease, and he had SIADH. Small-cell lung cancer should have been strongly considered, and the physicians should have been unwilling to give up on this diagnosis—despite the "negative" chest x-ray—

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PROBABILITY *(continued)*

until they had performed all reasonable tests (such as bronchoscopy or CT scan).

Instead, when the chest x-ray showed no obvious tumor and an unrelated finding (intestinal polyps) was uncovered in the process of an investigation for guaiac-positive stools, the SIADH was attributed to "an occult gastrointestinal lesion." Undoubtedly, the physicians knew with confidence and with little ambiguity how high the likelihood of lung cancer was in a male smoker with SIADH. But how confident were they of the likelihood that an occult gastrointestinal lesion could account for these findings? One might guess that they had little confidence.

This case raises an issue that we have not explored: confidence in probability judgments. Therefore, we shall discuss the concept of ambiguity. We think that the patient's physicians failed to consider this concept in their diagnostic hypotheses.

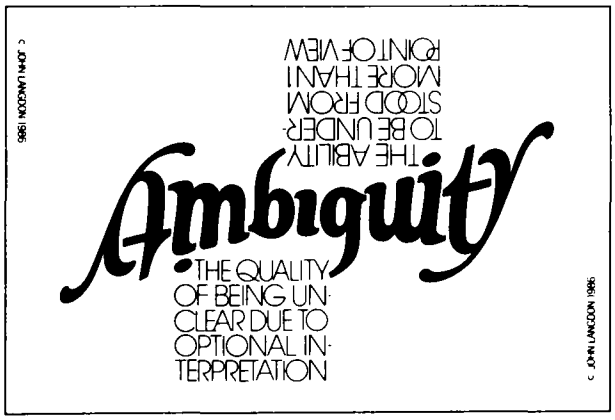
A busy clinician makes dozens, perhaps hundreds, of probability assessments each day on an array of probabilities: that one or more diseases may be present; that a patient will have a positive or negative (or some other) result of a diagnostic test; that, given a certain test result, one or more diseases are present or absent; that there might be an adverse reaction to a test or a treatment; that the patient might or might not respond to a regimen; and the probability of survival. Typically, each assessment is made without reference to a numerical value for the chance of the outcome. Instead, the probability is either categorical (high, very small, and practically nil) or ordinal (higher than, lower than, safer than).[1]

Even given the implicit categorical and ordinal descriptions of likelihood that we use every day, on the surface all probability assessments seem to be similar. Each requires the physician's judgment about the chance of some future event, and each is presumably grounded not only on personal experience but also on the physician's understanding of the pertinent medical literature. To be sure, they are beliefs about the state of a given patient, rather than "hard data," and they all require a judgment based on medical data.

But are all assessments of probabilities really the same? Even if we were to state our views of the likelihood of several different outcomes in numerical terms, would we have the same confidence about all of our judgments? If the initial reaction is that all probabilities have similar meaning to us, ponder this: Suppose we can choose between two treatments for a given disease. One treatment has been used for years and considerable data show that it cures 65% of patients. A second treatment has been introduced recently—only two studies have been published, each a small series—but the success rate is 70%. Are the two probabilities, 65% and 70%, comparable?

Most would agree that they are not. Large experience with the first treatment gives the physician confidence in a 65% probability of success. In the second treatment, there may be much uncertainty about the probability of 70% success, given limited data. Any probability needs to have a built-in factor that determines the confidence in which the value is held. The confidence in a probability often is described in terms of ambiguity. Ambiguity is uncertainty about a given probability. It sometimes is thought of as a "second-order" probability, or as a probability of a probability.

A certain amount of ambiguity characterizes all assessments of chance outcomes (see figure).



Nonetheless, considerable ambiguity is likely to exist when available information is scanty (e.g., when the sample size is small), when data are unreliable (e.g., when the credibility of the source is questionable), or when facts or opinions of putative experts are conflicting.[2] All of these are encountered regularly in medicine.

How to express ambiguity in probability assessments has yet to reach consensus. Some argue that the uncertainty of a probability should be expressed in terms used for characterizing outcome uncertainty: namely, as a probability range.

This would require establishment of a range for a given set of probabilities (hence, the probability of a probability). Finally, a measure of confidence has been applied by some to rate the degree of ambiguity.[3] Although a confidence rating seems superior in experimental settings for expressing uncertainty in a probability, its relevance to the real world is uncertain.

Many experts in probability have figuratively thrown up their hands when it comes to assessing ambiguity. Some have suggested that we simply ask people to state their views directly.[4] Some argue that such verbal answers may or may not reflect beliefs and judgments.[5] Some suggest that the only way to be sure how a person feels about a problem is to observe what action he or she takes.[4,6] Others point out that many probabilities for observable events cannot be identified simply by observing behavior.[7]

Does it matter whether we recognize ambiguity in assessment of likelihoods? It probably does, because people generally try to avoid ambiguity. Many reasons have been advanced to explain this: 1) People may reason that it is better to have more information than less; 2) they may be concerned that if not all information is available, they will have less control; 3) they may be concerned that their judgment will be evaluated by others (or even themselves after the fact); 4) they may wish to avoid uncertainty.[8,9] Although some of these seem to predominate in experimental settings in which subjects are asked to participate in monetary lotteries, we suspect that all or at least most obtain in day-to-day medical decision making.

Thus, we are left with an unresolved problem: Ambiguity in assessing likelihood in clinical practice certainly exists. It influences how we think about a given disease, test, or treatment, but we have not yet learned how best to express the uncertainty in our probabilistic beliefs. What do we do in the meantime? We can identify situations in which ambiguity is likely to be greatest (few data available, unreliable data, conflicting data) and appreciate that confidence in judgments about the probabilities of medical outcomes in these situations may not be unshakable.

When undertaking formal decision assessments, we can test the most ambiguous variables by multivariate sensitivity analyses. Or we can even use the so-called Monte Carlo simulation, which carries out sensitivity analysis on all variables simultaneously.[10] At the very least, an understanding of the roots of ambiguity should make us aware of the potential limitations of our assessment of probabilistic clinical data.

Perhaps the diagnosis of lung cancer would have been made sooner in the patient presented if the concept of ambiguity had been considered. Perhaps the extreme "softness" in the probability of an occult gastrointestinal lesion as the cause of the SIADH would have led his physicians away from this hypothesis toward others. Given the type of the patient's tumor, earlier diagnosis and treatment probably would not have extended his life by much, if at all. Yet because a similar error could well have substantial implications for a patient's survival or even for a patient's quality of life, we should be alert about how avidly we accept our numerous probability assessments. □

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