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Review Article

Probability At the Heart of Clinical Epidemiology

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Abstract

We know that statistics is the science of probability, and in relation to statistics and medicine Sir William Osler wrote that, "Medicine is a science of uncertainty and an art of probability" 1

I published in 2021, how medicine is part science and art 2 and now, while defining the role of statistics, we unveil another association of both.

Keywords: schizophrenia; electron microscopy; virus; mitochondria; brain; foetus

Introduction

We know that statistics is the science of probability, and in relation to statistics and medicine Sir William Osler wrote that, "Medicine is a science of uncertainty and an art of probability" [1]

I published in 2021, how medicine is part science and art [2] and now, while defining the role of statistics, we unveil another association of both.

In these times where complexity is the hallmark of the epoch and when, according to the late German physic Hans-Peter Dürr (*) we must discard reductionism, we should use statistics to understand the phenomena of nature. Albert Einstein insisted in his posture about determinism but lost the race to Nielhs Bohr whose work confirmed the uncertainty principle of Werner Heisenberg as the basis of quantum mechanics. You can read the beautiful book from Ian Stewart entitled “Does God Play Dice?” [3] and enjoy this beautiful dissertation.

Of course, at any moment it will rain if you are in the midst of a hurricane and of course you will die if you get the rabies, but in almost all other circumstances there will be a probability that events will occur. Medicine and meteorology are two examples where uncertainty is the rule of the game. In the simplest probabilistic statement, they will tell you the percentage probability of rain in the next 24 hours or the probability that pneumonia will resolve with certain treatment. If it does not rain or the infection persists, it should come at no surprise because there was a probability of this occurrence.

In biostatistics we express the probability that the calculated values in a sample reflect the parameters from the universe from which the sample comes from. The more used calculations are presented as confidence limits or as “p” values where the probability can be from 0 to 1.

We can express probability values as fractions, where the numerator is for example the number of cases of a disease and the denominator is the exposed population. For example the number of diabetics among obese males: 10/100. Furthermore, we can express it as 10%. This is the simplest form to measure uncertainty. But in biology, there are always other factors that influence the effect of the independent variable (obesity) on the dependent one (diabetes). We know that besides body weight, we can calculate the effect of age, gender, physical activity, genetics and many more factors. As you can notice, we are entering the realm of complexity and we will no longer be in the reductionism that so far has plagued medicine. Conditional probability is a statistical measure that indicates the probability of an event A occurring if another event B has happened. That is, the conditional probability P(A|B) refers to how likely it is that event A will happen once event B has already occurred. **(t**able 1**).**

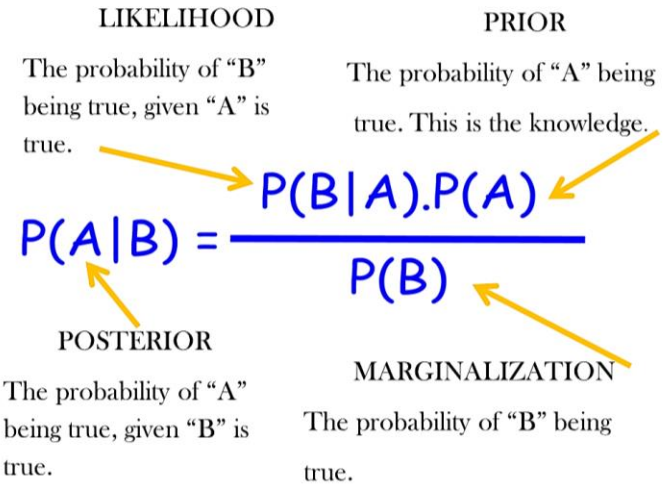

Table 1: Conditional probability or Bayes formula.

In clinical medicine every day we deal with multifactorial events, and it is a mystery how the mind of medical professionals evaluate the information and arrive to a decision. An example is a patient with chest pain and we can apply an algorithm separating first men from women, then by age groups and then according to the type of pain and arrive at a probability that the pain is of ischemic origin [4].

A situation where the concept of conditional probability is very useful is in the evaluation of laboratory and imaging tests. Our example will help in understanding that the values of sensitivity and specificity are not enough to assess the usefulness of a test. We have to calculate the predictive value of a positive or negative test and then proceed to estimate the prevalence of the disease in the group where an individual patient belongs (previous probability) and then using de Bayes proportion of probabilities (also known as likelihood ratio) calculate the posterior probability.

Let´s begin by portraying in a contingency table, the test´s results against the "reality" or the best estimation with the gold standard, accordingly with the state of the art (table 2)

ERRORS TABLE

			REALITY	
			Sick	**Healthy**
			Accept alternative hypothesis H_1	Accept null hypothesis H_o
TEST	**Sick**	Accept alternative hypothesis H_1	Correct ✓	Incorrect **type I error** ✗
	Healthy	Accept null hypothesis H_o	Incorrect ✗ **type II error**	✓ Correct

Table 2: The correct boxes are marked with ✓, while the wrong ones where the decision is incorrect are marked with ✗. We can see that the concept is the same as accepting or rejecting the null hypothesis in scientific investigation.

A good test correctly identifies most sick individuals (sensitivity) and the healthy ones (specificity). Now using the same table we will calculate sensitivity, specificity and the predictive values of a positive or a negative test. (table 3).

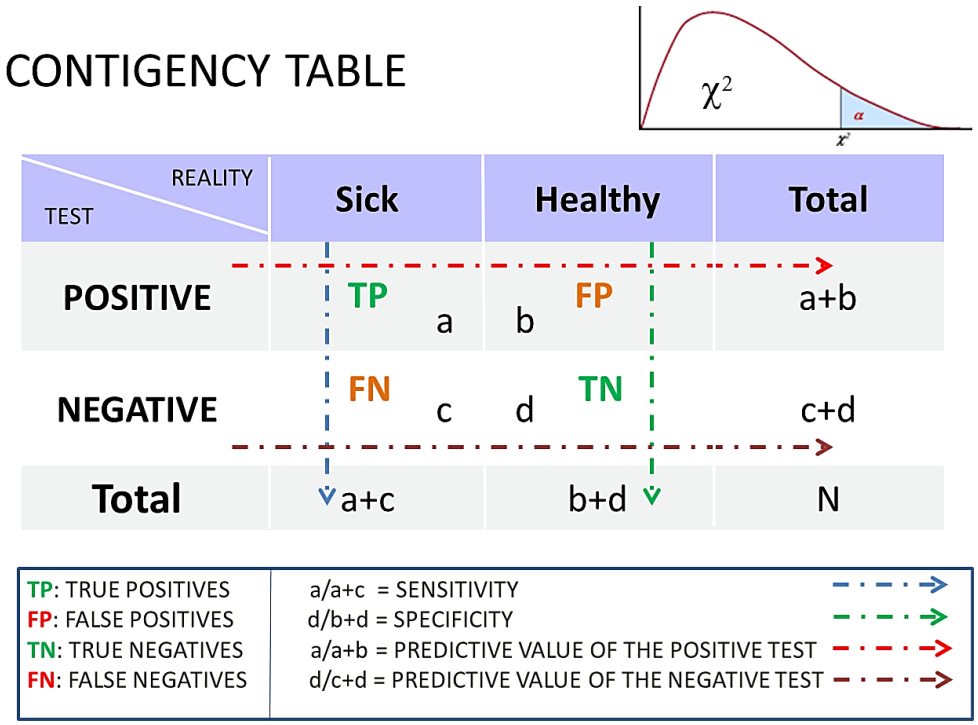

Table 3: We can visualize the sensitivity (a/a+c) and specificity (d/b+d) along with the false positive (FP) and negative tests (FN); this is shown in the vertical arrows. But to know the predictive value of a single patient, we calculate the proportion with the total number of positive (a/a+b) or negative (d/c+d) test as shown in the horizontal arrows.

We will use the sensitivity and specificity of troponin test, often used to evaluate patients with chest pain [5] (table 4).

	Miocardial infarction		
	SICK	HEALTHY	
TROPONINE +	TP A 95 (0.95) SENS	B FP 20 (0.2)	C 115
TROPONINE -	D FN 5 (0.05)	SPEC E 80 (0.8) TN	F 85
	G 100	H 100	200

Table 4: Shows the published sensitivity (95%) and specificity (80%) of the troponin test for myocardial infarction in patients with acute chest pain.

Then we calculate the Bayes or likelihood ratio for a positive or negative test. In table 5.

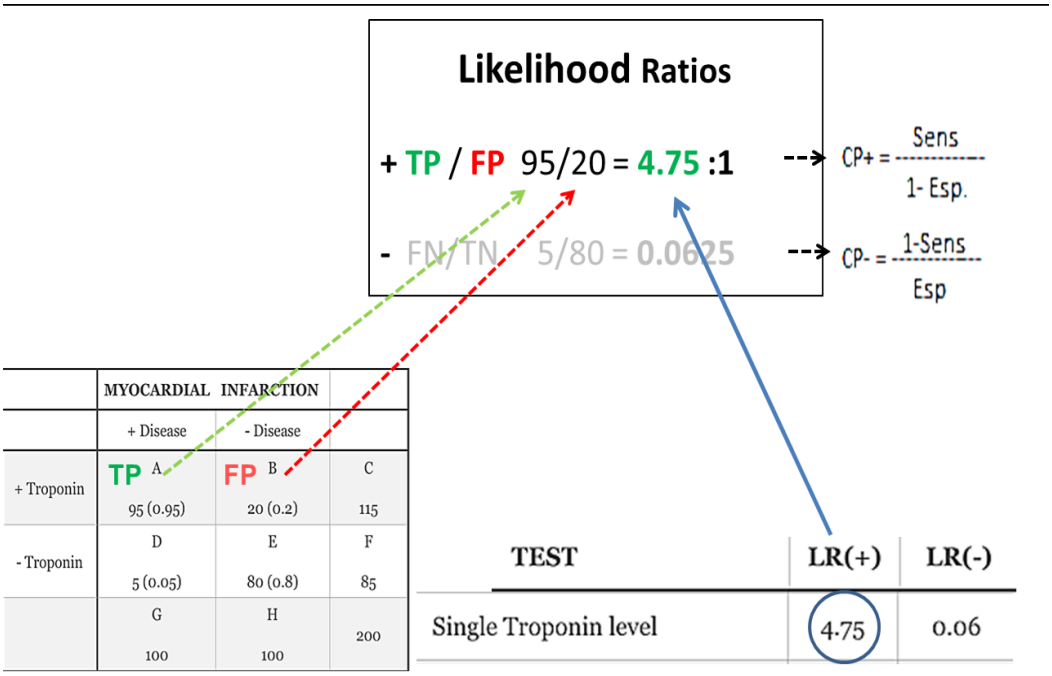

Table 5: The proportion of true positives and false positives is the probability quotient of a positive test.

we see that the ratio for a true positive test is 4.74 for every false positive. And in table 6

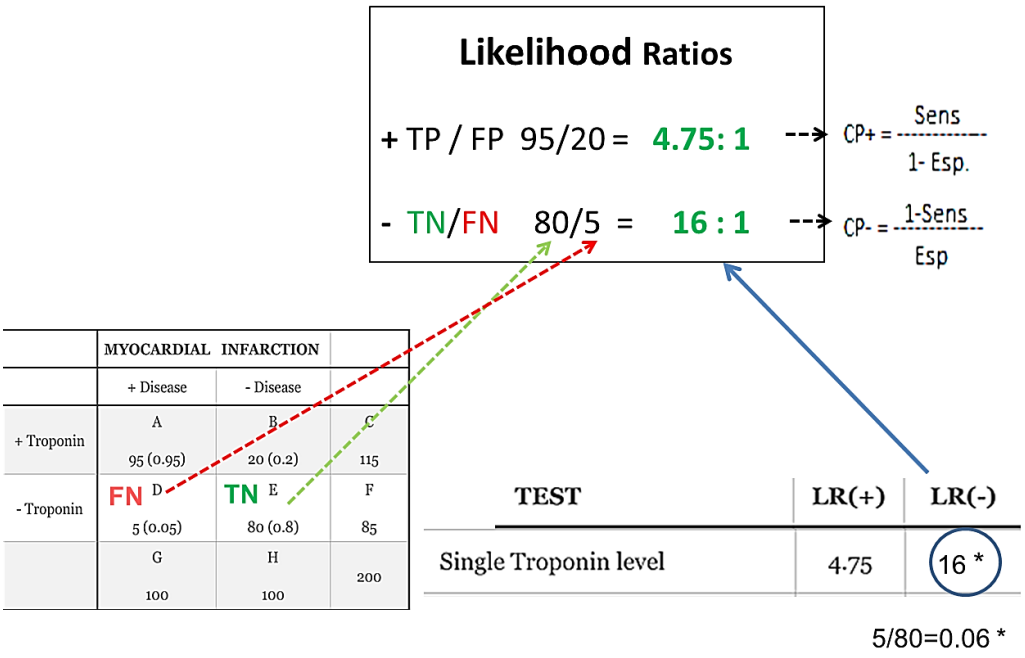

Table 6: The proportion of true negatives and false negatives is the probability quotient of a negative test.

We see 16 cases of a true negative test for every false negative, so the test has a better sensitivity than specificity and has a better predictive value to rule out the disease than to confirm it.

We will use this likelihood ratios in a nomogram published by Fagan [6], but to be able to illustrate the values for a negative or a positive test in the same graph, as the scale is exponential for the positive ratio and logarithmic for the negative one we will calculate the negative likelihood ratio as FN/TN instead of TN/FN and then the quotient will in this case, be a fraction (0.0625) that will fit properly in the nomogram (table 7).

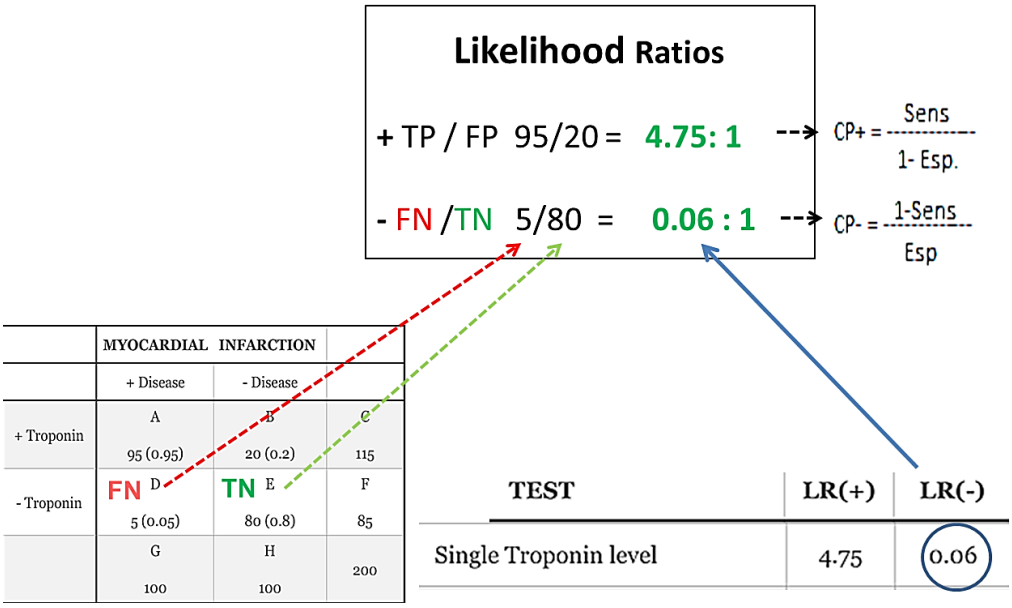

Table 7: Here we use the proportion of false negatives/true negatives, to be able to plot in a single nomogram the predictive value of a positive or negative test.

It has been shown that although there are no precise numbers because every disease has its own particular conditions, the usefulness of lab and imaging studies is larger in patients with intermediate probability of having the disease [7] (Table 8).

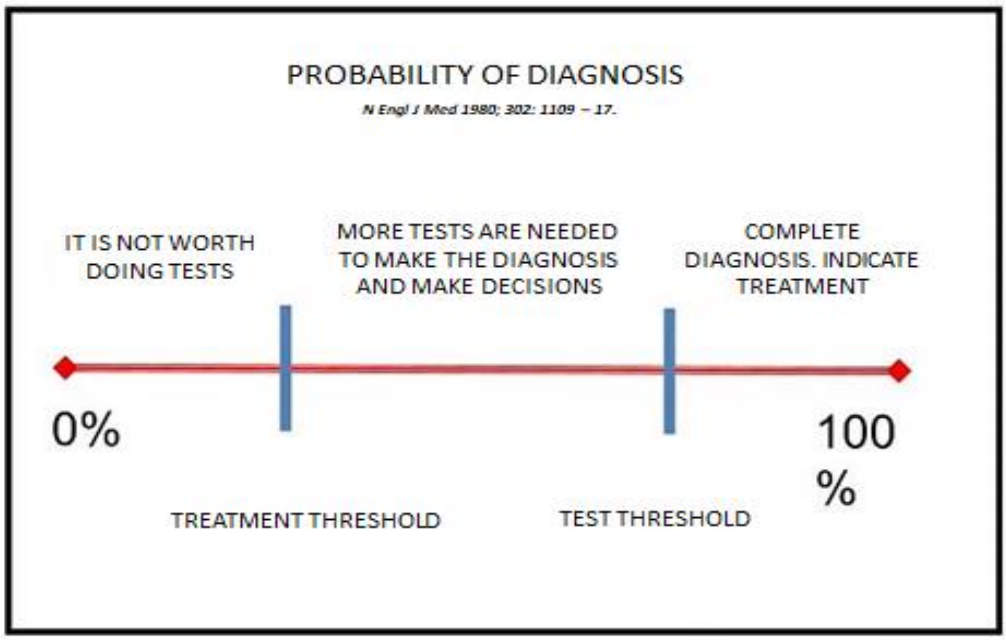

Table 8: Usefulness of lab and imaging tests according with the prior disease probability.

So, the next step as shown in table 9

Frequency of isquemic heart disease

Data from Diamond & Forrester

	High > 70%		Intermediate 10 – 70%		Low < 10%	
Age	Tipical angor		Atipical angor		Non angina pain	
	m	f	m	f	m	f
30 – 39	59	28	29	10	18	5
40 - 49	69	37	38	14	25	8
50 - 59	77	47	49	20	34	12
60 - 69	84	58	59	28	44	17
70 - 79	89	68	69	37	54	24
> 80	93	76	78	47	65	32

Table 9: We can estimate the pretest probability with the Diamond and Forrester pretest probability data. It uses 3 variables: age, sex and the type of pain as it is or not characteristic of angor pectoris. Numbers show the risk of coronary artery disease.

From Diamond & Forrester is to calculate the prior probability of a disease. The score is built by the risk factors gender, age and type of chest pain as published in the ESC guidelines [8,9] . Some critics of Bayes statistics argue that the estimation of pretest prevalence can be inexact, but it is better than doing the test in the general population where the number of false positives and negatives will be high since there is no test with 100% accuracy. It is easy to calculate that with a sensitivity and specificity of 98%, clearly superior to the tests used in clinical medicine, if you study a population with 5% prevalence of a disease, most positive and negative results will be false.

Then we will estimate the posterior probability of a disease with the combination of the pretest probability and the likelihood ratios of the test (table 10)

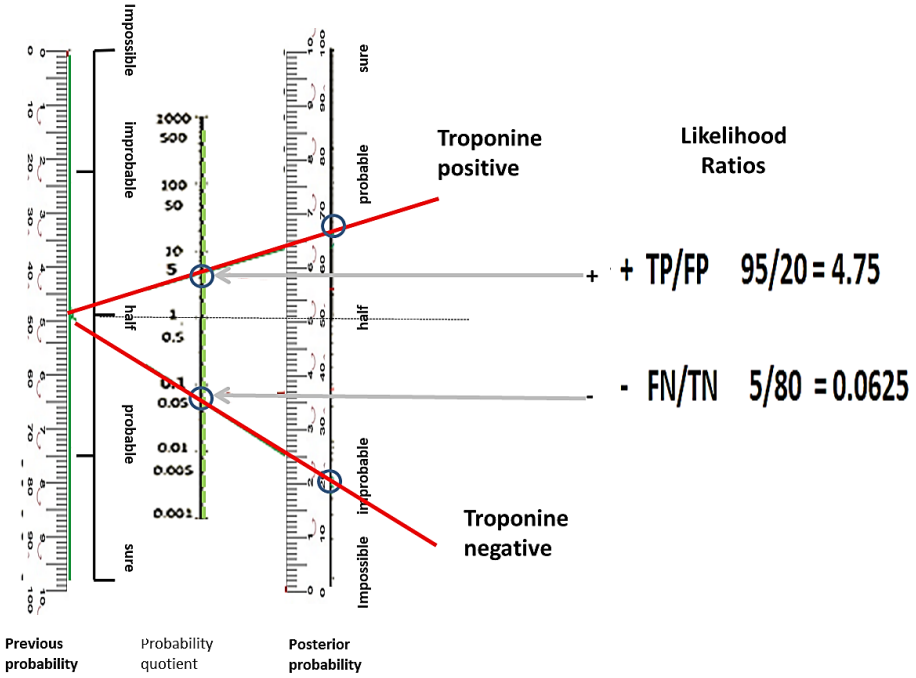

Table 10: Nomogram to calculate the posterior probability of ischemic heart disease based on the prestest probability and the likelihood ratio of the positive or negative test.

(Center column). Using an intermediate probability of 50% for CAD we can see that a positive troponin test increases the posterior probability to 80% and a negative one decreases the probability to 5%.

With low and high probabilities, you gain very little with additional tests as you can see in table 11.

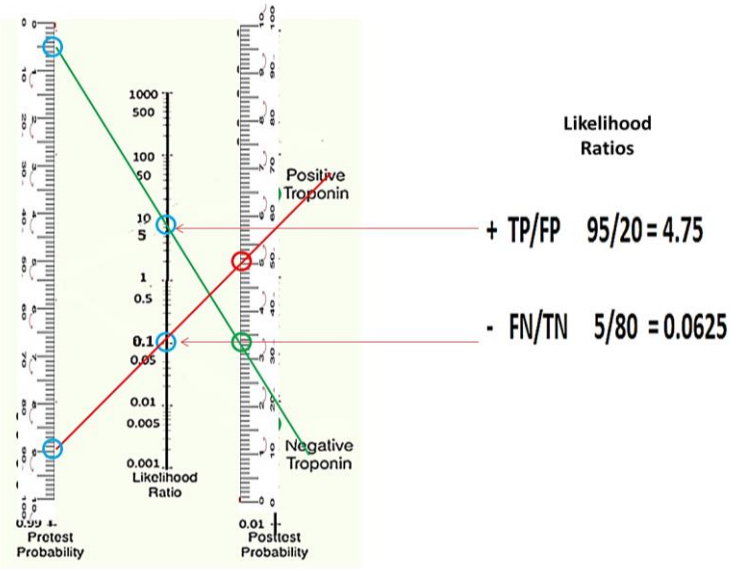

Table 11: If you begin with a low pretest probability (0.1), a positive test will at most, put the probability in an intermediate score (green line); and the same goes for a high pretest probability (0.9) where a negative test will not completely rule out the disease (red line). So studying patients with intermediate probability of a disease yields a larger benefit.

If you begin with a low pretest probability (0.1) as many disease have in the general population, a positive test will at most, put the probability in an intermediate score not enough to confirm the diagnosis; and the same goes for a high pretest probability (0.9) as in patients with typical symptoms and risk factors where a negative test will not rule out the disease. So studying patients with intermediate probability of a disease yields a larger benefit.

Conclusion

The era of reductionism in medicine has to come to an end. Not only physics is the realm of complexity, but biology has to be studied with many factors where the total results in a larger spectrum and functions than the sum of the individual parts. (figure. 1).

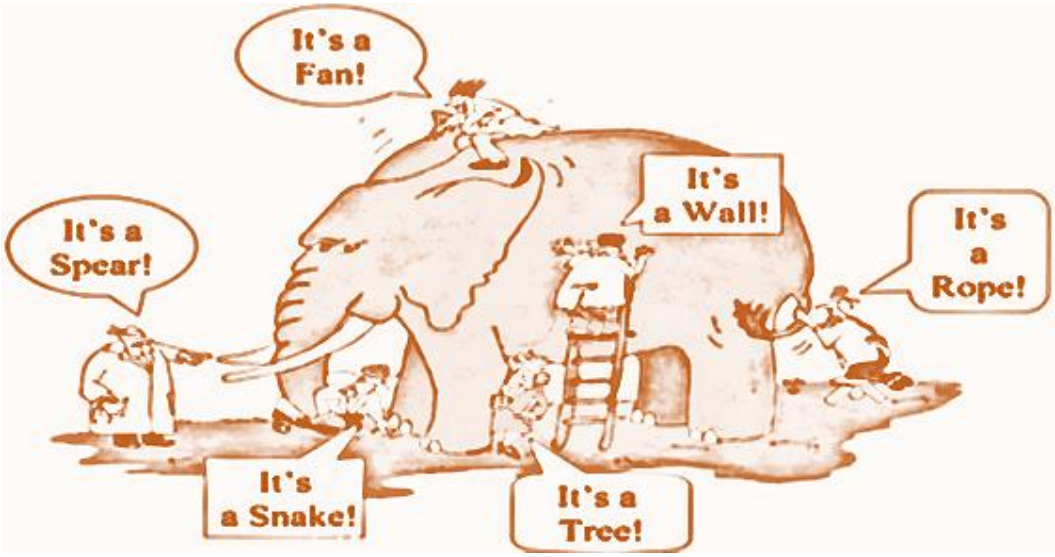

Figure 1: Wikipedia. The blind men and the elephant. John Godfrey Saxe:

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