On Probability Calculus in Application to Therapeutic Statistics*

By
Prof. C. Liebermeister
in Tübingen

1877

Typesetting and Translation from German by Leonhard and Valentina Held

From the theoretical side, it has often been shown irrefutably to us practical physicians that all our conclusions about advantages and disadvantages of individual treatment methods, provided that they are based on the statistics of the actual success, are completely vague as long as we do not apply the strict rules of probability calculus. In fact, if the observed outcomes have been more favourable in one treatment than in another, this may just as well be based on chance as it is undoubtedly based on chance if, in a game of hazard with equal chances, one person wins today and the other tomorrow. The simple fact that 20 of 100 patients died with one treatment method and 10 of 100 patients died with the other one, does not in itself prove that the second treatment method deserves to be preferred, and does not give any certainty that perhaps 30 of 100 will die next time this second treatment method is used. If we want to draw conclusions from the actual successes, the inevitable prerequisite to do so is to examine how large the probability is that the observed differences in success are not simply due to chance. And for this question only probability calculus gives the necessary indication. Page 935 Page 936

Certainly, with the accomplishment of this mathematical and formal part, our task is far from being completed. Rather, the question then arises as to whether the two series of observations, in which the difference in success occurred with different treatment, can really be regarded as comparable in every other respect. There might have also been a decisive change in the character of the disease, in the intensity of the cause of the disease, whether a change in the various other moments, on which the outcome of the disease may depend, has not caused the differences in the observed success. It would be wrong to demand the solution of this task from a mathematical analysis. The probability calculus shows us with all sharpness in which degree of probability it can

*The present work is essentially a chapter from a lecture about the main features of probability calculus applied to medicine and natural sciences.

be assumed that there was a difference in the constant conditions on which success depends. But it is completely incapable of giving any statement about the nature of this difference. The study of the causes, and the question of whether these are to be sought in the diversity of treatment or in the diversity of other constant conditions, is a matter for clinical analysis.

This latter and more difficult part of the issue has usually been treated with sufficient care and thoroughness in the better works in which therapeutic statistics have been used. This leads to the fact that the conclusions drawn often do not allow any objections from this side. In contrast, the purely formal mathematical part of the task has usually not been touched at all in these works. And yet it cannot be denied that the completion of this is the necessary precondition for the utilization of the observation.

The reason why physicians have made so little use of probability calculus so far is not so much that they have not given this discipline the importance it deserves. Rather, it is mainly based on the fact that the analytical apparatus has so far been too incomplete and inconvenient. Up to this point an admirable acumen has been applied by mathematicians to the elaboration of the methods necessary to solve the problems of probability calculus. Some parts of probability calculus, such as those which are important for the insurance industry, as well as individual methods which can be applied to the results of the observed natural sciences — I recall the method of least squares — have been perfected to such an extent that even the non-mathematician is able to use them with little difficulty. — To date, those analytical methods which would preferably be of use to the medical profession have not enjoyed the same degree of diligence. In particular, the application of probability calculus to therapeutic statistics has not yet been elaborated to the extent that the problems that occur can be solved with sufficient reliability. Mathematicians usually approach this problem only indirectly, but do not deal with it in a straight matter. Furthermore, what the non-mathematician has so far been offered in the form of practically applicable formulas cannot be regarded as an exact and comprehensive solution to the problem, but only as an alternative, which can provide a sufficient approximation to a solution in individual cases, but fails in most cases that occur in practice.

Page 937

The present problem has been discussed most thoroughly by Poisson. Although even this mathematician does not approach the task in a direct manner, the admirable mastery of the analytical methods by which he is distinguished has enabled him to produce relatively simple formulas which, within certain limits, allow calculation to be carried out with sufficient approximation. Certainly, these formulas could only maintain their convenient simplicity at the expense of accuracy by leaving out uncomfortable elements for the calculation. For this reason, they are only correct if the data series contain very large numbers. They require at least hundreds and often many thousands of individual observations. Mathematicians can easily say that if physicians want to draw safe conclusions, we must always work with large numbers; we must compile thousands or hundreds of thousands of observations. — After all, this is usually not practicable with therapeutic statistics. If the question is which method of treatment for pneumonia deserves to be preferred, or which method of surgery for a surgical disease is better, — how can a physician treat a few thousand cases one by one and then a

few thousand by another method? And if one wanted to help oneself by compiling the results of different observers, obtained at different times and places, then perhaps one would get those thousands. But then the compared groups would no longer be identical, and all conclusions would be illusory. Only in rare cases can therapeutic statistics meet the conditions that mathematicians have demanded so far. But if they are fulfilled, — then it can often seem questionable whether probability calculus is still Page 938
urgently needed. If, for example, one wants to compare the success of the antipyretic treatment of abdominal typhoid fever with that of the expectant treatment, if one sees that, without exception, wherever the antipyretic method has been applied in a reasonably appropriate manner, mortality has been reduced to a fraction of the earlier mortality, if for individual hospitals the cases to be compared already count in the thousands, — who will still consider probability calculus necessary to come to the conclusion that the antipyretic treatment is the better one? — Especially in cases, in which the mere consideration of the numbers is not sufficient to gain a certain conviction, in which therefore only by calculation it could be recognized, whether there is a certain degree of probability for the meaning of a difference and which degree of this probability exists, the formulas fail. And even with very large numbers, if the differences are small and therefore at first glance doubtful in their significance, those theorems can sometimes become disturbingly inaccurate.

The mathematicians' demand to always use large numbers for their conclusions has usually been accepted by the representatives of medical statistics without opposition. The same ones are ready to inculcate in physicians at every opportunity as an unshakable dogma that series of observations which do not consist of very large numbers cannot prove anything at all, that it is unscientific to want to draw conclusions from small numbers. — But is such an assumption really founded in the nature of things? If someone had treated only 12 cases of malaria expectantly and 12 other cases with quinine, would that not be enough to convince, that quinine is useful against malaria, even without any calculation? If the computation does not know what to do with such an unambiguous result, it is only a deficiency of it and a proof that the mathematical methods are still highly imperfect. In fact, the requirement of large numbers has only had some justification so far, when mathematicians have not yet provided us with a method that allows us to apply probability calculus to less large numbers. However, an exact and comprehensive solution to the problem must be equally applicable to small and large numbers. Of course, it will always result that for small numbers there must be a significant difference in the results of the observations in order to achieve a certain degree of probability, whereas for large series of observations for the same degree of probability even a small difference in the results is sufficient. But there are Page 939
circumstances in which even the comparison of observation series consisting of small numbers results in a probability for the exclusion of chance that comes very close to certainty.

Poisson's formulas have so far been the only method applied to therapeutic statistics. And in their application, physicians have not always been satisfied[1]. At first it was

[1] A good basic guide to using them can be found in: Fick, Medicinische Physik. 2nd edition. Brunswick

exploited by Gavarret[2], and later all physicians who dealt with medical statistics used the same formulas, namely Schweig[3], A. Fick, Oesterlen[4], Jessen[5], Hirschberg[6]. Gavarret, as Poisson had done with individual special tasks, takes a probability of 0,9953 or $\frac{212}{213}$, i. e. a probability that corresponds to a bet of 212 to 1, as sufficient, and the formulas are set up to indicate whether a therapeutic-statistical result with a probability of $\frac{212}{213}$ or odds of 212 to 1 is to be regarded as non-random, or whether this degree of probability is not reached. He has also calculated a table indicating the limits for which it can be claimed with the stated degree of probability that it will not be exceeded by the random deviations of statistical results. This table is also shared in more or less modified form by Fick, Jessen, Hirschberg.

It cannot be disputed that these tables may have a certain usefulness. But both the tables and Poisson's formulas, in the form in which they have been recommended so far for medical statistics, are far from being sufficient for the needs of the medical observer.

First of all, it is a deficiency that it can only be seen from this whether the assumed degree of probability of 212 to 1 is reached or not. But what if this degree of probability is not reached? Should all series of observations in which the odds of excluding chance are not quite 212 to 1 be completely worthless? Would it not already be a remarkable result if we had the odds of 100 to 1 that a certain observation series gave better results than another? And would we not even then, if the odds of preference of one observation series would only be 10 to 1, according to the experience available so far, apply this one rather than the other for the next case? Truly, we are not so rich in gold coins in the empirical foundations of therapy that we could be advised to throw all silver coins into the water! And a handful of silver coins is often worth more than a single gold coin. In fact, if the probability calculus is to be applied to the assessment of therapeutic results with benefit and in an extensive way, then it is necessary: not that one can convince oneself by means of a table or formula that for the exclusion of chance a certain arbitrarily assumed degree of probability is reached or not reached; but rather that one can calculate with certainty and accuracy for each available observation material with which degree of probability chance is excluded. Only when this is possible can we use all our series of observations in a scientific way, by giving each of them exactly the value it deserves[7].

Page 940

1866. Appendix.

[2] J. Gavarret, Allgemeine Grundsätze der medicinischen Statistik. Translated by Landmann. Erlangen 1844. — In this translation, certain formulas are distorted beyond recognition.

[3] Auseinandersetzung der statistischen Methode. Archive for physiological medicine. XIII. 1854. P. 305.

[4] Handbuch der medicinischen Statistik. Tübingen 1865. P. 60.

[5] Zur analytischen Statistik. Journal of Biology. III. 1867. P. 128.

[6] Die mathematischen Grundlagen der medizinischen Statistik. Leipzig 1874.

[7] In the correct recognition that adhering to the requirement of a probability of 212 to 1, even in cases where it cannot actually be achieved, does not meet the factual needs of medicine, Hirschberg calculated a second table in which only a probability of 0,916 or about 11 to 1 is required. This is a major improvement in that some observation series become at least to some extent usable, which they were not before. But the other deficiencies are also fully inherent in this table, and the natural requirement to determine the degree of probability for any observation material at hand is met neither.

Furthermore, it is very unfavourable for practical use that these tables usually start with the number 300, exceptionally with 200. Observation series which do not cover at least as many cases can therefore not be considered at all[8]. Apparently, this excludes most of the observation series occurring in practice from the application of probability calculus.

Finally, however, these tables cannot be applied directly to the problem at hand. And Page 941
if this did happen at times, it did not correspond to the real meaning of Poisson's formulas, and the results had to be incorrect. It happens that in case of a result the conditions of the table, as they are usually understood, are also not nearly fulfilled, i.e. the odds of excluding chance do not seem to reach 212 to 1, while in reality the odds are more than 1000 to 1.

These shortcomings of the methods have contributed significantly to making the results of therapeutic statistics appear even less certain than they actually are, and in general to discrediting therapeutic statistics more than they deserve. And if the physicians have not yet been able to decide to apply the methods presented by the representatives of medical statistics to their observations and to regulate their conclusions from them, this was probably less based on a misunderstanding of the high value of probability calculus or on an unscientific indifference towards strict methods, if they often believed that it was enough to have taken every care to carry out an accurate clinical analysis, if they did not just neglect mathematical analysis, but sometimes even declared to be superfluous or deceptive, it was certainly partly the opposition of the simple mind against too far-reaching assertions and demands.

A firm foundation of therapy is unthinkable without therapeutic statistics. Even where the therapy would be a so-called rational one, it could not do without the sample provided by experience, by the statistics of success. However, if therapeutic statistics are to stand on solid ground, it is necessary to apply probability calculus in its strictest form. It is therefore an urgent need for methods to be found which allow the significance of therapeutic experiences to be assessed with higher certainty than has been possible up to now.

For some time now, on the occasion of special therapeutic investigations, I have had the possibility to directly examine the task of applying probability calculus to therapeutic statistics. The fundamental formulas have resulted in a relatively simple form, without the necessity of neglecting uncomfortable links or the assumption of assumptions that are only approximate or only valid for large numbers. The formulas Page 942
are therefore just as valid for small numbers as for large ones. I have also succeeded in deriving other formulas from the fundamental ones, which hardly require any mathematical knowledge for their practical application, but which are suitable for solving the everyday questions of therapeutic statistics with any degree of accuracy desired. While the application of these formulas is also without difficulty for non-mathematicians, the complete derivation of them in a simple and understandable way

[8] Even Hirschberg's second table, which only demands odds of 11 to 1, starts with the number 300.

can only be given by partially applying higher analysis. In the following I have moved everything that requires special mathematical knowledge to supplemental notes. The essential discussions contained in the actual text will be understandable for everyone who is familiar with the initial principles of mathematics and probability. For orientation on the elementary theorems of probability, the work of Hirschberg is recommended for the physician, despite individual misunderstandings that occur during application, as well as the older work of Lacroix[9], which is still the best elementary representation of probability. Finally, the basic features of probability are excellently represented in the works of Hagen[10], which also contains a highly recommended explanation of the method of least squares. The actual fundamental works of Laplace, Gauss, Poisson, to which everyone who wants to work independently in this field will refer, are only accessible to those who are familiar with higher analysis. — Those who do not want to get involved in mathematical discussions can simply skim over them and use the formulas I. and II. on page 946, the application of which can be derived from the examples.

Let us assume that two different types of treatment have been used for a given disease; the first type of treatment has resulted in a deaths and b recoveries, the second type of treatment in p deaths and q recoveries. In the second series of observations, the mortality ratio was more favourable: $\frac{p}{p+q}$ was less than $\frac{a}{a+b}$. Before we can investigate what was the cause of the favourable mortality ratio in the second series of cases, the question whether this more favourable ratio has any significance at all has to Page 943
be answered, or whether it is perhaps simply due to chance. This question can be explained in an exact way by probability calculus. More specifically by indicating how large the probability is that the constant conditions were actually more favourable in the second series of observations, and how large the inverse probability is that the constant conditions were not more favourable. The comparison of these two quantities is then crucial for our verdict.

We can bring these and the numerous analogous tasks of therapeutic statistics to a pattern that corresponds to what has long been used in probability calculus.

Let us imagine two urns, each containing a very large number of partly black and partly white balls in any unknown ratio. We first draw individual balls from the first urn (which we throw back into it each time and mix with the others). In total we have drawn a black and b white balls. Then we draw from the second urn as well and get p black and q white balls. It would again be $\frac{p}{p+q}$ smaller than $\frac{a}{a+b}$. Now the question arises: Is the relatively smaller number of black balls received in the second case due to the fact that the second urn contained relatively fewer black balls? Or is it based on coincidence? Or more precisely: after the results of the two drawings, how large is the probability that the ratio of black balls to the total number of balls in the second urn is smaller than in the first? And what is the inverse probability that the ratio of black balls to the total number of balls in the second urn is equal to or greater than that of

[9] S. F. Lacroix, Traité élémentaire du calcul des probabilités. 4th edition. Paris 1864.
[10] G. Hagen, Grundzüge der Wahrscheinlichkeits-Rechnung. 2nd edition. Berlin 1867.

the first?

It is *certain* that the ratio of black balls in the second urn is either smaller or equal or larger than in the first urn. If we set the certainty $= 1$ and use P to represent the fraction which expresses the probability that the ratio of black balls in the second urn is smaller, then $1 - P$ is the probability that this ratio is equal or greater in the second urn than in the first.

It is now a matter of combining all equally possible cases which correspond to the probability P, on the one hand, and all equally possible cases which correspond to the probability $1 - P$, on the other.

Let in each of the two urns be very many, possibly an infinite number of balls. In the first urn, there are among n balls s black and $n - s$ white balls. Then, the probability to hit a black ball on the first draw is $= \frac{s}{n}$ and the probability to hit a white ball on the first draw is $= \frac{n-s}{n}$. The probability to draw only black balls in a draws is $= \left(\frac{s}{n}\right)^a$, the probability to draw only white balls in b draws is $= \left(\frac{n-s}{n}\right)^b$. The probability to draw first a black balls in a row and then b white balls in a row is $\left(\frac{s}{n}\right)^a \cdot \left(\frac{n-s}{n}\right)^b$. And the probability to draw in $a + b$ draws in total a black and b white balls but in any order is Page 944

$$= \frac{(a+b)!}{a!\,b!} \cdot \left(\frac{s}{n}\right)^a \cdot \left(\frac{n-s}{n}\right)^b$$

Here, $a!$ designates the so-called factorial of a, namely the product $1 \cdot 2 \cdot 3 \cdot \ldots \cdot a$. Likewise, it is $(a+b)! = 1 \cdot 2 \cdot 3 \cdot \ldots \cdot (a+b)$.

In the second urn, let the number of black balls among n balls be equal to t. Then the probability to draw from the first urn in $a + b$ draws in total a black and b white balls in any order, and to draw afterwards from the second urn p black and q white balls in $p + q$ draws in any order is

$$= \frac{(a+b)!\,(p+q)!}{a!\,b!\,p!\,q!} \cdot \left(\frac{s}{n}\right)^a \cdot \left(\frac{n-s}{n}\right)^b \cdot \left(\frac{t}{n}\right)^p \cdot \left(\frac{n-t}{n}\right)^q$$

The sizes s and t are unknown. As far as their behaviour towards each other is concerned, two possibilities come into consideration for us, which we have to compare according to their probability. These are the following two hypotheses:

First hypothesis: t is smaller than s. This hypothesis corresponds to the probability P that relatively fewer black balls are found in the second urn.

Second hypothesis: t is equal to or greater than s. This hypothesis corresponds to the complementary probability $1 - P$.

If none of a, b, p, q equals zero, the value of both s and t must be between 1 and $n - 1$, and for both s and t any value between these limits would be possible. We now make the assumption that, before the drawings began, there was no reason to consider any particular ratio of the black balls more probable than any other ratio, i. e. that a priori the assumption $s = 1$ or $s = 2$ had the same probability as $s = m$ or $s = m + 1$ or $s = n - 2$ or $s = n - 1$. The same applies to t. If, as may happen in special cases, this condition were not fulfilled, the a priori difference in the probability of the individual ratios would have to be taken into account (Supplemental Note 1). Page 945

Both for s and t, we now have to insert all numbers between 1 and $n-1$ and, for each of these possibilities, we have to examine the probability of the observed success both for the first and second hypothesis. If, for example, $s = m$, then for the first hypothesis all values of t which are smaller than m would be possible, and for the second hypothesis all values of t which are equal to or greater than m. We use the abbreviation

$$\frac{(a+b)!\,(p+q)!}{a!\,b!\,p!\,q!\,n^{a+b+p+q}} = Q$$

For $s = m$, the probability of the observed success in the first hypothesis is

$$= Q \cdot m^a (n-m)^b \left\{(m-1)^p (n-m+1)^q + (m-2)^p (n-m+2)^q + \dots + 1^p (n-1)^q\right\},$$

and in the second hypothesis

$$= Q \cdot m^a (n-m)^b \left\{m^p (n-m)^q + (m+1)^p (n-m-1)^q + (m+2)^p (n-m-2)^q + \dots + (n-1)^p 1^q\right\}$$

Using the common sigma notation, the sums in brackets can be written as

$$\sum_{t=1}^{t=m-1} t^p (n-t)^q \quad \text{and} \quad \sum_{t=m}^{t=n-1} t^p (n-t)^q$$

Next, we insert for s all numbers from 1 to $n-1$ one by one and determine the probability of the observed success for each of the two hypotheses. Since we are initially concerned only with relative probability, we can omit the factor Q which all expressions have in common. We then obtain the following values for the relative probability of the observed success:

	for the first hypothesis	for the second hypothesis
for $s = 1$	$1^a \cdot (n-1)^b \cdot 0^p \cdot n^q = 0$	$1^a \cdot (n-1)^b \cdot \sum_{1}^{n-1} t^p (n-t)^q$
for $s = 2$	$2^a \cdot (n-2)^b \cdot 1^p \cdot (n-1)^q$	$2^a \cdot (n-2)^b \cdot \sum_{t=2}^{n-1} t^p (n-t)^q$
for $s = 3$	$3^a \cdot (n-3)^b \cdot \sum_{t=1}^{2} t^p \cdot (n-t)^q$	$3^a \cdot (n-3)^b \cdot \sum_{t=3}^{n-1} t^p (n-t)^q$
for $s = m$	$m^a \cdot (n-m)^b \cdot \sum_{t=1}^{m-1} t^p \cdot (n-t)^q$	$m^a \cdot (n-m)^b \cdot \sum_{t=m}^{n-1} t^p (n-t)^q$
for all values together	$\sum_{s=1}^{n-1} \left\{ s^a \cdot (n-s)^b \cdot \sum_{t=1}^{s-1} t^p \cdot (n-t)^q \right\}$	$\sum_{s=1}^{n-1} \left\{ s^a \cdot (n-s)^b \cdot \sum_{t=s}^{n-1} t^p (n-t)^q \right\}$

Page 946

The probability of the first hypothesis is related to the probability of the second, just as the probability of the observed success under the first hypothesis is related to the probability of the observed success under the second. Since we denote the probability of the first hypothesis by P and that of the second by $1-P$, we have:

$$\text{(A)} \qquad \frac{P}{1-P} = \frac{\sum\limits_{s=1}^{n-1}\sum\limits_{t=1}^{s-1} s^a(n-s)^b \cdot t^p(n-t)^q}{\sum\limits_{s=1}^{n-1}\sum\limits_{t=s}^{n-1} s^a(n-s)^b \cdot t^p(n-t)^q}.$$

Similarly, we obtain by inserting the various possible values for t the following expression, which must necessarily be the same as the previous one.

$$\text{(B)} \qquad \frac{P}{1-P} = \frac{\sum\limits_{t=1}^{n-1}\sum\limits_{s=t+1}^{n-1} t^p(n-t)^q \cdot s^a(n-s)^b}{\sum\limits_{t=1}^{n-1}\sum\limits_{s=1}^{t} t^p(n-t)^q \cdot s^a(n-s)^b}.$$

With the achievement of this result, the task we had set ourselves has been solved. All that remains is to use purely mathematical manipulations to transform the obtained expressions in such a way that they become as convenient as possible for the calculation. Such transformations yield a large number of different formulas, which all give exactly the same results in the calculation, but some of which are more and others less difficult to calculate (Supplemental Note 2). I give here the two formulas which are the most convenient of all, and which we will therefore use exclusively.

$$\text{I.} \quad P = \frac{(a+b+1)!\,(p+q+1)!\,(a+p+1)!\,(b+q+1)!}{a!\,(b+1)!\,(p+1)!\,q!\,(a+b+p+q+2)!} \times \\ \times \left\{1 + \frac{a\cdot q}{(b+2)\cdot(p+2)} + \frac{a\,(a-1)\cdot q\,(q-1)}{(b+2)\,(b+3)\cdot(p+2)\,(p+3)} + \frac{a\,(a-1)\,(a-2)\cdot q\,(q-1)\,(q-2)}{(b+2)\,(b+3)\,(b+4)\cdot(p+2)\,(p+3)\,(p+4)} +++\right\}$$

$$\text{II.} \quad 1-P = \frac{(a+b+1)!\,(p+q+1)!\,(a+p+1)!\,(b+q+1)!}{(a+1)!\,b!\,p!\,(q+1)!\,(a+b+p+q+2)!} \times \\ \times \left\{1 + \frac{b\cdot p}{(a+2)\cdot(q+2)} + \frac{b\,(b-1)\cdot p\,(p-1)}{(a+2)\,(a+3)\cdot(q+2)\,(q+3)} + \frac{b\,(b-1)\,(b-2)\cdot p\,(p-1)\,(p-2)}{(a+2)\,(a+3)\,(a+4)\cdot(q+2)\,(q+3)\,(q+4)} +++\right\}$$

Only one of these formulas needs to be applied at a time, by calculating either P from formula I. or $1-P$ from formula II.. Usually, the latter method will be more convenient. Page 947

The notation must always be chosen such that $\frac{p}{p+q}$ is smaller than $\frac{a}{a+b}$.

In the derivation of the formulas, we have not made the otherwise common assumption that the number of observations is very large[11]. Therefore — and this is the essential advantage of these formulas — their validity does not depend on the number of available observations. The results are almost as accurate when the numbers are small as when they are large like thousands or millions. The degree of accuracy in a particular case depends on how far one wants to perform the calculation.

To show the application of the formulas, we start with an example consisting of very small numbers.

1. From an urn, about which we only know that it contains numerous black or white balls, 3 balls were drawn, 2 of which are black and 1 is white. From a second urn, 4 balls were drawn, of which 1 was black and 3 were white. The question is: after this drawing, how large is the probability P for the assumption that the second urn contains comparatively fewer black balls than the first? We have $a = 2$, $b = 1$, $p = 1$, $q = 3$, and obtain according to formula II.:

$$1 - P = \frac{4!\,5!\,4!\,5!}{3!\,1!\,1!\,4!\,9!}\left\{1 + \frac{1\cdot 1}{5\cdot 4}\right\}$$

The series in brackets consists only of 2 terms because for all following terms, the nominator of the fraction becomes $= 0$. By 4! we denote the factorial of 4, that is the product $1\cdot 2\cdot 3\cdot 4$; likewise 5! stands for $1\cdot 2\cdot 3\cdot 4\cdot 5$; $1! = 1$; etc. The numbers are so small that the calculation can be carried out without any further auxiliary means. It yields

$$\begin{aligned} 1 - P &= 0,1666666\ldots, \\ \text{hence } P &= 0,8333333\ldots, \quad \frac{P}{1-P} = 5. \end{aligned}$$

From formula I., one obtains in the same way:

$$P = \frac{4!\,5!\,4!\,5!}{2!\,2!\,2!\,3!\,9!}\left\{1 + \frac{2\cdot 3}{3\cdot 3} + \frac{2\cdot 1\times 3\cdot 2}{3\cdot 4\times 3\cdot 4}\right\}$$

$$P = 0,8333333\ldots.$$

You can therefore bet 5 to 1 that the ratio of black balls in the second urn is lower than in the first. If among similar cases of illness in one treatment 2 of 3 patients would have died and in another treatment only 1 of 4 patients, you could already bet 5 to 1 that this was not a coincidence, but that the conditions were more favourable in the second Page 948

[11]The number n is of course assumed to be very large or infinite; but this exactly corresponds to reality. Since this n corresponds to the number of observations which could possibly be made in the future; it is completely independent of the number of observations actually made.

series of cases. This result corresponds completely to the unbiased consideration, which would also find a request in the result of the second series compared to that of the first, to continue with the second treatment method until further notice.

In the chosen example, despite the small number of observations, the probability obtained is not entirely insignificant, because the difference $2/3 - 1/4$ is a very large one. If this difference were smaller, say $2/3 - 2/4$, by assuming that there were 2 black balls in the first draw among 3 balls and 2 black balls in the second among 4 balls, then by setting $a = 2$, $b = 1$, $p = 2$, $q = 2$ we obtain $1 - P = 5/14$ and $P = 9/14$. So we could not even bet 2 to 1 that there would be relatively fewer black balls in the second urn.

As soon as the numbers are slightly larger, the direct calculation of the factorials $a!$, $b!$ etc. is no longer possible. The factorial of 100, for example, is already a number of 158 digits, which begins with the digits 93326.... Such numbers, if you wanted to use them directly, would be difficult to handle for the calculation. But in probability calculus we usually do not need these factorials themselves, but only their ratio; and this is obtained exactly from the difference of their logarithms. In the table at the end of this paper[12], for all numbers from 0 to 1200 the logarithms of their factorials [Editor's note: to the base 10] are listed, and by means of this table the calculation of the factor consisting of factorials can be carried out with the highest convenience, as long as the values for $a + b + p + q + 2$ do not exceed 1200. Let us take a fictitious example again.

2. Suppose for some treatment of 15 ill patients, 6 have died while for another treatment of 32 equally ill patients, 7 have died. How large is the probability that the more favourable mortality ratio in the second case is not accidental?

I give, in order to show the arrangement of the calculation in detail, the calculation of the example in full detail. We have $a = 6$, $b = 9$, $p = 7$, $q = 25$, and obtain according to formula II.: Page 949

$$1 - P = \frac{16!\,33!\,14!\,35!}{7!\,9!\,7!\,26!\,49!}\left\{1 + \frac{7 \times 9}{27 \times 8} + \frac{7 \cdot 6 \times 9 \cdot 8}{27 \cdot 28 \times 8 \cdot 9} + \frac{7 \cdot 6 \cdot 5 \times 9 \cdot 8 \cdot 7}{27 \cdot 28 \cdot 29 \times 8 \cdot 9 \cdot 10} + ++\right\}$$

First we calculate with the help of the tables at the end of the issue the factor consisting of faculties, which we denote by F. [Editor's note: Throughout the article the symbol "log" denotes the logarithm to the base 10.]

log(16!)	=	13,32062
log(33!)	=	36,93869
log(14!)	=	10,94041
log(35!)	=	40,01423
log numerator	=	101,21395
−log denominator	=	102,35434
log F	=	0,85961 − 2

log(7!)	=	3,70243
log(9!)	=	5,55976
log(7!)	=	3,70243
log(26!)	=	26,60562
log(49!)	=	62,78410
log denominator	=	102,35434

[12] The table is an excerpt from the larger table of C. F. Degen, calculated to 18 decimal places, Tabularum ad faciliorem et breviorem probabilitatis computationem utilium Enneas. Havniae 1824.

The calculation of the other factor consisting of a finite series is easiest to perform with ordinary logarithms [Editor's note: to the base 10], taking into account that every new term can be obtained from the preceding one by multiplication with additional factors. We denote the separate terms of the series by $1, y_0, y_1, y_2$ and the sum of the series by S, so that

$$S = 1 + y_0 + y_1 + y_2 + y_3 + + + \quad \text{and} \quad 1 - P = F \times S.$$

The calculation can for instance be done as follows:

$$\begin{array}{rcl}
\log 7 & = & 0,84510 \\
\log 9 & = & 0,95424 \\
\hline
 & & 1,79934 \\
 & - & 2,33445 \\
\hline
\log y_0 & = & 0,45489 - 1 \\
\log 6 & = & 0,77815 \\
\log 8 & = & 0,90309 \\
\hline
 & & 1,14613 \\
 & - & 2,40140 \\
\hline
\log y_1 & = & 0,74473 - 2 \\
\log 5 & = & 0,69897 \\
\log 7 & = & 0,84510 \\
\hline
 & & 0,28880 \\
 & - & 2,46240 \\
\hline
\log y_2 & = & 0,82640 - 3 \\
\log 4 & = & 0,6021 \\
\log 6 & = & 0,7782 \\
\hline
 & & 0,2067 \quad - 1 \\
 & - & 2,5185 \\
\hline
\log y_3 & = & 0,6882 \quad - 4 \\
\log 3 & = & 0,477 \\
\log 5 & = & 0,699 \\
\hline
 & & 0,864 \quad - 3 \\
 & - & 2,570 \\
\hline
\log y_4 & = & 0,294 \quad - 5
\end{array}$$

$$\begin{array}{rcl}
\log 27 & = & 1,43136 \\
\log 8 & = & 0,90309 \\
\hline
 & & 2,33445 \\
\\
\log 28 & = & 1,44716 \\
\log 9 & = & 0,95424 \\
\hline
 & & 2,40140 \\
\\
\log 29 & = & 1,46240 \\
\log 10 & = & 1,00000 \\
\hline
 & & 2,46240 \\
\\
\log 30 & = & 1,4771 \\
\log 11 & = & 1,0414 \\
\hline
 & & 2,5185 \\
\\
\log 31 & = & 1,491 \\
\log 12 & = & 1,079 \\
\hline
 & & 2,570
\end{array}$$

If one requires the value of P only up to 5 decimal places, one can stop the series here [Editor's note: after six terms]. If one, as usually sufficient in practice, is prepared to accept a Page 950 lower degree of accuracy, then one could have stopped the calculation already earlier and could have taken even less decimal places for the logarithms. If one is familiar with the calculation with complements, then the form can be even further simplified. The combination of the terms of the series yields:

$$\begin{aligned} \log y_0 &= 0,46489 - 1 \\ \log y_1 &= 0,74473 - 2 \\ \log y_2 &= 0,82640 - 3 \\ \log y_3 &= 0,6882 \quad - 4 \\ \log y_4 &= 0,294 \quad\;\; - 5 \end{aligned}$$

$$\begin{aligned} & & 1,00000 \\ y_0 &= & 0,29167 \\ y_1 &= & 0,05556 \\ y_2 &= & 0,00671 \\ y_3 &= & 0,00049 \\ y_4 &= & 0,00002 \\ \hline S &= & 1,35445 \end{aligned}$$

$$\begin{aligned} \log S &= 0,13176 \\ \log F &= 0,85961 - 2 \\ \hline \log(1-P) &= 0,99137 - 2 \\ 1 - P &= 0,09803 \\ P &= 0,90197 \\ \frac{P}{1-P} &= 9,2 \end{aligned}$$

The calculation of P according to formula I., which is almost as easy to perform in this example, gives exactly the same result.

One can therefore bet a little more than 9 to 1 that the difference in the results for both series of observations was not accidental, i.e. that if all other constant causes from which the difference could be derived can be excluded, the same can be applied to the difference in treatment.

If the difference in the observation results had been larger, then despite the small numbers, a much larger probability of excluding chance would have been obtained. Assuming that in the same example only 2 of the 32 patients in the second series died, this would result in $P = 0,9968476$, i. e. one could bet 316 to 1 that the difference in the results was not due to chance.

3. In order to show how large the probability of excluding randomness can become even with small numbers, if the differences in the results of the observations are very large, we take an example mentioned earlier, for whose calculation the formulas used up to now were completely inadequate. Of a certain number of patients suffering from malaria, 12 had been treated with sufficient doses of quinine and 12 others had been treated purely prospectively without any active treatment. By the third day of treatment, 10 of those treated with quinine had become fever-free. Of those treated prospectively, only 2 were free of fever. How big is the probability that the quinine as an antipyretic method has any effect?

We set $a = 10$, $b = 2$, $p = 2$, $q = 10$, and get $P = 0,9993987$. We can bet 1666 to 1 that the difference in the results is not random.

Page 951

4. In no. 1 of the "Berliner Klinische Wochenschrift" of that year (1876), S t r i c k e r reported from the T r a u b e Clinic on the effect of salicylic acid in acute rheumatoid arthritis. He described that all fresh cases subjected to treatment with salicylic acid were free of all fever and local symptoms within 48 hours at the latest, but usually much earlier. Since we physicians are used to the fact that from time to time certain medicaments against certain diseases are advertised as infallible, but mostly prove to be ineffective or not very effective upon closer examination, it was not surprising that at the beginning this communication met with a decided scepticism from some physicians, especially since only 14 cases have been reported so far. The author himself says that he unfortunately has to admit that his statistical material "is composed of only 14 cases, for whom nothing is of value, who derives a decisive statistic only from thousands of cases". — In fact, this is the usual view in medical statistics. But the simple mind will certainly agree with the author when he ascribes a very large evidential value to the fact that all 14 cases without exception were so unusually favourable. — I applied my formula to that statement and convinced myself by a very simple calculation that, assuming the correctness of the observations and especially of the diagnoses as a matter of course, those 14 cases are perfectly sufficient to prove the existence of an unusual influence which only occurred in those cases and caused their favourable course, and that with a degree of probability which does not differ substantially from absolute certainty. — Also, the first tests which I myself carried out on sick people showed surprisingly favourable results; and since then, as is well known, S t r i c k e r's statements have not been confirmed in the most essential points.

For the execution of the calculation it is necessary to be able to compare a number of observations with indifferent treatment. It can happen, although rarely, that a single case treated prospectively also takes such a favourable course. In order not to judge the results of prospective treatment too unfavourably, we would like to assume that such a favourable course of treatment occurs in an average of 20 percent of cases. If we were to use 10 earlier cases for comparison purposes, of which 2 would have had the same favourable course, we would have $a = 8$, $b = 2$, $p = 0$, $q = 14$, or also, which gives exactly the same result, $a = 14$, $b = 0$, $p = 2$, $q = 8$. We obtain according to formula II.:

$$1 - P = \frac{11!\,15!\,9!\,17!}{15!\,0!\,2!\,9!\,26!} = \frac{11!\,17!}{2!\,26!}$$

Since b resp. $p = 0$, the series is reduced to the first term $= 1$. Note that $0! = 1$. The calculation with help of the table results in: Page 952

$$\begin{array}{rcr}
\log(11!) & = & 7,60116 \\
\log(17!) & = & 14,55107 \\
\hline
 & & 22,15223 \\
 & & 26,90665 \\
\hline
\log(1-P) & = & 0,24558 - 5
\end{array}$$

$$\begin{array}{rcr} \log(\ 2!) & = & 0,30103 \\ \log(26!) & = & 26,60562 \\ \hline & & 26,90665 \end{array}$$

$$\begin{aligned} 1 - P &= 0,000017603 \\ P &= 0,999982397 \end{aligned}$$

One could bet more than 56000 to 1 that the remarkably more favourable course of those 14 cases was not accidental.

If 100 indifferently treated cases had been used for comparison, 20 of which would have taken the short favourable course, one could bet more than 800 million to 1 that the result in those 14 cases would not be the product of chance.

If 1000 cases were available for comparison, of which 200 would have taken the favourable course, the odds would be more than 19000 million to 1.

If the difference of the observed results is less pronounced, then the probability of excluding chance is also lower, even if the number of observations is considerably larger.

5. In my ward at the Basle hospital, between 1867 and 1871, 38 of 230 patients with acute croupous pneumonia who were treated with antipyretic methods as far as necessary, died; the mortality rate was thus 16.5 percent. In earlier years, before the introduction of antipyretic treatment, 175 of 692 patients had died in the same ward; the mortality rate was 25.3 percent. Through precise clinical analysis it was established that the two series of observations were comparable in every other regard (see Fismer, Deutsches Archiv für klin. Med. volume XI. p. 391 ff.). So the only question left is: How large is the probability that the difference in results was not accidental:

We have $a = 175$, $b = 517$, $p = 38$, $q = 192$. The calculation according to formula II. gives $1 - P = 0,0028651$, thus $P = 0,9971349$. The odds for excluding chance are 348 to 1.

6. Finally, we want to calculate an example which at the same time is suitable to show in what striking way the meaning of the formulas used by representatives of medical statistics has been misunderstood by them. In the presentation of the mathematical principles of Hirschberg's medical statistics, the following example is given to explain the theorem that no weight should be placed on small fluctuations in statistical ratios: "If in one series of 300 cases of a disease, e.g. ileotyphus, a mortality of 22 per cent is found, and in a second series of 300 cases of ileotyphus a mortality of 16 per cent is found, the true value of mortality may be the same in both series, indeed it Page 953
is highly probable". Such an assertion does not at all correspond in fact to the usual

view of the general practitioner, who will certainly declare the result of the second series to be considerably more favourable; but it does not correspond to the result of an unbiased consideration either. The latter will certainly admit that the difference in the therapeutic results in the two series is not large enough to allow us to draw firm conclusions from it, even if the numbers are not very large. The possibility that this difference can only be accidental and meaningless will not be doubted; but that this is probable will certainly not be obvious to the simple mind. Now, even Poisson's formulas, if applied correctly, give a probability of 0,9397 for the assumption that the reduction in mortality in the second series is not random but is due to a constant cause; i.e. one can bet more than 15 to 1 that this reduction is not random. The question, of course, as to what is the cause of the reduction in mortality, whether a possible difference in treatment or a change in the nature of the epidemic or any other change in circumstances, is not a matter for mathematical analysis, but for clinical analysis. Odds of 15 to 1 are still far from absolute certainty; not as large as one might wish if one is to make difficult decisions, and especially not as large as the Gavarret formulas require; but certainly not meaningless. It will depend to a large extent on other circumstances and considerations whether one wishes to consider them sufficient to take an important decision in relation to future treatment or anything similar. Let us assume, for example, that the first series of observations were made in an ordinary hospital, the other under exactly the same conditions in a barrack hospital. These observations would then be a not inconsiderable hint. Where the construction of the barracks would be easy to carry out, one would probably proceed without question to that result. Where, on the other hand, there would be particular difficulties and inconveniences connected with it, and there would be no urgent need for a careful decision, it would be preferable to wait and see whether further observations would increase or decrease the probability. — In all cases, we can be certain that the result of a correctly applied calculation will not conflict with the result of a reasonable consideration carried out without an invoice. The calculation gives a result expressed in numbers and is therefore, where it can be applied, an irreplaceable aid. The importance and weight of these figures and the decisions to be taken on the basis of them are again a matter of debate.

If we apply our more exact formulas to the example, then, by setting $a = 66$, $b = 234$, $p = 48$, $q = 252$, we obtain $P = 0,96915$; we thus have for the exclusion of chance a probability of more than 31 to 1, and the result therefore has in reality an even somewhat larger significance than would be ascribed to it according to Poisson's formulas, which are not very exact for such small numbers. Page 954

If the factorials appearing in the formulas are larger than 1200! our table is no longer sufficient for calculation. But especially for large numbers, the factorials can easily be calculated according to Stirling's formula, which, if α is a large number

$$\alpha! = \alpha^{\alpha} \cdot e^{-\alpha} \cdot \sqrt{2\pi\alpha}$$

In this case e is the basis of the natural logarithms and π is the circumference of the circle for the diameter $= 1$. If all numbers are reasonably large, formula II. yields the following expression, which is convenient for calculations with logarithms:

$$\text{III.}\quad 1-P=\frac{\left(\frac{a+b+1}{a+1}\right)^{a+1}\cdot\left(\frac{a+b+1}{b}\right)^{b}\cdot\left(\frac{p+q+1}{p}\right)^{p}\cdot\left(\frac{p+q+1}{q+1}\right)^{q+1}}{\left(\frac{a+b+p+q+2}{a+p+1}\right)^{a+p+1}\cdot\left(\frac{a+b+p+q+2}{b+q+1}\right)^{b+q+1}}$$
$$\times\sqrt{\frac{(a+b+1)\cdot(p+q+1)\cdot(a+p+1)\cdot(b+q+1)}{2\pi\cdot(a+1)\cdot b\cdot p\cdot(q+1)\cdot(a+b+p+q+2)}}\left\{1+\frac{b\cdot p}{(a+2)(q+2)}+++\right\}$$

[Editor's note: The last factor in formula III. is given with more terms in formula II.]

7. Example. In the years 1843 to 1864, 469 patients with abdominal typhoid died in the Basle hospital during prospective treatment of 1718 patients with abdominal typhoid. In the years 1866 to 1874, only 130 patients died during antipyretic treatment of 1175 patients with the same average disease severity. What is the probability that the favourable mortality ratio with antipyretic treatment is not due to chance? We have $a=469$, $b=1249$, $p=130$, $q=1045$, and obtain with formula III.:

$$\begin{aligned}\log(1-P) &= 0{,}7310-28\\ 1-P &= 0{,}00000\,00000\,00000\,00000\,00000\,00538\ldots\\ P &= 0{,}99999\,99999\,99999\,99999\,99999\,99462\ldots\end{aligned}$$

So you can bet more than 1800 quadrillions to 1 that the difference in the results is not random.

The larger the numbers are, the easier it is to use Poisson's formulas for calculation. However, since they do not directly address our problem, they need to be slightly modified to be useful for our purposes. The results of the calculation are essentially the same as those obtained according to our formulas, only they are necessarily somewhat less accurate. For example, when applied to our typhoid fever statistics (7th example), the probability is even slightly higher; in the pneumonia statistics (5th example), on the other hand, the probability obtained is slightly lower than that calculated by us.

A few more hints about safeguards and auxiliary means should be mentioned, which in some cases can make the calculation easier. Page 955

For tasks where it is necessary to calculate a slightly larger number of terms, it is important to have a convenient control of the calculation to be sure of not making spelling and calculation errors. You can now easily calculate any term of the series directly and compare it with the value obtained by successive calculations. If we denote the terms of the series in formula II. by

$$1, y_0, y_1, y_2, y_3\ldots y_k\ldots y_n,\quad \text{then}$$

$$y_k = \frac{b(b-1)\dots(b-k) \times p(p-1)\dots(p-k)}{(a+2)(a+3)\dots(a+k+2) \times (q+2)(q+3)\dots(q+k+2)} = \frac{b!\,p!\,(a+1)!\,(q+1)!}{(b-k-1)!\,(p-k-1)!\,(a+k+2)!\,(q+k+2)!}$$

The latter term can be easily calculated with the help of the table of factorials if the individual numbers do not exceed 1200. If the result is correct with the result obtained by successive calculation, it is very likely that the logarithms of all preceding terms are also correctly calculated.

If the numbers are large and the differences of the observation results are small, it can happen that for an accurate calculation of $1 - P$ very many terms of the series would be necessary and therefore the calculation would be very time consuming. For the case, which is not uncommon in practice, that one can already be satisfied with a certain approximation, the sum of the series in formula II. can be easily estimated by the following approximation formula, which only requires the calculation of two terms, which then must be extended to at least 6 digits:

$$1 + y_0 + y_1 + y_2 + + + = \frac{y_0 + y_0 \cdot y_0 - 2y_1}{y_0 + y_0 \cdot y_1 - 2y_1}.$$

Once the series has been accurately calculated, this approximation formula provides some control over the calculation.

Finally, it should be mentioned that our formulas are not only applicable to therapeutic statistics, but also to a large number of other problems in probability calculus.

Page 956

Supplemental Notes.

---

1) When dealing with tasks concerning the so-called posterior probability, it is not uncommon to be under the illusion that one is approaching the observations without any preconditions. In reality, this is never the case and naturally cannot be the case. But the nature of the a priori assumptions has a significant influence on the results. Instead of the presupposition assumed in the text, which has usually been made tacitly for similar tasks up to now, other assumptions could be made; for example, it could be true for certain special cases if one were to presuppose that every single ball in the urn could be as good as black or white; and then, a priori, the different ratios would have a very extraordinarily different probability; they would behave like binomial coefficients.

2) From equations A and B on page 946 one obtains, for $n = \infty$ with mathematical rigour, the following four fundamental formulas, in which the abbreviation

$$\frac{(a+b+1)!}{a!\,b!} = \nu \quad \text{and} \quad \frac{(p+q+1)!}{p!\,q!} = \mu \quad \text{is used.}$$

$$(1) \qquad P = \nu \cdot \mu \cdot \int_0^1 \int_0^1 x^{a+p+1}(1-x)^b y^p \cdot (1-xy)^q dxdy$$

$$(2) \qquad 1-P = \nu \cdot \mu \cdot \int_0^1 \int_0^1 x^{b+q+1}(1-x)^a y^q \cdot (1-xy)^p dxdy$$

$$(3) \qquad P = \nu \cdot \mu \cdot \int_0^1 \int_0^1 x^{q+p+1}(1-x)^b y^b \cdot (1-xy)^a dxdy$$

$$(4) \qquad 1-P = \nu \cdot \mu \cdot \int_0^1 \int_0^1 x^{a+p+1}(1-x)^q y^a \cdot (1-xy)^b dxdy$$

The derivation of the formulas A and B given in the text is preferably intended for the understanding of those not familiar with higher mathematics. I will shortly give a derivation of the fundamental formulas in which the form corresponds more to that used in such discussions.

From the first urn a black and b white balls were drawn, from the second p black and q white balls, and $\frac{p}{p+q} < \frac{a}{a+b}$. — What is the probability that for the second urn the quotient of the number of black balls it contains by the total number is smaller than for the first?

According to the results of the drawings from the first urn, there is a probability that the quotient in question lies between the limits ρ and ρ' for the first urn:

Page 957

$$= \frac{\int_\rho^{\rho'} x^a(1-x)^b dx}{\int_0^1 x^a(1-x)^b dx} = \frac{(a+b+1)!}{a!\,b!} \int_\rho^{\rho'} x^a(1-x)^b dx.$$

And likewise, it is for the second urn according to the result of the drawings from the same.

As abbreviation, it will be used:

$$\frac{(a+b+1)!}{a!\,b!} = \nu, \quad \frac{(p+q+1)!}{p!\,q!} = \mu, \quad x^a(1-x)^b = f(x), \quad x^p(1-x)^q = \varphi(x).$$

$$\text{Then} \quad \nu \cdot \int_0^1 f(x)dx = \mu \int_0^1 \varphi(x)dx = 1.$$

If we apply the values of $\nu \cdot f(x)$ and $\mu \cdot \varphi(x)$ as ordinates to the axis of x vertically, the quotient of the black balls by the total number is smaller for the second urn than for the first, if the true value of the first urn is closer to zero in the figure than the corresponding value for the first urn. There is no other condition, and the true values of these quotients may fall on any point of the abscissa. However, the individual places have different probabilities according to the result of the drawings.

We divide the abscissa from $x = 0$ to $x = 1$ into numerous equal parts, each of which is $= \delta$.

$$\text{(5)} \qquad \text{Then} \quad P = \nu \cdot \mu \cdot \sum_{k=1}^{k=\frac{1}{\delta}} \left\{ \int_{(k-1)\delta}^{k\delta} f(x)dx \cdot \int_{0}^{(k-1)\delta} \varphi(x)dx \right\}$$

$$\text{(6)} \qquad 1 - P = \nu \cdot \mu \cdot \sum_{k=1}^{k=\frac{1}{\delta}} \left\{ \int_{(k-1)\delta}^{k\delta} f(x)dx \cdot \int_{(k-1)\delta}^{1} \varphi(x)dx \right\}$$

Two other formulas can be derived in a similar way by first performing the division of the abscissa for $\mu \cdot \varphi(x)$.

The smaller δ is taken, the more accurate the expressions are, and they become accurate to any degree when δ becomes infinitely small. In this latter case, except for infinitely small second-order sizes

$$\int_{(k-1)\delta}^{k\delta} f(x)dx = \delta \cdot f(k\delta);$$

is obtained by substitution of new variables:

$$\begin{aligned} P &= \nu \cdot \mu \cdot \int_{y=0}^{y=1} \int_{x=0}^{x=y} f(y)\varphi(x)dydx \\ &= \nu \cdot \mu \cdot \int_{0}^{1} \int_{0}^{1} x^{a+p+1}(1-x)^b \cdot y^p(1-xy)^q dxdy, \end{aligned}$$

i.e. formula (1), and in analogous manner the three other fundamental formulas.

Even in several other ways, the same formulas can be derived with the help of relevant considerations.

It can be seen from formulas (1) to (4), and can also be shown directly, that the value of the formula is not changed if a is swapped with q and b with p; further, that from each formula for P a formula for $1 - P$ and vice versa can be derived; by Page 958

either interchanging a with b and p with q,

or interchanging a with p and b with q.

Thus, with one of these formulas the other three formulas are given at the same time; and since this also applies to all formulas still to be derived (of which sometimes two become identical), I will, for the sake of simplicity, always give only one of the four formulas belonging together.

The integration of equations (1) to (4) is only possible by developing the factor consisting of a power of $(1 - xy)$, possibly with some transformation, into a series. In this way many different formulas are obtained, of which I will mention only a few. One obtains for example

$$(7) \quad 1 - P = \frac{(a+b+1)!\,(p+q+1)!)}{(a+b+q+2)!\,b!}\left\{1 + \frac{(a+1)(q+1)}{1\cdot(a+b+q+3)} + \right.$$
$$+ \frac{(a+1)(a+2)\cdot(q+1)(q+2)}{1\cdot 2\cdot(a+b+q+3)(a+b+q+4)} + \dots$$
$$\left. \dots + \frac{(a+1)(a+2)\dots(a+p)\times(q+1)(q+2)\dots(q+p)}{1\cdot 2\cdot 3\dots p\times(a+b+q+3)(a+b+q+4)\dots(a+b+q+p+2)}\right\}$$

This series is the beginning of a hypergeometric series but is broken off after $p+1$ terms. The complete series in combination with the factor consisting of factorials would be $=1$. Therefore, the rest of the series gives a value for P.

$$(8) \quad P = \frac{(a+b+1)!\,(p+q+1)!\,(a+p+1)!\,(b+q+1)!)}{a!\,b!\,(p+1)!\,q!\,(a+b+p+q+3)!} \times$$
$$\times\left\{1 + \frac{(a+p+2)(p+q+2)}{(p+2)(a+b+p+q+4)} + \right.$$
$$\left. + \frac{(a+p+2)(a+p+3)\cdot(p+q+2)(p+q+3)}{(p+2)(p+3)(a+b+p+q+4)(a+b+p+q+5)} \underset{\textit{in infin.}}{+++}\right\}$$

Using a transformation given by K u m m e r (Crelle's Journal, volume 15, p. 172), one obtains from formula (8) the formulas I. and II. on page 946, which are particularly convenient for practical use.

The following formulas, which can be obtained from the same double integral, are also quite useful for calculation, although somewhat less convenient:

$$(9) \quad 1 - P = \frac{(a+b+1)!\,(b+q+1)!\,(a+p)!\,(p+q)!)}{a!\,b!\,p!\,q!\,(a+b+p+q+2)!} \times$$
$$\times\left\{1 + \frac{p(a+b+p+q+2)}{(a+p)(p+q)} + \right.$$
$$\left. + \frac{p(p-1)\cdot(a+b+p+q+2)(a+b+p+q+1)}{(a+p)(a+p-1)(p+q)(p+q-1)} +++\right\}$$

$$(10) \quad 1 - P = \frac{(a+b+1)!\,(p+q+1)!\,(a+p)!\,(b+q)!)}{a!\,b!\,p!\,(q+1)!\,(a+b+p+q+2)!} \times$$
$$\times\left\{1 + \frac{p(b+q+2)}{(a+p)(q+2)} + \right.$$
$$\left. + \frac{p(p-1)\cdot(b+q+2)(b+q+3)}{(a+p)(a+p-1)(q+2)(q+3)} +++\right\}$$

Less useful are the series where the signs of the terms change.

Each of the formulas can be transformed into any of the others, even without going back to the original integral. When applied to numerical examples, the different formulas produce exactly the same results, which is obvious.

I also note that I presented my formulas to the professor of physics Mr. Hagenbach-Bischoff and the professor of mathematics Mr. Kinkelin in Basle, and that they confirmed the correctness of these formulas by arriving at identical results, partly by other methods.

Logarithms of the Factorials.

Page 959 bis 962

[Editor's note: Four pages of tables omitted. The tables give for all $\alpha = 0, 1, 2, \ldots, 1200$ the logarithm to base 10 of the factorial $\alpha!$ to 5 (for $\alpha < 450$) respectively 4 (for $\alpha \geq 450$) decimal places.]