ZUR TRANSFUSIONSFRAGE

Besprechung der Ponfick'schen Arbeit: Experimentelle Beiträge zur Lehre von der Transfusion.

By: DR. BRUBERGER

A TRANSLATION BY PHIL LEAROYD

A copy of this paper titled 'On the transfusion question - Discussion of Ponfick's work: Experimental contributions to the study of transfusion' by Dr. Bruberger, published in 1875 in the journal *Deutsche Militärärztliche Zeitschrift* (Vol. 4, No. 4, Pages 210-216), can be read or downloaded from the following site:

https://books.google.co.uk/books/about/Deutsche_milit%C3%A4r%C3%A4rztliche_Zeitschrift.html?id=mdttlRPh9xQC&redir_esc=y

This paper is published under the publisher's general heading of 'Reports and Reviews', and as the sub-heading identifies, it is essentially a critical appraisal of Dr. Ponfick's paper, which has the following reference:

Ponfick, E., Bamberg, J. (1875) Experimentelle beiträge zur lehre von der transfusion. [Experimental contributions to the theory of transfusion] *Archiv f. pathol. Anat.* [*Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medicin*], 62, 3, 273-335, which can be read or downloaded from the following site:

https://books.google.co.uk/books?id=whRQocAYfzEC&printsec=frontcover&source=gbs_ge_summary_r&cad=0#v=onepage&q&f=false

Note: Ponfick published an earlier paper about the fate of animal red cells in the human circulation, published in 1874, titled: Ueber die wandlungen des lammblutes innerhalb des menschlichen organismus: Ein beitrag zur lehre von der transfusion. [About the changes of lamb's blood within the human body: A contribution to the study of transfusion] *Berliner Klinische Wochenschrift*, 11, 28, 333-336, which can be read or downloaded from the following site:

https://babel.hathitrust.org/cgi/pt?id=mdp.39015049764577&view=1up&seq=343

I have produced a translation of this paper from German into English to enable its content to be appreciated by a wider audience. Whilst I am aware that instantaneous computer generated translation is available, this process struggles with accurately reading the original text and interpreting specialist terminology, as well as producing a 'colloquial style' not always representative of the original text. In addition, an 'automatic translation' may either purposely or inadvertently alter the wording to 'make it read better' but in doing so there has to be an element of interpretation involving something on the lines of 'I believe that this is what the author is actually trying to say'. I want to avoid that as much as possible and try to present what the author actually wrote and as a result the reader may find that the English text does not 'flow' as well as it could. Although I have taken great care in accurately identifying the original text and producing a true representative translation of the author's original wording I cannot guarantee that this work does not contain 'translational errors' and the reader is recommended to check specific details against the original text.

Note: Dr. Ponfick is frequently referred to in this paper only by the capital letter P. The paragraph settings and general layout of the paper have been maintained within the translation. ‘Per mille’, identified in the text, has been translated to be ‘per thousand’.

ON THE TRANSFUSION QUESTION
DISCUSSION OF PONFICK'S WORK: EXPERIMENTAL CONTRIBUTIONS TO THE STUDY OF TRANSFUSION.
Virchow’s Archiv Vol. 62

By: DR. BRUBERGER

The theory of transfusion has been brought to a certain conclusion in most of its main questions by Ponfick's classic work; the great importance of the matter requires a more detailed discussion of P.'s work and justifies the attempt to derive some useful applications for humans from the animal experiment.

Let us try to reproduce the results of P.'s work by following the investigations step by step.

In every transfer of blood, two series of moments must be distinguished: first, the mechanical effect is to be considered, which is caused by a considerable increase in the amount of fluid filling the vascular system, and then the chemical effect, in that special qualities of the blood supplied become effective in turn. The mechanical effect is first discussed by solving the question: what are the consequences of a sudden increase in the quantity of fluid contained in the vascular system? We already know from Berzelius, Stockvis and Lehmann that after injections of artificial serum (1 percent saline water with chicken egg white) protein, and interestingly the foreign albumin substance, appears in the urine, but that these solutions are well tolerated. P. now increased the amount of fluid in the vascular system by exactly half of the originally existing blood quantity using such an artificial serum. The symptoms after this procedure are limited to moderate oppression, copious defecation and peculiarities of urinary secretion. The quantity of the latter does not increase at all or only insignificantly in a 24-hour period, which is in contradiction with the abstractly predisposed plethora or the increased tension in the aortic system, the specific weight shows a significant decrease from 1045 to 1010-1025, although the food intake had not undergone any reduction, with alkaline reaction and strong protein content (egg protein) after just two hours. The situation was different if natural serum (very carefully prepared from lamb's blood) was used instead of the artificial one; even after the amount of fluid in the vascular system increased much further, there was no increase in the amount of urine, the specific weight is within normal limits, the reaction is clearly acidic and there is never even a trace of protein to be detected. This shows that the albuminuria after injection of artificial serum is not the result of the increase in blood pressure, which has never been precisely proven, but rather the result of the peculiar chemical constitution of the chicken egg white. What is extremely interesting is the agreement of P.'s results in this respect with those of Worm Müller, who, starting from completely different points of view, directly measured the pressure in the vascular system after increasing its contents and came to the conclusion that the vascular system has an a priori unimagined capacity for accommodation with regard to the pressure conditions against different degrees of filling.

With the plethora as such, of course, comes the deplethoric bloodletting, i.e. the bloodletting, which only has the purpose of balancing the abstractly supported plethora; a person choking on carbon oxide will still be allowed to have a blood-letting procedure and fresh blood can be substituted for the draining, poisoned blood.

After this mechanical mode of action of blood transfer, which is recognized to be relatively innocent, the chemical qualities inherent in the blood as such are examined. First of all, the question of how the own blood of the same individual and the blood of another individual of

the same species works is decided after various experiments to the effect that: dog blood is just as harmless to the dog as those liquids (natural serum) that are free of cellular elements but then it was found that the blood of different individuals of the same species was completely equivalent.

The question is different: does the blood of another animal species have the same effect as that of the same species? Even if the amount of something foreign injected into a dog, e.g. lamb's blood has not yet reached half of the previously transfused, similar blood, severe dyspnoea, collapse and death occur in rapid succession with complete cessation of the secretory activity of the kidneys; it is irrelevant whether the foreign blood was defibrinated or not defibrinated. This gives rise to the idea, first expressed by Prévost and Dumas, of the toxicity of any other type of blood. P. decides the question of whether each different type of blood is harmful by exchanging the blood of different domestic animals, but always testing the effectiveness of the blood of each subsequent type on the dog in a large series of experiments. The blood of lamb, cat, calf, pig, rabbit, chicken, duck and even human blood is then used in dogs. All types of blood agree with each other in that even transfused in small doses they cause blood urine, and in larger doses they cause severe, general disorders and death. The statement about the toxicity of different types of blood can therefore be generalized in the broadest sense. After the dose at which the lethal effect of the different types of blood begins has been established, the anatomical changes in which the deleterious effect is expressed are discussed. Haemorrhages and infarctions in the eye and in various other places, haemorrhagic erosions in the tractus intestinalis are of accidental and secondary importance; according to the consistent results of all P.'s observations, the condition of the kidneys is of outstanding importance: both in fatal and in minor cases, in cases interrupted by intentional killing, both kidneys are found to be very swollen, their tissue often appears noticeably pale, of a dirty gray-brown colour, in the peculiar brownish ground mass one can see numerous, sharply marked spots and streaks of a red-brown to dark coffee-brown colour, like the specks in haemorrhagic nephritis blasted in. On average, these spots in the cortex appear in large numbers. On closer inspection, one can distinguish brown and red stripes in the medullary cones, alternating with great regularity and extending radially towards the papilla. Pressure on the papillae drains a fluid that is sometimes black-brown, sometimes lighter. Microscopic examination shows that the brown spots and stripes in the cortex and the radial lines in the medullary substance are caused by one and the same change, by the presence of solid plugs in the lumen of twisted and straight tubules. The colour of these cylinders is initially that of blood cells, only later do they become brownish and darker; but at no time is it really based on the presence of coloured cells within the tubules, but on a uniform imbibition of a base, be it hyaline or granular, with a haemoglobin-like matter.

In this kidney affection P. finds the substrate for the serious disturbances during life, and he holds it responsible for the fatal outcome. He finds proof for this assertion in the fact that the severity of the course, the onset and the suddenness of death are in a certain constant relationship to the intensity of the kidney disease, and this in turn to the amount of blood transfused. As far as the nature of the haematuria after transfusion of dissimilar blood is concerned, this is not actual haematuria; the microscope is never able to detect a trace of a red blood cell in this ruby-red to varnish-coloured urine, neither whole nor stroma, but the spectroscope shows that this urine often contains an extraordinarily large amount of haemoglobin. In this case it is not haematuria, but haemoglobinuria. The average time of appearance of this haemoglobinuria is between 30-60 minutes after the start of the transfusion. The only physical component that can be found in the urine are brownish cylinders suspended sometimes sparingly, sometimes more abundantly, the substance of which is either completely hyaline or granular and the colour of which is uniformly yellow-brown; according to calibre, etc., they correspond to the grafts described from the kidney. As soon as the haemoglobin coloration occurs, the reaction of the urine becomes alkaline; the specific weight drops to an extremely low figure, a sign of the very remarkable lack of solid components in the urine.

The study of the dose of foreign blood necessary to produce haemoglobinuria shows that this latter is a fine reagent for determining the degree of toxicity of the individual blood species relative to one another. For example, haemoglobinuria occurs in dogs after a lamb blood transfusion of 1.2-1.25 per mille of body weight.

When discussing the question of where the haemoglobin that appears in the urine comes from, one can assume without a doubt that red blood cells have perished; it remains questionable whether those affected by the transition are those of the receiving animal itself or those of the donating animal, or finally those of both. Since we already know that lamb's blood serum is a safe medium for dog blood cells, the blood cells of the donating animal must be the ones that perish. The process of the destruction of the foreign blood corpuscles can be characterized firstly as a crumbling and then as a leaching of the haemoglobin of the whole cells without changing their configuration. If we now know that haemoglobinuria is derived from a dissolution of red blood cells in the transfused, dissimilar blood, it remains to be explained why such different quantities of different types are required to produce the symptom, or in other words, it remains to be explained, what becomes of the small doses of dissimilar blood, which are not sufficient to produce haemoglobinuria. Here P.'s experiments lead us to the view that we must assume certain devices in the body through whose intervention small amounts of haemoglobin are quickly converted without leaving us a trace - even if only in their dross - that thus up to a certain point there is a state of latency.

The conclusion of the work is the “Attempt at a theory of the toxicity of foreign blood.” Based on the investigations outlined above, it can be legitimately claimed that transfused, dissimilar blood is soon subject to dissolution, in which all of its coloured elements probably perish; with this, free haemoglobin gets into the plasma and all tissues, perhaps its presence in the bloodstream causes a variety of disorders in itself, but the haemoglobin does not stay in the bloodstream for long, a small part is converted into us through the circulation itself, the largest part reaches the kidneys, which are responsible for eliminating it. If the amount to be eliminated is not too large, this process can take place without too much difficulty. This performance of the kidneys is associated with anatomically well-characterized changes. In a very short space of time, such copious exudations can occur into the lumens of the urinary tubules that, under certain circumstances, any further excretion becomes impossible. This secretory insufficiency of the kidney is the beginning of the end. If the dose was lower, blockages of urinary tubules remained limited; between these tolerably benign cases and those that are quickly fatal, there are other cases in which an indecisive struggle between driving and inhibiting forces takes place in the kidney, often for a long time; here a strong diuresis can decide the victory of life, the excretion of haemoglobin can be completed. The kidney change must therefore be assigned a dominant role in an attempt to explain the toxicity of dissimilar blood. Many analogies cannot be mistaken between the overall picture of animals transfused with lethal or near lethal doses and the uremic symptom complex.

The answer to the question: "Whether similar or dissimilar blood is preferable for transfusion" is beyond the scope of the results, of P.'s work; at most, the question that needs to be discussed is: "Can dissimilar blood be effective at all?" The answer is: if dissimilar blood is to prove useful, it can only do so by virtue of its plasma and its colourless elements. Can similar blood be beneficial? After transfusion of the latter, haemoglobinuria never occurs, we can therefore conclude that when transfusion of both whole and defibrinated blood of the same type, the vast majority of blood cells remain unchanged in the foreign organism, so there remains no doubt that this is the case. The disorders that follow severe blood loss can be counteracted most effectively by the supply of peculiar blood, so that with the help of this healing remedy one is able to restore and maintain life and health.

At the end of his work, P. expresses the wish that it could be judged purely from within and for itself and he himself does not wish to immediately draw conclusions for humans from the results determined for animals - certainly! - but the heavy work requires every doctor who has transfused with similar and dissimilar blood to once again critically review the series of his experiences again; his attention is drawn to conditions to which he has previously paid little attention - and there seems to be no doubt in my mind that the animal blood transfusion, the praises of which Gesellius and Hasse sung so energetically in the discussion of the last

two years, Ponfick's work is the swan song forever sung. I myself was prompted to look again through the notes about the animal blood transfusions I had seen - these are the cases published by E. Küster (v. Langenbeck's Arch. XVII.), especially the information relating to kidney activity.

These are 14 animal blood transfusions that were carried out on 8 patients. I can only refer to these case histories contained in Sexton's work, because the transfusions carried out after this work was published have not been published, but I note that the later ones also did not give different results. Of the 8 case histories, one (case 6 from Sexton) must be ignored because information about renal secretion is missing; in another (case 1 amyloid of the kidneys) there was already severe kidney disease with albuminuria before the operation, so here the results of observation after transfusion appear clouded. In the remaining 6 cases, which were made on patients in whom the urine was normal before the operation, we see no albuminuria and no haemoglobinuria occurring after the transfusion twice (cases 2 and 3), albuminuria and bloody red haemoglobin staining are recorded three times (cases 4, 5 and 7), and once there was anuria with death soon following (case 8). I now calculated how much mutton blood the patients had received per mille of their body weight and came to the result: the haemoglobin-producing ability of mutton blood for humans is around 2.5 per mille of body weight, in such a way that haemoglobinuria certainly occurs when transfusions with this or a larger quantity, but also at lower doses, e.g. 1.9 per mille, can also occur; for doses lower than 1.9 per mille there is latency in the sense used by Ponfick.

We see from this that the preponderant factor in P.'s theory of the toxicity of foreign blood also applies to humans in the same way as to animals. It must be briefly mentioned here that haemoglobinuria in humans is not a pure haematuria, but a partial haematuria; blood cells are often actually seen in the urine and then in a human kidney after a lamb's blood transfusion, solid grafts analogous to Ponfick's are found in the urinary tubules, which - according to Orth’s confirmation - consisted of un-destroyed red blood cells.

As far as the theory itself is concerned, there is no doubt that the chain of phenomena as described by P., leaching of the blood cells, blockage of the urinary tubules by the leached haemoglobin, etc., the most dangerous cause of the toxicity of foreign blood, the theory does not fully explain the phenomena during the operation in humans, I believe that one still has Traube’s hypothesis of acute carbonic acid intoxication to explain the cyanosis and dyspnoea immediately after the start of the operation in humans, the hypothesis is supported by the fact that there are now three cases of animal blood transfusion known in the Augusta Hospital in which the transfusion was only started after the animal had been rendered apneic by excess oxygen supply (artificial respiration), and that in all of these three cases the cyanosis and dyspnoea did not occur.

Now the question remains, what is the justification for animal blood transfusions in humans in the future? I used to believe that the justification was unconditionally proven (cf. my work in this journal 1874, No. 10, page 526) by the successes recorded in the literature, even if they were often only temporary favourable. I did not yet know about dangerous haemoglobinuria at the time and only saw the dangerous symptoms quickly pass during the operation. To answer this, here is a small calculation example: if we assume the weight of the person in need of blood to be 100 pounds and calculate the blood mass according to the ratio of 1:13 of the body weight, we then only transfuse 100 cc. blood, this is already 2.0 per mille of foreign blood, and we are not even allowed to risk this dose, because after 1.9 per mille, as I showed above, haemoglobinuria can occur, after 2.5 per mille it will definitely occur. In order to operate safely, we would only have to transfuse about half, 50 cc. for this dose there would be latency for the haemoglobin; what do this 50 cc. mean for an anaemic person, at most it would mean that we have incorporated some protein-rich nutritional fluid into the blood. This is probably why the favourable results after lamb's blood transfusion are reduced compared to the danger in which we have placed the patient.