REVIEW ARTICLE

Renal Disease and Transplantation Forum
2023, vol. 16, no. 2, 93–100

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/RDATF.97780

VIA MEDICA

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Bloodletting. Medical dead end or an incessant inspiration for modern nephrology? Part 2.

ABSTRACT

Nowadays bloodletting is used as a treatment of polycythemia and hemochromatosis. However, for centuries it was used to treat numerous other disorders, mostly without any justification. The idea of bloodletting was to remove the excess of one of the "humors" — the blood. Indeed, for men with overproduction of red blood cells, iron overload, porphyria, or gout, phlebotomy could lead to an improvement in the patient's state. Bloodletting has now been replaced by drugs and extracorporeal blood purification methods. This manuscript presents an overview of the history and physiological basis of bloodletting.

Renal Disease and Transplantation Forum 2023, vol. 16, no. 3, 93–100

Key words: bloodletting, plasmapheresis, polycythemia, hemochromatosis, porphyria, extracorporeal blood purification methods

INTRODUCTION

In the first article devoted to bloodletting, apart from a historical perspective, the use of bloodletting as a method of removing water from the body was discussed [1–3]. However, apart from overhydration, it has also been used in other indications throughout history. Currently, bloodletting is a recognized form of therapy for polycythemia and hemochromatosis [2].

For many years, treatment with leeches or "bloody" cupping was also common and used to treat many diseases [4, 5]. Both of these methods are still widely used in some cultures [6], and leech therapy for selected indications has even gained the approval of the ever-demanding US Food and Drug Administration (FDA) [7].

HISTORICAL OVERVIEW — THE GOLDEN AGE OF BLOODLETTING

While the origins of bloodletting have been lost to time, the period when it flourished is well-documented. Until the 16th century, the humoral theory of Hippocrates and bloodletting were the indisputable foundations of medicine [8]. This changed with the advent of research into anatomy, physiology, and biochemistry, but also thanks to the observations of medical practitioners and the first clinical trials. From the moment William Havey (1578–1657) described the circulation of blood [3], the humoral theory began to crumble.

However, the tendency to use bloodletting lasted longer than the belief in the infallibility of Hippocrates. In the 18th century, the theory of disease according to the ideas of Brown and Broussais was proposed in place of the humoral theory. According to this theory, diseases were the result of altered excitability of the human body. Excessive excitability, or "sthenia" was treated mainly with... bloodletting. Patients with reduced excitability, or "asthenia", were spared the bloodletting [9]. Up until the 19th century, phlebotomy was a commonly held belief and habit among doctors and patients. Many fathers of medicine still favored bloodletting in the 18th and 19th centuries. Sir William Osler [1850–1919) recommended bloodletting for the treatment of pneumonia. The power of authority meant that this recommendation survived in his textbook until the 1942 edition [8]!

The popularity of phlebotomy reached its peak in the 18th and 19th centuries, but that was

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also a time when doctors started to ask themselves "To bleed, or not to bleed". This was the title of a 113-page (!) article from 1854 by Dr. Pliny Earle, who presented differing opinions on the efficacy of bloodletting in treating mental illnesses. It was the start of a debate and, fortunately, the beginning of the end of this bloody therapy in psychiatry [10]. However, this is not the end of the relationship between bloodletting and psychiatry. In 1967, Lasthénie de Ferjol syndrome was described, i.e. iron deficiency anemia associated with repeated bloodlettings performed by patients themselves. Nowadays this rare disorder is classified as a factitious disorder [11], similarly to the well-known Münchhausen syndrome [12].

REMOVAL OF EXCESS RED BLOOD CELLS

Red blood cells constitute approximately 44% of blood [13]. People were unaware of their existence for millennia, but red was invariably associated with blood. Excessive facial skin redness (plethoric face) was treated as an excess (plethora) of blood that had to be removed in order to restore the balance between the four fluids — "humors". Facial redness may have been due to an excess of red blood cells, but it is also typical for obese people with hypertension, whom bloodletting actually helped [14].

We now know that excess blood resulting from a significant increase in the number of red blood cells (polycythemia) is dangerous and that phlebotomy is an effective treatment [15]. Symptoms of polycythemia, such as shortness of breath, sleep disturbances, headaches, or tinnitus, are classic indications of bloodletting [15]. Phlebotomy is effective in primary polycythemia but is also used in secondary polycythemia (e.g. after a kidney transplant, in chronic lung diseases, in people living at high altitudes) [15]. It is a recognized method of treatment, although it is associated with complications such as increased risk of thrombosis and iron deficiency [2].

REMOVAL OF EXCESS IRON

Red blood cells are the main carriers of iron. As much as 65% of iron in the body is bound to hemoglobin [2], therefore removing red blood cells is the best method of removing excess iron from the body. Hemochromatosis, a disease involving excessive accumulation of iron, is a widely recognized indication for phlebotomy [16]. Hereditary hemochromatosis is quite common — 0.5% of the population is homozygous for the mutated HFE gene and 10% of the general population is heterozygous [17].

In everyday medical practice, filled with anticoagulants and antiplatelet drugs, we often struggle with the problem of bleeding and, consequently, iron deficiency. Maybe that is why we forget that the human body has practically no way to remove excess iron. It is not excreted in urine, although it can be excreted in bile, but it is then quickly reabsorbed in the gastrointestinal tract [17]. And this is the absorption of iron from the gastrointestinal tract that is physiologically the only way to regulate the body's iron metabolism. Especially the body of a modern, non-fighting man has few opportunities to remove iron [17].

As in polycythemia, bloodletting remains the basis of treatment for hemochromatosis. Typically, 500 ml of blood is removed every week, and then several times a year. The number and frequency of treatment depends on the levels of ferritin and hemoglobin. Another treatment method, often used in conjunction with phlebotomy, is chelation therapy using deferoxamine, where 1 g of deferoxamine binds 85 mg of iron (for comparison, 500 ml of blood removes 250 mg of iron) [2, 17].

OTHER INDICATIONS FOR BLOODLETTING

Bloodletting is also used in other diseases, in which excess iron is harmful. These are porphyria cutanea tarda (PCT) [2, 8, 16] and also gout [17].

Why gout? It has been observed that menstruating women rarely get gout attacks, similarly to men who regularly donate blood [17], On the other hand, people who have excess iron, i.e. mainly those who have a mutation in the HFE gene, and who do not lose blood, experience gout attacks more frequently. This is probably because iron-saturated transferrin increases xanthine oxidase activity [17]. This is why podagra, gonagra, chiragra, omagra, and rachidagra can occur in bronze diabetes.

A STEP FURTHER — FROM BLOODLETTING TO EXCHANGE TRANSFUSIONS

In case of bloodletting, if the medics got carried away or if the disease was "resistant" to a single treatment, therapy was often continued until the patient was finally exsanguinated. One of the patients killed in this manner was George Washington, who had approximately 2500 mL of blood removed due to symptoms of an infection [18]. One of the doctors who treated the dying president considered a trans-

fusion of sheep's blood [18], long before the modern science of transfusion was born.

Many years later, in 1901, Karl Landsteiner observed the phenomenon of agglutination of red blood cells and identified three blood types. We owe the description of the inheritance of blood groups and their classification as O, A, B, and AB to the work of Ludwik Hirszfeld and Emil von Dungern (1907-1911). These were the beginnings of the science of blood groups, which was the impetus for the development of transfusion medicine, and in 1937 the first hospital blood bank was established in Chicago [19].

The modern procedure of phlebotomy in hemochromatosis patients gave rise to a question — if we remove healthy blood from a person who has too much of it, maybe we could transfuse it to other patients. That is indeed what is currently happening in Polish blood donation centers [20]. This is one example of the link between bloodletting and its younger sibling - transfusion medicine. Another example is the use of autotransfusion as a form of doping by athletes [21].

The history of transfusion medicine is a topic for a separate article, but exchange transfusions are a point of interest for nephrologists. Because if "bad" blood could be removed and replaced with "good" blood, the combination of the two procedures became possible. This method was used to treat many disorders, including uremia, although some of the difficulties were obvious: *„It is obvious that replacement of uraemic patient's blood by fresh donor blood will remove protein breakdown products. The latter are, however, distributed throughout the extra-cellular water if not throughout the entire body water, and an exchange transfusion to be effective will require a very large volume of donor blood, of the order of 6o or more pints"* [22].

In his 1960 textbook "Kidney diseases", the father of Gdańsk nephrology, Professor Jakub Penson, wrote: *"Non-renal excretion as a method of treating acute renal failure. (...) The following methods of blood purification are known so far: a. Exchange blood transfusion consists of draining 5-6 liters of blood and administering the same amount of preserved blood into the second vein; thus approximately 70-80% of the blood is renewed. However, it is a very expensive method, because the blood exchange must be repeated several times. In addition, the obtained results are much worse than compared to an artificial kidney. Four patients underwent an exchange transfusion in the clinic. However, it is difficult to draw conclusions about the value of this method on the basis of these few cases (...). Today, however, this method is rarely used, because using the artificial kidney yields more reliable and better results. b. Peritoneal dialysis (...), c. Artificial kidney (...)" [23].*

Even with today's knowledge, technical and laboratory capabilities, it is difficult to imagine what an exchange transfusion treatment in a patient with severe uremia could look like. The pioneer doctors of nephrology were truly heroic. But does this heroism come as a surprise? Professor Jakub Penson, like the aforementioned professor Ludwik Hirszfeld, experienced the nightmare of the Warsaw Ghetto during the war.

▸▸ The pioneer doctors of nephrology were truly heroic. ◂◂

INSPIRATION — HOW TO GET RID OF THE DISEASE WITHOUT LOSING HEALTH?

Bloodletting can also remove an abnormal or excess blood component but with the loss of other valuable blood components. Exchange transfusion allows for the replacement of previously lost blood components, but the cost and technical issues limit this treatment. The progress of knowledge has made it possible to selectively remove blood components. However, these components had to be first identified and separated.

Blood outside of the body changes its appearance; it ceases to be a uniform liquid. A clot forms and the remaining clear fluid is called serum. If an anticoagulant is added to the collected blood and then left for a long time, or the sample is subjected to centrifugation, the blood cells separate from the plasma. Between the red layer of erythrocytes and the plasma, a light, narrow layer can be observed — a buffy coat composed of leukocytes and platelets. These simple experiments are now commonplace in every laboratory in the world [9, 13].

▸▸ The human body has virtually no ability to remove excess iron. ◂◂

It all began at the end of the 19th century. In 1897, Edmund Biernacki published the results of research on spontaneous sedimentation of red blood cells ("discs" in the original) in Gazeta Lekarska and Deutsche Medizinische Wochenschrift. To this day, the erythrocyte sedimentation rate (ESR, or odczyn Biernackiego, OB, in Polish) is a basic test, and one of the most sensitive and least specific laboratory tests [9].

Since blood can be separated into two main parts outside the body, it is possible to imagine that one part of the blood is perma-

Interestingly, clinical trials on the efficacy of bloodletting in the treatment of gout or hypertension are still being conducted.

nently removed and the other is given back to the patient. The removal of red blood cells is called erythrocytapheresis, removal of serum is called plasmapheresis (from Latin aphaeresis, Greek ἀφαίρεσις, aphaíresis, words meaning to take away).

This type of treatment can be performed with two intentions. Red blood cells can be removed because their excess is harmful to the patient, They can also be collected for a later transfusion to another patient. Similarly, plasma is removed because it contains harmful substances, or on the contrary, when it contains substances that can help others. In 2020 and 2021, the treatment of severe SARS-CoV-2 infections with convalescent plasma was extremely popular, and plasma donation was encouraged by the Ministry of Health on their official website. This happened despite the lack of evidence of the effectiveness of this treatment [24]. The debate around this therapy is still ongoing [25].

ERYTHROCYTAPHERESIS

Therapeutic erythrocytapheresis (TEA) is an alternative to phlebotomy. Similarly to bloodletting, this method is used in polycythemia and hemochromatosis. This is a more expensive method but preferred by patients, causing fewer hemodynamic disorders and preserving important blood components [2, 15]. Methods based on the separation of individual blood components by centrifugation are now indispensable in hematology and transfusion medicine. Leukocytapheresis and trombocytapheresis are also utilized in these fields [19].

PLASMAPHERESIS

Plasmapheresis is the process of plasma removal with a simultaneous transfusion of crystalloids, an albumin solution, or plasma of a healthy person. The concept of this procedure is reflected in the titles of the first articles in which the method was described in 1914: "Plasma removal with the return of corpuscles (plasmapheresis)" by Abel and "Washing the blood outside the organism and the survival of the red corpuscles" by Jurewicz [19].

Plasmapheresis, similarly to bloodletting, has been used to treat many diseases. Over time, its use has been limited to those diseases in which the component to be removed is found only or mainly in plasma, and has a fairly long half-life. It cannot be a kidney replacement therapy, as many uremic toxins have a volume of distribution much larger than the volume of blood. Currently, the list of indications for plasmapheresis is very precise and includes selected rheumatic, neurological, hematological, and nephrological diseases [19].

Over the years, plasmapheresis has undergone a metamorphosis in many indications — this is how LDL apheresis was created, and used in patients with familial hypercholesterolemia. The development of technology has made it possible to effectively remove selected components from the blood by using various types of filters, adsorption columns, dialysis, and substitution fluids. These methods have "technically" little to do with bloodletting, but the idea of removing "bad" blood has persisted.

RELATED THERAPIES

Bloodletting was usually done through a vein incision (venesection, phlebotomy), less often an artery (arteriotomy). Blood could also be removed by using leeches (leeching) or bloody, wet cupping. In these two methods, blood was sucked out of the skin cut by the leech or the medic.

Leech therapy is at least as old as classic bloodletting. It was described by Theocritus, Nicander, Horace, and Galen in antiquity [4, 8, 19]. Leeches were applied mainly to swollen, reddened places, around varicose veins, and localized inflammatory changes. This was due to the desire to remove excess blood from the place where it accumulated, after all, redness (rubor) is one of the main symptoms of inflammation [26]. The advantage of the treatment was that leeches could be applied to places where a lancet incision was difficult: around the mouth, eyes, nose, anus, or vagina. Performing bloodletting with leeches or cupping usually required less expertise on the part of the practitioner. However, there were exceptions to the rule. Some specialists applied leeches to the tonsils, inside the vagina or anus, and these treatments required dexterity and determination. Quite often there were predictable complications due to the high motility of the leeches [26].

The disadvantage of this treatment was also the unpredictable efficacy of the treatments. Each leech can drink 5–10 mL of blood, but poorly prepared leeches would drink any blood. On the other hand, an additional 40-50 ml of blood could be lost from the leech wound [27]. Therefore, there may have been significant bleeding. Up to 200 leeches were

attached at a time, but in young children, deaths were reported after using only one leech [26]. Another possible complication is a bacterial infection, typically with Aeromonas hydrophila, which is necessary for leeches to digest blood [27].

Anaphylactic reactions associated with proteins secreted by leeches are a complication of leech therapy [4]. However, leeches owe their medical success to the analgesic, anti-inflammatory and anticoagulant substances they secrete, both in the past and in the present. The strongest known anticoagulant substance secreted by leeches is hirudin [4], which was used during the first experimental dialysis by Abel in 1913 [28]. Bivalirudin, its derivative, was used more than 100 years later in individual dialysis patients [29], although this drug is contraindicated in patients with renal failure [30].

The list of known substances secreted by leeches is long: 1. blood coagulation inhibitors, e.g. hirudin; 2. platelet aggregation inhibitors; 3. hementin and hementerin, both with fibrolytic activity; 4. PC-LS — antiplatelet and blood pressure regulating factor; 5. triglyceridase and cholesterol esterase; 6. proteinase inhibitors with anti-inflammatory effect; 7. neurotransmitters; 8. endorphins; 9. factors that inhibit the growth of microorganisms; 10. steroids; 11.antielastase [31]. A whole pharmacy, and these are substances produced by only one of over 300 species of leeches. The local effect of proteins secreted by leeches is used in medicine to this day. Leeches are used in plastic and reconstructive surgery to improve microcirculation [27]. In 2004, the US Food and Drug Administration approved the use of leeches for these indications [31, 32]. The author was unable to find publications on the use of leeches in patients with complications after creating an arteriovenous fistula for dialysis. But maybe this is an idea for an unconventional research study.

As was the case with bloodletting, leech therapy reached its peak in the 18th and 19th centuries [32]. Even at the beginning of the 19th century, the popularity of leech therapy was so huge that more than 7 million leeches from continental Europe were imported to London annually [33]. Shortly thereafter, a shortage of leeches arose in France, and in 1833 alone 42 million leeches had to be imported to France [34]. It is a miracle that Hirudo medicinalis did not go extinct. In Poland, it is under species protection [35]. Clearly, the negative impact of medicine on the environment began long before the invention of plastic.

CUPPING

Wet cupping has been, and continues to be, an alternative to leeches. Its story begins in ancient Egypt [5] and is still alive today. An incision on the skin is made by the person performing the procedure, who then attaches the cup using suction. In the 20th century, "mechanical" leeches were also constructed [19]. Wet cupping is still popular around the world. Around 5% of the population of Iran has had cupping, called "hijamat", done at least once. This should not be surprising, since the prophet Muhammad himself emphasized the health benefits of cupping [6].

HISTORICAL OVERVIEW — DECLINE AND... EBM

We live in the era of clinical research and evidence-based medicine (EBM). When did clinical trials begin and did bloodletting have an effect on them? "Daniel's fast" is often considered to be the first "clinical" trial. The first "controlled study", described in the biblical Book of Daniel, is worth mentioning: *"Daniel then said to the guard whom the chief official had appointed over Daniel, Hananiah, Mishael, and Azariah: «Please test your servants for ten days: give us nothing but vegetables to eat and water to drink. Then compare our appearance with that of the young men who eat the royal food, and treat your servants in accordance with what you see». So he agreed to this and tested them for ten days. At the end of the ten days they looked healthier and better nourished than any of the young men who ate the royal food. So the guard took away their choice food and the wine they were to drink and gave them vegetables instead"* [36].

But let us go back to modern times and bloodletting. In 1662, a research project created by the "father of biochemistry" Jan Baptist van Helmont (1580-1644) was published. It is not known whether the study was ever conducted, but it is probably the first project not only with randomization, but also with a well-defined endpoint, and it concerned bloodletting [37]. "Let us take from the itinerants' hospitals, from the camps or from elsewhere 200 or 500 poor people with fevers, pleurisy etc., and divide them in two: let us cast lots so that one half of them fall to me and the other half to you. I shall cure them without blood-letting or perceptible purging, you will do so according

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to your knowledge (nor do I even hold you to your boast of abstaining from phlebotomy or purging) and we shall see how many funerals each of us will have: the outcome of the contest shall be the reward of 300 florins deposited by each of us" [37].

In 1809, a military surgeon called Alexander Hamilton conducted an experiment involving 366 sick soldiers and showed the harmfulness of bloodletting [38]. *„It had been so arranged, that this number was admitted, alternatively, in such a manner that each of us had one-third of the whole. The sick were indiscriminately received, and were attended as nearly as possible with the same care and accommodated with the same comforts. One-third of the whole were soldiers of the 61st Regiment, the remainder of my own (the 42nd) Regiment. Neither Mr. Anderson nor I ever once employed the lancet. He lost two, I four cases, whilst out of the other third [treated with bloodletting by the third surgeon] thirty-five patients died"* [38].

In the 19th century, Europe was hit by numerous cholera epidemics, during which bloodletting was the basic treatment [8]. Today, it is difficult to imagine the mortality rate of patients who were extremely dehydrated in the course of severe diarrhea, who were additionally bled at the end of their lives. Doctors were beginning to realize this, and they began to doubt the efficacy of bloodletting in treating other infections.

In 1828, Pierre-Charles-Alexandre Louis (1787–1872) published the results of a study on bloodletting in pneumonia. He compared the effect of bloodletting performed in the first 4 days of the disease with patients who were bled later. Mortality in the first group was 44%, and 25% in the second group [8, 34].

In addition to the results of what we would now call clinical research, there was also a truly Buddhist belief that "less is more". Therapeutic minimalism did not result from the influence of Eastern religions, but from the conviction that conventional treatment was ineffective. Doctors observed that it was not the therapies they used, but rest and a proper diet that contributed to recovery. In Poland, the advocate of therapeutic minimalism and spa treatment was Dr. Józef Dietl, well known to nephrologists, who, among other things, described the so-called Dietl orifice [39].

In his book published in 1852 entitled "On bloodletting in pneumonia from a clinicophysiological viewpoint", Dr. Dietl wrote: *"As a result of our experience, bloodletting in pneumonia is never advisable, that is: for the restoration of health, it is never needed. Bloodletting cannot suppress or reverse the inflammatory-pulmonary issue, it cannot reduce hepatization, it cannot stimulate excretion of sweats, at least in the greatest number of cases, nor accelerate recovery" [40].* The end of commonly used bloodletting came in the mid-nineteenth century.

Interestingly, clinical trials on the efficacy of bloodletting in the treatment of gout [41] or hypertension [42] are still being conducted. In 2018, a meta-analysis of studies on the role of bloodletting in the treatment of hypertension was published. It showed that treatment with bloodletting leads to a decrease in blood pressure, but it did not allow to draw final conclusions regarding the efficacy and safety of this method [42]. For European doctors, the mere publication of this type of meta-analysis is surprising. It seems that in view of the possibilities offered by modern pharmacological treatment and potential complications, bloodletting has no place in the treatment of hypertension, but that is a European point of view. All the cited studies included in the meta-analysis were authored by Asian researchers [42].

CONCLUSIONS

Many of the treatments used historically evoke an indulgent smile today. And yet, surprisingly many of the treatments we use today are derived from treatments used in the past. Although we do not believe that blood is the cause of all evil, it is a blood test that allows us to diagnose most diseases. Although we do not believe in the humoral theory of diseases, many treatments are based on the removal of excess substances from the body.

Bloodletting was a spectacular cure in a few cases in history, which became the justification for further attempts. However, this method has shortened the lives of many patients over the centuries.

One of the geniuses killed by bloodletting was Wolfgang Amadeus Mozart, who suffered from an infection, possibly a streptococcal one. It is tempting for the nephrologist to make a postmortem diagnosis of post-streptococcal glomerulonephritis. However, regardless of the primary cause, it was the loss of about 2 liters of blood and persistently repeated enemas that ended his life [43]. Many rules were bled, and the job of a court physician must have been dangerous. Napoleon, who survived a blood-

letting treatment, later stated that "Medicine is the science of murderers" [8].

Some not only survived but also greatly praised bloodletting. Prince Michał Kazimierz Radziwiłł, like many of his contemporaries, was glad of his bloodletting and meticulously noted his treatments, so that we know that he had 65 procedures in 34 years [14]. If these bloodlettings were performed today in a blood donation center, he would have received a "Honorary Blood Donor — Meritorious to National Health" badge [44].

Or maybe the prince could give some advice to Ernest Hemingway? Both gentlemen were well-built, and the adjective "plethoric" would fit both. Hemingway suffered from hypertension and hemochromatosis, for which there was no effective cure until the mid-twentieth century, and the era of bloodletting was long over. The great prose writer was treated ineffectively with electroconvulsive therapy [45]. Maybe if Hemingway had lived at the Radziwiłł court several hundred years earlier, the bloodletting would have protected him from disease complications and ultimately from suicidal death? In the dark months of the pandemic, we have repeatedly used treatments, the value of which we later doubted, and we have certainly made many mistakes believing in uncertain and unproven therapies. So let us appreciate the efforts of physicians, who for several thousand years had little more at their disposal than the bloodletting and enema proposed by Hippocrates. Enema... can it also inspire nephrologists today?

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