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HISTORY OF MEDICINE AND ETHICS

In memory of Ryan White, the boy with haemophilia who showed the world the other side of AIDS
Lest We Forget...

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Summary

In the 1980s, AIDS triggered a huge wave of fear, as always happens when unknown, deadly diseases emerge. The fact that gay men were among the first to be infected with HIV and to manifest the disease prompted public opinion to link the infection to behaviours that were, at least at that time, transgressive and therefore unacceptable and shameful. AIDS sufferers were therefore exposed to discrimination from the outset.

The case of young Ryan White prompted much-needed reflection in the mid-1980s. Born with a severe form of haemophilia, Ryan contracted AIDS through the therapeutic administration of an infected blood product. This demonstrated that AIDS was not a disease that affected only homosexuals and drug users; it could strike anyone.

Through the story of Ryan White, an "innocent victim" of AIDS, the authors highlight the changes that occurred between the 1980s and 1990s, and which led civil society – as well as researchers – to modify its perception of the disease.

This was no easy process, since discrimination and stigma have deep roots, exerting a cascading effect that is very difficult to counteract, and which sometimes proves even more harmful than the disease itself.

Introduction

In 1984, Ryan White was a teenager living in Kokomo, Indiana (USA). Born in 1971, Ryan suffered from a severe form of haemophilia A, but despite his potentially fatal disease, he tried to live his life as normally as possible, supported by his mother, Jeanne. To control his disease, Ryan underwent the administration of coagulation factor VIII, a clotting agent made from plasma collected from donors and used to treat episodes of bleeding in haemophiliacs.

THE HISTORY OF HAEMOPHILIA: GREAT VICTORIES AND A TRAGIC "BLIND SPOT"

The first description which we may say perhaps to mention to "haemophilia" are from the end of the 18th century when we can find various reports of families in which males suffered abnormally prolonged post-traumatic bleeding [1]: the anonymous obituarist of Isaac Zoll, writing in 1791 [2], Consbruch in 1793 and 1810, Rave in 1796 [3], and the "Haemophilia" was first described in 1803 by the American physician John Conrad Otto (1774-1844) [4] (Fig. 1).

He described an inheritable bleeding disorder in several families where only males born from unaffected mothers were affected [5]. He then called them the "bleeders. Conrad published the results of his studies on a predisposition to haemorrhage in some families in *An Account of an Hemorrhagic Disposition in certain Families* [6].

He understood the main characteristic of haemophilia, *i.e.*

Fig. 1. John Conrad Otto (1774-1844) - (Public domain - Wikipedia commons).

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that males tend to inherit the disease, while females are generally healthy carriers. This is because haemophilia is an X-linked inherited disease. Indeed, males have only one X chromosome; therefore, if they inherit a defective copy of this chromosome, they will always have the disease. As females have two X chromosomes, they usually have a healthy copy that compensates for the defective one; they are therefore either healthy carriers or affected by mild forms of the disease.

These accounts began to define a clinical syndrome on which the 19th century developed an extensive literature. The german physician and psychiatrist Christian Friedrich Nasse (1778-1851) (Fig. 2) was the first to publish the genetic description of "hemophilia" in "Nasse's Law", a dictum formulated by him in 1820 where he states that haemophilia is transmitted entirely by unaffected females to their sons [7, 8]. He states: *"women of bleeding families, although they marry men from normal families, carry the disease over from their own fathers to their children, and yet never suffer from the disease themselves"*. Not a hypothesis, not a conjecture, not a theory, but a full-blown law! [9].

In the historical evolution of this disease, different terms were used: *haemorrhoea, idiosyncrasia haemorrhagica, haematophilia, bleeding disease, hereditary haemorrhagic diathesis*, but the name then used and the current name *"haemophilia"* (the word was derived from the Greek words haima (blood) and phila (love or tendency), with the full term being haemorrhaphilia or "love of bleeding") arises only in 1828 [1].

"Hemophilia", as a term, was in fact first documented in 1828 by Johann Lukas Schönlein (1793-1864) (Fig. 3) a German naturalist and professor of medicine with his student Friedrich Hopff in his doctoral dissertation at the University of Zurich (Switzerland) which described the condition as "On hemophilia, or the hereditary predisposition to fatal bleeding". Schönlein was the physician also known for being the first who published the name "tuberculosis" (German: Tuberkulose) in 1832 [10]; before Schönlein's designation, tuberculosis had been called "consumption" [11].

However, historical evidence of the disease is much older. According to some scholars, Hippocrates of Kos (460 BC-post 377 BC) described a case of anomalous blood coagulation in a wounded soldier.

"Haemophilia" was acknowledged in ancient times; the Babylonian Talmud, one of the sacred texts of Judaism (a collection of Jewish rabbinical writings from the second century AD), affirmed that male babies should not be circumcised provided two brothers had already died owing to excessive bleeding from the procedure [12]; the disease is mentioned about a woman who had lost her first two sons from circumcision: *"If a woman has her first son circumcised and he dies as a result, and she then has her second son circumcised and he also dies, she should not have her third son circumcised, since the deaths of the first two prompt the presumption that this woman's sons die because of circumcision"* [13].

Similarly, in the year 1000, the Arab physician Abulcasis (Abū l-Qāsim Khalaf ibn ʿAbbās al-Zahrāwī, 936-1036), who is acknowledged by historians to be the "father of surgery", wrote a treatise entitled *al-Tasrif*, in which he described a disease that can certainly be identified as haemophilia. Albucasis, described a family with males who died from bleeding after trivial injury [14].

It was, however, only in the 20th century that fundamental discoveries were made that would enable haemophilia to be treated.

In 1952, the case of a patient named Stephen Christmas (1947-1993) led to the identification of two types of haemophilia (A and B), which are caused by the lack or deficiency of coagulation factors VIII and IX, respectively.

Again in the 1950s, the British researcher Ethel Bidwell (1919-2003), in the laboratory directed by Robert Macfarlane in Oxford, succeeded in

Fig. 2. Christian Friedrich Nasse (1778-1851) - (Public domain - Wikipedia commons).

Fig. 3. Johann Lukas Schönlein (1793-1864) **-** (Public domain - Wikipedia commons).

producing factor VIII in a concentrated form that could be administered to patients. Nevertheless, the availability of factor VIII remained limited by the fact that the preparation, which was made to order for each patient, could not be stored.

A few years later, however, in 1964, the American physiologist Judith Graham Pool (1919-1975) noticed that, on thawing previously frozen plasma, a sediment called cryoprecipitate was formed, and that this was extremely rich in factor VIII. Cryoprecipitation decisively changed haemophilia patients' lives and life expectancy, which at the beginning of the 1960s did not exceed 30 years; it even allowed them to undergo surgical operations that had hitherto been absolutely impossible.

However, the greatest advance in treatment stemmed from DNA studies and the cloning of the factor VIII gene in 1982 and the factor IX gene in 1984, which, in the late 1980s, enabled recombinant F VIII and subsequently F IX to be produced industrially [15].

The most recent studies in gene therapy involve the use of a modified virus, which does not cause disease, to insert a copy of the patient's missing gene which codes for the coagulation factor [16, 17].

In this process, which opened up the possibility of a cure for haemophilia, there remained, however, a short period of time, a sort of "blind spot", in which the therapeutic replacement of factors VIII and IX, obtained mainly from the plasma of healthy donors, was not supported by the tests needed in order to avoid contamination by infectious diseases.

Consequently, between the 1980s and the early 1990s, tens of thousands of people worldwide were infected by HIV and hepatitis B and C viruses through infected blood products.

A particularly significant portion of these were haemophiliacs. Indeed, according to data from the Hemophilia Federation of America (HFA), "in the 1980s, approximately 90% of patients with severe hemophilia were infected with HIV, and almost all patients with hemophilia who used factor products before 1988 were infected with hepatitis C virus (HCV)" [18]. One of these patients was Ryan White.

THE GLOBAL PERCEPTION STARTS TO CHANGE: NOT ALL AIDS VICTIMS ARE GAY OR DRUG ABUSERS

In the mid-1980s, epidemiologists began to hypothesize that AIDS might also be spread through blood products. This had serious implications for haemophiliacs who periodically received concentrates produced from large batches (pools) of plasma, much of which had been collected in the late 1970s and early 1980s, before the first cases of HIV infection had even been detected. This was exactly how Ryan White contracted AIDS – through the administration of contaminated blood products to treat his haemophilia.

Throughout the summer and autumn of 1984, Ryan was ill, plagued by stomach cramps, diarrhoea and exhaustion. In December of that year, he was admitted to the local hospital in Kokomo, where he was diagnosed with antibiotic-resistant pneumonia in both lungs. He was then transferred to Riley Hospital for Children in Indianapolis, where doctors began to suspect that Ryan had contracted *Pneumocystis carinii* pneumonia (PCP) from contaminated factor VIII.

In those years, the diagnosis of *Pneumocystis carinii* pneumonia (PCP) meant that the patient had AIDS. A biopsy revealed that Ryan had indeed contracted PCP, confirming the most dreaded diagnosis at the time: AIDS.

Despite this, Ryan was determined to live his life like any other 13-year-old. "Let's pretend I haven't got it", he told his mother, asking to return to school as soon as his condition improved.

"*Ryan White just wanted to go back to school. In much the same way that he had handled hemophilia, Ryan vowed not to let his AIDS diagnosis spoil his otherwise 'normal' childhood. A key component of living like a 'normal kid', Ryan's deeply held wish, was to attend school and socialize with friends and acquaintances"* [19].

But on July 27, 1985, officials of the Western School Corporation (WSC) in Russiaville, Indiana, prohibited Ryan from attending classes because of his illness, so as to ensure the safety of other students. Their decision suddenly shattered Ryan's dream of returning to normality despite his illness.

Two days earlier, on July 25, the American actor Rock Hudson (1925-1990), who was hospitalized following a collapse in Paris, where he had gone to undergo experimental treatments at the American Hospital and the Institut Pasteur, had his staff issue a press release in which he officially announced that he was suffering from AIDS [20].

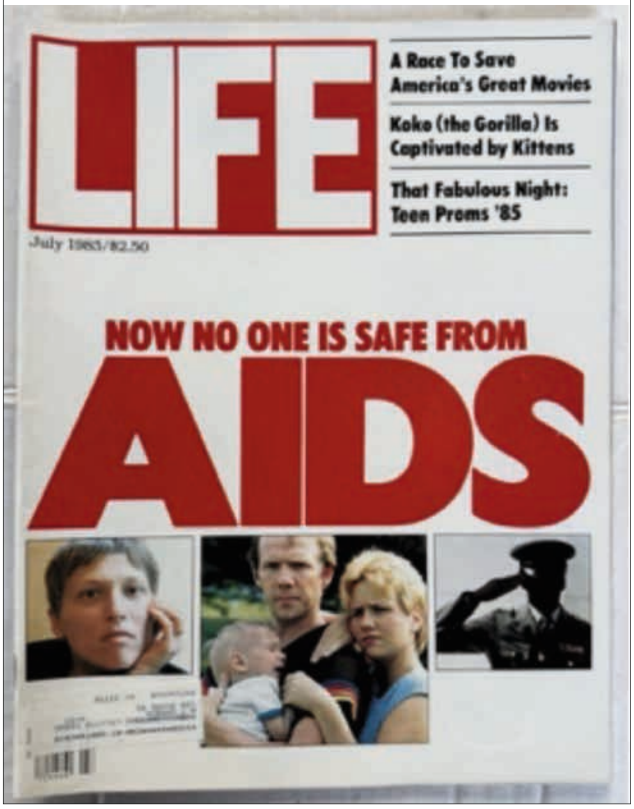
The two pieces of news had a profound impact on civil society. People's beliefs regarding AIDS were largely called into question; it was not a disease that exclusively affected promiscuous homosexuals and drug users. Life magazine headlined: "Now no one is safe from AIDS", above a photograph of a seemingly worried white, heterosexual family (Fig. 4).

THE YOUNG MAN WHO FOUGHT AGAINST THE STIGMA OF AIDS

The White family began a strenuous legal battle to uphold Ryan's right to attend school, bringing the AIDS issue into the national spotlight. In the spring of 1986, Ryan was granted the right to attend in-person classes. The media gave the case ample coverage and Ryan became one of the most well-known people in the United States, the face that raised awareness of the tragedy of AIDS, an "innocent victim" of a medical error.

With his readmission to school, the issue seemed to have been resolved. And yet, on the day of his return to class, two-fifths of the school's students were absent; a group of parents had even set up an alternative school in an old American Legion Hall, so as to stop their children from coming into contact with Ryan. Thus, Ryan became engaged in a new battle, alongside his fight against the disease: the fight against the discrimination and stigma that afflicted AIDS.

Fig. 4. The cover of Life magazine, July 1985 (Public Domain).



Ryan's battle to attend school also forced American society to confront widespread prejudices regarding the AIDS epidemic; this white, heterosexual, middle-class teenager from the American Midwest debunked the idea that AIDS affected only "deviant" groups.

He began appearing on the evening news and on the covers of popular magazines, thereby publicizing his story. Many prominent figures in the world of music and sport wanted to meet him and support him in his struggle. He was interviewed on ABC's "Good Morning America" programme [21] and took part in a charity event for the newly formed American Foundation for AIDS Research (amfAR) (Fig.5).

But the stigma hit hard, prompting people to focus on the concepts of "guilt" and "innocence" that imbued the social representation of the AIDS crisis; if Ryan was the innocent victim, then homosexuals and drug users, the outcasts of society, were the culprits [22]. Indeed, as Ryan's story grabbed national headlines, the media increasingly accused gay men and drug addicts of contaminating American society. As for Ryan himself, however, he never denigrated gays or blamed them for his illness.

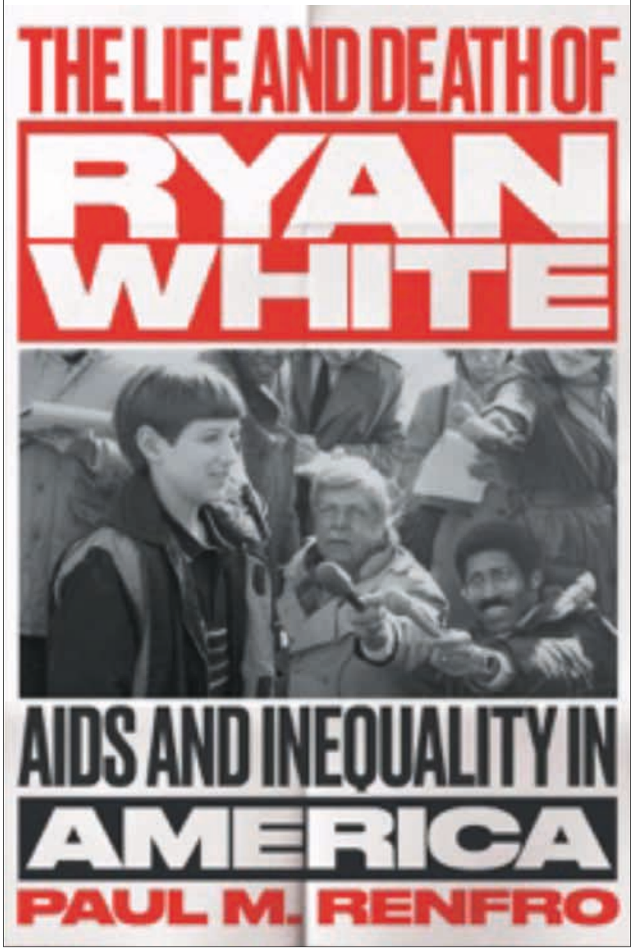
"In addition, during HIV's first decade, intense fear and stigma led to new HIV-specific criminal laws. In the name of public health, criminal laws were passed in more than 35 states that punished behaviors that might transmit HIV; states without HIV-specific laws used general criminal laws to accomplish the same end" [23]. People with AIDS were isolated from their families and friends; the stigma placed on them became a phenomenon of enormous proportions. In this context, Ryan White's testimony provided a glimmer of light and hope in an absolutely bleak landscape. His short life became a manifesto for the fight against the stigmatization of people with AIDS.

Similarly, the last days of life of another young AIDS patient, David Kirby (1957-1990), who was homosexual and a gay rights activist, made a fundamental contribution to the fight against discrimination and marginalization of those suffering from the so-called gay plague.

In November 1990, Life magazine published a photograph of Kirby on his deathbed, while his father hugged him lovingly. Therese Frare, at the time a student at Ohio University, immortalized the last moments of David Kirby, surrounded by his family, in what Life called "The Photo That Changed the Face of AIDS" [24].

Kirby's parents accepted not only their son's sexual identity, but also his illness, thus demonstrating how a true family could stay close to a terminally ill HIV-positive person: an extremely rare occurrence at the time. The publication of this photograph shocked the United States, but above all it sparked reflection, prompting many people to seek information and to take action.

Fig. 5. The cover of the book "The Life and Death of Ryan White: AIDS and Inequality in America" by Paul M. Renfro, showing the young Ryan White (Public Domain).



David Kirby died on May 5, 1990, at the age of just 32 years. Only a month earlier, on April 8, Ryan White had also died.

RYAN WHITE'S STORY DID NOT END WITH HIS DEATH

Ryan's death was perceived as a national tragedy. His funeral was a media event; CNN broadcast the ceremony live, and all three major American television networks showed footage of it [25]. His coffin was carried by Los Angeles Raiders' "defensive end" Howie Long, singer Elton John and television host Phil Donahue [26]. Among the more than 1,500 people who attended his funeral were First Lady Barbara Bush and Michael Jackson, who sat next to Ryan's mother, Jeanne White. The corpse lay in an open coffin at the entrance to the church – in stark contrast to the quiet, sparsely attended ceremonies that usually marked the funerals of AIDS victims.

Ryan's life, albeit brief, contributed to raising awareness of AIDS and, above all, to the realisation that this disease was not necessarily the of certain lifestyles.

Thus, Ryan's case helped to fuel a political debate that would prompt the federal government to allocate the funds needed to fight HIV infection and to approve an act that would bear Ryan's name. Indeed, shortly after Ryan's death, the United States Congress passed the Ryan White Care Act to support care for AIDS sufferers who did not have adequate health insurance or other resources. Signed by President George Bush Sr. on August 18, 1990, the act allocated $882 million in AIDS funds for 1991 and $4.5 billion in federal grants through 1995. This act was reconfirmed in 1996, 2000, 2006 and 2009, and is known today as the Ryan White Treatment Extension Act of 2009. The Ryan White programme constituted the US federal government's largest and most comprehensive commitment to improving the quality and availability of care for medically disadvantaged individuals and families affected by HIV.

Conclusion

Ryan White, in his short life – he died at the age of 19, having lived with the disease for years, despite the doctors' diagnosis in 1984 having been much more severe, granting him only 6 months to live – forced American society to confront AIDS, about which little or nothing was known at the time and which was associated exclusively with homosexuality. With his active testimony, he accompanied people in a profound reflection on their prejudices about the AIDS epidemic and those affected by this pathology, attempting to break down all forms of stigma [27].

White, along with many others, helped to raise public awareness of AIDS, a key factor in changing social perceptions and in promoting disease prevention. Thanks to Ryan, but also to many activists for patients' rights, HIV infection became a focus of research, and today AIDS is a preventable and treatable disease.

However, much remains to be done in terms of education, so that young people will not lower their guard and will take care to prevent any possibility of contagion. In this regard, WHO data indicate that 1.3 million [1.0-1.7 million] people contracted HIV in 2024 [28]. A great effort is also required to ensure that no one is ever stigmatized on account of a disease [29, 30]. Indeed, stigmatization has been shown to have a negative impact on HIV prevention, on individuals' decisions to undergo testing and to access health services, and on the healthcare management of people living with HIV [31]. "Ending the AIDS epidemic by 2030 will require addressing stigma more systematically and on a larger scale than current efforts" [32].

In this regard, it is necessary not only to strive to change society, but also to petition for laws that protect people and do not criminalise HIV and to make people understand the dangers of certain behaviours rather than simply prohibiting and sanctioning those behaviours [33].

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Authors' contributions

MM: conceived the study; DO: designed the study; DO & MM drafted the manuscript; performed a search of the literature; revised the manuscript; conceptualization and methodology; investigation and data curation; original draft preparation; review; editing. All authors have read and approved the latest version of the paper for publication.

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