

The fraud of Abderhalden's enzymes

Earlier this century, the German biochemist Emil Abderhalden deceived the scientific world with his spurious 'defence enzymes'. Unless there is a change in clinical thinking, such a fraud could happen again.

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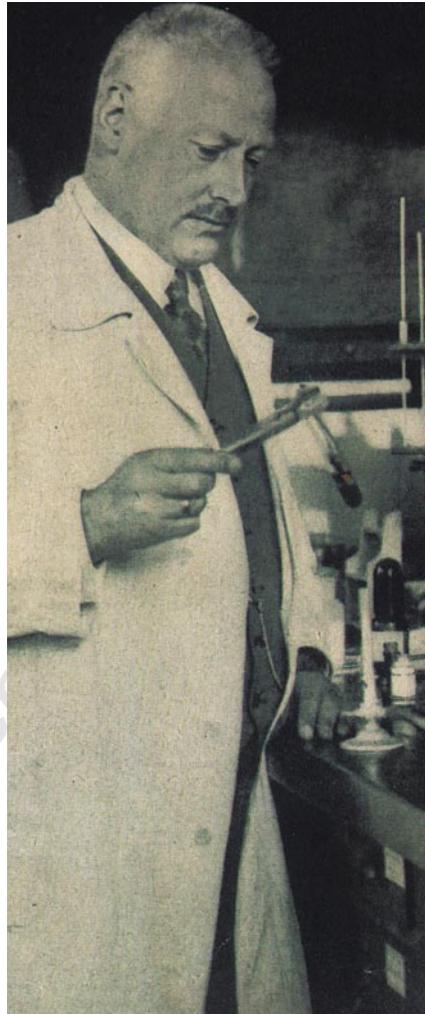
Is science a social construct, as some sociologists of science claim¹, or is its structure independent of social conditions? In the forefront of science, where everything seems possible, data may be misinterpreted and errors litter the path of science. In physics and chemistry such mistakes are usually quickly corrected by colleagues or the authors themselves. But what about fraud? Fraud assumes intention, which is difficult to prove. We think the deliberate invention and interpretation of data in science is a social construct. In physics and chemistry such social constructs are extremely rare; they are quickly detected and they have half-lives of just a few years. But we propose that this is different in medical science, in which science and social constructs may peacefully coexist.

We will demonstrate this by presenting the case of the non-existent *Abwehrfermente* (defence enzymes) created by Emil Abderhalden (1877–1950), who was professor of physiology and physiological chemistry at Halle University from 1911 to 1950, president of the Leopoldina—the oldest German academy of science—from 1931 to 1946, editor of several journals, and author of several books and more than 1,000 research papers².

Abderhalden's fraud

Abderhalden was born in 1877 in Switzerland. He received a medical education at the University of Basel, and in 1902 he went to Berlin to work with the great organic chemist Emil Fischer on the synthesis of peptides and the action of proteases, which are enzymes that break down proteins. In 1908 he became professor of physiology at the Tierärztliche Hochschule in Berlin, and three years later became professor of physiology and physiological chemistry at the University of Halle. He was due to become director of the Kaiser Wilhelm-Institut for physiology in 1914, but the First World War intervened. As a kind of compensation, the Kaiser Wilhelm-Gesellschaft financed his research with substantial grants until 1944.

Abderhalden's fame as a biochemist was achieved through two types of experiments. First, with Emil Fischer he began to synthesize and isolate peptides, and in his career he synthesized and isolated more than anyone else in Germany. Unfortunately, little use was made of them. In 1909 he published his first work on the second topic, the *Schutzfermente* (protection enzymes) or, as he called them later, the *Abwehrfermente*. In 1912 he published a book



Abderhalden: a convinced eugenicist.

about them, and considered them to be his most important discovery³; three new editions appeared before the end of 1914.

According to Abderhalden, animals and humans produce specific proteases, called *Abwehrfermente*, when they are challenged with foreign proteins. For example, the serum produced by pregnant women contains proteases specific to proteins of the placenta. The test for this claim is straightforward. Placenta is boiled, and the denatured, insoluble placental proteins are treated with serum from a pregnant woman. Peptides that arise through the action of the defence enzymes in the serum are dialysed and then identified by Biuret or ninhydrin reactions. Sera from non-pregnant women and men supposedly do not show this reaction.

This test intrigued gynaecologists and biochemists worldwide. Between 1912 and

1913, more than 25 papers from various gynaecological laboratories appeared that dealt with Abderhalden's pregnancy test, most of them with positive results³. In 1914, the directors of German university women's hospitals were asked by a medical journal to describe their experience with this test. Of the 15 that replied, all had more or less positive results, and none had negative results⁴.

The excitement increased. In the fourth edition of *Abwehrfermente* (1914), Abderhalden quotes 451 papers, many of them in non-German journals, which describe various uses of his test. As well as in pregnancies it was used successfully in three other contexts: the diagnosis of sarcomas and other carcinomas; the diagnosis of infectious diseases such as syphilis; and the diagnosis of psychiatric diseases such as schizophrenia. Cancer therapy using *Abwehrfermente* seemed just around the corner.

Why no one stopped him

We have to keep in mind that all these medical scientists deluded themselves: defence enzymes do not exist! It was a case of the emperor's new clothes: when everybody sees and admires his elegant clothes, just one child can destroy the social construct by pointing out that the emperor is naked. This 'child' was the German-Jewish biochemist Leonor Michaelis. In 1913 he had just published with Maud Menten the seminal paper on enzyme kinetics. Working in the biochemical laboratory of a hospital, he was asked by its director to establish the validity of Abderhalden's pregnancy test. He found that he and his collaborator were unable to repeat Abderhalden's experiments, despite spending a week in Abderhalden's laboratory in Halle. There was no difference between the sera of pregnant or non-pregnant women or between women and men: the pregnancy test did not work. In 1914, Michaelis and his collaborator published their negative results⁵; it marked the end of his academic career in Germany.

But Michaelis was not the only biochemist who could not repeat the results. Donald van Slyke from the Rockefeller Institute and Florence Hulton from the University of Pennsylvania failed too^{6,7}. In 1920 Jacques Loeb wrote⁸ to Michaelis, who was still in Germany: "Nobody speaks of the Abderhalden reaction any more in the United States and I am very much surprised to see that in his journal Abderhalden still continues that myth." The reply from Michaelis⁸ seems timeless: "In Germany one can succeed only when one presents practical,



applied science, however bad it may be. Anyone who wants to work on pure science is regarded a crank, and so he finally stops working". About Abderhalden he wrote⁸: "For me his type of work is disgusting. My position in Germany has suffered because of my opinion against his pregnancy test. There may be many who see through him, but nobody dares to say anything against him." Michaelis left Germany in 1922 to become visiting professor at a Japanese university, and later became a lecturer at Johns Hopkins University in Baltimore, Maryland, and then a member of the Rockefeller Institute in New York.

But how could Abderhalden continue with the *Abwehrfermente* from 1915 until his death in 1950? His strategy was simple and straightforward. He must have had collaborators who found what he wanted them to find (he dedicated the second edition of his book about the *Abwehrfermente* to his "faithful collaborators"). In general, he argued that the pregnancy test and other tests had worked in a large number of laboratories; so many scientists could not have deluded themselves. He conceded that in some laboratories the test did not work properly, and claimed that this demonstrated that the method was difficult, that it was not properly used, and — alas — that it was not perfect. So Abderhalden and his co-workers continued to streamline his method. The test became technically more and more complicated, and supposedly safer and safer. But the material to be tested became simpler. His research received a fresh impetus when he published a paper saying that the pregnancy test could work with urine, which was much easier to obtain than blood and supposedly contained more specific *Abwehrfermente* than blood. And so a second wave of users appeared.

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Sinister applications

In the 1930s and 1940s, a wide range of topics were analysed in half a dozen German institutes with the help of the *Abwehrfermente*⁹. There were tests for various forms of cancer; the final objective was cancer therapy. Tests for psychiatric diseases such as schizophrenia were developed; the *Abwehrfermente* were also used for effective shock treatment of psychotic patients. Tests were worked out to diagnose the various psychological types proposed by the psychiatrist E. Kretschmer¹⁰. (To test how patients dealt with fear, guns were fired behind their heads and pictures were taken; one schizophrenic patient is quoted as saying over and over again: "We want poison gas... why do they not give us poison gas?") The *Abwehrfermente* were used by Abderhalden's son Rudolf⁹ to diagnose various infectious diseases. They were even used to distinguish races of sheep⁹. Remember that none of these diagnostic tests could possibly work because the *Abwehrfermente* do not

exist, so the therapeutic value of the injections was dubious to say the least.

Some uses of the Abderhalden reaction were particularly disturbing. In November 1942, the human geneticist Otmar von Verschuer was appointed director of the Kaiser Wilhelm-Institute for Anthropology in Berlin. His former postdoc Josef Mengele joined him there in the winter of 1942–43. Mengele had been wounded in the war and spent some months convalescing in Berlin before moving in April 1943 to the Auschwitz concentration camp to become camp doctor. He must have discussed the scientific possibilities of Auschwitz with his teacher, because, when Mengele left, von Verschuer immediately applied for a grant from the Deutsche Forschungsgemeinschaft to finance Mengele's work in Auschwitz on the *Abwehrfermente* produced by members of various races deliberately infected with infectious diseases. They planned to use the Abderhalden reaction to demonstrate racial differences, and von Verschuer sent a technician to Abderhalden's laboratory in Halle to learn the technique¹¹.

Aware that the technique was not easy, von Verschuer called on Günter Hillmann to supervise the tests. Hillmann was an experienced biochemist who had worked in the laboratory of Karl Hinsberg, who had set out to improve the test of the *Abwehrfermente* for cancer cells; indeed, Hillmann himself had synthesized and tested a chemical that allowed a better quantification of the peptides released by the *Abwehrfermente*¹². But he had difficulties with Hinsberg, and in 1943 he moved to the laboratory of Adolf Butenandt, who had won the Nobel prize for chemistry in 1939.

Mengele sent blood samples from infected Jewish and Gypsy twins to Hillmann, who began analysing them. On 4 October 1944, von Verschuer wrote to a friend¹¹: "Precipitates have been prepared from the plasma of more than 200 individuals of various races, some twin pairs, some families. Abderhalden's method has been used and supplemented by a method newly discovered by Hillmann (who has joined us as collaborator). So very soon we can now begin our real research. The aim of our various efforts is now no longer to establish *that* the influence of heredity is important in various infectious diseases, but rather *how* hereditary factors act and what kind of events take place in their action."

A workshop on *Abwehrfermente* was held in 1947 in Tübingen, chaired by Butenandt. In a two-page report on the meeting¹³, Gerhard Mall, a collaborator of Kretschmer, wrote that Mall, Hinsberg, Kretschmer and Bersin had found specific defence enzymes. But Butenandt asked for the use of chemically homogenous proteins to re-test the claims.

That was not the last word on the *Abwehrfermente*, however. After Emil

Abderhalden's death in 1950, his son Rudolf declared that they were the perfect diagnostic tools to determine the optimal cell type for the *Frischzellen-Therapie* (fresh cell therapy) invented by Paul Niehans¹⁴, and so for a few years the Abderhalden reaction was used again. But two clinicians demonstrated that it made no difference whether the patient was healthy or sick; the sera reacted just the same¹⁵. We do not know when the *Abwehrfermente* finally disappeared as a diagnostic tool. Last year the *Frischzellen-Therapie* was outlawed in Germany by the Department of Health, but this ruling has been contested by doctors who claim it infringes the rights of both doctors and patients. The Supreme Court of Germany is pondering the problem, but this is likely to take a long time.

Behind the fraud

It is worth noting that Abderhalden was a convinced eugenicist. Given that his main scientific activity was based on self-deception and fraud, it is interesting that between 1922 and 1935 he edited a journal about ethics (*Ethik*). He wrote a textbook of biochemistry that appeared in 28 editions between 1906 and 1948 and was translated into four languages. He was president of the Leopoldina Academy from 1931 to 1950. After 1933, the notes "membership ended" or "membership extinguished" were secretly added to the file cards of the more than 90 Jewish members¹⁶ of the academy; the members were not informed, but they no longer received the academy's journal or invitations to events. All candidates for new international membership were discreetly vetted by the German foreign office to see whether or not they were Jewish¹⁶. After 1945, Abderhalden claimed that no Jewish member was ever expelled from the Leopoldina. Truth was not his business.

Historians of science have largely ignored Abderhalden and his *Abwehrfermente*. The biochemist Peter Karlson wrote¹⁷: "Emil Abderhalden certainly did not 'invent' the *Abwehrfermente*, he worked in many fields, he was a distinguished professor... and he certainly did not need to increase his fame through dubious publications... presumably one will have to classify the literature on *Abwehrfermente* as 'unconscious collection of wrong data', some kind of auto-suggestion." Theodor Wieland, a peptide chemist, calls Abderhalden¹⁸ "the founder of scientific biochemistry". About the *Abwehrfermente*, he wrote¹⁸: "Defence enzymes raised great hopes for theoretical biochemistry and also for practical medicine, which, however, in spite of intensive work, mostly with the participation of his son Rudolf, were not fulfilled. Thus they did not succeed in the isolation and characterisation of a defence proteinase."

The immunologist Otto Westphal told one of us (U. D., private conversation) that

his colleague Hans Brockmann wanted to work with Abderhalden on the *Abwehrfermente*: "Brockmann tested one or two systems, but was unable to reproduce them. He went to Abderhalden and told him that it worked the first time but not the second time. Abderhalden asked him why he repeated an experiment that worked well once. Brockmann left the institute immediately, considering Abderhalden to be a fraud." Westphal adds: "I had no doubt in the beginning myself, in fact I wrote a review on the *Abwehrfermente* in 1939. In 1942 or 1943 I spoke to Brockmann. The whole *Abwehrfermente* story was a fraud from beginning to end."

Never repeating an experiment that worked once, or discarding controls that did not work, is not science but pseudoscience or fraud. Abderhalden must have known this. It was his way of trying to seduce a young scientist to join him in the fake world of science as social construct. But Brockmann was a real scientist and fled. Westphal is listed as a participant at the Tübingen workshop on the Abderhalden reaction¹⁵. Was he critical? Did the participants use a double language that allowed the true scientist to abandon the non-existent defence enzymes and the believers to continue their social construct?

Can it happen again?

Abderhalden was a pure biochemist, but most of those using his method were medical, clinical biochemists. Such researchers often work during the day with patients in a hospital, and their experiments are confined to the afternoon or more likely the night. The senior author of research papers may be the director of a hospital. Clearly the universe of science is rather different from that of patients, who prefer to hear an optimistic diagnosis rather than the simple truth. It is difficult enough for the director of a large laboratory to validate all the experimental details of his collaborators, but for a physician, the director of a clinic who is responsible for many patients as well, this is clearly not possible. He must trust his collaborators, yet he is an authority. Truth may discreetly disappear.

In medical biochemistry, ideas or hope may be stronger than experimentally proven reality... The élite of today are students of the old élite, and learned the old values. Has medical, clinical science really changed that much?

Clinicians were offered the possible advantages of the *Abwehrfermente* for diagnostic breakthroughs. Most of them failed to admit that their tests did not work. Excellent non-clinical biochemists such as Butenandt and Kuhn kept silent too, at best stating that the specificity of the *Abwehrfermente* was not rigorously proven. The existence of the *Abwehrfermente* was seriously questioned only by Michaelis, van Slyke and Hulton, and the possibility of fraud was never mentioned in public. In medical biochemistry, ideas or hope may be stronger than experimentally proven reality. It is true that some antibodies have catalytic properties, but the question is whether the existence of specific defence proteases can be measured and proved in repeatable experiments. Here Abderhalden and almost all the people in the field failed.

At the time, Germany was regarded by many to be the leading country for medical science. The story is disturbing when we realise that it did not end in 1950 with the death of Abderhalden. The *Abwehrfermente* disappeared from the literature in the 1960s but nobody wrote a clarifying obituary. The élite of today are loyal students of the old élite, and they have learned and internalized the old values. Has medical, clinical science in Germany today really changed that much? We doubt it. The Brach-Herrmann-Mertelsmann affair¹⁹ provides a brief glimpse into the abyss of medical science in Germany. Will it be soon forgotten by the German medical élite, or will there be a real change in the spirit of true science? □

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