FERNAND WIDAL

by

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THE age into which Fernand Widal was born in 1862 was so unlike our own that it is difficult to see him in perspective without an effort of imagination.

In the medical world of one hundred years ago advances of major importance were being made against a background of traditional dogma and ignorance. In the year in which Widal was born Pasteur's paper discrediting spontaneous generation was only a year old. One of the fundamental principles of modern medicine, 'the specificity of disease' had been stated clearly for the first time only thirty-five years earlier by Pierre Fidèle Bretonneau. Bretonneau, as the result of a lifetime of experience in the ward and post-mortem room, stated that the dissimilar clinical and pathological features of diseases were not a matter of degree but the end result of different aetiological agents. To us this is common sense, but at the time it was a revolutionary idea. In 1835 the Italian Agostino Bassi had shown that the silkworm disease, muscardine, was due to a micro-organism. This was the first demonstration of a disease caused by a micro-organism. But although these basic discoveries had been made they were little known. Bretonneau could not make up his mind to publish and at first Bassi was ignored to such an extent that on several occasions he nearly starved. Men who were better known at the time, such as Charles Murchison, Senior Physician to the London Fever Hospital had some modern ideas on disease and its investigation. But they also had old ideas not susceptible to scientific demonstration. Murchison's impressive *Treatise on the Continued Fevers of Great Britain* which was published in 1862, for instance, contains very good statistical surveys of fevers and a clear and accurate account of the epidemiology of typhoid. But at the same time it affirms in many places that spontaneous generation occurs and recognizes that a large number of the medical profession think typhus and typhoid to be variants of the same disease. Widal therefore was the child of a decade in which old confusion reigned with new science.

Georges Fernand Isidore Widal came from a medical family. He was born on the 9 March at Dellys near Algiers, the son of 'a distinguished doctor' who was 'médecin inspecteur de l'armée'. An uncle, Mathieu Hirtz, was shortly to become Dean of the Faculty of Medicine at Strasbourg. His medical education took place in Paris. Both the evidence of people who knew him and the bare record of examination successes and appointments indicate that he was exceptionally brilliant and rose very rapidly to prominence. At twenty-two he became 'Interne des Hôpitaux', coming first in the highly competitive examination 'the Externat'. At twenty-six he took his doctorate with an important paper on streptococcal infections. He was appointed 'Médecin des Hôpitaux de Paris' at thirty. Two years later he was made 'Professeur Agrégé'—that is he was appointed into the group of doctors from whom professors were selected. In

1911, when he was forty-eight, he was elected Professor of Internal Pathology and at fifty-five he was made Professor of Clinical Medicine with a twenty year appointment.

Widal made three contributions to medicine. First, he brought laboratory experience to the bed-side. Second, he often put forward the view that scientific ideas and attitudes must be applied to medicine. Third, he started a school of medicine at the Cochin Hospital where people flocked to hear his unusually good teaching.

In his teachers can be seen the origins of his life's work. The sources I could find were all agreed that Dieulafoy was the major influence in Widal's education. Dieulafoy was the pupil of Trousseau who had himself been a pupil and close friend of Bretonneau. Widal was later to hold the same chair in pathology which his teacher had held. From the pathologist Cornil, Widal learnt the importance of the laboratory in medicine. He was taught by Roux and later by Metchnikoff, both of whom became his close friends. Roux was an outstanding teacher and a friendly, genial man. He worked with Pasteur on anthrax and rabies, showed that the lesions of diphtheria were caused by toxins, played an important part in the development of anti-toxins and worked on tetanus. Ilya Metchnikoff left his native Russia for good in 1887 to go to Paris where he started work in the newly founded 'Institut Pasteur' in 1888. He was the first to observe the phenomenon and develop the concept of phagocytosis. His friendship with Widal is important because he investigated agglutination and moreover realized that it was a phenomenon which might have great consequences.

In the available documents there is nothing about Widal as a student. But the life he would have led as a young doctor has been described by a doctor who worked in the same hospital a few years later. The interne would be on the wards at eight o'clock. He was responsible for 120 patients. He would see some of his patients and go on a round with students some of whom were sixteen years old. A round with the chief followed, by which time it was midday. The interne would then do post-mortems on patients under his care who had died, the chief frequently coming to watch. At one o'clock, according to this account, the doctors ' . . . had a quick luncheon, but very gay'—by which is meant a meal lasting an hour and a quarter with wine. The majority of the doctors present had a very broad culture and these meals were the scene of informed and entertaining discussions. After lunch, until five, the interne did all his own laboratory work at the Institut Pasteur, or at the Sorbonne, or in the hospital. Widal had a dirty old hut infested with rats in the grounds of the hospital where much of his routine and research bacteriology was done. At five o'clock the interne began a two hour visit to the wards. Most of his evenings, spent in a room in the hospital, were taken up with writing and preparing papers.

After living this sort of life for two years, at the age of twenty-four he started on his first research project. From 1886 he worked on the aetiology of typhoid with Chantemesse. He repeated and confirmed Eberth's work, studied the fermentation reactions of Eberth's bacillus and B. coli and showed that human

infections were usually from water. Lastly, but most important he showed in 1886 that rats could be made immune by the parenteral injection of heat killed cultures of the typhoid organism. He went on to find and identify the organism of bacillary dysentery in the cells of affected patients, an observation later studied far more completely by Shiga. In 1889 he published his doctoral thesis. In it he showed by correlating clinical observations, macro- and microscopic pathology and bacteriology, that puerperal fever, white leg, erysipelas, some forms of septicaemia following wounds and phlegmons were all caused by streptococci. He showed that the variety of the lesions could be attributed to variations in the virulence of the organisms. These facts are a commonplace today. At the time many doctors refused to believe that such different conditions could be caused by the same microbe.

Widal's best known contribution to medicine, the sero-diagnosis of typhoid, was first described before the Medical Society of the Hospitals of Paris on 26 June 1896. The agglutination of microbes by the serum of immunized animals had been discovered in 1889 by Charrin and Roger. In March 1896 Pfeiffer and Koll in Germany had shown that the serum of typhoid-immune animals or of human convalescents when added to typhoid bacilli present in the peritoneal cavity of guinea pigs caused agglutination. Grüber and Durham described this in vitro. Durham suggested its use in diagnosis in a communication to the Royal Society in January 1896. Widal and Sicard noted these basic observations. They also knew from Widal's earlier experiments that animals could be immunized with serum from patients actually in the febrile stage of typhoid fever. It was possible therefore that agglutination might occur not only as a result of immunity but during the disease itself. Widal wrote to the *Lancet* in November 1896,

> originally the phenomenon of agglutination had been considered as 'a reaction of immunity'. I was the first to show that it was indeed a reaction of infection—that it appeared in man during the first days of the disease, and I then arrived at the conception of sero-diagnosis and its applications.

The reaction was very simple, requiring only a pure culture of Eberth's bacillus, a drop of the patient's serum and a microscope. It aroused enormous interest, being repeated all over the world in the following months. It was important for two reasons. First, because it could be used to distinguish typhoid fever with certainty from difficult cases of pneumonia, acute miliary tuberculosis, mild cases of typhus and suppurative conditions. Second, because it could be used as a screening test for sorting out infected cases in epidemics and tracing carriers. A small but sad feud arose between Widal and Durham as to who should be credited with the idea.

In 1901 Bordet and Gengou first described their complement fixation reaction, or as they called it 'la déviation du complément'—complement deviation —which describes better what actually happens. Widal and Louis le Sourd applied this to the diagnosis of typhoid—the first time that complement fixation was used clinically. The test was rather complicated for the time and was little used. In 1906 the test was applied by Wassermann to syphilis.

In 1900 Widal with Ravaut and Sicard worked on what was called 'cyto-diagnosis of exudates'. That is, the microscopical examination of peritoneal, pleural and cerebro-spinal fluids. They laid down a series of diagnostic criteria in different diseases.

Widal's next work was on nephritis. He instinctively disbelieved the accepted classification of renal diseases based on anatomical criteria. He stated that what matters is how the functions of the kidneys are altered. Are all the substances to be excreted affected, or only some of them, and to what extent? Between 1903 and 1906 he published papers on the clinical features, chemical pathology and treatment of nephritis. He carried out blood urea estimations which were new at the time. He showed that raised urea levels were associated with anaemia, non-infective endocarditis, psychological changes, colitis and coma all in the absence of oedema. He showed that in another type of nephritis where oedema was present, salt deprivation reduced the oedema and a normal diet brought it on again. He observed that some of the effects of nephritis were due to hypertension and investigated the albumen and casts present in the urine of nephritics.

He did further bacteriological work on paratyphoid agglutinations and infectious jaundice, particularly spirochaetal jaundice. He worked on the immunization of the French Army against typhoid and paratyphoid. He devised sero-diagnostic tests for spirochaetal jaundice and actinomycosis. With Lemierre he developed a method for blood culture in typhoid.

From 1913 he investigated anaphylaxis, following up the work of Richet who discovered that phenomenon in 1902. Late in his life Widal followed up the work of Chauffard, his fellow-professor at the Cochin Hospital, on congenital haemolytic anaemias, by describing idiopathic acquired haemolytic anaemia (the Hayem-Widal type) and work on the cold type of paroxysmal haemoglobinuria.

The man who made these discoveries is described by his friends as of medium height and, despite a large head, handsome. He was somewhat rotund. He spoke with '. . . a very lively and enthusiastic voice'. His enthusiasm for his subject is mentioned almost as often as his '. . . alert and astonishingly penetrating eyes'. He remained young even in his sixties because he was very curious about the world around him and constantly in contact with young people. A friend (Edouard Rist) says of him, 'He loved his students and friends and treated them with bluff cordiality and laughing bonhomie which was his manner.' Photographs show a square rather Teutonic face with closely cut hair. He was a very reasonable man who was always prepared to be convinced by an opponent's argument if it was good. In what leisure he had he read history and particularly books about Napoleon whose genius had a strange fascination for him. Weissenbach, who knew him well, says 'He had a broad general culture and was interested in all the manifestations of the human spirit.' For this reason and because scientists occupied a very high social position in France he was often seen sitting next to his hostess at dinner in some salon, even when ambassadors were present. His study was decorated with Primitives. He was a fervent patriot. At the liberation parade in Strasbourg in 1919 he was quite

overcome with emotion. He was fond of travelling, for it satisfied his curiosity, but it is true to type that sometimes his journeys were cancelled at the last moment because there was some experiment to be done. He was married but had no children. It was medical science which was the passion of his life.

All accounts are agreed that Widal succeeded in narrowing the gulf between clinical and experimental medicine. As one doctor put it: 'He gave a sort of push to a whole generation by combining a clinical picture with laboratory work.' Widal described his own views in these words:

> I have always been firmly convinced that the study of the physical and biological sciences is the foremost task for the doctor who wishes to devote himself to research. These sciences, whichever they may be, constantly open up new horizons for him, equip him with precise methods of investigation, systematic techniques and measuring procedures, which enable him to bring the rigour of science to places where there were formerly only approximations and to replace what were only impressions with certainty. It is in applying scientific methods that medicine itself becomes a science. . . . The experimenter and the clinician can work in different ways, but their conclusions always arise from the same discipline. To the doctor who knows what he is looking for, observation sometimes affords very special cases which are so to speak 'spontaneous experiments'. These cases do not represent merely a fragment of the clinical picture, as is the case with many experiments conducted with animals; they represent the truth in its entirety for the very reason that they appear in the human subject. They can be sufficient of themselves to give the answer to a long unsolved problem.

With this outlook it was not surprising that Widal was made 'Membre de L'Institut' in 1919, an honour equal to the F.R.S. He had already in 1908 been made a member of the Academy of Medicine and in 1917 had received the highest French civil honour, the Grand Cross of the Legion of Honour.

Where he shone most was as a teacher. From his earliest days as an interne he possessed a talent for exposition and a remarkable command of words. For this reason crowds of people, students, housemen, registrars, and doctors from France and abroad flocked to his lectures. One of these left us the following description:

> Widal, who was complete master of his material as a result of long meditation, lectured without notes. He had lively and astonishingly penetrating eyes, and he would gaze at each member of his audience individually, one after the other. He understood almost infallibly which part of his exposition needed to be taken up again, presented in another way, recapitulated. And so it was that the idea which he wished to impress on the minds of his hearers always hit home and was fixed in the memory as often as not for good.

He died on 14 January 1929 at the age of sixty-seven.

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