It has been said that Graham (Figure 1) was the first to have proven the theory of the transmission of dengue by the mosquito. What was the exact contribution of Graham to the transmission of dengue fever? And who was Graham?

**GRAHAM AND DENGUE**

What about the exact contribution of Graham to the study of dengue? For a long time, I looked and searched for the publications of Graham on dengue fever, for a very long time, but I could not find anywhere a mention of this matter. I searched “A bibliography of AUB Faculty Publications” compiled by Suha Tamim [1] (who later became Mrs nimr `abdalfattâH Twqân) but there was no mention of any publication by Graham on the subject of dengue. One day in 1981, while I was perusing the unpublished index of Al-Kulliyah recently prepared by Professor Yusuf Khoury [2], I found that Dr najjîb `ardâtîy (Figure 2) had published in 1910 a paper on dengue fever.

Dr `ardâtîy was Adjunct Professor of Bacteriology at AUB; he lived just under the Beirut Old Lighthouse in his rosy colored multiarched house overlooking the blue Mediterranean. He was born in 1884 and graduated from AUB with an MD degree in 1906. He traveled to Vienna (1906-7, 1913, 1922), to Berlin (1906-7), to London (1922) and to Paris (1922).

While he was a member of the Sanitary Council of Beirut, he published a paper [3] on the typhoid epidemic that ravaged Ras Beirut in 1910. It had started in the second week of April and lasted until the third week. The number of patients seen in 10 days was about 1500, all of whom were clustered in an area bound by bâb idrîs, the lighthouse, rue Clémenceau and the sea. He investigated the matter very thoroughly and found out that the water main feeding the area in question was crossed by the sewer of the military barracks and hospital, and that it had been repaired two weeks before the beginning of the epidemic. Dr `ardâtîy goes on to say that most probably during the repair of the water main some contents from the sewer entered the drinking water [3]. Eight years later, Dr `ardâtîy became the Head of the Sanitary Department of Beirut (1918-21). He died on Mar 09 1944.

I pursued this line of search and tried for several years to obtain a copy of `ardâtîy’s paper on dengue which could perhaps lead me to the original work of Graham! First, I asked the Library of Congress for a copy of Dr `ardâtîy’s paper published in Al-Kulliyah, but to no avail. I tried the Libraries at Harvard and Princeton, also without success. Finally I remembered my very good friend Dr Yusuf Khoury {ywuf xwrî} from Yafet Library at AUB. He provided me with a xerox copy of `ardâtîy’s article. When I received it in the mail, only a few days after I had requested it, I was jubilant and ecstatic, as if I had won the lottery. Here at last came a ray of hope of finding the missing clue.

In fact, Dr najjîb `ardâtîy published his paper in 1910 [4]. It was entitled {Hummåy åldang} [Dengue Fever]. He referred to the original paper of Graham, which I finally located in 1993 in the National Library of Medicine, Bethesda, MD, where I also found a second paper on dengue by Graham [5].

In his paper, `ardâtîy mentions that Graham had performed several experiments on the transmission of dengue and that he was able to produce the disease by subjecting healthy humans to the bite of *Culex fatigans* which had been feeding on dengue patients.

A partial list of Syrian Protestant College (SPC) medical graduates between 1901 and 1909 is available [6, p 237]. Graham published his results in the Medical Record dated 1902 Feb 08 where he also reportedly found, in the red cells of patients, an active parasite which he named...
Haemameba (Hematozoon) dengui. These results could not be reproduced by other investigators. But ārdātāy was able to confirm this finding both with dark field unstained preparations and with smears stained with the Giemsa stain in patients who never had malaria. He gave a very vivid and clear description of these parasites, their growth and subsequent extrusion from the red cell. He also gave a differential between them and the malaria parasite saying that they were smaller, round, stained faintly, and had large granules. Ārdātāy also described with precision the symptoms of dengue fever and its complications which were not as mild as had been described before: subcuticular hemorrhage; epistaxis; severe hemorrhage from the stomach and the bowel which caused death in two patients; uterine hemorrhage; abortion in the 5th, 6th and 7th months; nausea and diarrhea; myocarditis that led to the death of two patients (a 4-year-old and a 14-year-old); conjunctivitis and edema which subsided with the defervescence of the dengue; recurrence and sometimes repeated recurrence; prolongation of the illness to more than three weeks [4].

Graham’s first publication on dengue fever was entitled Dengue: a study of its mode of propagation and pathology and was published in the Medical Record in 1902 [7]. The paper has eight figures. In it, Graham reviews the record and notes that dengue cannot spread to any extent when carried into dry and high places. Early in July of 1901, the city of Beyrouth in Syria was visited by an epidemic of dengue. The epidemic was settled to any extent when carried into dry and high places. Early in July of 1901, the city of Beyrouth in Syria was visited by an epidemic of dengue. The epidemic was settled when the house was ridden of the mosquitoes.

In Experiment 2: The house was ridden of mosquitoes and the children did not contract the disease from their sick siblings.

In Experiment 3: The dengue did not seem contagious when the house was ridden of the mosquitoes. Several other experiments of the same kind were recorded and in each case the result was the same: the dengue did not seem to be contagious when the mosquitoes were carefully kept out of the house.

A second group of experiments involved direct inoculation. Young men were used as guinea pigs “As the dengue is a disease not dangerous to life ... I believe these experiments to have been justifiable. It has been a very easy matter for a sum of five dollars, each, to run the risk of being sick, a week, with the dengue” [5]. Out of four cases, only three got the dengue, five, six and four days after the inoculation. The fourth case did not get the disease. He said that in the epidemic of 1889 he himself had a very severe attack lasting six days. During the epidemic of 1901, Graham himself escaped although constantly exposed, “I took no means to protect myself.”

Graham goes on to say that “I have carefully and systematically examined the blood ... in over one hundred cases; I was struck by the presence of an ameboid form in certain of the red blood corpuscles which was present in all the cases without exception ... It resembles the plasmodium malariae, but its cycle is longer and its phases much slower. It may not be absolutely proven that this hematozoon is the cause of the dengue, but its constant presence in the red blood corpuscle during the fever ... all point in the same direction and lead us to believe by analogy, if by no other way, that in this parasite we have the cause of dengue.”

In his second paper entitled The Dengue: a study of its pathology and mode of propagation and published in 1903 [5], Graham reiterates what he had written in his first article in the Medical Record in 1902 and adds the following supplementary remarks:

1. Graham saw over 500 cases of dengue in 1901.
2. He calls dengue “aboo-rikal”; this is probably a typoing or printing error; the actual and right word is “ābw ālrikāb”.
3. Culex fatigans is the culprit. Graham found it in all Lebanese villages up to 5000 feet.
4. “My excuse for exposing men to infection” wrote Graham “was that everyone was going to get it anyway, also that the disease is entirely without danger to life. The difficulty was not to find one willing to undergo the experiment but to select the best from many who offered.”
5. An inoculation experiment was carried out on two young men in a village in the mountain where no case of dengue had yet occurred. The first got the disease four days after sleeping in the netting. The second had his “initial chill after having passed five nights in the company of the mosquitoes”.
6. During this epidemic “a considerable number of cases occurred in the large village of Aley, which is 2300 feet above sea level. Few of the houses in this village were free of the Culex fatigans. bHamdwn is about 4000 feet above sea level and very dry with but few mosquitoes. Here, although the village is on the line of railway and several cases were imported from Beyrouth, yet the disease did not spread among those who did not descend to the city. Several cases occurred in Ainsofar, which is higher up (about 5000 feet) but which is not as dry as bHamdwn and which is more infested by mosquitoes. The villages like “arayyā, Cwaŷfât, etc. ... lower down and near Beyrouth, suffered almost as badly as Beyrouth”.
7. “An attempt was made to inoculate individuals with the salivary glands carefully dissected out and thoroughly mixed in a warm sterilized normal pep-
tonised saline solution. This solution was taken from a mosquito with a 27 day-old infection, and it was injected subcutaneously. On the third day the patient had a chill and high fever ... so strong that I desisted from further experiments in that line.”

8. I reproduce here Graham’s last paragraph:

“In the British Medical Journal of July 12th 1902, may be found a well-written article on the dengue by Dr F O Stedman of Hong Kong. He says among other things, ‘In several cases in which I have examined the blood during the relapse, I have found malaria parasites, and I hear that others have had the same experience; thus it seems that the attack of dengue either wakes up malaria, which has been lying dormant in the system, or else renders the patient particularly non-resistant to a chance fresh infec-
tion.’ I believe that Dr Stedman saw not malaria but the hematozoa of dengue ... the same means now used to pre-
vent malarial fevers must also be used to prevent communities from getting dengue. It is therefore a question of war against the mosquitoes, and when the Culex fatigans has been destroyed from among us I believe the dengue will be with us a thing of the past.”

DISCUSSION

A. After extensive experimentation, Graham concluded that dengue was due to an “ameboid hematozoon” which was transmitted by a Culex mosquito [5,7].

Today, it is believed that dengue is caused by four groups of B arboviruses, which are transmitted by the Anopheles mosquito. Several different varieties of dengue and denguoid conditions are recognized; one of them, West Nile fever, is transmitted by Culex univittatus.

In order to better understand Graham’s actions and conclusions, some medical events that occurred during this period (between 1880 and 1901) are recorded in the table below; they have most probably influenced him.

<table>
<thead>
<tr>
<th>MEDICAL DISCOVERIES AT THE END OF THE XIXth CENTURY</th>
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<tr>
<td>1880: Alphonse Laveran (1845-1922) discovered the malaria parasite.</td>
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<tr>
<td>1883: Robert Koch (1843-1910) discovered the vibrio of Cholera in Egypt [8].</td>
</tr>
<tr>
<td>1889: A dengue epidemic occurred on the Syrian coast.</td>
</tr>
<tr>
<td>1897: Ronald Ross (1857-1932) found out the role of the Anopheles mosquito in the transmission of malaria.</td>
</tr>
<tr>
<td>1901: A dengue epidemic ravaged Beirut and its surroundings in the autumn; it was summed “The great Dengue epidemic.”</td>
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B. We seem, after more than 100 years, to be faced with a challenging dilemma:

• We either accept the findings and conclusions of Graham and consider the epidemic which he studied a denguoid epidemic and call the disease Graham’s disease; in favor of this explanation is the fact that a denguoid disease (West Nile fever) is known to be transmitted by Culex mosquitoes.

• We assume that Graham erred when he considered the mosquito he used for the transmission to be a Culex. He also erred in thinking that he actually saw an ameboid hematozoon inside the red cells of his patients, when he may have been looking at some Giemsa precipitates that looked like hematozoans. In favor of this explanation is the fact that when I studied a malaria epidemic in 1950 [9], I used the same kind of microscope that was available to Graham (the old Leitz model) and I found it extremely difficult, almost impossible, to differentiate between the malaria parasite and precipitates of Giemsa, because of the pronounced chromatic aberration of the microscope. I had to use a new American made microscope to verify my observations.

C. Graham praises the climate of bHamduwn above that of çawfar and Aley and says that in general it is more salubrious. This observation has withstood the test of time. When I was taken ill with tuberculosis in 1943, Dr George Khayyat suggested that we spend the summer in bHamduwn instead of Aley, because the air in bHamduwn was dry and more salubrious. I presume that the teachings of Graham trickled down to Dr Khayyat who used them 21 years later.

D. Graham’s paper was published in February 1902, only a few months after the Beirut epidemic of dengue in July 1901, a remarkably short time compared to the delays we encounter nowadays. A paper published in Hong Kong in July 1902 is quoted in a paper written in Beyrouth and published in the United States in June 1903. Evidently the consideration and evaluation of submitted papers to the editor, the communications and the mail must have been faster in 1902 than they are now!!

E. It is interesting to note that, at the beginning of the 20th century, the microscope was a great instrument of research. It was so great that aspiring young physicians of any ambition were so impressed with the microscope that they wanted to be seen associated with the microscope which became a common feature in the photographs of physicians of the period (Figure 3).

F. One cannot fail to notice the following:

• The clarity, general style, logic, and precision of Graham’s two papers; this is an indication of the strong probity and great scientific acumen of the beloved teacher.

• When Graham mentions Beyrouth, he always adds the word “Syria”; because Beyrouth was then the capital of Ottoman Syria.

G. It is interesting to enumerate the salient events (the death of Virchow, Chekov, Caruso, Marie Curie, etc.) that represent the historical background against which Graham performed his experiments [6, p 244].
Dr Harris Graham
I knew from my Medical School days, from my old time teachers who, for the most part, were students of Graham (Professors Nimeh Nucho, Sami I. Haddad, Raif Abillama, Najib Saad, Hovsep Yenikomishian, Mustafa Khalidy, George Khayat, Philip Sahyun, and Philip Ashkar), that Graham was the famous Professor of Medicine at the Syrian Protestant College (SPC) renamed, in 1922, American University of Beirut (AUB). I also learned that Graham had a large clientèle that included the rich and famous socialite Lady L... His famous “takk” [two-wheel-one-horse-carriage] used to be seen frequently parked at her door, in Beirut, or at her summer home in Sofar (şawfar). I also learned that suspicious minds intimated that Lady L was not only a patient.

Actually, Graham became so famous that the Tramway station at the door of his house, in Ras Beirut, was named after him; and the long stairs East of the Dental School which lead from Avenue Perthuis down to mûnaö ālHuçn and which forms the Eastern boundary of the AUB Campus, was also named after him. When we moved from Háwwz ḥlsâ’atiyyé in 1932 to the dâ’wq house on Avenue Perthuis where Dr Ward used to live, I used to see Graham’s “takk” in the huge carriage garage of the house of Caýx sa’ýd ‘aýyâs where Graham used to live east of the dâ’wq House; only a stone wall separated the gardens of the two houses. We became friends with the two sons of Caýx sa’ýd: muHammad and ibrâhîm. There were many old carriages in that garage; I do not remember exactly how many; but at least three were eternally parked in there. We remained in the dâ’wq House, above the pharmacy, until the late fifties. Dr Ward had built, by the entrance of the House, a waiting room for the patients in the form of a beautiful octagonal kiosk, which we call today a gazebo.

Later on, I learned more about Graham from That they may have life and have it abundantly, the most wonderful book written by President Stephen B. L. Penrose Jr, a book which remains the ultimate storehouse of information and source book about the history of SPC and AUB; I learned that Dr Harris Graham was a Canadian from Toronto [13, pp 66-7], like Dr Charles Webster, Professor of Ophthalmology (Figure. 4) [14]. He graduated with an MD in 1885 from Ann Arbor, Michigan [15]. He first taught at Aintab (‘aýn tâb) Medical School, which closed in 1889. He was then appointed Professor of Pathology and the Practice of Medicine at the Medical School of SPC where he stayed until his sudden death in 1922.

Dr Graham was born on 1862 Mar 24 [15]; he would have been 60 years old when he died. “The sudden death of Graham on 1922 Feb 27, left a void in the Medical Faculty which was like a mortal wound.” [13, p 199]. “Dr Webster spoke of him … as ‘the central solid pillar of the Medical School’ [13, p 66]. Penrose writes: ‘Within three years of his appointment to Beirut, Dr Graham had so won the Turkish authorities that they sent him to the
Huleh district in Palestine to report on the cholera there. Later in the same year they asked him to study the spread of typhus, … among the pilgrims on the way to Mecca. He successfully performed both these tasks, which involved no little risk to himself … (he nearly died as a result of typhus infection acquired during the investigation). It was because of such services as these that both Dr Graham and Dr Webster, though technically enemies of Turkey, being Canadians, were permitted to practice freely in Beirut during the Great War. Both were called frequently to minister to high officials and their families.” [13, pp 66-7]; and again: “So great was his industry and all-round ability that it was necessary at his death to ask the Trustees to provide two men to take his place.” [13, p 66].

After his death, Mrs Graham (Ella T. Bray) became superintendent of the Hospital from 1922 until 1925 [13, p 226]. Graham died a little over two months before I was born (1922 May 04). In later years the great Lebanese painter, Mr ‘umar al’unsy, unknowingly, commemorated the date of death of Dr Graham (Feb 27) in his painting The cyclamens (Figure 5).

It was not until very recently that I got in touch with Ann Arbor Medical School to get more information about Dr Graham. I was referred to the Bentley Historical Library in Ann Arbor, which keeps material concerning the graduates of the Medical School. In the case of Graham this material included:

- Two photographs (Figure 6).
- Three obituaries: the first from the New York Evening Telegram of 1922 Mar 05 Sunday; the second from the New York Herald of 1922 Mar 06 contains the following details: “… later he took postgraduate courses in medicine in Germany and France. He was a specialist in tropical diseases.” The third obituary (most probably from a University publication) is slightly longer, gives a few more details, and is an exact reproduction of the next document.
- A letter (dated 1922 Mar 18) written by Dr WB Adams (Professor of Dermatology) who was a colleague of Dr Graham at the SPC; it was addressed to Mr RL Sensemann of the University of Michigan, and contains a little obituary: “… Directly after his graduation from Michigan Dr Graham was appointed a missionary to Turkey by the American Board. Immediately upon his arrival in Constantinople he was married to Miss Ella Bray, a fellow missionary, not without some difficulty, however. While in Michigan Dr Graham had taken out his first citizenship papers, but the American Legation at Constantinople could not issue a license on them, so he was obliged to revert to his British citizenship… He suffered many hardships in getting his work started in Aintab, his first position. The ship following his ship unfortunately sank, and took with her all Graham's possessions including his instruments, library and equipment… On the horseback journey to Aintab his horse kicked him and broke his leg (it must have been a mule ED). He reduced the fracture himself and continued his journey. For four years Dr Graham taught pathology and physiology in the Medical School connected with the Aintab Missionary College. When the Turks forcibly closed the school in 1889, Dr Graham was called to the Chair of Pathology of the American University of Beirut (SPC ED), which he filled with brilliant distinction for thirty-two years.”
- A hand written note on a small piece of paper, that stated he had obtained an AB from Toronto University in 1882, and another piece of paper dated 1922 Mar 24, stating that he died from encephalitis.

Figure 5. The cyclamens, by ‘umar al’unsy.

Figure 6. Medical Class of 1885, University of Michigan [15].
CONCLUSION

Whether we accept the facts as presented by Graham or we assume that he may have erred in some of his conclusions, we cannot but acknowledge the undeniable fact that Graham was and remains the first physician to have conclusively proven that dengue is transmitted by a mosquito.

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