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Medical progress

A historical view of alveolar echinococcosis, 160 years after the discovery of the first case in humans: part 1. What have we learnt on the distribution of the disease and on its parasitic agent?

Dominique Angèle Vuitton, WANG Qian, ZHOU Hong-xia, Francis Raoul, Jenny Knapp, Solange Bresson-Hadni, WEN Hao and Patrick Giraudoux

Keywords: *alveolar echinococcosis; Echinococcus species; epidemiology; history; Rudolf Virchow; western China*

Since the first 2 cases observed in southern Germany and the correct identification of a parasite at the origin of the disease by the famous scientist Rudolf Virchow in 1855, the borders of the endemic area of alveolar echinococcosis (AE) have never stopped to expand. The parasite was successively recognized in Switzerland, then in Russia, Austria and France which were long considered as the only endemic areas for the disease. Cases were disclosed in Turkey in 1939; then much attention was paid to Alaska and to Hokkaido, in Japan. The situation totally changed in 1991 after the recognition of the Chinese endemic areas by the international community of scientists. The world map was completed in the beginning of the 21st century by the identification of AE in most of the countries of central/eastern Europe and Baltic States, and by the recognition of cases in central Asia. Up to now, the disease has however never been reported in the South hemisphere and in the United Kingdom. In the mid-1950s, demonstration by Rausch and Schiller in Alaska, and by Vogel in Germany, of the distinction between 2 parasite species responsible respectively for cystic echinococcosis ("hydatid disease") and AE put an end to the long-lasting debate between the "dualists", who believed in that theory which eventually proved to be true, and the "unicists", who believed in a single species responsible for both diseases. At the end of the 20th century, molecular biology fully confirmed the "dualist" theory while adding several new species to the initially described *E. granulosus*; within the past decade, it also confirmed that little variation existed within *Echinococcus (E.) multilocularis* species, and that AE-looking infection in some intermediate animal hosts on the Tibetan plateau was indeed due to a new species, distinct from *E. multilocularis*, named *E. shiquicus*. Since the 1970s, the unique ecological interactions between the landscape, the hosts, and *E. multilocularis* have progressively been delineated. The important role of the rodent/lagomorph reservoir size for the maintenance of the parasite cycle has been recognized within the last 2 decades of the 20th century. And the discovery of a close relationship between high densities of small mammals and particularities in land use by agriculture/forestry has stressed the responsibility of political/economic decisions on the contamination pressure. Urbanization of foxes in Europe and Japan and the major role of dogs in China represent the new deals at the beginning of the 21st century regarding definitive hosts and prevention measures.

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Since the publication of the first cases in humans, in the middle of the 19th century, alveolar echinococcosis (AE) has been better and better identified in its geographical distribution and in its singularity as a cancer-mimicking parasitic disease. However, it has taken nearly one century to assess the responsibility of a distinct cestode, *Echinococcus* (*E.) multilocularis* at the origin of the lesions, and to delineate the extent of the geographical distribution of the parasite and of the infected patients. Both have not been fully determined yet, even though we may think that most is known regarding this subject. Progress in the elucidation of the interactions between the parasite and its hosts has not always been linear, and key-steps may be recognized in their understanding, which are associated with changes in concepts, improvement of techniques, and sometimes with random occurrence of simultaneous findings in various fields of research and/or particularly active or open-minded researchers. For more than a century AE has been a dreadful cancer-like disease, difficult to diagnose, nearly impossible to treat, and thus almost always fatal. Within less than half a century, it has become a chronic disease with a complete reversal of its prognosis. Most of reviews focus on the current state-of-the art, with little reference to history and on "how and by whom" progress

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has been made. Very old references are difficult to find; they were usually written in the local language of the physicians, surgeons and scientists who worked on the subject, i.e. nearly never English, since the disease was virtually not known in English-speaking countries for the first 100 years after the discovery of the first human case. These old references in German and French, and less old references in Japanese and Chinese are thus neglected by the English-speaking scientific community, whatever the country. In addition, not everything is published and a few key-events only persist in the memory of the actors! Moreover the content of the various MD or PhD theses which contain a lot of information is hardly accessible and rarely cited in scientific papers. In order to contribute to a better knowledge of the disease and the parasite among the young generation of physicians/researchers, a review of the existing literature, as well as personal experience of the authors and interviews of other researchers/physicians working in the field, have been combined to draw a comprehensive picture of the history of *E. multilocularis* and AE research which will be presented in 3 parts respectively dealing with what we have learnt since 1850 on: 1) the distribution of the disease and on its parasitic agent, which is the subject of this part of the review; 2) the interaction between the parasite and its host; and 3) the management of the patients with AE, which will be published in the second and third parts of the review.

ONCE UPON A TIME, IN GERMANY

Everything began as a German success-story, in the middle of the 19th century. In 1852, Franz Buhl, who worked in Münich[1] described the 1st case of a new condition in a patient from southern Germany;[1] in 1854 he had the opportunity to describe a second case of the same disease that he called "alveolar colloid";[2] he had found hepatic lesions consisting of many "alveoli" that contained a gelatinous mass, hence the name. He believed that the lesions were composed of degenerating tissue and not a form of a gelatinous cancer ("*gallertkrebs*") as proposed by Meyer[3] in his Thesis presented at the University of Zürich, Switzerland in 1854. In 1854 too, Zeller[4] reported a similar case in a patient who lived in Bad Urach, in the Schwäbische Alb, south to Stuttgart, in his thesis presented at the University of Tübingen, Germany. Both authors provided a detailed description of the new disease, but they were unable to determine its origin or the causative agent. It is the presence in Würzburg, not far from the places where these first cases were found, of the famous pathologist Rudolf Virchow (1821–1902) which certainly accelerated the discovery of the actual parasitic origin of the disease. Virchow had been offered a position as a professor of pathology at the University of Würzburg on the condition that he would no longer get involved with political activities, as he had distributed oppositional political pamphlets in Berlin and had been suspended from work![5] As early as 1855, Virchow[6] published the 4th case, with a systematic autopsy of the patient performed on March 5, 1855, and analyzed the findings reported by his colleagues on the 1st cases with a completely different interpretation. He stated that "*already the first glance at the specimen evoked the imagination of many little echinococcal vesicles*", an assumption confirmed by his careful microscopic examination which revealed fully developed protoscoleces in the vesicles. Such an observation, which is now considered to be a rather rare finding in humans, by chance favored his correct interpretation of "alveolar colloid" as an "AE", definitely a parasitic disease.[6] "Echinococcosis" was proposed as a name for the disease because protoscoleces were so typical of the "echinococcus" species of Taenia, already named and known at that time to be the agent of cystic echinococcosis, also called "hydatid disease". The parasite cycle of that "*Taenia echinococcus*" between dogs and sheep had just been elucidated in 1853 ought to the work of another German scientist, Carl Theodor Ernst von Siebold.[7,8] Von Siebold was contacted by Buhl and sent him animal samples which resembled his description in the human cases; such observations prompted Buhl to change his mind and consider that the disease he first described was indeed due to an "aberrant" *Taenia echinococcus*; he had nothing to do but agree with Virchow and to recognize that his Würzburger colleague had just been faster than him at publishing his remarkable pathological observations![9] The description of the clinical signs and symptoms of the disease as well as the meticulous account of the pathological findings which may be obtained in Buhl's and Virchow's papers are extraordinary in their precision and accuracy and their reading is highly recommended to those who are familiar with German! Those who are not may read the translation of the key-paragraphs in the historical vignette published in 2007 by Tappe and Frosch.[5] French readers will really enjoy reading the MD thesis of Perrin, published in 1932 (Figure 1), and which makes a synthesis of the situation regarding AE at that time and present clinical cases and pathological observations in detail![10]

AN "EUROPEAN DISEASE"?

Since the 1st case observed in Württemberg and Bavaria the borders of the endemic area of AE have never stopped to expand. Other AE cases were rapidly recognized in Germany and especially in Baden-Württemberg, especially in the Schwäbish Alb in the German Jura, and in Bavaria in the German Alps. In Switzerland, in the Zürich/St Gall area, and in Austria, in Tyrol in the Austrian Alps, several cases were discovered within the 1850s, not long after the 1st German cases;[11-13] in 1867, the 1st AE patient in a French-speaking area lived in a Swiss village distant of 10km from the French border in the Swiss Jura.[10] In 1886, Hermann Vierordt from Tübingen, Germany, published a total of 79 AE cases from Austria, Germany, and Switzerland.[14] The first published French case was observed in 1867 in Paris in a young Bavarian man,[15,16] but the first French autochtonous patient lived in Haute-Savoie, in the north of the French Alps, not far from Evian and Geneva Lake,

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L'Echinococcose alvéolaire du Foie
principalement chez l'Homme en France

THÈSE

présentée et soutenue publiquement le jeudi 14 janvier 1932
POUR OBTENIR LE GRADE DE
DOCTEUR EN MÉDECINE
PAR
PERRIN (Maurice-Louis-Henri-Marcel)

Ex Interne provisoire des Hôpitaux de Besançon
Ex Interne des Hospices de Bar-le-Duc
Diplômé d'Hygiène
né le 15 juillet 1906, à Besançon (Doubs)

Examinateurs de la Thèse : MM. MICHEL, professeur ..... Président.
ROBERT, professeur .....
THIRY, professeur ..... Juges.
ABEL, agrégé .....

Le Candidat répondra aux questions qui lui seront posées sur les diverses parties de l'enseignement médical

NANCY
IMPRIMERIE GEORGES THOMAS
28, RUE DE SOLIGNAC
1932

Figure 1. Cover page of the MD thesis of M Perrin, intern at Besançon hospital, Franche-Comté, France in the 1920–1930s, which comprehensively gives the epidemiological status of AE in Europe in 1930 and the arguments for the "*unicist*" versus "*dualist*" theory (Library of the Faculty of Medicine, Henri Poincarré University, Nancy, France).

and thus of Switzerland; the case was published in a MD thesis presented at the University of Geneva, Switzerland, in 1890.[17] In 1931, Maurice Perrin, cited above, an intern of the Besançon hospital, in his very well documented MD thesis presented at the University of Nancy, reported the 13 recognized French cases at that time, including 8 cases in the Jura area and 2 cases in German patients living in France (Figure 1).[10] Table 1 gives the epidemiological status of AE cases in Europe in the 1930s, according to Posselt[12] and Perrin.[10] If we compare European cases in humans between 1852 and 1928 and between 1982 and 2000 the main and striking differences are 1) the considerable increase in the number of cases: 307 patients within a 80-year-period in the 2nd half of the 19th century and the beginning of the 20th century, versus 559 cases within a 9-year-period at the end of the 20th century and beginning of the 21th; and 2) although the highest percentage of cases/total population was reported in Switzerland in the 2 periods, the number of cases proportionally decreased in Germany while it considerably increased in France. Major improvement in diagnostic methods and especially imaging techniques is certainly much involved in the increased prevalence of the disease over the centuries. It is difficult to say if the far lower number of cases in France and French-speaking Switzerland than in Germany and German-speaking Switzerland during the 80 years which followed the discovery of the 1st case in Germany was actually due to a real lower incidence of cases or to a lack of knowledge on the disease, since most of the medical literature was written in German and the political situation did not favor contacts between scientists at that time. However, it must be mentioned that the first publication in French may be found as early as 1866, as an article by Friedriech, translated from German,[18] and several French textbooks in the XIXth century mention the disease but they state that it is unknown in France.[10]

Table 1. Epidemiology of alveolar echinococcosis in Europe, comparison between the number of human cases collected between 1852 and 1928 (77-year period)* and between 1982 and 2000 (9-year period)†

Country region	Number of cases 1852–1928	Number of cases 1982–2000
Germany	159	132 (6)§
Bavaria	80	
Württemberg	53	
Bade	11	
Hessen (9), Hanover (4), Berlin (1)	14	
Mecklenburg	1	
Austria	96	54 (1)‖
Tyrol and Salzburg	77	
Carinthia	5	
Styria	14	
Switzerland	164 (2)‡	118 (6)‖
North-Eastern German-speaking "*cantons*"(Zurich, St Gall, Thurgau)	142	
South-Western French-speaking "*cantons*"	22	
Geneva	3	
Neuchâtel (*Val de Travers*)	1	
Vaud	6	
Bern (*currently Bern and Jura*)	12	
Other Alpine regions of Eastern Europe	4	
Czechoslovakia (currently Czech Republic)	2	
Moravia	2	
Poland	0	14
Belgium	0	3
France	13 (2)§	235
Jura/Ain area	8	
Alps/Savoy	1	
North of France	1	
Cantal (Massif central)	1	
Northern Italy	3	
USA	2 (2)§	
Total	600	559

*According to Posselt, 1928, and Perrin, 1932; †cases collected according to the same methodology in all European countries (EurEchinoReg project) and published by Kern et al, 2003; ‡includes 2 cases in French patients; §includes only German patients (within brackets); ‖includes 15 non-autochthonous cases (within brackets); 7 of them originated from neighboring countries, 3 from Turkey, 3 from the ex-Soviet Union, 1 from Kazakhstan, and 1 from Afghanistan.

TOWARDS EAST

For a while, it was considered that AE was restricted to the mountainous areas of Jura and Alps in central Europe. However, the discovery of the first case in Russia in 1879 was followed by many others, in the Moscow area, the Volga region (Kazan), and in Siberia (Tomsk and Irkutsk regions), which contradicted this belief;[19] in 1900, Posselt was able to list 213 recognized cases of AE, including 30 cases from Russia;[20] in 1928, the number of Russian cases amounted 209.[20,21] Posselt believed that the disease was initially originating from the Bavaria/northern Switzerland/Tyrol area and explained the discovery of AE cases in Russia by the export of animals from the Alpine regions to Russia in the past.[10] Subsequent studies and the molecular analysis of cases have since shown that the reverse situation was likely true: the original focus is Siberian, with an extension of the parasite cycle to the West and Central Europe, the South and Western China and Central Asia, and to the American continent through the Bering Detroit.[22,23] Cases were disclosed in Turkey in

1939;[24] then much attention was paid to Alaska and to Hokkaido, in Japan. After the discovery of the 1st human cases in Alaska, for half a century since the beginning of the 1950s and until the end of 1990s, the little and remote St Lawrence Island in Alaska, in the Bering Sea, was the focus of interest of major scientists such as Robert ("Bob"!) Rausch and Peter Schantz; and their studies were crucial for our understanding of the real agent of AE, *E. multilocularis*, and for the diagnosis and treatment of the disease in humans, respectively.[25-27] Such advances will be reported below.

In the first half of the 20th century, the "Hokkaido story" was emblematic of the responsibility of humans in the introduction of the disease in a previously free area: the first human case of AE was recognized in that northern island of Japan in 1936.[28,29] Map analysis of the progressive spreading of the disease led to the conclusion that *E. multilocularis* had been artificially introduced to Hokkaido in infected foxes transferred to Rebun Islands, northwest of Hokkaido, from the Kurile islands, to fight against rodents, a pest for Hokkaido farmers, in years 1924–1926. Another transfer of foxes took place in the 1960s. Spreading of the parasite and occurrence of human cases has followed, and the disease has become a public health problem and prompted physicians and scientists of Hokkaido to set up systematic screening programs in rural areas, and to develop research in the various domains of surgery, eco-epidemiology, serological and imaging diagnosis, and control and prevention, under the leadership of Junichi Uchino and Naoki Sato for the management of the clinical cases and of Masao Kamiya for epidemiological studies in animals.[30,31] A total of 383 AE cases were detected up to 1999, and currently 5–9 cases per year are newly disclosed by the Committee for Echinococcosis Control in Hokkaido.[31]

EMERGENCE OF CHINA AS "THE" ENDEMIC COUNTRY

Since the 1940s, the epidemiological situation regarding AE in the world seemed quite stable. AE was considered as a rare disease, mostly European, with the exception of Hokkaido. It totally changed in 1991 after Philip S ("Phil"!). Craig with the Chinese parasitologists working in Xinjiang Uygur Autonomous Region, LIU De-shan and DING Zhao-xun, stressed in Parasitology Today,[32] then in The Lancet[33] that the most important endemic area for AE might well actually be located in China. By the way, it may be mentioned that citation of authors in these publications used the 1st names and not the family names of the Chinese scientists (for instance Deshan L for Liu DS, Zhaoxun D for Ding ZX, or Dazhong S for Shi DZ), which may be confusing, since some of them were then authors of several papers in international journals, under their correct family names! In fact, human AE cases were firstly recognized in Xinjiang where first cases were discovered as early as 1956 and a cumulative report of 6 clinical cases published in 1965 by YAO Bin-li,[34] the head of the surgery department at the 1st Teaching Hospital of the Xinjiang Medical College in Urumqi (Figure 2). Cases in Qinghai Province, where the first reported patient was a 22-year-old man who died of AE brain metastases in 1959, were also published in the 1960s;[35,36] as well as in Gansu where JIANG Ci-peng[37] wrote several papers on the series of cases observed in the capital city of Gansu Province, Lanzhou. This however went totally unnoticed because the papers were published in Chinese language in Chinese medical journals, and because of the political situation of the People's Republic of China, largely left out from the rest of the world and totally engaged in the Cultural Revolution during that period. At the end of the 1970s, after the opening of China to the world, Chinese parasitologists and surgeons had contacts with researchers from the Liverpool School of Tropical Medicine and got their attention to the problem of echinococcosis in China. YAO Bing-li, who may be recognized as the founder of the very active community of scientists working in Xinjiang on alveolar echinococcosis, got in touch with his colleagues of western countries at the world congress of Hydatidology in Madrid, Spain, 1985 and, in 1986, published his experience of the surgical treatment of 52 cases.[38] Infected animals were first reported from central China in the 1980s .[39,40] Up to date, eight provinces or autonomous regions in China have been found endemic, including Qinghai, Xinjiang, Gansu, Sichuan, Tibet, Ningxia in west China where human cases and animal epidemiology are very well documented, and Inner Mongolia in the north as well as Heilongjiang in the northeast China where more studies are necessary to delineate the importance of the disease.[41,42] Details on the historical aspects and current findings, and especially original references in Chinese, may be found in PhD theses by ZHOU Hong-xia, for Xinjiang,[43] WANG Qian for Sichuan and the Tibetan plateau,[44] and YANG Yu-rong for Ningxia,[45] and related papers by these Chinese scientists. Under the leadership of Phil Craig, and after preliminary studies in Xinjiang and in Gansu, a series of

Figure 2. YAO Bing-Li (1919–1991), head of the Department of Surgery of the First Teaching Hospital of Xinjiang Medical College, Urumqi. He graduated from Zhongzheng Medical College of Nanchang University in 1946, and moved to Urumqi from Shanghai in 1957. Author of the first publication on alveolar echinococcosis in China, he was the first contact between Chinese scientists and the international scientific community and the founder of the research team on echinococcosis in Urumqi, Xinjiang (Sculpture, Research Building of the First Teaching Hospital of Xinjiang Medical University).

multinational, multidisciplinary and comprehensive epidemiological studies based on mass screening in rural villages using ultrasound examination of the liver and serology, combined with the study of risk factors, including behavioral, geographical, ecological and socio-economical parameters was initiated in 1994 in several Chinese provinces and autonomous regions. They were co-funded by the European Commission then the National Institute of Health of the USA and by the local institutions involved in the studies (Xinjiang Medical University and its 1st Teaching Hospital, Lanzhou Medical College, Ningxia Medical College, and Qinghai and Sichuan Centers for Endemic Diseases, currently CDCs) with additional support from Western and Asian universities (University of Salford, of Franche-Comté, of Asahikawa, etc.) and administrations (from the UK, France, Japan, Australia, etc.). The first campaign of mass screening in Gansu revealed the unique situation of some of the Chinese endemic areas, such as that found in Zhang and Ming Counties of Dingxi Prefecture where the prevalence of AE reached 16% in the village of Ban Ban Wan, Zhang county, the highest ever found in the world, and the average prevalence was 4% of the screened population.[46] This academic initiative, which now focuses onto more specific research issues, has currently been followed by a national program for surveillance and management of the disease in China, which involves 14 ministries and is certainly the most ambitious state-funded project ever implemented to diagnose and treat AE in the world.[47]

BACK TO EUROPE

The world map was completed in the 2000s by the identification of AE in most of the countries of central/eastern Europe and the confirmation of the presence of infected foxes in most of European countries. After the initiation by Dominique Angèle Vuitton and Peter Kern, in 1997, of the "EurEchinoReg Registry" aimed at updating the epidemiological situation in Europe[48] (Table 1), the discovery of an increase of fox infections in the previously known endemic areas and the urbanization of the life cycle, the re-emergence and public health threat of AE was stressed.[49,50] The pan-European "EchinoRisk" project, under the coordination of Thomas Romig and Patrick Giraudoux, stimulated research on the definitive hosts of *E. multilocularis* in Europe and led to the identification of human AE cases in Hungary, Czech republic, Slovakia, Romania, and to the evidence for the infection of foxes in all European countries, except Spain and Portugal.[51,52] The symposium on the Epidemiology of AE in Europe, held in Nancy/Malzeville, France, in September 2010, has allowed researchers to sum up their results and share their experience on the situation in Europe regarding AE. Emergence (or recent recognition?) of the disease in the Baltic States is the most striking epidemiological finding of the beginning of the 21th century. Lithuania, in particular, now definitely appears to be a major endemic area, with 80 patients diagnosed between 1997 and 2006 for a total population of 3535547 inhabitants, 57% of foxes, several farmer dogs, and various intermediate hosts found infected by *E. multilocularis.*[53] The parasite has also recently crossed the straits between Denmark and Sweden, reaching south-west Scandinavia, which was supposed *E multilocularis* free before.[54] Up to now, the disease has however never been reported in the South hemisphere and in the United Kingdom.[55]

TO BE ONE OR TO BE TWO, THAT IS THE QUESTION

It had taken only 3 years to attribute the disease found in a German farmer to a parasite of the genus *Echinococcus*; it took almost a century to clarify that the *Echinococcus* responsible for AE was distinct from that responsible for cystic echinococcosis! An excellent and detailed history of the famous controversy between "unicists" and "dualists" may be found in the review by Tappe et al in 2010.[56]

Virchow clearly believed that the disease he properly identified as a parasitic disease was nothing but a particular variety of hydatid disease, thus due to the parasite *Taenia echinococcus*, identified by von Siebolt who fully agreed with this interpretation, as well as Buhl. They were followed in their belief by several clinicians, and/or pathologists and researchers including Diesing, Naunyn, Küchenmeister, Klemm, Jenckel, and as early as 1863 by Rudolf Leuckart.[56] This physician and parasitologist from Leipzig, however, first stated that Virchow's description was actually different from the usual morphology of the hydatid cyst, and could thus be attributed to a different, "alveolar" larval "form", *Echinococcus multilocularis*, but was nevertheless due to the same *Taenia echinococcus* species. These scientists unexpectedly, given the political situation between France and Germany, received strong support from Félix Dévé, a French physician who was the head of a department of internal medicine in Rouen, in the North-West of France, an area endemic for CE but not for AE at that time. Initially in favor of 2 different species, Dévé nearly dedicated his life between 1900 and 1930 to find scientific evidence for the "*unicist*" theory, as it was called at that time, i.e. the responsibility of a single species for both "cystic" and "alveolar" echinococcosis.[57] He soon became the French champion of that cause. Against odds, Félix Dévé, in 1931, eventually observed a case of AE in a 27-year-old Germany patient from Württemberg and living in Le Havre, Normandy, France, who was hospitalized in his medicine department in Rouen after the surgical discovery of the disease![58] Detailed bibliography of Dévé and the description of this patient may be found in the thesis of Perrin, who went to Rouen to visit Dévé, the "echinococco-nut" of the "*années folles*", and had the opportunity to examine the patient.[10] Among the strongest arguments of the "*unicists*" was the similarity of "alveolar echinococcosis" described in humans and the "multilocular echinococcosis" observed in animals, and especially

cattle. In 1861, Johann Huber, from Memmingen in Bavaria at the border from Baden-Württemberg, discovered an alveolar lesion in cattle which had many traits in common with the alveolar echinococcosis found a few years earlier in humans in the same region; same observations were made by several German veterinarians and by the Swiss Guillebeau, from Bern, in 1890.[10,56,59] The French veterinarians, Raillet and Morot also published on cases of "bovine multilocular echinococcosis" in 1892;[60] Morot in 1899 estimated to one hundred the number of cows with the disease in the slaughterhouse of Troyes, in the North-East of France.[10]

Opposite to the "*unicists*" were the "*dualists*"! Led by Adolf Posselt, and among them the Swiss Morin who was the first in 1875 to evoke the possibility of 2 distinct species, and also Vierordt, Vogle, Mangold, Müller and the Russian Melnikow-Raswedenkow, they were convinced that the 2 diseases in humans, cystic and alveolar, were caused by 2 different parasites.[61] Animal experiments performed between 1875 and 1930 to demonstrate that feeding dogs with "alveolar echinococcosis" larval material could lead to the production of adult worms with distinct characteristics just added to the confusion. Despite all the efforts made by Posselt to conduct his animal experiments under rigorous scientific conditions, either the experimental design or the interpretation of the descriptions which showed anatomical differences were questioned and refuted by the "*unicists*"![10,56] Given the failure of that "anatomical/pathological argument", the "geographical argument", i.e. the restricted area where human AE cases were found and which were distinct from those where cystic echinococcosis was most prevalent, was among the best arguments of the *dualists*; the occurrence of "multilocular" lesions in cattle everywhere in Europe was explained by the exportation of Simmental cows from Switzerland to many countries, including to Russia through German immigrants! One century later, we may think that the "geographical argument" could never have been used if the first discovery of the disease had been made in China where both cystic and alveolar echinococcoses are present in the very same areas.[42] Anyway, despite the advantage given to *dualists* by the distinct geographical distribution of the 2 diseases in Europe, every new experiment or observation (as that of a "pseudo-alveolar echinococcosis" in Australia, a fief of "cystic", hydatid, disease) re-started the debate without solving it, and the 2 fierce opponents, Posselt and Dévé, never failed to fight at any meeting and in their publications, until Dévé stated peremptorily in 1948 that "the *dualistic* concept should definitively be abandoned"!

But scientific evidence has finally triumphed: in the 1950s, both in the far North of the world and in the very area where the first human cases were found, the "*dualistic*" concept was proven to be true. Robert Rausch and Everett L. Schiller, working on the helminth fauna in Alaska, discovered naturally infected northern voles, and conducted convincing experiments by infecting an artic fox from the lesions found in infected voles.[62] Together with the discovery of naturally infected foxes and of human cases of AE in Eskimos in the same area, these findings updated the suggestion of a possible "*E. multilocularis*", dear to the "dualists", which could be a true species identical to "*E. sibiricensis*", as named by Rausch and Schiller after their experiments in Alaska[25]. Inspired by these findings, Hans Vogel, parasitologist and physician at the Tropical Institute, Hambourg, Germany, conducted similar research in 1954–1957 in the Swabian Jura in Southern Germany, and found naturally infected *Arvicola* sp. voles with "alveolar" lesions, and adult worms in red foxes; he succeeded in infecting foxes from vole parasitic larvae, and voles from parasitic eggs found in the intestine of foxes:[63,64] the cycle was finally described and the parasitic agent was definitively named *E. multilocularis* Leuckart 1863, in memory to the first scientist who named it so, not regarding his "*unicist*" heretic religion! Opposite to *E. granulosus* which was soon split in several subspecies, some of which have now gained the status of species, [65] *E. multilocularis* has long been considered very homogeneous and attempts at finding subspecies using various tools, including usual molecular biology markers, have usually failed.[66,67] Identification of the tandemly repeated microsatellite marker EmsB (the "B" being for Besançon and Bart!) by Jean-Mathieu Bart and Jenny Knapp in the mid-2000s[68-70] has allowed a European consortium, as part of the European project Echinorisk, to map the genetic diversity of *E. multilocularis* in foxes at a continental scale, suggesting that the recent spreading of *E. multilocularis* may be the result of mainland – island processes from the traditional endemic areas of the northern Alpine arch to the northern new areas.[23,71] The speciation within *E. multilocularis* is nevertheless not questioned. And the infection of humans by the recently discovered new species *E. shiquicus*in China has never been demonstrated yet. This species, definitely different from *E. multilocularis*, as proven by DNA sequencing, and named after "Shiqu", the county of the Tibetan plateau in Sichuan where it was found, has similar but more "polycystic" pathological characteristics as *E. multilocularis* in its larval form in the intermediate host and a few morphological differences in the definitive hosts.[72]

OF MICE AND MEN

Bob Rausch in his studies on St Lawrence Island has been the first one to apply a holistic approach to understand *E. multilocularis* transmission. He pointed out the prominent role of community processes such as vole outbreaks in maintaining large transmission intensity.[25,70,73] Those seminal studies stressing on the role of a large reservoir of intermediate hosts to maintain the parasite cycle in a given area were followed later on in eastern France by Pierre Delattre and Patrick Giraudoux,[74,75] after *E. multilocularis* was found in a vole on the 1st plateau of the French Jura for the first time by René Houin and Martine Liance;[76] at the same time, Kenichi Takahashi

and his team in Hokkaido performed similar studies which were only published later.[77] Since the late 1980s, several studies carried out in France pointed out the correlation between land cover and transmission in wildlife: grassland landscapes were more likely to maintain intensive transmission by foxes.[78,79] Eco-epidemiology studies conducted by Patrick Giraudoux and his team in Franche-Comté, France in the 1990s found how ecological processes (landscape, small mammal population dynamics and prey/predator relationships) may lead to more intensive transmission and human exposure. This approach grounded on concepts of landscape ecology was thereafter successfully applied to various ecological systems and provinces/regions of China: Gansu, Ningxia and the Tibetan plateau.[80-83]

FOXES AND DOGS

The wild cycle which involves foxes and voles, as in the premonitory painting by Courbet in the French Jura endemic area in 1860 (Figure 3) just a few years after the discovery of the disease, was considered to be by far the most common one in Europe. The role of dogs in the transmission to humans was also shown soon after the discovery of the wild cycle in Alaska, and the discovery of a major role for dogs in China at the beginning of the 1990s stressed the public health significance of dog infection.[42] The significance of dog infection in terms of parasite burden in the environment and risk of contamination has been extensively studied on the Tibetan plateau by Paul Torgerson and Christine Budke and other participants in the "NIH-TransEch" multinational multidisciplinary project coordinated by Phil Craig from 2001 to 2008[81] The 1990-2000s have been crucial to elucidate the relationship between vole and lagomorph (*Ochotona sp.*) populations, dog infection and occurrence of AE in humans, as well as their links with socio-economical events, such as deforestation, land privatization, overgrazing of pastures, and/or rodent poisoning. Such studies have stressed the influence of changes in land use by agriculture, political decisions, and cultural habits on the functioning of *E. multilocularis* cycle, both in Europe and in China.[42,44,83-89] The growing importance of dogs as pets has made Johannes Eckert hypothesize that dogs could well also become a major source of contamination in Europe.[49,90,91] But the cunning fox had not said its last word! The increase in fox population partially due to the success of the anti-rabies vaccine has led to an increase both in fox population density and infection in all the endemic areas under study in Europe. The German team in Hohenheim in 1995 detected the possible re-emergence of *E multilocularis* in Germany,[92] re-emergence which revealed thereafter to be general in Europe.[50,93] A correlation was found between the increase in human cases within the first years of the 21st century and increase in the populations of infected foxes.[51] After preliminary reports on the situation in Sapporo, Hokkaido, Japan, Thomas Romig in Germany and Peter Deplazes, J Eckert's successor at the Institute of Parasitology in Zurich, Switzerland, were the first to conduct comprehensive studies on the potential risk represented by the new behavior of foxes, and especially their urban habitat;[50,94,95] such studies have been extended to several cities of the endemic areas, showing that the threat was real and this has prompted several teams to try and develop control measures.[96,97]

Figure 3. "Fox in the snow" *(Renard dans la neige)*, painted by Gustave Courbet in 1860 in the AE endemic area of the French Jura Mountains: a premonition of the key role for the predator/prey relationship in *E. multilocularis* parasite cycle and in human contamination? *(Dallas museum of art, USA).*

FROM EPIDEMIOLOGICAL OBSERVATIONS TO CONTROL MEASURES

Progress in the delineation of fox infection has been made possible thanks to new tools which could substitute for the time-consuming and most criticized counting of worms in the intestine of autopsied carnivores, especially foxes. The detection of *E. multilocularis* antigens in carnivore feces using ELISA was developed concomitantly by Phil Craig and Peter Deplazes,[98,99] and soon applied to field surveys in animal epidemiology and parasite transmission ecology.[100-102] A rather poor specificity prompted research teams to develop *E. multilocularis* DNA detection using PCR, firstly proposed by Stéphane Bretagne and René Houin in 1992.[103,104] Both techniques which are not yet completely adapted to the diagnosis of infection at the individual level[105] have, however, been largely used for epidemiological purpose and to assess the efficacy of control measures.[106-112] More recently host-fecal tests adapted to the regional fauna have been implemented in order to lift the ambiguity of feces identification when collected in the field.[111,113]

Opposite to the situation with *E. granulosus*, considered to only involve a domestic cycle, *E. multilocularis* present in wild animals was long considered to be inaccessible to control. However, because he considered dogs to be the main responsible definitive hosts able to disseminate infected feces on St Lawrence Island, Bob Rausch, once again a pioneer in that domain had long ago tried baits with praziquantel to decrease the parasite burden in the environment and thus the risk of human contamination, with apparent but not long-lasting success.[114] Thomas Romig and his team were the first to conduct aerial baiting and integrated methods in the early 2000s to control *E. multilocularis* in rural areas of Southern Germany, with foxes as definitive hosts, and

significantly reduced infection.[115,116] Masao Kamya and Narioki Nonaka from the Graduate School of Veterinary Medecine in Sapporo,[117] for Hokkaido, and Daniel Hegglin and Peter Deplazes, from the Institute of Parasitology in Zurich,[118] for Switzerland, have provided evidence that *E. multilocularis* could be controlled effectively by the hand-delivery of praziquantel locally in suburban and urban areas. Their example has been followed in France in cities such as Annemasse or Pontarlier, at the Swiss border (Comte et al, manuscript submitted for publication).

CONCLUSIONS

History of the epidemiology of alveolar echinococcosis has been marked for more than one century by a succession of short periods of accelerated discoveries and long periods of stagnation. Pace acceleration was usually favored by the introduction of new technologies such as ultrasonography and ELISA which transformed the diagnosis of the disease in humans in the 1970s, or detection of coproantigens and copro-DNA which made large surveys of the infection in the animal hosts possible in the 1990s. Unique geographical situations, such as islands (St Lawrence in Alaska, Hokkaido in Japan) where the parasite cycle could be followed nearly experimentally, or on the opposite wide regions with high prevalence (western China) where areas could be compared regarding prevalence of the disease both in humans and in animals, predator/prey relationship between definitive and intermediate hosts, and human behavior, have also contributed to major advances in knowledge as well as did unique personalities of researchers, both open-minded and rigorous in their scientific demonstrations (Virchow, Rausch, among others cited in this review). Since the 1980s, continuous progress has been mostly due to the efficacy of multidisciplinary networks of researchers all over the world, first in Europe, then between Europe and Asia, within the framework of common research projects and of the WHO-Informal Working Group on Echinococcosis, founded by Johannes Eckert and successively led by Dominique A. Vuitton, Peter Schantz, Phil Craig and Peter Kern. Such an exemplary cooperation, supported by public funding, may be regarded as essential to get proper knowledge and address appropriate public health issues regarding an “extremely neglected disease” such as alveolar echinococcosis.[119,120]

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