

Submitted: 18/10/2018

Accepted: 04/01/2019

Published: 22/01/2019

## Baseballs, tennis balls, livestock farm manure, the IDH1 mutation, endothelial cell proliferation and hypoxic pseudopalisading (granulomatous) necrosis: *Mycobacterium avium* subspecies *paratuberculosis* and the epidemiology, cellular metabolism and histology of diffuse gliomas, including glioblastoma

Ellen S. Pierce\*

13212 East Blossy Avenue, Spokane Valley, Washington, USA

### Abstract

An increased rate of diffuse gliomas, including glioblastoma, has been noted in livestock farmers in Western countries. Some researchers have suggested that a zoonotic virus or bacteria present in the livestock animal's feces or manure may be a possible etiologic factor. *Mycobacterium avium* subspecies *paratuberculosis* (MAP), the cause of a chronic enteropathy in domestic livestock and a probable zoonosis, is heavily excreted in an infected animal's feces or manure, contaminating soil and ground on the animal's farm. Once excreted in an animal's feces, MAP lasts indefinitely in a dormant but viable form, and easily spreads outside farms to the surrounding environment. MAP's presence throughout the soil in countries where MAP infection of domestic livestock is extensive and long-standing may explain the increased rates of glioblastoma in tennis and baseball players who handle balls coated with MAP-contaminated dirt. MAP infection is consistent with glioblastoma's two defining histopathologic characteristics: endothelial cell proliferation and pseudopalisading necrosis. MAP is a non-tuberculous or atypical mycobacterium, which can cause hypoxic necrotizing granulomas, granulomas that resemble areas of pseudopalisading necrosis. There are known bacterial causes of endothelial cell proliferation. Almost unique amongst intracellular bacteria, MAP's variant isocitrate dehydrogenase 1 (IDH1) enzyme, a type 2-oxoglutarate ferredoxin oxidoreductase, can use a host cell's cytosolic  $\alpha$ -ketoglutarate in its own Krebs or tricarboxylic acid cycle. MAP's ability to use a host cell's  $\alpha$ -ketoglutarate may explain the survival advantage of the cytosolic IDH1 enzyme mutation for patients with diffuse gliomas including glioblastoma, astrocytoma, and oligodendroglioma, a mutation that results in a reduced supply of cytosolic  $\alpha$ -ketoglutarate. MAP may therefore be one possible infectious cause of glioblastoma and the other histologic categories of diffuse glioma.

**Keywords:** Diffuse gliomas infectious etiology, Endothelial cell proliferation, *Mycobacterium avium* subspecies *paratuberculosis*, Necrotizing atypical mycobacterial granulomas, Transdifferentiation.

### Introduction: Suspected infectious causes of glioma

Infectious agents have been suggested as possible causes of nervous system tumors of several histopathologic types (Altieri *et al.*, 2006; Alibek *et al.*, 2013). Given their neurotropism, viruses have been the focus of investigation into possible infectious causes of brain cancers (Kofman *et al.*, 2011), including the human herpes viruses cytomegalovirus (Pandey, 2011; Dziurzynski *et al.*, 2012; Wick and Platten, 2014; Holdhoff *et al.*, 2017) and Epstein-Barr virus (Akhtar *et al.*, 2018). The parasite *Toxoplasma gondii* is a proposed non-viral infectious cause of brain cancer (Schuman *et al.*, 1967; Thirugnanam *et al.*, 2013). Two case reports relate the bacteria *Borrelia burgdorferi* to glioblastoma (Colpak *et al.*, 2014; MacDonald, 2018).

### Zoonoses on ruminant animal farms and the epidemiology of glioblastoma and other diffuse gliomas

There is a long noted increased rate of gliomas, including glioblastoma, in rural residents of Western countries who live in areas where domestic livestock farms are

located (Brooks, 1972; Wingren and Axelson, 1992; Howell *et al.*, 1995; Hansson and Ferguson, 2011). Farm residents (Choi *et al.*, 1970) and farm workers (Musicco *et al.*, 1982; Blair *et al.*, 1985; Khuder *et al.*, 1998), in particular, domestic livestock farmers (Reif *et al.*, 1989a,b; Lee *et al.*, 2002) including sheep (Reif *et al.*, 1989a) and dairy (Milham, 1976; Reif *et al.*, 1989a,b; Morrison *et al.*, 1992) farmers, have an increased risk for brain cancers, with a predominance of diffuse gliomas including astrocytoma and glioblastoma in one study (Choi *et al.*, 1970).

Pesticides have been extensively investigated as the possible reason for the increased rate of gliomas in rural and farm residents and workers but the research has been unable to confirm an association between pesticides and diffuse gliomas (Samanic *et al.*, 2008; Yiin *et al.*, 2012).

Investigators have occasionally suggested that it is not pesticides but a zoonotic microorganism, an animal virus or bacteria that may be responsible for the

increased rate of gliomas in rural and farm residents and workers (Carozza *et al.*, 2008; Efrid *et al.*, 2014). Zoonotic microorganisms are excreted in an infected animal's feces or manure and contaminate the ground the animal is defecating on (Manning and Collins, 2001). Rural residents who live near animal farms, live on animal farms or work on animal farms can become infected with a zoonosis by inhaling, ingesting, or directly contacting or handling pathogen-contaminated manure or manure-contaminated soil, dirt, and dust (The Center for Food Security and Public Health, 2017). Increased rates of glioblastoma in tennis players (Imbriano, 2012) and baseball pitchers (Martinez, 2016; Gartland, 2017), catchers, infield position players, and umpires (Franklin, 2011; Imbriano, 2012), including glioblastoma clusters of American professional baseball players from the Philadelphia Phillies, New York Yankees, and Kansas City Royals (Avril, 2013; Longman, 2017) suggest that the same zoonotic microorganism excreted in an infected domestic ruminant's manure, contaminating the soil of rural environments, may also be present in the baseline soil of baseball fields and in tennis grass and clay courts.

***Mycobacterium avium subspecies paratuberculosis: the zoonosis responsible for some cases of diffuse gliomas, including glioblastoma?***

*Mycobacterium avium subspecies paratuberculosis* (MAP) is a zoonotic microorganism present in domestic livestock feces or manure that may be responsible for the increased rate of diffuse gliomas, including glioblastoma, in domestic livestock farmers, rural residents living near domestic livestock farms and herds, and baseball and tennis players playing on fields and grass and clay courts far from domestic livestock farms (Pierce, 2017). MAP causes a chronic intestinal disease in domestic ruminants known as Johne's disease (Tiwari *et al.*, 2006). MAP is a long suspected cause of Crohn's disease (Uzoigwe *et al.*, 2007; Kuenstner *et al.*, 2017), but has also been implicated in a wide range of autoimmune diseases (Zhang *et al.*, 2017; 2018) as well as the neurologic disorders Parkinson's disease (Dow, 2014; Arru *et al.*, 2016) and multiple sclerosis (Sechi and Dow, 2015). A recent study describes MAP antibodies in sera from patients with neuromyelitis optica disorder (Slavin *et al.*, 2018). A significant segment of the medical community considers MAP to be a zoonosis (Davis, 2015; Davis *et al.*, 2017; Kuenstner *et al.*, 2017; Garvey, 2018). Like other zoonoses (Corbel, 2006), MAP may cause a range of diseases in its human host but MAP does not cause in its animal hosts.

***MAP in feces or manure and soil and dirt***

MAP is heavily excreted in an infected animal's feces or manure (McKenna *et al.*, 2006). MAP lasts indefinitely in the environment once excreted, and is diffusely distributed throughout the soil in countries where MAP infection of domestic livestock is long-standing (Rhodes *et al.*, 2013).

***How to catch MAP and other non-tuberculous or atypical mycobacteria***

MAP is a type of non-tuberculous or atypical mycobacterium. Non-tuberculous mycobacteria are environmental mycobacteria, bacteria which are present in soil, dirt, and dust (O'Brien, 1989; Falkinham, 2009; Nishiuchi *et al.*, 2017). Other non-tuberculous mycobacteria can be contracted by direct contact with or inhalation of the mycobacterium in dirt or dust. Children who contract non-tuberculous mycobacteria frequently get infected by putting soil or dirt into their mouths (Krantz *et al.*, 2016). Baseball pitchers often lick their fingers between pitches after holding balls coated with possibly MAP-contaminated dirt. Baseball catchers crouch in the possibly MAP-contaminated dirt above home base, have dirt thrown into their faces by players running on or sliding into home base, and repeatedly catch and handle balls coated with possibly MAP-contaminated dirt. Baseball infield players are positioned on possibly MAP-contaminated baseline dirt. Tennis players constantly handle tennis balls coated with possibly MAP-contaminated grass, dirt, and clay. Farmers who do not wash their hands after applying pesticides, and probably don't wash their hands after other farm work, have an increased risk of glioma (Ruder *et al.*, 2009).

***Areas of pseudopalisading necrosis in glioblastoma: are they hypoxic necrotizing mycobacterial granulomas?***

MAP may be responsible for the two pathognomonic histologic features of glioblastoma: endothelial cell proliferation and pseudopalisading necrosis. Areas of pseudopalisading necrosis in glioblastomas (Pathpedia, 2018) resemble necrotizing granulomas, which are characterized by a "pseudopalisading" lymphoproliferative reaction (Shah *et al.*, 2017). Both tuberculous and non-tuberculous mycobacteria as well as fungi are the major causes of necrotizing granulomas (Shah *et al.*, 2017). Necrotizing granulomas come in several shapes. If the location of the granuloma is cutaneous and the lymphoproliferative reaction has a more definite palisading shape, the necrotizing granuloma is described as a palisading granuloma. If the necrosis is in a wavy, curvilinear pattern, it is described as a serpentine granuloma. Non-tuberculous mycobacteria are known causes of palisading (Bartralot *et al.*, 2000) and serpentine (University of Medicine and Dentistry of New Jersey, 2018) granulomas. Areas of pseudopalisading necrosis in glioblastoma most closely resemble the palisading and serpentine granulomas caused by non-tuberculous mycobacteria.

Necrosis is not a feature of MAP infection of dairy and beef cattle, but is a feature of MAP infection of goats, sheep, and water buffaloes (Williams *et al.*, 1983; Kurade *et al.*, 2004; Sivakumar *et al.*, 2005).

Granulomas caused by *Mycobacteria* including *Mycobacterium tuberculosis* and non-tuberculous or atypical mycobacteria including *M. avium complex* species (of which MAP is a subspecies) are a result of

hypoxic insult to the mycobacteria-laden macrophages in the center of the granuloma (Via *et al.*, 2008; Cardoso *et al.*, 2015). Similarly, the areas of pseudopalisading necrosis in glioblastoma are also thought to result from hypoxia (Rong *et al.*, 2006).

What is the difference between a mycobacterial granuloma and a possibly MAP-associated glioblastoma granuloma are what the center granuloma cells consist of. In mycobacterial granulomas, the center cells are macrophages. In glioblastoma granulomas, the center cells are glioblastoma tumor cells.

#### **Endothelial cells and “glioblastoma granulomas”**

What are glioblastoma tumor cells? Glioblastoma tumor cells show transdifferentiation with vascular endothelial cells (Ricci-Vitiani *et al.*, 2010; Soda *et al.*, 2011). Glioblastoma tumor cells can be thought of as malignant vascular endothelial cells. These malignant vascular endothelial glioblastoma cells comprise the areas of pseudopalisading necrosis. Hypoxia within the areas of pseudopalisading necrosis of glioblastomas, which are otherwise characterized as among the most vascular of malignant tumors (Hardee and Zagzag, 2012), is similar to the simultaneous hyperemia and ischemia of the bowel wall in Crohn’s disease, another MAP-associated human disease (Hatoum *et al.*, 2005). Granulomas are usually composed of a central area of tissue macrophages called epithelioid histiocytes. The historical literature on Crohn’s disease describes another mechanism of granuloma formation, whereby Crohn’s granulomas are composed of non-proliferating lymphatic endothelial cells instead (Hadfield, 1939). Both vascular endothelial cell proliferation (Binion and Rafiee, 2009) and lymphatic endothelial cell proliferation (Hadfield, 1939; Warren and Sommers, 1948) have been described as histopathologic components of idiopathic inflammatory bowel disease. It is possible that the centers of MAP-associated glioblastoma granulomas are composed of MAP-infected vascular endothelial cells.

#### **MAP on the animal and human brain**

The evidence that MAP can infect a mammalian brain is almost non-existent. Animals having symptoms, usually gastrointestinal, of MAP infection are culled from a herd, and generally are not necropsied. A single study of goats experimentally infected with MAP demonstrated “cerebrocortical necrosis” in 3 out of 26 infected goats who had “neurological signs” (Kohler *et al.*, 2015). The authors did not state whether the cerebrocortical necrosis had a granulomatous histology. Cerebrocortical necrosis or polioencephalomalacia is a disease of ruminant livestock associated with thiamine deficiency or high-sulfate diets (Gould, 1998). The histology of polioencephalomalacia consists of multiple foci of necrosis in the cerebral cortex and endothelial cell proliferation (Adams *et al.*, 1956). The necrosis occurs in grey matter rather than white, and is of neurons rather than glial cells.

MAP may have a predilection for the human brain. The normal temperature of a dairy cow, the original and natural animal host of MAP, is 101.5°F. The human brain is the warmest part of the human body, although its “intense heat production” is rapidly cleared by cerebral blood flow, so only a small thermal gradient exists between the brain and the rest of the human body (Wang *et al.*, 2014). MAP may prefer the slightly higher temperature of the human brain compared to the rest of the human body.

#### **Is there any evidence of MAP causing vascular endothelial cell hyperplasia?**

A study of remote (non-gastrointestinal) MAP lesions in infected goats described MAP organisms being present in the endothelial cells of the intermediate sinuses of lymph nodes, and of causing increased glomerular tufting “due to the proliferation of vascular endothelium” (Sato *et al.*, 1968). A tiny literature suggests that endothelial cell proliferation is the precursor of granuloma formation in bovine MAP infection (Liang *et al.*, 2016). There are other known bacterial causes of endothelial cell proliferation, including *Mycobacterium lepromatosis* (Han *et al.*, 2008) and species of *Bartonella* (Berrich *et al.*, 2011).

#### **MAP and the cellular metabolism of diffuse gliomas: the isocitrate dehydrogenase 1 (IDH1) mutation**

In the World Health Organization (WHO)’s new (2016) central nervous system tumor classification system (Komori, 2017), diffuse glioma histology, categorized as glioblastoma, astrocytoma, oligodendroglioma, and oligoastrocytoma, has been almost completely superseded by the presence or absence of the isocitrate dehydrogenase 1 (IDH1) mutation (Tateishi *et al.*, 2017). According to WHO’s new classification, the only characteristic that ‘matters’ in a diffuse glioma, the most important characteristic in terms of patient survival, is whether or not the diffuse glioma has the IDH1 mutation (Lee, 2018). Patients whose glioblastomas have mutations, primarily the R132H mutation, in the IDH1 enzyme gene have an improved survival rate compared to patients with the wild-type or ‘normal’ IDH1 gene. How might the wild-type, normal IDH1 enzyme ‘help’ MAP proliferate or persist in an infected brain, and how might the mutant IDH1 enzyme ‘hurt’ MAP, suppressing MAP’s replication or persistence in an infected brain?

The normal or wild-type IDH1 enzyme catalyzes the conversion of isocitrate to  $\alpha$ -ketoglutarate, and vice versa, in the cytoplasm of a eukaryotic cell.  $\alpha$ -Ketoglutarate produced by wild-type or normal IDH1 is in the cytosol, and it can either translocate into a mitochondrion and participate in the tricarboxylic acid cycle (TCA) cycle, or it can remain in the cytosol and, via IDH1, undergo reductive carboxylation back into isocitrate, eventually resulting in the acetyl-coenzyme A necessary for lipid synthesis (Maus and Peters, 2017).

Intracellular bacteria usually lack the next enzyme in the TCA cycle,  $\alpha$ -ketoglutarate dehydrogenase, needed to convert  $\alpha$ -ketoglutarate to succinate (Munoz-Elias and McKinney, 2006). MAP has a unique type of  $\alpha$ -ketoglutarate dehydrogenase, called type 2-oxoglutarate (another name for  $\alpha$ -ketoglutarate) ferredoxin oxidoreductase, which can convert  $\alpha$ -ketoglutarate to succinyl-coenzyme A (Weigoldt, 2012; Weigoldt *et al.*, 2013) in MAP's version of the TCA cycle. Wild-type or normal IDH1, therefore, is helpful to MAP, it 'gives' MAP the  $\alpha$ -ketoglutarate it needs for its own variant TCA cycle.

The mutant IDH1 enzyme has a reduced ability to convert isocitrate to  $\alpha$ -ketoglutarate, and the little  $\alpha$ -ketoglutarate that is produced is converted to 2-hydroxyglutarate, resulting in a deficiency of  $\alpha$ -ketoglutarate. The lack of  $\alpha$ -ketoglutarate in an IDH1-deficient MAP-infected host cell may result in MAP going into a dormant, non-replicating mode. The dormancy of MAP resulting from host  $\alpha$ -ketoglutarate deficiency may be responsible for the improved survival rate in diffuse glioma patients with the IDH1 mutation. The fact that the IDH1 mutation occurs in the majority of what the 2016 WHO classification now just calls astrocytomas and oligodendrogliomas and correlates with their improved survival rate suggests that MAP may be involved in the pathogenesis of all diffuse gliomas, not just glioblastoma.

#### **Challenges to the identification of MAP in glioblastoma and other diffuse gliomas**

Several obstacles exist in identifying MAP organisms in human tissue. In the United States, laboratories handling animal tissue, that have commercial automated systems for culturing, histopathologic, and immunohistochemical identification of MAP in tissue, are not permitted to process human tissue. Identification of acid fast organisms using traditional acid fast stains require prolonged light microscopic examination at high (oil immersion) magnification (Shah *et al.*, 2017). Researchers have noted that MAP organisms are often not found within the histologic lesions of infected animals (Brady *et al.*, 2008).

#### **Conclusion: diffuse gliomas, including glioblastoma, as possible MAP-associated brain lesions**

There are epidemiologic, cellular metabolic, and histologic suggestions of a possible etiologic relationship between MAP and diffuse gliomas, including glioblastoma. A specific bacterial cause of some cases of diffuse glioma would have implications for their prevention by vaccination (Abdellrazeq *et al.*, 2018) and potential response to antimicrobial treatments (Wu *et al.*, 2016; RedHill Biopharma, 2017).

#### **Acknowledgments**

As always, my research would not be possible without the assistance of Dr. Beth Hill at the Providence Sacred Heart Medical Center and Children's Hospital's Health Sciences Library in Spokane, Washington, as well as

the other libraries that participate in the FreeShare Library Group within the DOCLINE National Network of Libraries of Medicine. Discussion of this idea with Ikbal E. AlKhafaji, M.D. and Michael T. Collins, D.V.M., Ph.D. is gratefully acknowledged.

#### **Conflict of interest**

The author declares that there is no conflict of interest.

#### **References**

- Abdellrazeq, G.S., Elnaggar, M.M., Bannantine, J.P., Park, K.T., Souza, C.D., Backer, B., Hulubei, V., Fry, L.M., Khaliel, S.A., Torkey, H.A., Schneider, D.A. and Davis, W.C. 2018. A Mycobacterium avium subsp. paratuberculosis relA deletion mutant and a 35 kDa major membrane protein elicit development of cytotoxic T lymphocytes with ability to kill intracellular bacteria. *Vet. Res.* 49, 53.
- Adams, O.R., Griner, L.A. and Jensen, R. 1956. Polioencephalomalacia of cattle and sheep. *J. Am. Vet. Med. Assoc.* 129, 311–321.
- Akhtar, S., Vranic, S., Cyprian, F.S. and Al Moustafa, A.E. 2018. Epstein-Barr virus in Gliomas: cause, association, or artifact? *Front. Oncol.* 8, 123.
- Alibek, K., Kakpenova, A. and Baiken, Y. 2013. Role of infectious agents in the carcinogenesis of brain and head and neck cancers. *Infect. Agent. Cancer.* 8, 7.
- Altieri, A., Castro, F., Bermejo, J.L. and Hemminki, K. 2006. Association between number of siblings and nervous system tumors suggests an infectious etiology. *Neurology* 67, 1979–1983.
- Arru, G., Caggiu, E., Paulus, K., Sechi, G.P., Mameli, G. and Sechi, L.A. 2016. Is there a role for Mycobacterium avium subspecies paratuberculosis in Parkinson's disease? *J. Neuroimmunol.* 293, 86–90.
- Avril, T. 2013. Four Phils and brain cancer: connection or coincidence? *Philadelphia Inquirer*. Retrieved September 12, 2018. Available at: [http://www.philly.com/philly/health/cancer/20130716\\_Four\\_Philis\\_and\\_brain\\_cancer\\_Connection\\_or\\_coincidence\\_.html?arc404=true](http://www.philly.com/philly/health/cancer/20130716_Four_Philis_and_brain_cancer_Connection_or_coincidence_.html?arc404=true).
- Bartralot, R., Pujol, R.M., Garcia-Patos, V., Sitjas, D., Martin-Casabona, N., Coll, P., Alomar, A. and Castells, A. 2000. Cutaneous infections due to nontuberculous mycobacteria: histopathological review of 28 cases. Comparative study between lesions observed in immunosuppressed patients and normal hosts. *J. Cutan. Pathol.* 27, 124–129.
- Berrich, M., Kieda, C., Grillon, C., Monteil, M., Lamerant, N., Gavard, J., Boulouis, H.J. and Haddad, N. 2011. Differential effects of Bartonella henselae on human and feline macro- and micro-vascular endothelial cells. *PLoS One.* 6, e20204.
- Binion, D.G. and Rafiee, P. 2009. Is inflammatory bowel disease a vascular disease? Targeting angiogenesis improves chronic inflammation in inflammatory bowel disease. *Gastroenterology* 136, 400–403.

- Blair, A., Malaker, H., Cantor, K.P., Burmeister, L. and Wiklund, K. 1985. Cancer among farmers. A review. *Scand. J. Work Environ. Health* 11, 397–407.
- Brady, C., O’Grady, D., O’Meara, F., Egan, J. and Bassett, H. 2008. Relationships between clinical signs, pathological changes and tissue distribution of *Mycobacterium avium* subspecies paratuberculosis in 21 cows from herds affected by Johne’s disease. *Vet. Rec.* 162, 147–152.
- Brooks, W.H. 1972. Geographic clustering of brain tumors in Kentucky. *Cancer* 30, 923–926.
- Cardoso, M.S., Silva, T.M., Resende, M., Appelberg, R. and Borges, M. 2015. Lack of the transcription factor hypoxia-inducible factor 1alpha (HIF-1alpha) in macrophages accelerates the necrosis of mycobacterium avium-induced granulomas. *Infect. Immun.* 83, 3534–3544.
- Carozza, S.E., Li, B., Elgethun, K. and Whitworth, R. 2008. Risk of childhood cancers associated with residence in agriculturally intense areas in the United States. *Environ. Health Perspect.* 116, 559–565.
- Choi, N.W., Schuman, L.M. and Gullen, W.H. 1970. Epidemiology of primary central nervous system neoplasms. I. Mortality from primary central nervous system neoplasms in Minnesota. *Am. J. Epidemiol.* 91, 238–259.
- Colpak, A.I., Isikay, I., Mut, M., Soylemezoglu, F., Kansu, T. and Foroozan, R. 2014. Acute visual loss: just the beginning? *Surv. Ophthalmol.* 59, 548–552.
- Corbel, M.J. 2006. Brucellosis in humans and animals. World Health Organization, Geneva, Switzerland.
- Davis, W.C. 2015. On deaf ears, *Mycobacterium avium* paratuberculosis in pathogenesis Crohn’s and other diseases. *World J. Gastroenterol.* 21, 13411–13417.
- Davis, W.C., Kuenstner, J.T. and Singh, S.V. 2017. Resolution of Crohn’s (Johne’s) disease with antibiotics: what are the next steps? *Expert. Rev. Gastroenterol. Hepatol.* 11, 393–396.
- Dow, C.T. 2014. M. paratuberculosis and Parkinson’s disease—is this a trigger. *Med. Hypotheses* 83, 709–712.
- Dziurzynski, K., Chang, S.M., Heimberger, A.B., Kalejta, R.F., McGregor Dallas, S.R., Smit, M., Soroceanu, L. and Cobbs, C.S. 2012. Consensus on the role of human cytomegalovirus in glioblastoma. *Neuro-oncol.* 14, 246–255.
- Efird, J.T., Davies, S.W., O’Neal, W.T. and Anderson, E.J. 2014. Animal viruses, bacteria, and cancer: a brief commentary. *Front. Public Health* 2, 14.
- Falkinham, J.O., 3rd. 2009. Surrounded by mycobacteria: nontuberculous mycobacteria in the human environment. *J. Appl. Microbiol.* 107, 356–367.
- Franklin, C. 2011. A cancer stat too obvious to ignore. *The Chicago Tribune*. Retrieved September 13, 2018. Available at: <http://www.chicagotribune.com/opinion/ct-xpm-2011-06-14-ct-oped-0615-cancer-20110610-story.html>.
- Gartland, D. 2017. Former Mets pitcher Anthony Young dead at 51. *Sport Illustrated*. Retrieved September 13, 2018. Available at: <https://www.si.com/mlb/2017/06/27/anthony-young-mets-pitcher-dead-brain-tumor>.
- Garvey, M. 2018. Mycobacterium avium subspecies paratuberculosis: a possible causative agent in human morbidity and risk to public health safety. *Open Vet. J.* 8, 172–181.
- Gould, D.H. 1998. Polioencephalomalacia. *J. Anim. Sci.* 76, 309–314.
- Hadfield, G. 1939. The primary histological lesion of regional ileitis. *The Lancet* 234, 773–776.
- Han, X.Y., Seo, Y.H., Sizer, K.C., Schoberle, T., May, G.S., Spencer, J.S., Li, W. and Nair, R.G. 2008. A new Mycobacterium species causing diffuse lepromatous leprosy. *Am. J. Clin. Pathol.* 130, 856–864.
- Hansson, H. and Ferguson, R. 2011. Factors influencing the strategic decision to further develop dairy production—a study of farmers in central Sweden. *Livest. Sci.* 135, 110–123.
- Hardee, M.E. and Zagzag, D. 2012. Mechanisms of glioma-associated neovascularization. *Am. J. Pathol.* 181, 1126–1141.
- Hatoum, O.A., Binion, D.G. and Gutterman, D.D. 2005. Paradox of simultaneous intestinal ischaemia and hyperaemia in inflammatory bowel disease. *Eur. J. Clin. Invest.* 35, 599–609.
- Holdhoff, M., Guner, G., Rodriguez, F.J., Hicks, J.L., Zheng, Q., Forman, M.S., Ye, X., Grossman, S.A., Meeker, A.K., Heaphy, C.M., Eberhart, C.G., De Marzo, A.M. and Arav-Boger, R. 2017. Absence of cytomegalovirus in glioblastoma and other high-grade gliomas by real-time PCR, immunohistochemistry, and in situ hybridization. *Clin. Cancer Res.* 23, 3150–3157.
- Howell, J., Coyne, M.S. and Cornelius, P. 1995. Fecal bacteria in agricultural waters of the bluegrass region of Kentucky. *J. Environ. Qual.* 24, 411–419.
- Imbriano, J. 2012. The untimely death of Gary Carter and what we can learn from what happened to the “kid”. Retrieved June 18, 2018. Available at: <https://thefullertoninformer.com/the-untimely-death-of-gary-carter-and-what-we-can-learn-from-what-happened-to-the-kid/>.
- Khuder, S.A., Mutgi, A.B. and Schaub, E.A. 1998. Meta-analyses of brain cancer and farming. *Am. J. Ind. Med.* 34, 252–260.
- Kofman, A., Marcinkiewicz, L., Dupart, E., Lyschkev, A., Martynov, B., Ryndin, A., Kotelevskaya, E., Brown, J., Schiff, D. and Abounader, R. 2011. The roles of viruses in brain tumor initiation and oncomodulation. *J. Neurooncol.* 105, 451–466.
- Kohler, H., Soschinka, A., Meyer, M., Kather, A., Reinhold, P. and Liebler-Tenorio, E. 2015. Characterization of a caprine model for the subclinical initial phase of *Mycobacterium avium*

- subsp. paratuberculosis infection. BMC Vet. Res. 11, 74.
- Komori, T. 2017. The 2016 WHO classification of tumours of the central nervous system: the major points of revision. Neurol. Med. Chir. (Tokyo). 57, 301–311.
- Krantz, A.M., Varnam, M. and Fernandez, C. 2016. Nontuberculous mycobacteria lymphadenitis: a case report. Cureus. 8, e846.
- Kuenstner, J.T., Naser, S., Chamberlin, W., Borody, T., Graham, D.Y., McNees, A., Hermon-Taylor, J., Hermon-Taylor, A., Dow, C.T., Thayer, W., Biesecker, J., Collins, M.T., Sechi, L.A., Singh, S.V., Zhang, P., Shafran, I., Weg, S., Telega, G., Rothstein, R., Oken, H., Schimpff, S., Bach, H., Bull, T., Grant, I., Ellingson, J., Dahmen, H., Lipton, J., Gupta, S., Chaubey, K., Singh, M., Agarwal, P., Kumar, A., Misri, J., Sohal, J., Dhama, K., Hemati, Z., Davis, W., Hier, M., Aitken, J., Pierce, E., Parrish, N., Goldberg, N., Kali, M., Bendre, S., Agrawal, G., Baldassano, R., Linn, P., Sweeney, R.W., Fecteau, M., Hofstaedter, C., Potula, R., Timofeeva, O., Geier, S., John, K., Zayanni, N., Malaty, H.M., Kahlenborn, C., Kravitz, A., Bulfon, A., Daskalopoulos, G., Mitchell, H., Neilan, B., Timms, V., Cossu, D., Mameli, G., Angermeier, P., Jelic, T., Goethe, R., Juste, R.A. and Kuenstner, L. 2017. The consensus from the *Mycobacterium avium* ssp. paratuberculosis (MAP) Conference 2017. Front. Public Health. 5, 208.
- Kurade, N.P., Tripathi, B.N., Rajukumar, K. and Parihar, N.S. 2004. Sequential development of histologic lesions and their relationship with bacterial isolation, fecal shedding, and immune responses during progressive stages of experimental infection of lambs with *Mycobacterium avium* subsp. paratuberculosis. Vet. Pathol. 41, 378–387.
- Lee, E., Burnett, C.A., Lalich, N., Cameron, L.L. and Sestito, J.P. 2002. Proportionate mortality of crop and livestock farmers in the United States, 1984–1993. Am. J. Ind. Med. 42, 410–420.
- Lee, S.C. 2018. Diffuse gliomas for nonneuropathologists: the new integrated molecular diagnostics. Arch. Path. Lab. Med. 142, 804–814.
- Liang, G., Malmuthuge, N., Guan, Y., Ren, Y., Griebel, P.J. and Guan le, L. 2016. Altered microRNA expression and pre-mRNA splicing events reveal new mechanisms associated with early stage *Mycobacterium avium* subspecies paratuberculosis infection. Sci. Rep. 6, 24964.
- Longman, J. 2017. The brain cancer that keeps killing baseball players. The New York Times. Retrieved March 18, 2018. Available at: <https://www.nytimes.com/2017/08/14/sports/baseball/brain-cancer-phillies-daulton.html>.
- MacDonald, A.B. 2018. Glioblastoma Multiforme—Borrelia DNA in 5 of 5 brain biopsies. Retrieved August 22, 2018. Available at: <https://durayresearch.wordpress.com/our-work/other-topics/glioblastoma-multiforme-borrelia-dna-in-5-of-5-brain-biopsies/>.
- Manning, E.J. and Collins, M.T. 2001. Mycobacterium avium subsp. paratuberculosis: pathogen, pathogenesis and diagnosis. Rev. Sci. Tech. 20, 133–150.
- Martinez, T. 2016. Mountain View graduate Rob Ramsay dies at age 42: former pitcher played for Mariners in 1999-2000. The Columbian. Retrieved March 30, 2018. Available at: <http://www.columbian.com/news/2016/aug/09/mountain-view-graduate-rob-ramsay-dies-at-age-42/>.
- Maus, A. and Peters, G.J. 2017. Glutamate and alpha-ketoglutarate: key players in glioma metabolism. Amino Acids 49, 21–32.
- McKenna, S.L., Keefe, G.P., Tiwari, A., VanLeeuwen, J. and Barkema, H.W. 2006. Johne's disease in Canada part II: disease impacts, risk factors, and control programs for dairy producers. Can. Vet. J. 47, 1089–1099.
- Milham, S. 1976. Occupational mortality in Washington State, 1950-1971. U.S. Dept. of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations.
- Morrison, H.I., Semenciw, R.M., Morison, D., Magwood, S. and Mao, Y. 1992. Brain cancer and farming in western Canada. Neuroepidemiology 11, 267–276.
- Munoz-Elias, E.J. and McKinney, J.D. 2006. Carbon metabolism of intracellular bacteria. Cell Microbiol. 8, 10–22.
- Musicco, M., Filippini, G., Bordo, B.M., Melotto, A., Morello, G. and Berrino, F. 1982. Gliomas and occupational exposure to carcinogens: case-control study. Am. J. Epidemiol. 116, 782–790.
- Nishiuchi, Y., Iwamoto, T. and Maruyama, F. 2017. Infection sources of a common non-tuberculous mycobacterial pathogen, *Mycobacterium avium* complex. Front. Med. (Lausanne). 4, 27.
- O'Brien, R.J. 1989. The epidemiology of nontuberculous mycobacterial disease. Clin. Chest Med. 10, 407–418.
- Pandey, J.P. 2011. Genetic and viral etiology of glioblastoma—a unifying hypothesis. Cancer Epidemiol. Biomarkers Prev. 20, 1061–1063.
- Pathpedia, L.L.C. 2018. Glioblastoma (GBM) - Slide 1. Retrieved March 29, 2018. Available at: [http://www.pathpedia.com/education/eatlas/histopathology/brain-and-cord/glioblastoma\(gbm\).aspx](http://www.pathpedia.com/education/eatlas/histopathology/brain-and-cord/glioblastoma(gbm).aspx).
- Pierce, E.S. 2017. Manure as the major source and aerosolization as the major route of infection of *Mycobacterium avium* subspecies paratuberculosis (MAP) from infected animals to humans: implications for disease etiologies and infection diagnosis and monitoring. A presentation for the

- 2017 Philadelphia MAP conference. Retrieved May 10, 2018. Available at: <https://vimeo.com/215736675/fd48f623cc>.
- RedHill Biopharma. 2017. RedHill Biopharma Announces QIDP Fast-Track Designation Granted by FDA to RHB-104 for Nontuberculous Mycobacteria Infections. Retrieved April 19, 2018. Available at: <http://ir.redhillbio.com/news-releases/news-release-details/redhill-biopharma-announces-qidp-fast-track-designation-granted>.
- Reif, J., Pearce, N. and Fraser, J. 1989a. Cancer risks in New Zealand farmers. *Int. J. Epidemiol.* 18, 768–774.
- Reif, J., Pearce, N. and Fraser, J. 1989b. Occupational risks for brain cancer: a New Zealand Cancer Registry-based study. *J. Occup. Med.* 31, 863–867.
- Rhodes, G., Henrys, P., Thomson, B.C. and Pickup, R.W. 2013. *Mycobacterium avium* subspecies paratuberculosis is widely distributed in British soils and waters: implications for animal and human health. *Environ. Microbiol.* 15, 2761–2774.
- Ricci-Vitiani, L., Pallini, R., Biffoni, M., Todaro, M., Invernici, G., Cenci, T., Maira, G., Parati, E.A., Stassi, G., Larocca, L.M. and De Maria, R. 2010. Tumour vascularization via endothelial differentiation of glioblastoma stem-like cells. *Nature* 468, 824–828.
- Rong, Y., Durden, D.L., Van Meir, E.G. and Brat, D.J. 2006. ‘Pseudopalisading’ necrosis in glioblastoma: a familiar morphologic feature that links vascular pathology, hypoxia, and angiogenesis. *J. Neuropathol. Exp. Neurol.* 65, 529–539.
- Ruder, A.M., Carreon, T., Butler, M.A., Calvert, G.M., Davis-King, K.E., Waters, M.A., Schulte, P.A., Mandel, J.S., Morton, R.F., Reding, D.J. and Rosenman, K.D. 2009. Exposure to farm crops, livestock, and farm tasks and risk of glioma: the Upper Midwest Health Study. *Am. J. Epidemiol.* 169, 1479–1491.
- Samanic, C.M., De Roos, A.J., Stewart, P.A., Rajaraman, P., Waters, M.A. and Inskip, P.D. 2008. Occupational exposure to pesticides and risk of adult brain tumors. *Am. J. Epidemiol.* 167, 976–985.
- Sato, H., Nakamatsu, M. and Fujimoto, Y. 1968. The pathological study of paratuberculosis in goats, centered around the formation of remote lesions. *Jpn. J. Vet. Res.* 16, 103–119.
- Schuman, L.M., Choi, N.W. and Gullen, W.H. 1967. Relationship of central nervous system neoplasms to *Toxoplasma gondii* infection. *Am. J. Public Health Nations Health* 57, 848–856.
- Sechi, L.A. and Dow, C.T. 2015. *Mycobacterium avium* ss. paratuberculosis Zoonosis—The Hundred Year War—Beyond Crohn’s Disease. *Front. Immunol.* 6, 96.
- Shah, K.K., Pritt, B.S. and Alexander, M.P. 2017. Histopathologic review of granulomatous inflammation. *J. Clin. Tuberc. Other Mycobact. Dis.* 7, 1–12.
- Sivakumar, P., Tripathi, B.N. and Singh, N. 2005. Detection of *Mycobacterium avium* subsp. paratuberculosis in intestinal and lymph node tissues of water buffaloes (*Bubalus bubalis*) by PCR and bacterial culture. *Vet. Microbiol.* 108, 263–270.
- Slavin, Y.N., Bo, M., Caggiu, E., Sechi, G., Arru, G., Bach, H. and Sechi, L.A. 2018. High levels of antibodies against PtpA and PknG secreted by *Mycobacterium avium* ssp. paratuberculosis are present in neuromyelitis optica spectrum disorder and multiple sclerosis patients. *J. Neuroimmunol.* 323, 49–52.
- Soda, Y., Marumoto, T., Friedmann-Morvinski, D., Soda, M., Liu, F., Michiue, H., Pastorino, S., Yang, M., Hoffman, R.M., Kesari, S. and Verma, I.M. 2011. Transdifferentiation of glioblastoma cells into vascular endothelial cells. *Proc. Natl. Acad. Sci. U. S. A.* 108, 4274–80.
- Tateishi, K., Wakimoto, H. and Cahill, D.P. 2017. IDH1 Mutation and World Health Organization 2016 diagnostic criteria for adult diffuse gliomas: advances in surgical strategy. *Neurosurgery* 64, 134–138.
- The Center for Food Security and Public Health. 2017. Transmission routes of zoonotic diseases of livestock. Iowa State University. Retrieved September 30, 2017. Available at: [http://www.cfsph.iastate.edu/Zoonoses/assets/English/zoonotic\\_dz\\_transmission.pdf](http://www.cfsph.iastate.edu/Zoonoses/assets/English/zoonotic_dz_transmission.pdf).
- Thirugnanam, S., Rout, N. and Gnanasekar, M. 2013. Possible role of *Toxoplasma gondii* in brain cancer through modulation of host microRNAs. *Infect. Agent Cancer* 8, 8.
- Tiwari, A., VanLeeuwen, J.A., McKenna, S.L., Keefe, G.P. and Barkema, H.W. 2006. Johne’s disease in Canada Part I: clinical symptoms, pathophysiology, diagnosis, and prevalence in dairy herds. *Can. Vet. J.* 47, 874–882.
- University of Medicine and Dentistry of New Jersey. 2018. Mycobacterial lymphadenopathy. Retrieved March 29, 2018. Available at: [http://pleiad.umdny.edu/hemepath/specif\\_react/mycobact\\_img.html](http://pleiad.umdny.edu/hemepath/specif_react/mycobact_img.html).
- Uzoigwe, J.C., Khaitsa, M.L. and Gibbs, P.S. 2007. Epidemiological evidence for *Mycobacterium avium* subspecies paratuberculosis as a cause of Crohn’s disease. *Epidemiol. Infect.* 135, 1057–1068.
- Via, L.E., Lin, P.L., Ray, S.M., Carrillo, J., Allen, S.S., Eum, S.Y., Taylor, K., Klein, E., Manjunatha, U., Gonzales, J., Lee, E.G., Park, S.K., Raleigh, J.A., Cho, S.N., McMurray, D.N., Flynn, J.L. and Barry, C.E., 3rd. 2008. Tuberculous granulomas are hypoxic in guinea pigs, rabbits, and nonhuman primates. *Infect. Immun.* 76, 2333–2340.
- Wang, H., Wang, B., Normoyle, K.P., Jackson, K., Spittler, K., Sharrock, M.F., Miller, C.M., Best, C.,

- Llano, D. and Du, R. 2014. Brain temperature and its fundamental properties: a review for clinical neuroscientists. *Front. Neurosci.* 8, 307.
- Warren, S. and Sommers, S.C. 1948. Cicatrizing enteritis as a pathologic entity; analysis of 120 cases. *Am. J. Pathol.* 24, 475–501.
- Weigoldt, M. 2012. Antigen expression and metabolism of *Mycobacterium avium* subsp. *paratuberculosis* *in vivo*. Doctor rerum naturalium, University of Veterinary Medicine Hannover.
- Weigoldt, M., Meens, J., Bange, F.C., Pich, A., Gerlach, G.F. and Goethe, R. 2013. Metabolic adaptation of *Mycobacterium avium* subsp. *paratuberculosis* to the gut environment. *Microbiology* 159, 380–391.
- Wick, W. and Platten, M. 2014. CMV infection and glioma, a highly controversial concept struggling in the clinical arena. *Neuro-oncol.* 16, 332–333.
- Williams, E.S., Snyder, S.P. and Martin, K.L. 1983. Pathology of spontaneous and experimental infection of North American wild ruminants with *Mycobacterium paratuberculosis*. *Vet. Pathol.* 20, 274–290.
- Wingren, G. and Axelsson, O. 1992. Cluster of brain cancers spuriously suggesting occupational risk among glassworkers. *Scand. J. Work Environ. Health* 18, 85–89.
- Wu, X., Hu, X. and Hamblin, M.R. 2016. Ultraviolet blood irradiation: is it time to remember “the cure that time forgot”? *J. Photochem. Photobiol. B.* 157, 89–96.
- Yiin, J.H., Ruder, A.M., Stewart, P.A., Waters, M.A., Carreon, T., Butler, M.A., Calvert, G.M., Davis-King, K.E., Schulte, P.A., Mandel, J.S., Morton, R.F., Reding, D.J. and Rosenman, K.D. 2012. The Upper Midwest Health Study: a case-control study of pesticide applicators and risk of glioma. *Environ. Health* 11, 39.
- Zhang, P., Minardi, L.M., Kuenstner, J.T., Zekan, S.M. and Kruzelock, R. 2018. Anti-microbial antibodies, host immunity, and autoimmune disease. *Front. Med. (Lausanne)*. 5, 153.
- Zhang, P., Minardi, L.M., Kuenstner, J.T., Zekan, S.M., Zhu, F., Hu, Y. and Kruzelock, R. 2017. Cross reactivity of antibodies against microbial proteins to human tissues as basis of Crohns disease and other autoimmune diseases. *bioRxiv*. 116574.