In the Literature

Eliminating Yaws


The identification of variants of Treponema pallidum subspecies pertenue in Guyana in 1999 recently led to the apparent elucidation of the origin of the treponematoses [1]. This work derived from the identification of infection with clinical elements suggestive of both yaws and syphilis in children of the Akwio tribe, among whom there have apparently no further cases identified. Just 2 countries are currently considered to be afflicted with endemic yaws: Indonesia and Timor-Leste (East Timor). India was recently declared by the World Health Organization (WHO) to have eradicated yaws.

Yaws, as a consequence of being limited to humans (and, possibly, great apes), together with its areas of endemicity being highly localized and its readily curable nature, is a disease that would appear to be a prime candidate for eradication. The lessons derived from experience in India are instructive.

Yaws was first identified in India in 1887. Arsenicals were administered in a mass control campaign in that country from 1935 to 1946. A WHO-UNICEF campaign administered 50 million “anti-yaws treatments” in 46 countries, including India, from 1952 to 1964, with a resultant ~95% overall reduction in prevalence. The prevalence in India during that campaign decreased from 14% to <0.1%. Then, in a story repeated with many other diseases of public health importance, the disease resurged in a number of countries, including parts of India, as attention was turned elsewhere. After the identification in 1977 of a number of cases in Madhya, Pradesh, the problem was eventually reexamined in India, and in the 1990s, a new eradication program was implemented. This multifaceted program included active surveillance and treatment of cases and contacts with a single dose of long-acting penicillin. This effort resulted in a decrease in the number of reported cases from 3571 in 1996, to 773 in 1997, and to 0 in 2004. On 19 September 2006, a formal declaration was issued, indicating that yaws had been eliminated in India. With continued active monitoring, it is hoped that it will be possible to declare the eradication of yaws in India in 2010. In the meantime, the WHO has set 2012 as the target date for the final elimination of yaws in Indonesia and Timor-Leste.

Reference


An Oncogenic Polyomavirus?


Merkel cell carcinoma (MCC) is an aggressive skin malignancy with a 5-year mortality rate of ~33%. It presents as a painless, reddish-violet–colored nodule or plaque and is of neuroendocrine origin, arising from Merkel cells, which act as mechanoreceptors in the response to touch. There are currently only ~1500 cases identified annually in the United States, but the incidence is on the rise.

The fact that MCC, like Kaposi sarcoma, predominantly affects elderly and immunocompromised persons has led to the suggestion that it may be associated with a viral pathogen. Feng and colleagues analyzed ~395,000 mRNA sequences from MCC tissue samples with digital transcriptome subtraction [1], by which they compared the analyzed gene sequences with those of the human genome, allowing the identification of nonhuman sequences. One such sequence showed similarity to a sequence of polyomavirus, with subsequent confirmation that it represented a polyomavirus after cloning of the complete viral genome. The polyomavirus sequence was identified in 8 of 10 MCC specimens and was found to be integrated into tumor cell DNA in a clonal pattern in 6 of the 8 tumors in which the viral sequences could be detected. None of 84 control samples contained the viral sequence.

These findings strongly suggest that the newly identified polyomavirus, which the investigators named the “Merkel cell polyomavirus,” may contribute to the pathogenesis of this tumor. There are 4 clades of polyomaviruses (mouse, bovine, simian/human, and KIPyV/WUPyV); phylogenetic analysis found that Merkel cell polyomavirus falls within the mouse clade. This is a somewhat unexpected finding, because previously identified polyomaviruses had appeared to be highly species specific. Despite extensive investigation, the oncogenic role of either BK virus or JC virus in humans remains inconclusive. Merkel cell polyomavirus, however, is the first polyoma virus genome to be demonstrated to be integrated into the DNA of a tumor cell. Thus, it represents a tantalizing candidate to be have a potentially oncogenic role—but many additional experimental data are required before this conclusion can be reached.

This study included another remarkable demonstration of a method capable of identifying novel pathogens. The method, which is a more automated, high-throughput modification of the method that 2 of these investigators previously used to identify human herpesvirus–8 in Kaposi sarcoma cells, has also been used by other investigators to identify a novel arenavirus in a cluster of transplant recipients with fatal febrile illnesses [2].

References

Bon Appétit, Mon Bactérie!


In the ~3 billion years of their existence on planet Earth, bacteria have evolved multiple mechanisms of resistance to molecules that threaten them. Rather than being a modern phenomenon of the “antibiotic era,” resistance to antibiotics likely predated the Cambrian explosion, which occurred approximately a half-billion years ago. In fact, a recent examination of the “antibiotic resistome” of soil streptomycetes identified a high prevalence of an amazing array of genes encoding an array of antibiotic resistance mechanisms, including some quite novel ones [1]. Dante and colleagues have taken this observation a step further by identifying soil bacteria that are not only resistant to high concentrations (1 g/L) of antibiotics but that also are capable of metabolizing them to the extent that they can serve as their sole source of carbon.

Soil samples were collected from diverse sites with varying potential exposure to commercial antibiotics, ranging from a cornfield fertilized with manure from antibiotic-fed cows to soil from nonurban areas with minimal human exposure in the previous 100 years. The investigators isolated large numbers of bacteria from these samples that were capable of using vancomycin, ciprofloxacin, penicillin, and carbenicillin as a sole carbon source; this was also true for trimethoprim for bacteria from 10 sites and for dicloxacillin for bacteria from 9 sites. Amikacin and kanamycin were each used by 10, whereas gentamicin was catabolized by 9. Each of the bacteria with this capability were resistant to the consumable antibiotic at a concentration of 1 g/L. The antibiotic-catabolizing bacteria were diverse, belonging to 11 different orders. Among the orders of bacteria most frequently implicated, 41% belonged to the order Burkholderiales, 24% to Pseudomonales, and 13% to Enterobacteriales. Genetic analysis found that some of the antibiotic metabolizers were closely related to known pathogens, including Serratia marcescens and members of the Burkholderia cepacia complex.

This close relationship increases the potential for horizontal transfer of these metabolic systems from soil organisms to bacteria that are pathogenic for humans. If this were to happen, we could then be faced with circumstances in which bacteria were not only resistant to an antibiotic but also benefited from its presence, by being provided with an ongoing meal. This adds insult to injury and even goes beyond phenomena in which bacteria depend on the presence of an antibiotic for their growth, as in the case of vancomycin-dependent enterococci [2].

References

Tuberculosis and Infliximab


A boxed warning regarding risks of activation of tuberculosis was added to the labeling of the 3 available anti-TNF products (infliximab, etanercept, and adalimumab) in October 2001. Raval and colleagues examined the spontaneous adverse event reports of cases of tuberculosis in patients receiving infliximab to the US Adverse Event Reporting System database. They identified 130 distinct patients, most of whom had received infliximab for the treatment of rheumatoid arthritis, with the infections diagnosed a median of 10 months (range, 1–72 months) after initiation of anti-TNF therapy. No information is reported regarding isoniazid administration. Most patients had additional risk factors for tuberculosis, including receipt of additional immunosuppressive agents in 68% and a history of latent or active tuberculosis in 25%; at least 25 patients had been born or resided in an area of endemicity. A tuberculin skin test was performed in 47 (70%) of 67 patients in whom infliximab therapy was initiated after October 2001, and 34 (72%) of the 47 patients were reported to have negative results. Eleven patients had received bacille Calmette-Guérin. The authors suggest enhancing the sensitivity of skin testing by using a 5-mm induration as a cutoff value and obtaining a detailed history of epidemiological and other risk factors, in addition to close monitoring during therapy.