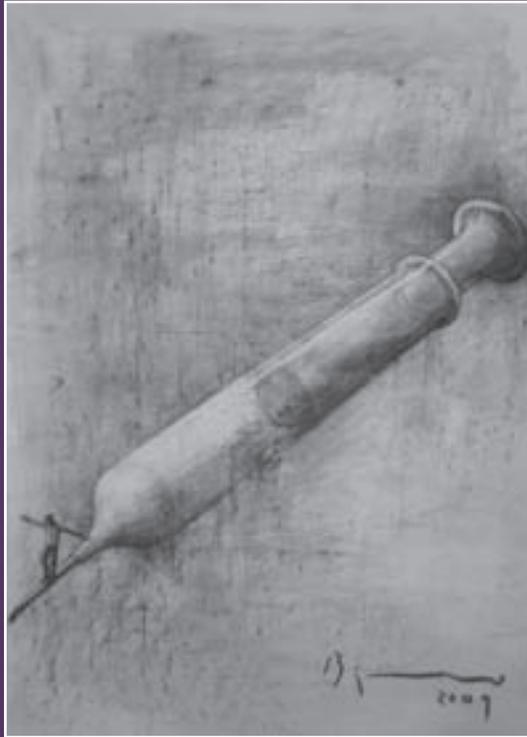


SECTION 3

New Approaches to Vaccination



**Hazardous ending of the
travel – Agustín Bejarano**
Charcoal/canvas
(120 x 80 cm)

'A smile rises up over the abyss: grows
like a tremulous abyss, bravely winged.
A smile lifts warmly upwards in flight...'

To Smile with the Sad Joy of the Olive-Tree
(Poem) – Miguel Hernández

Agustín Bejarano
Camagüey, Cuba

Agustín Bejarano graduated from the Higher Institute of Art in Havana, Cuba. Since the 1990s he has taken part in various art exhibitions held in Canada, Cuba, France, Mexico, Puerto Rico, Spain, Switzerland, and the United States. He received an award from the National Salon of Engraving (San Juan, Puerto Rico) during its IX Bienal de Grabado Latinoamericano y Caribeño, and the Grand Prize of the National Salon of Engraving, the Provincial Center of Fine Arts and Design, Havana.

His works are found in the Museo Nacional de Bellas Artes, (Havana); Colección Blasco & Lausín (Zaragoza); Colección Meter Ludwig, (Cologne); Collection Christie (Mexico); and at the Center for the Art (Florida), among others. He is a member of the Union of Writers and Artists of Cuba (UNEAC) and received a Distinction award from the Ministry of National Culture.

One hundred years ago, Albert Calmette and Camille Guérin started to continuously subculture a *Mycobacterium bovis* strain isolated from cow's milk. During this procedure, which lasted over 13 years and was not even interrupted by the First World War, the virulence was lost and the *M. bovis* strain became what is today referred to as Bacille de Calmette et Guérin (BCG)



Miracle of Weight – Alain Pino
Installation/acrylic, iron, cement

'From his dream, the man saw the giant
of a dream that was dreamt in Britain
and preparing the heart for the feat
he nailed the spur to Rocinant.'

The Witness (Poem) – Jorge Luis Borges

Alain Pino
Camagüey, Cuba

Alain Pino studied at the Professional School of Art and at the Higher Institute of Art, both in Havana. He also attended the Workshop in the BAC in Boston.

He has held solo exhibitions and participated in group exhibitions since 1994. These exhibitions were held in Argentina, Belgium, Canada, Costa Rica, Cuba, France, Germany, Italy, Malaysia, Spain, and the United States.

His works are in the collections of the Abraham Art Foundation (Texas); Beth Rudin Dewoody (New York); the Diane and Igal Silber Collection (Florida); Free University of Brussels (Brussels); Fundación Antonio Pérez (Cuenca); Galerie Barbara Farber (Trets, Chateau Vallat); Galerie Pierre Hubert, Art in Public (Geneva); International Creative Management (New York); and the pARTs Photographic Arts (Minneapolis).

CHAPTER 9

The History of BCG

Camille Locht

Introduction*

One hundred years ago, Albert Calmette and Camille Guérin started to continuously sub-culture a *Mycobacterium bovis* strain isolated from cow's milk. During this procedure, which lasted over 13 years and was not even interrupted by the First World War, the virulence was lost and the *M. bovis* strain became what is today referred to as Bacille de Calmette et Guérin (BCG). Tested for the first time in humans in 1921, BCG is today still the only vaccine available against TB. Its protective efficacy has been a subject of numerous clinical studies over the last 85 years, which collectively revealed that the vaccine affords rather good protection against severe and disseminated TB in children, but its protective efficacy against adulthood, pulmonary TB is very limited. In fact, it appears to protect better against leprosy than against TB. In addition to its use as a preventive vaccine against these two infectious diseases, BCG is also being used in a number of other indications, the most important of which being its therapeutic use for the treatment of superficial bladder cancer.

The Birth of BCG

In 1908, Albert Calmette, then Director General of the Institut Pasteur de Lille, and his co-worker Camille Guérin started cultivating a highly virulent

*Images in this chapter are provided by courtesy of the Institut Pasteur de Lille.

M. bovis strain (called strain 'lait de Nocard') received from Edmond Nocard, a veterinarian colleague of Guérin in Alfort, on a medium composed essentially of cooked potatoes and glycerinated ox bile. This led eventually to the generation of an attenuated vaccine strain today referred to as Bacille de Calmette et Guérin or BCG. Before 1908 many investigators had tried to attenuate the tubercle bacillus, inspired by the success of Louis Pasteur in developing live vaccines by attenuating virulent micro-organisms. However, none of them had succeeded in producing a strain that had completely and stably lost its virulence.

Following the 30-year-old hypothesis of Jean-Baptiste Chauveau that pulmonary TB was primarily not acquired by inhalation of the tubercle bacillus, but by ingestion and initial intestinal infection, Calmette and Guérin had since, for five years, accumulated extensive expertise in oral infection, first of goat (1) and then of cattle (2) with the bovine bacillus *M. bovis*. During the course of these experiments they noticed that a single oral administration of a low dose of fully virulent bacilli to cattle caused a transient sensitization of these animals to tuberculin, but did not cause disease. In contrast, oral administration of a high dose, or repeated administrations of low doses, resulted not only in TST conversion but also to the appearance of tuberculous lesions, mostly in the apical part of the lungs, and to TB disease that would not self-cure (3).

Interestingly, when young cattle were fed with a single low dose of bacilli, they became resistant to reinfection once their TST had become negative again, even with doses that killed non-immune cattle within weeks (4, 5). Immunity against TB could be achieved two to three months after ingestion of small amounts of live bacteria, harmless enough to not cause overt disease, and lasted for at least up to eight months. This observation prompted many workers, including Calmette and Guérin (4), to design methods to attenuate the virulence of the tubercle bacillus. Various chemical and physical methods were tried, which resulted in some degree of attenuation, without, however, yielding a stably attenuated vaccine strain.

One of the major challenges faced by all investigators working with the tubercle bacillus was the difficulty in obtaining homogenous emulsions of the organism, since, due to its fatty consistency, cultures grew as aggregated masses. Fortunately, Calmette and Guérin discovered that the addition of small quantities of sterilized beef bile to the culture dissociated these aggregates (6). They then determined that the bovine tubercle bacillus grew very well on glycerinated potato medium cooked in ox bile. In fact, the bacilli grew faster and acquired an altered colony morphology in the presence of ox bile, compared to growth in the absence of bile (7). The change in colony morphology was reversible. The growth on biliated medium also enhanced the virulence of the organism, as evidenced by a shortening of the time to death in infected guinea pigs (7). However, upon continuous passages at two-to-three week intervals,

the virulence of the bacilli gradually decreased. Already after 15 passages on biliated medium, the bacteria showed strong attenuation in guinea pigs and cattle (8). This attenuation was irreversible upon cultivation on non-biliated potato medium, although the change in colony morphology remained reversible. However, unlike guinea pigs and cattle the bacilli at passage 15 remained virulent for horses upon intravenous injection. Interestingly, despite the decrease in virulence the capacity of the passaged micro-organisms to induce resistance to challenge infection remained intact. In fact, resistance to challenge appeared much faster after vaccination with bacilli at passage 20 than with non-passaged bacteria, although total clearance of the challenge bacteria could not be achieved with either vaccination (9). Therefore, Calmette and Guérin concluded that this vaccination procedure did not induce true immunity but simple tolerance to the tubercle bacilli. Upon waning of this tolerance, the bacilli can reactivate.

After 34 passages, Calmette and Guérin felt that they had obtained a strain that had the characteristics that they were looking for, that is, not causing tuberculous lesions in cattle, even after administration of high doses, yet being able to induce resistance to challenge inoculation with virulent bacilli 30 days after vaccination. The 34e passage strain was also found avirulent in guinea pigs and non-human primates (10). They then decided to investigate whether any of the subcellular fractions could induce protection. Acetone- and benzene-soluble lipid fractions, various tuberculin preparations, heat-killed bacilli, and protoplasts were obtained and used to vaccinate eight-month-old cows. Upon challenge, none of these preparations induced durable protection, although vaccination with tuberculin delayed the onset of the disease somewhat (11). It was therefore concluded that durable 'tolerance' against tuberculous infection was directly related to the presence of live bacilli (Figure 9.1).

Although the attenuation appeared within a few months of passages at 3-week intervals, the investigators continued subculturing the bacilli on biliated potato medium for 13 consecutive years and a total of 231 passages (Figure 9.2). Even the First World War did not interrupt the regular subculturing every two to three weeks. In 1920, they concluded that the totally avirulent bacilli for both man and animals would be useful vaccines and succeed there, where the vaccine candidates of Emil Von Behring and Robert Koch had failed (12).

Extensive vaccination studies on cattle followed, as well as safety studies in a large number of mammals, including horses, cattle, sheep, dogs, rabbits, guinea pigs, primates, rats and mice, as well as in birds, including chicken and pigeons. The conclusion was that the attenuated *M. bovis* strain, now called Bacille de Calmette et Guérin (BCG), was totally safe in all species tested, unable to induce tubercles upon intravenous, intraperitoneal, subcutaneous or oral administration. Cultured on non-biliated potato medium, it did not reverse to virulence. However, young cattle vaccinated orally or subcutaneously with

Figure 9.1 Comparison of Protective Efficacy of Live BCG with that of Other Vaccine Preparations in Cattle



Note: Model representing the results of a vaccination trial in cattle with live BCG (*top row*), compared to a non-vaccinated control (*top row, left cow*) and different vaccine preparations (*bottom row*), including a killed BCG vaccine preparation (*bottom row, fourth pair of cows from the left*).

BCG were protected against experimental or natural challenge. Calmette and Guérin recommended systematic BCG vaccination in young cattle in the first days of life to protect them against infection with virulent *M. bovis*. Protection may be more problematic in older cattle, as most of them may already have been infected prior to vaccination, in which case BCG vaccination would not be effective (13).

The protective effect of BCG was not only shown in cattle, but also in rabbits, guinea pigs, and non-human primates (summarized in 14). Despite this success, Calmette and Guérin were hesitant to test the BCG vaccine in humans. However, Bernard Weill-Hallé, a physician at the Paris hospital, convinced them finally to use the BCG on a newborn child almost certain to acquire TB from his household contacts, as the child, whose mother had died from TB, was to be brought up by his grandmother suffering from severe TB. In July 1921 three doses of BCG were administered at the third, fifth, and

Figure 9.2 *M. Bovis* Passage Strains

Note: The original BCG strain has been lost, but intermediate passage strains from the virulent *M. bovis* ('lait de Nocard') are preserved at the Institut Pasteur de Lille. However, it is not known whether these strains are viable.

seventh days of his life, respectively. No harmful effect was noted, and the child remained healthy without any sign of TB disease. From then on many more newborns were treated with BCG, without any notable side effect. From 1924 to 1926 a first large-scale, multicentred efficacy trial was conducted on a total of 5,183 children all over France. Although this trial did not include a placebo control, the BCG efficacy against death caused by TB was judged to be 93 per cent during the first year of life, as evidenced by a historical comparison using the well established 25 per cent TB-caused death rate among children born in TB families (14). Soon, other efficacy trials were carried out in many different countries in Europe, Africa, South America, and Asia, with essentially the same results.

It was thus recommended to use BCG vaccination in neonates in all families with a high TB burden (Figure 9.3), and BCG was sent out to all corners of the earth with strong recommendations on how to cultivate the strain and how to use the vaccine (14). Over the years, this has resulted in the generation of more than a dozen different daughter strains. Although the vaccine was initially given orally, WHO currently recommends the intradermal route of BCG vaccination, primarily because the intradermal route allows for a more consistent dosing

Figure 9.3 Recommendations for Vaccination with BCG in France

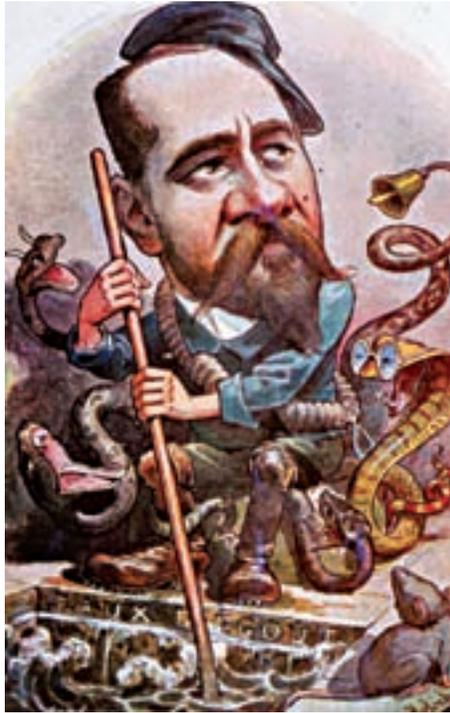
Note: Advertisement showing that BCG vaccination was recommended for children in France and delivered free of charge at the Institut Pasteur.

(15). This is probably due to the fact that the viability of BCG is reduced by 1 to 2 logs upon exposure to gastric secretions and low pH (16).

The Protective Effect of BCG against Tuberculosis

Since the very beginning, BCG vaccination has met with considerable controversy (17) (Figure 9.4), but is still today one of the most widely used vaccines in the world. Many clinical efficacy trials have been conducted in different parts of the world, with very different outcomes depending on a number of parameters. By the 1990s several hundreds more or less well-performed studies had been reported. In prospective trials, vaccine efficacy has ranged from 80 per cent

Figure 9.4 Caricature of Albert Calmette around the Vaccination Controversy



Note: Albert Calmette not only worked on BCG but had also been very active in the development of anti-snake venom antiserum, as well as in developing methods to purify sewage sludge.

down to 0 per cent (18). An important meta-analysis on 14 prospective and 12 case-control studies that were conducted in a sufficiently satisfactory manner was published in 1994 (19) and concluded that on average BCG vaccination significantly reduces the risk of TB by 50 per cent if all forms of TB are considered. Protection rates against TB meningitis, disseminated disease, and death, with respectively 64 per cent, 78 per cent, and 71 per cent, were higher than those of total TB cases. The efficacy of BCG vaccination increased with the distance from the equator, as the most important single variant linked to differences in efficacy. Age at vaccination, BCG strain variation, and differences in BCG preparations did not have a strong effect. However, a meta-analysis of studies on protection in newborns and infants against cases that were confirmed by laboratory tests indicated protection rates as high as 83 per cent (20). The meta-analyses provided no indication on the duration of protective immunity

induced by BCG. However, some recent studies suggest that it may last for as long as 20 years (21).

Probably the most extensive efficacy trial performed was the so-called 'Chingleput trial', carried out in South India over a period of twelve and a half years. Its outcome was disastrous, as in that trial BCG vaccination failed to show any benefit against pulmonary TB (20). However, curiously, the total numbers of TB cases, both in the vaccinated and in the non-vaccinated groups were unusually small, roughly seven times smaller than expected. One of the potential reasons for failure of BCG vaccination may be prior exposure to environmental mycobacteria (23). For more than 40 years it has been hypothesized that exposure to environmental mycobacteria may provide some level of protection against TB, and that in those cases BCG administration will not add much, if any, benefit. In addition, it is possible that in individuals sensitized by environmental mycobacteria, BCG take is affected, as immunity induced by the first infection may block the multiplication of the BCG (24). Already Calmette and Guérin suggested that BCG is best used in non-sensitized individuals or animals and, therefore, should be considered primarily for children sufficiently young to be unlikely infected prior to vaccination. This has been experimentally addressed in the aerosol challenge guinea pig model. Administration of *M. avium-intracellulare* appeared to protect against challenge with a low-virulence MTB strain isolated from the Chingleput population (25). Interestingly, a modest protective effect of BCG vaccination was observed in a 15-year follow-up of the Chingleput trial in the youngest age group, likely to be less sensitized by environmental mycobacteria (26).

Further evidence for a cross-protective effect of environmental mycobacteria and BCG comes from the fact that BCG can induce protection against other mycobacterial infections (27), including against leprosy. In fact, in trials in which the efficacy of BCG vaccination was tested simultaneously against TB and leprosy, the efficacy against leprosy was found to be greater than that against TB (28), including in the Chingleput district (26). The protective effect of BCG vaccination against leprosy was further documented by a meta-analysis performed on 26 published studies subdivided into experimental and observational studies. Whereas the overall average protective effect of BCG vaccination estimated by the observational studies was 61 per cent, the experimental studies provided a protective efficacy of 26 per cent against leprosy, both types with significant heterogeneity between the studies (29). Protection was better against multibacillary forms than against paucibacillary forms of leprosy and was greater among women as compared to men.

Another meta-analysis came to the conclusion that, considering BCG vaccination of infants has a demonstrated protective effect against TB meningitis and military TB in children during their first five years of life, BCG vaccination

is a highly cost-effective intervention against severe childhood TB. It should therefore be continued in high-incidence countries (30).

However, BCG-induced immunity is likely to wane with time after vaccination (31) and, therefore, revaccination with BCG during adolescence has been considered and extensively used in several countries. A cluster-randomized trial involving more than 200,000 school-aged children has addressed whether revaccination with BCG is effective in Brazil (32). The crude incidence of TB was found to be 29.3 per 100,000 in the intervention group and 30.2 per 100,000 in the control group, indicating that revaccination of children aged 7–14 years did not provide any substantial additional protection. Revaccination was ineffective against both pulmonary and extrapulmonary TB and in all age groups. However, these results do not exclude that protection by revaccination may perhaps increase with time.

Nevertheless, the conclusions of this study are similar to those of a previous study where the effectiveness of revaccination was tested in Malawi, where the first vaccination did not provide significant protection against TB but afforded 50 per cent or more protection against leprosy (33). At a five- to nine-year follow up after the second vaccination, no benefit of a revaccination with BCG was noted for protection against TB, although a slight increase in protection against extrapulmonary TB by repeated BCG vaccination was noted in this study. In contrast, the rate of pulmonary disease was actually higher among the revaccinated individuals compared to those who had received placebo. However, interestingly, revaccination with BCG provided increased protection, of roughly 50 per cent, against leprosy compared to a single BCG vaccination. These findings indicate that a second vaccination with BCG can increase protection against leprosy, but not against TB, a conclusion that was also drawn from a recent meta-analysis (29). However, the increased protection against leprosy by revaccination was very recently questioned. Cunha et al. (34) found no evidence of enhanced protection against leprosy conferred by a second dose of BCG given to schoolchildren aged 7–14 years. In fact, there was a slight increase in the leprosy rate during the first year of follow-up in the intervention arm.

BCG and Non-Mycobacterial Diseases

In addition to its use as a vaccine against TB and leprosy, several studies suggest that BCG administration has also an overall beneficial effect on the general child survival, including that of low birth weight immature infants (35), independent of its effect on TB or leprosy, providing an indication for non-specific bystander effects of BCG (36, 37). The presence of a BCG scar or

a positive tuberculin response was associated with better survival of children below 12 months of age, whereas a positive response to tetanus or diphtheria antigens was not, indicating a BCG vaccine-specific effect (38). Some studies estimated a lowering of child mortality by 50–75 per cent after BCG vaccination (34). However, confounding effects, including a better socio-economic, cultural, and educational status for households in which children had received the vaccine, may make it difficult to draw definitive conclusions from such studies. On the other hand, it is known that BCG vaccination can influence immune responses to other vaccines, both quantitatively and qualitatively (39), which conceivably may in turn have effects on survival from diseases other than mycobacterial infections.

BCG vaccination induces a strong Th1 immune response in newborns (40). The association between child survival and TST positivity could thus be related to enhanced overall CMI in reacting children, compared to non-reacting children. Interestingly, in the elderly, CMI was also shown to be a good predictor of general morbidity and mortality (41). At the two extremes, very young and very old age, cellular immunity often defaults, unless immuno-interventions are applied, such as BCG vaccination at birth.

In agreement with this hypothesis, BCG vaccination has been reported to diminish the incidence, prevalence, and intensity of hookworm infections in children (42). A strong inverse association was also observed between TST responses and a range of atopic disorders (43). In both cases these conditions are characterized by an exacerbated Th2-type immune response, normally inhibited by Th1 cytokines (44). Asthmatic symptoms were one-half to one-third as likely in TST responders compared to non-responders, although estimated allergen exposure was similar in the two groups. Moreover, remission of atopic symptoms was six to nine times as likely in responders. In parallel, TST responders had significant lower levels of Th2 cytokines and higher levels of Th1 cytokines than non-responders.

Although in the study of Shirakawa et al. (43), the TST responsiveness was mostly due to previous MTB exposure, the effect of BCG vaccination on atopic conditions has been tested in several studies. In a study carried out in Brazil, neonatal BCG vaccination was associated with a 37 per cent reduction in the prevalence of lifetime asthma (45). In Spanish schoolchildren BCG vaccination at birth also appeared to offer a weak but significant protection against asthma and hay fever (46). However, the protective effect of BCG vaccination against asthma is controversial (47), as other observational studies have provided no support for a significant relationship between receipt of BCG in the first year of life and the likelihood of acquiring asthma in childhood or adolescence (48). Thus, the effect of BCG immunization on asthma and allergies may perhaps be at best a very weak one.

In mouse models, nasal administration of BCG has been found to suppress the development of experimentally induced airway eosinophilia (49). Interestingly, when different routes of BCG administration were tested, by far the best route for this suppressive effect was the nasal route, which constitutes obviously an important difference between these mouse studies and the human studies described above, as BCG is mostly given intradermally to human newborns. The suppression of eosinophilia in mice was correlated with reduced IL-5 production and, using IFN- γ receptor knock-out mice, the suppressive effect was shown to be mediated by IFN- γ . In agreement with these findings, when a recombinant BCG strain producing the cytokine IL-18 was used, airway eosinophilia was further decreased (50). IL-18 is an IFN- γ inducing factor and acts in synergy with IL-12, a cytokine that is induced by mycobacterial infections, lending further support for the role of BCG-induced Th1 cytokines in inhibiting allergic disorders.

Studies in diabetes-prone mice have shown that a single injection of BCG given at an early stage can prevent the development of type I diabetes (51). This was also tested in 17 children with newly diagnosed type I diabetes, where a single intracutaneous dose of BCG was found to lead to long-term clinical remission in 11 of those children (52). However, subsequent randomized controlled trials did not confirm a favourable effect of BCG vaccination on remission rates for children with type I diabetes (53). The effect of BCG on other inflammatory diseases has also been investigated, including Crohn's disease. In general, the data on the protective outcome are conflicting, and a better understanding on how BCG vaccination may affect such chronic health conditions is clearly needed.

Probably the most investigated and used 'non-specific' property of BCG is its effect against cancer. Based on hundreds of years of observations relating spontaneous recovery and regression of certain cancer patients to concurrent bacterial infections, several experimental infections and clinical trials have been carried out to identify the best bacterial cocktail for cancer treatment [reviewed in (54)]. Some of them have been extensively used until the 1960s, albeit with very questionable effects. In particular, it was noted that patients with TB rarely developed malignant neoplasms (55). BCG has, therefore, been investigated for its effect against many different cancers. It has been tested as an adjuvant combined with autologous cryoconserved tumour cells in the treatment of cancer, including colorectal (56) and non-small cell lung cancer (57). In a prospective randomized trial only 3 out of 20 patients treated with cryoconserved tumour cells in the presence of BCG had recurrences in a 28-month follow up, and none had died, whereas 9 out of 20 control patients had recurrences, and 4 had died (56). In contrast, no apparent benefit from therapeutic vaccination with tumour cells and BCG against non-small cell lung

cancer was observed (57). BCG has also been used for the treatment of a variety of other cancers, with or without autologous antigen, including melanoma and leukaemia. Despite considerable excitement over initial encouraging results in immunotherapy for acute lymphoblastic leukaemia (58), subsequent controlled studies failed to confirm the initial results.

Clearly the most striking benefit of BCG therapy was observed in the treatment of bladder cancer. It was known that the bladder is capable of mounting strong immune responses, making it therefore a potentially suitable model for BCG immunotherapy. In 1976, Morales et al. (59) were then the first to describe the successful treatment of bladder cancer with BCG. In a small group of nine patients with recurrent superficial bladder tumours treated with vesical and intradermal administration of BCG, the pattern of recurrence was altered favourably. Similarly, the addition of BCG therapy to nephrectomy significantly prolonged the survival of stage IV renal cancer patients (60). Unequivocal benefits of BCG treatment against bladder cancer were established in a controlled randomized study carried out 4 years later on 37 patients (61). Standard surgical therapy was compared to standard therapy plus BCG. After one year of follow up, 42 per cent of the control patients had recurrent tumours compared to 17 per cent for the BCG-treated patients. This led to wide acceptance of BCG therapy for the treatment of bladder cancer (62). Compared to all other forms of intravesical chemotherapy, BCG appears today as the most effective one. Remission upon BCG treatment averages 70 per cent over 5 years. A meta-analysis on 9 randomized trials including 700 patients concluded that 68 per cent of the BCG-treated patients had a complete response compared to 51 per cent in the group of patients treated by intravesical chemotherapy (63). However, BCG is not effective against muscle-invasive disease, or tumours that lie out of direct contact with BCG.

During the 30 years since the first recognition of a beneficial BCG effect on superficial bladder cancer, the mechanism by which BCG exerts its effect has been the subject of many studies [reviewed in (64)]. Both cancer-specific and non-specific mechanisms play a role. Upon instillation, BCG adheres to the urothelial lining and induces the local production of proinflammatory cytokines, especially Th1 cytokines, and the accumulation of inflammatory and effector T cells. These may by themselves have more damaging effects on tumour cells than on normal cells. At the same time, BCG may also induce the expression of adhesion molecules on tumour cells, thereby facilitating binding of immunocompetent effector cells that are active against target cells expressing specific tumour-associated antigens. Perforin-mediated lysis of tumour cells may represent the predominant effector mechanism.

Conclusion

In addition to its first aim to protect newborns (humans and cattle) against TB, BCG has thus been tested and used for a number of indications with various levels of success. Its protective effect against TB is more than ever under debate, and much effort is employed to develop vaccines with improved efficacy against this disease. However, considering that BCG is globally the most widely used vaccine, with more than 3 billion administrations so far, all new vaccines have to take this into consideration, and their efficacy will necessarily be compared to that of classical BCG. The first new vaccines are in their first phases of clinical trials (see 65), and it will still be a long way until BCG can be successfully replaced.

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