Section for the Study of Disease in Children.

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Preventive Vaccination Against Tuberculosis with BCG.

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SINCE Robert Koch discovered the tubercle bacillus, experimental evidence has been obtained, especially during the last thirty years, that the majority of human beings are spontaneously vaccinated against tuberculosis in the first period of life by the absorption of a few bacilli present in milk or any other food, or penetrating into the organism by way of mucous membranes or even of the skin. Such spontaneous infections are nearly inevitable, because of the ubiquity of the tubercle bacillus expectorated by consumptives and propagated everywhere by dust and flies contained in non-sterilized or unboiled milk and even present in the fæces of apparently healthy individuals who suffer from latent tuberculosis. It is quite exceptional to succeed in preventing such infections, in the long run, by preventive measures.

Such "paucibacillary" infections—as they are called to-day—being caused by a few bacilli, are unable to cause any pathological trouble in the organism. They only sensitize it against tuberculin, and this *allergy*, which, incidentally, is not constant, may be transient or lasting.

Such infections are frequently quite harmless but only if they are not repeated within a sufficiently long time; they are then followed by a specific immunity against further and even more abundant infections.

This specific immunity against re-infections can be compared with those present in syphilis, glanders, brucellosis, piroplasmosis, malaria, and most probably in other diseases like lepra; it depends on the presence in the organism of some *living* specific parasites sufficiently few not to cause serious or even mortal lesions.

It cannot be obtained, except for a very short time, by injecting bacilli killed by heat or any other physical or chemical agent nor are bacillary extracts able to bring it about. That is why first Mafucci in 1898, then MacFadyean, Pearson and Gilliland, and finally Behring, with Römer and Ruppel in 1902, proposed to utilize the human bacillus for the vaccination of bovines, Theobald Smith having been the first to demonstrate the low virulence of human bacilli for cattle.

Unhappily, the experiments on a large scale begun in different countries to test the practical value of Behring's method of bovine vaccination, had soon to be abandoned; the subcutaneously or intravenously vaccinated animal excreted intermittently, and often during long periods, bacilli, which being sometimes virulent for guinea-pigs, could be dangerous for man and animals.

Other experimenters, hoping to avoid this drawback, have tried to vaccinate bovines with avian bacilli or with paratubercle bacilli isolated from tortoises, reptiles, frogs or fishes.

All their endeavours were vain. We know to-day that no antigenic value whatever can be attributed to "paratubercle bacilli," such as Friedmann's tortoise bacillus, which is actually being advocated in various countries, especially in France, as a curative and preventive remedy against tuberculosis. Such bacilli are absolutely useless in prophylaxis as well as in therapeutics.

Those failures led Gerald Webb and W. Williams in America and more recently Selter, of Bonn (Germany), to take the responsibility of inoculating very small doses of virulent *human* tubercle bacilli, not only into animals, but even into children of various ages.

It is extremely improbable that a method, consisting of the inoculation of virulent bacilli in man and in domestic animals could become a common practice; individuals so *infected* (and not *vaccinated*) are likely to become sources of infection for their environment, and live under the constant menace of a generalization of their infection—started by a caseous tubercle.

Neither is it possible to use cultures of bacilli—modified by age or spontaneously attenuated—such as those isolated from certain lesions of the skin, bones or glands (e.g., the R 1 strain from Saranac, or Uhlenhuth's Tb. 18). It is true that such cultures are generally well tolerated by susceptible animals even when they are injected in massive doses; nevertheless, they cause local tuberculous lesions, which can be *re-inoculated from animal to animal.*

To secure preventive vaccination against tuberculosis with the least risk, and as efficaciously as can be obtained by spontaneous infection with a few virulent bacilli, it is absolutely necessary to discover a strain of bacilli, definitely incapable of causing progressive tuberculosis, even in high doses, in animals and man. Such a strain should be inoffensive too for all kinds of susceptible animals and birds. but it should have the same antigenic properties as virulent bacilli, and be able to provoke antibody formation; for resistance to re-infections which characterizes immunity in tuberculosis seems to depend on the presence of such defensive substances.

For more than thirty years my co-worker, C. Guérin and myself have been devoting our attention to this problem of obtaining a *vaccinal* attenuated strain of *fixed* virulence, comparable to Pasteur's living vaccines (anthrax, chicken septicæmia, hydrophobia, etc.). Future generations will decide if we have succeeded in solving it. But experimental and clinical observations have already shown that it is possible to combat tuberculous infection efficaciously with our strain, when it is used in accordance with the conditions which we have elaborated, and which I am presently going to describe. Especially when used for new-born infants it notably reduces general infantile mortality.

As early as 1901 certain experiments on roebucks and young bovines had shown Guérin and myself that the absorption of virulent bacilli by the mucous membranes of the digestive tract plays a predominant part in tuberculous infection of the lungs, just as it does in pulmonary glanders in horses. In studying this mode of infection we tried to imitate as closely as possible the conditions of natural infection. The animals absorbed carefully prepared suspensions of bacilli, mixed with their food, or by means of a œsophageal tube. To obtain fine emulsions of bacilli we first ground them in an agate mortar, with egg-yolk, and later with pure sterilized bile, the latter giving the best results. This gave us the idea that it might be easier to emulsify bacilli grown on potatoes, cooked in ox-bile and kept in hour-glass tubes containing sterile pure 5% glycerinated bile, the potatoes being dipped at one end in this extremely alkaline liquid, rich in lipoids.

We were able to establish that tubercle bacilli grew very well on this culture medium, on which they presented a characteristic appearance, resembling that of *B. mallei*. They could be easily emulsified in physiological saline solution, much more so than cultures that had grown on ordinary glycerine broth or potato, and it was much easier to infect animals with small doses of such suspensions. Hence it became our rule to cultivate our strain on bile potato. It was a virulent bovine strain, isolated in 1902, by Nocard, from milk obtained from a tuberculous udder.

After thirty passages on bile potato we remarked that the strain ceased to kill guinea-pigs. After sixty passages on bile it was still slightly virulent for rabbits and horses, but it had become absolutely avirulent for guinea-pigs, monkeys and calves. We then pursued our research work in this direction, and in 1912 we undertook experiments on a large scale on calves, placed in special stables, under conditions most favourable to natural infection. These experiments were prematurely interrupted by the war, but had already provided us with valuable information, published by us in 1920 in the *Annales de l'Institut Pasteur*, 1920, vol. xxxiv, p. 553.

We were able to demonstrate, that intravenous—or better, subcutaneous—injections of our bile bacillus (50 to 100 mg.) in young calves could make them manifestly resistant to natural or experimental virulent infections, and we had ascertained that this resistance against experimental infections persisted during 12 to 18 months. We then had to try to establish immunity against tuberculosis by impregnating as early as possible—i.e., immediately after birth—the lymphatic system of the young animal with attenuated bacilli which, having kept all their antigenic properties, were incapable of causing progressive tuberculosis. This impregnation had to be attained by the natural way of access, that is to say, *by the intestinal tract.*

Our bile bacillus, which is to-day shortly designated as BCG (bacillus Calmette-Guérin), was at that moment at its 230th passage on bile medium, and no more modifications of its characteristics took place. Intraperitoneal injection of as much as 10 mg. BCG in guinea-pigs was followed by the formation of nodules in the epiploön, persisting several weeks without doing any damage to the animal, and finally vanishing by resorption without leaving a trace, so that when the animal was killed 5 or 6 months after the injection, it was impossible to discover the smallest lesion, even under the microscope. It seemed that we had obtained a real vaccine, of hereditarily fixed attenuation, like Pasteur's anthrax vaccines ; indeed, all our efforts to restore its virulence by passage in animals or by mixed inoculations of BCG and tuberculin or other irritating substances, were unsuccessful.

That is the point to which our investigations had led us, and we were just beginning an experiment on the large scale of methodical vaccination of a gravely infected herd of young bovines, belonging to M. Legrand, at Gruville (near Fécamp, Department of Seine-Inférieure), when on July 1, 1921, Dr. Weill-Hallé, who was then physician to the Infant Department of the Charité Hospital in Paris, came to consult us on a subject, which well might excite the conscientious scruples of the experimenter. He told us of a baby, born of a tuberculous mother, who had died shortly after delivery The baby was to be brought up by a grandmother, herself tuberculous, and consequently its chances of survival were precarious. Could one risk on this child a trial of the method which, in our hands, had been constantly inoffensive for calves, monkeys, guinea-pigs and which had proved to be efficacious in preventing experimental tuberculous infection in these animals ? We considered it our duty to make the trial, and the results were very fortunate, as the infant, having absorbed 6 mg. BCG in three doses per os, has developed into a perfectly normal boy, without ever having presented the slightest pathological lesion, notwithstanding constant exposure to infection during two years.

When we saw that this child developed normally during the six months following the vaccination, we thcught we need not wait any longer to try the

method on other children. Weill-Hallé, Turpin and Miss Coloni agreed with us, and proceeded to vaccinate during the next three years (up to July, 1924) 317 infants sixty-seven of whom were born and brought up in tuberculous families, the others in families apparently free from tuberculosis. The doses of BCG ingested by these children were fixed at 30 mg., instead of 6 mg., divided in three portions of 10 mg. each, absorbed at 48-hour intervals.

We insisted on the vaccination taking place immediately after birth, and by ingestion, for the following reasons:—

(1) Tuberculous infection is far more dangerous to young infants than to adults. An infant fed and brought up by a tuberculous mother or in a family including a bacillus-spreading consumptive, is almost invariably seriously or fatally infected. Heynsius van den Berg, Amsterdam, found that infection during the first three months of life leads to a tuberculous mortality as high as 71·5% during the first and second years of life. It is a well-known fact that in children born and brought up in contact with tubercle bacilli, mortality during the first year of life reaches from 7 to 25% or even more (the figures depending on the intensity and efficacy of antituberculosis measures provided by each country), whereas in children belonging to apparently healthy families it does not exceed 2%.

It is therefore necessary to provide the lymphatic organs of the newborn with inoffensive bacilli acting as antigen, to create a state of immunity before any virulent infection has taken place. Now the development of immunity takes about four weeks, and consequently one must act quickly. It is essential during this "negative" period before the appearance of immunity, to avoid carefully all occasions and sources of infection. The best way to do this is to separate the baby immediately after birth from its tuberculous mother and to place it in a special babies' home until the full development of immunity. If this separation is impossible, special prophylactic measures should be taken at home.

(2) Vaccination of the newborn offers another advantage. It can be carried out by ingestion. Disse's researches have shown that during the first days after birth the cylinder cells covering the internal intestine wall, do not yet form an uninterrupted mucous membrane, and microbes still penetrate it with the utmost facility. Later on, about the fifteenth day, the internal intestinal surface becomes much less permeable, and thereafter the best way to vaccinate will be by subcutaneous or intramuscular injection.

Of course one could not think of introducing this method of vaccination against tuberculosis into general practice, without being absolutely convinced of its innocuousness. Now the innocuousness of BCG has been proved by thousands of inoculations in all sorts of animals. So many convincing proofs of it have been furnished at the commission of expert bacteriologists and clinicians, appointed in Paris by the Hygiene Section of the League of Nations, October, 1928, as well as at the recent International Conference at Oslo, August, 1930, that no one can have any further misgivings about it.

When Weill-Hallé and Turpin began their first vaccinations on babies, we did not yet know if the infantile organism would tolerate BCG as well as young animals did. It was therefore necessary to be careful and that is why we waited three years before we decided to put cultures of our strain at the disposal of foreign laboratories, and to deliver vaccine doses to the doctors of our own country who asked for them.

During that period of three years, and the eight following years, we never ceased to keep before our eyes one important question, and to encourage others to study it: *Is it to be feared that BCG vaccine should eventually become virulent in the organism?* In other words: Is it possible that BCG bacilli, after having lived a certain time in the organism without being killed or eliminated, become capable of causing progressive tuberculous lesions?

A large amount of research work has been devoted to the solution of this problem, in many foreign laboratories as well as in our own, but the most ingenious experimental combinations have failed to restore to our BCG strain the pathogenic properties of the original culture from which it was derived.

Some facts have been published that seemed at first sight disturbing, but we know now that they were due to errors of interpretation or of technique, and not a single one of them has been verified by other experimenters.

I mention, in the first place, S. A. Petroff in America, and E. A. Watson in Canada, who claimed to have demonstrated the possibility of a return to virulence of BCG. They inoculated high doses of BCG (20 to 100 mg.) in a great number of guinea-pigs, which they kept alive during at least eighteen months. At the end of this period they found authentic progressive tuberculous lesions in from 1 to 2% of their animals, and they were able to reinoculate these lesions in new guinea-pigs, while all the other animals remained normal, though they had received the same doses of BCG.

Now tens of thousands of guinea-pigs and rabbits the world over have been inoculated with all imaginable doses of BCG. We have kept such animals for a period of two years and a half, much longer indeed than did Petroff and Watson. Countless passages from animal to animal have been made by us and by investigators elsewhere. Never have we observed a development of progressive tuberculous lesions capable of re-inoculation in passage. Therefore the facts, published by the aforementioned authors, must be regarded as accidental, due to the animals having already been used for other inoculations, or to spontaneous infection, which is not exceptional in animals bred and kept in the neighbourhood of a sanatorium or a hospital where tuberculous patients are admitted.

Further, Petroff claims to have dissociated BCG into two types of colonies, the R type, very abundant, and the S type, much less frequent, the incidence being of one S type colony on 50,000 of the R type. Petroff claims that the progressive tuberculous lesions observed in some of his guinea-pigs are due to those S type colonies.

Now dissociation of BCG and of virulent cultures in R. S. and intermediate type colonies can be easily realized, but in no other laboratory of the world has it been possible to discover a virulent S colony in authentic pure BCG. None of the most distinguished bacteriologists such as C. Prausnitz, Bruno Lange, R. Kraus, Gerlach, Tzeknowitzer, Stanley Griffith, Reed, Cantacuzene, J. Bordet, Malvoz and van Beneden, not to speak of my own co-workers, has ever succeeded in isolating a virulent S colony from BCG. Professor Neufeld, director of the Robert Koch Institute at Berlin, made the following statement at the international conference at Oslo, August, 1930: having secured some specimens of R and S type colonies from Petroff, he had studied them in his laboratory, and both were found to be contaminated with virulent bacilli of the human type.

We, ourselves, already knew that Petroff's cultures were contaminated with a human bacillus, very slightly virulent for rabbits.

More recently other authors have joined the discussion: Hormaeche, of Montevideo, Sasano and Medlar, of the Mount Gregor Sanatorium (New York), and G. Dreyer of Oxford. During an epidemic of streptococcus infections in his guinea-pigs, Hormaeche succeeded in isolating a pathogenic streptococcus from his animals, and he observed that when he inoculated this streptococcus in animals previously vaccinated with BCG it caused a recrudescence of virulence in BCG, which was followed by the appearance of tuberculous lesions that could be reinoculated in passage.

This author has not succeeded in repeating the experiment with another strain of BCG than that which had been used in his first experiment. Charles Nicolle, who visited Montevideo recently, has been so kind as to bring me a sample of Hormaeche's streptococcus, and Dr. A. Saenz has studied it in my laboratory. He

has not been able to confirm Hormaeche's results, nor has P. Nelis in Brussels, who studied two streptococcus cultures, one isolated from a cow's udder, the other from an abscess in a horse.

K. T. Sasano and E. M. Medlar, at Mount Gregor, having stated the perfect innocuousness of BCG for guinea-pigs and rabbits, claimed to have obtained its return to virulence by cultivating it on Sauton's synthetic medium, with the addition of fresh rabbit's serum. The authors remarked that the experiment succeeded less well with heated serum. Three passages on this medium should suffice to obtain a virulent culture, 1 mg. of which kills rabbits in thirty to fifty days. This is the degree of virulence of a normal bovine culture.

Most probably the culture has been accidentally contaminated in this experiment by the addition of unheated fresh rabbit's serum. A. Boquet is actually now repeating it in my laboratory, and, till now, after three passages on Sauton's medium, with the addition of fresh and sterile rabbit's serum, the virulence has not increased.

Finally, G. Dreyer, in an article in the *Lancet*, 1931, i, 9, claims to have obtained a virulent culture, killing guinea-pigs and rabbits just as an ordinary bovine strain, by cultivating BCG in the depth of peptonized glycerol veal broth. About one in every five flasks implanted in this way is reported, after two to four passages in the same medium, to contain such a virulent culture, though not constantly, neither are all BCG strains capable of giving this striking result.

Now for many years we and many other experimenters have studied deep cultures of tubercle bacilli. Not the least increase of virulence has ever been observed in such deep cultures. Indeed, S. Arloing (Lyons) formerly used deep cultures to obtain attenuated tubercle bacilli for bovine vaccination.

Till now none of the many attempts to render BCG cultures virulent has been successful, and no one has succeeded in proving that BCG can be transformed into a virulent bacillus by sudden mutation, as some supposed. Since the Lübeck disaster many efforts have been made in this direction. It has been supposed that such a mutation could be favoured by culturing BCG on other mediums than Sauton's, e.g., Dorset's egg-medium, or Hohn's egg-hematine medium. But to-day we are assured that this is not to be feared, as has been proved by the experiments of P. Zeyland at Poznan, of Bruno Lange at Berlin, C. Prausnitz (Breslau), F. Gerlach (Vienna) and W. Park (New York). No one of these experimenters has succeeded in modifying the pathogenic properties of BCG. Consequently we have a right to consider BCG as a fixed virus, because of its absolute stability in vitro as well as in vivo. Indeed, for six years all our attempts to detect a late-developing variation have been unsuccessful.

Does this give us a right to conclude that no laboratory artifice will ever succeed in obtaining a transformation of BCG into a virulent bacillus, just as Guérin and myself succeeded in transforming a virulent bacillus into BCG? I would be the last to claim it! We are acquainted with laboratory artifices, by which we may transform Pasteur's anthrax vaccines into virulent anthrax cultures. Do we not know that hydrophobia virus can be attenuated by passage through monkeys, but becomes virulent for rabbits by passage through this animal species? Have not some authors claimed to transform Jenner's vaccine into smallpox virus by successive inoculations in horses? Why should such a transformation be impossible, *a priori*, in the case of BCG, and, if so, why should it be an argument against preventive vaccination against tuberculosis? Should we refuse ourselves the immense benefits of Jenner's vaccine, Pasteur's vaccines against anthrax, hydrophobia, etc., the living vaccines against bovine septicæmia or sheep-pox, because such vaccines may sometimes become virulent under very particular conditions?

Some have told us that the use of living vaccines may entail certain dangers, but they failed to specify the nature of the dangers. They forget that only living viruses are able to cause solid and durable immunity, as does the disease itself.

Killed viruses, such as an antityphoid, paratyphoid, pest or cholera vaccines never give satisfactory results, causing only transitory and unreliable immunity.

As for preventive vaccination against tuberculosis with BCG, a great number of experimenters have studied the properties of BCG bacilli, isolated from children, in whom they had remained during a whole year or even more. They have never succeeded in finding the slightest modification in virulence. Many times BCG cultures have been isolated from mesenteric glands or other organs, at autopsies of children, who have died after vaccination from various non-tuberculous diseases. Such cultures have never been found to be virulent.

One can no longer doubt the perfect innocuousness of BCG, which remains avirulent in the organism of the vaccinated, in which it only acts as an antigen.

Experimental and clinical evidence of the innocuousness of the method having thus been obtained, extensive and precise information about its efficacy had to be collected. Experimental research work on young bovines and anthropoid apes, such as has been done in West Africa by our co-workers, Wilbert and Delorme, in Vienna by R. Kraus and F. Gerlach, and in San Francisco by Meyer, had already convinced us of the efficacy of BCG vaccination.

To measure the value of BCG as a means of antituberculous prophylaxis, it is of course necessary to wait until the protective effects of the first vaccination at birth, and of the revaccinations, recommended by us at the ages of 3, 7 and 15, have become evident.

Even now, however, we may judge its influence in the diminution of tuberculous and general mortality of young infants.

Unhappily no comparative information can be obtained from the study of the death-rates published by most civilized countries, the notification of tuberculosis not being obligatory except in certain North American States, in Switzerland and, lately, in Great Britain. The figures, indicating the tuberculosis death-rates at different ages, are quite useless for us: in the first place, because they are not exact, being based upon inaccurate or fantastic statement, and secondly, because they regard the population as a whole, and do not concern those individuals, *born and brought up in tuberculous families*, in whom we are specially interested.

Hospital statistics are not more useful, because they deal only with diseased individuals, and, consequently, the tuberculosis mortality at different ages, as figured in such statistics, is much higher than it would be when one considered whole families, of which only one or more members are tuberculous. So we are bound to look for information to the dispensaries in different countries, generally directed by specialists and intelligent visiting nurses who know what becomes of the children belonging to the families controlled by those institutions. When we do this, it becomes evident that general mortality (including tuberculosis mortality) during the first year of life in children, born and brought up in tuberculous environment, ranges from at least 7·4% (William H. Park, New York) to 71·5% (as indicated by Heynsius van den Berg, in Amsterdam). It must be noted, however, that this last figure applies only to children aged under 2 years, who have been exposed to infection during the three first months of life.

In France, the general mortality in children aged from 1 day to 1 year, as calculated by the dispensaries, varies from 16% to 25% in different departments. In Roumania, according to J. Cantacuzene and his co-workers, it reaches 25%. In vaccinated children of the same age, living under the same conditions, and controlled by the same dispensaries, tuberculous mortality becomes nearly zero, and general mortality is four times less than it is in non-vaccinated children. And this striking fact has been observed in every country and in every city where vaccination has been introduced on a large scale for a certain number of years.

Our own first statistics on this subject, published in 1926-1928, have been sharply criticized by some professional statisticians, principally by Greenwood (London),

Rosenfeld and Götzl (Vienna). They reproached us with not taking into consideration the "tables of life" and methodological rules, which is justifiable criticism. But they unjustly reproached us with choosing infants to be vaccinated among those belonging to better-controlled families who were protected by better precautions against infection, whereas the non-vaccinated lived under less favourable conditions. This criticism is unjust and erroneous, for we took the utmost care to deal with exactly comparable groups of infants.

Our figures have been confirmed by all observers in different countries—principally in Roumania, Sweden, Belgium, Holland, Spain, Greece, in New York, Montreal, Montevideo, etc.—though many of them have been controlled by professional statisticians, thus proving that our statistics were not incorrectly compiled. Nevertheless some prejudiced adversaries of BCG continue to attack them, without being able to justify their attitude. But we still hope to convince these obstinate adversaries (though this may seem a vain hope), and therefore the computation of the results of our latest inquiry (regarding children living in a tuberculous environment, controlled by the dispensaries, and vaccinated between 1924 and January 1, 1930, *consequently all at least one year old on January* 1, 1931), has been entrusted to the statistician of the French National Antituberculosis Committee; the outcome of his investigation is as follows: The general mortality of 8,075 vaccinated children exposed to tuberculous infection, aged from one month to one year[1]), controlled by 114 dispensaries, has been 4·6%, whereas in non-vaccinated children of the same age, living under similar conditions, it is at least 16%, and often exceeds 25%.

Further, of 579 children who were vaccinated more than four years ago, and who have lived continuously in tuberculous family surroundings, not one has died. This proves that BCG has at least been innocuous for those 579 children, and has protected them against bacillary infection to which they have been exposed during four consecutive years. Can one wish for a clearer demonstration of the preventive advocacy of BCG?

How can this difference between general mortality in vaccinated and in non-vaccinated groups be explained? Disregarding children born and brought up in tuberculous families, in whom we know tuberculous mortality to be formidable, tuberculosis is generally supposed to kill about two infants in 1,000 during the first year of life, though certainly a much greater number of children are infected, in whom infection remains latent for several years. Can it be that tuberculous infection plays a more important part in infant mortality than we have supposed? I only mention in this connexion the possibility of an infection by filterable virus, impossible to detect at autopsy and difficult to suspect in the living. Or does the harbouring of BCG, followed by its digestion and elimination, confer on the organism a special aptitude to resist those other infections which are so frequent in young children?

At any rate this resistance is so often and so manifestly observed that it cannot be denied and can only be ascribed to preventive vaccination with BCG immediately after birth.

General mortality being constantly lower in vaccinated individuals than in non-vaccinated living under similar social conditions and exposed to the same sources of infection, the innocuousness of BCG becomes once more evident. If tuberculosis mortality is not completely abolished by it this is probably due to the fact that vaccination is sometimes incorrectly performed and, especially, that the necessary precautions—on which I have insisted—to avoid repeated and massive infections during the first four or five weeks after birth, are not always taken. The organism needs this period to acquire resistance against virulent superinfections.

[1] Infants, vaccinated or not-vaccinated, who have died during the first month of life, have been deliberately disregarded, vaccination being inoperative during that period.

This resistance is frequently, but not always, accompanied by a more or less manifest and durable tuberculin allergy.

So we must reckon with a certain number of failures, due not to the method in itself, but to imperfect knowledge or negligence.

In the beginning we began timidly, as I have mentioned, to vaccinate seriously endangered infants. When, however, we saw that not only was BCG innocuous, but that vaccinated children showed more resistance to infants' diseases, and nearly always developed better than did non-vaccinated ones, we decided to extend the benefit of the method to the children of apparently normal families. We all know examples of children, born from healthy parents, but infected by a maid, a grandfather, a grandmother, or other contact.

Among fifty children who died from tuberculosis at St. Louis' Hospital, Paris, J. Renault found that twenty-two had tuberculous parents, but twenty-eight had been brought up by healthy parents and in surroundings free from tuberculosis.

Nobécourt made analogous observations at the Enfants Malades Hospital, and we ourselves have often heard the narratives of colleagues who came to consult us with regard to children whom they had omitted to vaccinate because the mothers had seemed to be healthy at first, but had become tuberculous when it was too late to have the children vaccinated.

So we find ourselves placed in this dilemma: if BCG is inefficient, it is paradoxical to give it to babies born from tuberculous parents who are less resistant to an eventually dangerous virus. If on the other hand one is convinced of its utility, why should one refuse its beneficial influence to children of apparently normal families who may some day be exposed to a fortuitous infection?

And what risk does one run in vaccinating a child with innocuous BCG, instead of allowing it some day to absorb the inevitable virulent tubercle bacillus, which, though it may not immediately endanger its life, constitutes a perpetual menace of progressive tuberculosis?

And finally, so large an experience has now been gathered in the last seven years in most civilized countries, nearly one million children having been vaccinated the world over without any established accident due to BCG, that even the most hesitant may be reassured.

In Europe, only Great Britain, Portugal and Austria have hesitated up to now. Everywhere else vaccination has been practised, either on very large numbers of children, belonging to tuberculous and normal families, or on children born in tuberculous surroundings only. It has been observed that both procedures give equivalent and constantly favourable results. These results are particularly demonstrable in certain countries, e.g., in Roumania, Sweden, Poland, Bulgaria and Greece, and in certain cities, e.g., New York, Montreal, Montevideo, Barcelona and Amsterdam.

In Roumania, where more than 80,000 children have now been vaccinated, the general mortality since 1927 has been 50% less in the vaccinated than in the non-vaccinated.

In Sweden, 4,009 infants were vaccinated in the province of North Bothnia alone between September, 1927, and May 1, 1930; 8,342 children have not been vaccinated, serving as controls. The general mortality has been 2·3% in the vaccinated, 9·5% in the non-vaccinated.

Analogous figures have been found in the other countries and cities above indicated. The experiment, undertaken by William H. Park, at New York, is particularly suggestive, because it deals with a small number of children, all born from tuberculous mothers in hospitals, and regularly controlled. Up to January 1, 1930, 208 of these children have been vaccinated, 350 non-vaccinated remaining as controls. After three years the following results were noted by the author:—

Tuberculous mortality during the first year of life was 8% in non-vaccinated,

0·9% in vaccinated children. During the second year it was 3·8% in non-vaccinated, zero in vaccinated children.

What doctor, what sanitary authority, knowing these facts, and with all the necessary information now available, would deliberately refuse to apply this simple method of defence against the most virulent of all human diseases?

CORRIGENDUM.

Proceedings, Vol. xxiv, p. 65, "Jaw-Winking Phenomenon (Marcus Gunn) with Cinematographic Demonstration."—LEONARD FINDLAY, M.D.

By a printer's error figs. 3 and 4 in the illustration of this case were transposed. The correct sequence is given below.

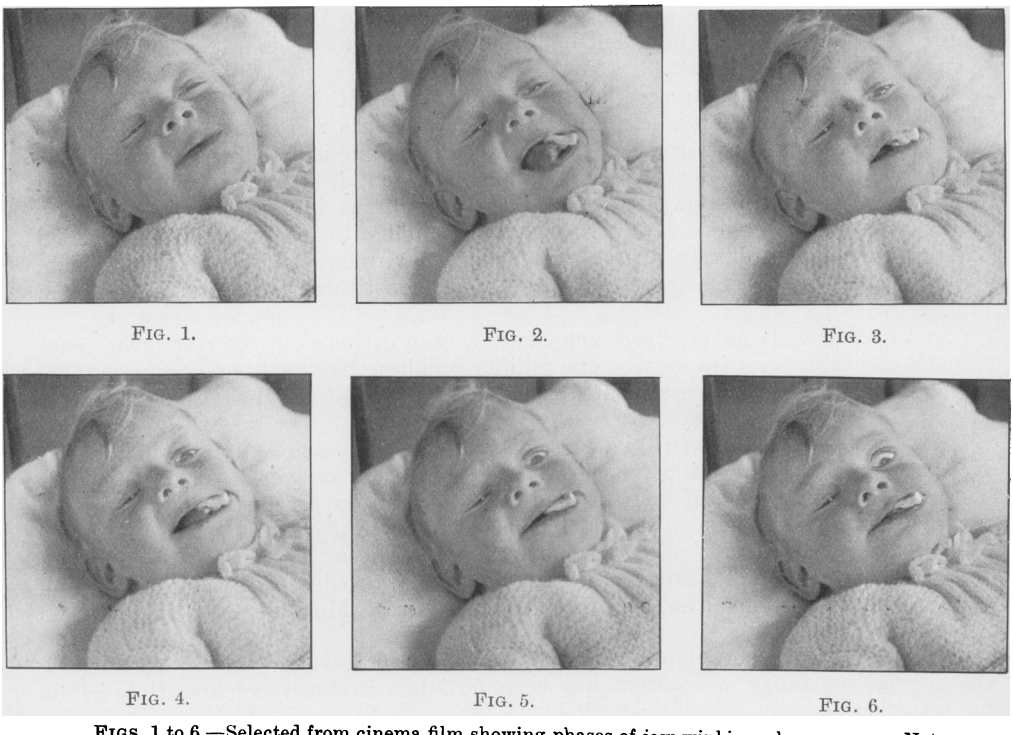

FIG. 1. FIG. 2. FIG. 3.

FIG. 4. FIG. 5. FIG. 6.

FIGS. 1 to 6.—Selected from cinema film showing phases of jaw-winking phenomenon. Note absence of contraction when child is at rest (fig. 1), and when the mouth is open (figs. 2 and 3); but marked contraction of levator palpebræ superioris of left eye during biting movement (figs. 4, 5, 6).