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EDITORIAL

VACCINATION AGAINST TUBERCULOSIS

The BCG (bacille Calmette-Guérin) vaccination against tuberculosis, first used in France more than 30 years ago, has been the subject of much controversy. It has, however, come to be accepted in many countries as an effective method of preventing progressive tuberculosis. The vaccine has been used in various ways, for instance in the newborn and in Mantoux-negative persons exposed to contact with infectious cases of tuberculosis; but no adequate statistical study has been made of the contribution it might make to the further control of tuberculosis in western communities where without its aid the substantial reduction in the prevalence of the disease has taken place which has been a feature of recent decades. Accordingly the Medical Research Council, in 1949, appointed a special committee to plan and direct an investigation in England. This committee has now presented its first report[1]—a progress report—which proves to be a most important document. The report is published in the *British Medical Journal*, and a summary of the report will be found in our present issue (page 388).

A live bacillus prepared from the microbacterium of vole tuberculosis has been used for vaccination against tuberculosis, though on a smaller scale than BCG, and the MRC investigation was planned to assess the value of both of these vaccines.

The investigation was designed to afford a comparison of the incidence of tuberculosis over a period of years in adolescents, divided according to their reaction to the tuberculin test and, in negative reactors, according as they were vaccinated with BCG, vaccinated with vole-bacilli, or unvaccinated.

Between September 1950 and December 1952 about 56,000 volunteers had entered the research—boys and girls nearly all aged between 14½ and 15 and all in their final year at schools in the north of London, at Birmingham and at Manchester. Every entrant had first been

VAN DIE REDAKSIE

INENTING TEEN TUBERKULOSE

Die BCG-entstof (*bacille Calmette-Guérin*) teen tering, wat meer as 30 jaar gelede al vir die eerste maal in Frankryk gebruik is, het baie opspraak verwek. Dit is egter in die loop van jare in baie lande erken as 'n doeltreffende metode om toenemende tuberkulose te voorkom. Die entstof is al op verskillende maniere gebruik, bv. by pasgebore babas en by Mantoux-negatiewe mense wat blootgestel was aan aansteeklike gevalle van tering. Dusver was daar egter nog nie genoeg statistiese navorsing op die bydrae wat dit kan maak tot die verdere beheer van tuberkulose in die westerse lande nie, waar die belangrike afname in die voorkomssyfer van tering—sonder die hulp van hierdie entstof—'n kenmerk van die laaste jare was. Die mediese navorsingraad het dientengevolge in 1949 'n spesiale komitee ingestel om 'n ondersoek in Engeland te beplan en te beheer. Hierdie komitee het so pas sy eerste verslag[1] voorgelê—'n vorderingsverslag—wat 'n baie belangrike dokument blyk te wees. Die verslag het in die *British Medical Journal* verskyn, en op bladsy 388 in hierdie uitgawe van die *Tydskrif* is 'n opsomming daarvan.

'n Lewende basil, voorberei uit die mikrobakterie van tering by die woelmuis (*Microtus agrestis*) word ook as entstof teen tering gebruik, hoewel op kleiner skaal as BCG, en die navorsingraad se ondersoek was ingestel om die waarde van albei vaksines te bepaal.

Die ondersoek was só beplan dat 'n vergelyking getref kon word insake die voorkoms oor 'n aantal jare van tuberkulose by puberteitsjariges. Die proefpersone was verdeel volgens hulle reaksie op die tuberkulientoets, en dié wat negatief gereageer het, is weer verdeel in groepe wat met BCG, met muisbasil, of glad nie geënt is nie.

Tussen September 1950 en Desember 1952 het ongeveer 56,000 vrywilligers hulle vir navorsing aangebied—almal seuns en meisies tussen 14½ en 15 jaar oud, en almal in hul laaste jaar op skool in noord-Londen, Birmingham en Manchester. Van elke kind is eers 'n roentgenbeeld opgeneem, en dié wat teringlyers geblyk het, of wat kort tevore tuis met 'n teringlyer in aanraking was, is uitgesluit uit die ondersoek. (Onder dié wat as toetreders geslaag het, was daar 'n paar wat

X-rayed and any found to be suffering from tuberculosis, or to have been in recent contact with a case at home had been excluded from the investigation. (A few of those who had been passed as entrants were afterwards excluded because they developed tuberculosis which was adjudged to have started before entry.)

At the initial examination each entrant was also given an intracutaneous tuberculin test with 3 TU (tuberculin units), and those who reacted negatively were then tested with 100 TU. Those negative to both strengths were divided into 3 'random' groups, of which one group was at once vaccinated with BCG and one with vole-bacillus, and the third group was left unvaccinated. The positive reactors were divided into 2 groups, viz. those positive to 3 TU and those negative to 3 TU and positive to 100 TU. Thus the 56,000 entrants were divided for purposes of comparison into 5 groups, every member of which from then on has been subjected to a carefully designed and rigorous follow-up, which is still continuing.

Besides the initial examination, many of the participants recieved a second examination (including tuberculin tests and chest X-ray) while still at school, and after leaving school they have all been followed up by means of a cycle of enquiry and examination lasting 14 months and consisting of a postal enquiry, a home visit by a health visitor, and an examination which again included a chest radiograph and tuberculin tests. As a result, contact was made during the cycle with 94% of the participants, and has since been made with many of the remaining 6%. Besides these sources, information was also obtained from notification lists of medical officers of health and from the chest clinics. After the completion of the first cycle a second 14-months cycle of enquiry was put in operation, and so on.

Of the participants who were vaccinated with BCG, 99·6% became tuberculin-positive; of those vaccinated with vole-bacillus 94·4% (the vole-bacillus vaccine used for the earlier participants was below standard strength; of the 1,900 vaccinated with the later batch all became positive).

All definite and suspected cases of tuberculosis that were discovered were examined by an independent assessor, who was kept unaware of the results of the tuberculin tests and whether vaccination had been performed.

A total of 165 definite cases of tuberculosis began within 2½ years after entry to the trial. Of these 63% were of pulmonary tuberculosis and 22% of pleural effusion without evidence of pulmonary tuberculosis; 68% were severe enough for the patients to be taken off work for at least 3 months. There was no death from tuberculosis in any participant during the 2½ years.

The annual incidence of tuberculosis (over the 2½ years) in the tuberculin-negative unvaccinated group was 1·94 per 1,000, in the BCG-vaccinated group 0·37 per 1,000, and in the vole-bacillus-vaccinated group 0·44 per 1,000.

According to the results of the test, if *none* of the tuberculin-negative entrants had been vaccinated 165 cases of tuberculosis would have been expected among them within 2½ years of entry; if all of them had received

later weer uitgesluit is omdat hulle tering, wat na vermoede al vóór inskrywing begin het, ontwikkel het.)

By die eerste ondersoek is 'n tuberkulien-veltoets met 3 TU (teringeenhede) op elke inskrywer gedoen, en dié wat negatief gereageer het, is vervolgens met 100 eenhede getoets. Dié wat op albei konsentrasies negatief gereageer het, is toe weer in 3 ‚toevallige' groepe verdeel, waarvan een dadelik met BCG, en een groep met die muisbasil geënt is. Die derde groep is nie geënt nie. Die positief-reagerendes is weer in 2 groepe verdeel, nl. positief op 3 eenhede en positief op 100 eenhede. Dus is die 56,000 medewerkers vir vergelykingsdoeleindes in 5 groepe verdeel, en elke lid is van toe af onderwerp aan 'n noukeurig beplande, streng opvolging wat nog aan die gang is.

Benewens die eerste ondersoek, is baie van die kinders vir die tweede maal—weer met inbegrip van tuberkulientoetse en X-straalbeelde van die borskas—ondersoek terwyl hul nog op skool was. Nadat hulle die skool verlaat het, is almal opgevolg deur middel van 'n kringloop van navraag en ondersoek wat oor 14 maande gestrek het en wat bestaan het uit navraag deur die pos, tuisbesoek deur 'n gesondheidsamptenaar, en 'n ondersoek wat wéér straalondersoek en tuberkulientoetse ingesluit het. As gevolg van hierdie metodes het die navorsers gedurende die kringloop met 94 persent van die deelnemers in aanraking gekom, en sedertdien is die meeste van die oorblywende 6 persent ook opgespoor. Afgesien van hierdie bronne, is inligting ook geput uit die kennisgewinglyste van mediese gesondheidsbeamptes en borsklinieke. Na afloop van die eerste kringloop is 'n tweede navraagprogram van 14 maande ingestel, en so voort.

Van die deelnemers wat met BCG geënt is, het 99·6 persent tuberkulien-positief geword, en van dié wat met die muisbasil geënt is, 94·4 persent. (Die muisbasil-entstof waarmee die eerste klomp deelnemers geënt was, was onder die normale sterkte; die 1,900 wat met 'n latere voorbereiding geënt is, het almal positief geword.)

Alle uitgesproke en verdagte gevalle van tering wat ontdek is, is deur 'n onafhanklike geneesheer ondersoek wat nie ingelig is oor die uitslag van die tuberkulientoetse en wat nie geweet het of die pasiënte geënt was of nie.

'n Totaal van 165 uitgesproke gevalle van tuberkulose het binne 2½ jaar na toetrede tot die proefneming begin. Uit hierdie totaal was daar 63 persent gevalle van longtering, en 22 persent gevalle met borsvlies-uitvloeisel sonder tekens van longtering; 68 persent was so ernstig siek dat hulle ten minste 3 maande lank moes ophou werk. Gedurende die 2½ jaar het geeneen van die deelnemers aan tuberkulose gesterf nie.

Die jaarlikse voorkomssyfer van tuberkulose (oor die 2½ jaar) in die nie-geënte tuberkulien-negatiewe groep was 1·94 op 1,000; in die BCG-groep was dit 0·37 op 1,000; en in die groep wat met die muisbasil-entstof geënt was, was dit 0·44 op 1,000.

Bereken op die uitslag van die proefneming, kon dit verwag word dat 165 gevalle van tering binne die 2½ jaar na toetrede sou voorkom onder die tuberkulien-negatiewe groep, as *geeneen* van hulle geënt was nie. As almal van hulle met BCG geënt was, kon 30 gevalle verwag word—dit beteken 'n afname van 82 persent in die verwagte voorkomssyfer van tuberkulose in die tuber-

BCG vaccine 30 cases would have been expected—a reduction of 82% in the expected incidence of tuberculosis in the tuberculin-negative group. This convincing result may be taken as a fair expression of the protection afforded during the first 2½ years to the BCG-vaccinated adolescents in this experiment. The results with vole-bacillus vaccine are equally convincing. Later reports on the experiment must be awaited for an answer to the question how long the protection will endure in the vaccinated subjects; incomplete follow-up results extending to 4 years which are recorded in this first report disclose no falling off.

This figure of 82% applies, as stated, to the tuberculin-negative section, who constituted 60% of the test population of adolescents. The remainder (the tuberculin-positive) could not have the benefit of vaccination. Including them so that the whole of the test population is is under consideration, if *none* had been vaccinated 246 cases of tuberculosis would have been expected in the 2½ years; if *all the negative reactors* had received BCG vaccination 111 cases would have been expected—a reduction of 55% in the incidence of tuberculosis in the whole test-population.

However, 134 cases of previously unsuspected definite tuberculosis which were present on entry were excluded from the trial, nearly all as the result of the initial radiographic examination. In the absence of this X-ray, many of these cases would have been thought to arise after entry, and the apparent reduction in the total incidence of tuberculosis would have been only of the order of 35%.

These figures constitute a strong case in England, and other countries in like case, for proceeding with the vaccination of school children against tuberculosis. The high proportion (40%) of positive reactors at the age of 14 or 15 in this experiment suggests that the vaccination should be undertaken at a younger age; however, more data is needed before the optimum age can be determined. The *British Medical Journal*[2] says: 'Not enough is known to allow the prescription of an optimum age for vaccination, and if there is indeed such an age it may well vary with changing circumstances. The best compromise might be to offer vaccination to school-children as a routine at the age of about 12....and to make vaccination against tuberculosis conveniently available at any age to children whose parents request it.'

The tuberculosis situation in the White population of South Africa is much the same as in the people of Britain. It is known that the Union Government has been seriously considering a scheme of anti-tuberculosis vaccination. The results to date, therefore, of this English experiment should go far in deciding the issue here. There is perhaps an even stronger case for the application of a vaccination scheme to the Native, Coloured and Indian population, who suffer from a greater prevalence of tuberculosis and mostly live in conditions which favour a high incidence of the disease. This view is supported by the results obtained in experimental work in North American Indians,[3, 4, 5] who suffer from a high prevalence of tuberculosis.

In conclusion reference should be made to the significant results obtained by the follow-up of the 40% of participants in the MRC investigation who gave a kulien-negatiewe groep. Hierdie oortuigende uitslag kan beskou word as 'n redelike bewys van die beskerming wat die BCG-entstof gedurende die eerste 2½ jaar van die proefneming aan die kinders verleen het. Die resultate met die muisbasil-entstof is ewe oortuigend. Latere verslae oor die proefneming sal 'n antwoord lewer op die vraag van hoe lank die beskerming by geënte persone sal duur; die tot nog toe onvolledige opvolgingresultate van 4 jaar, wat in hierdie eerste verslag opgeteken is, dui aan dat daar nog geen afname in onvatbaarheid is nie.

Soos aangestip, het die syfer van 82 persent betrekking op die tuberkulien-negatiewe groep, wat 60 persent van al die deelnemers in die proefneming uitgemaak het. Aan die res (die tuberkulien-positiewes) kon die voordele van inenting nie verstrek word nie. As ons hulle ook insluit om ons berekening oor die hele proefpopulasie uit te brei, kon 246 teringgevalle in die 2½ jaar verwag word as geeneen van hulle geënt was nie; gestel *al die negatiewes* het die BCG-enting gekry, kon daar 111 gevalle verwag word—'n afname van 55 persent in die voorkomssyfer van tering in die hele proefneminggroep.

Daar was egter 134 gevalle van voorheen onvermoede maar definitiewe tering aanvanklik teenwoordig, wat toe uit die proefneming uitgesluit is, meestal as gevolg van die eerste radiografiese ondersoek. Sonder hierdie straalondersoek sou die navorsers gedink het dat baie van hierdie gevalle eers na toetrede ontwikkel het, en dan sou die klaarblyklike afname in die totale voorkomssyfer van tuberkulose maar omstreeks 35 persent gewees het.

In Engeland, asook in ander vergelykbare lande, pleit hierdie syfers oortuigend ten gunste daarvan dat die inenting van skoolkinders teen tering voortgesit word. Die groot proporsie (40 persent) in hierdie proefneming van positief-reagerendes op 14 of 15 jarige ouderdom, suggereer dat die inenting miskien op 'n jonger leeftyd gemaak moet word; meer gegewens is egter nodig om die beste ouderdom te bepaal. Die *British Medical Journal*[2] doen die volgende verklaring: ‚Not enough is known to allow the prescription of an optimum age for vaccination, and if there is indeed such an age it may well vary with changing circumstances. The best compromise might be to offer vaccination to school-children as a routine at the age of about 12....and to make vaccination against tuberculosis conveniently available at any age to children whose parents request it.'

In Suid-Afrika is die tering posisie by Blankes min of meer dieselfde as in Brittanje. Dit is bekend dat 'n skema van inenting teen tering die ernstige aandag van die Unie-regering geniet. Die huidige resultate van hierdie Engelse proefneming kan heel moontlik baie help om die deurslag te gee. Miskien is die toepassing van 'n inentingskema meer dringend by die Naturelle-, Kleurling- en Indiër-bevolking waar die voorkomssyfer van tering soveel groter is en wat gewoonlik onder omstandighede lewe wat 'n groot voorkomssyfer begunstig. Hierdie mening word ondersteun deur die resultate van proefnemings by Noord-Amerikaanse Indiane[3, 4, 5] by wie die voorkomssyfer van tering baie hoog is.

Ten slotte moet daar verwys word na die betekenisvolle opvolgingsresultate van die 40 persent deelnemers aan die Britse navorsingraad se ondersoek wat positief gereageer het op die eerste tuberkulientoets. Dit is

positive reaction in the initial tuberculin test. It was found that in those with a positive reaction to 3 TU the annual incidence of tuberculosis (in 2½ years) was 1·75 per 1,000, and in those negative to 3 TU and positive to 100 TU 0·74 per 1,000. The incidence was particularly high amongst those with *strong* reactions to 3 TU. In those with 15 mm. induration or more the annual rate was 2·93 per 1,000 and in those with 5-14 mm. induration 0·78 per 1,000. These figures are to be compared with the annual incidence of 1·94 per 1,000 in the tuberculin-negative unvaccinated group. They point to the desirability of keeping persons with *strong* tuberculin reactions under close observation.

A further interesting feature of the follow-up was that in the unvaccinated negative reactors the tuberculosis incidence rate was low in the first year and higher in the second year, by which time it reached the same levels as those with high tuberculin sensitivity. This may possibly be correlated with the fact that after the adolescents leave school they begin, in employment, to run a greater risk of infection. On the other hand, in the positive reactors on the whole the incidence of tuberculosis was fairly even over the first 3 years.

1. *Tuberculosis Vaccines Clinical Trials Committee* (1956): Brit. Med. J., **1**, 414.
2. *Editorial* (1956): *Ibid.*, **1**, 444.
3. Aronson, J. D. (1948): Amer. Rev. Tuberc., **58**, 255.
4. Aronson, J. D. and Aronson, D. F. (1952): J. Amer. Med. Assoc., **149**, 334.
5. Stern, S. C. and Aronson, J. D. (1953): Amer. Rev. Tuberc., **68**, 695.

bevind dat die jaarlikse teringvoorkomssyfer in die 2½ jaar 1·75 op 1,000 was by dié wat positief reageer het op 3 eenhede, en 0·74 op 1,000 by dié wat negatief was op 3 eenhede en positief op 100 eenhede. Die voorkomssyfer was veral groot by dié wat *sterk* gereageer het op 3 eenhede. By die proefpersone met 'n verharding van 15 of meer mm. was die jaarlikse voorkoms 2·93 op 1,000, en by dié met 5-14 mm. verharding was dit 0·78 op 1,000. Hierdie syfers moet vergelyk word met die jaarlikse voorkomssyfer van 1·94 op 1,000 by die tuberkulien-negatiewe, nie-geënte groep. Hulle dui op die wenslikheid daarvan om mense met sterk reaksies op tuberkulien noukeurig dop te hou.

Nog 'n interessante kenmerk van die opvolging was dat die voorkomssyfer van tuberkulose by die nie-geënte, negatief-reagerendes laag was in die eerste jaar, en hoër in die tweede jaar, toe dit dié van die hoogs sensitiewe tuberkulien-reagerendes ingehaal het. Moontlik kan dit in verband gebring word met die feit dat die jongmense groter gevaar van aansteking loop as hulle eers die skool verlaat en begin werk. Aan die ander kant was die voorkomssyfer by die positief-reagerendes oor die algemeen taamlik eweredig oor die eerste 3 jaar.

1. *Tuberculosis Vaccines Clinical Trials Committee* (1956): Brit. Med. J. **1**, 414.
2. *Editorial* (1956): Ibid., **1**, 444.
3. Aronson, J. D. (1948): Amer. Rev. Tuberc., **58**, 255.
4. Aronson, J. D., en Aronson, D. F. (1952): J. Amer. Med. Assoc., **149**, 334.
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PORPHYRIA

Porphyria is a disease of special interest because of its familial incidence and its habit of remaining latent until on specific provocation which can be avoided if the danger is realized, it breaks out into its serious, and often fatal, acute phase. The disease is not uncommon in South Africa, in both Europeans and non-Europeans. In Europeans nearly all cases are of old Afrikaner stock, and it has been shown to be a non-sex-linked Mendelian dominant.

Dr. Geoffrey Dean, whose article is published in this issue (page 377), has traced the genealogies of 32 porphyric families, in which a total of 324 members (168 male and 156 female) are known to have shown clinical manifestations of porphyria. One of these groups, which was intensively investigated (Dean and Barnes), descends from an ancestor who was born in 1814 and had had 478 descendants, 434 of whom were still alive. With these, contact was established and specimens of urine were obtained from them. One porphyric parent in the group has 125 descendants (excluding those under 18 years old), of whom 60 are porphyrics, extending over 5 generations; and the history of the disease in this branch conforms entirely with the requirements of a non-sex-linked Mendelian dominant.

In the latent stage of porphyria the symptoms may be mild or absent. It usually causes no symptoms during childhood. The commonest manifestation is abnormal sensitivity of the exposed skin, which blisters and abrades easily and is sometimes more pigmented than usual. This skin condition is commoner in men; in women preauricular hypertrichosis may occur. Most male porphyrics remain well throughout life, but many of the women complain of abdominal discomfort, which sometimes leads to a laparotomy, with its special dangers for a porphyric. During pregnancy symptoms are often more pronounced, and a history may be given that previous pregnancies were terminated because of pains, vomiting and hysteria. Often a family group is found to be porphyric only when one of its members has an acute attack.

The diagnosis of porphyria is determined by analysis of the urine and faeces. In the latent stage the urine is normal in appearance and the increase in porphyrin may be so slight as not to be easily detected; it may even be absent. In the acute stage the diagnosis may be suggested by a dark urine of reddish-brown colour. In both stages the urine should also be tested for porphobilinogen which, however, is seldom present in the quiescent stage. More precise information can be obtained by a quantitative analysis of faecal porphyrin. For analysis, 4 oz. of urine, with a few drops of chloroform added, and a sputum-jar half full of faeces, should be sent to a biologist skilled in porphyrin analysis.

An acute attack is readily provoked by drugs, chemicals or alcohol, and, in Dean's experience, is always precipitated in this way. A wide range of drugs has this action,

particularly sedatives such as barbiturates. Thiopentone as an anaesthetic is extremely dangerous. If an operation is necessary, gas, oxygen and ether may safely be given. Penicillin is not harmful, but sulphonamides are dangerous.

In the acute attack of porphyria the behaviour is very emotional, the patient complains of severe pain all over the body and especially in the abdomen, nutrition is impaired, usually with marked loss of weight, and vomiting and constipation may occur. Weakness of the limbs may follow, which may at first be attributed to hysteria but is in fact caused by a lower-motor-neurone type of paralysis; the reflexes disappear, pupils are dilated, pulse is rapid, and blood pressure may be raised. There is evidence of impared liver-function and usually leucocytosis. Sometimes epileptic convulsions occur. Acute porphyria is much commoner in women than in men.

We cannot do better than quote in conclusion the last paragraph of Dr. Dean's article:

'Once a case of porphyria has been diagnosed it is the doctor's responsibility to investigate the family history fully.... Enquiry must be made to discover which side of the family is affected.... The urine and faeces of the relatives on the affected side should be examined for porphyrins. It must not be forgotten that the syndrome will present in different ways in different members of the family. Some may have complained of symptoms the cause of which will not have been known, and the doctor will be able to make the correct diagnosis in patients who have long been regarded as neurotic. All affected members of the group should be interviewed, and they should be given a letter stating the evidence on which the diagnosis has been made and mentioning the danger of barbiturates and other drugs in this condition; this letter they should show to any doctor they may consult in future.'