# A FIELD EXPERIENCE OF MASS PERCUTANEOUS BCG INOCULATION AS AN IMMUNIZING AND DIAGNOSTIC PROCEDURE

I. W. F. SPENCER, M.B., B.CH., D.P.H., D.T.M. & H.; M. E. E. COSTER, M.B., B.CH.; A. V. MCPHAIL, M.B., B.CH.; AND M. RICHTER, M.B., B.CH., *City Health Department, Johannesburg*

The objective was a trial of rapid field application in a selected community of a procedure already established as safe and effective in raising general immunity to tuberculosis and providing preliminary diagnostic data.

## THE CONTROL OF TUBERCULOSIS

Accumulated international experience has resulted in significant advance toward control of the disease. Work in all branches has produced an increasing wave of factual information that confuses by its complexity, and a return toward basically simple thinking, with reappraisal of fundamental epidemiological concept, was thought necessary prior to this study.

### *General*

Primarily, assessment may be made under 3 considerations, viz. (a) the infector pool, (b) the epidemiological instrument, and (c) adjustment of the instrument to the needs of individual communities.

(a) *The infector pool.* Canetti,[1] in an extensive review of the problems of control, referred to the 'infector pool' of tuberculosis, which consists of cases excreting tubercle bacilli. We consider that the infector pool so described is, in fact, the only significant source of infection in man, particularly in South Africa, where bovine strains are not important, and that it emerges as the crucial centre against which control measures must be directed. The magnitude of the problem of tuberculosis in any community is related to the size of its infector pool. Clearly, control measures fall into two groups, one directed toward the prevention of new subjects entering the pool and the other toward removal of infected subjects from the pool by rendering their sputa free of tubercle bacilli. Both groups should operate concomitantly and the epidemiological instrument of their application should be adjusted to the circumstances of individual communities.

(b) *The epidemiological instrument.* Among problems met in arranging control programmes is the influence of advocates of various control measures, e.g. chemotherapy, mass radiology, or BCG vaccination, some of whom might consider that any one of these is the prophylactic procedure of universal choice, irrespective of the existing socio-economic and environmental circumstances of the community to which the control programme is to be applied. To clarify the broad adjustment of control measures necessary, we formulated a simple postulate represented in Fig. 1 to indicate the priority rating of prophylactic procedure applicable to any given situation. The postulate is based on the relationship between the infector pool and socio-economic circumstance; the poorer the socio-economic circumstance the larger the infector pool and *vice versa.* The priority rating of prophylactic procedures is dependent upon and adjusted according to this factor. These procedures, represented as parts of the epidemiological instrument in Fig. 1, require simultaneous application, and must overlap and interlock to retain an unbroken ring of encirclement. Where this is not attained the control programme will lose effectiveness in accordance with the gaps created. Control measures applicable for a community of high socio-economic status with a small infector pool will be all those represented in Fig. 1. Similarly, they will all be applicable to a community of low socio-economic status with a large infector pool, but their proportional representation in the ring of encirclement will be different.

(c) *Adjustment of the instrument to the needs of individual communities.* In communities with high socio-economic status and a small infector pool, socio-economic measures and BCG vaccination will form a small part of the control programme, which will be concentrated on case finding and treatment. BCG

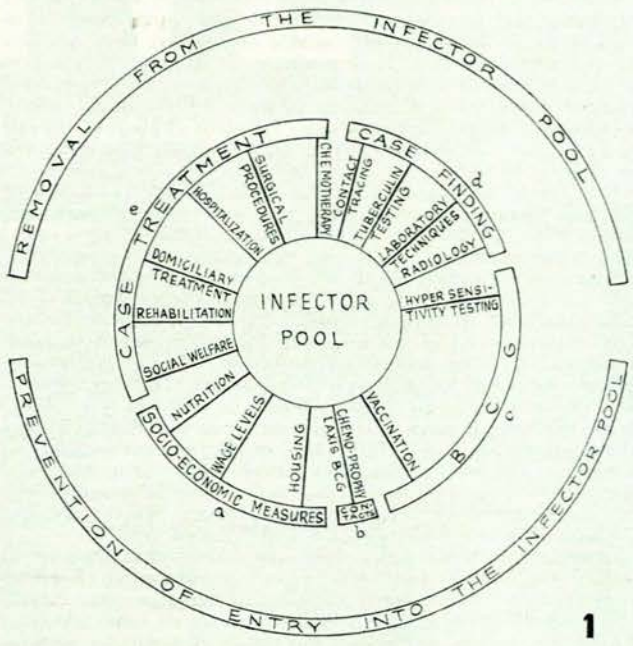


*Fig. 1.* Diagrammatic representation of the epidemiological instrument in tuberculosis.

vaccination would be reserved for small groups at especial risk such as nurses attending tuberculotics, or for contacts of cases. Conversely, in communities with a low socio-economic status and a large infector pool, prevention of entry into the pool (Fig. 1) will become the primary objective, while further adjustment will be necessary between a and c (Fig. 1), for socio-economic measures are long-term projects and BCG vaccination therefore has to be an absolute priority within this category.

Extreme hypothetical examples are shown in Figs. 2A and 2B, and gradation to the needs of individual communities will lie between the two. There can be no single policy applicable to every country, nor can there be one for the whole of any

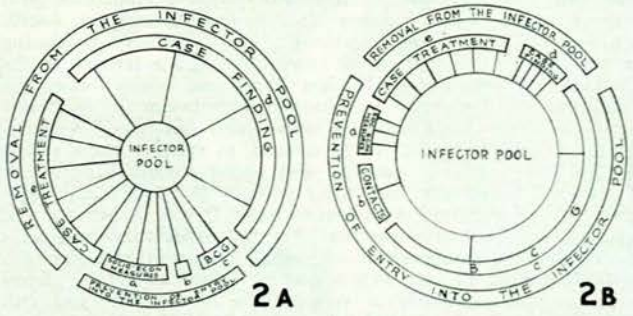


*Fig. 2A.* The epidemiological instrument in an affluent metropolitan group (see Fig. 1).
*Fig. 2B.* The epidemiological instrument in an undeveloped tribal Bantu group (see Fig. 1)

specific country. In most instances it is not possible to have one policy even for a single city, where the principles laid down in Figs. 1 and 2 are likely to determine different priority

ratings for control measures against tuberculosis in the affluent areas and in the slums.

In addition to these basic factors there are complex considerations bearing on each control measure which do not fall within the scope of this paper. Nevertheless, some of the more salient features have a secondary effect on planning, and are briefly considered. Over and above fundamentals of geographic circumstance, population structures, evolutionary standards and attitudes, and economic resources for the undertaking, it is well to recall that no communicable disease has thus far been eradicated in the history of medicine. It is more accurate to reason in terms of control rather than eradication, for, at best, control measures can only be effective to the point where incidence and mortality become virtually negligible though the infection remains slumbering in its habitat. The reasoning of highly effective control rather than eradication has the advantage of keeping in mind the truth that any relaxation of control meaures, even though a disease has virtually disappeared, will result in unfortunate and forceful recurrence. The recent outbreak of smallpox in England gives grounds for thought. It is likewise significant that treatment alone does not control a disease to the point of low incidence unless it be combined with established epidemiological methods to cut the chain of its survival, as instanced by yellow fever, malaria, smallpox, trypanasomiasis, spirochaetosis, plague, typhus, typhoid, poliomyelitis, diphtheria, and others. Thus in tuberculosis no misplaced confidence should be directed toward the hope that case finding and treatment alone will finally control the disease. They only form part of the epidemiological instrument, and in the countries where tuberculosis has been reduced to a level of low threat, this has been brought about by combination with measures and factors that inhibit the passage of new subjects into the infector pool.

Apart from these generalities, there are other matters to which the worker must give expert consideration. Even in communities where mass radiological surveys are clearly indicated to detect unknown infectious cases of tuberculosis, it becomes necessary to pinpoint the survey at particular sections of the community. Brightman and Hilleboe[2] drew attention to this aspect and further considered that a goal of finding one new case per 1,000 persons examined should be established, and that coverage of high socio-economic groups with yields of less than 0·5 new cases per 1,000 was wasteful of time and effort.

The advent of effective chemotherapeutic agents in the form of streptomycin, isoniazid, P.A.S., ethionamide, and more recent additions, has completely altered the prognosis for the individual sufferer, and has held high promise as a most effective element in the epidemiological instrument of control. However, in this field, too, serious problems are encountered. Multiple drug regimes to meet the difficulty of drug resistance are of little value where continuation of therapy cannot be maintained because of sociological circumstances. Where chemotherapy is inadequate, drug resistance is a serious sequel, not only for individual patients, but from the epidemiological aspect where these persons excreting drug-resistant bacilli cause primary resistant infections in their contacts, producing a new chain of danger to the community and a setback to the control of tuberculosis. In less developed communities the maintenance of therapy over long periods becomes completely unsatisfactory. MacFadyen, Klopper and Shongwe,[3] working in the Hlatikulu district of Swaziland, in spite of their efforts to use all available medical and social means for regular treatment, found that half their patients (52% of adult cases and 50% of children) were lost to sight. It was of interest that one of their problems was that they failed for various reasons to obtain the cooperation of tribal chiefs in reducing the defaulter rate. In our experience in urban and rural Bantu communities, especially in view of the motivations and attitudes of the Bantu toward tuberculosis, it was found essential to bring any programme of control to the people through the medium of their own respected persons of authority and status who well understand their traditional fears and concepts in regard to this disease. This feature remains the same whether the worker is in a tribal area or in a Bantu residential complex in a large city like Johannesburg. Menon[4] reported that in Hyderabad, of 472 patients treated with isoniazid alone, 48% were excreting resistant bacilli after a year. An even more important finding was that 15% of previously untreated patients gave cultures resistant to isoniazid, which caused concern over the potential epidemiological threat arising from these cases. In a leading article in the journal in which Menon's paper was published the view was held that his experience confirms yet again that isoniazid alone is unsatisfactory chemotherapy for mass treatment, and that it might be argued that the eventual burden to the State may be added to by the spreading of isoniazid-resistant infection. This view is of significance in Bantu areas in South Africa, where the issue of isoniazid under conditions and attitudes that often preclude assurance of adequately continued therapy should be given cautious consideration. Moodie[5] stated that drug resistance is one of the main problems in Hong Kong, where it was found that 40% of patients attending the public clinics for the first time admitted to having had previous treatment. In a comprehensive national survey in Great Britain by a research committee of the British Tuberculosis Association[6] the number of treated patients who were excreting tubercle bacilli was estimated to be at least 3,500, of whom 1,800 were excreting bacilli resistant to all 3 major drugs. If these findings show the extent of the problem caused by inadequate treatment in a community like that of Great Britain, it constitutes a warning of what may be anticipated in Africa, including South Africa, where circumstances often prevail which would not permit adequate continuation of chemotherapy. Moreover, it lays emphasis under these conditions to use every possible means with minimal delay to prevent the uninfected becoming infected, and to use BCG vaccination, not in fitful pockets over protracted periods, thus allowing great numbers of persons to enter the infector pool who could have been protected in a mass campaign, but in as extensive and rapid a method of application as local circumstances permit.

BCG vaccination does not protect the infected, but, with modern vaccines, techniques, and readings of local skin reaction to inoculation, an immediate indication is given in these persons that they require further investigation as potentially active tuberculotics in need of treatment; while the view is held that it causes no harm to persons with established tubercular pathology and may boost immunity levels in persons harbouring quiescent foci. A problem related to large-scale BCG vaccination is that resultant specific hypersensitivity precludes the use of the valuable tuberculin test for simple preliminary diagnosis. In great part the loss is compensated for by the modern dual role of BCG vaccine as an immunizing agent and for concomitant detection of Koch's phenomenon of hypersensitivity, though should any non-infected vaccinees contract tuberculosis at a later stage the tuberculin or BCG sensitivity tests would be of no value in these cases. In practice we found that a register of BCG immunization, to which reference could be made to ascertain whether a person had been vaccinated or not, was little used by clinicians faced with differential diagnoses of tuberculosis. Clearly, in communities where socio-economic factors and a high incidence of tuberculosis indicate the need for a priority rating to be given to mass BCG vaccination, the loss of the tuberculin test as a diagnostic procedure is of little comparable consequence. BCG is a safe vaccine and carries no threat similar to drug resistance and a consequently more potent infector pool. Finally, the level of protection afforded by BCG vaccination is not maintained indefinitely, and necessity arises for recurrent inoculation. However, protection levels were found to be substantial 7½ - 10 years after inoculation in the precisely controlled study of the Medical Research Council[7] in Great Britain, involving 54,239 children.

Chemoprophylaxis has little place in large-scale control programmes, for its effect is no longer exerted after cessation of administration and it cannot be continued indefinitely. Its major use is in protection of contacts of active cases.

*The Problem in the Bantu Residential Areas of Johannesburg*

Tuberculosis control programmes in South Africa are complicated by the widely differing social and economic status of population groups, not only as between Whites, Bantu and other groups, but among the Bantu themselves, many of whom have rapidly attained advanced socio-economic, environmental,

scholastic and academic standards, while a large proportion remain at tribal level, with the mass of the people in various transitional stages between the two. In terms of our postulate, basic data for broad adjustment of control measures are tabulated in Table I.

TABLE I. INCIDENCE OF TUBERCULOSIS

| Year | Republic of South Africa | | | | Johannesburg* | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases notified | | Rate† | | Cases notified | | Rate† | |
| | Bantu | Eur. | Bantu | Eur. | Bantu | Eur. | Bantu | Eur. |
| 1960 | 50,224 | 1,221 | 462·4 | 39·6 | 2,990 | 159 | 606 | 42 |
| 1961 | 49,233 | 1,224 | 443·1 | 39·1 | 2,712 | 150 | 536 | 41 |
| 1962 | 53,801 | 1,261 | 473·6 | 39·6 | 3,002 | 157 | 613 | 42 |

*Cases among miners excluded †Notification rate per 100,000 population

The size of the infector pool among Bantu in the Republic is so much greater than among Whites that the priority rating of control measures for the two population groups must be unlike. Adjustment for the Bantu population demands maximum rapid application of measures to prevent entry of new subjects into the infector pool and, while all possible urgency is applied to long-term socio-economic progression, immediate priority should be given to large-scale BCG inoculation. In the White population, on the other hand, adjustment requires maximum emphasis upon case finding and treatment with reservation of BCG vaccination for groups at especial risk.

This study is only concerned with the Bantu residential areas of Johannesburg. In previous communications[8, 9] dealing with mass diphtheria, whooping cough, tetanus, poliomyelitis, smallpox, and measles live-virus vaccination in these areas, the residential complex and the development of mass immunization techniques to meet the epidemiological needs of the community were described. In brief summary, the complex covers 26 square miles and houses about half a million Bantu varying from the recently detribalized to professional levels. The area has an extensive integrated hospital and clinic network. The clinics operated by the Johannesburg City Council provide curative, midwifery, dental, health-visitor, child-welfare, tuberculosis, immunization and domiciliary services and are staffed by 520 medical and other personnel, and there were 935,052 patient attendances, 12,135 district confinements and 72,299 ambulance removals during 1961. In addition, private practitioners have established practices in the area. During mass immunization procedure the community therefore has a medical service to which they would report abnormal reaction. The gradual development over recent years of techniques for bringing large-scale immunization campaigns to the homes of the people was discussed.[8, 9] It has resulted in a population group conditioned to large-scale, swift immunization drives involving the whole area in a systematic linear progression and in which they have evolved considerable trust.

The tuberculosis sections of the City Health Department are extensive, with satisfactory hospitalization, diagnostic, domiciliary and social welfare services. In 1962 there were over 180,000 attendances at tuberculosis clinics, 27,167 visits by domiciliary staff, with 7,478 patients on ambulatory treatment and 1,212 in hospital at the end of that year. In the 3-year period 1960 - 1962, apart from tuberculin-negative case contacts, 11,046 tuberculin-negative pre-school and school children were vaccinated with BCG vaccine.

Considerable strides have been made in housing but notwithstanding better housing and effective medical services, the rise in wage level, though marked, has not yet attained a standard to provide the necessary socio-economic level to combat tuberculosis. An analysis of the notification rates and death rates of pulmonary tuberculosis in Johannesburg in Table II shows that the Bantu incidence was greater in 1962 than 1961. The rise may be attributed to better case finding by an expanded tuberculosis service. The death rate is falling. Nevertheless, the tuberculosis morbidity in these areas remains critical notwithstanding the standard of diagnosis and treatment, indicating the need of adjustment of the epidemiological instrument to meet the circumstance and provide increased prevention of entry into the infector pool. This is further evident when related to the improvement in other health aspects, exampled by a fall in the Bantu infantile mortality

TABLE II. PULMONARY TUBERCULOSIS IN JOHANNESBURG

| Race | 1958 | | 1959 | | 1960 | | 1961 | | 1962 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NR | DR | NR | DR | NR | DR | NR | DR | NR | DR |
| E .. | 47 | 4 | 51 | 4 | 37 | 5 | 37 | 4 | 38 | 4 |
| C .. | 753 | 60 | 428 | 43 | 331 | 23 | 449 | 18 | 523 | 44 |
| A .. | 146 | 15 | 115 | 4 | 101 | 8 | 158 | 25 | 233 | 4 |
| B .. | 696 | 44 | 636 | 50 | 527 | 35 | 514 | 34 | 591 | 30 |
| Total .. | 429 | 28 | 382 | 30 | 319 | 22 | 320 | 22 | 364 | 20 |

*NR* = Notification rate. *DR* = Death rate.
E = Europeans. C = Coloured. A = Asiatics. B = Bantu.

rate from 132·70 in 1958 to 122·75 in 1960 and 61·20 in 1962, and by downward trends in other communicable disease.

Finally, in applying our postulate to the problem in these areas, the extensive infector pool demands priority for rapid large-scale BCG inoculation for immunizing and diagnostic purposes, followed by indefinite maintenance BCG immunization of the newborn, while routine services should be retained at peak efficiency and, in addition, provide a programme of investigation and therapy for cases detected as a result of preliminary diagnostic data obtained from BCG inoculation.

## BCG VACCINE

In 1908 Calmette and Guérin[10] studied a virulent bovine strain of the tubercle bacillus isolated 6 years previously by Nocard. They used a bile-glycerine-potato medium and found that the cultural characteristics of the organism became permanently modified and related to progressive attenuation of virulence. They subsequently rendered the strain completely avirulent after 230 transfers on ox bile-glycerine-potato medium over a period of 13 years (1908 - 1921). The strain was designated as BCG (*Bacille Calmette-Guérin*) and became of particular significance in active immunization against tuberculosis. The vaccine was first given by mouth to newborn infants in 1921 and has since been administered by various techniques to well over 100 million people throughout the world.

*Safety.* BCG has proved one of the safest vaccines used in medicine, especially freeze-dried vaccine, which permits precise standardization and sterility in preparation, and has replaced the former liquid type. Pollock,[11] after a meticulous review of BCG vaccination in man, concluded that objections to its safety were not substantiated by experience. An indication of safety is the introduction of BCG vaccination as a compulsory measure in France, Denmark, Norway, Brazil and Japan.

*Immunology.* Various immunological considerations in regard to the vaccine have a bearing on our study. Anergic and depressive changes in tuberculin sensitivity are known in various conditions, for example the terminal stages of tuberculosis, advancing age, after parturition, exposure to roentgen or ultraviolet radiation, corticosteroid therapy, and some infectious diseases. Von Pirquet[12] in 1908 noted depression of tuberculin sensitivity in measles. Bloomfield and Mateer[13] in 1919 recorded the general belief that the skin test altered during acute infectious disease and commented on constant depression in measles. Mitchell *et al.*[14] in 1935 investigated a group of 1,487 cases of different infectious diseases, and found a depression of allergy during the acute stages of scarlet fever and measles. Mellman and Wetton[15] recently reported on depression of the tuberculin reaction by attenuated live measles-virus vaccine. They studied a group of 17 children with positive tuberculin reactions, of whom 10 received measles vaccine with gamma-globulin and 7 without. There was no change of tuberculin reaction in those who received the measles vaccine with gamma-globulin, but the tuberculin reaction was depressed in the children given measles vaccine alone. Pre-vaccination sensitivity returned in 2 - 11 weeks in 6 of the 7 children but one child was still tuberculin negative after 5 months. Previous natural measles infection did not seem to alter the depression of tuberculin sensitivity by the measles vaccine suggesting the action of some principle in the vaccine, and the authors observed that the depression of sensitivity may not have been specific.

The report of Mellman and Wetton's work was received immediately before the BCG vaccination campaign here described, and had relevant significance. Four months previously 105,636 inoculations had been given in the same area in the fourth (booster) phase of a diphtheria, whooping cough and tetanus immunization campaign in children 3 months to 9 years old. Children aged 3 years to 9 years received diphtheria and tetanus antigens, while those aged 3 months to 2 years received diphtheria, whooping cough and tetanus antigens and, simultaneously, Edmonston-strain live measles-virus vaccine without gamma-globulin. 22,289 children received measles vaccine in this age group.[9] Possible effect on conversion by BCG vaccine was considered. It was felt that it was not likely to alter protective efficiency, but might have an effect on the reading of diagnostic reaction to BCG vaccine if local hypersensitivity were depressed by any residual effect of measles vaccine given 4 months previously. This, however, seemed improbable in the face of Mellman and Wetton's findings. Moreover, their sample of 17 cases was small and further investigation by these and other workers will be important. There was no time to initiate a properly controlled study during our undertaking.

Eighteen years ago Pilcher[16] had made the interesting observation that the local reaction to a non-specific whealing agent (codeine solution) was

lessened in measles and scarlet fever and, even more interesting, so was an ordinary atropine flush.

Emphasis has fallen on the loss of the tuberculin test as a diagnostic aid after BCG vaccination. Major interest has been focused in the past on the hypersensitivity reaction in diagnosis, no doubt because antibodies to the tubercle bacillus are present in such low titre that they are of little diagnostic value. In our opinion the tubercle bacillus in many respects initiates reactions in the body not dissimilar to the host-parasite relationship established in parasitic invasions like toxoplasmosis.[17] It is possible that the loss of the tuberculin test after BCG vaccination may in turn stimulate greater interest in a suitable test of a haemagglutination type for antibody reaction to the tubercle bacillus, in the same way as the danger of the Sabin-Feldman dye test for toxoplasmosis stimulated the evolution of a haemagglutination test for that disease. Of further significance in regard to the tuberculin test was the recent demonstration by Singer and Rodda[18] of antigens common to the *Mycobacterium tuberculosis* and other mycobacteria and fungi, groups which are genealogically related, and that these organisms are able to produce tuberculin conversion, especially fungi of known infectiousness, for man. Their work suggested that the degree of specificity of the tuberculin test may need reassessment, particularly in areas where warm moist conditions are suitable for rapid multiplication of fungi and mycobacteria that may be related to the high tuberculin positivity found in tropical areas.

An advantage of BCG vaccine over tuberculin in sensitivity-reaction readings is that it will demonstrate infratuberculin allergy in subjects with partial hypersensitivity who are negative to the tuberculin test.

*Efficacy.* The many well-known and extensive trials reported from different parts of the world bear irrefutable testimony to the efficacy of BCG vaccination in man. A classic among these was that of Aronson *et al.*,[19] who in a 20-year survey of BCG vaccination among American Indian tribes showed that 12·5% of all deaths in the vaccinated and 45·3% in the unvaccinated were due to tuberculosis. The Medical Research Council[7] of Great Britain in a significant investigation involving 54,239 children over a period of 7½ - 10 years showed that the incidence of tuberculosis in the vaccinated was one-fifth of the incidence in the unvaccinated, and found that it greatly diminished the danger of miliary tuberculosis and tuberculous meningitis. Shennan,[20] after a critical statistical analysis of a 3½-year BCG vaccination campaign in Southern Rhodesia, found that the vaccine conferred about 78% protection in African school children, with probability limits of 61% - 91%. He therefore concluded that BCG vaccination in the Bantu appears as effective as in various other races and nations studied.

Hyge[21] reported an instance where 94 tuberculin-negative unvaccinated children and 106 vaccinated children were exposed to a tuberculous teacher. 41 of the unvaccinated children developed progressive tuberculosis while only 2 among the vaccinated children developed the disease, giving a protection rate of 96%. This report was recalled during the course of our campaign when a reading team indicated at the end of a day that they thought there had been a class in one of their allotted schools with an unusually high number of positive hypersensitivity reactions. The routine statistical review at the end of each day proved this so, and immediate investigation found the teacher to be an advanced undiagnosed pulmonary tuberculotic.

With careful techniques tuberculin conversion rates in the region of 96% can be anticipated.

*Complications* were not infrequently encountered with intradermal inoculation of liquid BCG vaccine and were related to individual resistance, variation of vaccine potency and dose magnitude, and inelegant intradermal procedure. The complications, occasionally generalized and serious but usually minor, were sometimes troublesome and protracted; they included ulceration at the site of inoculation, lymphadenitis and suppuration, skin rashes, erythema nodosum and other manifestations. However, with the adoption of painless, simple percutaneous techniques and accurately standardized freeze-dried vaccine these complications have ceased to be a problem. Hsing,[22] in describing local reactions after intradermal inoculation of over 6 million people since 1950 in Taiwan, drew attention to cases of unpleasant keloid formation that had resulted from BCG vaccination 6 - 10 years previously and had caused resentment. In view of the predisposition of Bantu to keloid formation this observation is of interest, but percutaneous techniques are unlikely to result in this development.

The opinion is commonly held that people should not be vaccinated with BCG when they are being immunized against other infections, because of the possibility of complications, or of the depression of the antigenic properties of weaker antigens by the more potent. In compliance with this idea we discontinued our routine diphtheria, whooping cough, tetanus and smallpox immunization 1 month before, during, and 1 month after the mass BCG campaign. Routine BCG immunization was discontinued during this period to avoid confusion, but routine maintenance immunization of newborn children and pregnant women with oral trivalent poliomyelitis vaccine was not interrupted. However, as we have previously stated,[9] multiple immunization techniques are of especial potention value in Africa, where mass immunization procedure is often necessary and where environment and population attitudes often preclude return on numerous occasions for different inoculations. We have described mass campaigns[8, 9] in these areas of combined diphtheria, whooping cough, tetanus and smallpox immunization, and combined diphtheria, whooping cough, tetanus and live measles-virus immunization, without untoward reaction. Further, Winter *et al.*[23] have demonstrated the satisfactory combination of immunization against poliomyelitis, diphtheria, whooping cough, tetanus and smallpox in this country. In view of these trends, and provided other inoculations are not given on the same arm as the BCG vaccination, combination with other immunization procedures may well be practicable with percutaneous BCG techniques.

*Improved Vaccines and Techniques*

Freeze-dried vaccines, which have replaced the former type of liquid vaccine, are much more uniform in constitution and effect owing to greater stability after lyophilization, and may be used 6 months to 1 year after manufacture if properly stored under refrigeration. The vaccine contains living organisms, of which a minimal number are necessary for satisfactory vaccination, and accordingly has to be protected from raised temperatures. However, the work of Ungar *et al.*[24] produced a freeze-dried vaccine with increased stability to heat by growing the cells in a glycerol-free medium. The improved heat resistance is only maintained in unopened ampoules and is lost immediately on reconstitution. Thus short unrefrigerated periods during transportation and accidental exposure to higher temperatures for a little time will not render the vaccine ineffective; nevertheless, no latitude or abuse is permissible in carrying out manufacturers' requirements for storage, transport and reconstitution.

Methods of administration used are oral, scarification, intradermal, and multiple-puncture procedures. Oral methods are less certain and give less marked and shorter lasting tuberculin conversion, requiring frequent revaccination. Scarification is slow and permits too much variation in technique. Intradermal injection has been generally accepted and is considered to give better and more lasting conversion than multiple puncture, but takes longer, requires greater skill, and is related to minor complication in a proportion of cases to which multiple puncture is not. Vaccination using multiple-puncture inoculation was described by Rosenthal[25] in 1939 and Birkhaug[26] in 1947. Modern percutaneous application requires the use of apparatus that causes simultaneous skin puncture by 20 needles to a set depth and force of penetration through a film of BCG vaccine of greater strength than that used for intradermal inoculation and of minimal standards of viable organismal count (200 - 300 million organisms at a needle pressure of 10 lb.). With correctly applied multiple-puncture methods giving sufficient needle force and a full pattern of penetration, the tuberculin conversion rates have become as satisfactory as with intradermal inoculation, but insufficient time has elapsed to draw accurate conclusions about the duration of conversion. Percutaneous isoniazid-resistant vaccine is not yet available, and contacts on prophylactic isoniazid should be vaccinated with isoniazid-resistant vaccine by intradermal injection. Various sterilization methods are advocated for multiple-puncture apparatus some of which include flaming the instrument. Heat and antiseptics inactivate the vaccine. Instrument surfaces coated in inflammable sterilizing fluid and subsequently ignited undergo little sterilization by heat, because heat at a flame base is insufficient to sterilize, but this procedure is useful for removing excess sterilizing fluid. Sterilization by flame requires insertion in the upper hot regions of the flame, and Hopper[27] found that as the needles became blunter through the effects of flaming and clogging with carbon deposits so the clinical results deteriorated.

Reading of smallpox and BCG vaccination scars in assessment of immunization status is becoming difficult. Lorber[28] after a one-year follow-up of 240 infants vaccinated with percutaneous BCG vaccination by multiple puncture found that the site of vaccination was virtually not visible in all.

Over a decade ago Frappier and Guy[29] drew attention to the use of BCG vaccination as a preliminary diagnostic procedure. Normal local reaction to BCG develops 10 - 12 days after inoculation. Using scarification as the method of inoculation, they showed that in negative allergy the inoculation was reduced to simple lines or mere traces in 48 - 72 hours, while positive allergy showed as a local reaction in 24 hours. This reaction was still present at 96 hours, though after 48 hours

the intensity diminished each day and had virtually subsided at the end of a week. The authors gave as criteria of positivity oedema, redness, or a different shade to controls without any vaccine application, and that the reading at first sight was strikingly apparent and palpable, even though superficial. They concluded that not only did this test assess total skin allergy, but also infratuberculin states of partial hypersensitivity, thus showing greater accuracy than tuberculin testing, and that it was an economic and efficient substitute for tuberculin testing before BCG vaccination. Similarly Friedman and Silverman[30] in 1952 expressed the opinion that BCG vaccine provided a more sensitive and specific test than ordinary tuberculin tests, and many reports, mainly of Continental origin, have substantiated these earlier views. Heaf[31] concluded that it was possible to dispense with tuberculin and use the vaccine itself for sensitivity testing. A logical development has been the dual purpose use of the vaccine for combined immunizing and diagnostic procedure. Indeed, in view of the difficulty in many Bantu communities of maintaining patient contact for procedures and observation on numerous occasions, successful mass BCG vaccination campaigns in these circumstances become impracticable unless the preliminary tuberculin test is dispensed with.

De Assis,[32] quoted in other reports, described the vaccination of over 3 million persons in Brazil by frequently repeated oral administration without tuberculin testing, and claimed a 100% conversion rate without untoward reaction. The attractive theoretical course of combining oral BCG feeds in established programmes of oral poliomyelitis immunization for the newborn lends stimulus to the thought that reappraisal and improvement in oral techniques would not be inappropriate.

## THE CONTROL PROGRAMME

Shortly before this study the State Department of Health issued a policy directive making the following specific requirements in respect of Bantu in these areas:

(a) Persons of all ages were to be inoculated with percutaneous BCG vaccine without prior tuberculin testing.

(b) The local reaction to inoculation was to be read after 24 hours in persons up to and including the age of 20 years.

(c) No further steps were to be taken where there was no local reaction to inoculation at 24 hours.

(d) The management of cases showing local reaction to inoculation after 24 hours was to be as follows:

(i) Those under 5 years of age were to be treated with isoniazid for 2 years as active cases.

(ii) Those 5 - 10 years of age who showed clinical evidence of tuberculosis, or who gave a history of having been a contact of a tuberculosis case, were to be radiologically examined on 100 mm. film, and any tuberculotics thereby detected were to be treated.

(iii) Those 11 - 20 years of age were to be radiologically examined on 100 mm. film and any tuberculotics thereby detected were to be treated.

(e) Those over 20 years of age were to be radiologically examined on 70 mm. film without any reading of the reaction to inoculation, and any tuberculotics thereby detected were to be treated.

There was no stipulation whether inoculation with percutaneous BCG vaccine was to be introduced as a mass campaign, or over a protracted period with persons living in circumscribed areas being inoculated and positive reactors investigated before another similar group was inoculated. Decision regarding individual control programmes in different places was obviously dependent upon local conditions, facilities and resources for the programme.

Our primary objective was the introduction of measures that would meet the requirements of the State Department of Health and coincide with the epidemiological needs of the community in accordance with the principles of our postulate (Figs. 1 and 2). On these grounds it was evident that a rapid, mass BCG immunizing and preliminary diagnostic campaign was indicated; that its effect should be maintained by continued immunization of the newborn and revaccination conducted in accordance with eventual determination of the duration of conversion after percutaneous inoculation; that it should be preceded by pilot reaction and field studies and be followed by routine follow-up procedure complying with the requirements of the State Health Department; that existing tuberculosis services should be maintained at highest efficiency; and that the immunization campaign should be directed especially at the age group (0 - 20 years) considered to be most at risk.

The control programme for the Bantu areas of Johannesburg therefore fell into the following defined stages: (a) a pilot BCG reaction study; (b) a pilot field study; (c) a mass immunization campaign, with assessment of local accelerated reaction; and (d) follow-up procedure.

## THE PILOT REACTION STUDY

In the pilot field study local reaction to percutaneous BCG inoculation was observed and related to known clinical tuberculotic states. In the mass immunization campaign, reading teams had to follow mobile inoculation teams at 24-hour intervals, and required a precise simple directive regarding the recording of reaction assessment. The objective of the pilot study, therefore, was to obtain practical experience of 24-hour local reaction to inoculation and to present the data in precise form to reading teams in order to achieve a reasonably uniform assessment by multiple observers in the field.

The extent of the study was limited by the time interval remaining before the date of commencement of the mass campaign, which had to conform with school terms and annual examinations. It was further limited by the available amount of percutaneous vaccine, for supplies for the mass campaign only became available shortly before the campaign was to begin.

The field team consisted of one of us, one health visitor, and a nurse when necessary. In order to eliminate the uncontrollable variable of multiple observation the medical officer was the only observer of reactions. The sample of subjects consisted of 120 persons, who were selected and not random, and had a median age distribution of neonate

TABLE III. CRITERIA IN PILOT REACTION STUDY

| | *Infected* | | | |
|---|---|---|---|---|
| | *High risk (active)* 20 *subjects* | *Intermediate risk (inactive)* 20 *subjects* | *Less risk (potential)* 20 *subjects* | *Not infected* 60 *subjects* |
| Tuberculin test | + | + | + | − |
| Clinical signs | + | − | − | − |
| *Bacteriological investigation | + | − | − | − |
| Radiological investigation | + | + | − | − |

*In young children bacteriological investigation was waived.

to middle age. It was divided into 2 groups, viz.: (a) 60 subjects infected with tuberculosis and not on therapy, and (b) 60 subjects not infected with tuberculosis and not previously inoculated with BCG vaccine. The criteria of infection and non-infection used are shown in Table III.

A control was considered advisable but impracticable. Local reaction would consist of reaction to the trauma of introduction, to the residual menstruum and additives of the reconstituted vaccine and, lastly, to the organism. A true control would require inoculation with the menstruum and additives containing no growth of bacteria. Inactivation of bacilli in reactivated vaccine would be unsatisfactory because of contained killed organisms, while filtrate would not necessarily be free of bacterial products. No true samples suitable for a control were available in the time at our disposal. However, as a control measure, observations were made of the traumatic pattern of needle

penetration on arms dried after the application of cleansing fluid (ether 25%, water 25%, ethyl alcohol 50%) but without any application of vaccine.

Reaction survey forms were drawn detailing in their top half full personal data of the subjects, including the following: sex, age, nutritional status, time of inoculation, whether in the category of non-infected or infected persons and, if in the latter, whether in the high-, intermediate-, or minimal-risk groups. At the bottom of the form was a tabular questionnaire to be completed by the medical officer regarding details of diameter, induration, swelling, colour, local temperature, papule formation, and other data related to the local reaction. To avoid observer bias the personal information at the top half of the form was completed by someone other than the medical officer, and the form was folded before presentation to him for completion of the questionnaire. He had no knowledge of the clinical status of the subject.

The data of the completed survey forms were critically analysed by the other two co-authors of this paper, who were unbiased, unprejudiced observers, with no knowledge of the subjects in the study. Their statistical deductions were then taken to an independent study group of doctors and nurses by the remaining co-author for evaluation, and were finally compared with the recorded clinical impressions (made available at this stage) of the original field team who inoculated and read local reaction. There was no variation between their field impressions and the final criteria drawn after the evaluation outlined.

The reactions were either positive or negative, and no degrees of positivity were elicited. The criteria were simple and suitable for field reading teams. Negative reactions showed no plateau of swelling at the inoculation site, no colour change, and no increase of local temperature; and showed signs of needle penetration varying from a few small traumatic elevations to a pattern of puncture marks that were barely visible. Positive reactions invariably showed a plateau of swelling upon which papules were present and distributed according to the pattern of needle penetration. The papules were usually much more obvious than the elevations caused by traumatic swelling at the points of needle penetration in negative reactions. In addition, positive reactions in most instances showed a faint purple colour change related to each papule, which in the pigmented skin of our Bantu subjects was not as obvious as in unpigmented skins and was best seen out of doors. There was a slight increase of local temperature in a proportion of cases. The pattern of needle penetration tended to vary in a few cases where inaccurate skin contact from unsatisfactory application of the multiple puncture apparatus caused inadequate skin puncture by needles in one or other half or quadrant of the circle of inoculation. An obvious positive reaction in this series is shown in Fig. 3. Observation in a group of positive reactors 48 hours after inoculation showed the changes to be more marked than at 24 hours, but in no way indicated that reading at 24 hours was not entirely satisfactory; this was a factor additionally important in the mass campaign to follow, because, in our experience, the longer the delay after inoculation the more difficult it becomes to make contact with vaccinees in Bantu areas.

All the 60 persons in the infected group showed positive reactions except for 2 patients with anergic response, one of whom was found to be an advanced toxic pulmonary tuberculotic and the other has not yet been elucidated. All the 60 persons in the non-infected group showed negative reactions except 3 in whom positive infratuberculin reactions were obtained.

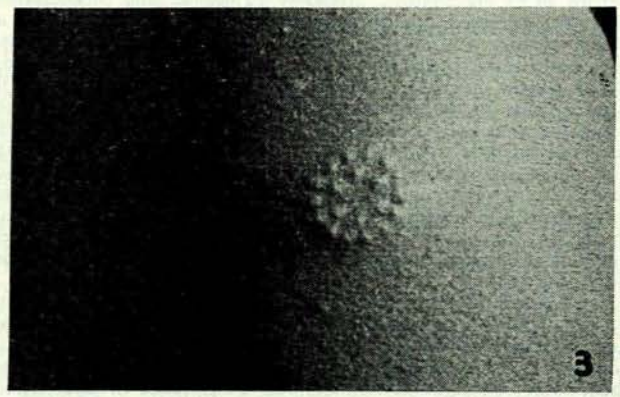

*Fig. 3.* Photograph of a positive BCG reaction.

We were unable to relate any variation in the changes of positive reaction to the degree of severity of the tuberculosis infection.

Reading teams in the mass campaign consisted of 54 persons, 45 of whom were Bantu nurses and 9 White. Both groups were fully qualified nurses and many were health visitors with post-basic qualifications. They were therefore competent observers of whom, however, only relatively few had any extensive experience in the reading of tuberculin-test reactions. In fact, we were firmly in favour of allocating persons to reading teams who were accurate observers but who had not had specific experience in skin hypersensitivity readings. Such observers we thought better able to base opinion on what they saw in relation to simple criteria laid down, without bias arising from correlation with previous experience; and, paradoxically, we considered that as the readers became more experienced so would they less accurately apply the simple criteria drawn. This opinion was supported by later experience in the mass campaign, and by the findings of Loüdon *et al.*[33] (1963), who investigated inter-observer variation between readers, mostly inexperienced, in assessing Mantoux, Heaf, and tine tuberculin tests, and found consistent reader bias apparently interpretive in origin. As the majority were inexperienced, they assumed that interpretive bias might have been reduced by experience, but the conspicuous degree of variation between two physicians of many years experience in reading the Mantoux test caused surprise. Likewise Griffith[34] in Heaf-test studies found that two nurses trained in the same department disagreed on the grading of 21% of tuberculin-positive children (70 of 336), and that an experienced nurse on repeating her readings gave a different grading on the second occasion in 15% of the tuberculin-positive children; however, the difficulty was confined to borderline reactions between one grade of positivity and another, and there was no difficulty in reading the tuberculin-negative children. The experience

of our pilot study indicated that difficulty in reading reactions in the mass campaign would be minimal, for cases were either clearly negative or positive, with little gradation between the two.

### THE PILOT FIELD STUDY

Three weeks before the mass campaign we undertook a field trial in a small Bantu township of about 600 houses in the eastern sector, the only one of its kind remaining in Johannesburg. All the other Bantu residential areas are part of the single massive Bantu complex of over 70,000 houses, with trading and recreational amenities, lying to the south-west of the city, and in which the mass campaign of this study took place.

The trial was a small but accurate duplication of the propaganda, organization, control and field procedures for the mass campaign. The purpose was to test the probable response to propaganda methods and the applicability of proposed field methods.

Two inoculating teams operated in the area for 1 day and were followed by 2 reading teams 24 hours later. Experience of minor technical problems was gained, but it was evident that the completed planning for the mass campaign required no modification, except for one obvious point overlooked, which was the provision of returns to show the number of persons inoculated in the age group 0 - 20 years. On this account the figures for the pilot field study reflected in the statistical summary in Table IV show only the totals of persons of all ages who were inoculated, namely 2,100. The following day the reading teams traced 1,404 of these who were in the age group 0 - 20 years. In many instances the ages of vaccinees were not known and had to be assessed by the readers. They experienced no difficulty in applying the criteria of negative and positive response. A total of 573 of the 1,404 reactions recorded were found to be positive, but a large proportion of the tuberculin-negative contacts and school and pre-school children vaccinated with BCG during the previous 3 years had been in this township.

### THE MASS CAMPAIGN

In view of previous experience[8, 9] the campaign was conducted on a domiciliary basis, with rapid progression of teams through the whole area in 18 working days between the scheduled dates 7 - 31 October 1963. Rapid progression was essential. It had been found difficult to sustain public interest under non-epidemic conditions for longer periods. Neither could the tempo of teams, the strain on depleted staff complement left to operate extensive routine medical services, nor the cooperation of school and crèche personnel be extended for a longer time. Inoculation was offered to persons of all age groups but an absolute priority was the age group 0 - 20 years.

#### *Propaganda Methods*

In this community of Bantu, in all stages of transition toward the European way of life, the propaganda methods used in mass immunization against diphtheria, whooping cough, tetanus, smallpox, poliomyelitis and measles had been satisfactory. They were based on the realization that, for the majority, methods suitable for the European were not optimal, and that posters, press and radio announcements were of limited value and often misinterpreted. The paramount channel of information was word of mouth by those who knew, namely Bantu medical, nursing and clinic personnel, informed people of status in the community, and the families of those safely inoculated. It was essential to present simple, accurate data in a manner acceptable to the concepts of the people. Achievement of some understanding of requirement necessitated a degree of experience of African attitudes to disease, which vary from one area and race to another, but have an element of basic uniformity. Even in an urban area like Johannesburg, Bantu tradition and custom remain woven in the minds of the people. Endeavour to thrust entirely European concept against this fabric leads to varying degrees of failure. It is necessary to respect and understand these attitudes and motivations, and to direct propaganda in a way that does not try to penetrate the fabric of traditional concept, but to run parallel with it and gain support from it. In many places the old and basic concept of African medicine was that disease was not only an adverse process that affected the body or the mind, but anything that affected the well-being of the person, family, homestead, crops, animals or other possessions. Thus disease included illness, injury, death, failures, accidents, misfortune and disaster. Disease within this meaning could have been caused by an act of Nature, incurring the wrath of the Ancestral Spirits, or the actions of jealous or ill-disposed persons. Many infectious diseases were considered to be due to natural causes, for example those against which immunization campaigns had already been completed. Tuberculosis, however, was related to other causes such as the machinations of an ill-disposed person. Further, the disease affected not only the physical state of the sufferer, but caused disruption of the family and homestead and a falling away of possessions. As an element of unfounded stigma attached to tuberculosis in earlier European thought, so it is sometimes said to bring 'disgrace' to a Bantu family. Mothers bringing apparently well children for immunization who were subsequently traced as tuberculotics as a result of positive reaction would be faced with this problem. Skilled educative procedures aimed at tuberculotics and their families in some instances meet an indefinable barrier that confuses the expert educator who fails to look sufficiently far back to see forward. Likewise, obstacles to protracted chemotherapy are formidable. However, as the obtaining of protection from adverse influence is fundamental to African medicine, immunization procedures offered by modern techniques are perhaps the more easily acceptable. Many of these things may not be in the scope of this paper but, nevertheless, are significant when working in Bantu communities, where medical propaganda methods require careful modification, especially in regard to tuberculosis. What might seem insignificant may be critical to the success of an undertaking.

As on previous occasions,[9] the proposed conduct of the campaign and suggested propaganda methods were submitted to regularly held discussion groups attended by less senior medical field workers. Those members of the groups who were Bantu have invariably given an accurate estimation of the reaction of the community. The groups drew attention to the necessity not to emphasize the relationship

between simple immunization, in which the people had evolved considerable trust, and subsequent follow-up of positive cases, with associated family disruption in some instances, and that the two procedures should not run concurrently. It was essential to offer inoculation to grandmothers because many mothers were not able to care for their children for some reason, or children had reverted to the maternal grandmother. Many grandmothers would not have brought children for inoculation, but did so to get inoculation for themselves. The sick, bearers of wrist bands indicating steroid therapy or sensitization, and persons with obvious skin disorders, were not inoculated in the campaign on medical grounds. Neither were pregnant women inoculated; this was not on medical grounds, but because some spontaneous abortions might have coincided with BCG vaccination, brought it into disrepute, and caused difficult problems of rumour. We further thought it wise that all inoculations should be given by a medical officer.

As in preceding campaigns no fee was charged and consent was required in all cases, introducing an essential element of trust in the minds of the people. Seventy thousand printed forms in the 2 official and 2 Bantu languages were distributed to householders. They simply set out the threat of tuberculosis in the area, that vaccination strengthened and protected against the disease, that if vaccinated persons still contracted the disease it would tend to be mild, that they were to wait at their homes for the teams to come to them, they would be informed in advance of the arrival of a mobile inoculating team, and that a nurse would come to their homes to see whether the vaccination was protecting well, the nuance being that in cases with reaction further help would have to be brought to the individual. Precise explanatory letters were issued to all school principals, with the approval and cooperation of the Education authorities, and to crèche supervisors. A medical officer visited each of the 160 schools and crèches in the area and arranged exact appointments for the arrival of inoculating and reading teams. Schools were given forms for parents or guardians of children, with consent forms that had to be signed and returned. No children in any institution were inoculated unless they presented with a signed consent form. Propaganda vans with public address systems patrolled each area for 2 days before the commencement of the campaign and gave details of the scheduled date and time of arrival of an inoculating team. Regular announcements were made at all clinics, and information was disseminated by domiciliary health-visiting, nursing and midwifery staffs. All private practitioners and hospitals in the area were informed by letter, and the attention of hospital authorities drawn to the increased necessity of checking whether a patient had been inoculated with BCG vaccine if a positive tuberculin test was obtained.

Finally, when an inoculating team reached a scheduled area during the campaign, its transport van equipped with a public address system combed the area informing the people of the arrival of the team and the place where it had set up operation.

*The Organization*

The functioning of the organization of 125 persons and 27 transport vehicles was uneventful and the reaction of the community exemplary. Six mobile domiciliary and 3 school and crèche inoculating teams were employed. Each domiciliary team was covered by a team of 8 readers, who visited the homes and recorded local reaction 24 hours after inoculation in persons aged 0 - 20 years, or as soon afterwards as possible if a weekend or public holiday intervened. Similarly each of the school and crèche teams was covered by a team of 2 readers. Teams assembled at a field headquarters each morning and persons in charge of sections were briefed. A discussion group for collation of data and research was held each day.

Records have always constituted a bottleneck controlling the tempo of team operation. Yet it was essential that each individual could at a later stage be related without delay to his or her record. The method of taking immunization to the community, instead of requiring large numbers to present themselves at established centres, avoided uncontrollable crowds which on later analysis often showed that the apparently large numbers inoculated were only a fraction of the total at risk.[9] With the resultant better-regulated flow of vaccinees adequate record keeping became more possible. A card system used in the first of our domiciliary campaigns proved particularly ineffective, for it was almost impossible to relate any individual to a card long after the campaign. It is an absolute requirement to retain simplicity and limit data to what is completely essential. Measures could have been taken, to record totals of vaccinees not only in the age group 0 - 20 years, but also 0 - 4, 5 - 10 and 11 - 20. However, all that was fundamental during the campaign was to know how many persons were inoculated in the age group 0 - 20 years in order to assess the target for reading teams as a control of their success rate. Further assignment into age groups would not be necessary until the regular tuberculosis services, engaged on follow-up procedure, arrived at the recorded addresses of positive reactors. Unnecessary duplication would have added to the load of record keeping, and prevented many persons from being immunized because of operative retardation owing to collection of data more simply done at a later stage, and when actually required.

Loose-leaf, hard-covered record files were made in the Department, one for each of 92 areas within the residential complex. The loose leaves had columns for entry of consent, names, house numbers, BCG inoculation, history of tuberculosis in the home, and reaction. Over 70,000 house numbers were entered in files of the appropriate areas before the start of the campaign. Each domiciliary inoculating team carried about 15 of the files, corresponding to their allotted areas of operation. A clerk entered information opposite the house number in the file of the area of domicile of each individual who presented to a team. He issued a blue ticket to those up to and including 20 years of age, and a pink ticket to those over 20 years. No person presenting at an inoculation table was vaccinated unless in possession of a ticket, which had to be placed in an enumeration box. Tickets in these boxes therefore gave the daily total of persons inoculated and the numbers in the age groups 0 - 20 years and over 20 years.

Members of reading teams carried two folders. In one was inserted a specific map and schedule of house numbers to be covered each day. The other, a loose-leaf folder, had the criteria from the pilot reaction study attached to the back together with a photograph of a positive reaction (Fig. 3). At the end of each day, record sheets completed that day by domiciliary inoculating teams were removed from their files and inserted into the folder of the reader who would be covering that area the next day. She entered the reaction of persons 0 - 20 years old and whether there was a history of tuberculosis in the house. When she returned at the end of the day these sheets were returned to the files of the inoculating team. She was further required to submit a daily statistic sheet. The completed files of the domiciliary inoculating teams therefore constituted a final record to be delivered to the routine tuberculosis services to trace positive reactors through the names and addresses recorded for each.

School and crèche records required collection at the time of inoculation of all consent forms signed by parents or guardians, which also showed the name and address of each child. As only children with signed forms were inoculated, collection of a form was a record of inoculation. Consent forms were then placed in envelopes for each class or group, and retained by school or crèche staff until the next day, when staff issued them to reading teams. Reading teams entered the reaction to inoculation on each form. The forms together with statistic sheets were brought in every day, filed under schools, classes and crèches, and constituted the record for subsequent follow-up procedure.

A detailed daily statistical analysis was kept of each inoculating team and every reader. Comparative analysis indicated where advice or assistance was needed. Further, by comparison with similar statistical records of previous campaigns, abnormal area response became obvious and received attention. A statistical review indicated any pockets of poorer response, which received additional visits from the inoculating teams on the day after completion of their schedules.

The task of compiling daily maps, routes and schedules for inoculating and reading teams before the commencement of the campaign was complex, but there was no instance of alteration or failure during the 18 working days of operation.

The freeze-dried percutaneous BCG vaccine used was of 2 types: a British vaccine in ampoules of 25 mg./ml. moist weight and reconstituted by addition of 0·3 ml. of sterile water, and a Swedish vaccine reconstituted by addition of 0·5 ml. of prepared dissolving fluid issued with the ampoules. Vaccine loses potency if exposed to temperatures higher than a range of 4 - 10°C. Stock supplies were refrigerated at 4°C and batches issued to teams for daily requirement. In the field, ampoules of vaccines and fluid were kept in fibre-glass bags, containing cans of previously refrigerated cooling agent, and suspended beneath operating tables for protection from the sun. Temperature readings in the field indicated satisfactory compliance with temperature-range requirement. Reconstituted vaccine was used forthwith and care taken that amounts reconstituted should not exceed the number of vaccinees presenting at any given time. In our experience, up to 18 adequate doses could be obtained from an ampoule of British vaccine and up to 25 from an ampoule of the Swedish. Criteria of adequacy were an unbroken film of vaccine between the skin and the whole area of the base plate of the multiple puncture apparatus and the appearance of satisfactory papules 10 - 20 days after inoculation. Gentle addition of reconstituting fluid was necessary to avoid troublesome frothing. The reconstituted vaccine was drawn into 1 ml. Record syringes fitted with No. 18 hypodermic needles from which the bevelled points had been removed. The blunt ends prevented inadvertent pricking of arms during application over right deltoid insertions, and tended to limit waste of vaccine from droplets extruded from needles by capillary action between applications. Medical officers retained a record of batch numbers of vaccine used in the various areas.

Percutaneous vaccine inoculation was obtained with Heaf's pattern multiple-puncture apparatus supplied by the State Department of Health. The instrument used discharged a set of 20 needles through a perforated base plate applied to the skin. The needles were individually mounted in a removable needle block and were individually replaceable. Three depths of precise skin penetration of 1 mm., 2 mm. or 3 mm. were obtainable by rotating a collar to the required setting. The needles were simultaneously discharged when pressure was applied to a plunger. A depth of penetration of 2 mm. was used throughout the campaign irrespective of age or skin texture.

An inoculating team consisted of a record clerk; an untrained person to clean arms and marshal queues; a qualified nurse for reconstitution of vaccine, loading of applicator syringes, and sterilization of equipment; a clinic assistant to apply the vaccine; and a medical officer to inoculate. School and crèche teams, who were not slowed as the domiciliary teams were, by more detailed record requirement and more complex gathering of vaccinees, achieved rates of up to 360 inoculations per hour with this instrument. Assessed over the whole campaign, including time taken for transport, establishment of new operating points, and other interruptions, school and crèche teams averaged 239 inoculations per hour and domiciliary teams 148 per hour. 60 instruments were in use by teams; 6 to each domiciliary team and 8 to each school and crèche team. This minimal number, without replacements, was necessary for the speed of the teams and to allow proper sterilization and cooling.

Various factors in relation to the instrument and technique were determined during the pilot field study and the campaign. The apparatus withstood hard but careful usage very well. Each was examined at the end of every day and worn or bent needles replaced (1,024 needles during the campaign). A large capped screw that retained needles in position in the needle block required periodic tightening to prevent loosening of needles, which affected depth of penetration. Faulty application of the base plate to the skin surface resulted in a partial pattern of needle penetration, especially in obese subjects, where tensing of the skin was difficult, or in thin subjects, where pressure tended to produce deflection to one or other side of the humerus. With high-pressure usage the head of the instrument tended to work loose, as a result of which needles did not pass squarely through the perforations of the base plate but struck the edges of the perforations with the sides of the bevel of their points, which resulted in premature wear of needles. This was overcome by periodic tightening of the head

or, more effectively, by rotating the whole gun in a clockwise direction when applied to the vaccine on the skin before discharging the needles. This movement spread the vaccine effectively and, by friction of the base plate against the skin, kept the head of the apparatus firmly screwed to the barrel. Again under periods of stress, the collar that altered depth of penetration tended to move from its setting, also contributing to interference with needle alignment and affecting depth of penetration. Teams checked this point regularly. Several times toward the latter half of the campaign needles failed to discharge when the plunger was depressed. This was at first attributed to operator fatigue, but eventually increasing numbers of instruments ceased to function. It was found after extracting the plunger that a disc that was threaded into the barrel, against which the discharge mechanism operated, gradually worked loose. The suppliers of the instrument then provided a small tool that fitted into the barrel and into holes in the disc, permitting easy tightening where necessary at the end of each day; and no further difficulty was encountered. The instruments withstood boiling well. There was evident variation at the site of inoculation in the pattern produced by different operators, in spite of their all having had the same preparatory instruction.

In previous immunization campaigns, where inoculation of antigens was performed by subcutaneous injection, the threat of serum hepatitis was effectively controlled by providing a freshly sterilized needle for each person inoculated and avoiding drawback into syringes. Parallel technique was not possible with multiple puncture apparatus. Arms of those to be inoculated were cleaned with a mixture of ethyl alcohol 50%, ether 25% and water 25%, and queue movement so arranged that they were completely dry before inoculation. As the fluid constituted a fire hazard, suitable precautions were taken and team transport carried sand buckets and fire extinguishers. Needles and base plates of instruments were immersed in the fluid in a container, vigorously shaken, the plunger pumped several times to remove excess fluid, and the remaining fluid removed with a sterile pledget of cottonwool before each inoculation. Instrument heads were not flamed in view of Hopper's experience.[27] Serum-hepatitis virus, which is variably estimated to be carried by about 5% of people, is not satisfactorily inactivated by alcohol and ether. At regular intervals fluid in which needles and base plates were immersed was discarded and the containers thoroughly boiled before recharging. Chlorine in solution has effect on the virus but would be detrimental to BCG vaccine. Neither has the thermal death point of the virus been finally determined. Autoclaving in the field was desirable but totally impracticable. Accordingly, block barriers to the potential spread of virus were introduced by thorough boiling of each multiple-puncture apparatus after it had completed 25 successive inoculations. The person applying vaccine notified the nurse responsible for vaccine reconstitution and sterilization of equipment, at the end of every 25 applications. The nurse then removed the multiple puncture apparatus in use and replaced it with a boiled instrument that had been allowed to cool. Boilers were heated by gas camping stoves, which have proved convenient, economical and efficient in all campaigns.

The experience of the reading teams was varied. As this was the first operation of its kind it was necessary to make provision for the possible maximum of commitment, which was assessed at 60 readings per day for each of the 54 members of the reading teams. In practice it was found that the load per reader was considerably less, and averaged 45 readings a day. The average of homes falling to each reader covering mobile domiciliary inoculation teams was 28 houses a day, often scattered throughout her area of operation. In instances where readers completed a daily schedule more rapidly than anticipated, they were allocated routine nursing duties for the remainder of the day. In view of these factors it was possible that fewer readers could have been employed, but statistics do not record frustration and fatigue. Readers reported that the more readings they performed during a day, the less their fatigue. In many homes parents stated that only some of the children had been taken for inoculation as this was the first time that an immunizing campaign was offered for tuberculosis and they wished to test its effects on a few. They were impressed that medical services came back to read the portent of the procedure. Reading by school and crèche teams was quick and easy in view of organized groups passing in file before each reader. The criteria of negative and positive reaction at 24 hours were found precisely satisfactory. Readings were a little more obvious at 48 hours and still easily read at 72 hours. At a study group that analysed reader and public reaction, a number of readers stated that they felt more confident of their reading ability at the beginning of the campaign than at the end, which supported our previous contention.

*Untoward Reaction*

Apart from 2 instances of evanescent micro-papular eruption that was possibly related to inoculation, no cases of established untoward reaction had been reported to the clinic services up to the time of writing (4 weeks after the campaign).

*Statistical Results*

Final statistical analysis is summarized in Table IV. 160,298 inoculations were given to all age groups in the mass campaign. In addition 2,100 persons were inoculated in the pilot field study. 124,997 were inoculated in the priority age group 0 - 20 years, being 71·4% of the calculated target of 175,000 people in this age group living in these areas. Of these 124,997 inoculated, in whom the reaction to percutaneous BCG inoculation was to be assessed 24 hours later, 91,966 persons were traced and the reactions recorded by the reading teams. Reading teams therefore traced 73·6% of their possible target. A total of 12,759 positive reactions was recorded.

The total of positive reactions obviously included conversion to positivity from previous BCG vaccination (which has been relatively limited in these areas), instances of exposure to infection without clinical disease, and previously diagnosed cases who happened to present for inoculation. The relationship to active disease will not be determined until investigation of positive reactors is completed in the scheduled follow-up procedure.

In general, progression of reading teams was made to parallel that of mobile domiciliary teams so that inoculations done late on one day would not be read the morning of the next, but in the afternoon, to provide an interval not shorter than 24 hours. In some areas the intervention of weekends or a public holiday caused the reaction not to be read until 48 or 72 hours had elapsed. Analysis of the percentage of positive and negative reactions 24, 48 and 72 hours after inoculation throughout the campaign showed insignificant differences and suggested that there was no valid variation in reading assessment at these times. However, the shorter the time after inoculation the easier it was to trace the vaccinee.

Table IV reflects an apparently considerable lag between children inoculated in schools and crèches on one day and the number of these read by reading teams on the next. When these lags were analysed for all the schools and

TABLE IV. STATISTICAL SUMMARY: BCG INOCULATION AND PRELIMINARY DIAGNOSTIC CAMPAIGN, 7–31 OCTOBER 1963

| October 1963 | Persons inoculated | | | | | | | | | Reactions read | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A. Mobile teams | | | B. School and crèche teams | | | Total A and B | | | A. Mobile teams | | B. School and crèche teams | | Total A and B | Total A and B | Total reactions read |
| | 0–20 yrs | Over 20 | Total | 0–20 yrs | Over 20 | Total | 0–20 yrs | Over 20 | Total | Positive | Negative | Positive | Negative | positive | negative | |
| 7 .. .. .. | 2,774 | 1,501 | 4,257 | 3,067 | 58 | 3,125 | 5,841 | 1,559 | 7,400 | | | | | | | |
| 8 .. .. .. | 3,587 | 1,860 | 5,447 | 2,874 | 57 | 2,931 | 6,461 | 1,917 | 8,378 | 163 | 1,580 | 149 | 2,862 | 312 | 4,442 | 4,754 |
| 9 .. .. .. | 4,437 | 2,027 | 6,464 | 3,524 | 73 | 3,597 | 7,961 | 2,100 | 10,061 | 138 | 1,899 | 205 | 2,064 | 343 | 3,963 | 4,306 |
| 11 .. .. .. | 3,661 | 1,857 | 5,518 | 3,174 | 68 | 3,242 | 6,835 | 1,925 | 8,760 | 285 | 2,528 | 469 | 2,834 | 754 | 5,362 | 6,116 |
| 14 .. .. .. | 3,152 | 1,411 | 4,563 | 3,231 | 67 | 3,298 | 6,383 | 1,478 | 7,861 | 230 | 1,664 | 469 | 2,268 | 699 | 3,932 | 4,631 |
| 15 .. .. .. | 4,159 | 2,085 | 6,244 | 3,537 | 74 | 3,611 | 7,696 | 2,159 | 9,855 | 172 | 1,656 | 306 | 2,756 | 478 | 4,412 | 4,890 |
| 16 .. .. .. | 4,614 | 2,073 | 6,687 | 3,207 | 53 | 3,260 | 7,821 | 2,126 | 9,947 | 286 | 2,338 | 393 | 2,810 | 679 | 5,148 | 5,827 |
| 17 .. .. .. | 4,041 | 2,169 | 6,210 | 4,006 | 60 | 4,066 | 8,047 | 2,229 | 10,276 | 217 | 2,019 | 426 | 2,763 | 643 | 4,782 | 5,425 |
| 18 .. .. .. | 4,030 | 2,059 | 6,089 | 3,410 | 60 | 3,470 | 7,440 | 2,119 | 9,559 | 329 | 2,239 | 633 | 2,996 | 962 | 5,235 | 6,197 |
| 21 .. .. .. | 3,306 | 1,619 | 4,925 | 3,545 | 81 | 3,626 | 6,851 | 1,700 | 8,551 | 322 | 2,276 | 527 | 2,492 | 849 | 4 768 | 5 617 |
| 22 .. .. .. | 4,272 | 2,011 | 6,283 | 3,131 | 61 | 3,192 | 7,403 | 2,072 | 9,475 | 287 | 2,384 | 598 | 2,490 | 885 | 4,874 | 5,759 |
| 23 .. .. .. | 3,546 | 1,913 | 5,459 | 3,855 | 62 | 3,917 | 7,401 | 1,975 | 9,376 | 209 | 2,229 | 576 | 2,487 | 785 | 4,716 | 5,501 |
| 24 .. .. .. | 1,455 | 2,441 | 6,896 | 3,530 | 64 | 3,594 | 7.985 | 2,505 | 10,490 | 266 | 2,010 | 697 | 2,978 | 963 | 4,988 | 5,951 |
| 25 .. .. .. | 4,407 | 2,410 | 6,817 | 3,560 | 79 | 3,639 | 7 967 | 2 489 | 10 456 | 252 | 1 837 | 659 | 2 485 | 911 | 4,322 | 5,233 |
| 28 .. .. .. | 2,445 | 1,096 | 3,541 | 3,294 | 54 | 3,348 | 5,739 | 1,150 | 6,889 | 315 | 2,161 | 562 | 2,569 | 877 | 4,730 | 5,607 |
| 29 .. .. .. | 4,303 | 2,111 | 6,414 | 3,255 | 67 | 3,322 | 7,558 | 2,178 | 9,736 | 246 | 1,492 | 398 | 2,725 | 644 | 4,217 | 4,861 |
| 30 .. .. .. | 4,187 | 2,400 | 6,587 | 2,984 | 56 | 3,040 | 7,171 | 2,456 | 9,627 | 338 | 2,462 | 648 | 2,439 | 986 | 4,901 | 5,887 |
| 31 .. .. .. | 1,750 | 1,170 | 2,920 | 667 | 14 | 681 | 2,417 | 1,184 | 3,601 | 369 | 2,191 | 620 | 2,224 | 989 | 4,415 | 5,404 |
| | 67 126 | 34 213 | 101,339 | 57,851 | 1,108 | 58,959 | 124,977 | 35,321 | 160,298 | 4,424 | 34,965 | 8,335 | 44,242 | 12,759 | 79,207 | 91,966 |
| *Pilot field study** | | | | | | | | | | | | | | | | |
| | | | 1,234 | | | 866 | | | 2,100 | 186 | 398 | 387 | 433 | 573 | 831 | 1,404 |

*9 and 10 September 1963.

crèches in the whole campaign, the rate of inoculated children not traced was surprisingly small. Scholars over 20 years old are not infrequent in these areas, but the totals of persons over 20 inoculated by school and crèche teams also included teaching and supervisory staff who wished to be vaccinated.

## FOLLOW-UP PROCEDURE

Record files of inoculating teams containing the names and addresses of positive reactors have been distributed, according to the area each covered, to the subsidiary tuberculosis clinic serving that area. The totals of positive reactors allocated on this basis is shown in Table V. Investigation

TABLE V. FOLLOW-UP PROCEDURE: ALLOCATION OF POSITIVE REACTORS TO CLINICS

| Subsidiary tuberculosis clinics | Positive reactors | | |
|---|---|---|---|
| | Schools and crèches | Domiciliary | Total per clinic |
| 1(M) | 1,548 | 705 | 2,253 |
| 2(J) | 1,586 | 1,898 | ,4843 |
| 3(O) | 1,830 | 471 | 2,301 |
| 4(S) | 2,112 | 970 | 3,082 |
| 5(P) | 1,259 | 380 | 1,639 |
| | 8,335 | 4,424 | 12,759 |

will be pursued as expeditiously as possible by domiciliary staff at the subsidiary clinics, by a mobile X-ray service, and by referral to the tuberculosis master clinic in the area for radiologica! investigation where necessary.

Therapy will be conducted in accordance with the directive of the State Department of Health. We shall try to persuade persons over 20 years of age to submit to X-ray examination, and BCG maintenance immunization of the newborn will be introduced. On completion, this follow-up phase will form the subject of a final communication.

## SUMMARY

1. Aspects of tuberculosis control and application to the Bantu residential areas of Johannesburg are discussed.

2. A study to establish field criteria of local hypersensitivity reaction to percutaneous BCG inoculation is described.

3. A mass campaign of percutaneous BCG inoculation without prior tuberculin testing is outlined.

4. The field experience of reading local hypersensitivity reaction 24 hours after inoculation is described.

Views of the authors do not necessarily reflect the opinion of the State Health Department or the Johannesburg City Health Department.

We are indebted to the State Health Department for facilitating the supply of vaccine and multiple-puncture apparatus, and to Dr. J. W. Scott Millar, Medical Officer of Health, Johannesburg, for permission to publish this paper.

## REFERENCES

1. Canetti, G. (1962): Tubercle (Edinb.), **43**, 301.
2. Brightman, I. J. and Hilleboe, H. E. (1962): Amer. J. Publ. Hlth, **52**, 749.
3. MacFadyen, D. M., Klopper, J. M. L. and Shongwe, S. P. N. (1963): Tubercle (Edinb.), **44**, 82.
4. Menon, N. K. (1963): *Ibid.*, **44**, 34.
5. Moodie, A. S. (1963): *Ibid.*, **44**, 334.
6. Research Committee of the British Tuberculosis Association (1963): *Ibid.*, **44**, 1.
7. Medical Research Council (1963): Brit. Med. J., **1**, 973.
8. Spencer, I. W. F. and Coster, M. E. E. (1962): S. Afr. Med. J., **36**, 881.
9. Spencer, I. W. F., Coster, M. E. E., Richter, M. and Maher, M. (1964): *Ibid.*, **38**, 103.
10. Calmette, A. and Guérin, C. (1908): C.R. Acad. Sci. (Paris), **147**, 1456.
11. Pollock, T. M. (1959): Tubercle (Edinb), **40**, 399.
12. Von Pirquet, C. (1908): Dtsch. med. Wschr., **34**, 1297.
13. Bloomfield, A. L. and Mateer, J. G. (1919): Amer. Rev. Tuberc., **3**, 166.
14. Mitchell, A. G., Nelson, W. E. and LeBlanc, T. J. (1935): Amer. J. Dis. Child., **49**, 695.
15. Mellman, W. J. and Wetton, R. (1963): J. Lab. Clin. Med., **61**, 453.
16. Pilcher, J. D. (1935): Amer. Rev. Tuberc., **31**, 568.
17. Spencer, I. W. F. (1959): S. Afr. Med. J., **33**, 156.
18. Singer, E. and Rodda, G. M. J. (1963): Tubercle (Edinb.), **44**, 268.
19. Aronson, J. D., Aronson, A. B. and Taylor, H. C. (1958): Arch. Intern. Med., **101**, 881.
20. Shennan, D. H. (1963): Cent. Afr. J. Med., **9**, 53.
21. Hyge, T. V. (1956): Acta tuberc. scand., **32**, 89.
22. Hsing, C. T. (1963): Amer. Rev. Resp. Dis., **88**, 402.
23. Winter, P. A. D., Mason, J. H., Kuhr, E., Schaafsma, A. W., Robinson, M., Saayman, L. R. and Spence, R. G. (1963): S. Afr. Med. J., **37**, 513.
24. Ungar, J., Muggleton, P. W., Dudley, J. A. R. and Griffiths, M. I. (1962): Brit. Med. J., **2**, 1086.
25. Rosenthal, S. R. (1939): Amer. Rev. Tuberc., **39**, 128.
26. Birkhaug, K. (1947): Amer. J. Clin. Path., **17**, 751.
27. Hopper, J. M. H. (1960): Med. Offr, **103**, 311.
28. Lorber, J. (1959): Tubercle (Edinb.), **40**, 21.
29. Frappier, A. and Guy, R. (1950): Canad. J. Publ. Hlth, **40**, 72.
30. Friedman, E. and Silverman, I. (1952): Pediatrics, **9**, 280.
31. Heaf, F. R. G. (1955): Lancet, **1**, 315.
32. De Assis, A. (1953): Hoja tisiol., **13**, 325.
33. Loüdon, R. G., Lawson, R. A. and Brown, J. (1963): Amer. Rev. Resp. Dis., **87**, 852.
34. Griffith, A. H. (1963): Med. Offr, **110**, 161.