THE PRESENT POSITION OF B.C.G. VACCINATION

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Introduction

It is now generally recognized that a primary tuberculous infection evokes a definite degree of acquired resistance to reinfection. This primary infection, though usually innocuous to the European, may produce progressive disease. For the last seventy years research has been directed towards finding a vaccine that will produce an avirulent primary infection and evoke acquired resistance in safety; from this has emerged the B.C.G. vaccine and, more recently, the Vole vaccine.

The history of B.C.G. up to 1948 has been dealt with in detail elsewhere (Irvine, 1949); this article is primarily concerned with advances which have occurred since then and with its recent introduction into this country.

Safety

For the first time in the last twenty years some investigators have reported that they have been able to produce progressive disease in animals with B.C.G. Hauduroy and Rosset (1951) have produced progressive disease and death by inoculating B.C.G. into hamsters; Vorwald *et al.* (1950) have had similar results in silicotic guinea-pigs and Dubos (1949) in mice suffering from avitaminosis. These results are noteworthy, but, as Hauduroy and Rosset (1951) themselves point out, the production of progressive disease in hamsters does not necessarily imply that B.C.G. is dangerous for man.

There is still no report of any case of progressive tuberculosis occurring in a vaccinated human being, but Despierres *et al.* (1951) mention one case in which death may have occurred from the toxæmia produced by the massive breakdown of glands. An infant, vaccinated by scarification on the arm at birth and segregated from infection, developed extensive clavicular and cervical adenitis at the tenth week; a large quantity of sterile pus was evacuated from these regions which gave negative results on guinea-pig and rabbit inoculation; the infant became febrile and died at three

months. No autopsy is reported and, as B.C.G. was not grown from the pus, the case can only be regarded as strongly suggestive. As the global figure of forty million vaccinations must now be well passed, this does not compare unfavourably with the average of four deaths a year in this country, from vaccination against smallpox.

A case of accidental overdosage is reported by Saie and Chevé (1950). A four-day-old infant was given an injection of 50 mg. B.C.G.; though this was 1,250 times the usual intracutaneous dose, no worse harm resulted than a large local abscess and some suppuration of a regional lymph gland.

Efficacy

There is little new information concerning the efficacy of the vaccine. The two annual reports of the International Tuberculosis Campaign which is operating in forty countries have no control figures and do not attempt an evaluation. In this country the M.R.C. are still engaged in the vaccination of certain groups of school-leavers and their results will not be available for some time. Dahlström and Difs (1951), however, in an excellent study of 36,235 vaccinated Swedish conscripts and 25,239 controls showed that the tuberculosis morbidity rate was markedly lower in the vaccinated group; the ratio for primary tuberculosis was 1:7.1 and for post-primary 1:3.7. There seems little reason to change an earlier generalization that B.C.G. protects roughly four out of five.

The duration of the efficacy of vaccination, which at present can only be assessed by the length of time between vaccination and reversion, is still a subject about which there is a wide divergence of reported results; the assessment of duration by the reversion date is further complicated by the possibility of superinfection with a natural infection as the artificial resistance is waning. To expect 80 per cent. of the vaccinated still to be positive reactors five years after vaccination would seem to express the general consensus of opinion, but it is to be hoped that in a

few years the Ministry may be able to answer this problem from their returns.

Policy

Though few are still rabidly opposed to the use of B.C.G., the question as to whether it should be used wholesale or in selected groups is still being debated. In countries where the detection and segregation of all infectious cases of tuberculosis is precluded by the question of expense, personnel, and accommodation, it would seem logical to employ the method of mass vaccination of all negative reactors. This has been the policy of the International Tuberculosis Campaign, operating in war-devastated countries where tuberculosis is rife.

Mass vaccination to be practicable requires a very simplified technique and can hardly be expected to produce accurate statistical evidence. The International Tuberculosis Campaign recommends a single preliminary tuberculin test to discover reactors followed by vaccination without segregation; conversion testing is only carried out on samples of the whole. What constitutes a single preliminary test which is both safe and effective is not yet generally agreed; the International Tuberculosis Campaign has decided on a single Mantoux 5 T.U. with O.T.; Ranganathan (1951) reports that the same technique has been used on 750,000 persons in India. In this country Arblaster (1951) uses a single Jelly test. Heaf (1951) has recently devised a six-point multiple-puncture test through adrenalized pure O.T.; his report suggests that it may give nearly as good results as the Mantoux 100 T.U. without any risk of a fierce reaction.

Sergeant (1950) has had to simplify his technique even further in the difficult task of vaccinating the nomad Bled tribes of North Africa and vaccinates all apparently healthy persons without a tuberculin test before or after; Oppers (1951) adopted the same technique for the 30,000 inhabitants of the island of Timor. Though Ustvedt (1950) agrees that no harm results from the vaccination of healthy positive reactors, a deterioration of the clinical picture may occur if B.C.G. is given to tuberculous patients; this is confirmed by Levi-Valensi and Miguères (1951). In the present state of our knowledge this degree of simplification would only appear to be justified in exceptional circumstances.

On the other hand, where the problem is not considered to be so pressing the more conservative line of vaccinating only those at known risk has been practised; this is the case in this country where only nurses, medical students and contacts are supposed to be given B.C.G. Why the dental student has not been included amongst those at

known risk is not clear; he would appear to be more continuously and directly exposed to droplet infection than the medical student. The diabetic might also be added with little additional strain to the existing organization; the lowered resistance to tuberculous infection produced by this condition is now generally recognized.

In such places as Minnesota, where Myers (1951) has reduced the tuberculosis mortality rate over the last 30 years from 106.1 to 13.6 by the systematic hunting down and isolation of all infectious tuberculosis, there is understandable opposition to the introduction of a measure which would rob the positive tuberculin reaction of its detective value. This policy, analogous to that of producing a tuberculin-negative herd of cattle, is excellent in theory and would be also in practice if it were universally accepted. Unfortunately, as has occurred in the island of Bornholm, the immigrant negative-reactor may find himself in a vulnerable position on entering a less perfect world outside. At the present time this attitude would appear unrealistic.

Standardization of Technique

Though the controlled use of B.C.G. greatly facilitates the collection of accurate statistics, unless a strict standard technique is followed by all vaccinators the results will be rendered invalid by the number of possible variables. The Ministry's Memo. 322/B.C.G. only sets out the general principles of vaccination and it was clear that for any reliable statistical survey some standardization would have to be set up within its framework. For this reason the following standards have been agreed throughout the Oxford region:

1. A negative reactor is defined as one who fails to show an area of induration of an average diameter of 6 mm. or over on the 2nd-4th day after a Mantoux 100 T.U. (1/100 O.T. or 1/500 P.P.D.); all segregated neonatals are assumed to be negative reactors.

2. No stronger tuberculin test should be used at any time after vaccination than was used before it.

3. Only those who have converted by the 13th week should be classified as successfully vaccinated.

4. Where possible, segregation from *known infectious* tuberculosis is carried out for six weeks before proving a reactor negative, and until conversion after vaccination.

5. All persons are followed up yearly on or about the anniversary of their vaccination and all reverts are immediately revaccinated.

If any variation from this scheme occurs it is shown in the records and is punched on the

Powers-Samas cards from which the statistics are made; such cases can be rejected in the mechanical sorting. The Mantoux 100 T.U. may be criticized as an unnecessarily high standard for a negative reactor, but as the degree of allergy produced by B.C.G. is not great, the 100 T.U. may ultimately save a lot of revaccinating of reverts; it is obviously unsound in any statistical study to use a stronger tuberculin test after vaccination than was used before.

Conversion testing is carried out at four and eight weeks, except in infants when it is delayed to six and ten weeks as they tend to convert more slowly. To attribute a conversion months later to successful vaccination is clearly unwarranted, so an arbitrary limit of 13 weeks has been fixed. Negative reactors to both tests are immediately revaccinated with double the original dose and again tested for conversion after the same intervals; so far only two cases in the region have failed all four conversion tests and in each instance an inhibitory substance to tuberculin allergy has been demonstrated in their serum. Cornbleet (1950) has shown that cases of sarcoidosis often fail to convert after B.C.G.; whether this is due to the same inhibitory factor would make an interesting piece of research.

A point of considerable importance in the Oxford Regional Scheme is that all the work by A. Q. Wells on the vole vaccine is kept on the same record form; a direct comparison between these two methods of vaccination should be possible as the work develops. As the B.C.G. scheme has only been in operation for two years, it is too soon to venture into statistics.

Segregation

There are as yet no B.C.G. hostels in this region, but every attempt is made to obtain segregation by other means; the tuberculin testing of contacts six weeks after the source of infection has been removed to a sanatorium, followed by the vaccination of all negative reactors, is one method used. Medical students are vaccinated in the pre-clinical stage and nurses as probationers; in this way conversion takes place before exposure occurs. As probationers rarely come from tuberculous homes, they have not usually been in contact with known infectious tuberculosis during the six weeks before joining, so testing and vaccination may be begun at once; this means that they are given their conversion test in the fifth week of training and may go on the wards immediately afterwards.

The existing staffs of hospitals present a greater problem, but where tuberculous cases are isolated in special wards a preliminary tuberculin survey will produce enough positive reactors to staff

these wards for three months; meanwhile the negative reactors are segregated for six weeks, retested, and vaccinated. On conversion they take up all duties as before.

In sanatoria, where segregation of the existing staff is impossible, it is thought better to vaccinate without segregation than not to vaccinate at all. To vaccinate without prior segregation is to risk vaccinating in the pre-allergic phase of a natural infection; Bøe (1949) and Ustvedt (1950) have shown that this does no harm but may produce an accelerated reaction—that is a somewhat fierce local reaction which attains its height in 1-3 weeks instead of the usual 4-6; it is a modified form of the Koch reaction. To fail to segregate between vaccination and conversion is to risk infection before the vaccination has become effective; as there appears to be no negative phase after B.C.G. (Ustvedt, 1950), this does no harm. But in either instance a natural infection may develop into tuberculous disease shortly after vaccination, and the apparent cause and effect to the lay mind may bring unmerited discredit on the vaccine.

Segregation is frequently a difficult problem to surmount, but it appears to be an important factor for the efficacy of the vaccination; Dahlström and Difs (1951) found there was no statistically significant difference between the incidence of tuberculosis in vaccinated and controls when infection occurred during the segregation period.

Variations in the Vaccine

No B.C.G. vaccine is as yet made in this country and we depend on supplies of fresh vaccine from Copenhagen and on freeze-dried vaccine from Paris. Houghton and Horne (1950) report that the clinical picture produced by these two is slightly different; the Danish produces some local breakdown in three-quarters of the vaccinated and a high conversion rate at four weeks, while the French produces a milder local reaction but conversion takes longer. Though this may be due to the one being fresh and the other dried, van Deinsen *et al.* (1950) have shown that there is a morphological difference between the two organisms. The French strain, grown according to Calmette's original instructions, has not varied throughout the thirty years of its existence and the average bacillus measures 3μ in length. The Danish, maintained in Sauton's medium, measures only 2μ ; the ultra-microscope has shown it to be proportionately diminished in its other two dimensions also. As the dose of the vaccine is based on the wet weight of the bacillary mass, it follows that a given dose of the Danish vaccine might contain over three times as many organisms as the same dose of the French.

Further instances of variations in the vaccine

are reported. The Danes have for some time been troubled with alterations in the antigenicity of their strain; Rochat (1950) complains that in 1949 they increased the strength of their vaccine without warning from 0.25 to 0.75 mg./ml. and caused a sudden inexplicable increase in the severity of his vaccination reactions. Dubos (1949) has shown that the grinding of the bacillary mass to produce a uniform suspension may result in the destruction of the great majority of the living organisms. Birkhaug (1951) reports that there is a loss of viability during the freeze-drying of his vaccine, but that no deterioration occurs during storage; van Deinse and Sénéchal (1950) report no loss during the freeze-drying of the French vaccine, but a steady deterioration during storage.

All this does not simplify a study which is already sufficiently complicated by variables.

Complications

The introduction of B.C.G. into the human body results in a pathological process of a benign nature which regresses when it has reached a certain point. By using a radio-active isotope and following the spread with a Geiger-Müller chamber, Ström (1950) showed that about half the organisms had reached the regional lymph glands within ten minutes of vaccination; a blood-stream dissemination of a number of the bacilli also takes place. A pathological process is then set up at the site of vaccination, in the regional glands, and possibly elsewhere.

The local reaction after intracutaneous vaccination takes the form of a 5-10 mm. papule which makes its appearance about the second week and increases up to the 4th-6th week; after this it slowly regresses. In the majority of cases the fresh Danish vaccine produces some skin breakdown in the centre of the papule at the height of the reaction; this may take the form of a vesicle which dries off to a crust, or, in severer reactions, of an open ulcer. The glandular reaction is usually clinically undetectable, though enlarged glands may sometimes be palpable; the peak of this reaction appears to be later, usually about the third month.

There should be no general reaction. A temporary check in the weight curves of vaccinated infants is reported by Giraud *et al.* (1949) and Gyllenswärd (1949); Sacrez *et al.* (1951) found none.

This is the standard picture of what the French call 'Bécégéite'—a word which has mercifully not been translated into English; 'itis' attached to the name of a bacillus is clearly wrong, but 'Beecegeeoosis' (*cf.* Spirochetosis), though more correct, is equally horrible. Any pathology caused by B.C.G. over and above this standard picture

must be regarded as a complication. Local ulceration of over 10 mm. is unusual, but should be regarded as a severe reaction rather than a complication.

The local complication is a cold abscess. This is usually due to the vaccine having been given entirely subcutaneously, for if even a portion of the injection goes intracutaneously when breakdown occurs the pus has a free exit and a deep ulcer results. Local abscesses do not only occur in the hands of the novice; a good intracutaneous injection into the thin tough skin of a struggling infant can be an extremely difficult procedure even in the hands of the expert. They do not occur with multiple-puncture or scarification, which is a point in favour of these methods.

The glandular complication is enlargement of the regional glands to a size at which they become obvious or uncomfortable for the patient; when this occurs the glands are in danger of breaking down and producing a glandular abscess. The incidence of these abscesses varies enormously; nearly all occur in infants under 18 months of age—particularly if vaccinated in the leg. In 1,015 vaccinated newborn infants, Gaisford and Griffiths (1951) reported 47 cases of inguinal abscesses in a group (number unspecified) who were given 0.15 mg. into one leg; only three axillary abscesses occurred after the same dose in the arm. This is an unusually high incidence and was probably due to the double dose being given in the same site; Wallgren (1947), using Swedish B.C.G., reports an average of one abscess a year for the whole of Sweden.

Other complications are so rare that they are only found by a search of the world literature. Instances of transient hilar enlargement have been reported by Brun and Plauchu (1947), Fourestier and Saint-Germain (1950), Giraud *et al.* (1949), and Le Melletier *et al.* (1950); the condition regresses within a few weeks and produces no symptoms. Gaisford and Griffiths (1951) reported a more serious result of glandular enlargement; an infant developed intestinal obstruction from adhesions in a mass of pelvic glands after vaccination on the leg. Kostic-Yoksic (1951) has reported seven cases of erythema nodosum at the time of conversion which he thinks were due to B.C.G. Mimouni (1951) reported one case of multiple tuberculides with bone involvement from which B.C.G. was grown.

In the treatment of severe local reactions or complications it should always be borne in mind that the condition ultimately regresses whatever is done. Ulcers may be dressed with PAS powder or treated with ultra-violet light. Abscesses should be aspirated; Gaisford and Griffiths (1951) recom-

mend replacement of the pus with 10,000-20,000 units of streptomycin.

The Vole Vaccine

A survey of B.C.G. would be incomplete without a reference to the vole vaccine. While investigating epidemics in animals, A. Q. Wells found that the periodic outbreaks of disease in voles was due to a tubercle bacillus. On examination he found that the strain conformed to no known type; though pathogenic for the vole, it did not produce progressive disease in laboratory animals. Young and Paterson (1947) have since shown that one vole strain can produce tuberculosis in guinea-pigs.

Finding that vaccination with the vole bacillus increased the resistance of guinea-pigs to tuberculosis, Wells (1946) compared it with B.C.G.; he found that the degree of resistance produced by the vole vaccine was greater. After exhaustive experiments on its safety, he started vaccinating human beings; by the third week all his cases had converted. It is now ten years since human vaccination was begun and several thousand vaccinations have been carried out with vole vaccine. Though it is still too early to assess the exact degree of its efficacy, the preliminary reports are very encouraging.

Weight for weight, vole vaccine is about ten times as strong as B.C.G., judged by the reactions produced in man. Conversion rates of 100 per cent. are usual after multiple-puncture through 2 mg. ml. vole vaccine, while for comparable results 20 mg. ml. B.C.G. is required. The optimum intracutaneous dose is being worked out at the moment.

The advantage of the vole vaccine is that it can be maintained at a steady degree of virulence. Should any variation in the strain be observed after repeated subculture, the normal virulence can be restored at once by passage through a vole. There is no animal through which a similar passage can be made with B.C.G. and it has had to be maintained on artificial media for 44 years; the only way of correcting variations in its virulence is to alter the medium in which it is grown. The disadvantage of the vole vaccine is that it grows poorly on any artificial medium and the production of sufficient vaccine for large-scale vaccination is at the moment difficult.

The Future

Up to the present the Ministry has restricted the use of B.C.G. to medical students, nurses and contacts. In some quarters pressure is already being brought to bear for an extension of these limits; in particular the vaccination of all school-leavers is being advocated. To those of us who

have seen this group leave the shelter of home life and launch into the world of industry at a period when natural resistance is low, this matter would appear to be urgent.

The authorities seem loath to take the first step from a controlled use of B.C.G. in special groups to a mass vaccination of one age-group of the general population. There are two reasons for this. First, the M.R.C. is in the process of conducting an investigation into the efficacy of B.C.G. on a section of this very age-group; their work should be completed by midsummer and, as these school-leavers will have left school by August, any general release after this cannot possibly interfere with the follow-up of either vaccinated or controls. Secondly, as Norman Smith and Heaf (1951) have pointed out, there is little justification for extending vaccination further until all nurses, medical students and contacts have been vaccinated. This would seem logical, but it is hard that even in the sphere of medicine the pace of the fastest should be set by that of the slowest. In the Oxford region, the staff of every hospital has an appointed vaccinator and nearly every chest clinic is using B.C.G.; that this and similar regions should be denied an opportunity to progress because some other regions have not yet put the Ministry scheme into operation would seem unjust.

The task of extending vaccination to school-leavers should not be underrated; though this organized section of the population is ideally suited to such a programme, at least six months' preparatory work would be necessary before launching such a scheme. Even if approval were given before this paper is published, it would be difficult to start vaccinating by the autumn. The chest physician—that ever-willing horse—cannot be expected to cope with this as well, and it is upon the school doctor that the burden must fall; this means that the M.O.H. must see that his school doctors are properly trained in vaccination, probably by a chest physician. Then the school doctor must discuss the whole problem with the school authorities and their intelligent co-operation must be obtained. Finally, as the scheme is launched, B.C.G. vaccination must be explained to the parents themselves (this is most easily done by a pamphlet such as that issued by the Oxford Regional Hospital Board, 'B.C.G. Vaccination—What it is and How it Works'), for without their co-operation and consent no vaccination can take place.

And next? The protective value of B.C.G. against tuberculous meningitis is the least challenged of its claims. For this reason the vulnerable 0-3 years age-group would appear to be indicated; vaccination of the population at birth

alone would reduce this lethal disease to a rarity. But unfortunately it is in this very age-group that most of the problems occur; conversion is slow, glandular complications are common, and the vaccination itself is no easy task.

The work of de Assis (1949) in Brazil suggests that the discredited oral route may be after all effective for infant vaccination. By adding a dose of 100 mgm. B.C.G. to an infant's feed at monthly intervals from birth to six months—a technique that he calls 'concomitant vaccination'—good conversion figures have been obtained without complications; Rosenberg (1950) also reports satisfactory results with this method and Ustvedt (1951) is trying it in Sweden. Some years must elapse before the school-leaving programme is properly established; this time might well be spent in research into this possible simplification of the problem of the newborn infant.

And finally? Assuming, as would seem justifiable on the available evidence, that B.C.G. normally produces acquired resistance for about five years, vaccination at birth would protect the vulnerable 0-3-year-old period; the natural resistance of the 4-15-year-old child is high and in an environment sheltered: the entry of the adolescent into the world at 16 would be safeguarded by the vaccination of school-leavers. It is only after 20 that the problem will once again arise.

Mass radiography has become an acknowledged part of industrial medicine. Already in some quarters it has become linked with tuberculin testing. The completion of the picture by the mass radiography and tuberculin testing of adults together with the vaccination of all who are found to have become negative-reactors, should go far to exterminate a disease that Bunyan once called 'the captain of the men of death.'

BIBLIOGRAPHY

- ARBLASTER, P. G. (1951), *Lancet*, **ii**, 734.
 ASSIS, A. de (1949), *Dis. Chest*, **16**, 266.
 BIRKHAUG, K. (1951), *Amer. Rev. tuberc.*, **63**, 85.
 BÖE, J. (1949), *Acta tuberc. Scand.*, **23**, 123.
 BRUN, J., and PLAUCHU, M. (1947), *Rev. Tuberc.*, **2**, 361.
 CORNBLEET, T. (1950), *Arch. Dermatol. Syph.*, **62**, 697.
 DAHLSTRÖM, G., and DIFS, H. (1951), *Acta tuberc. Scand.*, **25**, suppl. 27.
 DESPIERRES, G., et al. (1951), *Rev. tuberc.*, **15**, 451.
 DUBOS, R. J. (1949), *Amer. Rev. tuberc.*, **60**, 67c.
 FOURESTIER, M., and SAINT-GERMAIN, E. DE (1950), *Rev. Tuberc.*, **14**, 868.
 GAISFORD, W., and GRIFFITHS, M. (1951), *Brit. med. J.*, **ii**, 702.
 GIRAUD, P., et al. (1949), *Pédiatrie*, **4**, 663.
 GYLLENSWARD, C. (1949), *Acta paediatr.*, **38**, 215.
 HAUDUROY, P. and ROSSET, W., (1951), *C.R. Acad. Sci.*, **232**, 445.
 HAUDUROY, P., and ROSSET, W. (1951), *Presse méd.*, **59**, 121.
 HEAF, F. (1951), *Lancet*, **ii**, 151.
 HOUGHTON, H. G. H., and HORNE, N. W. (1950), *Ibid.*, **ii**, 533.
 IRVINE, K. NEVILLE (1949), 'B.C.G. Vaccination in Theory and Practice,' Blackwell Scientific Publications, Oxford.
 KOSTIC-YOKSIC, S. A. (1951), *Arch. franc. Pédiat.*, **8**, 245.
 LE MELLETTIER, J., et al. (1950), *Rev. tuberc.*, **14**, 350.
 LEVI-VALENSI, A., and MIGUÈRES, J. (1951), *Arch. Méd. soc.*, **7**, 24.
 MIMOUNI, J. (1951), *L'Algérie méd.*, **55**, 1138.
 MYERS, J. ARTHUR (1951), *Pediatrics*, **7**, 793.
 OPPERS, V.-M. (1951), *Ann. Inst. Pasteur.*, **81**, 43.
 RANGANATHAN, K. S. (1951), *Lancet*, **ii**, 529.
 ROCHAT, P. (1950), *Gegen die Tuberk.*, **8**, 141.
 ROSEMBERG, J. (1950), *Rev. tuberc.*, **14**, 490.
 SACREZ, R., et al. (1951), *Pédiatrie*, **40**, 535.
 SAIE, J., and CHEVE, J. (1950), *Rev. tuberc.*, **14**, 315.
 SERGENT, E. (1950), *Arch. Inst. Pasteur d'Algérie*, **28**, 41.
 SMITH, N., et al. (1951), *Public Health*, **64**, 187.
 STRÖM, L. (1950), *Acta paediatr.*, **39**, 453.
 USTVEDT, H. J. (0000), 'Oral Vaccination with B.C.G.', *Medicine Dept. IX, Ullevål Hospital*.
 USTVEDT, H. J. (1951), *Bull. World Hlth. Orgn.*, **23**, 469.
 VAN DEINSE, F., et al. (1950), *Ann. Inst. Pasteur*, **78**, 596.
 VAN DEINSE, F., and SENECHAL, F. (1950), *Tubercle*, **31**, 15.
 VORWALD, A. J., et al. (1950), *Amer. Rev. Tuberc.*, **42**, 455.
 WALLGREN, A. (1947), 'Calmette-Vaccination in Sweden,' Swedish National Association against Tuberculosis, Stockholm.
 WELLS, A. Q. (1946), M.R.C. Report No. 259.
 YOUNG, J. A., and PATERSON, J. S. (1947), *Lancet*, **i**, 707.

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of *B. Proteus* to feed on tubercle bacilli. He first grew the strain on a mixture of broth and dead tubercle bacilli. By gradual reduction of the amount of broth in the mixture, he finally achieved a strain which lives entirely on tubercle bacilli. From this he has now extracted an antibiotic substance (*Protaptin*) which is enormously potent against the tubercle bacillus and has been highly successful in the treatment of infected guinea pigs. Clinical trials were about to begin last July. Not only the substance, but the method has tremendous possibilities.

As to man's pertinacity and his powers of appli-

cation, we need only mention the story of streptomycin, which was the only one of more than a thousand similar compounds investigated in great detail by Waksman which has proved useful.

For these and many other reasons we take the view that advance continues; that ingenuity is still with us as it always has been, like the golden thread of romance showing itself here and there, sometimes in the least expected quarters. We believe that, at the present moment, no line is likely to be more productive than that of the prevention and eradication of tuberculosis. We pray that in our lifetime may hold similar views on the subject of cancer.