tuberculosis in England have already been taken up in an editorial comment in the issue of the *British Medical Journal* in which his article appears. I therefore need not enter upon this subject.

Wilson does not stand alone in criticizing B.C.G. vaccination. I myself, 20 years ago, strongly censured the manner in which B.C.G. vaccination was then carried out, as well as the conclusions drawn (Wallgren, 1927); but later, when it was performed in a satisfactory way, I became a fervent supporter of the method. Levine and Sackett have expressed very strong opinions on the B.C.G. studies of other workers, but Wilson does not accept the work even of these authors, as the vaccinations were carried out without consideration of the fact that protection does not arise until the vaccine has taken. These two B.C.G. opponents had finally to admit that if they comply with that condition the mortality among the non-vaccinated infants is three times greater than that of the vaccinated infants; how many times greater then is the morbidity, of which one does not receive any information? Aronson and Palmer were rather sceptical with regard to B.C.G. when they undertook their investigation, intended to demonstrate whether B.C.G. had any effect. They learned by experience that B.C.G. satisfies even rather large demands as a protective measure. I am confident that Wilson also, if he really is willing to perform adequate investigations with B.C.G. under scientifically unimpeachable conditions, will by degrees come to be a protagonist of this method of vaccination.

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THE EFFICACY OF B.C.G. VACCINATION

BY

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Last year hundreds of thousands of young children and adolescents in war-ravaged Europe were tuberculin-tested and the non-reactors vaccinated against tuberculosis with B.C.G. This extensive campaign, which was initiated and financially sponsored by the Danish Red Cross Society, does not appear to be very well motivated if B.C.G. vaccination does not confer an increased protection against tuberculosis. According to Prof. G. S. Wilson (1947) the value of B.C.G. vaccination is rather problematic and in any case not definitely proved.

Difficulty of Procuring Control Material

The great difficulty in getting fully comparable control material is the reason why there is still debate about the efficacy of a prophylactic measure which has been in use for many years. In his famous novel *Martin Arrowsmith* Sinclair Lewis describes the difficulties met with when a scientific experiment is consistently conducted with living human beings as objects and alternate patients are taken as controls. Where mass investigations are concerned,

which require a certain amount of propaganda to induce the public to take active part, it is soon found to be impossible to treat only every other person. There will be letters to the daily press from agitated members of the community who have been refused permission to share in the new medical discovery. If it be announced that the method is still uncertain and must first be tested, the rumour arises that it is something dangerous. The result will be that only a small proportion of the public will volunteer, and hence, statistically viewed, the material will be to some extent a selected one. Nor is it possible in our modern community to inject sterile saline instead of vaccine into every alternate subject without publicly giving notice of this from the outset. Should such a measure be adopted in secret, the whole investigation would immediately become discredited when the first cases of disease appeared among those who had received only a simulated vaccination.

The difficulties enumerated here have been so great that at all centres in Scandinavia where the Calmette method has been used it has been considered necessary to abandon the statistically most trustworthy method of vaccinating alternate cases.

Primary Infection at Adult Age

How, then, has B.C.G. vaccination become so popular in Scandinavia without definite proof of its reliability? First we are convinced that pulmonary tuberculosis is nowadays very often a direct consequence of primary infection in adults (Heimbeck, 1928, 1929, 1936; Arborelius, 1930; Kristenson, 1932, 1933, 1942; Malmros and Hedvall, 1938, 1940; Törnell, 1939; Ustvedt, 1932; Frostad, 1944; S. Holm, 1947; and others). Consecutive tuberculin-testing has perhaps been used to a greater extent in Scandinavia than elsewhere, and we have been able to observe continually that previously Mantoux-negative adolescents fall ill with tuberculosis. Sometimes the primary infection produces symptoms similar to those of influenza or a "heavy cold." As a rule the radiographs then disclose a primary focus in the lung and enlarged hilus glands. In other cases it may have its onset as pleural effusion. Often, however, it initially runs an entirely symptomless course. In some of these cases, and in many of those that have had an initial fever or pleural effusion, the first radiographic lung changes that can be classed as genuine pulmonary tuberculosis appear some months later. Malmros and Hedvall showed that genuine progressive pulmonary tuberculosis often begins in these cases as small cloudy spots in the supraclavicular part of the lung or in the first intercostal space (subprimary initial foci). According to Heimbeck, Frostad, Hedvall (1946), and S. Holm, pulmonary tuberculosis can develop in some cases direct from the primary focus by progression out into the surrounding lung tissues or by liquefaction of the primary focus. The last-named has shown that no less than 34% of the cases that exhibit x-ray changes at the primary infection will later develop into genuine pulmonary tuberculosis.

Systematic tuberculin tests carried out before the onset of the disease—e.g., on probationer nurses and medical students—proved that those who were formerly tuberculin-negative were more liable to succumb. Some had relatively mild changes, others became seriously ill, and some cases were fatal. Heimbeck showed that a positive tuberculin reaction can be produced by B.C.G. vaccination, and it was a quite natural step to make an attempt to protect these tuberculin-negative adolescents by means of vaccination. Experience of the past few years seems to confirm the assumption that B.C.G. vaccination confers a certain amount of protection. Very few cases of tuberculosis have been observed among the vaccinated.

Personal Tests With B.C.G.

Since 1942 B.C.G. vaccination has been used to a great extent in Oerebro. The district covers an administrative area with about 230,000 inhabitants. Practically all the newborn are vaccinated. The whole population is successively and systematically tuberculin-tested and the non-reactors are vaccinated if they give their consent. So far, 22,413 persons have been vaccinated, 8,040 being newborn infants, 7,836 children over 1 year, and 6,537 adults. Within the district there are two tuberculosis sanatoria, one central hospital with medical and paediatric departments, and some smaller hospitals. When a case is admitted to any hospital with the diagnosis of tuberculosis or suspected tuberculosis it is ascertained whether the patient has been vaccinated with B.C.G. By this means it is possible to find out whether any of those vaccinated have developed tuberculosis. During the period 1942-7 only one such case has been discovered. This case is of special interest, and a brief report of it follows.

A probationer nurse aged 22 was B.C.G.-vaccinated before starting her hospital duties in 1943. A test one month later showed that she reacted very slightly to tuberculin (Mantoux 1 mg.). In 1944 the tuberculin reaction was checked and found to be negative; she was therefore again B.C.G. vaccinated. After this inoculation the tuberculin reaction was distinctly positive. At a control examination at the end of 1945, just before she was to begin service at a tuberculosis sanatorium, a tuberculin test did not give a definitely positive reaction. On account of shortage of staff, however, the physician allowed her to start work there in spite of her negative reaction. X-ray films showed no pulmonary changes. Two months later she was again tuberculin-tested, and was then found to be a strong reactor. Another x-ray film showed normal conditions. Some months later, however, she developed pleurisy with effusion. No tubercle bacilli could be demonstrated on culture and inoculation of pleural fluid. She is now healthy again, without x-ray changes in the lungs, and at full work. Nevertheless the case must be interpreted as tuberculosis—up to that time the only one known among 22,000 vaccinated persons. It is obvious that in this case vaccination had not given sufficient resistance, and this was doubtless due to a deficient power of reaction.

Other Scandinavian Investigations

My material is certainly large, but the observation period is as yet too short to allow of any definite conclusions regarding the efficacy of B.C.G. vaccination. Investigations from other areas in Scandinavia, however, point in the same direction. In the small Danish island of Bornholm, where, according to Olsen (1943), more than 23% of the population have been vaccinated with B.C.G., the whole situation on the tuberculosis front has altered. As is shown in Graphs 1 and 2, the number of recognized new cases of tuberculosis in the age groups between 15 and 35 years has diminished considerably since B.C.G. vaccination was instituted on a

GRAPH 1.—New cases of pulmonary tuberculosis by age groups, in Bornholm, Denmark, 1936-40.

GRAPH 2.—New cases of pulmonary tuberculosis by age groups, in Bornholm, Denmark, 1941-5; 23% of the population are now B.C.G.-vaccinated.

large scale. It is within these ages that most cases of pulmonary tuberculosis are found. If in other countries, too, an appreciable change in the morbidity curve, with the disappearance of the high peak of pulmonary tuberculosis in the years of adolescence, should be obtained in the course of some ten years, this could be interpreted as a rather tangible manifestation of the efficacy of B.C.G. vaccination. This does not, however, amount to absolute proof, since the reduced number of cases might depend on improved hygiene, fewer bacillus-carriers, and other unknown factors.

An Epidemic of Tuberculosis

Tage V. Hyge (1947) has published a work that would seem to furnish the best evidence hitherto advanced for the efficacy of B.C.G. vaccination. Although it only records a number of cases of tuberculosis at a school, the whole is as clear and unmistakable as if it had been a question of a well-planned laboratory experiment on hundreds of guinea-pigs. The events were briefly as follows.

At a girls' school in Copenhagen a case of pulmonary tuberculosis was discovered among the pupils in October, 1941. This led to a careful examination of all the pupils and the educational staff. In February, 1942, this examination was repeated, with the disclosure on tuberculin tests of 200 non-reactors among the pupils. Of these, 144 volunteered for B.C.G. vaccination. At a new compulsory examination of the whole school in December, 1942, the finding was 130 spontaneously tuberculin-positive, 133 tuberculin-positive after Calmette inoculation, and 105 tuberculin-negative (mainly newly admitted pupils).

In January-February, 1943, there broke out at the school an influenza-like epidemic which closer examination showed to be due to another tuberculous infection. The infection originated from a female teacher who taught in several forms. It was found that among 94 tuberculin-negative pupils who had been exposed to infection 70 had become tuberculin-positive. Of these, 41 had radiographic lung changes, and 37 had bacilli in the gastric lavage. The disease ran a benign course among all the younger pupils. Among those of 16-18 years, however, progressive pulmonary tuberculosis developed in nine cases, this generally starting as subprimary foci of the type described by Malmros and Hedvall. In only two cases did the pulmonary tuberculosis start from a primary focus (in one of these progression did not begin until two years after the infection). In six cases pneumothorax had to be carried out. One of the patients died of pulmonary tuberculosis.

Among 106 B.C.G.-vaccinated who had been exposed to infection there were two cases of pulmonary tuberculosis, and among 105 originally tuberculin-positive there were four cases (only two of these are considered by Hyge to be connected with the infection at the school). It is accordingly clear that B.C.G. vaccination does not, any more than does a tuberculous infection previously passed through, bring absolute protection. Compared with the tuberculin-negative, however, these categories are in a substantially better position.

Hyge's investigations clearly indicate the path we must take if we are to combat tuberculosis effectively—B.C.G. vaccination of all tuberculin-negative persons.

Supposed Difficulties and Disadvantages

In his article Wilson also discussed the difficulties and disadvantages which are thought to be involved in the use of B.C.G. vaccination. I fully agree with him when he maintains that very great care has to be taken in the preparation of the vaccine and in its distribution. All B.C.G. vaccine used in Sweden during the past few years has been prepared in a single laboratory and under Dr. A. Wassén's constant supervision. The strain employed for the preparation of the Swedish B.C.G. vaccine was obtained in 1926 from the Pasteur Institute in Paris and has since been kept "active" continuously. In the course of years vaccine has been prepared for hundreds of thousands of vaccinations. In not a single case has it been possible to demonstrate that the attenuated B.C.G. strain has regained its virulence.

Nowadays we are using only the intracutaneous method of injection, which was first proposed by Wallgren (1928). If the injection is made strictly into the superficial layers of the skin large ulcers are very seldom seen. In our series small ulcerations occurred in 11.6% of adults, in 10.4% of children, but in only 2.3% of infants (see Table I).

TABLE I.—Size of Ulceration in the Various Age Groups.

Group	No. Vaccinated	Ulcerations					
		Small		Somewhat Larger*		Total	
		No.	%	No.	%	No.	%
Newborn	8,040	185	2.3	0	0	185	2.3
Children 1-15 years ..	7,836	816	10.4	126	1.6	942	12.0
Adults	6,537	756	11.6	47	0.7	803	12.3
Total	22,413	1,757	7.8	173	0.8	1,930	8.6

* Diameter more than 15 mm.

The vaccination may very well be left to nurses, who quickly learn the injection technique when they have some practice with sterile saline.

I tested Birkhaug's needle-puncture method with a vaccine twenty times stronger in a small number of cases, but the result was not satisfactory. For instance, of 282 newborn children vaccinated by Birkhaug's method, only 57% were tuberculin-positive on being tested seven to eight weeks afterwards. On the other hand 8,040 newborn babies vaccinated by Wallgren's intracutaneous method with 0.05 mg. of vaccine reacted positively in 94.3% of the cases on being tested six to seven weeks later. Moreover, Birkhaug's apparatus is difficult to sterilize. If it is used for mass vaccination there may be a risk of, for instance, hepatitis virus being transmitted from one patient to another.

As is evident from Table II, the intracutaneous method gives very satisfactory results in newborn infants and older

TABLE II.—Results of Vaccination by the Intracutaneous Method.

Group	No. Vaccinated	Tuberculin-positive 6-7 Weeks after Vaccination
Newborn ..	8,040	94.3%
Children 1-15 years vaccinated at the Central Hospital	2,061	96.8%
Adults vaccinated at the Central Hospital	2,735	93.7%
Adults and children vaccinated in Örebro City	7,475	99.1%

children, as well as in adults, a positive tuberculin reaction being obtained in over 90% in all the groups. Formerly it was thought, on the basis of theoretical speculations, that the newborn would not react so well. As experience now shows that this is not the case, there is no reason to postpone vaccination until a later period. On the contrary,

vaccination immediately after birth has five great advantages: (1) As most children are nowadays born in the lying-in wards of hospitals, this time is the very best if we want to vaccinate as many as possible. (2) There is no necessity for tuberculin-testing the children before vaccination, as all of them are undoubtedly tuberculin-negative at birth. (3) Abscesses very seldom occur in infants. I have never seen any large abscess develop after vaccination of the newborn. Such do occur, however, now and then in older children and in adults. (4) No difficulty is experienced in getting the mothers to allow their newborn babies to be B.C.G.-vaccinated. Close upon 100% consent to the procedure. There does not seem to be any risk of B.C.G. vaccination of the babies causing the mothers to be scared of all kinds of protective inoculation. On the contrary, this vaccination is free from pain and gives such slight complications—if it is properly performed—that, if anything, it is a good advertisement for all preventive medicine. (5) After B.C.G. vaccination at infantile age the subsequent tuberculin-testing can be done without risk by the Mantoux method direct with 1 mg.

That infants of tuberculous mothers must be segregated for six to eight weeks after the vaccination can scarcely be ranked as a disadvantage of the method. Every medical officer conscious of his responsibility surely considers it a self-evident duty always to remove the newborn infant from a tuberculous infectious mother quite independently of whether the child has been vaccinated or not. If the child is not vaccinated, this segregation ought to continue until the mother recovers or dies. If the infant has been vaccinated, however, possibly the mother may be allowed to have charge of her child again when the latter has become definitely tuberculin-positive after the vaccination. It is obviously of the greatest importance that the infectiousness of the mothers should be discovered in time. For this reason all prospective mothers should be controlled by miniature radiography. (This procedure has been employed for many years as routine examination of all patients admitted to the Central Hospital.)

It has been claimed that the antibody-producing mechanism is not sufficiently developed in infants and that it would therefore be better to postpone the vaccination to a later point. As this can hardly be experimentally determined in man, one must content oneself with studying the behaviour of the tuberculin reaction. As stated earlier, a positive tuberculin reaction can be produced in the newborn by vaccination with the same dose of vaccine as is used for adults. The reaction becomes positive as early as six weeks afterwards and therefore does not argue in favour of a deficient reactivity. It has not been shown earlier whether the tuberculin reaction remains positive in cases of vaccination immediately after birth as long as in those in which vaccination has been undertaken at an older age. So far as can be judged from our material, however, no difference seems to exist in this respect. The period of observation is admittedly still short, but it seems that those vaccinated immediately after birth retain their positive reaction for several years. Thus, at an investigation of 284 children five years after they had been vaccinated at birth we found 95.1% still tuberculin-positive. By way of comparison it may be mentioned that of 638 children vaccinated at the age of 4 years, 99.2% were still tuberculin-positive on being tested three years later.

What People Ought to be Vaccinated?

The B.C.G. campaign should not by any means be confined to the newborn. Wherever a non-reactor is encountered he ought to be vaccinated. As indicated in Table III, there are also numerous non-reactors in the middle-age

TABLE III.—*Tuberculin Tests in the Rural Districts of Örebro County*

Age in Years	Non-reactors	Age in Years	Non-reactors
1-5 ..	90%	30-40 ..	11%
5-10 ..	83%	40-50 ..	6%
10-15 ..	83%	50-60 ..	4%
15-20 ..	35%	60-70 ..	4%
20-25 ..	23%	>70 ..	6%
25-30 ..	16%		

groups, especially in the rural districts. The administrative area of Örebro, where these investigations have been conducted, has many big industries and good communications. It is therefore probable that the high number of non-reactors found there is not an exceptional phenomenon but one applicable to many other districts both in Sweden and in other countries. If the B.C.G. vaccination of all non-reactors should meet with organizing difficulties, it could be initially confined to the newborn and to school-children just before the age of puberty. In addition, of course, all medical students, probationer nurses, and other hospital staff ought to be vaccinated, for it has been established by numerous investigations that these fall victims to tuberculosis to a greater extent than others.

Tuberculin Control and Revaccination.—Every vaccinated person ought to be tuberculin-tested six to seven weeks after the vaccination. Should the reaction not be positive, revaccination ought to be done. Later on controls should also be undertaken now and then to see whether the tuberculin reaction is still positive, and in case of need vaccination should be repeated. Children vaccinated at birth may be conveniently controlled in the first and the last form at school. Probationer nurses and other hospital staff should be controlled before they start service at a sanatorium or other hospital ward where the risk of infection is particularly great.

Summary and Conclusions

The harmlessness of B.C.G. is established beyond doubt. If Wallgren's method is used and the vaccine in a dose of 0.05 mg. is injected strictly intracutaneously, large abscesses very seldom appear (0.8%). Small abscesses occur in about 7.8%. They heal, however, relatively soon and without giving any persistent lesions. In newborn infants abscesses occur much more rarely (2.3%) than in older children and in adults. Nor does B.C.G. vaccination involve any other unpleasant effects. Birkhaug's needle-puncture method cannot be recommended.

The newborn become tuberculin-positive after vaccination to the same extent as older children and adults, subsequently remaining positive for several years.

Of the 22,413 B.C.G.-vaccinated cases during the period 1942-7, only one developed tuberculosis—a pleuritis in a probationer nurse who was tuberculin-negative in spite of two B.C.G. vaccinations.

In other places where B.C.G. vaccination has been employed to a great extent a definite impression has been made that it gives good protection against tuberculosis, although on account of the absence of controls this cannot be regarded as proved.

In earlier investigations published conjointly with Hedvall I have shown that pulmonary tuberculosis in adolescents often develops in connexion with a recent primary infection. Several other Scandinavian investigators have arrived at a similar view. Hyge's investigation of a tuberculosis epidemic in a school would seem to have placed it beyond all doubt that B.C.G. vaccination can prevent a development of progressive pulmonary tuberculosis in the majority of cases.

B.C.G. vaccination of all newborn infants and the vaccination of non-reactors, first proposed by Heimbeck, ought for this reason to be utilized to the greatest possible extent.

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EXPOSURE TO D.D.T.

BY

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Since 1943 some millions of people must have been exposed to D.D.T. in various forms and for varying periods of time, and it would appear from common experience that poisoning from D.D.T. in its insecticidal forms is most unlikely. Individual cases of poisoning have been recorded, but the effects of any solvent or vehicle used have seldom been completely ruled out. This applies especially to the common mixture of D.D.T. in kerosene.

In July, 1946, D.D.T. residual spraying on a large scale was started in Abadan, South Iran. The solvent used was commercial kerosene, and fairly frequent chemical examinations showed that a concentration of D.D.T. ranging from 3 to 4% was being obtained. Also in use was a 2.5% solution of D.D.T. in "black oil" (a mixture of 75% gas oil and 25% fuel oil), which meant that there were three broad groups of exposed persons—the sprayers, the "black oilers," and the mixers.

The sprayers were young men of the sweeper class who were trained to apply D.D.T. in kerosene to the walls of quarters and outhouses as a residual spray. The apparatus used was a standard "Four Oaks" knapsack spraying machine with a fine nozzle. The sprayers were organized in gangs, each gang being responsible for the spraying of a given housing area once every two months. The exposure was twofold—by the skin and by inhalation.

The "black oilers" were trained searchers for mosquito larvae. They carried a 1-litre can full of 2.5% solution of D.D.T. in gas-oil-fuel-oil mixture, and when they found mosquito larvae they sprinkled this solution on the breeding-place and reported it on returning to the office at night. The exposure was by the skin only.

The mixers prepared both solutions in a yard. The first step was to prepare a sludge of D.D.T. by crushing the powder in solvent in a 4-gallon (18-litre) tin and transferring the sludge to a 30-gallon (136-litre) drum of solvent. Difficulty in obtaining rapid solution was experienced, especially in the winter, which accounts for the fluctuation in the final concentrations obtained. The exposure in this case was by the skin only.

After nine months of this fairly continuous exposure it was felt that an opportunity presented itself of attempting to assess the occurrence of any deterioration in health. Accordingly, those who had been exposed to D.D.T., numbering 32 in all, were clinically examined and the results recorded on a standard card. A control group of 36 sanitary workers were examined by the same means. The sanitary