MASS B.C.G. VACCINATION IN MALTA

REPORT ON THE B.C.G. VACCINATION CAMPAIGN

HELD BY I.T.C.* in MALTA IN 1950

BY

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Between March and June 1950, a Norwegian medical team, together with four Maltese medical teams (which the Norwegians trained), carried out a survey of the tuberculin reaction of the section of the population of Malta aged 1-18 years, and vaccinated with B.C.G. the "negative" reactors. The campaign, the first of its kind in Malta, was held on an entirely voluntary basis, and was carried out under the auspices of the I.T.C. under the direction of Dr. A. Weidemann, of Norway, and myself. The tuberculin and B.C.G. vaccine used were prepared at the State Serum Institute in Copenhagen; while the costs were borne mainly by the I.T.C. but in part also by the Government of Malta.

Altogether 48,319 children and youths aged 1-18 years came for testing. The result of 42,986 of these tests is known, while 36,320 were vaccinated with B.C.G.

Of 6,009 persons over 18 years who were tuberculin-tested, 2,361 were vaccinated during the campaign. This report also includes the results obtained in this group.

Reasons for the Campaign

The situation in Malta in respect of tuberculosis can be studied from Table I, which is taken from the 1949 Annual Report of the Chief Government Medical Officer, Malta.

TABLE I.—Deaths from Pulmonary Tuberculosis in Malta and Gozo

Year	Estimated Population at End of Year	Cases Notified	Case Rate per 1,000 Population	No. of Deaths	Death Rate per 1,000 Population
1939	269,912	189	0.70	118	0.43
1940	270,755	232	0.86	139	0.51
1941	271,359	294	1.08	178	0.65
1942	269,090	415	1.54	227	0.84
1943	272,121	314	1.15	192	0.70
1944	279,187	261	1.00	146	0.52
1945	286,596	236	0.82	134	0.49
1946	295,247	273	0.92	133	0.48
1947	303,998	220	0.72	161	0.52
1948	304,991*	202	0.66	104	0.34
1949	310,985*	228	0.73	97	0.31

*Mid-year population.

It will be seen that the number of deaths from pulmonary tuberculosis in 1949 was only 97, which gives a rate of 31 per 100,000. As the death rate from other forms of tuberculosis was 12 per 100,000, the total tuberculosis death rate for 1949 was thus 43 per 100,000. It will be agreed that, statistically at least, there was no cause for undue alarm.

*The International Tuberculosis Campaign (I.T.C.) is a joint international effort of: (1) The United Nations International Children's Emergency Fund (Unicef), which furnishes most of the supplies and equipment. (2) The Danish Red Cross, Swedish Red Cross, and Norwegian Relief for Europe, which provide specially trained physicians and nurses. (3) The World Health Organization (W.H.O.), which sets standards, provides technical advice and assistance, and evaluates the results. (4) The Ministry of Health of the country in which a campaign is being conducted, which provides local supplies, facilities, and medical teams.

Other factors, however, had to be taken into consideration. The 1939-45 war brought about the destruction of a considerable proportion of Malta's habitable dwellings, and the ensuing housing shortage resulted in severe overcrowding in the homes, very large families often being segregated together in small houses of one to three rooms.

Material collected by the tuberculosis home visiting service during 1949 showed that the average tuberculous family consisted of 5.7 persons housed in 2.5 rooms; and that 69% of the patients shared their bedrooms with one to three members of the household, while 17% shared their bed with another member of the family. Of the new cases of pulmonary tuberculosis, 52% preferred domiciliary to hospital treatment.

Finally, the severity of the cases of primary intra-thoracic tuberculosis detected in children attending the contacts' clinic could be attributed to the persistent and intimate contact of these children with open cases in a very restricted environment.

All the conditions favouring the spread of the disease certainly existed, and called for the immediate adoption of effective preventive measures. It was recognized that mass B.C.G. vaccination alone would not, indeed could not, solve the whole problem. It was felt, however, that immunization against tuberculosis was the most practical and the speediest weapon with which to combat the conditions created by war. A mass B.C.G. vaccination campaign could allow the nation to tide over the critical period while long-term measures were being developed.

Practical Procedure

An education programme was carried out on the lines of the following principles. Ways and means of public information were devised which most suited local conditions; which gave a true and full picture of the relevant medical facts concerning B.C.G. vaccination; which did not create a nation-wide tuberculophobia, but allowed the people to see the tuberculosis problem in its real perspective; which could reach most of the people most effectively; and which were so spaced and repeated as to keep the interest of the population in B.C.G. vaccination alive throughout the whole campaign.

The island was divided into 42 districts, and each team covered from six to eight of these districts. Each team consisted of one vaccinator, two nurses, and a clerk, and worked in one district for a week. With the co-operation of the education authorities very suitable premises were found in the Government school of each district.

Pre-vaccination Tuberculin Test

For the pre-vaccination tuberculin test the adrenaline-Pirquet (A-P) technique was adopted, mainly because the "Mantoux" necessitated more attendances and the Moro patch test could not be relied upon to give definite and easily interpreted results.

Old tuberculin, of a strength 1.7 times that of the international standard and to which 0.5% phenol had been added during preparation, was used for testing. To each millilitre one drop of 1% adrenaline was added, and every week the adrenaline-tuberculin solution was renewed.

The test is made as follows. The prepared skin of the flexor side of the left forearm is stretched and with a scarificator two scratches 0.5 cm. long and 2-3 cm. apart are made through the epidermis, but preferably neither deep enough to produce prompt bleeding nor too superficial. Adrenaline-tuberculin is rubbed into the two scratches by means of a glass rod, and the arm is kept

uncovered for 5 minutes, after which any tuberculin remaining can be wiped off.

The test is read after 72 hours, the infiltration being measured across the scratches at the point where the reaction is strongest. The higher of the two figures is recorded and any vesicular reaction or lymphangitis present noted. The reaction is considered "positive" when the infiltration definitely measures 3 mm. or more.

Complications of the Test

In the "positive" reaction the induration varied from 3 to 22 mm., though most reactions were from 4 to 9 mm. in size.

Vesiculation occurred in 97 individuals, whose ages ranged from 1 to 18 years and whose reaction measurements ranged from 5 to 12 mm.

Lymphangitis was reported in 102 individuals, whose ages varied from 4 to 18 years and whose reaction measurements ranged from 5 to 17 mm.

Secondary infections with pyogenic micro-organisms were found in 27 cases.

Dispersed local reaction was found in 15 cases. During testing the tuberculin solution had accidentally soiled the rolled-up shirt-sleeve, which, acting in the manner of a percutaneous test, produced this "positive" reaction.

Febrile Reaction.—Five children between 6 and 15 years old complained of a mild fever (99–101° F.—37.2 to 38.3° C.) for one to three days after the test. Three of these had a "clear" chest skiagram, while calcifying hilar nodes were noted in two, one having in addition a calcified spot (Ghon) in the right lower zone.

Erythema Nodosum.—A girl aged 5 years, giving a 13-mm. "positive" tuberculin reaction, developed a nodular eruption three days after the test. Her chest skiagram showed an adenitis in the left hilum with collapse of the left upper lobe. On contact investigation her father was found to be suffering from open pulmonary tuberculosis.

Erythema Multiforme.—The following typical case was confirmed by a skin specialist. It is natural to ask whether the tuberculin test might have precipitated the eruption, especially in view of the known aetiological relationship of drugs, sera, etc., to this condition.

A married woman aged 37, with a healthy past and family history, was tuberculin-tested on May 3, 1950, on the volar aspect of the left forearm. That same evening she developed an intense itching and redness on the dorsal aspect of the left hand. She applied some balsam locally and bandaged her hand. Next day she developed a rash affecting her forehead, face, and neck as well as her forearms and legs. The eruption came out all at once and in no definable order. No itching was complained of.

On examination her temperature was 99° F. (37.2° C.), pulse 78, and respirations 18. No abnormality was detected on examination of the lungs, heart, abdomen, and central nervous system. The urine contained no abnormal elements. A blood count showed: red cells, 5,000,000; haemoglobin, 14.2 g.; colour index, 0.9; white cells, 19,000 (polymorphs 78%, lymphocytes 22%). A skiagram of the chest revealed calcified foci in the left lung; no evidence of any

active lesion. The Wassermann reaction was negative. The rash consisted of large discrete raised papulo-vesicles, circular or oval in shape. Each of these was set on a more diffuse erythematous base and exhibited a central depression and centrifugal radiations. The rash was bilateral and roughly symmetrical, and on the whole was confined to exposed parts. All the mucous membranes accessible to inspection were healthy. The local reaction to the tuberculin test appeared in every way a normal one. There was no evidence of vesiculation, lymphangitis, or secondary infection.

Results

Roughly 85% of the results read were "negative," while the incidence of infection in the first 15 years of life was practically identical in the two sexes (Table II). In the last three age groups (16 to 18 years), however, there was a

TABLE II.—Results of Tuberculin-testing

Age in Years	Year of Birth	No. Tested	No. Read	Results Known	Positive Reactors	Negative Reactors
Males						
1	1949	818	119	699	13 (1.8%)	686 (98.2%)
2	1948	1,590	239	1,351	28 (2.1%)	1,323 (97.9%)
3	1947	1,785	232	1,553	52 (3.4%)	1,501 (96.6%)
4	1946	1,731	216	1,515	75 (4.9%)	1,440 (95.1%)
5	1945	1,861	222	1,639	78 (4.7%)	1,561 (95.3%)
6	1944	1,777	201	1,576	100 (6.4%)	1,476 (93.6%)
7	1943	1,293	139	1,154	94 (8.2%)	1,060 (91.8%)
8	1942	1,094	116	978	111 (11.4%)	867 (88.6%)
9	1941	1,172	126	1,046	155 (14.8%)	891 (85.2%)
10	1940	1,450	148	1,302	209 (16.1%)	1,093 (83.9%)
11	1939	1,487	156	1,331	272 (20.5%)	1,059 (79.5%)
12	1938	1,668	179	1,489	355 (23.8%)	1,134 (76.2%)
13	1937	1,501	156	1,345	315 (23.5%)	1,030 (76.5%)
14	1936	1,458	187	1,271	360 (28.4%)	911 (71.6%)
15	1935	1,020	132	888	262 (29.5%)	626 (70.5%)
16	1934	770	104	666	242 (36.4%)	424 (63.6%)
17	1933	645	108	537	207 (38.5%)	330 (61.5%)
18	1932	532	78	454	200 (44.1%)	254 (55.9%)
		23,652	2,858	20,794	3,128 (15.1%)	17,666 (84.9%)
Females						
1	1949	782	112	670	11 (1.5%)	659 (98.5%)
2	1948	1,571	213	1,358	42 (3.1%)	1,316 (96.9%)
3	1947	1,728	203	1,525	38 (2.5%)	1,487 (97.5%)
4	1946	1,723	179	1,544	58 (3.7%)	1,486 (96.3%)
5	1945	1,762	179	1,583	101 (6.4%)	1,482 (93.6%)
6	1944	1,803	179	1,624	109 (6.7%)	1,515 (93.3%)
7	1943	1,325	147	1,178	114 (9.6%)	1,064 (90.4%)
8	1942	1,122	107	1,015	97 (9.5%)	918 (90.5%)
9	1941	1,171	116	1,055	130 (12.4%)	925 (87.6%)
10	1940	1,580	139	1,441	223 (15.5%)	1,218 (84.5%)
11	1939	1,559	132	1,427	263 (18.5%)	1,164 (81.5%)
12	1938	1,620	140	1,480	288 (19.5%)	1,192 (80.5%)
13	1937	1,490	126	1,364	324 (23.7%)	1,040 (76.3%)
14	1936	1,432	140	1,292	351 (27.2%)	941 (72.8%)
15	1935	1,099	96	1,003	289 (28.8%)	714 (71.2%)
16	1934	1,092	99	993	304 (30.6%)	689 (69.4%)
17	1933	959	82	877	292 (33.3%)	585 (66.7%)
18	1932	849	86	763	292 (38.3%)	471 (61.7%)
		24,667	2,475	22,192	3,326 (15.0%)	18,866 (85.0%)

steady tendency for the proportion of "positive" male reactors to exceed the female one. This tendency continued in the groups aged 19 to 20 years (years of birth, 1931–30), as may be seen from Table III. (This table deals with 5,933 cases, 76 of the 6,009 being unavailable for analysis.)

It is probable that these differences are a reflection of the fact that Maltese lads aged 16 to 20 are more likely than

TABLE III.—Result of Tuberculin-testing 5,933 Persons Over 18 Years Old

Year of Birth	Males			Females		
	Tested	Positive	Negative	Tested	Positive	Negative
1931	209	102 (48.8%)	107 (51.2%)	392	154 (39.3%)	238 (60.7%)
1930	154	80 (51.9%)	74 (48.1%)	366	168 (45.9%)	198 (54.1%)
1929/25	536	362 (67.5%)	174 (32.5%)	1,234	626 (50.7%)	608 (49.3%)
1924/20	341	271 (79.4%)	70 (20.6%)	931	522 (56.1%)	409 (43.9%)
1919/15	190	156 (82.1%)	34 (17.9%)	534	335 (62.7%)	199 (37.3%)
1914/10	153	135 (88.2%)	18 (11.8%)	432	290 (67.1%)	142 (32.9%)
1909/05	86	78 (90.6%)	8 (9.4%)	217	153 (70.5%)	64 (29.5%)
1904/00	49	43 (87.7%)	6 (12.3%)	109	78 (71.5%)	31 (28.5%)
Total ..	1,718	1,227 (71.4%)	491 (28.6%)	4,215	2,326 (55.2%)	1,889 (44.8%)

girls of that age to have left the relatively sheltered life of their homes and to be engaged in occupations entailing a wider contact with the community.

Some of those infected with tubercle bacilli eventually develop tuberculosis, and, since more cases of phthisis had been occurring among males than among females of the age group 16 to 20, one had expected that more males would also be found infected than females in this group. The results of the campaign confirmed this expectation.

On the other hand, since the incidence of phthisis was in actual fact higher in the male, one would have expected a higher male mortality in this age group, or at least in the next group (20-25). Contrary to expectation, in the period 1944-50 there were many more female deaths than male in both age groups. It seems, therefore, that at ages 16-20 more males than females are infected with tubercle bacilli and in consequence more males develop pulmonary tuberculosis, which, however, is less likely to progress to a fatal issue than in the female.

District Analysis of Results

For the purposes of this investigation the districts covered during the campaign were divided into 14 rural, 10 semi-rural, 11 suburban, and 7 urban areas (Table IV).

TABLE IV.—Results of Tuberculin-testing in Four Types of Districts

Districts	Total Population	Population Aged 1-18			Incidence of Pulm. Tub. per 1,000 Population
		No.	% Tested	% Positive Reactors	
Rural (14)	38,125	15,503	40.9	8.6	0.22
Semi-rural (10)	79,555	31,178	31.1	14.0	0.51
Suburban (11)	92,881	37,178	41.8	16.7	0.66
Urban (7)	68,550	25,201	37.1	20.0	0.61

This district analysis has shown that the incidence of tuberculous infection and of pulmonary tuberculosis is decidedly lower in the rural areas than in any other part of Malta, and that in the semi-rural, suburban, and urban areas conditions are approximately identical.

B.C.G. Vaccination

Immunization was carried out by means of Wallgren's intradermal injection technique, in preference to the scarification method of Bretey and to Rosenthal's multipuncture method, chiefly because it was felt that the method chosen was the only one that allowed the dosage to be measured with accuracy and therefore to be standardized.

The following is a description of the vaccination technique used during the present campaign. The ampoule containing the vaccine is shaken vigorously in order to ensure an even suspension of the bacilli. Then 0.1 ml. of the vaccine is aspirated in a 1-ml. syringe, and through a very small platinum-iridium needle (No. 20) it is injected intradermally into the skin overlying the left deltoid. After a correct injection a 10-mm. wheal forms, in which the hair follicles stand out prominently. The vaccine supplied by the State Serum Institute of Copenhagen contains 0.025 mg. of B.C.G., or about 1 million "B.C.G. bacilli," per 0.1 ml. The number of persons vaccinated is shown in Table V.

The Reaction to B.C.G. Vaccination

Briefly, the events following vaccination are: (1) the development of a primary focus at the site of inoculation through the multiplication of the bacilli injected; (2) lymphogenic spread of the process to the regional glands; (3) haematogenous dissemination of the bacilli to distant organs and probably their partial elimination in the urine; (4) the development of allergy after an incubation period of three to four weeks.

The local changes vary. Normally the small wheal made by the intradermal injection of the vaccine disappears within

TABLE V.—Number of Persons Vaccinated with B.C.G.

Year of Birth	Negative Reactors			B.C.G. Vaccinations		
	Males	Females	Total	Males	Females	Total
Aged 1-18:						
1949	686	659	1,345	672	650	1,322
1948	1,323	1,316	2,639	1,304	1,295	2,599
1947	1,501	1,487	2,988	1,480	1,473	2,953
1946	1,440	1,486	2,926	1,428	1,478	2,906
1945	1,561	1,482	3,043	1,555	1,470	3,025
1944	1,476	1,515	2,991	1,468	1,502	2,970
1943	1,060	1,064	2,124	1,058	1,059	2,117
1942	867	918	1,785	863	913	1,776
1941	891	925	1,816	889	922	1,811
1940	1,093	1,218	2,311	1,091	1,216	2,307
1939	1,059	1,164	2,223	1,058	1,161	2,219
1938	1,134	1,192	2,326	1,131	1,191	2,322
1937	1,030	1,040	2,070	1,026	1,039	2,065
1936	911	941	1,852	909	939	1,848
1935	626	714	1,340	625	712	1,337
1934	424	689	1,113	422	685	1,107
1933	330	585	915	329	583	912
1932	254	471	725	253	471	724
Total	17,666	18,866	36,532	17,561	18,759	36,320
Over 18:						
1931	107	238	345	107	237	344
1930	74	198	272	73	196	269
1929/25	174	608	782	172	604	776
1924/20	70	409	479	70	407	477
1919/15	34	199	233	33	197	230
1914/10	18	142	160	18	139	157
1909/05	8	64	72	8	63	71
1904/00	6	31	37	6	31	36
Total ..	491	1,889	2,380	487	1,874	2,361

10-30 minutes, and for some time thereafter nothing is seen at the site of inoculation. At the end of three to four weeks a red nodule appears, which may or may not become a small pustule or, following the discharge of the pus, a tiny ulcer. Finally after a variable interval scarring occurs.

The variations in the local reaction to vaccination are to a large extent due to variations in the natural resistance of persons vaccinated as well as to differences in dosage and technique of administration of the vaccine. In order to minimize the risk of abscess formation locally and in the draining regional glands, during the campaign great stress was laid on the importance of: shaking the ampoules to avoid clumps of bacilli, checking the dosage (0.1 ml.) during each inoculation, and avoiding subcutaneous inoculation.

Koch Phenomenon

An accelerated reaction at the site of inoculation may follow the vaccination of those already infected with tubercle bacilli. This premature abnormal reaction, known as the Koch phenomenon, is to be expected in a mass campaign, since no known tuberculin test can be relied upon to detect 100% of those already infected.

In order to check its incidence during this campaign and to ascertain the characters of the local reaction within the first week of immunization, various unselected groups of vaccinated individuals were examined quite soon after vaccination.

TABLE VI.—Results of Examination of Local Reaction to B.C.G. Vaccination

Day After B.C.G. Vacc.	Total No. of Exams.	Age Group in Years	Size of Infiltration		Size of Erythema		No. Having Pustule	No. Showing Koch Phen.
			0-8 mm.	9-12 mm.	8-10 mm.	10-20 mm.		
3rd	268	6-16	267	1	260	8*	9	1
4th	541	6-19	541	—	534	7	4	—
5th	261	6-16	260	1	256	5	1	—

* Of these, one had a 35-mm. erythema.

The presence of a pustule so soon after vaccination was puzzling. Its cause could not be determined with any certainty. It is possible that these pustules were being produced by a mild secondary infection of the site inoculated, in spite of the fact that the hypodermic needles used for the intradermal injection of the vaccine were made red-hot immediately before each vaccination.

Throughout the whole campaign 11 cases of Koch phenomenon were referred to me. The commonest finding was a darkish circular ulceration with a tendency to sloughing at the site of vaccination three to six days after inoculation. Other findings included: (1) a "positive" tuberculin reaction in the test-scratches which before vaccination had given a "negative" reaction; (2) enlargement of lymph nodes in the axilla on the side of vaccination unaccompanied by enlargement of other groups of palpable glands; (3) fever ranging from 99 to 102° F. (37.2 to 38.9° C.) accompanied by chilliness, malaise, and headache; and (4) x-ray evidence of healed or active tuberculosis. Clinical and x-ray supervision of these cases has not revealed any complication in any of them.

Ulcers and Local Abscesses

In all, 23 cases of discharging ulcer were referred to the clinic. The condition tended to appear between the 30th and 53rd days after vaccination. The ulcers were usually punched out, were between 13 and 37 mm. in diameter, and were discharging greenish purulent matter. On the whole the ulcers tended to heal rapidly, but it was difficult to ascertain the duration of the discharge because in many cases the scab formed was scratched away and the purulent secretion started all over again. In two cases fever and constitutional symptoms were noted. Oral administration of para-aminosalicylate (8 to 10 g.) to these cases brought about an improvement in the local and general conditions within two to three weeks.

Secondary infection was definitely a contributory factor in several of these cases, which healed rapidly after the local application of a sulphonamide powder thrice daily, the area being covered during the day with gauze soaked in acriflavine solution 1/1,000.

Glandular Reaction

We did not consider glandular enlargement to be a complication of B.C.G. vaccination unless it accompanied suppurative reaction at the site of vaccination, caused pain or discomfort or limitation of movement of the arm, or the adenitis showed a tendency to suppurate. Of the 54 cases referred to us for glandular enlargement in the axilla following B.C.G. vaccination, two had a secondarily infected B.C.G. ulcer, two complained of discomfort on movement, while in 21 cases the condition progressed to suppuration.

This complication occurred in 13 boys and 8 girls aged 1-6 years, and 17 of the 21 were between 2 and 3 years old. It will be seen, therefore, that it showed a marked tendency to occur in very young children. Of the 5,552 aged between 2 and 3 years 17 developed a glandular abscess after vaccination; and of 15,775 children aged 1-6 years 21 developed a suppurative adenitis.

In all the cases the local reaction to B.C.G. vaccination consisted of a small (4-7 mm.) ulcer discharging greenish purulent matter. A second tuberculin test revealed a "positive" reaction with an infiltration varying between 5 and 8 mm. The interval between vaccination and the appearance of an axillary lump varied between two and four months. The adenitis became suppurative in a further one to three months. All these glandular reactions without exception occurred on the side of vaccination. The abscess developed in the anterior axillary fold in 13 cases and in the mid-axilla in four cases. Three children had a supra-clavicular abscess and one boy an infraclavicular one. The constant rubbing of the skin by tight clothing overlying abscesses at the anterior axillary fold precipitated rupture of the abscess. Most of these children developed a secondary anaemia with mild leucocytosis during the period of suppuration. Two cases had fever and loss of appetite for a few days, but these symptoms subsided quickly after rupture of the abscess. Chest skiagrams were taken of all the cases. No abnormal intrathoracic glandular reaction was detected.

Oral administration of para-aminosalicylate, 8 g. a day, in 10 cases did not seem to affect materially the progress

of the adenitis towards suppuration. When fluctuation was noted these abscesses were aspirated through adjacent healthy skin. In some cases this was followed by a sinus formation or by re-formation of the abscess. From 2 to 10 ml. was aspirated at one sitting. The purulent matter extracted was examined and acid-fast bacilli were seen microscopically. In none of the cases was secondary infection detected. When these abscesses burst or formed a sinus, a sulphonamide powder and para-aminosalicylate were applied thrice daily and the site was protected with gauze soaked in 1/1,000 acriflavine solution. At the time of writing (10-14 months after vaccination) 12 cases have ceased to discharge and have formed a scar.

Scar

It has not been possible to give the exact number of people whose reaction to vaccination has been examined 6-10 months after the inoculation. The group, however, includes several hundreds, and in most of them a scar has formed. Its size varies from 4 to 15 mm. It is usually circular, being purplish in colour peripherally and thin and translucent at the centre. In a very small minority of those seen a scab is still present at the site of vaccination.

Post-vaccination Tuberculin Test

Very extensive experience with the vaccine had proved it capable of achieving a 98-99% conversion rate. To check the efficacy of both the vaccine and the technique of its administration, 2,421 unselected vaccinated individuals were tested. In 1,975 (98.95%) of these the result was "positive" and the size of the reaction obtained varied between 3 and 10 mm.; while in 21 persons (1.05%) aged between 1 and 17 years, of whom four were 5 years and four were 11, the results obtained were "negative" as follows: 6 with a 0-mm. reaction, 3 with an infiltration of 1 mm., and 12 with a 2-mm. reaction.

In order to gain experience in the matter of revaccination an effort was made to find and follow-up as many post-vaccination "negative" reactors as possible. Instead of revaccinating these, they were followed up with A-P tests every four weeks to see if and when conversion would eventually take place. Eight cases of this nature which were followed up for three to six months eventually did give a "positive" (3-5 mm.) reaction. It is possible, therefore, that conversion does not always occur as promptly as one would expect, and that eagerness to revaccinate too soon after a post-vaccination "negative" tuberculin reaction may be unjustified in at least some cases.

In 367 post-vaccination "positive" reactors, periodic retesting over a period of six months with the A-P technique failed to show any significant increase or decrease in the size of the reaction to the test.

Finally, 17 persons who were known to be "tuberculin-negative" six months after vaccination were subjected to the B.C.G. diagnostic test described by Ustvedt and Aanonsen (1948). With a gramophone-needle-holder two intradermal punctures were made through a drop of B.C.G. vaccine. Two to four days after the test 11 of the cases developed a local darkish reaction, which in three proceeded to ulceration. The result resembled a Koch phenomenon. In two cases a transient erythema was noted locally, but nothing else eventually developed; while in another four cases the result two to three weeks after the test was similar to that obtained after a normal B.C.G. vaccination.

It is Ustvedt's opinion that the early reaction that occurred in 11 of the cases is one denoting that the previous B.C.G. vaccination had successfully infected these individuals despite the repeatedly "negative" A-P tuberculin tests. It is quite probable that this diagnostic B.C.G. test is more sensitive and specific than the A-P test and therefore eminently suitable for application on post-vaccination "negative" reactors. In view of the limited size of this experiment the conclusion reached must be regarded only as a tentative one.

X-ray Examination of Positive Reactors.—Mass x-ray examination of "positive" reactors could not, however, be considered owing to the lack of a mass radiography apparatus in Malta. Those in charge of the tests were asked to give priority to the following: (1) young "positive" reactors aged 1-3 years; (2) members of families in which the incidence of "positive" reactions in the children suggested the presence of a source of infection in the home; and (3) "positive" reactors who complained of ill-health or suspicious symptoms.

Complications in B.C.G. Vaccination Subjects

Febile Syndromes

Considering the universal tendency to regard in the light of cause and effect every medical ailment occurring after vaccination, the number of cases of fever after B.C.G. immunization that have been referred to us are surprisingly few. In some the fever could be attributed to a severe local reaction, and these cases have already been mentioned. Others in whom the local reaction was quite normal complained of fever accompanied by malaise and decreased energy, or lack of appetite and loss of weight. These symptoms had come on one to four weeks after vaccination and lasted from a few days to a few weeks.

Systematic clinical inquiry, physical examination, diverse laboratory examinations, and chest x-ray examination were carried out in each case. Only in three or four cases could the suspicion of a specific B.C.G. effect be entertained. In these no plausible explanation for the fever could be found.

Allergic Syndromes

These include one case of erythema nodosum and 17 cases of phlyctenular conjunctivitis.

Erythema Nodosum.—A girl aged 7 was vaccinated with B.C.G. following a 0-mm. "negative" tuberculin reaction. Twenty-nine days later she developed typical erythema nodosum. One brother and two sisters had also been vaccinated. All the members of her family had a "chest clear" x-ray report. Her parents denied any family history of tuberculosis. The post-vaccination tuberculin reaction was "positive" (4 mm.). She had a clear chest x-ray film and no past history of similar rashes or of sore throat or tonsillitis, etc. Inspection of her throat did not reveal any abnormality. Throat swabs showed no haemolytic streptococci. The E.S.R. was 5 mm. in the first hour. Fever ranged from 99 to 101° F. (37.2 to 38.3° C.).

This case is interesting, and raises the question whether erythema nodosum can occur as a pure B.C.G. effect.

Phlyctenular Conjunctivitis.—I am indebted to Dr. F. Damato and Dr. V. Tabone for the following particulars.

Dr. Tabone writes: "I have seen six cases of phlyctenular conjunctivitis following B.C.G. vaccination. In most cases the conjunctivitis came on two to three weeks after vaccination; it ran the usual course, and all cases cleared up eventually on the usual treatment (mainly symptomatic). It appears that during the building of specific antituberculous immunity there can be an allergic ocular manifestation with the production of the phlyctenules."

Dr. Damato writes: "I saw 11 cases of phlyctenular conjunctivitis and keratitis in children vaccinated with B.C.G. Their ages varied between 4 and 8 years. A chest x-ray film was taken in all these cases: none showed signs of infiltration; enlargement of hilar glands was the only finding. The number of phlyctens was usually one. Subjective symptoms were rather marked; were it not for this fact the children would never have been brought for examination. All cases responded very well to treatment by sulphacetamide 30% instilled three-hourly and ung. hydrargyri oxidi flavi applied twice a day, and cod-liver oil by mouth. There was no recurrence of the ophthalmia."

As Dr. Damato pointed out to me, these cases are interesting because they constitute some evidence against an ectogenous origin of the condition and would seem to confirm

the view that the phlyctens are an allergic manifestation of tuberculous infection even when this is as mild as that produced by B.C.G. vaccination.

Vaccination in Pre-allergic Phase

A female nurse aged 23 was vaccinated with B.C.G. on March 17, 1950, after a 0-mm. "negative" tuberculin reaction. Before vaccination she had been working in an orthopaedic ward where cases of surgical tuberculosis were admitted. About March 30 she began to get easily tired, to lose her appetite, and to feel feverish. She eventually reported sick on April 20. On examination she looked tired, had a temperature of 100° F. (37.8° C.), and her chest skiagram revealed an active adenitis in the left hilum but no pulmonary lesion. She now gave a "positive" tuberculin reaction (9 mm.). She was kept in bed and x-rayed every two to four weeks, and was on a sanatorium regime. Her temperature subsided and her general condition improved. She is still under observation, and serial x-ray examinations show regression of the hilar lesion. This case is important because she appears to have been inoculated with B.C.G. while in the pre-allergic phase of the adenitis. Convalescence was rapid and uneventful, and vaccination does not seem to have affected the condition, which on the whole has been quite benign.

Tuberculous Disease

The Tuberculosis Control Section, to which all forms of tuberculosis are notified, made it a point of inquiring, in every case notified since the campaign started, whether or not the patient had been vaccinated with B.C.G. Up to 12-15 months after the campaign none of the cases of tuberculosis that have been reported had been vaccinated with B.C.G.

Comments

Certain points connected with the investigation require further comment.

(1) **Age Limit.**—We did not include infants less than 1 year old, because their immunogenic powers are limited and many would have required revaccination, and because their very thin skin would have made intradermal inoculations difficult and many a local abscess would have resulted from too deep an injection of the vaccine.

(2) **Isolation.**—At its meeting in Paris on June 15, 1948, the W.H.O. Subcommittee on Tuberculin Testing and B.C.G. Vaccination recommended: "That for the mass-vaccination programme isolation of vaccinated persons was not necessary, and that segregation of open cases, even though desirable for other reasons, is considered not to be an essential measure for a mass B.C.G. vaccination programme." In view of these recommendations isolation of vaccinated contacts with open cases of tuberculosis was not carried out, though, whenever possible, infectious subjects were asked to keep away from their homes for at least a few weeks either by entering hospital for treatment or by seeking other accommodation temporarily.

(3) **Follow-up.**—Plans have been devised for the future follow-up of all the cases vaccinated. It is further proposed to hold regular campaigns of this nature. It is also intended to offer vaccination to all contacts, nurses, and medical students, and to patients suffering from diabetes mellitus. Unicef has provided us with the necessary transport and with clerical and medical equipment, and thus made possible the fulfilment of these plans.

(4) **The difficulties** we have encountered were: those arising from the need of adapting general principles and procedures to suit local customs and conditions, and those created by prejudices and fears which are the almost inevitable accompaniment of any new venture.

(5) **The impressions** we have formed are: (1) that it is possible by factual, sober propaganda to obtain that degree of public response which justifies the effort and expense involved in such a campaign; (2) that valuable information may be obtained by relating the results of the tuberculin

tests to other data collected from the clinical and administrative control of tuberculosis; (3) that the adrenaline-Pirquet test is harmless, reliable, and easily applied, and gives straightforward results; (4) that B.C.G. vaccination is harmless; it is very rarely attended by complications, and these are on the whole quite benign; (5) that if reliable information is to be obtained the follow-up of those vaccinated should be centralized both clinically and administratively.

(6) *Tuberculosis control* has benefited from the campaign in three main ways. First, it has stimulated in the public a healthy interest in tuberculosis; secondly, the age, sex, and district analyses of the results of tuberculin-testing have given us a fairly clear picture of the way tuberculous infection is affecting the community; finally, through B.C.G. vaccination we have conferred on 40% of our younger generation a degree of protection from tuberculous disease which they could not, with equal safety, have otherwise secured.

It is for the future to show us not only the duration of the immunity we have conferred but also: (1) whether in Malta, by comparing the incidence of tuberculosis before and after the present campaign, further evidence can be obtained that B.C.G. vaccination is in reality the effective preventive measure we now believe it is; and (2) whether, by comparing the incidence of tuberculosis in those vaccinated with B.C.G. and in those unvaccinated, it can be shown that B.C.G. offers efficient protection from tuberculous disease, as we now believe it does.

Summary

Between March and June, 1950, 54,328 persons in Malta were tuberculin-tested and 38,681 were vaccinated with B.C.G. The reasons for this campaign and the methods of its actuation are given.

The tuberculin-testing results are subjected to age, sex, and district analyses; while the results of vaccination, together with the local reactions seen and the complications encountered, are described.

The methods adopted for following up the campaign, such as the retesting of those vaccinated and the x-ray examination of selected groups of initially "positive" reactors, are included.

It would not have been possible to carry out this campaign but for the generosity of the I.T.C. Organization, which, in addition to sending a skilled team, supplied all the necessary equipment, tuberculin, and vaccine, and, together with the Malta Government, bore all the expenses involved. I am indebted to all who took part in the campaign and particularly to the teams so ably led by Dr. A. Weidemann, I.T.C. Chief of Mission, and his Norwegian staff. I wish to thank the Chief Government Medical Officer and his staff for their valuable administrative help; Dr. H. J. Ustvedt for his interest and advice; Miss Nordahl, of W.H.O., for her statistical work; and Miss C. Busuttill and Mr. J. R. C. Agius, of this department, for their help during the campaign and in the preparation of this paper. My thanks are also due to Professor A. C. Briffa, Chief Government Medical Officer, Malta, for permission to publish this paper.

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The Canadian National Research Council is supporting investigations for devising artificial hearts, reports the division of medical research. Three workers at the Sick Children's Hospital, Toronto, have built an artificial heart, designed to shunt the blood from the heart of a child suffering from congenital heart disease while the surgeon is repairing the heart. In their preliminary work they have demonstrated that the instrument may safely be used in surgery. The council has made 10 other grants to medical scientists to investigate various phases of cardiac failure.

GALL-STONES: A CLINICAL SURVEY

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Gall-stones have been recognized as a clinical entity for several hundred years. Indeed, Robertson (1945), in an exhaustive review of the historical aspect, quotes a publication by Benevenius dated 1506 on gall-stones, very aptly entitled *On the Hidden Causes of Disease*. Although we have progressed some distance since those early days, gall-bladder disease still remains an unsatisfactory chapter, containing far too many loose ends.

Aetiology

Davidson (1944) discusses the aetiology of cholecystitis and cholelithiasis, and states that a considerable diversity of opinion exists about the relative significance of the various possible causative factors. Weiss (1944) suggested that there is probably a hereditary predisposition to cholelithiasis; the anamnesis frequently reveals that members of several generations show the disease or that several siblings suffer from it. The same writer also mentions the patient's mode of life (sedentary habits), tight garments (corsets and belts constricting the abdomen and checking the flow of bile), infectious diseases (typhoid, pneumonia), dietary indiscretions, and pregnancy—the well-known so-called predisposing factors. As an explanation Weiss suggested that there may be a hereditary disturbance of cholesterol metabolism in the gall-stone patient, but Davidson in the same year stated that there is no proof of any general metabolic defect in cholesterol metabolism, but suggested that some other factor, such as infection, is needed to bring about the precipitation of cholesterol or pigments in the form of gall-stones. It seems to be more generally agreed that a sedentary life and an unbalanced diet play an essential part. Commenting on the well-recognized high incidence of gall-stones in the middle-aged and elderly, Davidson suggests that failing function and decreased efficiency in certain essential functions of the liver and gall-bladder are also probable factors.

But more recent work on steroid metabolism tends to support the views of Weiss, that a fundamental disturbance in cholesterol metabolism may be the principal factor in gall-stone production. Hitherto unknown disturbances of steroid metabolism have recently been recognized in another quite distinct disorder, and may well prove to be of great significance in its aetiology: we refer to rheumatoid arthritis. Sommerville *et al.* (1950) demonstrated that rheumatoid arthritics of both sexes excrete an unusually high proportion of intramuscularly injected progesterone in the urine as pregnanediol, a finding supported later by Copeman *et al.* (1950).

Cholesterol is a constituent of every cell in the body; like progesterone it is a steroid, although little is known about its site of origin, function, or metabolism (Davidson, 1944). It is well known that large amounts of cholesterol are present in most gall-stones, and that the highest concentration of the steroid is to be found in the suprarenal glands. There is a known association between pregnancy and cholelithiasis (Weiss, 1944), and we also know that the sex incidence and age incidence of this disease run closely parallel with those of rheumatoid arthritis, in which abnormal steroid metabolism is known to occur. It is not, perhaps, stretching imagination too far if we press the analogy between the two diseases and suggest that abnormal steroid metabolism may be the basic factor in the lithogenous process. A virtue of this