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ADDENDUM.—Since this essay was written cases of tuberculous mesenteric adenitis have been encountered with undiminished frequency, and another case of tuberculous rheumatism has been seen. The main problem encountered has been the diagnosis of cases in which the clinical picture is typical, the tuberculin test is positive, no other tuberculous lesion can be found, but no calcification is seen on x-ray examination. In these cases the diagnosis is vague, being arrived at by exclusion and therapeutic test. The use of radioactive calcium for tracing the process of calcification in the glands might be of value. Unfortunately no suitable isotope has yet been discovered.

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A COMPARISON OF VACCINATION WITH VOLE BACILLUS AND B.C.G. VACCINES

BY

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B.C.G. vaccine was first used as a measure to prevent tuberculosis in human subjects in 1922. While, so far, there is no direct evidence that B.C.G. vaccination does in fact protect against tuberculosis, the experience gained in many countries, such as Denmark, goes far to support such a contention, and the vast majority of tuberculosis physicians throughout the world advocate the extension of anti-tuberculosis vaccination, believing that if it was adopted on a wide scale it would quickly reduce the number of new cases. A murine form of acid-fast bacillus found in voles was described in 1937 by Wells (1946), and from this organism he prepared a vaccine which he showed produced tuberculin conversions and acted in a manner very similar to B.C.G.

The course of vaccination with B.C.G. has been fully described; it is usually uneventful and produces little or no discomfort. However, there appear to be good reasons for carrying out investigations into new forms of vaccination. B.C.G. vaccine is not necessarily the ideal immunizing agent, as it is an artificial organism which might lose its potency. It would be wise to have available a proved substitute, and vole vaccine might well be suitable.

Any investigation of the action of vole vaccine must be controlled by a corresponding group treated with B.C.G., and all the conditions regarding surroundings and observations must be identical.

As vaccination with either B.C.G. or vole vaccine is a harmless procedure, neither giving rise to any systemic reactions, a comparison between the two vaccines can best be made by noting the ease of administration; the conversion rates; the early local reactions; the reversion rates; and the late reactions, or the late cosmetic effects. The final comparison must obviously include a note of any subjects who subsequently develop tuberculous disease. This is a matter of a long-term observation and cannot be completed until a period of at least fifteen to twenty years has elapsed.

The present investigation, which is being carried out at the Orphan Homes of Scotland, Bridge of Weir, began in the autumn of 1951. Of the 783 children between 1 and 15 years of age resident in the homes, the 575 included in the initial series and the 130 in subsequent series were negative reactors to 100 I.T.U., using old tuberculin. Details of the preliminary tuberculin survey have already been reported (Frew *et al.*, 1953). In all the cases x-ray examination by the M.M.R. unit failed to show any chest lesions. For the principal series, in 1951, two equal groups were selected by random methods, care being taken to ensure that both groups were as nearly as possible equal in regard to sex, age, school class, and cottage. B.C.G. was given to 288 children and vole vaccine to 280.

Administration

The B.C.G. vaccine was obtained from normal supplies prepared in the State Serum Institute in Copenhagen and given in the normal manner.

The vole vaccine used was in three forms: (a) Dry, reconstituted vaccine (2 mg. dry weight per ml.), used in 1951. (b) Liquid vaccine (2 mg. dry weight per ml.), used in 1952. (c) Liquid vaccine (half-strength) (1 mg. dry weight per ml.), used in 1953.

In 1951 the under-5-year group (numbering 55) were given the vole vaccine by intradermal injection, the dosage and method being identical to those used for B.C.G. In the case of the children of 5 years and over, vaccination was carried out by multiple puncture. The apparatus used consists of a spring-loaded gun which, on release of the trigger, projects 40 needles through a predetermined distance. For the present work the needles were adjusted to penetrate a depth of 2 mm. A sterile circle of rice paper of the same diameter as the end plate of the gun was dipped into the vaccine, applied smoothly to the skin, and the punctures were made through it. Little pain was felt, many of the children stating that they felt only a dull knock, and no dressings were required.

Conversion Rates

1951 Group.—Routine tuberculin-testing was begun at the end of the second week and was continued at weekly intervals until each case was recorded as positive. In children of 5 years and over, Mantoux-testing, using 100 units old tuberculin, was used, while in children under 5

years the tuberculin jelly test was used without flourpaper. The conversion rates for the various groups are shown in Table I. Very rapid conversions were noted in the B.C.G. group, the percentage after three weeks being 93% (99% in those over 5 years of age). The conversion rate in the vole group was slower, being 66% after three weeks and 79% after four weeks. Table I shows, however, that by

TABLE I.—B.C.G./Vole Conversion Rates

	Total	Positive				
		2nd Week	3rd Week	4th Week	6th Week	8th Week
B.C.G.						
Kindergarten (1-4 yrs.)	56	18 (32%)	39 (70%)	48 (86%)	53 (95%)	55 (98%)
Primary	174	86 (49%)	171 (98%)	172 (99%)	173 (99%)	174 (100%)
Sec. and outside schools	58	48 (82%)	58 (100%)	58 (100%)	58 (100%)	58 (100%)
	288	152 (53%)	268 (93%)	278 (96.5%)	284 (98.6%)	287 (99.6%)
Vole						
Kindergarten (1-4 yrs.)	55	18 (32%)	42 (76%)	53 (96%)	54 (98%)	55 (100%)
Primary	169	27 (16%)	102 (60%)	119 (70%)	160 (94%)	167 (98.8%)
Sec. and outside schools	56	27 (48%)	40 (71%)	49 (87%)	53 (95%)	56 (100%)
	280	72 (26%)	184 (66%)	221 (79%)	267 (95%)	278 (99.3%)

the sixth week the percentages were B.C.G. 98.6% and vole 95%; and 99.6% and 99.3% at the eighth week. Further testing at 12 weeks showed that in both groups there was a final 100% conversion. It was also noted that in the under-5-year group (intradermal vole) the rate of conversion was more rapid than in the corresponding B.C.G. group, and it is interesting to note that subsequent tuberculin testings at 6, 12, and 24 months have shown that no reversions have occurred in this vole group.

1952 and 1953 Groups.—In these groups tuberculin-testing was carried out at three and six weeks, and by the latter date complete conversion had taken place (Table II).

TABLE II.—Vole Vaccine Conversion Rates

	Total	3rd Week	6th Week
1952	38	{ -5 years 42% +5 " 92% }	100%
1953	49	{ -5 " 38% +5 " 86% }	100%

Local Reactions : 1951 Series

B.C.G.—The reactions followed the usual course—macule, papule, and ulcer. On the whole they were rather more severe than expected and greater than met with in similar groups vaccinated as contacts or school-leavers. In the under-5-year group ulceration was noted in 96% and enlargement of the axillary glands in 48%. This adenitis was first noticed at five weeks, but in two cases it did not develop until the fourteenth week. In only one case did the condition progress to abscess formation. The average diameter of the ulcers noted was 4–5 mm. They were usually at their largest at approximately seven weeks, and healing occurred in from eleven to twenty weeks. In the children of 5 years and over ulceration was noted in the majority. The ulcers were on an average from 5 to 8 mm. in diameter (in nine it exceeded 8 mm.); they were at their greatest size at from five to eight weeks and healing took place in a very variable time from nine to twenty-six weeks. In five cases an axillary abscess formed between the third and ninth months, and in two cases acid-fast bacilli were demonstrated in the pus obtained from the abscesses. The presence of pus did not seem to have any adverse effect on the rate of healing or on the rate of conversion. Auto-inoculation was noted in a number of cases—usually on the skin of the arm adjacent to the vaccination.

Intradermal Vole.—The local reactions in this group were marked by their severity. Deep ulcers were noted in 100% of the cases, and all showed enlargement of the axillary glands. This adenitis was first noted at three weeks, and in all cases was present by eight weeks. Axillary abscesses occurred in 25 cases, or 45%. Several of these axillary abscesses were late in developing. Examination of the pus obtained from these glands showed acid-fast bacilli in 18 out of the 25 cases. The ulcers were 7 to 8 mm. in diameter, were deep, and reached their largest at seven to eight weeks, and, on an average, healing took place in from fourteen to twenty-eight weeks. A feature of this group was the very satisfactory healing which followed the admittedly very severe local reactions.

Multiple Puncture Vole.—In vaccination by multiple puncture no generalized reactions were noted and no child complained of pain or discomfort. The typical rosette began to develop in two to three weeks and varied greatly in size. Ulceration was noted in one case, but this was due to secondary infection following a severe blow on the vaccination site. In only three cases did an abscess develop in the axillary glands—one at a very late date—and in none of these cases was this complication accompanied by any systemic upset. Acid-fast bacilli were demonstrated in the pus obtained from the glands in all three cases. In no case was there any suggestion of auto-inoculation.

Local Reaction : 1952 and 1953 Series

The multiple-puncture vole vaccinations followed the pattern already described. The development of the rosettes was more satisfactory and the percentage of complete rosettes greater than in 1951. A 100% conversion was obtained by the sixth week.

Reversion Rates : 1951 Series

The data so far collected, relating to reversions, concerns the 1951 series only. Tuberculin-testing was carried out at six months, one year, and two years. As before, Mantoux-testing was employed in those aged 5 years and over, and the tuberculin jelly tests—without using flourpaper—in the under-5-year group. The initial Mantoux tests were carried out using 10 I.T.U. and all negative reactors were retested with 100 I.T.U.

Since the beginning of the investigation an increasing number of children have left the homes. We have made every effort to have these children followed up by the local public health departments, but unfortunately it has not been possible to carry out the periodic tuberculin-testing in all. The number of reversions reported here are a percentage of the children actually tested at the periodic surveys.

Table III shows that the percentage of reversions at six months and one year showed little difference between B.C.G. and vole groups, but by the end of the second year the

TABLE III.—Reversion Rates

	Under 5 Years				5 Years and Over			
	Vole		B.C.G.		Vole		B.C.G.	
	No. Tested	Reversions	No. Tested	Reversions	No. Tested	Reversions	No. Tested	Reversions
Start	55		56		225		232	
6 months	54	0	55	0	223	0	219	2 (0.9%)
1 year	53	0	54	1	221	4 (1.8%)	217	4 (1.8%)
2 years	50	0	45	1	200	14 (7%)	195	20 (10.3%)

percentage of reversions was higher in the B.C.G. group. Furthermore, no reversions had occurred in the intradermal vole group at the end of the second year. No case which had reverted to negative at one year was found to be tuberculin-positive at two years. It was noted at each routine tuberculin-testing that a number of cases required retesting with 100 I.T.U. The number of such cases was small at six months, larger at one year, and much greater at two

years. The number of children requiring retesting was definitely greater in the B.C.G. than in the vole group (Table IV).

TABLE IV.—Cases Requiring Retesting with 100 I.T.U.

	Vole					B.C.G.				
	No. Tested	-5	5+	Total	%	No. Tested	-5	5+	Total	%
6 months	277	—	12	12	4	274	1	19	20	7.3
1 year	274	3	37	40	14.6	271	1	71	72	26.6
2 years	250	4	61	65	26	240	10	86	96	40

It is too early to place much importance on these figures, but they appear to suggest a greater diminution of allergy in the B.C.G. than in the vole group.

The percentage of reversions would seem to be high. Routine retesting of a group of contacts in the County of Renfrew shows a reversion rate of 1.5% after two years and 5.2% after three years. In this connexion it should be noted that the children in the homes were all examined by the M.M.R. unit each year and that no cases of active tuberculosis were found at any of these visits. They therefore did not receive the minimal doses of infection such as one would expect if they had been living outside the homes, and this fact is very possibly responsible, at least to some extent, for the high reversion rate.

Reversion Rates: 1952 Series

Routine tuberculin-testing carried out at one year confirmed these findings. The fact that further tuberculin-testing with 100 I.T.U. was required in 26.5% of the B.C.G. group as against only 5.1% of the vole group again suggests that the allergy produced by the vole vaccine is more permanent, or at least stronger, than that resulting from vaccination with B.C.G.

Late Cosmetic Results: 1951 Series

The late results of the B.C.G. vaccinations were those normally observed, and no ugly or objectionable scarring was noted. It was particularly pleasing to note the excellent healing and absence of bad scars which followed intradermal vole vaccination in spite of the severe early reactions. In multiple-puncture vole vaccinations the routine weekly inspections showed that the individual puncture marks developed induration which became progressive and subsequently increased over a period of nearly one year. This induration was first noted in the older children during the seventh and eighth weeks, and in the younger ones during the tenth week. At the final reading of the entire series, at the end of six months, induration was noted in 62 cases (30% of those available for inspection). At the end of the first year 154 (67%) out of the 229 cases still resident in the homes were inspected, and the results of this inspection are summarized in Table V.

TABLE V.—Cosmetic Results with Vole Vaccine

	1951 Series				1952 Series	
	After 1 Year		After 2 Years		After 1 Year	
	No.	%	No.	%	No.	%
A. Complete healing, with no residual marks	50	32.5	60	44.1	4	10.5
B. Small needle pricks (size of original ones) still seen (no induration)	20	13.0	14	10.3	11	28.9
C. As for B, but individual marks a little larger	66	42.9	30	22.1	19	50.0
D. Indurated arms	8	5.2	20	14.7	2	5.3
E. Complete healing, with residual scarring	10	6.5	12	8.8	2	5.3
Total	154		136		38	
Satisfactory		95%		89.7%		95%

It was noted that complete fading had occurred in 32.5% ; almost complete fading in 13% ; while in a further 42.9% the resultant scars were slight and could not cause any

adverse criticism. In 88.4% the rosette had completely or almost completely disappeared. The 6.5% which showed scarring were not in any way unsightly, and our inspections have therefore shown that in almost 95% of the cases the late appearances of the vaccinations were satisfactory. In 5.2% of the cases, however, definite induration of the individual parts of the rosette was noted, and in 4% this was severe.

Inspection of the rosettes was repeated at the end of the second year and 136 arms were seen at this examination. The results are classified in Table V.

During the second year the proportion of arms with complete healing and no residual marks increased from 32.5% to 44.1%. Arms showing induration of the lesions rose from 5.2% to 14.7%, being slight in 4.4% but definitely unsightly in 10.3%. All these reactions were in children vaccinated by the multiple-puncture method. The term "induration" is used to describe local reactions of a lupoid character, varying from a few dry, indolent, crusted spots to a confluent, raised patch, similar in size to the area of the multiple-puncture gun. The increase in the proportion of lesions of this type between the observations made after one and two years was surprising and quite unexpected. Equally unexpected and disappointing was the fact that the appearances noted in arms showing marked induration at one year showed practically no change at the inspection at the end of two years. Several recorded at two years were seen in arms which had been regarded as healed at the end of one year and no explanation can yet be advanced to account for them. They are lupoid in appearance. While their cause is obscure we feel that trauma and possibly superinfection in the wide area of vaccination by the multiple-puncture gun are contributing factors. There has never been any suggestion of any lupoid reaction in any of the children receiving intradermal vole vaccine.

The 1952 series of vole multiple-puncture vaccinations were inspected at the end of one year, and the results were similar to those noted in the previous series. These late reactions are tabulated for comparison in Table V.

Discussion

After considerable experience with both methods we believe that multiple puncture has many advantages. There is no danger of injecting the vaccine at too deep a level, as may happen with the intradermal method in young and nervous children.

It is too early to draw firm conclusions on the results. Even though conversions take place more quickly with B.C.G. vaccine, the fact that by six to eight weeks the rates in the B.C.G. and vole are equal, and that conversions ultimately took place in 100% of our cases, indicated that the allergy produced is equally satisfactory with both vole and B.C.G. vaccines. When the reversion rates are considered there is no doubt that those relating to vole vaccine are more favourable. In our first series of cases, which have already been followed up closely for over two years, the proportion showing late lupoid reactions after multiple-puncture vole vaccine is, we consider, too high, and although the vaccine has distinct potentialities, we feel that it cannot be employed on more than an experimental basis until these difficulties have been overcome. We have noted that conversion always took place if any part of the rosette developed. We felt that satisfactory results could be obtained with half-strength liquid vaccine. The 1953 vaccinations were carried out to test this point, and so far we can report 100% conversion after six weeks.

All our 1951 cases have been followed up for over two years, and no case of tuberculous infection has yet been reported. One point which must be kept in mind is the definite loss of allergy after two years. What percentage of reversions can be expected after three, four, or five years? Any final comparison and decision regarding the merits of the vaccines must obviously await further testing of each of the three (and any other) groups over a further period of at least three to four years.

Summary

This report describes an investigation designed to compare vaccination with B.C.G. and vole bacillus vaccines, and records the preliminary results after one and two years. The B.C.G. was given in the routine intradermal manner and the vole vaccine by multiple puncture to those of 5 years and over and intradermally to those under 5 years. Vaccination by the multiple-puncture method is probably slower than by intradermal injection, but it is considered to be the method of choice and is simpler and more certain in young children.

The rate of conversion after vole vaccination is a little slower than after B.C.G., but the percentages—95% after six weeks and 100% after twelve weeks—are very satisfactory, and compare closely with those obtained with B.C.G.

We believe that vaccination with vole bacillus has certain advantages because of the milder clinical course and the smaller rate of reversions.

The periodic surveys showed that induration developed in a substantial proportion of the cases receiving vole vaccine by the multiple-puncture method, and that, later, lupoid reactions occurred in the vaccination area. These later complications were noted in 5% and 15% of the cases inspected after the first and second years. The discovery of lupoid reactions at the second yearly inspection in arms regarded as healed at the first yearly inspection was unexpected and unfortunate, and we regard the rate of these reactions to be too high to permit of the routine use of the vaccine until these difficulties have been overcome.

We are indebted to the Council of Management of the Orphan Homes of Scotland for permission to carry out the investigation; to Dr. J. S. M. Gray, County Medical Officer of Health, Renfrewshire, for help in carrying out the work; and to Professor F. R. G. Heaf, Dr. A. Q. Wells, and Dr. K. Neville Irvine for advice and assistance.

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At the North of England Education Conference held in Sheffield on January 6, Mr. L. J. BARNES, director of Social Training at Oxford University, unfurled, in the words of the *Manchester Guardian* (January 7), "the banner of professional syndicalism." "We know," Mr. Barnes said, "that health centres don't exist because in the main the doctors don't want them." There was no evidence, however, of any opposition among teachers to county colleges. If the doctors wanted health centres they would get them; educationalists did not get county colleges whether they wanted them or not. The difference lay in the different types of professional organization in the two fields. The National Health Service, Mr. Barnes said, had come into being on the basis of professional syndicalism, subject only to parliamentary control. The doctors had managed it very cleverly and ingeniously, and he believed they were right to have done so. Professional syndicalism, subject only to lay control at the top, was the traditional pattern of the British public services; in education alone there was not yet any trace of it. "That fact is a great misfortune," Mr. Barnes concluded. "We shall never get anywhere in the field of adolescent education and welfare until the teaching profession takes effective steps in the direction of professional syndicalism."

TREATMENT OF PAPILLOMA OF BLADDER WITH RADIOACTIVE COLLOIDAL GOLD AU¹⁹⁸

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Villous papillomata of the bladder are usually multiple, and the possibility of distinguishing between benign and malignant tumours is an open question, both from the urologist's point of view, depending on interpretation of cystoscopic appearances at one and successive examinations, and from the point of view of the interpretation by the pathologist of the histological findings. In a proportion of patients papillomata in other situations, such as the larynx, breast, large intestine, and rectum, undergo malignant change, and it may be that villous papilloma of the bladder could correctly be regarded as a pre-malignant condition, as suggested by Riches (1948).

Buerger (1915) suggested that changes in size and staining properties, atypical mitoses, and multinucleate cells are evidence of malignant change. These changes would probably now be called "carcinoma *in situ*," but the further changes which he has described—invasion of the basement membrane and subsequent infiltration of the connective-tissue stroma of the papilloma and the presence of epithelial cells in the bladder wall and in blood vessels—are undoubted evidence of carcinoma. In 30% of 52 cases of carcinoma of the bladder reported by Buerger the carcinoma had been preceded by a papilloma. The true proportion of such malignant changes is masked by the fact that the papillomatous nature has been lost when a large, frankly malignant tumour is first found. These facts, and the fact that clinically benign and malignant papillomata often co-exist in the same bladder, accord with the view of Willis (1953) that pathological distinction between benign and malignant papillomata may be impossible.

Methods of Treatment

The treatment of these lesions by cysto-diathermy has for many years been the method of choice, but the results of such treatment are difficult to find. It is certain, however, that a number of patients develop incurable malignant disease after many years' cystoscopy and diathermy. Others may be cured by total cystectomy, which has been advocated as the treatment of choice even in relatively early cases. Total cystectomy, however, has a mortality and a morbidity which seem a high price to pay in the early cases.

X-ray treatment is used, but involves treating the whole bladder and some of the surrounding pelvic organs to a high dose of radiation.

The use of an intravesical rubber balloon containing radioactive solutions (Walton and Sinclair, 1952) or a central solid radioactive source emitting gamma radiation (Cones and Gregory, 1952) in a suitable balloon has also been tried, but, although the dose falls off relatively rapidly from the surface of such a balloon, the dose given to the subepithelial connective tissue is likely to be 70–90% of the dose to the bladder wall, and is likely to result in undesirable vascular and connective tissue changes which may, after some years, produce atrophic or metaplastic changes in the bladder epithelium.