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.

Rationale of a New Method of Treatment

Because of these considerations, when presented with a patient suffering from haematuria due to myriads of papillomata covering the whole bladder surface, it was decided to explore the possibilities of using beta radiation to treat the papillomata. If the radioactive fluid could be used to fill the bladder without any containing balloon, the papillomata would float freely in it and be irradiated from all sides. The normal bladder wall, on the other hand, would be irradiated from only one aspect and the limited range of the beta emission would provide a very rapid fall in dose. Thus only the epithelium of the bladder would be treated and the subepithelial connective tissue would be almost unirradiated.

For such a method radioactive colloidal gold from A.E.R.E., Harwell, appeared to be the most suitable material available, since its beta emission (0.96 MeV) had a

FIG. 1.—Relation of the half-value layer to thickness of the papilloma.

his bladder. It was estimated that some 300 mc. should be given in about 100 ml. of saline, so that, taking account of the dilution by urine passing into the bladder from the ureters, the dose to the bladder wall in two to three hours would be of the order of 3,000 r.

Preliminary Tests

Dangers in using such a large amount were anticipated from two points of view: (1) The absorption into the blood or lymph of 5 or 10% of such a large dose might have undesirable consequences. (2) The retention by sticking to the bladder wall of a relatively small amount could result in huge doses (about 1,000,000 r for 1 mc. per square cm.) of radiation to the bladder epithelium. (This had been found to occur in similar work with thorium-X before artificially produced isotopes were available. Thorium-X is an alpha-particle emitter with a range of only about 10 microns, however, and only beneficial results were observed.)

It was necessary to confirm that the colloid would remain in suspension while in the bladder. The solution is supplied slightly alkaline (about pH 8 in samples tested), and it was considered that the gelatin might become unstable and the colloid precipitate in acid conditions. Alkalinization of the urine would prevent acidity in the bladder but lead to a large excretion, diluting the radioactive solution and limiting the maximum period of retention.

Actually a sample of inactive gold colloid was acidified with HCl to about pH 2 without any precipitation occurring immediately, on standing, or after incubation at 56° C. for about half an hour. Therefore 95 ml. of this inactive gold was introduced into a male patient's bladder through a catheter, which was then tied off. After two hours 340 ml. of fluid was drained off. The pH was only about 7 and no precipitation could be observed.

On the next occasion a similar volume of colloid was used with a total activity of about 400 μ c. After two and a half hours 235 ml. of fluid was drained off and the bladder washed out three times with saline, each lot of fluid being retained. Also urine was collected for the next 12 hours. The activities of these samples, determined by comparison with a standard dilution from the original colloid,

were 97%, 4.5%, 0.5%, 0.05%, and 0.05% respectively in fluid drained from the bladder, in the first, second, and third rinses, and in the urine. This total (102%) corresponded to the whole of the injected activity within the experimental accuracy. The gamma count rate over the bladder was not significantly above background, and a blood sample taken just before the bladder was drained showed no detectable activity.

Treatment

As these tests showed that the colloid was not precipitated in the bladder or absorbed, it was decided to proceed with treatment. Following cystoscopy, a Foley catheter was passed into the bladder. Three hundred mc. of radioactive colloidal gold in 100 ml. was taken into a syringe, a small sample was retained for making a standard dilution, and the rest was introduced into the bladder after the balloon of the Foley catheter had been inflated with 5 ml. of fluid. The end of the catheter was then securely tied off and the catheter fixed by strapping so that the balloon was used to close the neck of the bladder. After two and a half hours the bladder contents were drained off and the bladder washed out eight times with warm saline, by which time the washings were practically colourless.

The fluid and rinses were retained for activity measurements, and urine was collected for 24 hours. Care was taken to avoid leakage round the catheter and spillage of the active fluids during injection, draining, and rinsing. Gamma counter measurements were also made over the patient immediately and about 24 hours after the bladder was emptied. It was estimated that very much less than 0.5% of the injected gold was retained in the bladder and no other site of activity was observed. The dose received by the bladder epithelium was estimated to be 3,000 r (2,700 rep beta dose, 300 r gamma dose).

After two months the treatment was repeated, using an ordinary catheter, and a dose of about 2,400 r was delivered to the bladder wall.

When examined cystoscopically six weeks later, no papillomata could be seen except for a ring of small nodules around the internal urethral meatus where the contact of the Foley bag had protected them from the beta radiation. It was decided to treat these locally with radioactive cobalt so arranged in a Foley balloon at the neck of the bladder as to give a dose of 3,000 r, using a source-epithelium distance of 1 cm.

The patient is now well and symptom-free, and at his last cystoscopy, 15 months after the last treatment, his bladder wall was normal in appearance throughout. No other treatment has been given. The case summary is given below.

A man aged 67 was referred on September 8, 1952, by Mr. Till. He had had three weeks' haematuria in June, 1952, and occasionally since, and dysuria and nocturnal frequency since June, 1952: now D/N=3-hourly/2-hourly. Cystoscopy on August 29 had shown that the bladder was covered with villous papillomata, the main mass of growth being above the right ureteric orifice and around the left ureteric orifice.

October 10.—Biopsy: transitional-cell papilloma. Injection of non-radioactive colloidal gold into the bladder for two hours to test for possible precipitation. Blood: Hb, 81%, white blood cells, 5,000 per c.mm.

October 14.—110 ml. slightly active colloidal gold for two hours to ensure that no residual radioactivity remained after washing out the bladder.

October 18.—Radioactive colloidal gold, 377 mc. in 105 ml. for three hours. Total dose to surface, 3,000 r.

January 9, 1953.—Cystoscopy. Two papillomata: (A) above right ureteric orifice; (B) medial to left ureteric orifice; (C) fronds at bladder neck. Suggested diathermy of (A) and (B). Radium in Foley catheter to (C) and another treatment with colloidal gold.

January 27.—Coagulation of (A) and (B) (Mr. A. S. Till). Second injection of radioactive colloidal gold, 274 mc. in 100 ml. for three hours. Total dose to surface, 2,950 r.

April 14.—Radioactive cobalt in Foley catheter to treat neck of bladder, 3,000 r in 5 hours 20 minutes. Blood urea, 27 mg. per 100 ml.

June 16.—Cystoscopy. Redness of bladder wall. No neoplasm.

December 1.—Cystoscopy. Normal bladder mucosa. Symptom-free except for nocturnal frequency. The patient says this is a habit—he empties his bladder whenever he wakes up. Blood: Hb, 96%; white blood cells, 5,100 per c.mm.

April 20, 1954.—Symptom-free. Cystoscopy: normal bladder.

Suggested Routine

As a result of this treatment, experience has now been gained which makes it possible to recommend the following routine procedure in centres where the drill for the handling of isotopes is established.

1. It is necessary to get the permission of the Medical Research Council to use the method.

2. After cystoscopic examination the plan of treatment of the case is decided, bearing in mind the morbid anatomy and pathology and the possible effects of the various surgical and radiotherapeutic steps in treating and possibly spreading the growth. For instance, in a recent case with multiple large malignant papillomata the plan decided upon was 3,000 r x rays (275 kV) to the bladder, 4,000 r with radioactive cobalt in a balloon introduced via a perineal urethrotomy, diathermy of any residues six weeks later, and then gold to be used only if seedlings began to develop subsequently.

3. Having decided to use the colloidal gold method, fluid intake is forbidden on the day of treatment. An ordinary rubber catheter of a large size is introduced, the bladder emptied, and the end of the catheter double tied. In females a purse-string linen suture is passed around the catheter at the external urethral meatus and tied tightly so as to prevent any risk of leakage.

4. Using the special protective gun (see Figs. 2 and 3) which has been made to enclose a 100-ml. syringe, some 300 mc. of colloidal gold is drawn into the syringe and made up to 100 ml. with saline.

FIG. 2.—Lead-protected gun for 100-ml. syringe.

D/R in MR/min. for 300 mc. Au¹⁹⁸ in 100 ml.

FIG. 3.—Diagram of the syringe gun with 5-mm. lead protection.

5. The solution is injected, using a thin Record needle passed obliquely through the wall of the catheter.

6. Two samples of about 2 ml., one taken at the start and one at the end of the injection, are retained as standards for measurement of the activities of the fluid drained from the bladder and washes.

7. The patient is returned to the ward and put to bed. If he is active the solution mixes well with the urine passing into the bladder, but if he is sleepy following an anaesthetic it is necessary to move him about, tilting the bed and turning him on to his side so as to ensure mixing. This has been done because in one patient, who was asleep and stationary until the bladder was emptied, the bladder contents showed definite lack of mixing.

8. At the appropriate time (two and a half hours to three hours, determined as being likely with the dose used and the expected dilution to have given a dose of 3,000 r), with suitable precautions, the contents of the bladder are run off into a glass jar, and the bladder is washed out five or six times with warm saline into a succession of glass jars until the washings are free from the colour of the gold colloid.

9. The percentage of the gold in these washes is determined and the gamma-ray measurements are made over the suprapubic region with a counter, so as to determine if further washing is needed. This has not been necessary so far.

10. The urine is collected for 24 hours.

11. The dosage is estimated as described in the Appendix below.

Discussion

The points which it is required to know in connexion with any new method, apart from its rationale and technique, are: (a) if it is safe and if there are any untoward effects; (b) the type of case in which it is effective; and (c) other possible uses.

Safety

The method as detailed above has now been used on 22 occasions with no untoward effects on the patient and no suggestion of danger to staff. All patients have been sufficiently free of radioactive material and free of symptoms to leave hospital the next day.

Type of Case

(i) As previously indicated, the method was designed to treat cases of *multiple villous papillomatosis*. We have had only one such case referred. This has been described in detail above.

(ii) The method has been used also to treat the bladder in cases of papillomatosis with carcinoma. It is clear that the thickness of the tumour must determine the dose it receives, and so, when there are thick papillomata or a carcinoma, the dose received at a depth below the surface will be too small to be effective. Nevertheless, in some cases a rapid shrinkage may easily be obtained of part of a tumour, making easier a decision regarding subsequent treatment. This is illustrated by the following case summary:

A married woman aged 79 was referred by Mr. D. C. Corry on January 9, 1953. Her history was that she had the first attack of painless haematuria three years ago for two to three days and the second attack two weeks ago. She saw Dr. Wase after one week and continuously since.

January 5, 1953.—Cystoscopy. Papilliferous tumours of base of bladder obscuring both ureteric orifices. Suggested radioactive gold to clear the bladder and diminish the size of the tumour. Then Co⁶⁰ balloon.

January 20.—Radioactive colloidal gold, 289 mc. in 86 ml. for three hours. Total dose to surface, 3,050 r.

February 24.—Cystoscopy. Tumour much smaller. Ureteric orifices seen. Three papilliferous tumours seen close to right ureteric orifice.

March 10.—Co⁶⁰ in balloon. 5,500 r in ninety-three hours at 3.3 cm. distance.

May 1.—Cystoscopy. Tumours still smaller, but three papillomata still present.

August 14.—Cystoscopy. Biopsy of one lesion remaining just above right ureteric orifice. Transitional cell carcinoma—Broders's Grade 1.

August 21 to 28.—Treatment by uterine and vaginal radium to base of bladder—2,500 mg.hr. in uterus and 2,500 mg.hr. in vagina.

(iii) Treatment with radioactive colloidal gold has also been used as a method of treating the bladder to diminish the surface activity of a malignant growth three to four weeks before opening the bladder in cases in which cystostomy for implantation of radium, radon, or radioactive tantalum or for partial cystectomy was intended.

(iv) It would theoretically be possible to treat with radioactive colloidal gold the pelvis of a kidney which is the seat of papillomata. However, it is doubtful whether accurate diagnosis of such cases or adequate follow-up afterwards will ever be possible.

Summary

A technique is described for the treatment of multiple villous papillomatosis of the bladder whereby some 300 mc. of radioactive colloidal gold (Au^{198}) may be introduced per urethram so as to deliver a dose to the bladder epithelium of about 3,000 r in three hours. The recommended course is two such treatments with about two months' interval.

The procedure is safe for the patient and for the staff, if properly carried out.

It has caused complete disappearance for fifteen months of myriads of papillomata in a 67-year-old man, leaving him symptom-free.

In cases unsuitable for complete treatment by this method it may be used to bring about the disappearance of multiple small tumours and to stop haemorrhage. Accurate cystoscopic examination may thereby be rendered possible and the surface of a carcinoma devitalized preparatory to subsequent cystostomy.

APPENDIX

Estimation of Dose.—Beta Dose: The maximum range of the Au^{198} beta particles is only some 3.8 mm., so that with any layer of active fluid of thickness greater than this the dose rate at the surface will be half that in an infinite medium and will be proportional to the specific activity. From data given by Marinelli, Quimby, and Hine (1948) the dose rate at the surface for an activity of 1 mc. per ml. would be 405 rep/h.* (340 rad/h.†). The depth dose will be small, falling to 50% at 0.3–0.4 mm. depth. **Gamma Dose:** Au^{198} also emits gamma radiation of 0.41 MeV energy, and the gamma dose rate at the surface will depend on both the specific activity and the dimensions of the cavity. If the bladder is considered as a sphere of radius r cm., the dose rate is given by 15.1 r (see Mayneord, 1950). This figure is based on a dose rate of 2.4 r/h. at 1 cm. from 1 mc. The depth dose here will be greater, but will have fallen to 50% at depths of 0.75–1.5 cm. for radii of 2.5–5 cm.

Deducting the volume of the catheter itself, the initial bladder volume is taken as equal to the volume of fluid injected, and the volume of fluid drained from the bladder is measured. It is assumed that urine drains into the bladder to increase the fluid volume at a constant rate, and the initial and final beta and gamma dose rates are calculated from the corresponding specific activities and volumes. The gamma dose rate does not, of course, increase linearly with volume, but, as this contributes only 10–15% of the total, the surface dose is given with sufficient accuracy from the average beta and gamma dose rates.

A nomograph for calculating these dose rates is given in Fig. 4.

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*1 rep=83.5 ergs/g.

†1 rad=100 ergs/g.

FIG. 4.—Nomograph for calculating the surface dose rate in the bladder. Read volume on "A" and mc. on "E" to give beta D/R on "C"; then from this value on "C" and volume on "B" read gamma D/R on "D".