courses. No patient in this series received the antibiotic. The good results with nitrofurantoin confirmed the original bacteriological findings, and in view of its relative lack of toxicity suggest that it is the drug of choice. In one case the infection was cured only when nitrofurantoin was given with an antibiotic. Apart from the value of combined therapy in removing resistant organisms or delaying the emergence of resistance, such combinations would perhaps also be useful in severe pyelonephritis, since effective blood and tissue levels of nitrofurantoin cannot be attained.

The patients were not all observed for a long period following treatment, and the incidence of relapse and reinfection was not determined. In view of this and the consequent criteria accepted for cure it is recognized that perhaps little can be concluded regarding the ultimate effects of therapy. Complicated infections especially are prone to relapse, in addition to their relatively poor response to treatment. However, the object of the investigation was to correlate and compare the relative ability of various drugs in removing infecting *Proteus* strains from the urinary tract with their activity *in vitro*. The results showed that this was in the main achieved. In any case, a final cure in many instances may depend more upon the relief of complicating factors than upon antibacterial therapy alone, and, as McGeown (1956) remarked, a relapse does not detract from the therapeutic value of a drug, but merely indicates the proneness of a damaged renal tract to become infected. Richards *et al.* (1955) observed a relapse of proteus infections which had been treated with nitrofurantoin. However, the relative freedom of the drug from toxic effects and the slow emergence of resistant bacterial strains to it would fit it well for repeated administration or long-term therapy.

Summary

A series of 58 patients with a proteus infection of the urinary tract, of whom 46 (79%) had local complicating factors, were observed in order to compare the results of treatment with sensitivity tests *in vitro*.

The *Proteus* strains isolated were typed biochemically. *P. mirabilis* was the pathogenic species in 49 cases (84%), and in 27 cases (47%) there was a mixed infection with an enterococcus.

Sensitivity tests were performed *in vitro* with nitrofurantoin and 12 antibiotics. All the strains tested were sensitive to nitrofurantoin.

Nitrofurantoin, streptomycin, or a sulphonamide was given to the majority of patients, and these treatment groups were comparable. Nitrofurantoin proved superior to the other two in curing the infection.

There were occasional discrepancies in the correlation between individual sensitivity tests and therapeutic outcome.

Twenty-three patients received nitrofurantoin, and only three failures were recorded with prolonged therapy. The only toxic effect noted was vomiting in two cases.

The results indicated that nitrofurantoin was the most effective drug used, even in complicated cases and mixed infections, and that it is worthy of further trial in a larger series of cases.

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STABILITY OF H. PERTUSSIS VACCINE ESTIMATED BY MOUSE-PROTECTION TEST

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The Whooping-cough Committee of the Medical Research Council (1956) has reported an average deterioration rate of 0.2 log unit per annum for the vaccines used in its trial. This deterioration rate was determined from the results of mouse-protection tests and was not in conflict with the clinical results. In the treatment of the results the Committee regarded the deterioration as a sample value and did not quote the significance of its difference from zero. Moreover, the Committee states that its conclusions are unaltered if the deterioration rate is ignored.

TABLE I.—Results of Mouse-protection Tests on *H. pertussis* Vaccine BIV. (Survivors/Total in Group)

Date of Test	Dose of BIV		
	40 × 10 ⁶ Cells	200 × 10 ⁶ Cells	1,000 × 10 ⁶ Cells
19/3/51	5/15	9/15	14/15
10/4/51	2/15	2/15	15/15
16/4/51	2/15	5/15	11/12
8/5/51	3/15	4/14	12/15
22/5/51	4/14	9/12	9/14
29/6/51	4/18	5/19	9/10
20/7/51	0/15	7/15	13/15
16/8/51	0/15	3/15	13/15
11/9/51	1/15	6/15	10/15
2/5/52	0/14	2/15	12/15
28/5/52	1/15	4/15	10/20
6/8/52	2/18	9/17	20/20
15/9/52	1/13	1/12	11/15
23/12/52	1/19	1/20	8/18
23/2/53	0/18	2/18	14/18
8/5/53	4/16	7/16	17/20
26/2/54	8/15	10/15	13/14
5/3/54	2/14	3/16	14/16
11/3/54	1/15	2/15	10/13
23/3/54	3/14	5/14	14/15
9/4/54	7/15	11/15	13/15
27/5/54	0/13	7/11	11/15

TABLE II.—*ImD*₅₀ Values

Time in Months from January 1, 1951	<i>ImD</i> ₅₀	Time in Months from January 1, 1951	<i>ImD</i> ₅₀
3	102	19	170
3	350	20	703
4	210	24	563
4	290	26	1,900
5	110	28	180
6	230	38	51
7	240	38	310
8	400	38	490
8	410	39	220
16	510	39	45
17	870	41	200

Graph showing dose and age of vaccine, and proportion of mice surviving.

We have observed no deterioration of certain vaccines, and our finding agrees with that reported by Kendrick, Eldering, Hornbeck, and Baker (1955). In particular we have records relating to one vaccine, BIV, stored at 4° C. over a period of three years. In this paper we assess the highest rate of deterioration for this vaccine to be legitimately inferred from mouse-protection tests. The supply of BIV being now exhausted, no further tests are possible with it.

Statistical Note

In Table I are shown all the available results from 22 sets of three doses as the number of survivors out of the total in each group of mice obtained over a period of 41 months; Table II gives the ImD_{50} values. A plane was fitted to log dose, time, and probit of percentage survivors with a single cycle of weighting (Finney, 1947). The regression equation for log dose and time on probits was calculated. The ratio of the two regression coefficients was used as a measure of the rate of deterioration. Heterogeneity was found, as was expected (Ungar and Basil, 1957), and provided for. The lower fiducial limits of this ratio (Fieller, 1944) were calculated for $P=0.05$ and $P=0.01$ (single tail) and expressed as log units per annum and half-life in years. The procedure is illustrated in the graph. This is a projected graph in which the dose of vaccine, the age of the vaccine, and the proportion of mice surviving are plotted at right angles. The 66 observed values are marked as solid circles, and for each the deviation from the fitted plane is marked by a line. The plane between dose of vaccine and age of vaccine is also shown at the 50% level. The two planes, the fitted one and the one between dose and age of vaccine, intersect in a line that is the regression of the ImD_{50} dose of vaccine on the age of the vaccine. The slope of this line measures the rate of deterioration.

Results

The deterioration as determined above is not different from zero. Indeed, the sample value indicates a slight increase in activity. Its lower fiducial limit ($P=0.05$) is 0.05 log unit, or a half-life of 5.76 years. At $P=0.01$, the lower limit is 0.09 log unit, or a half-life of 3.23 years. Although, as can be seen, an appreciable deterioration may have

occurred, the limiting value found is much smaller than the one given in the Whooping-cough Committee's report.

Discussion

The reasons for the deterioration of the vaccine, as given in that report, are a matter of speculation. One could lie in the method of preparing the vaccine—namely, incomplete killing of the organisms and destruction of enzymes. It is known that certain chemicals will act as bacteriostatic or slow bactericidal agents—for example, organic mercurial compounds—without at the same time inactivating proteases. The enzymes can in the course of months affect the antigenicity of the prophylactic, particularly if it happens to have been kept at room temperature.

Another explanation of the alleged deterioration may be found in the assay method. The mice used might vary with time in their response to the antigen, unless precautions are taken to use a specially uniform strain of mice and a stable standard is available for comparison. Further, the challenge strain of *Haemophilus pertussis* used in the method may vary in virulence.

Finally, the possible effect of changes in the diet of the animals must be kept in mind.

Summary

The mouse-protection test has been used to show that *H. pertussis* vaccine stored at 4° C. does not deteriorate appreciably and that there could be a half-life of 5.76 years ($P=0.05$) or, at worst ($P=0.01$), of 3.23 years.

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BRITISH STANDARD FOR PERTUSSIS VACCINE: ITS USE IN ROUTINE CONTROL OF COMMERCIAL VACCINES

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Pertussis vaccine has been used in this country for a number of years on a fairly wide scale. Control of the vaccine for safety and potency has been carried out in the usual way through the Regulations made under the Therapeutic Substances Act and through the monograph on the vaccine in the *British Pharmacopoeia*. Up to the present time the control measures have not included any direct test for potency, and indirect methods depending upon opacity, etc., have been the only ones applied. In recent years several large-scale field trials of the protective power of pertussis vaccine have been organized by the Medical Research Council. All vaccines used in