- Kleeman, C. R., Rubini, M. E., Lamdin, E., and Epstein, F. H. (1955). *J. clin. Invest.*, **34**, 448.
 Leaf, A., and Mamby, A. R. (1952). *Ibid.*, **31**, 54, 60.
 Levinsky, N. G., Davidson, D. G., and Berliner, R. W. (1959). *Amer. J. Physiol.*, **196**, 451.
 Pearson, C. M., and Rose, A. S. (1960). In *Neuromuscular Disorders*, p. 422. Association for Research into Nervous and Mental Disorders, Baltimore.
 Roberts, H. J. (1959). *Ann. intern. Med.*, **51**, 1420.
 Schuermann, H. (1951). *Arch. Derm. Syph. (Berl.)*, **192**, 575.
 Schwartz, W. B., Bennett, W., Curelop, S., and Bartter, F. C. (1957). *Amer. J. Med.*, **23**, 529.
 — Tassel, T., and Bartter, F. C. (1960). *New Engl. J. Med.*, **262**, 743.
 Turner, P., and Williams, R. (1962). *Brit. med. J.*, **1**, 287.
 Van 't Hoff, W., and Zilva, J. F. (1961). *Clin. Sci.*, **21**, 345.
 Verney, E. B. (1946). *Lancet*, **2**, 781.
 — (1947). *Proc. roy. Soc. B.*, **135**, 25.
 Walton, J. N., and Adams, R. D. (1958). *Polymyositis*. Livingstone, Edinburgh and London.

CONTROLLED TRIAL OF A.B.O.B. IN MEASLES, CHICKEN-POX, AND MUMPS

BY

M. P. CURWEN, M.A.

Department of Medical Statistics, St. Bartholomew's Hospital, London

R. T. D. EMOND, M.B., M.R.C.P., D.T.M.&H.

Consultant Physician in Infectious Diseases, Coppetts Wood Hospital, London

AND

G. DONALD W. McKENDRICK, M.A., B.M. M.R.C.P.

Consultant Physician in Infectious Diseases, St. Ann's Hospital, London

In November, 1960, a synthetic material—N¹,N¹-anhydrobis (β-hydroxyethyl) biguanide hydrochloride (A.B.O.B.)—became available in Great Britain, marketed as "virugon." It was introduced as an antiviral agent of low toxicity, claims being made that it was effective in the treatment of a wide variety of common infections, including influenza, measles, chicken-pox, herpes zoster, and mumps.

The published reports available at that time (Sjöberg, 1960; Farquhar, 1960) were somewhat difficult to evaluate but did provide sufficient evidence to justify further investigation. In view of the imminence of a measles epidemic, it was decided by the Association of Infectious Diseases Physicians to carry out a double-blind trial to determine the value of the drug in the treatment of measles and at the same time to assess its value in the treatment of mumps, chicken-pox, and herpes zoster. However, the number of cases of herpes zoster was insufficient for analysis, and no account has been taken of this condition.

Statistical Analysis

Twelve hospitals agreed to take part. The following patients were admitted into the trial: *measles*—all uncomplicated cases admitted within 24 hours of the onset of the rash; *mumps*—all cases with salivary-gland involvement admitted within four days of onset of illness; *chicken-pox*—all cases admitted within four days of onset of illness.

The measles trial ran from January to May, 1961, and the other trials from January to December, 1961. Identical numbered boxes of tablets were made up as follows:

A.B.O.B.—The active tablet contained 400 mg. of A.B.O.B. instead of the 100 mg. in the standard "virugon" tablet and did not contain the solanaceous alkaloids.

Placebo.—Starch lactose tablet flavoured to match A.B.O.B. tablet.

The active and dummy tablets were allocated to successive patients (regardless of which disease) by means of random lists held centrally.

A.B.O.B. dosage.—Adults, 400 mg. three times a day for seven days; children under 12 years, 200 mg. three times a day for seven days; and children under 5 years, 100 mg. three times a day for seven days.

Brief case histories were reported on special forms (a different form being used for each disease).

Results

Twenty-one patients were excluded from the trial, either for administrative reasons or because there was doubt about the diagnosis. Table I shows the number of cases included, together with the age and sex distribution.

TABLE I.—Age and Sex Distribution

	Total	M	F	Age					
				0-4	5-9	10-14	15-19	20-24	25-
Measles	392	202	190	284	80	2	6	10	10
Chicken-pox	100	42	58	12	22	4	10	27	25
Mumps	26	12	14	6	8	1	2	5	4

Measles.—It was realized that it would be difficult to assess any results of A.B.O.B. in a disease whose course is usually so mild; the most satisfactory criterion seemed to be the number of days between that on which the tablets were first given and that on which the temperature returned to normal. This was defined as the first day—midnight to midnight—on which the axillary temperature, recorded four-hourly, did not rise above 98.8° F. (37.1° C.). All but 9 of the 392 patients had raised temperatures when the trial started. Table II shows that

TABLE II.—Measles Results

	A.B.O.B.	Placebo
Total No. of patients	194	198
No. of days before temperature returned to normal*	3.3 ± 0.13	3.6 ± 0.15
No. of days before patient "felt well"	4.9 ± 0.23	5.0 ± 0.23
" " " " " was discharged*	13.7 ± 0.58	13.2 ± 0.44
No. of patients developing { Pneumonia	12	13
{ Otitis media	10	7
{ Other	27	28

* Mean ± standard error.

there was virtually no difference between the two groups of patients assessed, either on the temperature basis or taking account of the number of days before the patient "felt well" or was discharged. There were few serious complications, the numbers being remarkably similar in each group. The 25 cases of pneumonia complicating measles were all confirmed by chest x-ray examination. There were no cases of encephalitis. Complications shown in Table II under the heading "other" were a miscellaneous assortment of relatively mild conditions. Just under half the patients in each group were treated with an antibiotic and all but about 5% had an antipyretic. The age and sex distributions were similar in the two groups.

Chicken-pox.—Not all the patients with chicken-pox had a raised temperature on admission. Table III shows

TABLE III.—*Chicken-pox Results*

	A.B.O.B.	Placebo
Total No. of patients	48	52
No. admitted with raised temperature	33	39
No. of days before temperature returned to normal*	2.5±0.27	3.2±0.21
No. of days before patient was discharged*	12.1±0.58	13.0±0.67

* Mean±standard error.

the average time before the temperature returned to normal in 72 patients with a raised temperature on admission. The proportion of patients in the A.B.O.B. group whose temperatures fell to normal in less than three days was 20 out of 33 (61%), compared with 11 out of 39 (28%) in those receiving the placebo. The average time was, in fact, 0.7 day shorter in the A.B.O.B. group. The difference cannot, however, be regarded as of more than borderline significance ($t=2.0$; $p=0.05$ approximately). On the other hand, the difference, such as it is, persists when the figures are further analysed by age, sex, or hospital. In each group the longest period of raised temperature was seven days. The patients in the A.B.O.B. group returned home on the average a day earlier than those on the placebo; but this might well have been due to chance, as the difference does not approach statistical significance. The date of discharge is often determined as much by social as by medical considerations. Hospitals were asked to report the severity of the rash on the fourth day, but in only eight cases (five on A.B.O.B. and three on placebo) was there any improvement compared with the state on admission.

Mumps.—There were barely enough cases of mumps to permit an adequate assessment of the efficiency of A.B.O.B. in this condition. Sixteen patients received A.B.O.B. and 10 the placebo; in each group the average time before the swelling disappeared was about eight days. Pancreatitis was reported in two patients, one in each group, and orchitis in one patient in the A.B.O.B. group.

Side-effects.—It is difficult to be certain whether or not there were any toxic effects attributable to A.B.O.B. Several children in each group developed diarrhoea within the first few days; in some cases this was caused by Sonne dysentery and in others it was thought to be a complication of the antibiotic used.

Conclusions

Measles.—We were unable to find any difference between the control cases and those treated with A.B.O.B. The duration of the illness and the incidence of complications were the same in both groups. A.B.O.B. in the dosage used would therefore appear to have no value in treating measles. Our findings confirm the results already obtained in two smaller series (Hopkins *et al.*, 1961; Brown *et al.*, 1962).

Chicken-pox.—The duration of the fever was shorter in the treated than in the control group. The difference is only of borderline significance, and it would seem in itself to have little clinical importance. Under the conditions of the trial it was found difficult to assess accurately the development of the rash and whether it was modified by the drug.

Mumps.—We could not demonstrate that A.B.O.B. had any effect on the course followed by mumps.

The trial was arranged by the Association of Infectious Diseases Physicians, and we would like to thank the following physicians who also took part: Dr. G. E. Breen, South

Middlesex Hospital; Dr. D. L. Brown, South Lodge Hospital; Dr. E. H. Brown, Hither Green Hospital; Dr. E. James, Rush Green Hospital; Dr. W. H. Kelleher, Western Hospital; Dr. J. J. Linehan, Waddon Hospital; Dr. J. C. McEntee, St. George's Hospital; Dr. W. F. T. McMath, Neasden Hospital; Dr. F. M. Stammers, City Hospital, St. Albans; Dr. R. W. Tannahill, Chadwell Heath Hospital. Our thanks are also due to Miss J. Letchner, of the department of medical statistics, St. Bartholomew's Hospital, who compiled the statistics; and to Bayer Products, who supplied the tablets and record cards.

REFERENCES

- Brown, A. G., Renton, G. H., and Griffiths, P. (1962). *Brit. med. J.*, **1**, 374.
Farquhar, J. (1960). Read at Symposium, Stockholm, October 28.
Hopkins, E. J., Pye, A. M., Solomon, M., and Solomon, S. (1961). *Brit. med. J.*, **2**, 1263.
Sjöberg, B. (1960). Read at Symposium, Stockholm, October 28.

Preliminary Communications

Simultaneous Active and Passive Immunization Against Tetanus

It is now generally recognized that prophylaxis against tetanus is best achieved by active immunization with tetanus toxoid, and it should be practised on as wide a scale as possible. If fully immunized persons are wounded, then protection can be further enhanced by a booster injection of tetanus toxoid; they do not require to be passively immunized by an injection of tetanus antitoxin.

Active immunization, however, cannot be used to protect non-immunized persons who are wounded, since it is not until some weeks after two spaced doses of toxoid that adequate immunity to tetanus develops. Prophylaxis in non-immunized persons therefore depends on the protection provided by injecting tetanus antitoxin, but such protection is less reliable than that given by active immunization and is accompanied by certain dangers, such as hypersensitivity reactions to horse serum. Furthermore, if patients develop antibodies against horse serum the passive antitoxin may be so rapidly eliminated as to give only transient protection. The risk of hypersensitivity reactions and of the rapid elimination of antitoxin is probably greater in those who have received antitoxin on previous occasions. It is most desirable, therefore, that all who are passively immunized with antitoxin are in addition actively immunized so as to avoid the use of antitoxin should injuries occur on subsequent occasions.

Simultaneous active and passive immunization, however, is not widely practised, since there is evidence that when plain tetanus toxoid is given at the same time as antitoxin the response to the toxoid is inhibited (Barr and Sachs, 1955). Parish and Cannon (1962) therefore advocate delaying active immunization until six weeks after the injection of antitoxin, but this delay undoubtedly results in many patients not receiving active immunization. Simultaneous active and passive immunization has, however, proved effective in the field of diphtheria prophylaxis (Fulton *et al.*, 1941) where the diphtheria toxoid used is an alum-precipitated preparation. Furthermore, reports have been published from countries other than Britain in which simultaneous active and passive immunization of patients against tetanus using adsorbed preparations of toxoid has produced adequate active immunity (Gold and Bachers, 1943; Ericsson, 1948; Tasman and Huygen, 1962). It was