vaccinated regions was initiated in November, 1958, and repeated random collections of stool specimens were made throughout 1959 and 1960. In 1958–9 a total of 2,322 specimens was collected in the four vaccinated regions, and 2,964 specimens in 10 non-vaccinated provinces; in 1960 a total of 7,486 stool specimens was collected from healthy children throughout the whole country. At least three important observations can be made from the results gained hitherto. (1) The initial spread of viruses which follows their mass introduction into the child population is self-limited, and the attenuated strains (Sabin) do not appear to persist in a community longer than a few months. (2) There is no evidence that the attenuated viruses spread beyond the regions into which they had been introduced. (3) An extraordinarily reduced spread of polioviruses could be demonstrated at the peak of the season, after the nation-wide use of oral vaccine in the spring of 1960.

We are indebted to many co-workers without whose help this programme, completion of surveillance, could not have been carried out. Special acknowledgment is made to the staff of the Epidemiological Department of the Ministry of Health of Czechoslovakia; epidemiologists and virologists from the Hygiene and Epidemiological Service in many regions, particularly Drs. Anna Mayerová, Jaroslav Pešek, Irena Poledníková, Vladislav Potužník, Mojmír Suchánek, Michal Tarabčák, Milada Tesaříková, Jaroslav Valihrach, Helena Vojtová, and others; and to the staff of the Virus Departments of the Institute of Sera and Vaccines, Prague.

Addendum

Since this paper was prepared for publication a new nation-wide oral vaccination was carried out in 1961 in Czechoslovakia. In April, 1961, approximately the same number of children of the same age-groups as in 1960 received type 1 live poliovirus followed in June by a mixture of types 2 and 3. This means that about 90% of the child population have been revaccinated.

As regards the incidence of poliomyelitis, not a single virologically confirmed case of paralytic poliomyelitis was revealed in Czechoslovakia up to December 20, 1961.

In our virological surveys, carried out in the same manner as in previous years, not a single poliovirus strain was recovered from about 2,800 stool specimens collected at random from healthy children in March as well as approximately 600 samples collected in September, 1961, and tested up to the time of writing.

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ANTIBODY RESPONSE IN INFANTS TO THE POLIOMYELITIS COMPONENT OF A QUADRUPLE VACCINE

BY

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The two regimes recently recommended by the British Ministry of Health (*Brit. med. J.*, 1961b) for the active immunization of children against diphtheria, tetanus, pertussis, and poliomyelitis during the first two years of life involve either three or four injections of combined diphtheria, tetanus, and pertussis vaccine (triple vaccine) and three injections of Salk poliomyelitis vaccine, thus making a total of six or seven injections. The number of injections would, of course, be considerably reduced by replacing Salk vaccine by the Sabin oral vaccine, and the Ministry of Health has already put out a scheme for such a replacement (*Brit. med. J.*, 1962).

Although oral vaccine may eventually prove to be the vaccine of choice throughout the world, one must not lose sight of the fact that Salk vaccine may serve a useful purpose in many instances, especially if it were combined as a quadruple preparation with diphtheria, tetanus, and pertussis vaccines. The use of such a preparation would likewise reduce the number of injections necessary during early childhood. Already quadruple vaccine has been used in the U.S.A. (Bordt *et al.*, 1960) and in Canada (Wilson *et al.*, 1960), but there has been no routine use of it in the Republic of Ireland or in the United Kingdom. It was therefore considered advisable to carry out a study to investigate its value, and a comparison was made of the poliomyelitis antibody levels obtained in infants after immunization with quadruple vaccine with those after triple vaccine and poliomyelitis vaccine given at the same time but in separate injection sites.

Procedure

The study was made between December, 1960, and November, 1961. Fifty-eight infants, resident in five children's homes in Ireland, received either quadruple vaccine (group A) or triple vaccine and poliomyelitis vaccine separately (group B). In making the allocation to one of the two groups the infants in each home were ranked in order of age and, taking them in pairs, one or other regime was allocated at random. Six infants, four in group A and two in group B, did not have the appropriate blood samples examined and were excluded from the subsequent analysis. Group A finally consisted of 24 infants and group B of 28. In both groups the age range of the infants and their mean age were similar (Table I).

TABLE I.—*Age of Infants in Each Vaccination Regime*

Age (Weeks)	No. of Infants Receiving	
	Quadruple Vaccine (Group A)	Triple and Polio Vaccines (Group B)
5–16	11	12
17–28	6	7
29–40	6	6
41–48	1	3
Total	24	28
Mean age	22·8	22·8

All injections were given intramuscularly in a dose of 1 ml. Infants in group A were given the quadruple vaccine into the left deltoid and those in group B the poliomyelitis vaccine into the left deltoid and the triple vaccine into the right deltoid at the same visit. With both groups injections were given on three occasions at intervals of one month. Serum samples were obtained approximately one week before the first injection and two weeks after the third injection; they were titrated for neutralizing antibody to all three types of poliovirus.

In the months following this primary immunization some of the infants left the children's homes. Approximately six months after the primary immunization 36 infants were followed up and given a booster dose of poliomyelitis vaccine. Serum samples were obtained two weeks after the booster dose and titrated for neutralizing antibody to all three types of poliovirus.

Neutralizing antibodies in the sera collected from the participants before and after vaccination were titrated simultaneously by the colour test (Shand, 1961), using a range of twofold dilutions from 1/4 to 1/2048. Titres are expressed as the reciprocal of the final dilution of the serum in the virus–serum mixture. A titre of less than 4 was recorded as no antibody.

Vaccines

The vaccines were prepared at the Wellcome Research Laboratories; they were plain suspensions containing no adjuvant. Both the triple and the quadruple vaccines contained 30 Lf of diphtheria toxoid, 6 Lf of tetanus toxoid, and 20×10^9 *Bordetella pertussis* per ml. The poliomyelitis vaccine was a routine batch blended in the proportions of three parts type 1 (Brunenders), two parts type 2 (MEF-1), and one part type 3 (Saukett). The quadruple vaccine was prepared by suspending the concentrated diphtheria, tetanus, and pertussis components (the same batches as those in the triple vaccine) in the poliomyelitis vaccine, and, although this resulted in a 16% dilution of the poliomyelitis vaccine, antigenicity tests in animals indicated that there was no significant reduction in potency.

Results

Pre-vaccination Antibody

The pre-vaccination antibody titres to the three virus types are given in Table II and show that many of the infants had maternal poliomyelitis antibodies before vaccination and that the distribution of antibodies was broadly similar in both groups. Of the 52 infants taking part in the study, 6 had antibody to all three types, 12 to two types, and 18 to one type, while the remaining 16 were triple-negative. Among the 29 infants aged 24 weeks or less when the pre-vaccination serum sample was taken, 23 had antibody to one or more types, whereas, among the remaining 23 infants, who were more than 24 weeks old, 13 had antibody to one or more types.

TABLE II.—*Distribution of Pre-vaccination Antibody Titres According to Vaccination Groups*

Pre-vaccination Titre	Quadruple Vaccine (Group A)			Triple and Polio Vaccines (Group B)		
	No. of Infants with Antibody to Types					
	1	2	3	1	2	3
<4	17	12	14	21	17	15
4	3	6	3	3	5	5
8	0	1	2	1	3	1
16	1	3	1	2	1	4
32	1	0	1	1	1	3
64	0	0	0	0	0	0
128	2	2	1	0	1	0
256	0	0	2	0	0	0

Post-vaccination Antibody

The antibody responses to three doses of vaccine are shown in Fig. 1 and are summarized in Table III for those infants without pre-vaccination antibody. Among those without antibody to type 1 before vaccination 6 of 17 in group A had type 1 antibody after vaccination compared with 20 out of 21 in group B. All infants in both groups without pre-vaccination antibody to types 2 and 3 had antibody to these virus types after vaccination.

TABLE III.—*Proportion of Infants with No Detectable Antibody Before Vaccination who Responded After the Third Injection*

Vaccine Group	Type 1	Type 2	Type 3
Quadruple vaccine (group A)	6/17	12/12	14/14
Triple and polio vaccines (group B)	20/21	17/17	15/15

Among the infants with maternal antibody to type 1 before vaccination, 2 of the 7 in group A and 3 of the 7 in group B had an increase in titre after vaccination. Of those with maternal antibody to type 2 before vaccination, 8 of the 12 in group A and 10 of the 11 in group B had an increase in type 2 antibody after vaccination. As regards the type 3 antibody, 6 of the 10 infants with maternal antibody in group A and 12 of the 13 in group B had an increase in antibody titre after vaccination.

An analysis was made among all those infants in both groups who had no pre-vaccination type 1 antibody to determine if a response to type 1 was influenced by age. Although the figures are small they showed that an antibody response to type 1 was as common in the younger infants as in the older ones. Thus of the 12 aged 14 weeks or less 9 responded; of 7 aged 15 to 24 weeks 6 responded; and of the 19 aged more than 24 weeks 11 responded.

Vaccination Reactions

No reactions, either local or general, occurred in any of the infants after the first or third injections with

either regime. Sixteen of the 25 infants from a single home developed vomiting, pyrexia, and diarrhoea after the second immunization session, but two others in the same home, who had not been vaccinated, also developed similar symptoms. In all cases the illness lasted a few days and was followed by complete recovery. Although examinations of faecal specimens were made there was no indication of the cause of the outbreak; it did not appear, however, to have been caused by the immunization procedure.

Antibody Response to Booster Dose

As already mentioned, poliomyelitis antibody levels were also determined in 36 infants after a booster dose of the poliomyelitis vaccine. Of these, 16 were in group A and 20 in group B. The post-booster sera were titrated in parallel with the sera taken from the same children after the third dose given approximately six months previously. The results obtained from these parallel titrations are compared in Fig. 2. With both regimes there was a general increase in antibody titre to each virus type; in every infant tested antibody was now present to all three virus types. The levels of antibody obtained with types 2 and 3 were very similar with both regimes, but with type 1 considerably higher levels were obtained in group B. This can also be clearly seen from the results in Table IV, in which the geometric mean titres to each virus type after the third dose and after the booster dose of poliomyelitis vaccine are given.

Discussion

In this study the antibody responses obtained in infants to poliomyelitis vaccine when given in the form of a quadruple vaccine containing diphtheria, tetanus, pertussis, and poliomyelitis vaccines were compared with those obtained when poliomyelitis vaccine was given separately but concurrently with a triple vaccine containing diphtheria, tetanus, and pertussis vaccines. The components of the quadruple vaccine were identical with those of the poliomyelitis and the triple vaccines; moreover, the infants were allocated to the two regimes by a method of random selection which gave two groups of very similar age. The findings thus constitute a valid comparison of the antibody responses resulting from the two different regimes.

In infants without maternal antibody both regimes, each consisting of three doses at intervals of four weeks, produced adequate responses to both types 2 and 3. In the quadruple-vaccinated group the proportion of infants responding to type 1 was unsatisfactory and was less than in the group which received the triple and the poliomyelitis vaccines separately. It is possible that the lower proportion of responders to the type 1 component of the quadruple vaccine was due to antigenic competition resulting from the increased number of antigens given at one site. In order to counteract such competition it may be essential either to use a more potent type 1

TABLE IV.—*Geometric Mean Titres of Antibody to Each Virus Type in Both Groups After (a) Third Dose and (b) Booster Dose*

Serum Sample Taken	Type 1		Type 2		Type 3	
	Group A	Group B	Group A	Group B	Group A	Group B
After third dose	9	49	167	175	448	256
After booster dose	79	431	1,068	1,023	792	955

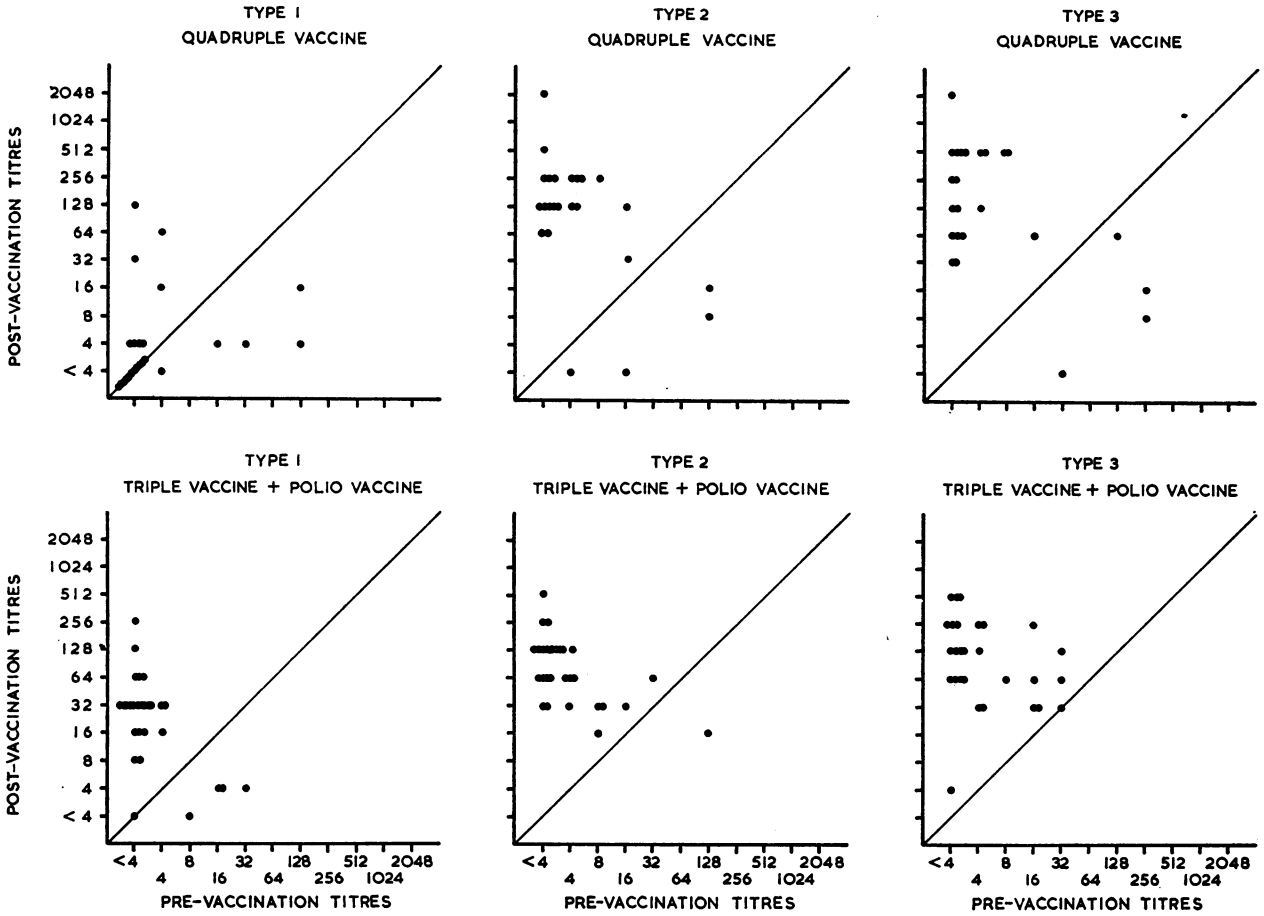

FIG. 1.—Antibody responses to three doses of vaccine in infants without pre-vaccination antibody.

component (Charney *et al.*, 1961) or to incorporate in the vaccine a mineral adjuvant. Quadruple vaccine containing an adjuvant has been used by Bordt *et al.* (1960), who obtained more promising antibody responses.

In those infants with maternal antibody at the time of vaccination both regimes produced unsatisfactory responses in the majority to type 1 and even in a few to types 2 and 3. The effect of maternal antibody in inhibiting the antibody responses to vaccine has been demonstrated with poliomyelitis vaccine when given alone (Perkins *et al.*, 1959) and also when given in a quadruple vaccine (Brown and Kendrick, 1960). It is possible, however, that the use of a more concentrated vaccine (*Brit. med. J.*, 1961a) or the incorporation of a suitable adjuvant would also be of value in overcoming this inhibitory effect, and it would thus seem advisable to investigate such possibilities further.

Although the antibody responses to the three primary injections were not always satisfactory, those obtained after the booster dose of poliomyelitis vaccine given approximately six months later were much more promising with both immunizing regimes, and especially with the one where triple and poliomyelitis vaccines had been given separately. These findings are in agreement with those of Perkins *et al.* (1961), who also obtained adequate responses in infants after a booster dose of poliomyelitis vaccine given alone. It would therefore appear desirable, until a more satisfactory quadruple vaccine is available, to use triple vaccine and poliomyelitis vaccine separately when immunizing infants of 3 months or less, and to give each vaccine simultaneously in three primary doses followed by a fourth booster dose of poliomyelitis vaccine 6 to 12 months later.

Summary

Fifty-two infants were vaccinated with either Salk poliomyelitis vaccine and triple (diphtheria, tetanus, and pertussis) vaccine concurrently, or with quadruple (diphtheria, tetanus, pertussis, and poliomyelitis) vaccine made from the same components.

The poliomyelitis levels of the two groups were compared after a primary course of three injections and again after a booster dose given six months later.

The post-primary responses of the two groups were similar and satisfactory for types 2 and 3, but the type 1 response was much less in the quadruple group than in the group receiving the triple and poliomyelitis vaccines at separate sites. The presence of maternal antibody affected the antibody response adversely in both groups.

After a booster dose of poliomyelitis vaccine six months later all infants had antibody to all three virus types. Higher levels for type 1 were obtained in the group which had received primary immunization with triple and poliomyelitis vaccines separately.

We are indebted to the medical officers in charge of the children's homes—namely, Dr. V. Coffey, Dr. B. Cullen, Dr. J. Finn, Dr. B. O'Sullivan, and Dr. R. Sutton—for permission to carry out this investigation on infants under their care, and to their nursing staffs for their unlimited patience and co-operation. We also thank Mr. F. L. Shand, who made the antibody titrations; and Miss M. Simpson,

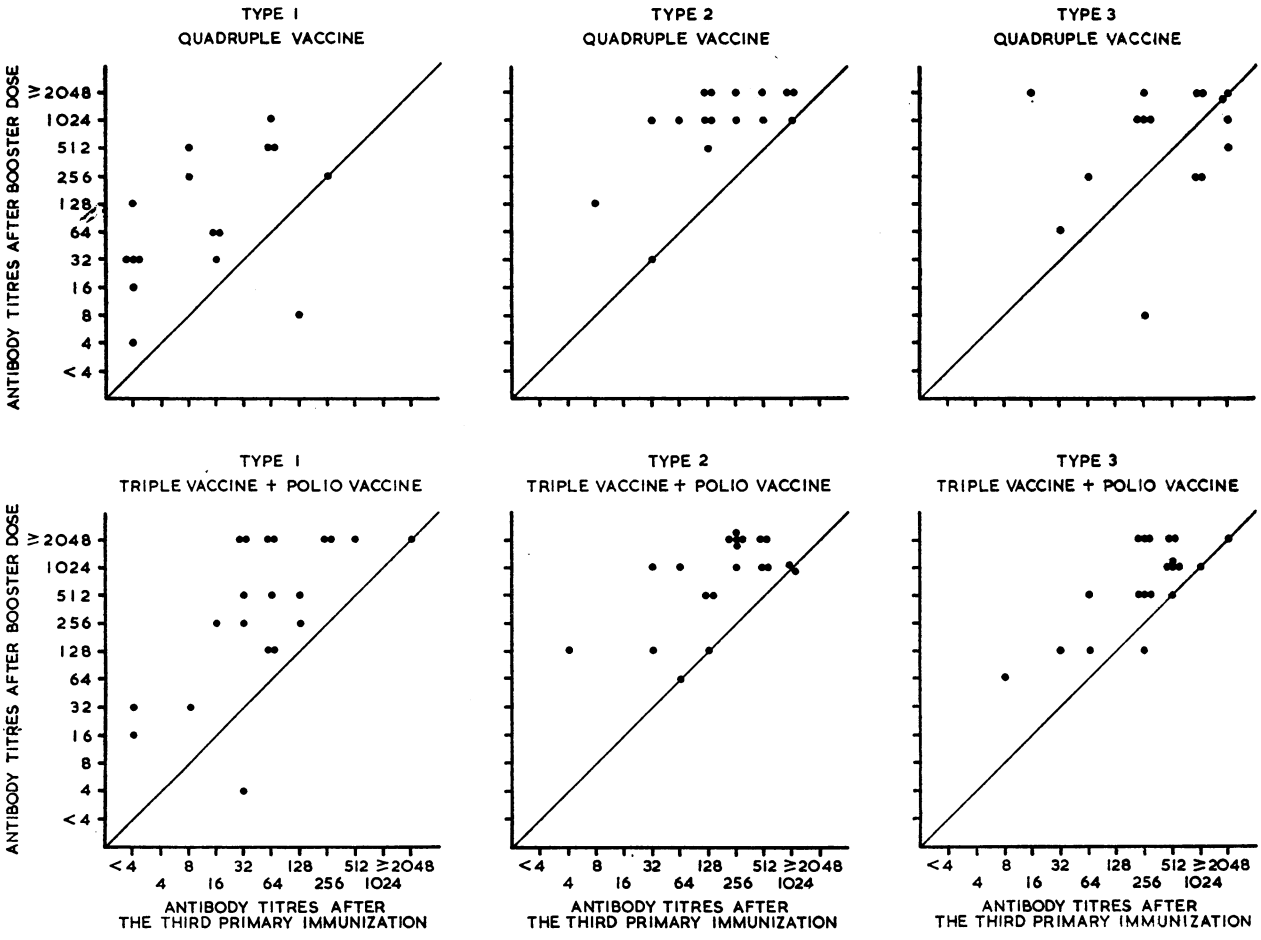

FIG. 2.—Antibody response to booster dose.

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DETERIORATION AFTER MITRAL VALVOTOMY—II*

BY

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Multifactorial Degeneration

The majority of patients with severe mitral stenosis can be divided into three main groups. There is a relatively large group in which surgical treatment is clearly advisable, and a smaller one with clear contraindications, such as age over 65, gross cardiac enlargement, intractable congestive failure, cirrhosis of the liver, or *important* incurable concomitant disease. In the third group the decision is more difficult because of various combinations of relative contraindications such as age over 50, atrial fibrillation, considerable cardiac enlargement, heavy calcification of the valve, aortic valvular disease, and associated mitral incompetence. The decision whether to operate or not is an anxious one because it must be assumed that the operative risk is above average and the chances of maintaining a good result are relatively poor. Yet without operation the outlook is hopeless. Unfortunately, a proper policy can only be determined in retrospect by actually observing the effects of surgical treatment in a large number of cases. Obviously the decision whether to advise treatment must be made on a balance of probabilities, but in this particular instance we feel more weight than usual must be given to the patient's own viewpoint once it has been appreciated that there may be only moderate improvement at best, and possibly little or none, and that there is a somewhat increased risk. Some patients will gladly accept this chance, but others prefer to continue their restricted lives for a limited period.

A combination of adverse factors may weigh the balance against advising operation at all or towards deciding, with otherwise so bleak an outlook, that the risk must be taken. The decision may be very difficult, and in order to try to get some factual information on this problem we have analysed a group of patients with multiple adverse factors who were treated by valvotomy for severe stenosis. There are obvious difficulties in making the assessment of each case on a "points" system because of variation between individuals in incidence, severity, and relative importance of each factor.

Seventy-eight patients qualified for this "multifactorial" group through having a combination of arbitrarily graded adverse features. Each had either (1) atrial fibrillation *and* heavy calcification *and* a cardiothoracic ratio of 60% or more, or (2) two of these three features and *in addition* two or more of the following: age 50 or over, aortic valvular disease, mitral incompetence, tricuspid stenosis, congestive failure, or (if not in group 1) light calcification suggesting a rigid valve, or a cardiothoracic ratio of 55–59%. On this basis each patient had at least four relative contraindications to operation.

In order to include only cases with definite associated mitral incompetence only those in which reflux was confirmed at operation have been selected. A few severe cases were excluded despite the severity of their condition, as shown, for example, by a very large heart and congestive failure because they were in sinus rhythm and had no calcification or other valvular defects and therefore did not fit into the *multi*factorial grouping. Also a few patients who were thought to be relatively "good risks" despite a multiplicity of adverse factors have been included because each of these appeared to be mild.

The incidence of each factor is shown in Table XXX. Over half the 31 operative deaths in the whole series of 500 patients came from this multifactorial group, giving a mortality of 21%. This is certainly a high figure, but it must be remembered that this group contains all the most severe cases in the series and the "medical" mortality for such a group without operation will also be high within a short period.

TABLE XXX.—*Multiple Adverse Factors* (78 *Cases*)

Factors	No.	%
Atrial fibrillation	75	96
Cardiothoracic ratio ≥60% ..	59	76
,, ,, =55–59% ..	19	24
Heavy calcification	43	55
Light ,, ...	16	21
Age 50+	20	26
,, 45–49	20	26
Aortic valvular disease	55	71
Mitral incompetence	38	49
Tricuspid stenosis	5	6
Congestive failure	45	58

Nine of the 16 deaths were from cerebral embolism, and this is related to the high incidence of clot (30%). Five deaths were due to cardiac arrest or circulatory failure, both conditions being almost confined to seriously ill patients, and two were from traumatic mitral incompetence.

Of the 62 survivors, 26 have now been followed for more than six years, and it can be seen from Fig. 7 that "good" or "fair," that is to say worth-while, improvement has been maintained by the majority.

*The first part of this article appeared in last week's issue at p. 1027.