knowledge of would be quite unacceptable here but this would be true even if the psychiatrists concerned were acting in good faith.

Of the three types of conceptual difference that I have mentioned, the first, which is political, is by far the most important. It completely alters the value attached to the others. The second (the concept of mental illness) is much more amenable to discussion, and so are some aspects of the third (the concept of responsibility).

Another area of concern where some practical advance might be made is procedural. Someone who, by our standards, is perfectly capable of conducting a defence, may be prevented from contacting his relatives during the course of the investigation, which may be six months or more, denied access to a defence lawyer, and kept out of court at the time of trial. Moreover, the court need not necessarily see the accused person at all if the written recommendation of a commission of psychiatrists is accepted. Needless to say, the accused person's own wishes are not consulted when deciding upon a recommendation on non-imputability by reason of mental illness.

My personal view is that, so long as our differences on these issues can be frankly acknowledged and discussed, communications between British and Soviet psychiatrists should continue. Doctors are not likely to bring about much change in the political system, nor should they expect to do so, but they can attempt to influence each other's practice in their own professional sphere. Representations about individual cases may be more effective if stated in these terms.

The other thing that we can do, as I suggested in my paper at the recent conference in Yerevan, is to consider these issues in their international context. Complaints of malpractice have been made about medical services in several parts of the world, notably the United States and the Soviet Union, but our own country has not been immune from criticism. The initiative of the Royal College of Psychiatrists in suggesting a commission of inquiry to be set up by a number of national associations is therefore to be welcomed. This group would be concerned with the detailed investigation of individual cases, during the course of which there would inevitably be much discussion of ethical principles and of medicolegal procedures. I very much hope that such a body will be established, with active co-operation from the two largest national associations, as well as from those in Western Europe.

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For Debate

A Randomized Controlled Trial of Acetyl Salicylic Acid in the Secondary Prevention of Mortality from Myocardial Infarction

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Summary

The results of a randomized controlled trial of a single daily dose of acetyl salicylic acid (aspirin) in the prevention of re-infarction in 1,239 men who had had a recent myocardial infarct were statistically inconclusive. Nevertheless, they showed a reduction in total mortality of 12% at six months and 25% at twelve months after admission to the trial. Further trials are urgently required to establish whether or not this effect is real.

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Introduction

A definite and prolonged inhibition of platelet aggregation by acetyl salicylic acid (aspirin) has been shown by several workers,[1-3] and confirmed subsequently. It has repeatedly been suggested that because of this effect aspirin is likely to have a prophylactic effect in thromboembolic conditions, particularly in coronary artery thrombosis. Clinical evidence of such an effect is conflicting and clearly direct evidence of benefit can come only from randomized controlled trials. This paper reports such a trial of aspirin in the preven-

tion of death in men who had recently had a myocardial infarct.

Method

The trial began in February 1971. Hospital physicians in six hospitals in South Wales agreed to notify us of the names of all men under 65 discharged from their wards with a confirmed diagnosis of myocardial infarction. No steps were taken to standardize diagnostic criteria but discussions indicated that there was likely to be close agreement among physicians.

With his general practitioner's agreement, each patient was visited at home. The purpose of the trial was explained and if the patient agreed, he was supplied with specially prepared gelatine capsules. These contained either powdered aspirin (300 mg once a day) or an inert placebo and were to be taken once a day before breakfast to ensure rapid absorption. Preliminary laboratory studies on volunteers consistently showed that this dose affects platelet function. Men receiving anticoagulant therapy and those with evidence suggestive of peptic ulceration were not included. To detect aspirin taken independently of the trial, each man was asked to keep a detailed record of all medicaments taken for any reason.

The men were visited weekly at first, then monthly for the duration of the trial except for a few who, when established in the trial, were subsequently visited at about three-month intervals. Details of any further cardiovascular episode were noted, but from the beginning we intended to base conclusions on mortality alone. Furthermore, because of uncertainties in the certified cause of death in men who had had a recent infarct, we decided to draw conclusions from total mortality.

In the spring of 1972 we were contacted by the group conducting the Boston Collaborative Drug Surveillance Programme. In confidence, they presented preliminary data based on patients who had survived a myocardial infarct which suggested a substantial protective effect of aspirin but were also consistent with a raised incidence of early mortality in aspirin takers. To help resolve this important dilemma we agreed that the code of our trial should be broken and the results disclosed to the Boston workers. At that time there had been 17 deaths and these were inconsistent with a harmful effect of aspirin (six deaths in those on aspirin, 11 in the controls). We therefore decided to continue the trial but to increase the rate of admission to obtain more data as rapidly as possible.

Physicians in hospitals throughout the rest of South Wales and in some hospitals in Oxford, Sutton Coldfield, Birmingham, Manchester, Swindon, Northampton, Nuneaton, Reading, Altrincham, Crewe, Stockport, Walsall, and Macclesfield were therefore asked to co-operate. A nurse was appointed in each of the new main centres (Sutton Coldfield, Oxford, Swansea, and Manchester) so that patients could be visited at regular intervals. The original design of the trial was adhered to with two important changes. Firstly, the age restriction was removed and, secondly, the physicians contacted after May 1971 were asked to notify, in addition to recently discharged patients, patients who had been discharged during the previous six months. In fact, some patients were admitted to the trial after an even longer interval. The original intention to base the main conclusions on deaths alone was maintained.

In view of the possible magnitude of the effect of aspirin indicated by the Boston data, we agreed that the data from our trial should be monitored by an independent group—to ensure that if a convincing beneficial effect (or an unacceptable effect) became apparent before the trial was due to be concluded it could be stopped. Other than when the code was broken in spring, 1972 and apart from the operations of the monitoring group after this, the trial was conducted double-blind.

During the trial some men withdrew. The reasons for some withdrawals were clear: a few men moved away from the areas of the study; some were withdrawn by their own physicians because of illness—for example, a suspected re-infarction after which anticoagulants were prescribed; and several men complained of minor side effects, occasionally gastrointestinal. In a few cases men simply refused to continue to co-operate, or their general practitioner asked for them to be withdrawn for psychological reasons or for reasons other than those given above.

Admissions to the trial continued until July 1973 and the trial concluded on 1 September 1973.

Results

A total of 1,239 men were admitted to the study (table I and II). During the trial 113 patients had to be withdrawn, 49 from the aspirin group and 64 from the placebo group (table III). No man was withdrawn because of serious side effects, and no man is known to have had a gastrointestinal haemorrhage. Table IV gives the distributions of age and interval between infarction and entry to trial for these men, together with the length of time in the trial before withdrawal. There is little difference in these age distributions and both are very similar to the total groups (table II). Again, there is little difference in the distributions

TABLE I—*Admission to Trial and Allocation to Aspirin or Placebo*

Area	Number of Men		
	Aspirin	Placebo	Total
Cardiff	338	341	697
Manchester	58	63	121
Oxford	68	61	129
Sutton Coldfield	64	66	130
Swansea	87	93	180
All Areas	615	624	1,239

TABLE II—*Initial Characteristics of Men admitted*

Characteristic	Aspirin	Placebo
Age <55 yr	266 (43%)	286 (46%)
55-64 yr	264 (43%)	271 (43%)
65 + yr	85 (14%)	67 (11%)
Mean age	55·2	54·8
Interval between infarction and entry to trial:		
<6 weeks	302 (49%)	319 (51%)
6-13 weeks	165 (27%)	154 (25%)
14 + weeks	148 (24%)	151 (24%)
Mean interval	9·8	10·0
Mean length of time in trial (Months)	12·2	11·7

TABLE III—*Patients who left Trial and Reasons for Withdrawal*

Reason For Withdrawal	Number of Men Withdrawn (% of total admitted)		Total
	Aspirin	Placebo	
Left Area	0 (0%)	4 (0·6%)	4 (0·3%)
Illness	20 (3·3%)	24 (3·8%)	44 (3·6%)
Side Effects	22 (3·6%)	20 (3·2%)	42 (3·4%)
Refusal to continue	7 (1·1%)	16 (2·6%)	23 (1·9%)
Total withdrawals	49 (8·0%)	64 (10·3%)	113 (9·1%)
Total admitted	615	624	1,239

TABLE IV—*Initial Characteristics of Men withdrawn and Length of Time in Trial*

Characteristic	Aspirin	Placebo
Age <55 yr	25 (51%)	28 (44%)
55-64 yr	18 (37%)	26 (41%)
65 + yr	6 (12%)	10 (16%)
Mean age (yr)	54·9	55·9
Interval between infarction and entry to trial:		
<6 weeks	19 (39%)	23 (36%)
6-13 weeks	15 (31%)	18 (28%)
14 + weeks	15 (31%)	23 (36%)
Mean interval (Weeks)	11·7	13·7
Mean length of time in trial (Months)	4·2	8·0

of the interval between infarction and entry to the trial for the two groups. Both, however, differ considerably from the group as a whole, reflecting the fact that a greater than expected proportion of the withdrawals came from the areas outside Cardiff, where the intervals between infarction and entry were considerably larger than for the Cardiff area.

Of the patients who withdrew, those in the aspirin group had been in the trial for a considerably shorter period than those in the placebo group (table IV) and this difference was consistent in each area. This would be the expected pattern if aspirin does cause side effects at the dosage used. The difference is, however, in the same direction for each of the three main reasons for withdrawal (table V). This would be explicable if the separate reasons are all considered to be different manifestations of side effects to aspirin. Nevertheless, the fact that there were more withdrawals in the placebo than in the aspirin group negates this possibility. On balance, however, the apparent differences do not appear to be important, and clearly aspirin was not an important cause of side effects in the dosage used.

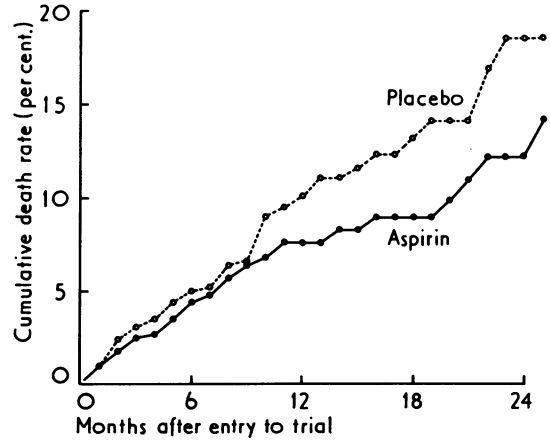
TABLE V—*Length of Time in Trial by Reason for Withdrawal*

Reason for withdrawal	Mean Length of time in Trial in Months (Number of Men Withdrawing)	
	Aspirin	Placebo
Left area	— (0)	9·8 (4)
Illness	5·6 (20)	9·2 (24)
Side effects	3·3 (22)	6·5 (20)
Refusal to continue	3·2 (7)	7·9 (16)
Total	4·2 (49)	8·0 (64)

DEATHS

During the trial 108 deaths occurred, 61 in the placebo group and 47 in the aspirin group. The differences in mortality rates among areas (table VI) were not important and that they did occur is not surprising in view of the relatively small numbers in some areas. the different durations between infarction and admission to the trial, and the different lengths of time spent in the trial by men in the different areas. What is important is whether the aspirin/placebo difference was consistent among the areas. Quite clearly it was not the same in all areas but a statistical test to check for heterogeneity in the aspirin/placebo difference among areas gives χ^2 (4 d.f.) = 2·4 (0·50 < P < 0·70) suggesting that the data from the five areas were well within sampling variation and can be pooled.

To test whether aspirin had any effect on total mortality the data from the five areas were pooled and a standard life table[4] constructed. This includes the men withdrawn during the trial as cases "lost to follow-up" at the point when they ceased treatment. The longest time that any man was in the trial was 30 months but the cumulative mortality rates are given for only 25 months as relatively few men were in the trial for longer. As shown, all the deaths have been included except for one in the aspirin group which occurred in the 27th month after admission to the trial. Table VII shows the death rates at 6, 12, 18, and 24 months, together with their standard error calculated using the method of Greenwood.[5] The differences between the death rate curves are small, particularly during the first eight or nine months but the death rate in the placebo group was always higher than in the aspirin group.



Cumulative death rates—all men.

At no time was the difference between the aspirin and placebo death rates statistically significant as judged by conventional *t* tests using the given standard errors. Though the statistical tests employed should take into account the fact that the results were repeatedly evaluated by the monitoring committee, such a test would be more stringent than the *t* test, and therefore seems unnecessary in view of the non-significance of the latter.

TABLE VI—*Mortality by Area and Treatment Group*

Area	Aspirin			Placebo		
	Total*	Deaths	% Mortality	Total*	Deaths	% Mortality
Cardiff	318	28	8·8	317	43	13·6
Manchester	49	2	4·1	55	2	3·6
Oxford	60	5	8·3	51	5	9·8
Sutton Coldfield	59	4	6·8	54	5	9·3
Swansea	80	8	10·0	83	6	7·2
Total	566	47	8·3	560	61	10·9

*The total numbers of men given here are the numbers of men admitted minus the withdrawals.

EFFECT OF AGE

Mortality was consistently higher in the placebo group for each of the three age groups considered (table VIII). Within both aspirin and placebo groups, the percentage mortality increased with age, as would be expected. Two age groups were analysed: under 55, and 55 and older. The age of 55 years was chosen as the cutting point purely because it produced two groups of similar size, and different dividing points produced essentially similar patterns. In the younger men the death rate in the placebo group was always higher than that in the

TABLE VII—*Cumulative Mortality Rates* (± *S.E.*)

Age Group	Mortality rates at:							
	6 months		12 months		18 months		24 months	
	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo
All ages	4·4 (0·9)	5·0 (0·9)	7·6 (1·2)	10·1 (1·4)	9·0 (1·4)	13·2 (1·9)	12·2 (2·3)	18·5 (3·2)
Under 55 yr	2·4 (1·0)	4·8 (1·3)	6·1 (1·7)	9·2 (1·9)	6·1 (1·7)	9·2 (1·9)	8·6 (3·0)	11·9 (3·2)
55 yr and over	5·9 (1·3)	5·1 (1·3)	8·6 (1·6)	10·8 (1·9)	11·2 (2·2)	17·0 (3·2)	15·1 (3·4)	25·3 (5·5)

TABLE VIII—*Mortality by Age*

Age (yr)	Aspirin			Placebo		
	Total*	Deaths	% Mortality	Total*	Deaths	% Mortality
<55	241	15	6·2	258	23	8·9
55-64	246	23	9·3	245	28	11·4
65 +	79	9	11·4	57	10	17·5
Total	566	47	8·3	560	61	10·9

*The totals are those admitted minus the withdrawals.

aspirin group though nowhere was the difference statistically significant (table VII). In these younger men the death rate remained nearly constant after they had been in the trial for a year and only two subsequent deaths occurred one in each treatment group. In the older men there was no difference in the death rate up to 9 or 10 months after admission and from this time onwards the rate was always greater in the placebo group—but, again, nowhere was the difference statistically significant (table VII).

EFFECT OF INTERVAL

The numbers of deaths and the percentage mortality by arbitrary interval between infarction and entry (table IX) showed a clear basic pattern: in men admitted shortly after their infarction the placebo death rate was considerably higher than that for the aspirin group. In men admitted later there was little or no difference. Life-table analysis here is particularly difficult. The numbers of men and deaths are not sufficient to allow a split into more than two groups and, unlike age, the choice of the dividing point is absolutely crucial. Divisions at less than, and greater than or equal to, 4, 6, and 14 weeks produce three quite different sets of life tables, as indeed one would expect from table IX. For this reason, we present none of them, but there is absolutely no evidence that the apparent advantage of aspirin in men admitted shortly after infarction was due to a considerable reduction in death rate during a short period immediately after admission to the trial, followed by little subsequent difference. Had this been the case the differences in effect in table IX could be explained, but it was not, and the difference between aspirin and placebo in the men admitted early increased fairly steadily during the whole trial.

TABLE IX—*Mortality by Interval between Infarction and Entry to Trial*

Interval (weeks)	Aspirin			Placebo		
	Total*	Deaths	% Mortality	Total*	Deaths	% Mortality
<4	138	9	6·5	157	15	9·6
4-5	145	13	9·0	139	24	17·3
6-13	150	15	10·0	136	14	10·3
14 +	133	10	7·5	128	8	6·3
Total	566	47	8·3	560	61	10·9

The effect of interval between infarction and entry, is further complicated by the fact that the "early" group was disproportionately made up of men from the Cardiff area. For example, of the 579 men admitted within six weeks, 486 (84%) were from the Cardiff area, whereas the Cardiff men made up only 55% of the overall total. It is thus impossible to be certain whether the effect is one of "interval" or "area."

Discussion

The results of this trial were inconclusive. None of the differences detected was statistically significant at conventional levels and there were possible inconsistences in the data. Though inconclusive, the observed differences showed that aspirin reduced total mortality by 12% at six months and 25% at twelve months after admission to the trial. If real, this effect appeared to be largely independent of age within the range included in the study, but the interval between infarction and starting aspirin or, possibly "area," or both, might have been important. It is difficult to envisage a real "area" effect. However, there are possible reasons why the interval between infarction and beginning of treatment may affect the outcome, particularly the number of deaths actually due to a further thrombosis and that due to ventricular fibrillation. The proportion of the latter is likely to be high soon after an infarct and thereafter to fall. If aspirin affected thrombosis but not ventricular fibrillation this would give a pattern the reverse of that observed (table VIII).

Further trials are obviously essential before it can be decided with any confidence whether or not the effects observed are real or are simply due to chance. Nevertheless, it is profitable to consider in some detail possible sources of bias in the study.

The regularity of tablet taking is unknown. We did attempt, by blood tests conducted without prior warning, to examine salicylate levels and platelet aggregation in some of the men. These attempts were not very successful as blood salicylate levels are very low after the dose used, and transport of the blood samples seemed to affect platelet aggregation. Nevertheless, based on experience in many clinical trials, all involved in the field work are convinced that almost all these men were exceptionally co-operative. At the same time, the inconsistencies we have noted with respect to "area" and "interval" could have arisen if men admitted to the trial soon after their infarct are better motivated than those admitted later, and are therefore more likely to take treatment. The fact that men withdrawn from the trial had been, on average, admitted to the trial 2-4 weeks longer after infarction than the men as a whole, and that the proportion (12·7%) of men withdrawn among those admitted 14 weeks or more after their infarct is higher than the proportion (6·8%) in those admitted within six weeks (see tables II and IV), provides some support for this possibility.

On the other hand, possibly if aspirin does have a protective effect, the difference between the groups has been diminished by casual aspirin-taking by the control subjects. Of the men admitted to the trial early on, 341 returned record sheets listing all tablets taken for any reason, and most of these covered at least six months. Twenty-four (7%) of these mentioned aspirin or aspirin-containing preparations and indicated that 3% of men had taken aspirin on more than six occasions in one year (or pro rata) and 4% had taken it less frequently. It is unlikely, therefore, that this is a source of serious bias but possibly some reduction in the aspirin-placebo differences might still have occurred.

It could also be argued that the dose of aspirin used in this trial was unrealistic. A dose of 300 mg once a day was chosen because this is well above that necessary to affect platelet aggregation to collagen and to ADP as measured by the Born and similar techniques.[6 7] Nevertheless, this may not be the most relevant measurement of the context of coronary artery thrombosis. Indeed, possibly higher doses are required to affect other aspects of platelet function aggregation measured by other techniques, and no dose of aspirin appears to affect platelet survival, which may be an even more relevant index in cardiovascular disease.

There are obvious uncertainties in the cause of death as obtained from death certificates. Two of the certificates gave carcinoma as the cause (both men had been on placebo) and one death occurred by suicide (aspirin). All the other deaths were stated to be due to cardiovascular causes, and, while this cannot be taken as certain in every case, it is probably true of most deaths. Nevertheless, even accepting that most deaths were due to cardiovascular causes, there can be no certainty as to which deaths, or even what proportion occurred because of a further thrombosis. We have separated out cases in which death was said to have occurred very suddenly, as this would be consistent with an electrical mechanism rather than an arterial occlusion by a thrombus. Relevant evidence is available in only a relatively few cases, and 10 of these had received aspirin and 11 placebo.

The evidence from this trial is therefore inconclusive. Nevertheless, when taken together with that from the Boston

study[8] a clear and urgent case for further randomized controlled clinical trials is obvious.

This trial elicited an immense amount of goodwill and support from hospital physicians, general practitioners, and other medical and ancillary workers, to all of whom we express sincere thanks. The work also necessitated considerable help from colleagues in the M.R.C. Unit and in Nicholas Research Laboratories, to whom we are most grateful. We also thank Professor J. P. D. Graham of the Welsh National School of Medicine and colleagues in the M.R.C., D.H.S.S., and the Office of Population Censuses and Surveys who advised on the conduct of the trial after May 1972; the monitoring group (Professors Sir Richard Doll, F.R.S., Jerome Cornfield and D. D. Reid in addition to P.M.S.); and the nurses who handled the extended field work (Nurses L. Baker, E. R. Hill, S. P. Hill, T. Saunders, and W. Softley).

Requests for reprints to P.C.E.

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Regular Aspirin Intake and Acute Myocardial Infarction

BOSTON COLLABORATIVE DRUG SURVEILLANCE GROUP

British Medical Journal, 1974, 1, 440-443

Summary

The results of two large independent studies involving a combined total of 776 patients treated in hospital with a discharge diagnosis of acute myocardial infarction and 13,898 patients with other discharge diagnoses showed a negative association between regular aspirin intake and non-fatal myocardial infarction. The data are consistent with the hypothesis that aspirin protects against this disease. Clinical trials are needed to determine whether this hypothesis is correct.

Introduction

Since 1966 the Boston Collaborative Drug Surveillance Program has used nurses to carry out intensive monitoring of medical patients in several hospitals in four countries.[1] As part of the routine data collection, information has been obtained on drug intake before admission and on discharge diagnoses. For some time a strong negative association between regular aspirin intake before admission and a discharge diagnosis of acute myocardial infarction has been observed in these data (Study I). During the first ten months of 1972 a separate study was undertaken to obtain additional data on the relation of drug use to disease. This entailed a survey of drug exposure and discharge diagnoses in about 25,000 consecutive admissions to the medical and surgical wards of 24 hospitals in the Boston area.[2] The second study again showed a negative association between regular aspirin use and the development of acute myocardial infarction (Study II). Detailed analyses of both sets of data are presented here.

Subjects and Methods

STUDY I

Information on "regular" drug intake in the month before admission and on discharge diagnoses was collected in a standard fashion by nurse monitors in over 9,000 patients admitted to various medical wards in eight hospitals. On admission, patients were asked whether they took drugs regularly for a wide variety of indications (for example, contraception, pain, headache, etc.). Regular drug intake was defined as "regular use of the same medication on a scheduled basis" (in the case of aspirin intake the definition was generally interpreted as "daily" use). When such a history was given for any drug, the duration of consumption was recorded, but no effort was made to determine the dosage taken. Diagnoses were obtained from the attending physicians at the time of discharge.

This programme was not designed to test any particular hypothesis, but rather to evaluate relationships between a large variety of drugs and diseases. Thus, at the time of obtaining the data, no specific interest was directed towards either aspirin use or acute myocardial infarction.

For the purposes of the present evaluation of the relation between regular aspirin intake and acute myocardial infarction, patients receiving any preparation containing aspirin were combined to form an "aspirin-exposed" group. Certain patients were excluded from the final analyses. These were: (1) patients below the age of 40 and above the age of 69 years; (2) patients with *first* diagnoses which are likely to be associated with aspirin intake—namely, cancer, headache, any form of arthritis, any other musculoskeletal disorder, any form of gastrointestinal bleeding, alcoholism, and anxiety or any psychological disturbance. With these restrictions, the final analyses of data from Study I were based on a population of 325 patients with a discharge diagnosis of acute myocardial infarction and 3,807 controls.

Among the controls the discharge diagnosis was: 60% cardiovascular disease; 28% respiratory disease; 16% diabetes; 11% gastrointestinal disease; 10% renal disease; and 15% none of these diagnoses. The percentage frequency of regular aspirin use in these categories was 4·5, 5·1, 4·1, 5·5, 6·9, and 7·1, respectively. Angina pectoris or coronary insufficiency, or both, was a discharge diagnosis in 270 controls with cardiovascular disease. Among them the frequency of regular aspirin use was 4·4%.

STUDY II

Study II was based on a special multipurpose survey carried out from January to October 1972 in the general medical and

Boston Collaborative Drug Surveillance Group, Boston, U.S.A.
See end of article for membership