Antihypertensive therapy in elderly patients

NINTH INTERIM REPORT

THE EUROPEAN WORKING PARTY ON HIGH BLOOD PRESSURE IN THE ELDERLY (EWPHE)*

Summary

Over 800 hypertensive patients above the age of 60 years have now been entered into the double-blind multicentre trial of the European Working Party on High Blood Pressure in the Elderly (EWPHE). After stratification and randomization, half were treated with one capsule daily containing 25 mg hydrochlorothiazide and 50 mg triamterene, and half were given matching placebo. If blood pressure control was insufficient a second capsule was given and, if necessary, up to 2 g methyldopa daily.

Prior to randomization, no significant differences were present between the two groups. A significant blood pressure difference between the groups was attained during the initial phase of the trial and maintained during 5 years of follow-up. No major disturbances in serum sodium or serum potassium were observed. However, serum creatinine and serum uric acid rose in the active treatment group, but not in the placebo group.

A favourable influence of active treatment on prognosis can be expected on the basis of the blood pressure reduction and in the absence of major electrolyte disturbances. However, since the other treatment effects may offset this potential benefit, conclusions can be drawn only on the basis of observed statistical differences in terminating events between the groups. The trial still continues and more patients are being admitted. Neth J Med 1984; 27:165.

Introduction

Hypertension is one of the major risk factors for stroke and coronary heart disease in both middle-aged and elderly subjects[1,2]. However, such an association does not necessarily imply that morbidity and mortality are reduced when blood pressure is lowered by antihypertensive drugs. Controlled trials with antihypertensive agents in elderly subjects have not shown increased mortality or morbidity associated with active treatment, but either no difference or some possible but not necessarily statistically significant benefit[3-9].

In view of the uncertainties regarding treatment in aged people, the European Working Party on High Blood Pressure in the Elderly (EWPHE) initiated a study to assess the effects of antihypertensive drug therapy in patients above the age of 60 years. A double-blind multicentre trial was designed, which started in 1973. Several interim reports have been published so far; the present paper (ninth interim report) reviews data observed up to June 1983. The report deals only with treatment effects which are not end-points for the study. Mortality and morbidity data are deliberately omitted, since they are known only to the co-ordinating office; revealing these data would destroy the nature of the trial.

Patients and methods

Study protocol

Elderly patients with high blood pressure are admitted to the study if they fulfil certain criteria. Before final admission of a patient, his or her initial record form is sent to the co-ordinating office after a run-in period on placebo capsules.

Address for correspondence: Dr A. Amery, Co-ordinating Office of the EWPHE, Academisch Ziekenhuis Sint-Rafaël, Kapucijnenvoer 33, 3000 Leuven, Belgium.

*The following members are participating in the EWPHE: A. Amery[1], K. Beard[2], W. Birkenhäger[3], M. Bogaert[4], P. Brixko[5], C. J. Bulpitt[6], D. Clement[4], P. de Leeuw[3], J. F. de Plaen[7], M. Detuyttere[8], A. de Schaepdryver[4], R. Fagard[1], H. Feltkamp[9], F. Forette[10], J. Forte[11], R. Grauwels[1], R. C. Hamdy[12], J. Hellemans[1], J. F. Henry[10], A. Koistinen[13], G. Leonetti[14], P. Lewis[6], P. Lund-Johansen[15], J. P. R. MacFarlane[2], K. Meurer[9], P. Miguel[11], J. Morris[16], A. Mutsers[4], A. Nissinen[13], E. O'Brien[17], W. O'Callaghan[17], K. O'Malley[17], P. Omvik[15], J. C. Petrie[18], L. Terzoli[14], J. Tuomilehto[13], J. Webster[18], B. O. Williams[2], and P. Willemse[3].

1. University Hospital St Rafaël, Leuven, Belgium; 2. Victoria Geriatric Unit, Glasgow, Scotland; 3. Zuiderziekenhuis, Rotterdam, The Netherlands; 4. University Hospital, Gent, Belgium; 5. Geriatric Hospital Le Valdor, Liège, Belgium; 6. Hammersmith Hospital, London, United Kingdom; 7. University Hospital St Luc, Brussels, Belgium; 8. Medisch Centrum voor Huisartsen, Leuven, Belgium; 9. University Hospital Köln, West-Germany; 10. Hôpital Charles Foix, Ivry, France; 11. University Hospital Santa Maria, Lisboa, Portugal; 12. St John's Hospital, London, United Kingdom; 13. North Karelia Project, Kuopio, Finland; 14. Istituto di Recherche Cardiovascolari, Milano, Italy; 15. University Hospital Haukeland, Bergen, Norway; 16. St Charles Hospital, London, United Kingdom; 17. Royal College of Surgeons, Dublin, Ireland; 18. Aberdeen Royal Infirmary, Aberdeen, Scotland.

The positive (selection) criteria are as follows: 1) age of 60 years or more at admission to the study; 2) sitting blood pressure (average of readings on three separate visits) on placebo during the run-in period within certain limits: 160 to 239 mm Hg for systolic and 90 to 119 mm Hg for diastolic blood pressure; 3) patient's willingness to co-operate and to be followed-up regularly (informed consent).

Negative (exclusion) criteria are: 1) curable causes of increased blood pressure; 2) certain complications of hypertension, i.e. retinopathy grade III or IV, congestive heart failure, enlarging aortic aneurysm, severe renal failure, past history of cerebral or subarachnoid haemorrhage; 3) concurrent diseases such as hepatitis or cirrhosis, gout, malignancy, etc.

Patients are classified for each collaborating centre into one of eight categories according to age, sex, and the presence or absence of cardiovascular complications of hypertension. After classification, patients are randomly allocated to an active treatment or placebo treatment group for the duration of the study. The corresponding drugs are sent to the different centres where the patient can be admitted to the study if he or she continues to fulfil the admission criteria. Treatment randomization is restricted so that, in each of the categories for a participating centre, approximately the same number of patients will receive active or placebo treatment (restricted randomization per centre and per category).

At first, all patients receive 1 capsule containing either 25 mg hydrochlorothiazide and 50 mg triamterene, or a matching placebo. The dosage may be increased, after at least 2 weeks, to 2 capsules per day. If the blood pressure remains high after 1 month, methyldopa in the treated group or matching placebo in the other group can be added in an initial dose of 500 mg, increasing eventually to four 500 mg tablets daily. Both capsules and tablets are identical in shape, taste and colour to their matching placebo.

Patients may end the study for one of the following reasons: 1) by completion of 7 years' observation; 2) by being lost to follow-up; 3) by interruption of all study treatment during more than 3 months; 4) by

TABLE I. SOME CHARACTERISTICS AT ADMISSION

	Placebo		*Active*		*Probability of between-group differences*
Total number (n)	423		420		
Age (in years)	72.1 ± 0.30		71.7 ± 0.40		
Sex: male (n)	126		131		
female (n)	297		289		
Body weight (in kg)	67.2 ± 0.6 (416)		66.7 ± 0.6 (414)		
Height (in cm)	159 ± 0.5 (407)		159 ± 0.5 (402)		
Recumbent blood pressure (in mm Hg)					
systolic	185 ± 0.9 (418)		184 ± 0.9 (415)		$p > 0.1$ for all items
diastolic (phase 5)	100 ± 0.4 (418)		99 ± 0.4 (413)		
Recumbent pulse rate (in beats/min)	77.8 ± 0.5 (406)		78.8 ± 0.5 (409)		
Eye fundus	R (420)	L (420)	R (414)	L (414)	
grade I (n)	140	135	158	152	
grade II (n)	168	173	158	159	
lens opacity (n)	28	25	18	20	
normal (n)	61	63	64	66	
unknown (n)	23	24	16	17	
Central nervous system disturbances present (n)	70 (422)		72 (420)		

In this and the following table mean ± standard error of the mean are given, together with, in brackets, the number of patients from whom this item is available.

one of the specific study terminating events, including death, cerebral or subarachnoid haemorrhage, development of hypertensive retinopathy grade III or IV, enlarging or dissecting aneurysm, congestive heart failure not controllable without diuretics or antihypertensive drugs, hypertensive encephalopathy, increase in left ventricular hypertrophy and a rise in blood pressure exceeding the defined limits.

All patients' data are recorded and sent to the co-ordinating office every 3 months.

Statistical methods

A paired t-test was used for within-group changes and a standard unpaired t-test for comparison between the active and placebo groups.

Results

Characteristics at admission

On 1st June 1983, a total number of 843 patients had been admitted into the trial. Their characteristics are given in the tables. No significant differences between the two groups were generally found at admission, and both groups were therefore comparable at the start of the trial, except for cardiothoracic ratio ($p = 0.004$).

The average age was 71.9 (tabel I) and patients up to 97 years of age were admitted to the trial. Only 30 per cent of the patients were males. In the total study population, obesity was not a major problem since the mean body weight was 67.0 kg for an average height of 1.59 m. The cardio-thoracic ratio averaged 52.4 per cent, which could be considered high in a middle-aged population but is frequently seen in a population over age 60.

The cause of hypertension was not determined in the majority of cases, since in most patients examinations such as renal arteriography were not performed. Renal parenchymal disease was considered to be the cause in 7 per cent. Renovascular hypertension was suspected in 15 patients. In some cases a tentative diagnosis was made and an additional possible diagnosis suggested. The total number of aetiological diagnoses therefore exceeds the number of patients entered.

Drug intake

The drug intake in the actively treated patients is given in table II. The intake of the diuretic was relatively constant throughout the trial period; only a few patients were taking methyldopa after 3 months, while from one year on the methyldopa intake averaged about 317 mg daily.

TABLE II: AVERAGE DRUG INTAKE IN THE ACTIVE TREATMENT GROUP (IN MG)

	Hydrochlorothiazide	*Triamterene*	*Methyldopa*
After 3 months (n = 353)	34 ± 0.7	67 ± 1.3	43 ± 10
After 1 year (n = 285)	38 ± 0.8	76 ± 1.6	245 ± 26
After 2 years (n = 221)	37 ± 0.9	74 ± 1.8	325 ± 37
After 3 years (n = 156)	37 ± 1.1	73 ± 2.2	325 ± 45
After 4 years (n = 109)	37 ± 1.3	74 ± 2.6	330 ± 54
After 5 years (n = 70)	40 ± 1.6	80 ± 3.1	360 ± 71

Blood pressure

The sitting systolic and diastolic (phase 5) blood pressures before and during the study are given in fig. 1. In the placebo group, both the systolic and diastolic blood pressure fell significantly ($p < 0.001$) between the initial pressure and the blood pressure after 3 months; subsequent changes in pressure were small and not significant. In the actively treated group the fall in blood pressure during the first three months was 23/10 mm Hg and at 3 months the fall in blood pressure was significantly larger in the actively treated group ($p < 0.001$): this difference was mainly due to administration of the diuretic. After 3 months the systolic and diastolic blood pressures continued to decrease in the actively treated group, probably as

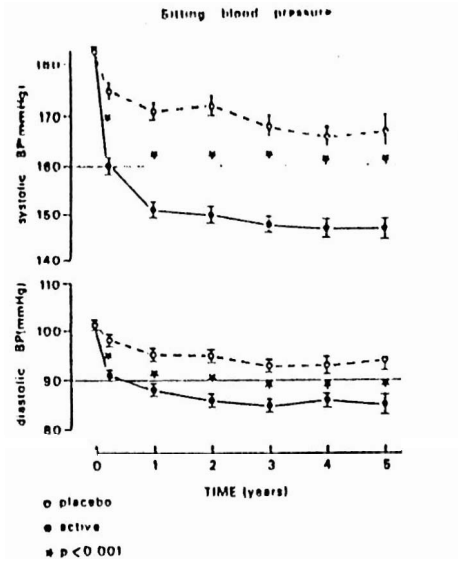

Fig. 1. Changes in sitting systolic and diastolic blood pressure during the 5-year treatment period: mean ± SEM values. In this and in the following figures numbers refer to the number of patients studied at the end of each time period.

a consequence of administration of methyldopa (table II). At 5 years the average sitting blood pressure was 20·0 mm Hg higher in the placebo-treated group than in the actively treated group.

A minority of patients have been followed for five years and not all have been followed for three months.

Body weight

At admission the body weight was similar in both groups (table I); at no time during the first five years was there a significant difference in body weight between the two groups.

Serum creatinine

The serum creatinine levels were similar in both groups at admission. In the placebo group serum creatinine changes were not significant. In the active treatment group an increase in serum creatinine was observed, and during the trial serum creatinine was significantly higher in the active treatment group than in the placebo group (fig. 2). In this active treatment group, the change in sitting systolic blood pressure (x) over the first three months was inversely correlated with the change in serum creatinine (y) according to the regression equation: $y = 7.434 - 0.230\,x$ ($n = 336$; $r = -0.21$; $p < 0.001$).

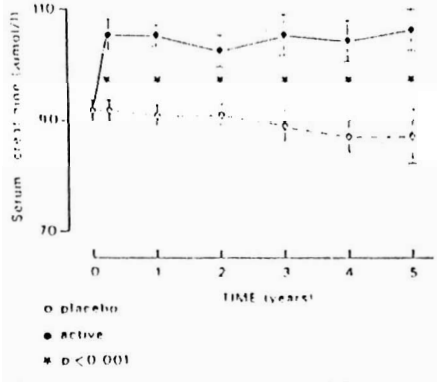

Fig. 2. Changes in serum creatinine levels during the 5-year treatment period: mean ± SEM values.

Serum uric acid

The serum uric acid levels in the two groups were not significantly different at admission. In the placebo group no significant increase was observed, but in the active treatment group serum uric acid increased by 0.07 mmol/l during the first year and remained high during the subsequent years (fig. 3). Changes in serum uric acid (y) within the first year were significantly correlated with changes in serum creatinine (x) according to the following formula: in the placebo group: $y = 0.0008 + 0.0009\,x$ ($n = 246$; $r = 0.24$; $p < 0.001$); in the active treatment group: $y = 0.0494 + 0.0011\,x$ ($n = 260$; $r = 0.30$; $p < 0.001$).

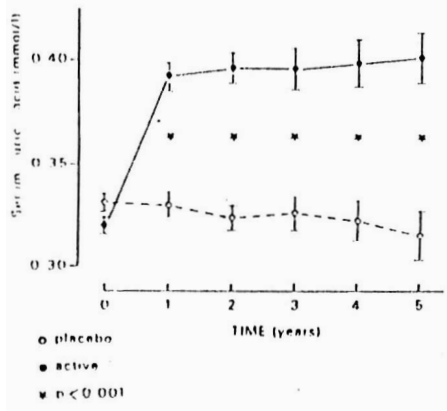

Fig. 3. Changes in serum uric acid levels during the 5-year treatment period: mean ± SEM values.

Serum potassium and sodium

The combination of a thiazide diuretic with a potassium-sparing agent provoked only small changes in serum potassium; but the small differences in serum potassium level between active treatment and placebo group reached statistical significance (fig. 4).

The serum sodium concentrations were similar in both groups at admission, and subsequent changes were small and statistically insignificant.

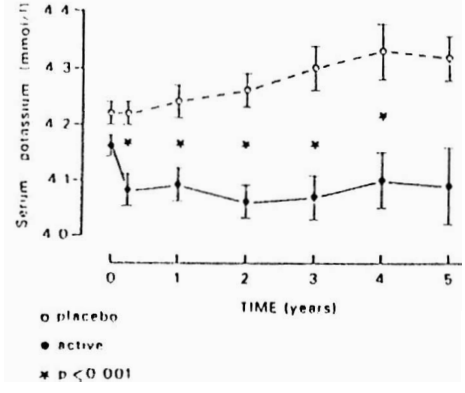

Fig. 4. Changes in serum potassium levels during the 5-year treatment period: mean ± SEM values.

Blood glucose

As reported elsewhere[10] the fasting blood glucose level did not change significantly in the placebo group during the first three years, but rose significantly in the active treatment group (fig. 5).

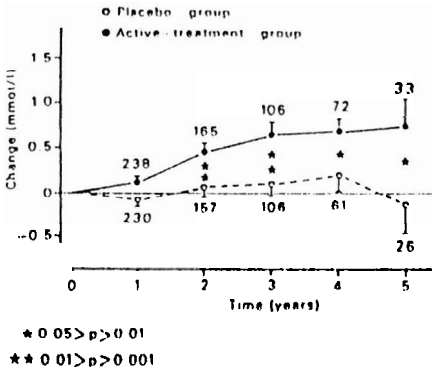

Fig. 5. Changes in fasting blood glucose levels during the 5-year treatment period: mean ± SEM values.

Serum cholesterol

The serum cholesterol level was similar in both groups during the run-in period. In the course of time a slight decrease was noted in the two groups, but so far no significant difference has emerged between the placebo and the active treatment group.

Discussion

The ultimate goal of antihypertensive therapy is to reduce mortality and morbidity while maintaining the quality of life. The purpose of the present multicentre trial is to evaluate whether this aim can be achieved in elderly subjects, but a definite answer cannot yet be given since it was decided in the study protocol that: 1) these data should not be communicated during the trial, and 2) the trial should be terminated when significant results are found. However, it was already shown in the pilot trial[11] that initiation of hypotensive therapy can produce a slow, progressive reduction in pressure without an excess of terminating events in the active treatment group as compared with the placebo group.

A blood pressure difference of 23/10 mm Hg between the groups was already achieved after three months of therapy and this difference was well maintained during the 5 years of observation. According to Kannel et al.[1] the risk of an atherothrombotic brain infarction increases by about 30 per cent for each 10 mm Hg increase in systolic pressure. The present trial might therefore be expected to detect a difference in stroke incidence. However, it has not been clearly established how long such a difference in blood pressure has to be maintained or whether reduction in pressure from a previously high level has the same beneficial effect as that calculated from observed casual blood pressure differences in epidemiological studies not involving intervention. Furthermore, one has to realize that any potential benefit resulting from the fall in blood pressure may be offset by unwanted side effects of treatment. For instance, diuretics may cause a variety of metabolic derangements, including impairment of renal function, electrolyte disturbances and deterioration of glucose tolerance.

Serum creatinine, indeed, rose during the first three months of active treatment and remained increased as compared with the placebo group during the follow-up. The increase in serum creatinine was clearly associated with the hypotensive effect, due to either a non-specific effect of blood pressure reduction on GFR or a direct effect of the diuretic on renal secretory function. In the placebo group there was little change in serum creatinine or serum uric acid. In the active treatment group, however, the serum uric acid level was increased by 0.07 mmol/l and increases in uric acid occurred even in patients in whom creatinine did not change. Nevertheless, changes in serum creatinine were accompanied by parallel changes in serum uric acid. As previously reported, the change in serum uric acid level with diuretic treatment does not only reflect the changes in glomerular filtration as indicated by serum creatinine.

With the drugs used in the present trial, the reduction in pressure was maintained without major disturbances in the serum potassium level. This may be a result of using triamterene as a potassium-sparing compound in the diuretic. Serum sodium, too, was not adversely affected.

Glucose intolerance also is a major risk factor for coronary artery disease and, in this study, treatment enhanced this risk factor: a significant increase in fasting blood glucose was observed in the active treatment group but not in the placebo group. On the other hand, no major differences were found with regard to cholesterol, suggesting that the spontaneous decrease in this variable which seems to occur at a high age[12] is not altered by the thiazide-methyldopa treatment.

In conclusion, the results of the present study indicate that effective lowering of blood pressure with a combination of diuretics and methyldopa is associated with a rise in serum creatinine and uric acid, while glucose tolerance is impaired. The balance between the presumed benefit associated with blood pressure reduction and the possible harm related to enhancement of other risk factors remains to be determined. The overall result of this trial, which continues until 1987, should provide this information.

Acknowledgements – This study is supported by the Belgian Hypertension Committee, the Belgian Medical Research Found (FGWO) and the World Health Organisation.

Capsules of hydrochlorothiazide + triamterene and placebo are supplied by Smith, Kline and French and tablets of methyldopa by Merck, Sharp and Dohme. Their support is gratefully acknowledged.

References

1. Kannel WB, Dawber TR, Sorlie P, Wolfe PA. Component of blood pressure and risk of atherothrombotic brain infarction: The Framingham Study. Stroke 1976;7:327-31
2. Amery A, Wasir H, Bulpitt C, et al. Aging and the cardiovascular system. Acta Cardiol (Brux) 1978;33:443-67.
3. Carter AB. Hypotensive therapy in stroke survivors. Lancet 1970;1:485-9
4. Hypertension – Stroke Co-operative Study Group. Effect of antihypertensive treatment on stroke recurrence. JAMA 1974;229:409-18
5. Sprackling ME, Mitchell JRA, Short AH, Watt G. Blood pressure reduction in the elderly: a randomised controlled trial of methyldopa. Br Med J 1981;283:1151-3.
6. Report by the Management Committee. Treatment of mild hypertension in the elderly. A study initiated and administered by the National Heart Foundation of Australia. Med J Aust 1981;2:398-402.
7. Veterans Administration Co-operative Study on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. I. Results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. JAMA 1967;202:1028-34.
8. Veterans Administration Co-operative Study on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 1970;213:1143-52.
9. Veterans Administration Co-operative Study on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. III. Influence of age, diastolic pressure and prior cardiovascular disease. Further analysis of side-effects. Circulation 1972;45:991-1004.
10. Amery A, Berthaux P, Bulpitt C, et al. Glucose intolerance during diuretic therapy. Results from the European Workjng Party on Hypertension in the Elderly Trial. Lancet 1978;1:681-3.
11. Amery A, Berthaux P, Birkenhäger W, et al. Antihypertensive therapy in elderly patients. Pilot trial of the European Working Party on High Blood Pressure in the Elderly. Gerontology 1977;23:426-37.
12. Amery A, Birkenhäger W, Bulpitt C, et al. Influence of antihypertensive therapy on serum cholesterol in elderly patients. Acta Cardiol (Brux) 1982;37:235-44.

Announcement

Op zaterdag 19 mei 1984 zal van 10.00 – ca. 15.00 uur in het Academisch Ziekenhuis te Utrecht (Grote Collegezaal) een NIV-symposium plaatsvinden over 'De betekenis van monoclonale antilichamen voor diagnostiek en therapie'.

Inlichtingen te verkrijgen bij het Centraal Secretariaat N.I.V., Lomanlaan 103, 3526 XD Utrecht, tel. 030-885411, toestel 310, van 9.00 – 15.30 uur.

NOTE TO AUTHORS – VANCOUVER STYLE

Most medical journals agreed to accept articles prepared in accordance with the Vancouver style, and will introduce this system from January 1980 on. Consequently, the Editors of *The Netherlands Journal of Medicine* decided to adapt the Instructions to Authors accordingly.

The Netherlands Journal of Medicine publishes original articles, editorials, reviews and short abstracts on clinical and experimental aspects of internal medicine. Contributions from outside The Netherlands are accepted. Manuscripts should be sent to:

L. Offerhaus
Chopinstraat 9
1077 GL Amsterdam

Authors should retain a complete copy of the manuscript, as the Editors do not accept responsibility for loss of papers submitted. Submission of a paper is held to imply that it does not contain material reported or published elsewhere, except as an abstract of 600 words or less.

Manuscripts should be written in English. All papers are published in English. The entire paper (including figures and tables) should be submitted in triplicate, typewritten (double-spaced) on one side of the paper (A4 format) and with margins of about 4 cm. Generally, the paper should be organized as follows: separate title page, summary, introduction, methods, results, discussion, acknowledgements, references, figure legends, and tables.

The *title page* should carry the title of the paper, the names of the authors, and the department or institute and the town where the work was performed. A short running title should also be supplied.

The summary should summarize the important information in the paper and not exceed 200 words.

No abbreviations without definition should be used in the text except those listed below. Mention the statistical method employed. Use a capital initial letter for proprietary names of substances and materials. At first mention of a chemical substance, use the correct chemical designation as well as the generic name.

Number *footnotes* to the texts as follows: (1), and type them at the foot of the page where they belong. Refer to footnotes in the title and the tables with the following symbols and in this order: *, **, ***, †, §.

To indicate *references* in the text, use superior numbers: [1,2,3]. Journal citations in the reference list should be typed double-spaced on a separate page and numbered consecutively in the order in which they appear in the text. The complete title should be given. Names of journals should be abbreviated according to *Index Medicus*, US National Library of Medicine. Examples:

Articles

1. Clemmons DR, Van Wyk J, Ridgway EC, et al. Evaluation of acromegaly by radioimmunoassay of somatedin-C. N Engl J Med 1979; 301:1138-42.

Books

2. Smith JM. Scientific analysis on the pocket calculator. New York: J. Wiley, 1975:12-6.

Articles in books

3. Bird GWG, Wingham J. Sensitization of cells with protein antigens. In: Thompson RA, ed. Techniques in clinical immunology. Oxford: Blackwell Scientific Publications, 1977:56-7.

Enclose figures (unmounted photographs with good contrast printed on glossy white paper, width preferably 78 or 164 mm) in a separate envelope. Note on the back (with a *soft* pencil) the number of the figure and the name of the first author, and clearly indicate which is the top side. Lettering in drawings and diagrams should be large enough to be legible after reduction to column width. Doublespace legends consecutively on a separate sheet. Legends should be concise and clearly explain the figures without reference to the text.

Tables should be typed double-spaced on separate sheets. Quotation-marks and vertical lines should not be used. Tables should be numbered with Roman numerals and should have a brief heading. The use of SI units is allowed.

Seventy-five *reprints* will be supplied to the first (or senior) author free of charge. Additional reprints can be ordered when proofs are returned.

Receipt of the manuscript should be acknowledged by the editor within one week.