Risk Factors for Ischemic Stroke
Dubbo Study of the Elderly

Leon A. Simons, MD; John McCallum, DPhil; Yechiel Friedlander, PhD; Judith Simons, MACS

Background and Purpose—One in 10 deaths in Australia is due to stroke. The predictors of ischemic stroke have not been well defined, although hypertension, atrial fibrillation, and previous stroke have been consistently reported. We report on 98 months' follow-up in a prospective study of cardiovascular disease in the Australian elderly, the Dubbo Study.

Methods—The cohort, first examined in 1988, was composed of 2805 men and women 60 years and older. The prediction of ischemic stroke by potential risk factors was examined in a Cox proportional hazards model, after linkage to hospital and death records.

Results—Three hundred six men and women manifested an ischemic stroke event (ICD-9-CM 433 to 437), and 95 subjects suffered a fatal stroke event. In the multivariate model, the significant independent predictors of stroke were advancing age, female sex (48% lower risk), being married (30% lower risk), prior history of stroke (227% higher risk), use of antihypertensive drugs (37% higher risk), belonging to the highest category of blood pressure reading (67% higher risk), presence of atrial fibrillation (58% higher risk), HDL cholesterol (36% lower risk for each 1-mmol/L increment), impaired peak expiratory flow (77% higher risk for tertile I than for tertile III), physical disability (59% higher risk), and depression score (41% higher risk for tertile III than for tertile I).

Conclusions—These findings suggest that morbidity and mortality associated with ischemic stroke can be predicted by various clinical indicators, some of which may be amenable to intervention. The matters of impaired peak expiratory flow, depression score, and ischemic stroke require further study. (***Stroke***. 1998;29:1341-1346.)

Key Words: elderly ∎ prospective studies ∎ risk factors ∎ stroke, ischemic

One in 4 deaths in Australia in 1994 was due to CHD; 1 in 10 was due to stroke.[1] Current treatment for patients with established stroke is relatively ineffective. Surveys of stroke survivors indicate that more than 50% have severe and permanent disability.[2] Compared with the volume of prospective studies in CHD, there have been relatively fewer population studies investigating the precursors of stroke. Although most strokes occur in elderly people, exposures at younger ages may be significant ones. Effective risk factor intervention offers a real hope of reducing stroke morbidity and mortality. Randomized, controlled intervention studies have demonstrated significant prevention of stroke with management of hypertension[3] or hypercholesterolemia.[4]

Certain risk factors have consistently been identified as significant predictors of stroke outcome (mainly fatal stroke): age, hypertension, antihypertensive treatment, alcohol intake (inverse prediction), previous stroke, and atrial fibrillation.[5–9] Other risk factors much less consistently associated with stroke include smoking, diabetes, previous CHD, ECG evidence of left ventricular hypertrophy, excessive alcohol intake, and family history of stroke.[5,7,9,10] The relationship between serum cholesterol and stroke remains somewhat

elusive,[8] possibly because of a negative association with hemorrhagic stroke on one hand[11,12] and a positive association with ischemic stroke on the other.[9,12] The present report examines the prediction of ischemic stroke by demographic, psychosocial, behavioral, and conventional cardiovascular risk factors in a cohort of elderly Australians followed for 98 months since 1988.

Subjects and Methods

Subjects and Baseline Examinations

The Dubbo Study is an ongoing prospective study of cardiovascular disease in an elderly Australian cohort first examined in 1988 to 1989.[13] All noninstitutionalized residents of the town of Dubbo born before 1930 were eligible; participation rate was 73% (1235 men and 1570 women). Methods and measures have been described in detail elsewhere.[2,13] Briefly, baseline examinations comprised demographic, psychosocial, and standard cardiovascular risk factor assessments. The medical examination included height and weight, blood pressure (10 minutes' seated rest; phase V diastolic; mean of two readings), resting ECG (Minnesota Code),[14] and peak expiratory flow rate (Wright peak flowmeter; best of two attempts).[15] We obtained venous blood (after 12 hours' fast) for assessment of total serum cholesterol and triglycerides by automated enzymatic methods,[16,17] high density lipoprotein (HDL) cholesterol after precipita-

tion with phosphotungstic acid/MgCl$_2$,[18] and lipoprotein(a) using a commercial ELISA kit.[19] The laboratory participated in the Australian Lipid Standardization Program and used standards traceable to the Center for Disease Control, Atlanta, Ga.

A baseline questionnaire was administered to explore measures of social support, depression status,[20] education, cognitive function, alcohol and tobacco use, medications, general medical history, family history of CHD, myocardial infarction and chest pain, physical activity, self-rated health, and physical disability. The study was approved by Institutional Ethics Committees at St Vincent's Hospital Sydney, the University of New South Wales, and the Australian National University. All participants gave informed written consent.

Follow-up Procedures For Stroke Outcomes

Stroke outcomes were ascertained exclusively by review of hospital and death records (the latter used only in case of death outside hospital). Postal surveys were conducted every 2 years to confirm vital status and identify any outcomes that might have been treated outside the single regional hospital. The latest postal survey in 1997 successfully traced more than 98% of participants. Hospital records were coded internally according to ICD-9-CM[21] and then reviewed by our own staff. Most subjects were admitted to the hospital when stroke or transient ischemic attack was suspected. CT of the head was performed in 70% of stroke cases. Cerebral arteriography was not routinely performed. Subjects with hemorrhagic stroke events (codes 431 and 432) were few (n=29) and excluded from all analyses. Ischemic stroke was taken as the inclusive coding 433 to 437. Transient ischemic attack (code 435) was included in the grouping "all strokes," as in the Framingham Study.[6] However, code 438 was excluded, since this represented only 9 subjects in whom the precise diagnosis was uncertain. Outcomes up to June 30, 1997, were included in this analysis, a median 98 months' follow-up.

Statistical Methods

For the purpose of risk factor studies, subjects were followed until the first in-study presentation of stroke. Stroke at study entry was based on any previous diagnosis by a physician. CHD at study entry was defined as a positive myocardial infarction questionnaire, and/or positive angina (Rose) questionnaire,[14] and/or ECG changes (Q waves, T-wave inversion, or left bundle branch block). Many of the variables used are self-explanatory, but some require specific definition:

(1) Blood pressure (4 categories): SBP <140 mm Hg and DBP <90 mm Hg; SBP 140 to 159 or DBP 90 to 94; SBP 160 to 199 or DBP 95 to 99; SBP ≥200 or DBP ≥100.

(2) A separate variable indicating the intake of antihypertensive medication.

(3) Cigarette smoking: never, former, or current.

(4) Diabetes mellitus: prior history, fasting plasma glucose level of ≥7.8 mmol/L, and/or using medication for diabetes.

(5) Lipoprotein(a): quintiles, because of the skewed distribution.[18]

(6) Peak expiratory flow: tertiles, with tertile I indicating the greatest impairment.

(7) Self-rated health (3 categories): very good to excellent, good, and fair to poor.

(8) Disability (in 3 categories based on physical ADL): no disability, one impairment in ADL, and >1 impairment in ADL.

TABLE 1.   Baseline Characteristics of Study Population

No. of subjects	2805
Men	1235 (44%)
Mean age (range), years	69 (60–98 years)
Proportion 60–69 years of age	1585 (57%)
Prior coronary heart disease	607 (22%)
Prior stroke	155 (6%)
Current smoker	426 (15%)
On antihypertensive drugs	1348 (48%)
SBP 160–199 or DBP 95–99	658 (24%)
SBP ≥200 or DBP ≥100	197 (7%)
Atrial fibrillation	66 (2%)
Left ventricular hypertrophy	78 (3%)
Cholesterol	
5.00–6.49 mmol/L	732 (26%)
≥6.50	430 (15%)
Disability: >1 impairment in ADL	636 (23%)
Self-rated health: fair-poor	592 (21%)

(9) Depression score: tertiles, tertile III indicating greater evidence of depression.

The independent contribution of any risk factor to stroke outcome was examined in a Cox proportional hazards model, which was used to account for the variable follow-up time. Point estimates and 95% confidence intervals for the RR of stroke were calculated from the regression coefficients. Variables were entered into the model in a single block. A final model was recalculated as the most parsimonious version, including only significant variables or others that were potential confounders. Variables were introduced as continuous or categorical variables, as indicated in "Results." With categorical variables, the lowest or opposite category served as the reference group. Interaction terms between various independent predictors were also explored in the final model. The proportional hazards model assumes constant relative hazard over the length of follow-up. This assumption was confirmed by a log-minus-log hazard plot demonstrating parallel curves over all categories for various predictors. Statistical analyses were conducted with *SPSS for Windows, Release 7.0* (SPSS, Inc).

Results

Table 1 presents a brief summary of the baseline characteristics of the population in 1988 to 1989. Of note was the prior history of stroke in 6% of the subjects and evidence of prior CHD in 22%. Over a median 98 months' follow-up, 306 men and women (11%) manifested a stroke outcome. Of these outcomes, 95 were fatal events. There were 683 deaths (24%) from all causes over the period. Sex- and age-specific

TABLE 2.   Age- and Sex-Specific Incidence Rates for Ischemic Stroke During Median 98-Month Follow-up

	Men		Women		Total Population	
	No.	Rate/100	No.	Rate/100	No.	Rate/100
60–90 years	61	8.3	34	4.0	95	6.0
70–79 years	78	19.0	70	12.8	148	15.4
80+ years	18	20.7	45	25.9	63	24.1
Age-standardized rate*		12.3		9.6		10.8

*Based on new world standard population,[22] calculated by direct method.

TABLE 3.   Proportional Hazards Models For Ischemic Stroke Outcome

	Relative Risk (95% Confidence Intervals)	
	All Stroke	Fatal Stroke
Demographic		
Age	1.06 (1.04–1.09)*	1.10 (1.06–1.14)*
Female sex	0.52 (0.38–0.70)*	0.45 (0.25–0.79)†
Currently married	0.70 (0.54–0.91)†	0.46 (0.28–0.76)†
Cardiovascular risk factors		
Prior stroke	3.27 (2.39–4.47)*	3.07 (1.81–5.21)*
Prior CHD	1.15 (0.87–1.51)	1.05 (0.64–1.71)
Diabetes	1.23 (0.82–1.84)	0.97 (0.43–2.16)
Blood pressure medication	1.37 (1.04–1.80)‡	1.44 (0.87–2.38)
SBP 140–159 or DBP 90–94	1.01 (0.74–1.37)	1.03 (0.59–1.81)
SBP 160–199 or DBP 95–99	1.26 (0.92–1.72)	1.06 (0.60–1.88)
SBP ≥200 or DBP ≥100	1.67 (1.09–2.57)‡	2.08 (1.01–4.29)‡
Atrial fibrillation	1.58 (0.91–2.75)§	3.11 (1.38–7.00)‡
Total cholesterol	1.02 (0.92–1.14)	0.95 (0.78–1.17)
HDL cholesterol	0.64 (0.44–0.94)‡	0.54 (0.27–1.07)§
Triglycerides	1.06 (0.97–1.16)	1.09 (0.92–1.29)
Smoking		
Former	0.94 (0.70–1.26)	0.91 (0.53–1.58)
Current	1.14 (0.78–1.67)	1.07 (0.52–2.18)
Body mass index	0.96 (0.93–0.99)‡	0.87 (0.81–0.93)*
Peak expiratory flow		
Tertile I	1.77 (1.26–2.50)†	1.99 (0.96–4.13)§
Tertile II	1.26 (0.89–1.80)	1.52 (0.71–3.23)
Psychosocial and behavioral		
Disability		
1 ADL	1.11 (0.81–1.52)	1.54 (0.83–2.86)
>1 ADL	1.59 (1.15–2.21)†	2.23 (1.18–4.22)‡
Self-rated health		
Good	0.88 (0.66–1.16)	0.83 (0.49–1.41)
Fair-poor	0.74 (0.53–1.04)	0.68 (0.38–1.24)
Depression		
Tertile II	1.17 (0.84–1.64)	1.73 (0.85–3.52)
Tertile III	1.41 (1.01–1.96)‡	2.30 (1.14–4.64)‡

For categorical variables, the opposite or missing category served as reference group with RR=1 (eg, male sex, no prior stroke, never smoked, peak expiratory flow tertile III, no disability). For continuous variables, RR relates to each unit increment (e.g., 1 year of age, 1 unit of body mass index, 1 mmol/L cholesterol).

*$P<0.001$; †$P<0.01$; ‡$P<0.05$; §$P<0.10$.

incidence rates for all ischemic stroke events are presented in Table 2. The incidence rates were higher in men than in women up to 79 years of age; thereafter, they were higher in women. Overall, rates increased with age.

The following variables were removed from the final multivariate model because they did not predict stroke outcome and were not considered major confounders: lipoprotein(a), alcohol intake, ECG evidence of left ventricular hypertrophy, and family history of premature CHD. The final Cox proportional hazards models included many significant
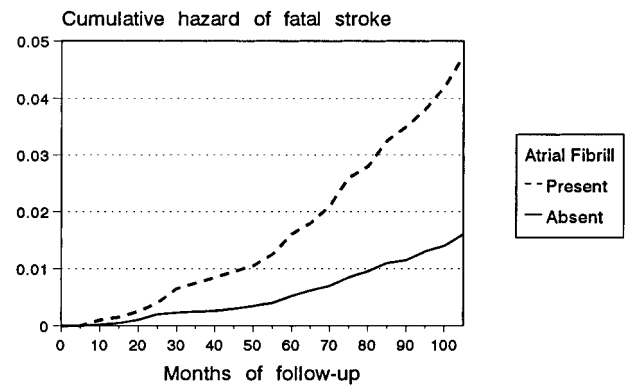

Figure 1. Cumulative hazard of fatal stroke by presence or absence of atrial fibrillation in the proportional hazards model.

predictors, and the results are presented in Table 3 for all stroke events and for fatal stroke events.

The significant independent predictors of stroke were increasing age, female sex (48% lower risk than males), being married (30% lower risk), prior history of stroke (227% higher risk), use of antihypertensive medication (37% higher risk), belonging to the highest category of blood pressure reading (67% higher risk than for the lowest category), presence of atrial fibrillation (58% higher risk; $P<0.10$), HDL cholesterol (36% lower risk for each 1-mmol/L increment), body mass index (minimally lower risk with increasing values), peak expiratory flow rate (77% higher risk for tertile I than for tertile III), physical disability (59% higher risk for those with >1 impairment in ADL) and depression score (41% higher risk for those in tertile III than in tertile I). Notable by their absence of significant prediction were prior CHD, diabetes, total cholesterol and triglycerides, current cigarette smoking, and alcohol intake.

There were generally similar predictors for fatal stroke events, although statistical significance was reduced because of smaller event numbers. The following contrasts, though, were noted in regard to prediction of fatal stroke: the presence of atrial fibrillation was associated with a >200% higher risk of fatal stroke and a 58% higher risk of any stroke; depression score tertile III was associated with a 130% higher risk of fatal stroke and a 41% excess risk of any stroke. Fig 1 and 2 illustrate the cumulative hazard in the multivariate model for
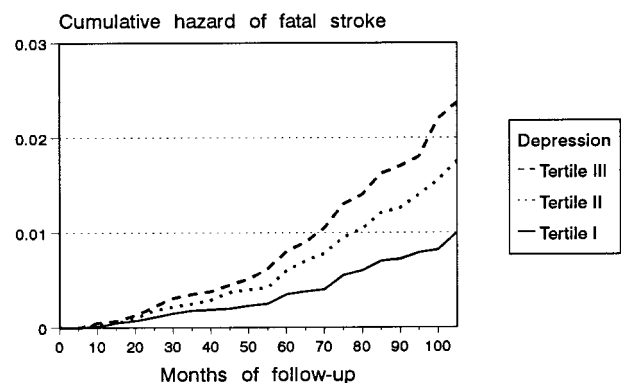

Figure 2. Cumulative hazard of fatal stroke by depression score tertile in the proportional hazards model.

TABLE 4. Age- and Sex-Specific Models for Prediction of Ischemic Stroke

	Relative Risk (95% Confidence Intervals)	
	60–69 Years	70+ Years
Depression		
Tertile II	1.08 (0.64–1.84)	1.28 (0.82–1.99)
Tertile III	0.83 (0.46–1.48)	1.83 (1.18–2.83)*
	Men	Women
Currently married	0.85 (0.60–1.25)	0.54 (0.36–0.82)*
SBP 140–159 or DBP 90–94	0.91 (0.60–1.39)	1.18 (0.73–1.89)
SBP 160–199 or DBP 95–99	1.27 (0.84–1.93)	1.31 (0.81–2.14)
SBP ≥200 or DBP ≥100	1.11 (0.55–2.23)	2.46 (1.36–4.43)*

Proportional hazards models were calculated separately for age categories 60–69 and 70+ years and for men and women. Only those variables having significant interactions with age or sex from Table 3 are shown.

*P<0.01.

fatal stroke by presence of atrial fibrillation and by tertile of depression score.

The multivariate model was recalculated to explore interaction terms between significant predictors of stroke events and age, sex, and past history of stroke. The significant interactions were blood pressure reading and sex (P<0.02), marital status and sex (P<0.05), and depression score and age (P<0.001). The model was recalculated for the separate sexes and for those 60 to 69 years and 70+ years of age (Table 4). Being married significantly predicted stroke outcome only in women (RR, 0.54). Blood pressure reading significantly predicted stroke only in women and in a graded fashion (RR for highest category, 2.46). Depression score tertile III significantly predicted stroke only in the age group 70+ years (RR, 1.83).

Discussion

This is the first report on stroke outcomes from the prospective Dubbo Study of cardiovascular disease in the Australian elderly. Our earlier reports have explored the more frequent CHD outcome.[23] To our knowledge, only one other Australian study, the Busselton Study, has reported prospective risk factor data for stroke.[9] Although stroke is predominantly a disease of the elderly, nearly all other longitudinal studies of stroke followed subjects from middle age into old age.[8] The Dubbo Study differs in this major respect; it commenced with senior citizens having a mean age of 69 years. Other studies performed specifically in the elderly have yet to publish definitive stroke analyses.[24,25] A study of cardiovascular disease specifically in the elderly represents a study of selected "survivors," and this could bias some of the risk factor relationships. However, this type of study is important because it explores risk factor relationships in the "well elderly."

We have confirmed certain risk factors for ischemic stroke that have been consistently identified in earlier studies; namely, increasing age, hypertension and use of antihyper-

tensive treatment, prior stroke, and presence of atrial fibrillation.[5–9] We have identified additional risk factors that have been much less consistently associated with ischemic stroke: namely, male sex, HDL cholesterol, body mass index, and physical disability. We have identified additional risk factors not previously linked to increased stroke risk: namely, being unmarried, having impaired peak expiratory flow, and having some evidence of depression. Finally, we have failed to confirm prediction of ischemic stroke by important vascular risk factors, such as cigarette smoking, diabetes, previous CHD, left ventricular hypertrophy, total cholesterol or triglycerides, lipoprotein(a), and alcohol intake.

Antihypertensive treatment predicting future stroke or coronary disease is a finding that sometimes excites comment.[9,23,24] It may be speculated that an increased risk of stroke in the presence of hypertension may not be fully reversible, or perhaps treatment has been inappropriate or inadequate. However, clinical trials in the elderly have clearly demonstrated cardiovascular disease prevention by antihypertensive drug therapy,[3] albeit under strictly controlled circumstances.

Approximately 85% of strokes result from cerebral infarction. Emboli from the heart may be responsible for up to 20% of these cases.[26,27] Almost one half of these events complicate nonvalvular atrial fibrillation.[28] Given the age of the Dubbo cohort, it is possible that a very small proportion of subjects with atrial fibrillation may have rheumatic valvular disease. We possess no specific data on this point, but it is likely that atrial fibrillation in the majority of our subjects was nonvalvular in origin. In the presence of atrial fibrillation, we have identified a 60% excess risk of stroke and a 200% excess risk of stroke death (Table 3). The Framingham Study reported an RR of stroke with atrial fibrillation of 2.6 in the age group 60 to 69 years, 3.3 in those 70 to 79 years, and 4.5 in those older,[6] suggesting an interaction with age. We found no similar interaction between atrial fibrillation and age in the prediction of ischemic stroke. In the Busselton Study the RR for stroke mortality in the presence of atrial fibrillation was 5.9.[9] Anticoagulant therapy with warfarin has been shown to reduce the future risk of stroke in patients with atrial fibrillation but would not be indicated below 65 years in the absence of other major risk factors.[29]

The serum cholesterol–stroke association remains an enigma. If low serum cholesterol concentration is associated with an increased risk of hemorrhagic stroke[11,12] and increased cholesterol is associated with an increased risk of ischemic stroke,[9,12] this could be the reason that an examination of 13 000 strokes in 450 000 persons drawn from 45 prospective cohorts failed to find an association between serum cholesterol and stroke (ie, hemorrhagic and ischemic stroke combined).[8] In the present study there was no evidence of a quadratic relationship between total cholesterol and stroke. However, HDL cholesterol was an important predictor of ischemic stroke, as we have already shown for CHD in this elderly cohort[23] and others have shown for asymptomatic carotid atherosclerosis.[30] Confusion in the relationship between total cholesterol and stroke may only be settled when studies can report a greater number of events in carefully documented, different stroke types. To add to the present

interest, it is becoming clear that statin drugs used to lower cholesterol levels do indeed reduce future stroke risk.[4] But it is recognized that statin drugs do more than merely lower serum cholesterol level.[31]

The relationship between impaired peak expiratory flow and ischemic stroke has not, to our knowledge, been previously reported. There has been renewed interest in the relationship between CHD and obstructive airways disease or chronic bronchitis.[32] We have previously reported[33] that peak expiratory flow tertile I was associated with increased risk of all-cause mortality (62% excess risk in men and 92% in women) and CHD mortality (75% excess risk in men and 158% in women). Peak expiratory flow rate, one measure of obstructive airways disease, is influenced by age, height, and gender.[15] Our CHD findings were obtained in a multivariate model that controlled for these and many other variables. Our present findings vis-a-vis stroke were not materially influenced if height was introduced into the proportional hazards model. A Swedish study noted a trend toward increasing risk of stroke in those with reduced vital capacity.[5] The Cardiovascular Health Study is another prospective study in the elderly that has assessed forced expiratory volume in one second and vital capacity, but it has not yet reported specific prospective findings in the stroke area.[25] The pathways from impaired peak expiratory flow and respiratory disease to CHD or stroke are unclear. Cigarette smoking is one suggested linkage, although not supported in the present data. Other pathways may include changes in blood coagulation[34] or the presence of specific infection.[35]

Currently married women had a 46% lower risk of stroke, while marital status was not predictive for men. This contrasts with our finding that marriage predicted a 25% lower all-cause mortality rate in both men and women.[36] The smaller surviving cohort of married women (50% of women) may be less exposed to stroke risk than the larger group of surviving married men (79% of men). The reasons for this are unclear but may relate to stronger selection biases for women or differential benefits from social support in marriage. We have observed apparent negative effects of marriage on all-cause mortality for male and female diabetics,[37] so these factors are known to be complex in this population.

We have not assessed clinical depression. However, subjects in tertile III of the depression score distribution would have more depressive symptoms than those in tertile I.[20] There is evidence from MRI studies[38,39] that changes in the brain (deep white matter hyperintensities and reduction in basal ganglia volumes) are associated with onset of depression in late life. These changes appear to be associated with vascular risk factors such as hypertension or diabetes,[39] but this will require confirmation in ongoing studies. If late-onset depression has a vascular basis, we have another plausible marker for future stroke. It is not suggested that depression per se leads to stroke. Rather, it is possible that depression and ischemic stroke share a common etiology. At entry to the Dubbo Study, 50% of subjects having a past history of stroke belonged to depression score tertile III compared with 35% of subjects having no past history. The corresponding proportions in depression score tertile I were 14% and 31%. However, cross-sectional data of this type should be viewed with extreme caution, since these subjects were manifesting increased evidence of depression after the onset of stroke or other serious illness. This was similarly true for cross-sectional relationships with physical disability. Almost 50% of subjects with prior stroke had >1 impairment in ADL, the proportion being only 21% in those without prior history. In many ways physical disability acted as a surrogate for prior stroke in predicting ischemic stroke.

To summarize some of our key findings (and those of others), hypertension predicts ischemic stroke and blood pressure management has been shown to prevent future strokes.[3] Nonvalvular atrial fibrillation predicts ischemic stroke and anticoagulant therapy with warfarin has been shown to reduce the risk of future stroke.[29] This therapy is presently underutilized.[40,41] Impaired peak expiratory flow predicts future stroke, but the benefits of treatment in prevention of stroke are unknown. Depression predicts ischemic stroke, and both conditions may have a common etiology. Treatment of stroke risk factors might conceivably reduce the future risk of depression or stroke.

Acknowledgments

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Leon A. Simons, John McCallum, Yechiel Friedlander and Judith Simons

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