

41

Neoplasms of the central nervous system

Epidemiologic considerations

Alan K. Percy, M.D., Lila R. Elveback, Ph.D.,
Haruo Okazaki, M.D., and Leonard T. Kurland, M.D.

THIS PAPER REPORTS the incidence and survivorship for various neoplasms affecting the central nervous system (CNS) in the resident population of Rochester, Minn., for the thirty-four-year period 1935 through 1968. It is desirable to have such statistics for various populations. Information of this type might disclose trends and population selection of disease which could provide relevant clues to etiology. Also, where comparisons can be extended to regional or national populations, such incidence data would be of value in planning for research and the provision of medical care.

Most of the earlier reports dealing with the frequency of neoplasms affecting the central nervous system have been based on the experience of individual neurosurgeons, autopsy series, or proportionate rates of hospital admissions. While providing valuable descriptions of clinical or pathologic experiences, these data do not necessarily reflect an accurate picture of the incidence of neoplasms or their frequency by type in the population.

Since the early part of this century, the medical practice in Rochester has been centered mainly at the Mayo Clinic. For several decades, approximately one-half of the Rochester population has been seen annually at one of the Mayo Clinic facilities for the diagnosis or treatment of minor or serious accidents or illnesses or for routine examinations. Diagnoses made by clinic physicians, whether at the clinic, in affiliated hospitals, or at autopsy,

have been entered on a master sheet of the patient's record, cross-indexed, and processed for automated retrieval.

In 1958, Kurland¹ presented the results of an earlier survey in which it was noted that primary intracranial tumors represented 1% of the deaths in the Rochester population during the years 1945 through 1954. That survey, one of the first based on a defined population, yielded incidence rates for neoplasms of the central nervous system that exceeded the rates from all other population studies. The age-specific incidence rate of primary brain neoplasms was noted to increase dramatically with increasing age. However, the population and the number of cases ascertained in Kurland's survey were admittedly small, perhaps allowing for chance fluctuations of some magnitude. The current investigation enlarges the study period to include all cases available through the enlarged diagnostic index of the Rochester epidemiology program and to explore possible

From the Department of Medical Statistics, Epidemiology, and Population Genetics and the Department of Experimental and Anatomic Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Dr. Percy was the recipient of Teacher-Investigator Award NS-11,016.

This work was supported in part by research grant GM-14231 from the National Institutes of Health, Public Health Service.

Submitted for publication April 5, 1971; accepted April 12, 1971.

Reprint requests to Section of Publications, Mayo Clinic, Rochester, Minn. 55901.

trends.
study.

METHO.

The
and an
resident
vous sy
diagnos
A reside
home w
ester for
of the a
individu
tate dia
symptom

All c
or meta
tumors
spinal c
plasms
few ne
the CN
classifi
or prob
logic or
servatio

All ca
dently
to the
diagnos
neurolo
slides ob
by the d
cation.

Incide
date of
the three

Primary
Primary
Primary
Primary
Metastatic
Total

Total (M)

trends during the nearly thirty-five years under study.

METHODS

The review of records of the Mayo Clinic and ancillary resources was confined to those residents of Rochester in whom a central nervous system neoplasm was suggested on the diagnostic cross-index from 1935 through 1968. A resident was defined as any individual whose home was within the physical limits of Rochester for at least one year prior to the diagnosis of the disease. Care was taken to exclude any individual who moved to Rochester to facilitate diagnosis or treatment after the onset of symptoms.

All cases were categorized as being primary or metastatic lesions. The cases of primary tumors were subdivided as neoplasms of the spinal cord, pituitary, or brain. Primary neoplasms of the nerve roots and meninges and a few neoplasms from adjacent tissues affecting the CNS were also included. All cases were classified as definite (confirmed histologically) or probable (strongly suspected on roentgenologic or clinical grounds alone or by direct observation of an otherwise inoperable lesion).

All case abstracts were reviewed independently to establish proper placement according to the above classification. Almost all clinical diagnoses had been made by Mayo Clinic staff neurologists. One of us (H.O.) reviewed all slides obtained at operation or autopsy to verify the diagnosis and provide histologic classification.

Incidence rates per 100,000 population by date of diagnosis were calculated for each of the three decades from 1935 through 1964 and

for the four years from 1965 through 1968 by using the number of cases in the numerator and the respective decennial census in the denominator. For the period 1965 through 1968, an estimate of the population was based on a special 1965 census.

RESULTS

During the thirty-four-year period of this study, 297 cases of intracranial and intraspinal neoplasms were identified among the resident population of Rochester. One hundred seventy-four patients had primary neoplasms, including 1 patient with 2 histologically distinct primary neoplasms. The remaining 123 patients had metastatic tumors to the brain or spinal cord, including 4 patients who also had a primary tumor of the brain. Of the 686 cases reviewed, 389 were not included because of nonresidency (131), neoplasm not of the central nervous system (256), or onset prior to 1935 (2).

The numbers of primary neoplasms of the brain, pituitary, and spinal cord, as well as the number of metastatic lesions, are presented in Table 1 by sex for each of the study periods. Of the 174 primary neoplasms, 93% were histologically confirmed and the remainder were diagnosed by direct visualization or by roentgenologic evidence. If the pituitary neoplasms, which are often diagnosed on the basis of clinical and roentgenologic evidence, are excluded, 95% of the diagnoses of primary neoplasms of the brain and spinal cord were established histologically. Two of the neoplasms lacking histologic confirmation were observed directly at operation but no biopsy could be obtained.

In this study, 63 (36%) of the 174 primary central nervous system neoplasms were first

TABLE 1
NEOPLASMS OF THE CENTRAL NERVOUS SYSTEM BY SITE, SEX,
AND STUDY PERIOD, ROCHESTER, MINN., 1935-1968

Type	1935-1944		1945-1954		1955-1964		1965-1968		1935-1968	
	M	F	M	F	M	F	M	F	M	F
Primary in brain, certain	6	7	9	23	31	36	9	12	55	78
Primary in brain, probable	0	0	0	1	0	1	1	3	1	5
Pituitary	3	1	5	1	4	5	2	0	14	7
Primary in spinal cord	2	2	2	4	2	0	1	1	7	7
Metastatic	4	8	9	24	24	39	9	6	46	77
Total	15	18	25	53	61	81	22	22	123	174
Total (M and F)	33		78		142		44		297	

diagnosed at autopsy (Table 2). In 24 (38%) of the 63 cases, there were some neurologic symptoms or signs or both but the diagnosis had been other than neoplasm. In 2 cases, autopsy was performed for medicolegal reasons after automobile accidents. In the remaining 37 cases there were no symptoms. These 63 cases included 36 meningiomas, 12 gliomas, and 15 other histologic types; the ratio of meningiomas to gliomas was 3:1. Among those lesions diagnosed while the patient was living, there were 25 meningiomas, 37 gliomas, and 48 others; the ratio of meningiomas to gliomas was 0.7:1. The ratio of all meningiomas (61) to all gliomas (49) in this study was 1.2:1. These ratios contrast with those from neurosurgical and hospital series in which gliomas usually outnumber meningiomas 2:1 or 3:1.²⁻⁴ The methods and level of case ascertainment in the present study are believed to provide a more realistic frequency distribution of central nervous system neoplasms by type.

Eighty percent of the 174 primary central nervous system neoplasms were intracranial, and 80% of the intracranial lesions were meningiomas or astrocytomas (Table 3). The 4 intracranial sarcomas represented 2% of the total, in good agreement with the 3% found in a surgical series of 8,000 intracranial neoplasms at the Mayo Clinic.⁵ Chromophobe adenomas were the most common primary tumors involving the pituitary, and schwannomas were the most common type in the spinal cord.

Incidence rates are presented in Table 4. The rates for neoplasms of the pituitary were 1.6, 2.1, and 2.3 for the first three decades, 1.1

TABLE 2
PRIMARY NEOPLASMS OF THE CENTRAL NERVOUS
SYSTEM DIAGNOSED AT AUTOPSY,
ROCHESTER, MINN., 1935-1968

Period	Total No. of neoplasms	Neoplasms diagnosed initially at autopsy	
		Total	With neurologic symptoms or signs
1935-1944	21	7	3
1945-1954	45	14	4
1955-1964	79	32	14
1965-1968	29	10	3
1935-1968	174	63	24

TABLE 3
PRIMARY NEOPLASMS* OF THE CENTRAL NERVOUS
SYSTEM BY TYPE, ROCHESTER, MINN., 1935-1968

Type	Number	Percent of total
Spinal cord	14	8
Schwannoma	6	
Ependymoma [†]	3	
Meningioma	2	
Chondroblastoma*	1	
Melanoma	1	
Teratoma	1	
Pituitary	21	12
Chromophobe adenoma	11	
Craniopharyngioma	4	
Eosinophilic adenoma	2	
Unknown	4	
Intracranial		
Meningioma	61	35
Astrocytoma	49	28
Schwannoma	9	5
Other	20	12
Ependymoma	4	
Sarcoma	4	
Retinoblastoma*	2	
Chordoma*	2	
Lipoma	2	
Medulloblastoma	2	
Epidermoid	1	
Hemangiopericytoma	1	
Dermoid or parathyroid cyst	1	
Unknown	1	

* Includes selected neoplasms of adjacent tissues affecting CNS

for the last four years, and 1.9 for the entire thirty-four-year period; they do not differ significantly. For neoplasms primary in the spinal cord, the rates were 1.6, 2.1, and 0.5 for the first three decades, 1.1 for the last four years, and 1.3 for the entire period; these also do not differ significantly. The rates shown in Table 4 were lower during the first decade than during succeeding periods; this could be due to underdiagnosis. Diagnostic techniques and neurosurgical procedures were still being developed, and it is unlikely that they were being fully utilized by the population at all ages. Furthermore, autopsy rates, particularly the percentage including central nervous system examinations, were lower in the first period than in later years.

1935-1944
1945-1954
1955-1964
1965-1968
1935-1968

0-24
25-44
45-64
≥65

95% conf

The r.
not signi-
fically tw
when the
all diag-
noses b-
diagnose
the reco-
gnized
diagnosis
until the
autopsy
for 1965
of earlier
currently
group—the
undergo
lesions. I
four-year
be suffi-
cient type
other and
Age-spe-
cific rates
1968 also
of primary
significant
results of
Other stu-
dies and
subsequent
rates also
and spinal
toward in-

TABLE 4
AVERAGE ANNUAL INCIDENCE RATES PER 100,000 POPULATION FOR NEOPLASMS
OF THE CENTRAL NERVOUS SYSTEM, ROCHESTER, MINN., 1935-1968

	Primary in brain			Primary in CNS			Metastatic to CNS			Total in CNS			
	No.	Rate	CI*	No.	Rate	CI*	No.	Rate	CI*	No.	Rate	CI*	
By period													
1935-1944	13	5.2	3-9	21	8.5	5-13	12	4.8	2-8	33	13.3	9-9	
1945-1954	33	11.7	8-16	15	15.9	11-21	33	11.7	8-17	78	27.6	22-35	
1955-1964	68	17.4	14-23	79	20.2	16-26	63	16.1	13-21	142	36.3	31-44	
1965-1968	25	13.4	9-20	29	15.5	10-22	15	8.0	4-13	44	23.6	17-32	
1935-1968	139	12.5	11-15	174	15.7	14-18	123	11.1	9-13	297	26.8	24-30	
By age for entire period													
0-24	19	3.9	2-6	27	5.5	4-8	3	0.6	0-2	30	6.1	4-9	
25-44	18	5.6	3-9	22	6.9	4-10	17	5.3	3-9	39	12.3	9-17	
45-64	39	18.9	14-26	53	25.7	20-34	64	31.1	25-41	117	56.8	48-69	
≥65	63	69.0	54-90	72	78.9	63-101	39	42.7	30-59	111	121.6	101-148	

*95% confidence interval for the rate

The rates for the last four-year period are not significantly lower than those in the previous two decades; however, it is likely that when this review was made early in 1969, not all diagnoses of central nervous system neoplasms for 1968 had been entered into the diagnostic index. Also, it is likely that with the recognition of symptoms of a possible central nervous system neoplasm, a definitive diagnosis would not be entered on the chart until the patient's operation or demise and autopsy or death certification. Since our rates for 1965 through 1968 are based on the date of earliest neurologic symptoms, that rate is currently deficient, especially in the metastatic group—these patients would be less likely to undergo operation than those with primary lesions. The deficiency in data entry for the four-year period, however, is not believed to be sufficiently selective by age, sex, or histologic type to preclude use of these data in our other analyses.

Age-specific incidence rates for 1935 through 1968 also are shown in Table 4. The incidence of primary neoplasms of the brain increased significantly with age, corresponding to the results of the previous Rochester survey.¹ Other studies^{2,4} have suggested a peak in the fifth and sixth decades and a decrease in the subsequent decades. Age-specific incidence rates also were computed for primary pituitary and spinal cord neoplasms. There was a trend toward increase with age in each, although

the number of cases was small and the standard error so great that no conclusion is warranted. Incidence rates for metastatic neoplasms showed a similar increase with age; however, the confidence limits are relatively large in the older age groups.

Age-specific incidence rates were calculated for astrocytomas and meningiomas (Table 5). With each type of neoplasm, the age-specific incidence rate increased with age. In terms of sex-specific incidence, a sex difference was observed with the meningiomas—the female:male ratio was 2:1. This is in agreement with published statistics.⁶ Previous evidence, particularly from Sweden⁷ and Israel,⁸ has suggested that astrocytomas occur more frequently in males. In this study the difference in rates (4.7 for males and 4.2 for females) is not significant.

TABLE 5

AGE-SPECIFIC INCIDENCE RATES PER 100,000
POPULATION FOR ASTROCYTOMAS AND
MENINGIOMAS, ROCHESTER, MINN., 1935-1968

Age	Astrocytomas		Meningiomas	
	No.	Rate	No.	Rate
0-24	9	1.8	1	0.2
25-44	6	1.9	5	1.6
45-64	15	7.3	19	9.2
≥65	19	20.8	36	39.4
Total	49	4.4	61	5.5

19 (17%) of 109 primary intracranial neoplasms were first discovered at autopsy; this is about one-half of the proportion noted in the present study. The clinical diagnoses in these 19 cases included trauma, toxic encephalopathy, suspected infection, and behavior disorders. The importance of complete autopsy data in a population survey of central nervous system disorders cannot be stressed too strongly.

As it appears in most publications, the distribution of central nervous system neoplasms by histologic type is the result of a hospital series or a pathology collection in which the special interests or talents of the investigator can be expected to lend some bias to the statistics. Thus, metastatic tumors are infrequently encountered in most surgical series, and certain tumors occur with unusual frequency, such as pituitary tumors in Cushing's report of his surgical experience. In the series reported by Cushing,² Olivecrona,³ and Zülch,⁴ the relative occurrences were: gliomas, 43 to 53%; meningiomas, 13 to 19%; neurinomas,* 7 to 9%; pituitary adenomas, 7 to 18%; and metastases, 3 to 4%. Data from Israel,⁸ derived from a review of the Tumor Registry for 1961 through 1965, yielded a somewhat different distribution: gliomas, 27%; meningiomas, 17%; neurofibromas, 12%; and pituitary adenomas, 5%. No statistics were reported for metastases. The Carlisle study¹⁰ revealed 25% gliomas; metastases comprised 45% of all intracranial neoplasms. In the present study the distribution of primary neoplasms was: gliomas, 28%; meningiomas, 35%; schwannomas, 5%; and pituitary adenomas, 7%. Metastatic tumors represented 41% of the neoplasms. In the present study, the nearly complete histologic confirmation allows for reasonable certainty of the diagnosis, and the large number of autopsy-discovered neoplasms suggests more complete case ascertainment.

The lack of histologic confirmation in one-third of the Israeli cases⁸ could explain some of the discrepancy by histologic type as compared to the current study. However, the current study was a population survey whereas the Israeli study had to rely on case reporting to a central registry, a situation that would favor the detection of malignant or sympto-

matic lesions over silent or indolent tumors. In addition, the Israeli survey included hemangiomas (2%). Twenty-three cases of hemangioma (vascular malformations) of the central nervous system were identified in the Rochester study, all but 1 at autopsy. Since these lesions were not regarded as true neoplasms, the cases were not included in the computations.

It is difficult to believe that the marked difference between the rates in Rochester and in Connecticut (Table 7) reflects a true difference in disease incidence. It seems more reasonable that more complete case ascertainment related to the extensive diagnostic index and high autopsy rate in Rochester accounts for most, if not all, of the difference noted.

The proportion of metastatic tumors, 41%, in the present study is considerably higher than the 1 to 8% reported¹⁴ in neurosurgical series but lower than the 62.7% reported from chronic disease hospitals providing terminal care for patients with any type of malignancy. In the present study, it is likely that there is more underreporting of metastatic cerebral cancer than of the primary neoplasms of the brain. The metastatic cases were included only when involvement of the central nervous system was specified on the diagnostic master sheet of the patient's record or in the autopsy protocol. In most instances, signs of cerebral dysfunction, focal seizures, or localized paresis had developed; it was not unusual that metastasis was observed and recorded for the first time at autopsy. It seems reasonable that, if all brain neoplasms were correctly diagnosed, about 50% would be metastatic, as suggested by Kurland.¹

In the earlier Rochester study,¹ there was a preponderance of females with primary neoplasms of the brain and meninges and with metastases. The present results, based on appreciably larger numbers, indicate that females still more commonly have meningiomas, but gliomas and most other neoplasms occurred with equal frequency in the two sexes.

The present study substantiates one of the more interesting results of the previous Rochester study¹—that the age-specific incidence for primary neoplasms of the central nervous system increases with age. Other studies of tumor incidence by age at diagnosis often failed to

account for this, thus yielding peaked age-specific rates¹⁵ which are not a convincing intra-cohort response (Dorn and Stratton).

Other loma¹⁷ are studied to show the advancing age equivalents for the disease, and, therefore, including ability of all ages.

Average age at primary age, for R

* In these series neurinomas were included in the glioma group.

tumors.
led he-
of be-
the cen-
in the
Since
ne neo-
in the

ked dif-
and in
ference
asonable
related
d high
n most,

ns, 41%,
higher
surgical
ed from
terminal
quency
is
ebral
of the
ed only
ous sys-
master
utopsy
erebral
paresis
metas-
the first
at, if all
agnosed,
uggested

re was a
ary neo-
and with
on ap-
females
as, but
occurred

of the
is Roch-
ence for
hus sys-
of tumor
to

account for the size of the population at risk, thus yielding the impression that incidence peaked at the fifth and sixth decades. This is specifically pointed out by Doll and associates¹⁵ who compiled age-specific rates for five continents. In those countries where the standards of medical practice are relatively high and methods of reporting are reasonably well controlled, the age-specific incidence rates for major subgroups and for all tumors combined tend to increase with age. However, this was not a consistent finding in the subgroup including intracranial neoplasms in which the rates corresponded to the age-distribution found by Dorn and Cutler¹⁶ in a ten-city study (see illustration).

Other neoplasms, such as multiple myeloma¹⁷ and breast cancer,¹⁸ have recently been studied in the Rochester population and also show this trend of increasing rates with advancing age. The Mayo Clinic provides the equivalent of general as well as specialty care for the elderly members of the community, and, therefore, there is a greater likelihood of including older patients. This, plus the availability of diagnostic facilities for patients of all ages and the high autopsy rate in this com-

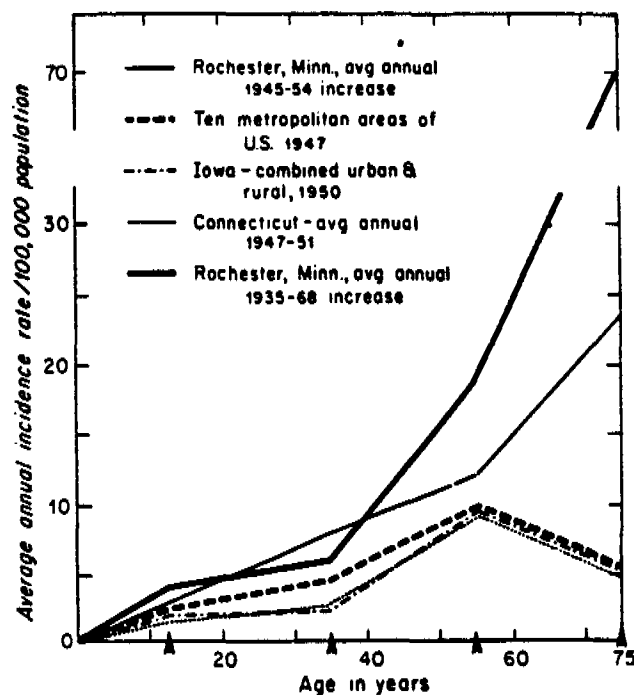
munity, may account for the difference between age-specific incidence rates in this study and those derived from hospital, surgical, or population surveys elsewhere.

SUMMARY

Incidence rates were computed for central nervous system neoplasms for the resident population of Rochester, Minn., for the thirty-four-year period 1935 through 1968. The records of the Mayo Clinic were the major source of data for the cases; the ancillary records in other medical facilities in and near Rochester could be identified and were available through the expanded diagnostic index of the Rochester epidemiology program. There were 174 primary and 123 metastatic CNS neoplasms. Ninety-five percent of the primary brain and spinal cord neoplasms were histologically confirmed.

During the study period, 36% of the primary CNS neoplasms were first diagnosed at autopsy. Meningiomas accounted for more than one-half of this group. Average annual incidence rates per 100,000 population were 12.5 for primary brain neoplasms, 1.9 for pituitary neoplasms, 1.3 for primary spinal cord neo-

Average annual incidence rates for primary neoplasms in brain, by age, for Rochester and other areas



plasms, and 11.1 for metastases to the CNS. No consistent trend over time was observed in the incidence rates for meningiomas, gliomas, or all primary CNS tumors combined.

Age-specific incidence rates for primary brain neoplasms increased significantly with age; the rates for pituitary and spinal cord neoplasms showed a trend toward increase with age. No sex predilection could be found for primary brain, pituitary, or spinal cord or metastatic tumors. Meningiomas were found significantly more frequently in females.

Five-year survival, determined by the direct method, was 22% for gliomas and 59% for meningiomas.

REFERENCES

1. Kurland LT: The frequency of intracranial and intraspinal neoplasms in the resident population of Rochester, Minnesota. *J Neurosurg* 15:627-641, 1958
2. Cushing H: *Intracranial Tumors*. Springfield Ill, Charles C Thomas, 1932
3. Olivecrona H: The cerebellar angiodysplasias. *J Neurosurg* 9:317-330, 1952
4. Zulch KJ: *Brain Tumors, Their Biology and Pathology*. 2nd ed. New York, Springer Publishing Company Inc, 1965, pp 62-69
5. Kernohan JW, Uhlenhuth A: Sarcomas of the brain. *Progr Clin Cancer* 1:414-437, 1965
6. Earle KM, Richany SF: Meningiomas: A study of the histology, incidence, and biologic behavior of 243 cases from the Frazier-Grant collection of brain tumors. *Med Ann DC* 38:353-358, 1969
7. Ringertz N, Tornberg B, Sjöström A, et al: Cancer Incidence in Sweden 1959. Stockholm Sweden, National Board of Health, The Cancer Registry, 1962
8. Lebowitz U, Alter M: Tumors of the nervous system: Incidence and population selectivity. (abstr) *Neurology (Minneapolis)* 19:292, 1969
9. Schoenberg BS, Christine BW: Neoplasms of the brain and cranial meninges: A study of incidence, epidemiological trends, and survival. (abstr) *Neurology (Minneapolis)* 20:399, 1970
10. Brewis M, Poskanzer DC, Rolland C, et al: Neurological disease in an English city. *Acta Neurol Scand* 42(Suppl 24):1-89, 1966
11. Cohen A, Modan B: Some epidemiologic aspects of neoplastic diseases in Israeli immigrant population. III. Brain tumours. *Cancer* 22:1323-1328, 1968
12. Guomundsson KR: A survey of tumors of the central nervous system in Iceland during the 10-year period 1954-1963. *Acta Neurol Scand* 48:538-552, 1970
13. Huntington RW Jr, Cummings KL, Moe TL, et al: Discovery of fatal primary intracranial neoplasms at medicolegal autopsies. *Cancer* 18:117-127, 1965
14. Wagner JA: Neuropathology of neoplastic metastases to the brain. *Southern Med J* 48:302-305, 1955
15. Doll R, Payne P, Waterhouse J: *Cancer Incidence in Five Continents: A Technical Report*. Berlin, Springer-Verlag, 1966
16. Dorn HF, Cutler SJ: Morbidity from cancer in the United States (Public Health Monograph No. 29). Washington DC, Government Printing Office, 1955
17. Kyle RA, Nobrega FT, Kurland LT: Multiple myeloma in Olmsted County, Minnesota, 1945-1964. *Blood* 33:739-745, 1969
18. Snyder J, Payne WS, Kurland LT: Unpublished data.