The Natural History of Homocystinura Due to Cystathionine β-Synthase Deficiency

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SUMMARY

An international questionnaire survey has been conducted to define better the natural history of homocystinuria due to cystathionine β-synthase deficiency and permit evaluation of treatment. Data were compiled for 629 patients. Among patients not discovered by newborn screening, B_6-responsive individuals on the average have significantly better mental capabilities (mean IQ, 79) than do B_6-nonresponsive individuals (mean IQ, 57). Time-to-event curves are presented for the other major clinical abnormalities produced by this disease. Each occurred at significantly lower rates in untreated B_6-responsive than in untreated B_6-nonresponsive patients, as shown by the following examples: (1) dislocation of optic lenses (at age 10, chances of dislocation: 55% and 82%, respectively); (2) initial clinically detected thromboembolic events (at age 15, chances

of having had such an event: 12% and 27%, respectively); (3) radiologic detection of spinal osteoporosis (at age 15, chances of such osteoporosis having been detected: 36% and 64%, respectively); and (4) mortality (at age 30, chances of not surviving: 4% and 23%, respectively). Methionine restriction initiated neonatally prevented mental retardation, retarded the rate of lens dislocation, and may have reduced the incidence of seizures. Pyridoxine treatment of late-detected B_6-responsive patients retarded the rate of occurrence of initial thromboembolic events. Following 586 surgical procedures, 25 postoperative thromboembolic complications occurred, six of which were fatal. Reproductive histories were reported predominately for B_6-responsive patients. Living offspring of either men or women patients had few abnormalities. The evidence is inconclusive whether untreated maternal cystathionine β-synthase deficiency leads to excessive fetal loss. Only 13% of patients detected in screening programs of newborns and classified as to B_6-responsiveness were B_6-responsive, compared to 47% among late-detected patients. Current screening programs that identify neonatal hypermethioninemia may be preferentially failing to detect B_6-responsive patients.

INTRODUCTION

Homocystinuria due to cystathionine β-synthase deficiency is a genetically determined inborn error of the transsulfuration pathway biochemically characterized by increased plasma homocyst(e)ine and methionine and decreased cyst(e)ine. The disease was discovered in 1962, when mentally retarded individuals were screened for abnormal urinary amino acids [1, 2]. Two years later, the enzyme defect, deficient activity of cystathionine β-synthase, was demonstrated [3].* The major clinical manifestations include mental retardation, dislocation of the optic lens (ectopia lentis), skeletal abnormalities, and a tendency to thromboembolic episodes [6].

    Once the enzyme defect and the major biochemical aberrations had been defined, dietary therapy based upon methionine restriction and L-cystine supplementation was suggested. This regimen resulted in some degree of control of the biochemical abnormalities, and largely anecdotal evidence emerged that such treatment from the newborn period could prevent or delay clinical manifestations [7–10]. Subsequently, it was found that some patients on normal diets respond biochemically to large doses of vitamin B_6† with decreases in plasma homocyst(e)ine and changes of plasma methionine and cyst(e)ine concentrations toward normal [11], while others do not so respond. Evidence now available strongly indicates that such

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* Several other enzyme lesions are now known that also lead to excretion of excess homocystine (homocystinuria) [4, 5]. In this paper, we will deal only with homocystinuria due to cystathionine β-synthase deficiency, and the condition will be designated by the latter name.

    † Vitamin B_6 will hereafter be referred to as B_6 or pyridoxine.

B_6-responsiveness, or lack thereof, is one manifestation of a considerable hetero-geneity in the mutations producing deficiencies of cystathionine β-synthase activity [6]. Since 1967, many patients have been given trials or prolonged periods of dietary and/or pyridoxine therapy. These therapeutic trials were carried out in the absence of any randomly selected, untreated control population. More recently, the use of aspirin and dipyridamol has been suggested to prevent thrombosis [12], but neither has been subjected to rigorous testing. Other workers have advocated the administration of betaine to reduce concentrations of homocysteine [13, 14].

Only a few years elapsed between discovery of cystathionine β-synthase de-ficiency and initiation of various therapies. Consequently, there was little op-portunity to accumulate knowledge about the natural history of the condition. It is clear, however, that the age of onset and the severity of clinical manifestations vary widely among affected individuals. Thus, the prevalence and natural history of each of the pleiotropic features remain uncertain. Few data are available upon the impact of maternal cystathionine β-synthase deficiency on reproductive potential and on the fetus. The effects of genetic heterogeneity, as indicated, for example, by B_6-responsiveness or B_6-nonresponsiveness, on each of these manifestations are largely undefined. These gaps in our knowledge impede realistic assessment of the efficacy of various therapies. Since homocystinuria due to cystathionine β-synthase deficiency is a relatively rare disease [6], no single physician or center has accumulated a sufficiently large sample of patients to address these questions. Therefore, we have conducted a worldwide questionnaire survey and collected information in a standardized format on more than 600 patients with homocystinuria due to proven or presumed deficiency of cystathionine β-synthase. Our results, presented in this report, clarify some of the major uncertainties about the natural history of the disease and the role of genetic heterogeneity. They also establish baselines for future evaluation of the effects of treatment in this disease.

METHODS

Data Base

A standardized questionnaire was designed and mailed to each clinician known from a previous study [15] to be caring for patients with cystathionine β-synthase deficiency. Physicians were asked to complete a questionnaire for each such individual about whom they had appropriate information. To encourage participation, the questionnaire was kept relatively simple.* Each patient was identified by first name, first two letters of family name, birth date, and sex. Affected relatives were specified. Further questions focused upon the factor(s) that led to ascertainment, whether the patient was responsive to B_6, and upon the presence and age of appearance of major clinical manifestations. A detailed history of therapy was requested, as well as a reproductive history. To permit use of rel-evant published material, the respondent was asked to identify articles concerning a given patient. Additional sources of information were identified by a review of the literature and by contacting centers around the world specializing in diagnosis and management of inborn errors of metabolism. Further, physician cooperation was solicited by notices in

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* Copies of the questionnaire are available through the National Auxiliary Publications Service (see footnote † to page 10).

appropriate journals. For some patients upon whom recent information could not be obtained, the study coordinators completed questionnaires chiefly or solely on the basis of published material. Such patients were included only when sufficient details were available to prove that they did not overlap with any patient otherwise included in the study. Data collection occurred during 1982 and early 1983. Data from the completed questionnaires were entered into a computer and verified by proofreading a print-out of the computer data against the original questionnaires. A computer search for duplication due to a single patient having been reported upon by two different physicians detected several such instances, and the redundant information was deleted.

Statistical Analyses

Time-to-event curves were calculated according to the product-limit estimate method of Kaplan and Meier [16]. Comparisons among the curves for statistically significant differences were performed by the procedures of Gehan [17] and Breslow [18]. For evaluation of treatments, numbers of expected events were calculated according to the nonparametric procedures described by Turnbull et al. [19]. Differences between numbers of observed and expected events were tested for statistical significance according to the same procedure.

RESULTS

The Study Population and Criteria for Acceptance into Study

For the present survey, updated information was received concerning 532 homocystinuric patients with proven or presumed cystathionine β-synthase deficiency. To this group was added material on an additional 97 patients obtained primarily from published reports [7, 9, 20–55], bringing the total to 629 patients. All patients admitted to the study had been demonstrated to be excreting homocystine. To restrict the population to cystathionine β-synthase-deficient individuals (thus excluding other causes of homocystine excretion [4–6]), either (1) cystathionine β-synthase deficiency had to have been demonstrated directly by enzyme assay or (2) the patient had to have either hypermethioninemia or dislocated optic lenses. Table 1 shows the similar percent distributions of these findings in patients with and without confirmation of the diagnosis by enzyme assay.

TABLE 1

CRITERIA FOR ACCEPTANCE OF PATIENTS INTO STUDY

	ENZYME ASSAY	
	Performed*	Not performed
Dislocated lens and hypermethioninemia	147 (68.0%)	274 (66.3%)
Dislocated lens only	21 (9.7%)	75 (18.2%)
Hypermethioninemia only	39 (18.1%)	64 (15.5%)
Neither of above	9 (4.2%)	0 (0%)
Total	216 (100%)	413 (100%)

* The following tissues were used for enzyme assays (followed by no. patients, in parentheses): liver (27); both liver and cultured fibroblasts (13); cultured fibroblasts (170); brain (1); phytohemagglutinin-stimulated lymphocytes (3); transformed lymphocytes (1); cultured fibroblasts and phytohemagglutinin-stimulated lymphocytes (1).

TABLE 2

CLINICAL FEATURES LEADING TO INVESTIGATION FOR HOMOCYSTINURIA

Clinical feature	Sole cause (% of patients)	Contributory cause* (% of patients)	Total in which a cause (% of patients)
Ectopia lentis	20.6	65.0	85.6
Mental retardation	4.0	51.7	55.7
Developmental retardation	1.5	21.0	22.5
Early thromboembolic disorder	1.1	15.0	16.1
Marfanoid characteristics	0.9	36.0	36.9
Bony abnormality	0.2	23.3	23.5
Seizures	0.2	3.0	3.2
Behavioral or psychiatric disorder	0	2.8	2.8
Other†	0.4	10.6	11.0

NOTE: Based on data for 472 patients not ascertained as a result of screening of newborns or screening of all sibs of a proband.

* Includes all patients with the specified feature, as well as at least one other, reported as leading to investigation for homocystinuria.

† Includes a variety of manifestations, none of which was a cause in as many as 2% of the population.

Of the 629 patients, 307 were females and 321 males, close to the expected ratio of 1:1. The sex of one patient was not specified. Sixty-four patients (10.2%) were dead at the time of reporting.

Ascertainment

Data on factors leading to investigation of patients for homocystinuria were available for 618 patients. Of these, 58 were discovered during screening of newborns, and an additional 88 were discovered by screening all siblings after detection of homocystinuria in a proband, leaving 472 patients ascertained on the basis of clinical features. Table 2 displays the frequencies at which each of the major clinical manifestations was the sole reported cause of investigation for homocystinuria or was a contributory cause. Most patients were investigated because of more than one clinical feature, the major exception being the almost 21% initially investigated solely because of ectopia lentis.

B_6-Responsiveness

Of the 629 patients, 231 (36.7%) were classified as biochemically responsive to B_6 when not folate depleted; 231 (36.7%) were classified as nonresponsive to B_6; 67 (10.7%) were judged intermediate in response; and 100 (15.9%) had not been classified. For subsequent analyses in this presentation, neither the "intermediate-response" group, although this may include patients with a biochemically significant response, nor unclassified patients were included in groups designated as "B_6-responsive" or "B_6-nonresponsive."

The relative frequencies of B_6-responsive and B_6-nonresponsive patients among at least two subgroups of the total population differed markedly from the overall frequency. Among the 55 patients who had been both discovered by newborn screening and classified with respect to B_6-responsiveness, seven (12.7%) were B_6-responsive, 43 (78.2%) were nonresponsive, and five (9.1%) were intermediate

in response. Thus, the ratio of responders to nonresponders was 1:6 in this subgroup. Among 25 patients who were not hypermethioninemic when untreated and who had been classified with respect to B_6-responsiveness, 21 (84%) were responsive, two (8%) were nonresponsive, and two (8%) were intermediate in response, yielding a ratio of responders to nonresponders of 10:1.

For many sibships, more than one affected member had been classified as to B_6-responsiveness. Table 3 shows that among such sibs there was almost complete concordance of responsiveness or nonresponsiveness. In no case was a patient judged fully responsive when one of his or her sibs was judged fully nonresponsive.

Hypermethioninemia

Among the patients for whom data were available concerning the presence or absence of hypermethioninemia in the untreated state, 524 (93.6%) were hypermethioninemic and 36 (6.4%) were not. As expected from the relative preponderance of B_6-responsive patients among those who were not hypermethioninemic, 10% of untreated B_6-responders were not hypermethioninemic, whereas less than 1% of untreated B_6-nonresponders were not hypermethioninemic.

Mental Capabilities

Responding physicians were asked to rate the mental capabilities of patients in several ways:

(1) IQ. A plot of the distribution of IQ's among all patients for whom such data were available is shown in figure 1. To eliminate any effect of very early therapy, data on patients discovered by newborn screening were not used in constructing these plots of IQ or in the alternative analyses of mental capabilities discussed in the following sections. Figure 1 demonstrates a very wide range in patient IQ's—from 10 to 138. The median of the cumulative frequency curve was at an IQ of approximately 64. The curve for patients classified as B_6-responders was shifted toward higher IQ's (median 78), whereas that for patients classified as B_6-nonresponders was shifted toward lower IQ's (median 56). As a result, only about 4% of B_6-nonresponders had IQ's of 90 or above, but 22% of B_6-responders had values in this range. The difference between the mean IQ for B_6-

TABLE 3

CONCORDANCE OF B_6-RESPONSIVENESS IN SIBLINGS

ADDITIONAL SIBS:	FIRST SIB: B_6-RESPONSIVENESS			
B_6-RESPONSIVENESS	Yes	Int.*	No	Σ
Yes	56	· · ·	· · ·	56
Int.*	1	10	2	13
No	· · ·	· · ·	50	50
Σ	57	10	52	119

NOTE: Based upon 104 sibships (total of 223 sibs) in which more than one sib had been classified with respect to B_6-responsiveness.
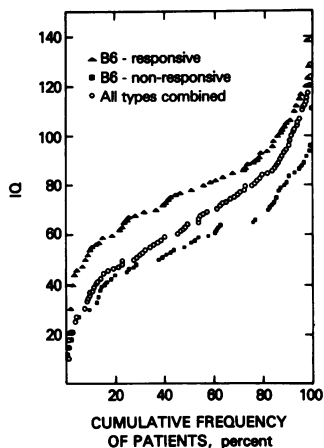
* Int. = intermediate.

FIG. 1.—Distributions of IQ's among patients not detected by newborn screening. *The curves* are based on the following nos. of patients with reported IQ's: all B_6 categories, 284; B_6-responders, 107; B_6-nonresponders, 115. *For any specified IQ value, the plots* show the total percent of each category of patients with IQ's equal to, or less than, the specified value.

responders (79) and that for nonresponders (57) was highly significant ($P \leqslant$ .0001).

(2) If no IQ value was available, physicians rated the patients as being either "grossly retarded," "mildly retarded," "average or above average intelligence, but with a learning disability," or "average or above average intelligence." Table 4 shows the proportions of patients in each of these categories. The trends are clearly the same as those resulting from IQ measurements, with 61% of the patients being either grossly or mildly retarded, but only 38% of B_6-responders being so rated, and almost 85% of B_6-nonresponders showing retardation. The difference between the distributions of B_6-responders and nonresponders was again highly significant ($P \leqslant$ .0001).

(3) If a proband had one or more documented nonhomocystinuric sibs, responding physicians were asked to rate the proband's intelligence as either "below," the "same" as, or "above" that of unaffected sibs. The results, table 4, follow a similar trend, again with very significantly ($P \leqslant$ .0001) higher ratings for B_6-responders than for B_6-nonresponders.

To evaluate further the validity of the results described above, for each rating method, the analyses were repeated after prior division of the patients into subgroups consisting of those with a diagnosis confirmed by enzyme assay and those without such confirmation. No substantial differences were noted between these two subgroups.

To gain some insight into the influence of ascertainment bias on the ratings of mental capabilities, the above analyses were repeated (1) after removal of the few patients ascertained solely on the basis of mental retardation and (2) after removal of all patients with mental retardation included as one factor in ascertainment. The first procedure produced virtually no change; the second led, as expected, to shifts toward higher IQ's among all groups. The medians of the

TABLE 4

QUALITATIVE ESTIMATES OF MENTAL CAPACITY

PATIENTS	MENTAL STATUS				INTELLIGENCE RELATIVE TO UNAFFECTED SIBS		
	Grossly retarded	Mildly retarded	Average or above with learning disability	Average or above	Below	Same	Above
All B$_6$ categories	21.9*	39.2	5.7	33.2	76.7	22.3	1.0
B$_6$-responsive	5.2	32.7	11.2	50.9	63.2	34.2	2.6
B$_6$-nonresponsive	38.3	46.6	4.1	11.0	94.4	5.6	0

NOTE: Patients were those not discovered by newborn screening. Ratings of mental status and intelligence relative to unaffected sibs, respectively, were available for the following numbers of patients: all B$_6$ categories, 283 and 305; B$_6$-responders, 116 and 117, and B$_6$-nonresponders, 73 and 107.
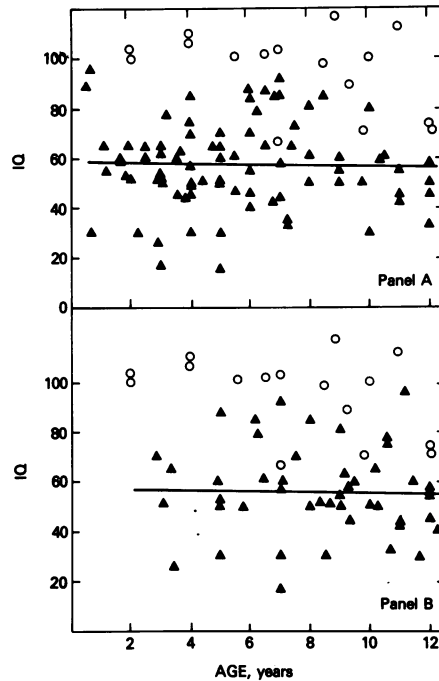
* Nos. are % of rated patients.

FIG. 2.—Effect of early treatment on IQ of B6-nonresponsive patients. B6-nonresponsive patients ascertained by newborn screening and treated with methionine restriction from early ages are each represented by *an open circle*. The same patients are plotted in both *panels A* and *B*. *The ages* are those at which the IQ's were measured. The comparison populations consist of B6-nonresponsive patients not ascertained by newborn screening. Each such patient is represented by *a closed triangle*. For comparison populations, the ages are: *panel A*, age at ascertainment; *panel B*, age at last follow-up. *The lines* are regression lines calculated for the IQ's of the comparison populations: *panel A*, IQ = 57.27 − (0.01567) × (age at ascertainment, in mos); mean IQ = 55.7 ± 2.6 (SEM); *panel B*, IQ = 58.81 − (0.01827) × (age at last follow-up, in mos); mean IQ = 57.6 ± 1.9 (SEM).

cumulative IQ curves rose to 81 for patients in all B6 categories combined, to 86 for B6-responders, and to 64 for B6-nonresponders. Thus, the difference in median IQ between B6-responders and nonresponders was essentially unchanged (about 22 points), and the difference in mean IQ remained highly significant ($P \leq$ .0001). Similar shifts occurred in the more qualitative alternative estimates of mental capabilities, and again the differences between B6-responders and nonresponders remained highly significant (data not shown).

Effect of early treatment on mental capability. General experience with cystathionine β-synthase-deficient patients has shown that late treatment rarely, if ever, completely reverses mental impairment [6], although methionine restriction or treatment with pyridoxine [56, 57] or betaine [13] have been reported to lead to behavioral improvement and moderate increases in IQ [57], suggesting a reversible component to the mental disturbance of the untreated disease [57]. Early treatment, however, might prevent the mental damage [10]. The effect of early treatment is illustrated in figure 2. IQ's for B6-nonresponsive patients identified as neonates and treated from very early ages with methionine restriction, usually

accompanied by L-cystine supplementation (early-treated), are compared to IQ's of B_6-nonresponsive patients not detected by newborn screening (late-detected). If treated at all, very few of the latter patients had commenced therapy at ages of less than 1–2 years. IQ's of early-treated patients are plotted at the age of measurement of the latest reported IQ. The ages of measurement of the IQ's for the late-detected patients were not specified in the questionnaire. These IQ's are plotted alternatively as a function of the age at ascertainment (panel A) or the age at last follow-up (panel B). It is apparent that for these late-detected patients severe impairment of IQ was manifest from early ages, and this impairment did not change markedly as a function of age.* The IQ's of the early-treated patients are higher, with little overlap with the late-detected groups at ages up to 7 to 8 (mean IQ = 94 ± 4 [SEM]; $P \leqslant .001$ compared to mean IQ of either late-detected group).

Qualitative estimates of mental capabilities for the early-treated group are in agreement with the above results. Of 23 patients without IQ measurements, one (4%) was estimated to be grossly retarded, three (13%) mildly retarded, one (4%) average with learning disability, and 18 (78%) to be average or above. These values are very favorable compared to those in table 4 for late-detected B_6-nonresponsive patients.

For the 15 patients detected by newborn screening who were B_6-responsive, or were intermediate or unclassified as to B_6 response, reported IQ's ranged from 82–110 (six patients), and all other patients were estimated to be of "average or above average" intelligence. Most of these patients had been treated with methionine restriction from the time of diagnosis, several had received B_6 in addition, and four (three responders, one intermediate) had been treated solely with vitamin B_6. Again, these results are highly favorable compared to those in table 4.

Dislocation of Optic Lenses

Data on ages of lens dislocation were analyzed according to the Kaplan and Meier method, with the important stipulation that for each patient the only interval considered was that prior to initiation of treatment specific for cystathionine β-synthase deficiency. Hence, a patient was removed from the group at risk for lens dislocation (censored) at the time he or she started such treatment. The resulting time-to-event graphs are shown in figure 3.† These plots demonstrate that,

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* The apparent tendency of IQ in the early-detected group to decrease after age 8 may to some extent be due to a change in the method used to determine IQ. Prior to age 6, methods that measure only verbal ability (e.g., Stanford-Binet) are generally used; thereafter, methods that evaluate performance as well as verbal ability (e.g., WISC) are used increasingly. Some patients we have observed received a markedly higher "verbal" than "performance" score on the WISC test and, correspondingly, had lower overall IQ scores at ages when this test was used than at a younger age. The questionnaire did not ask the responding physician to specify the type of IQ test used, and further data would be needed to evaluate fully the effects of this possible methodological change.

† The numerical values upon which this figure is based have been deposited with, and are available through, the National Auxiliary Publications Service. See NAPS document no. 04244 for 17 pages of supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163. Remit in advance in U.S. funds only $7.75 for photocopies or $4.00 for microfiche. Outside the U.S. and Canada, add postage of $4.50. $1.50 for microfiche postage.
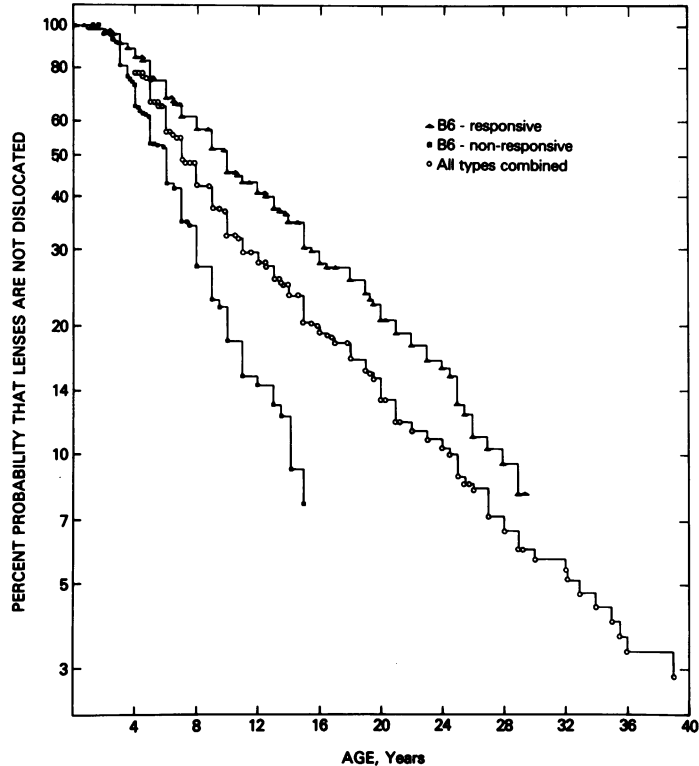
FIG. 3.—Time-to-event graphs for lens dislocation in untreated patients. Patients were removed from the at-risk groups upon commencement of any therapy. *Probabilities* were calculated according to the Kaplan and Meier method [16] and are plotted on a logarithmic scale. *Time points* are plotted only when they are the first or last for a given probability. Based on data for following nos. of patients: B_6-responsive, 231; B_6-nonresponsive 231; all types, 628. *Each plot* is discontinued at the time the no. of patients remaining at risk decreases to 10. For clarity, *the graph for "all patients"* is plotted starting at age 4.

for all groups of patients, there was a lag period of approximately 2 years before appreciable lens dislocation occurred. After age 2, lens dislocations began to be detected, but at different rates in B_6-nonresponders and B_6-responders, so that 50% of untreated nonresponsive patients had dislocated lenses by age 6, whereas for untreated B_6-responsive patients, 50% dislocation was attained at approximately age 10. After age 3, smoothed logarithmic plots are reasonable approximations of straight lines for both groups. Thus, during this phase, approximately half of the B_6-nonresponsive patients who start an interval with intact lenses can be expected to dislocate during the next 40 months, while for untreated B_6-responders, half can be expected to dislocate each 95–100 months. Statistically, the difference between the time-to-event graphs for B_6-responders and B_6-nonresponders was highly significant ($P < .0001$). Note, however, that these plots most correctly represent the detection of lens dislocation rather than its actual occurrence. If a patient had dislocated lenses at ascertainment, and his or her history did not establish a prior time of dislocation, then dislocation was placed at the time of

ascertainment. As a result, these curves represent maximum ages. Serial exam-
inations of untreated patients from early ages might well result in curves shifted
to earlier ages in such plots.

Effect of treatment on lens dislocation. An important property of the Kaplan-
Meier curves shown in figure 3 is that they furnish a statistical prognosis for an
untreated patient starting at any specified age. This permits assessment of the
effect of treatment on lens dislocation in an assorted group of patients who start
treatment at different ages and have been maintained on treatment for different
intervals. For each such patient, one can calculate the probability that, during
the interval he or she is at risk on treatment, lens dislocation would have occurred
had he or she not been treated.* The combined probabilities for a group of such
patients yield a predicted number of dislocations if they had been untreated or if
treatment is without effect. This number can be compared to the actual number
of dislocations that occurred during treatment. Table 5 displays such comparisons.
Among 24 B_6-responsive patients with lenses intact who were given pyridoxine
(with or without folate) as initial and continuous treatment (column A), 8.4
dislocations would have been expected to occur during treatment, as calculated
from the time-to-event graph (fig. 3) if treatment had no effect. Five dislocations
occurred. This decrease is not statistically significant ($P > .05$). Column C takes
into account additional experience by including intervals of treatment that took
place after temporary interruption of the initial treatment or in which B_6 therapy
followed earlier periods of dietary treatment. The decrease in the number of lens
dislocations observed below those expected now became statistically significant.

In table 5, B_6-nonresponsive patients are separated into "late-detected" and
"early-treated" (i.e., those identified by newborn screening). No effect of therapy
was observed among the few "late-detected" B_6-nonresponsive patients who had
intact lenses at the time they were started on dietary therapy. Among "early-
treated"patients, however, for each treatment regimen evaluated, the number of
dislocations observed was significantly below the number expected ($P \leq .001$),
suggesting that therapy may be beneficial when begun in early infancy. Since six
of these patients had suffered lens dislocations, the benefit may be more in delaying
the time of lens dislocation rather than in absolute prevention. Follow-up of these
patients to older ages is necessary to clarify this issue.

Thromboembolic Events

From the thromboembolic events originally reported, nine described as "pos-
sible" or "partial" and two that were only questionably related to the underlying
condition were deleted. There remained a total of 253 events, occurring in 158
patients. No reported events occurred in 471 patients. Of these 253 events, 81
(32%) were cerebrovascular accidents, 130 (51%) affected peripheral veins (with

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* The interval at risk is the time from onset of treatment in a patient with lenses not yet dislocated
until the earliest of one of three events: (1) treatment termination, (2) time of last follow-up (if the
patient is on continuing treatment), or (3) lens dislocation. The probability that an untreated patient
will develop dislocation during the interval t_1 to t_2 is $(1 - p_2/p_1)$, where p_1 and p_2 are the probabilities
that lenses are not dislocated (fig. 3) at times t_1 and t_2, respectively.

TABLE 5

EFFECT OF THERAPY ON LENS DISLOCATION AND ON INITIAL THROMBOEMBOLIC EVENTS

	LENS DISLOCATION (TREATMENT EVALUATED)			THROMBOEMBOLIC EVENTS (TREATMENT EVALUATED)		
	A*	B†	C‡	A*	B†	C‡
B6-responsive, late-detected:						
No. patients	24	...	26	120	...	135
Expected events§	8.4	...	10.8	14.9	...	19.9
Observed events	5	...	5	3	...	4
Normal deviate	−1.57	...	−2.44‖	−3.54#	...	−4.14#
B6-nonresponsive, late-detected:						
No. patients	10	13	23	26	41	68
Expected events§	3.6	4.6	6.9	2.1	4.1	6.2
Observed events	4	7	9	1	2	8
Normal deviate	0.30	1.46	1.10	−0.83	−1.15	0.82
B6-nonresponsive, early-treated:						
No. patients	30	31	39	30	32	41
Expected events§	11.7	12.5	16.2	1.7	2.1	2.9
Observed events	3	4	6	0	0	1
Normal deviate	−4.15#	−4.01#	−3.99#	−1.38	−1.55	−0.96

* Treatment for B6-responsive patients is pyridoxine with or without folate. Treatment for B6-nonresponsive patients is methionine restriction, with or without cystine supplementation. For all groups, the treatment in question was the initial one and was given continuously.

† Treatment for B6-nonresponsive patients as in column A, except that pyridoxine and/or folate could be added to the dietary measures.

‡ Treatments evaluated are those specified in column A for B6-responsive patients and in column B for B6-nonresponsive patients. However, in column C, such treatments were no longer required to be the initial ones or to be given continuously. In the latter instance, the treatment being evaluated was interrupted by an interval of no therapy or by an interval of a therapy not being evaluated.

§ Expected events were calculated by use of the time-to-event curves (figs. 3 or 4) and the cumulative expectations of the individual patients, as explained in the text.
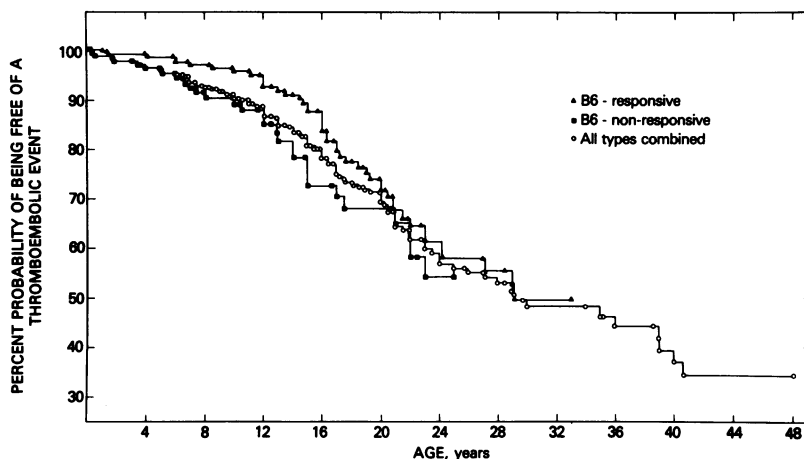
‖ P < .05.

# P < .001.

FIG. 4.—Time-to-event graphs for first thromboembolic event in untreated patients. The methods and *symbols* used are the same as those detailed in the legend to figure 3, except that *probabilities on these graphs* are plotted on a linear scale and data for 627 patients were used for *the "all types" curve.* For clarity, *the graph for "all patients"* is plotted starting at approximately age 7.

32 resulting in pulmonary embolism), 10 (4%) produced myocardial infarctions, 28 (11%) affected peripheral arteries, and four (2%) fell into none of these categories. The distributions of these types of thromboembolic events were only marginally related to the B_6-response category of the patients.

Time-to-event graphs for first thromboembolic events in untreated patients are shown in figure 4.* The occurrences of both thromboembolic events and lens dislocation are age-dependent, but they differ in several other characteristics. The lag for thromboembolism is longer: 8–12 years before maximal rates are attained. The rates of occurrence of thromboembolic events are far less. For example, for the total group, the chances of suffering such an event were only about 25% by age 16 and 50% by age 29. While the overall curves for B_6-responders and for B_6-nonresponders remain significantly different from one another ($P = .02$), the extent of the difference is not as striking as in the case of lens dislocations.

The effect of therapy on thromboembolic events. The effect of treatment on thromboembolic events is shown in table 5. Experience was available for substantial numbers of B_6-responsive patients, and for each treatment regimen evaluated, the number of events observed during pyridoxine therapy was far less than the

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* The numerical values upon which this figure is based have been deposited with, and are available through, the National Auxiliary Publications Service. See NAPS document no. 04244 for 17 pages of supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163. Remit in advance in U.S. funds only $7.75 for photocopies or $4.00 for microfiche. Outside the U.S. and Canada, add postage of $4.50. $1.50 for microfiche postage.

number expected if therapy were without effect. The decreases were statistically significant. No significant beneficial effect was apparent for late-detected B_6-nonresponsive patients treated by methionine restriction, alone or in some combination. Because many of the early-treated B_6-nonresponders have not yet attained ages when thromboembolic events are most likely to occur (fig. 4), few events were expected among this group. Therefore, the fact that almost none have occurred, although encouraging, is not yet proof of the efficacy of treatment.

Thromboembolic events after the first clustered in a nonrandom way in specific patients. Therefore, the appearance of an initial event in a patient signified that that patient should thereafter be regarded as being at higher risk of suffering a thromboembolic event than another patient, matched for age and B_6-response category, who had not had an initial event. Thus, the expectation for recurrent thromboembolic events over any time interval could not be calculated by reference to the time-to-event graphs of figure 4, which specify the risk of an initial event only. Sufficient data were not available to permit construction of time-to-event curves for untreated patients after first episodes. To see if vitamin or dietary therapy had any major effect on the rate of occurrence of thromboembolic events subsequent to the first, it was therefore necessary to use a simplified analysis that included the assumption that the rate of such events is a constant, regardless of the age of the patient. For each patient, starting after his or her first thromboembolic event, months of exposure and number of episodes off treatment were compared to months of exposure and number of episodes on treatment to be evaluated. These values were summated and used to calculate events per year on and off treatment. B_6-responders off relevant treatment had 24 events during 3,744 months of exposure and seven events during 2,028 months of exposure on pyridoxine treatment (with or without folate), yielding rates of 0.08 and 0.04 events per year, respectively. B_6-nonresponders off treatment had 11 events during 1,264 months and four events during 836 months on methionine restriction. The corresponding rates were 0.10 and 0.06 events per year.

Postoperative thromboembolic complications. Among 164 patients with 241 major surgical procedures, 14 postoperative thromboembolic events occurred, four of which were fatal. Among 238 patients with 345 eye operations (the majority lensectomies), 11 postoperative thromboembolic events occurred, two of which were fatal [20, 21]. Of all operations, 258 were in B_6-responsive patients with one fatal and eight nonfatal thromboembolic events. Only two of these events occurred during B_6 therapy. B_6-nonresponsive patients underwent 193 operations, which were followed by one fatal and 10 nonfatal thromboembolic events.

Osteoporosis

Osteoporosis on the basis of a lateral radiograph of the spine was the definition of this finding. Time-to-event graphs for such spinal osteoporosis (fig. 5) again demonstrate a progressive appearance that is significantly less rapid in B_6-responsive patients than in B_6-nonresponsive patients ($P < .002$).
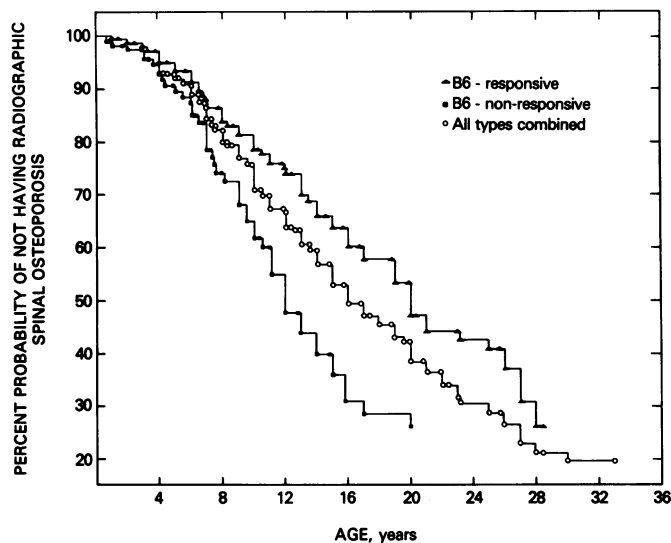
FIG. 5.—Time-to-event graphs for radiologic spinal osteoporosis in untreated patients. *The curves* are based on only those patients who were reported to either have or not to have osteoporosis on the basis of a lateral radiograph of the spine. Nos. of patients: B_6-responsive, 154; B_6-nonresponsive, 137; all types, 364. The methods and *symbols* used are the same as those in figure 3. For clarity, *the graph for "all B_6 categories"* is plotted starting at age 4.

Seizures

Among all patients in the late-detected group, 114 were reported to have had seizures, and 422 were said not to have had seizures (incidence, 21.3%). Among late-detected B_6-responsive patients, the incidence was 36/214 (16.8%), and among late-detected B_6-nonresponsive patients, 43/184 (23.4%). Although this difference is not statistically significant, time-to-event curves (not shown) indicated that seizure onset tended to occur somewhat earlier in untreated B_6-nonresponsive (e.g., 20% chance of having seizures by age 12 years) than in untreated B_6-responsive patients (20% chance by age 21). The difference between the curves overall attained marginal statistical significance ($P = .04-.05$). Grand mal seizures accounted for 69%, 69%, and 76% of the seizures characterized as to type among, respectively, the total group, B_6-responsive patients, and B_6-nonresponsive patients.

Very limited evidence was reported as to the effect of dietary or pyridoxine therapy upon seizures in late-detected patients. Seizures in several B_6-nonresponsive patients were not alleviated by diet. Among B_6-responsive patients, seizures decreased in frequency during pyridoxine treatment in only a few.

Information on the presence or absence of seizures was available for 55 patients detected in newborn screening programs and started early on therapy. Only one was reported to have had seizures. This patient was a B_6-nonresponsive infant who had generalized seizures at 18 hrs of age, 4 days before dietary therapy was started. By use of the time-to-event curve for seizures in untreated B_6-nonresponsive patients, it was calculated that among 40 B_6-nonresponsive patients detected by newborn screening, 4.2 would have been expected to have had seizures had

therapy been without effect. The lack of seizures in this group during therapy is thus encouraging, although more data are required to provide definitive proof of the preventive effect of early treatment.

Mortality

Of the 629 patients covered in this study, 64 were deceased. The cause of death was unknown for three patients, and two died for reasons apparently unrelated to cystathionine β-synthase deficiency (accidental drowning at age 8; metastatic abdominal carcinoma at age 61). Of the remaining 59 deaths, thromboembolism was known to be the chief causative factor in 42 (71%) and was a probable, but less clearly established, major contributing factor in at least five others (8%). Pneumonia, other pulmonary infections, or sepsis were reported as the cause of death in seven patients (12%). The latter were all grossly mentally retarded with IQ's less than 50. For five patients, the causes were of uncertain relationship to the underlying disorder (heart failure at 15 years in a severely retarded patient; subarachnoid hemorrhage at age 10 from two aneurysms of the basilar artery; spongy degeneration of the central nervous system with toxic sepsis [58]; pulmonary hemorrhage in a 36-day-old infant; suicide at age 18).

The time-to-event graphs for deaths are shown in figure 6. Many of the patients who died had had brief periods of therapies that would be expected not to be effective (e.g., B_6 given to nonresponsive patients or methionine restriction that did not alter abnormal plasma amino acid patterns) or were treated only after several thromboembolic events had already occurred. Therefore, to give a more accurate representation of the overall mortality, patients were not removed from the groups at risk upon initiation of therapy.

Mortality among patients classified with regard to B_6 response was 5.5% (29 of 529 patients). Survival (fig. 6) for B_6-responders was significantly higher than that for B_6-nonresponders ($P < .0001$). For example, the expected mortality at
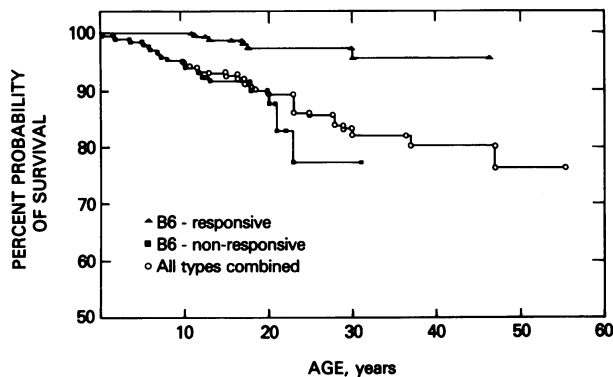

FIG. 6.—Time-to-event graphs for deaths. Patients were not removed from the at-risk groups upon initiation of therapy. Otherwise, the methods and *symbols* were the same as those described in the legend to figure 3 except that data for 629 patients were used for *the "all-types" curves. For "all patients,"* the graph is not plotted prior to age 10, but was virtually the same as that for B_6-nonresponsive patients.

age 20 was less than 5% among those responsive to B_6 and approximately 20% in those not responsive. The incidence of mortality among those whose response to B_6 was unknown was disproportionately high (35%). Several factors appeared to contribute to this result: the deaths occurred either before the effect of pyridoxine on cystathionine β-synthase deficiency was well known [11] or in patients in whom sudden death or profound retardation precluded evaluation of B_6-responsiveness.

Patients Ascertained by Complete Sibship Screening

To what extent has ascertainment bias contributed to these results? Patients ascertained by screening of all siblings following diagnosis of cystathionine β-synthase deficiency in a proband form a special group that provides some insight into this question. Ninety patients detected by such complete sibship screening were included in the present study. Of these, two were detected as newborns and treated early, and 88 were late-detected. Major clinical manifestations in these 88 patients were compared to those in late-detected patients ("probands") who came to attention because of clinical complication(s). (1) Mental capabilities. The "complete-sibship-screened" group of B_6-responsive patients had a mean IQ 21 points higher than the B_6-responsive probands, a difference which was statistically significant. When IQ scores were not available, however, the proportions of each of these groups judged to be mentally retarded were not significantly different. Among B_6-nonresponsive patients, no significant difference was present in the mean IQ scores for the "complete-sibship-screened" group compared with probands, but only 65% of the former were judged to be retarded, as compared to 91% of the probands ($P < .05$). (2) Seizures. In the "complete-sibship-screened" group, seizures were reported in 16 of 85 patients (19%), an incidence not significantly different from that in the proband group: 98 of 449 (22%). (3) Lens dislocation. There were no statistically significant differences in the time-to-event curves for any of the "complete-sibship-screened" groups when compared with the proband groups. (4) First thromboembolic events. The results were the same as those for lenses. (5) Osteoporosis. The results were the same as those for lenses and first thromboembolic events, except that for B_6-responders the time of detection of osteoporosis in the "complete-sibship-screened" group was slightly delayed compared with that in the proband group (e.g., 60% chance of not having detected osteoporosis at age 20 years in the former, as compared to 45% in the latter). Statistical comparison showed these time-to-event curves were barely significantly different ($P = .04-.05$).

Reproductive Performance

Eighty-eight pregnancies were reported among 40 homocystinuric women. To these were added 20 pregnancies among seven women included in previous reviews [6, 59] but not covered in the present survey, yielding a total of 108 pregnancies. Of these pregnancies, six were terminated by elective abortion. The outcomes of the remaining 102 pregnancies are summarized in table 6. Most occurred in B_6-responsive women (79 of the 90 pregnancies occurring in women classified

TABLE 6

OUTCOMES OF PREGNANCIES IN CYSTATHIONINE β-SYNTHASE-DEFICIENT HOMOCYSTINURIC WOMEN

	B₆-RESPONSIVE THERAPY DURING PREGNANCY		B₆-NONRESPONSIVE	INTERMEDIATE RESPONSE	RESPONSE UNKNOWN
			THERAPY DURING PREGNANCY		
	None	B₆	Folate, aspirin, and dipyridamole	None	None
Full-term, normal child	25	18	1	5	11*
Child with abnormality	2†	1‡	. . .	. . .	. . .
Premature birth	· · ·	1§	. . .	1‖	· · ·
Stillborn	5	2	. . .	. . .	1#
Spontaneous abortion	19	4	. . .	3	. . .
Ectopic pregnancy	1	1	1	. . .	. . .
Total	52	27	2	9	12

NOTE: Includes data from the present survey and from additional patients included in the reviews by Mudd and Levy [6] and Lamon et al. [59], but not covered in the survey. Six pregnancies (five spontaneous abortions in an untreated B₆-responsive patient and one normal child born to the same patient following B₆ therapy) were deleted from the pregnancies summarized in [6] and [59] since they were found to be duplications (V. Shih, personal communication, 1983). One patient, previously taken to be B₆-nonresponsive [6] (patient 1 in [60]) has since been reclassified as B₆-responsive on the basis of further studies (patient 1 in [61]).

    * Includes one patient who was not specified as either treated or not treated.

    † One child with coloboma of iris, otherwise normal at age 4; one child with fused sagittal suture and mental retardation.

    ‡ One child with trisomy 21 [62].

    § Normal child delivered at 33 weeks.

    ‖ Died of hyaline membrane disease.

    # Hydrocephalic child, stillborn as a result of a decompression procedure done to permit delivery [56].

as to B₆-response). Among these B₆-responsive patients, fetal loss (stillbirth, spontaneous abortion, and ectopic pregnancy) occurred in 25 of 52 pregnancies (48%) in which the patient was not treated with pyridoxine and in seven of 27 pregnancies (26%) in which the patient received pyridoxine. These results, however, were strongly influenced by major contributions from three patients: (1) a woman who had 10 spontaneous abortions without pyridoxine treatment, (2) a woman who had five stillbirths or spontaneous abortions prior to B₆ administration followed by two stillbirths after commencement of such treatment, and (3) a woman who had five spontaneous abortions prior to B₆ therapy, followed by two normal deliveries after initiation of pyridoxine treatment. Removal of the data from these three women would leave 32 B₆-responsive patients with 55 pregnancies that ended other than by elective abortion. Fetal losses in this subgroup were 5/32 (16%) in the absence of B₆ treatment and 5/23 (22%) during B₆ administration. These values were not significantly different statistically.

    Twenty-one male patients were reported to have sired 34 fetuses whose fates were known. Of these recognized conceptions, 33 resulted in apparently healthy offspring and one spontaneously aborted. To these may be added three normal children sired by two patients previously reported [56] but not included in the present survey. Of the total of 37 fetuses, 29 were sired by patients responsive to B₆, two by patients not responsive, one by a patient intermediate in response,

and five by patients with unknown responses. The one fetus who aborted was fathered by a B_6-responsive patient.

DISCUSSION

A major aim of the present study was to gather standardized data on a sufficient number of patients with homocystinuria due to cystathionine β-synthase deficiency so that questions requiring statistical treatment could be considered. Information upon 629 patients was included in the study (532 on the basis of questionnaires; 97 chiefly on the basis of published material). We are aware of some 75–100 additional patients for whom we were unable to obtain reports. In spite of the relatively satisfactory coverage attained, the possibility must be considered that the patient sample is subject to bias in several ways. (1) There may have been relative underreporting of deceased patients as information about them became less current for responding physicians. Every effort was made to obtain reports covering all known deceased patients, but to the extent these efforts fell short, the sample would be biased toward less severely affected patients. (2) Bias in the opposite direction, toward more severely affected patients, may have occurred because most of the patients included in this survey were ascertained due to the presence of one or more clinical features typically associated with cystathionine β-synthase deficiency. In the sections that follow, the effect of such bias on each clinical manifestation is discussed in light of data on ascertainment (table 2) and, more quantitatively, of comparison of patients discovered during complete screening of sibships with probands. However, even the latter tactic may not completely eliminate ascertainment bias in a situation, such as the present, in which there is a strong impression of general concordance within sibships of severity of symptoms. As early as 1978, the experience in New South Wales [63] suggested that mild cases of cystathionine β-synthase deficiency are more frequent than had been thought and that underascertainment of patients with this disease might be occurring. Data from screening programs of newborns furnish one means to arrive at a crude estimate of the possible magnitude of such underascertainment. This was done for the United States, the country from which the greatest number of patients were reported (37% of all those classified as B_6-responsive or nonresponsive). Combination of the results from screening programs of newborns in the Rocky Mountain states [64], Georgia (L. Elsas and P. Fernhoff, personal communication, 1984), New England (H. L. Levy and J. Simmons, unpublished observations, 1984), and Maryland and Delaware (S. R. Panny and J. M. Joseph, personal communication, 1984) leads to a rate of detection of cystathionine β-synthase deficiency of one per 209×10^3 newborns (based on a total of 3.34×10^6 screened). Extrapolating this combined ratio to the country as a whole, assuming from the results reported here that 78% of those detected are B_6-nonresponsive and taking into account the age structure of the population of the United States [65] and the less than normal survival of B_6-nonresponsive patients (fig. 6), one may estimate that in the United States the number of living B_6-nonresponsive cystathionine β-synthase-deficient persons 25 years of age or younger should be 299, an incidence of one per 738×10^3 persons in the total population. Reports were obtained for the survey concerning 63 patients of this sort, or one per

3.5×10^6. Although the above estimate is no better than a very rough approximation, it appears that a substantial portion of potential B_6-nonresponsive subjects in the United States have been both diagnosed and reported upon in the present survey. However, probably an even greater portion remain to be diagnosed or (in our opinion less likely) are known to physicians but were not reported upon.*

The analogous calculation for B_6-responders indicates that in the United States there should be only 55 such patients alive at age 25 or less (one per 4.7×10^6). The low estimate is due to the fact that only 13% of patients detected in screening of newborns have been B_6-responsive. In actuality, reports were obtained upon 47 such patients. Since it seems unreasonable to suppose that such a high proportion of all such patients have been both diagnosed and reported upon, these combined results support the likelihood (discussed further in the section below on newborn screening) that B_6-responders are being missed in current screening programs of newborns, so that the above estimate of the potential number of these patients is probably too low.

B_6-responsiveness or nonresponsiveness. In considering clinical manifestations, an effort was made to control as much as possible for the extensive heterogeneity known to occur in the mutations producing cystathionine β-synthase deficiency [6]. This was done simply by asking responding physicians to classify patients as either B_6-responsive, B_6-nonresponsive, or intermediate in response. Rigid guidelines as to how to make this classification were not set up for the responding physicians, because it was realized from the outset that, at best, this division is an oversimplification. There is ample evidence that, if sufficient studies are performed, patients with genetic lesions differing in many details will be found within any one of these categories of response to B_6 [6, 66, 67]. Classification on the basis of more detailed data, however, would not have been possible for the majority of cystathionine β-synthase patients, for whom such studies have not been carried out. Furthermore, studies of the properties of a particular mutant enzyme from a given patient do not yet permit unambiguous prediction whether that patient will be clinically responsive to pyridoxine or not (although most responsive patients have some residual cystathionine β-synthase activity whereas most nonresponsive patients do not [6, 68]). Clinical classification based on B_6-response was also in accord with the widespread impression that it is among B_6-responsive patients that those with milder manifestations of cystathionine β-synthase deficiency are to be found [6]. In practice, B_6-responsiveness or non-responsiveness turned out to be concordant within sibships (table 3), providing evidence that this classification has a genetic basis. Further, classification in this

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* The United States provides a useful example for this sort of calculation, not only because far more patients were reported from this country than from any other, but also because, in terms of patients reported per unit population, the United States fell at neither the upper nor the lower extreme of the range. Considering only patients classified as B_6-responsive or B_6-nonresponsive, reports were obtained from the United States at a rate of one patient per 1.28×10^6 persons in the population. Ten countries (Australia, Belgium, Canada, Ireland, the Netherlands, New Zealand, Norway, Sweden, Switzerland, and the United Kingdom) had higher rates of reporting. The rate for Australia was highest, one per 390×10^3. Rates for the other nine areas ranged from one per 560×10^3 to one per 1.27×10^6. The rates for 13 countries were less than that for the United States.

manner did result in statistical differences between B_6-responsive and B_6-non-responsive patients with respect to the severity of most of the major clinical manifestations.

Newborn screening. Among the patients in this survey who had been detected by screening of newborns, and classified as to B_6-responsiveness, only 13% were B_6-responsive. Among late-detected patients, the corresponding value was 47%. The possibility that this discrepancy is due to high and preferential early mortality among B_6-nonresponsive patients cannot be excluded, although the likelihood that this is so appears very remote, based upon the survival curve for B_6-non-responsive patients once they have been detected (fig. 6). Much more probable, as suggested from the experience of the Massachusetts newborn screening program [69], and from the above comparison of the estimated number of B_6-responders in the United States with the number actually reported, B_6-responsive patients are being missed in current screening programs that base detection upon hyper-methioninemia during the first days of life. Further evidence from the present survey that this may be so is provided by the finding that 21 B_6-responsive patients were reported not to be hypermethioninemic when untreated, compared to only two B_6-nonresponders. Since, as discussed below, available evidence now supports the effectiveness of early treatment in ameliorating mental retardation, incidence of seizures, and the rate of lens dislocations, these findings suggest the need for an improved method of detecting cystathionine β-synthase deficiency during screening of newborns.

Mental capability. The results presented in figure 1 and in table 4 emphasize the wide range of mental capabilities found in cystathionine β-synthase-deficient patients and the fact that there is extensive overlap in this regard between B_6-responsive and -nonresponsive patients. Nevertheless, there is clearly a tendency for B_6-responsive patients to be less severely affected, and virtually all patients with IQ's of 90, or above, are B_6-responsive.

Many of the patients in the survey sample had mental retardation as at least one factor contributing to their ascertainment (table 2), raising the possibility that ascertainment bias influenced quantitatively the apparent extent of the mental impairment caused by cystathionine β-synthase deficiency. Comparison of patients ascertained by complete sibship screening with those in the proband group confirmed that ascertainment bias did exert such an influence. To estimate the maximum contribution of ascertainment bias, relevant analyses were repeated after prior removal of patients for whom mental retardation was a factor in ascertainment. The difference in IQ's between B_6-responsive and nonresponsive patients remained, with the median IQ's for B_6-responsive and B_6-nonresponsive patients each increasing by eight points.

Optic lenses. The results in figure 3 provide the first time-to-event curves for lens dislocations in large untreated groups of both B_6-responsive and B_6-nonre-sponsive patients. Both curves display a lag during the first 2 years of life, but thereafter differ in the rates of lens dislocation between the two groups. If ascertainment bias is not present, these curves also confirm the impression that eventually the great majority of cystathionine β-synthase-deficient patients develop

dislocated lenses, as shown by the probability that only 3% of all such patients will have lenses in place by age 39. However, the data in table 2 suggest that ascertainment bias might be particularly marked for ectopia lentis, which was the sole feature leading to ascertainment of almost 21% of patients discovered because of clinical stigmata and a contributory factor in an additional 65%. Cystathionine β-synthase-deficient patients without dislocated lenses are probably especially likely to remain undiagnosed, and the occurrence of significant numbers of such patients would help explain the probability, discussed above, that, at present, there has been marked underascertainment of the total group of patients with this disease.*

Thromboembolic events. The time-to-event graphs for initial thromboembolic events in the untreated state (fig. 4) provide for the first time data based upon sufficiently large numbers of both B_6-responsive and B_6-nonresponsive patients that realistic estimates can be made of the chances of suffering a clinically detected event of this sort over given age intervals. As with lens dislocations, these prob- abilities change with the age of the patients: initial lags are followed by progressive increases in the probability of suffering a thromboembolic disorder. The cumulative probabilities of having thromboembolic events are, perhaps, lower than might have been expected from the general impression in the literature. Both B_6-responders and B_6-nonresponders have about a 70% chance of reaching age 20 free of clinically apparent thromboembolic disorder. Of course, additional events may have occurred that would have become apparent through the use of more extensive or sophisticated examinations.

Since early thromboembolic events were the sole cause of ascertainment in relatively few patients (table 2) and the time-to-event curves for first events were not significantly different for patients discovered by complete sibship screening and probands, there is little indication that ascertainment bias distorts the results reported for such events toward a falsely high incidence. On the other hand, at least some patients who present as young adults with thrombotic events and none of the other "typical" clinical features of cystathionine β-synthase deficiency may be remaining undiagnosed [63, 70]. If so, our present picture of the incidence of thromboembolism in this disease may be falsely low.

The relative infrequency of clinically apparent events means that evaluation of the effects of therapies is correspondingly difficult. Calculated over 5-year intervals, the maximum likelihood for B_6-responders of having such an event occurred over the interval of approximately 20–25 years, when the chances were 0.038 per year. For B_6-nonresponders, the maximum likelihood occurred between approximately 12.5–17.5 years, and was equal to 0.040 per year. These values correspond to about 25 years/event. Thus, even if patients were studied during

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* Using the data from figure 3, it can be calculated that at any moment in the United States approximately 26%–27% of the B_6-nonresponsive cystathionine β-synthase-deficient individuals alive at age 25, or less, will not yet have developed ectopia lentis. This group should therefore comprise 79 patients of the estimated potential total of 299. For B_6-responsive patients, the analogous value is 44% of the potential total.

these intervals of maximum risk, it would be necessary to follow 50 patients for 5 years each to accumulate the expectation that, had these patients not been treated, 10 detected thromboembolic events would have occurred. If patients were studied at earlier ages, before the periods of maximum risk, the numbers of patients and/or the periods of observation would have to be increased to attain the same expectation.

Postoperative thromboembolic complications. Early reports on cystathionine β-synthase-deficient patients drew attention to the possibility that they are at increased risk for postoperative thromboembolic complications [20, 21]. Considerable attention has subsequently been devoted to development of suitable procedures for pre- and postoperative management and for anesthesia [53, 71–76]. Information on the specific procedures employed during the operations reported in the present survey was not obtained. Nevertheless, the data indicate that it is certainly possible for the great majority of operations, including ophthalmologic and other forms of major surgery, to be carried out without producing thromboembolic complications. In this respect, B_6-responsive and B_6-nonresponsive patients fared about equally well.

Osteoporosis. The time-to-event graphs presented in figure 5 for detection of radiographically demonstrated spinal osteoporosis should be regarded as setting upper limits for the ages at which this condition is present in given proportions of patients. More than the other clinical manifestations discussed here, osteoporosis could have been present, yet gone undetected, until patients were ascertained for other reasons. Some effect of ascertainment bias on these curves is indicated also by the significant difference between the curve for B_6-responsive patients discovered by complete sibship screening and the curve for probands. Certainly, better serial data, optimally using more sensitive and quantifiable measures of osteoporosis, will be required to provide baselines that permit satisfactory evaluation of the effects of therapies on this manifestation.

Mortality. The survivorship data (fig. 6) drawn from the present survey indicate mortality rates much less rapid than those reported by McKusick et al. [56]. Because in that early series patients were not subdivided according to B_6-response, comparisons are possible only between total group experiences. McKusick et al. found that approximately 50% of patients had died by age 20, and 75%, by age 30. For the present series, the values were 11% by age 20 and 18% by age 30. These differences cannot be ascribed to the fact that a greater proportion of the patients now being reported upon had probably received treatment. Survivorship curves constructed taking into consideration mortality only among patients who had not yet received treatment were not appreciably steeper than those in figure 6 for any single B_6-response category, or for the overall group. Three additional factors may be considered as possibly contributing to the difference between the earlier study and our survey. First, as noted above, it is possible, although judged unlikely, there was relative underreporting of deceased patients for the present survey. Second, during this survey, we received reports upon a number of siblings of acknowledged cases of cystathionine β-synthase deficiency. These siblings had died with clinical manifestations characteristic of cystathionine β-synthase deficiency, but prior to the recognition of this disease in the early 1960s. Con-

sequently, urine and/or plasma samples were not examined for homocystine. To avoid circularity in defining the clinical picture of cystathionine β-synthase deficiency, we did not include such patients, whereas a number of these patients, or others with somewhat similar circumstances, were included in the former series [56]. Inclusion of these patients would have added 25 subjects to our survey, and resulted in slightly, but not strikingly, greater rates of mortality. For example, for the overall group, the modified mortality would have been 14% at age 20 and 19% at age 30. Third, and probably most important, the early series may have included on the average more severely affected patients than those in the present series because, as greater familiarity has been gained with the clinical picture of cystathionine β-synthase deficiency, more mildly affected patients with this disease have been recognized. If this is so, the actual prognosis for patients with cystathionine β-synthase deficiency is far better than had been thought previously.

Reproductive performance. For both men and women, many fewer conceptions were reported for B_6-nonresponsive than for B_6-responsive patients. This result may well reflect the more marked mental retardation, poorer survival, and generally inferior clinical condition of B_6-nonresponsive individuals, but a specific effect upon fertility is not excluded. The offspring of male subjects did not suffer excessive losses up to the time of birth and were generally reported to be normal. Since these children are presumptive heterozygotes for cystathionine β-synthase deficiency, one may conclude that the genetic load from such heterozygosity is minimal both in utero and at least in the early years of life. Higher rates of fetal loss were experienced by presumptive heterozygous fetuses carried by cystathionine β-synthase-deficient mothers (48% in untreated B_6-responsive women; 26% in such women during B_6 administration). However, these overall figures were strongly influenced by the results from three women, each of whom had multiple stillbirths or spontaneous abortions. It is uncertain whether the latter fetal losses can be attributed to cystathionine β-synthase deficiency or were incidentally associated. Whether or not they were receiving B_6 therapy, the remaining B_6-responsive women had reported fetal losses near 20%, a rate not excessive compared to that for the general population [77]. Especially for untreated women, this rate is much more favorable than those reported in previous reviews [6, 59], a result probably due to the fact that many normal pregnancies in untreated homocystinuric women had previously gone unreported. Phenylketonuria in the mother often results in mental retardation, microcephaly, congenital heart disease, and low birth weight in the offspring [78]. These, or other, abnormalities were not prominently reported among living offspring of cystathionine β-synthase-deficient mothers.

Treatment. Methionine restriction, usually accompanied by cystine supplementation, was the first treatment devised for cystathionine β-synthase-deficient patients, and, for B_6-nonresponsive patients, far more experience has been accumulated with this treatment than with any other. The results of this survey clearly indicate the efficacy of such therapy in preventing mental retardation in B_6-nonresponsive patients who are detected as newborns and started early upon therapy (fig. 2). An improvement of the order of 35 points in mean IQ was

observed in such patients. The evidence available tentatively suggests that such therapy may also decrease the rate of lens dislocations (table 5) and reduce the incidence of seizures. More definitive information on these manifestations will be acquired in the near future as further experience with these patients accumulates. Likewise, it is still too early to assess the effect of early-onset methionine restriction therapy on thromboembolic events (table 5), mortality, or osteoporosis.

Methionine restriction, sometimes accompanied by pyridoxine therapy, has also been used for the majority of patients detected as newborns who are B_6-responsive. Because of the relative infrequency of patients in this group, data are more limited, but, nevertheless, indicate that most subjects will attain normal or near normal intelligence when so treated.

Methionine restriction has apparently not produced statistically significant benefit upon lens dislocation or the rate of occurrence of first thromboembolic events in late-detected B_6-nonresponsive patients. These observations should be interpreted with caution, however, since it is very likely that for many of the patients reported here compliance with the restricted diet was poor. Thus, the possibility that a very strictly managed group of late-detected B_6-nonresponsive patients would benefit from methionine restriction has certainly not been excluded. The experience reported by Carson [79] furnishes a suggestive example of this possibility.

Pyridoxine administration is currently the most widely used therapy for late-detected B_6-responsive patients. A statistically significant reduction in the number of initial thromboembolic events seems to have been brought about by this treatment. Certainly, this observation is encouraging, but in view of the relatively small numbers of events, should probably be regarded more as suggestive than as definitive. Evaluation of the effect of pyridoxine treatment on lens dislocation awaits observation of more patients started on therapy at earlier ages, and, for osteoporosis, of conducting longitudinal studies of this condition.

More recently, several additional modes of therapy have been suggested. Aspirin and dipyridamole may reverse decreased platelet survival time [12], although evidence on this point has varied [80]. These agents would be expected to affect chiefly thrombotic events. Betaine or choline reduce homocyst(e)inemia [13, 14] and might affect the whole array of consequences due to this chemical aberration. Because hypermethioninemia may be enhanced, the long-term effects of this treatment will require especially careful evaluation. In practice, these agents are currently being used chiefly for late-detected B_6-nonresponsive patients who present the most difficult problems in therapy among cystathionine β-synthase-deficient patients. In some B_6-responders, aspirin and/or dipyridamole are superimposed on pyridoxine treatment. Preliminary observations suggest that betaine significantly improves patient behavior [13, 14]. The data obtained during the present survey were not sufficient to permit evaluation of the long-term effects of either of these therapeutic regimens on thromboembolism or that of betaine upon dislocation of optic lenses and development and progression of osteoporosis. It is hoped that the data reported here will provide the baselines necessary for design of future studies that are statistically meaningful and for evaluation of the results of such studies.

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