EFFECT OF THE HEMODIALYSIS PRESCRIPTION ON PATIENT MORBIDITY

Report from the National Cooperative Dialysis Study*

E. G. LOWRIE, M.D., N. M. LAIRD, PH.D., T. F. PARKER, M.D., AND J. A. SARGENT, PH.D.

Abstract This report summarizes morbidity in 151 patients in a cooperative trial designed to evaluate the clinical effects of different dialysis prescriptions. Four treatment groups were divided along two dimensions: dialysis treatment time (long or short), and blood urea nitrogen (BUN) concentration averaged with respect to time (TAC_{urea}) (high or low). Dietary protein was not restricted. There was no difference in mortality between the groups. Withdrawal of patients from the high-BUN groups for medical reasons was significantly greater than withdrawal from the low-BUN groups. Hospitalization was also greater in the high-BUN groups, but dialysis treatment time had no significant effects.

The data indicate that the occurrence of morbid events is affected by the dialysis prescription. Increased morbidity appears to accompany prescriptions associated with a relatively high BUN. Conversely, morbidity may be decreased by prescriptions associated with more efficient removal of urea if the dietary intake of protein and other nutrients is adequate. (N Engl J Med. 1981; 305:1176-81.)

PHYSICIANS who prescribe hemodialysis therapy have long been confronted by the difficult problem of how to determine an appropriate "dose" of dialysis for individual patients. In clinical practice, most patients in a dialysis program undergo treatment for similar lengths of time and with dialyzers that have similar performance characteristics. The needs of individual patients are often not considered or, if they are considered, are judged more by clinical impression than by quantitative measures to guide therapy. Any difference between treatment regimens is usually influenced more by different needs for removal of fluid than by different metabolic needs; individual requirements for solute removal are often ignored.

The National Cooperative Dialysis Study (NCDS) was initiated because of the perceived need to develop a quantifiable definition of adequate long-term dialysis treatment within the domain of current clinical therapies. The study was designed to evaluate two concentrations of blood urea nitrogen (BUN: about 50 and about 100 mg per deciliter [20 and 40 mmol per liter]) at two different treatment durations (TIME: about three hours and about 4½ hours) with a thrice-weekly treatment schedule. There were four treatment groups representing all combinations of BUN and TIME. It should be noted that the target BUN concentration was the value averaged over a dialysis cycle,[1] so that BUN might typically oscillate between 120 mg per deciliter (40 mmol per liter) (before dialysis) and 80 mg per deciliter (30 mmol per liter) (after dialysis) in the high-BUN groups and between 70 and 30 mg per deciliter (20 and 10 mmol per liter) in the low-BUN groups.

The dependent variables consisted of major organ-system indexes, psychosocial data, and measures of general morbidity, such as death, hospitalizations, and withdrawal from the study. Although most of the data were analyzed at the end of the study, morbidity analysis was ongoing to ensure that patients would not be subjected to a continuing and potentially preventable risk. In March 1980 there were sufficient data to demonstrate significantly higher morbidity in the high-BUN groups, and the NCDS Patient Safety Committee — whose members were not involved in the day-to-day management of the study — recommended that these groups be discontinued. This report describes those data.

METHODS

General

Urea nitrogen averaged with respect to time (TAC_{urea})[1] and the length of the dialysis treatment were used as the primary independent variables. TAC_{urea} is an integrated parameter computed as the mean BUN during a full dialysis cycle and was considered more appropriate for controlling therapy than an arbitrary pretreatment value. Nonetheless, the two target TAC_{urea} values of 100 mg per deciliter and 50 mg per deciliter correspond clinically to midweek (second dialysis on a thrice-weekly schedule) pre-dialysis values of 120±10 mg per deciliter (range) and 70±10 mg per deciliter, respectively. The dietary prescription included a daily protein intake of 0.8 to 1.4 g per kilogram of body weight.

The test therapies were divided on two dimensions: BUN concentration and dialysis treatment time. The four possible combinations were designated as follows: Group I — standard therapy with relatively long dialysis times (4½ to five hours) and a relatively low urea nitrogen concentration (TAC_{urea} = 50 mg per deciliter); Group II — a long dialysis time while permitting urea nitrogen to rise (TAC_{urea} = 100 mg per deciliter); Group III — a shortened dialysis time (3±0.5 hours) while maintaining a low urea nitrogen concentration; and Group IV — a reduced dialysis time while permitting urea nitrogen to rise.

The desired BUN concentrations were achieved by manipulating dialyzer urea clearance at the prescribed treatment times. Clearance was manipulated, in turn, by combining four operating variables[2]: the membrane and surface area of the artificial kidney, the rate of blood flow to the dialyzing membrane, the flow rate of

*National Cooperative Dialysis Study: Lead Center: (Harvard University with major affiliates at Quantitative Medical Systems, Inc., Vanderbilt University and Damon Medical Laboratories): E. G. Lowrie (Principal Investigator), J. A. Sargent (Co-Principal Investigator, Kinetics and Treatment Control), J. M. Lazarus (Co-Principal Investigator, Outcome Variables), R. R. Henry (Nutrition), N. M. Laird (Statistics), R. K. Neff (Systems), D. C. Olivier (Systems), R. Frankel (Laboratory Quality Assurance), J. R. Bourne (Neurobehavioral), P. E. Teschan (Neurobehavioral), B. A. Maher (Psychosocial), and B. J. Murawski (Psychosocial). Participating Centers: M. N. Gottlieb (Peter Bent Brigham Hospital), P. Y. Schoenfeld (University of California, San Francisco), H. E. Ginn (Vanderbilt University), T. F. Parker (Dallas Kidney Disease Center), T. K. Rao (Downstate Medical Center), G. C. Santiago (Henry Ford Hospital), B. P. Teehan (Lankenau Hospital), D. M. Roxe (Northwestern University Hospital), and H. R. Harter (Washington University Medical School).

Address reprint requests to Dr. Lowrie at the National Cooperative Dialysis Study Coordinating Center, 1055 Commonwealth Ave., Boston, MA 02215.

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the dialysate, and the relative directions of blood and dialysate flow (countercurrent, co-current, or completely mixed dialysate). The clearance required to achieve the desired BUN for individual patients was computed with a mathematical model of urea nitrogen metabolism.[3-7] This model, based on material balance of nitrogen, permits calculation of the net rate of urea generation between dialysis treatments and estimation of the corresponding net rate of protein catabolism.[4,6,7]

Patients

All patients were between the ages of 18 and 70 years, inclusive; they all received treatment in a dialysis center, and their residual creatinine clearance was no more than 3 ml per minute.[8] Patients were excluded if they were known to have cancer, diabetes mellitus, uncontrolled hypertension, reversible renal failure, systemic disease such as lupus erythematosus, or unstable cerebral or coronary vascular disease. Patients with clinically important pulmonary disease or hepatic dysfunction were also excluded. One hundred fifty-one patients from eight centers were randomized into one of the four experimental groups during the initial 22 months of the study and are the subject of this report.

Protocol

Each center selected dialyzers from one manufacturer. In practice, there was one manufacturer whose dialyzers use regenerated cellulose membranes (C-DAK series from Cordis Dow providing 1.3 m^2, 1.8 m^2, or 2.5 m^2) and one whose units use Cuprophan membranes (CF series from Travenol Laboratories providing 1.2 m^2, 1.5 m^2, or 2.3 m^2). This prospective dialyzer selection was based on the practical range of urea clearance for each device and the range of clearance that would be required for control in patients in each of the groups. The dialyzer was selected for each patient before he or she was assigned to a treatment group.

The NCDS protocol is described in detail elsewhere.[9,10] All patients gave a medical history after providing appropriate informed consent. Their status before the study was evaluated by collecting base-line data while they remained on their pre-study dialysis regimen. Patients then entered the study, and data were collected for no less than three months while they were maintained on standard therapy, as defined by Group I. Patients in whom standard therapy produced successful control were then randomly assigned to one of the four treatment protocols. The randomization was performed by the Lead Center according to a schedule determined before the study began. In order to test the randomization procedure patients were evaluated according to group with respect to potential medical risks, including age, history of heart disease, hypertension, peripheral vascular disease, pulmonary disease, and gastrointestinal disease; there were no statistical differences between the groups. Pre-randomization hospitalization was also evaluated, and again, there was no significant difference between groups.

Data on removal of patients from the study protocol were obtained with a study-exit form. Up to four reasons for withdrawal, with comments, were allowed. These included death, withdrawal for medical reasons, transplantation, and "other." The latter category included unspecified patient preference, moved from area, and completion of the protocol. For purposes of this report, a patient was classified as removed for medical reasons if any medical diagnosis was given on the exit form. Data describing hospitalization were taken from the treatment log. Multiple diagnoses were allowed. Diagnoses thought not to be related to uremia were eliminated prospectively.* The large majority of excluded hospitalizations were for vascular access surgery. When more than one diagnosis was listed, the most serious was selected (the choice of most serious was validated by an exterior, blinded, independent review).

*See NAPS document no. 03906 for a one-page list of diagnoses, including those eliminated prospectively. 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 for microfiche. Outside the U.S. and Canada add postage of $4.50 ($1.50 for microfiche postage).

Statistical Methods

An analysis of variance was used to compare the treatment groups with respect to the independent variables: dialysis time, midweek BUN, and TAC_{urea}. As is usual with a 2-by-2 factorial design, the total between-groups variance was partitioned into the variance due to the overall effect of BUN, the variance due to the overall effect of TIME, and the variance due to the interaction between TIME and BUN. Thus, the results of three F-tests are reported for each variable in Table 1.

Time to withdrawal and time to first hospitalization were analyzed with covariance analysis methods for life-table data.[11,12] An exit due to death or medical reasons was counted as a "death"; all patients who did not die were considered to have withdrawn alive at their time of exit or on April 1, 1980, whichever came first. First hospitalization or death was counted as "death" in evaluating hospitalization data. Center, base-line medical risk, and hospitalization before randomization were used as covariates in these analyses.

Results

Control Achieved

Table 1 shows the four group means and their standard errors for duration of dialysis treatment, midweek pre-dialysis BUN, and TAC_{urea}. Overall, the objectives for control were achieved, but the two high-BUN groups fell somewhat below target, so that the actual values of TAC_{urea} compared in this study were about 52 and about 89 mg per deciliter (19 and 32 mmol per liter). Nonetheless, good separation between the groups was achieved. Note that the P values for TIME in columns two and three of Table 1 indicate that the two long-TIME groups had slightly lower BUNs than the two short-TIME groups. The difference is only marginally significant.

Patients Removed from Study for Death or Medical Reasons

Figure 1 shows the proportion of patients remaining in each study group as a function of time on protocol dialysis. By nine months, an estimated 11 per cent, 45 per cent, 6 per cent, and 46 per cent of the patients in Groups I, II, III, and IV, respectively, had been removed because of death or medical reasons. The values at one year were 18 per cent, 45 per cent, 6 per cent, and 62 per cent. Statistical analysis of the group withdrawal rates indicates a highly significant BUN effect ($P<<0.0001$) and no significant TIME or interaction effects ($P>0.5$ for both tests).

Table 1. Control Achieved According to Study Group.*

Group and Factor Analyzed	Duration of Dialysis (Hr:Min)	Midweek Pre-dialysis BUN	Time-Averaged BUN
I	4:29±0:03	71.2±1.4	51.3±1.1
II	4:31±0:03	104.9±1.7	87.7±1.4
III	3:19±0:03	73.1±1.4	54.1±1.1
IV	3:14±0:03	109.1±1.5	89.6±1.2
TIME	P<0.0001	P<0.05	P<0.05
BUN	P>0.1	P<0.0001	P<0.0001
Interaction	P>0.1	P>0.1	P>0.1

*Data are reported as means ±S.E.M., and BUN is given in milligrams per deciliter (to convert to millimoles per liter, multiply by 0.357). The probabilities indicate the significance of differences between means for the variable with respect to the experimental factor.

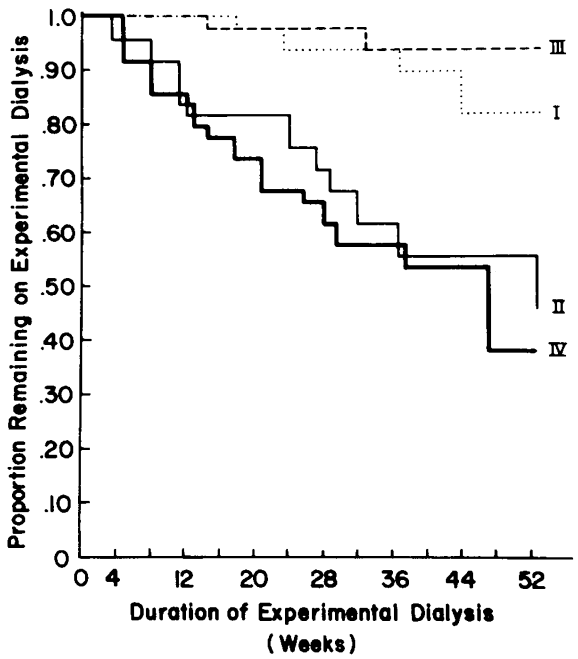

Figure 1. Proportion of Patients Not Withdrawn for Medical Reasons or Death as a Function of Time on Experimental Dialysis in the Four Study Groups.

Loss of patients from the high-BUN groups (II and IV) was greater than loss from the low-BUN groups (I and III). The numbers of patients represented at 24 weeks in Groups I through IV, respectively, were 30, 18, 35, and 23. The corresponding values were 19, 10, 25, and 13 at 36 weeks and six, seven, 13, and five at 52 weeks.

Table 2 shows the numbers of patients randomized and removed for death, medical reasons, or other reasons, and Table 3 shows the primary diagnoses associated with medical removal or death.

Three deaths occurred among randomized patients after their removal from the protocol; one patient had been in Group II, and two had been in Group IV. Thus the total number of deaths after randomization in Groups I through IV were two, one, zero, and three. These differences, controlling for exposure time, were not statistically significant.

Hospitalizations during Experimental Dialysis

Figure 2 shows the proportion of patients remaining non-hospitalized as a function of time on protocol therapy, estimated from a standard life-table analysis. In Group I, 100 per cent, 94 per cent, 86 per cent, and 86 per cent of the patients remained non-hospitalized after three months, six months, nine months, and one year, respectively. The corresponding values were 81 per cent, 70 per cent, 58 per cent, and 46 per cent in Group II; 90 per cent, 79 per cent, 69 per cent, and 69 per cent in Group III; and only 57 per cent, 47 per cent, 31 per cent, and 31 per cent in Group IV.

Differences in time elapsed before the first hospitalization were also analyzed (Table 4). There were 48 first hospitalizations during the 22 months analyzed. The right-hand column in Table 4 (observed/expected) indicates that the two high-BUN groups had excessive hospitalizations — a difference that was highly significant ($P<<0.0001$). Note that the short-TIME groups tended to have more hospitalization than the long-TIME groups when compared within the same level of BUN. For example, within the low-BUN groups less hospitalization was observed if TIME was long (observed/expected, 0.31 vs. 0.54). A similar pattern is observed in the high-BUN groups (observed/expected, 1.62 vs. 3.09). The effect of TIME however, appears quite small in comparison to the effect of BUN.

A percentage of days hospitalized was calculated for each patient in both the control and experimental phase by dividing the number of days hospitalized by the total number of days in the control or the experimental phase. The group averages were 0.67 per cent, 1.98 per cent, 1.86 per cent, and 1.14 per cent during the control phase in patients ultimately assigned to Groups I through IV, respectively. These values declined by 0.11 per cent (to 0.56 per cent) and by 0.46 per cent (to 1.40 per cent) in Groups I and III but rose by 2.81 per cent (to 4.79 per cent) and by 5.35 per cent (to 6.49 per cent) in Groups II and IV. The primary diagnoses associated with these hospitalizations are shown in Table 5. Cardiovascular diseases and miscellaneous medical problems predominate.

Discussion

Throughout the history of hemodialysis therapy for end-stage renal disease, finding a method for prescribing adequate removal of "uremic toxins" has been the goal of many investigations.[3-7,13-23] The goals of therapy and the methods for achieving these goals have been elusive. Hemodialysis practitioners have never professed to replace normal renal function, with its complex feedback mechanisms and hormonal and metabolic involvement. Rather, the aim has been to remove adequate amounts of accumulated metabolic products and water while balancing certain electrolytes. The question, then, of how to prescribe adequate dialysis is foremost, but questions concerning how one can best determine that the prescription is adequate are also important.

Table 2. Data on Removal from Experimental Protocol as of April 1, 1980.

Group	No. of Patients Randomized	No. of Deaths	No. Withdrawn for Medical Reasons	No. Withdrawn for Other Reasons *	No. Not Withdrawn
I	41	2	2	21	16
II	32	0	11	13	8
III	41	0	2	19	20
IV	37	1	17	13	6
Totals	151	3	32	66	50

*Including all other reasons for removal, such as completed protocol, patient preference, and renal transplantation.

The adequacy of dialysis treatment is inextricably linked to the physical and biochemical nature of uremic toxicity. Historically, there have been attempts to isolate a uremic toxin[24] or at least to define clinically the molecular size of the offending substance or substances.[13-15,18] The results of these investigations have generally been contradictory.[21] In this study, patient morbidity was used to reflect the adequacy of treatment. The biochemical concept of toxicity was expanded to include a broad category of protein-derived catabolites as represented by their easily measured surrogate — urea.

When data concerning removal of patients from the study for medical reasons are analyzed, one finds that significantly more patients left Groups II and IV. This suggests that TAC_{urea} is associated with patient withdrawal more often than TIME is. A wide range of diagnoses were associated with withdrawals from Groups II and IV. The four groups did not differ in death rate during or after the study.

Another method for evaluating morbidity involved determining the need for hospitalization in each of the study groups. Although physicians and patient-care personnel were not "blinded" in this study, precautions were taken to minimize bias against any of the groups based on preconceived notions about the therapies. Study teams were informed about the potential benefits and risks of each therapy, and examples of each were described from clinical practice. It seems unlikely that any potential bias led to hospitalization. Figure 2 shows that 86 per cent, 46 per cent, 69 per cent, and 31 per cent of the patients treated according to Group I through Group IV therapy remained non-hospitalized at the end of one year, and the observation implies a higher relative risk in the high-BUN groups. Finally, the fraction of days hospitalized increased during the protocol dialysis in the high-BUN groups.

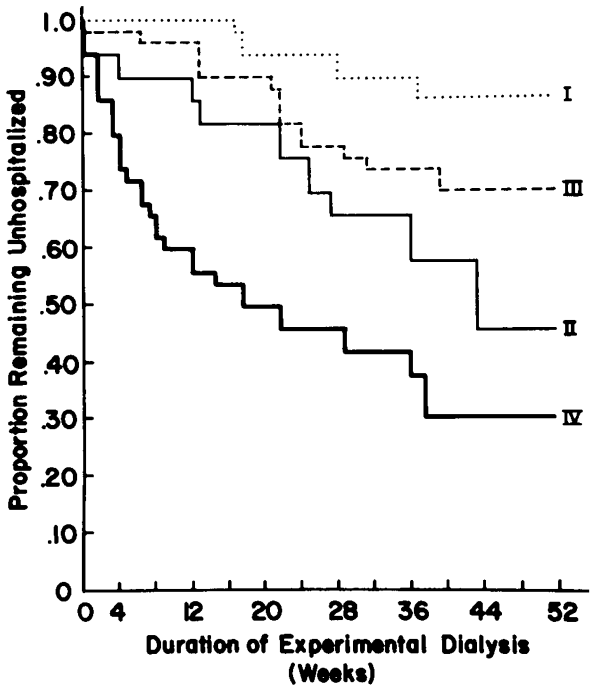

Figure 2. Proportion of Patients Remaining Non-Hospitalized as a Function of Time in the Four Study Groups.
The proportion was lower in the high-BUN groups (II and IV) than in the low-BUN groups (I and III).

Table 3. Primary Diagnoses Associated with Death or Removal before 24 Weeks.

Diagnosis	Group			
	I	II	III	IV
	no. of patients			
Anorexia or nausea		4	1	7
Fatigue		1		
Dialysis dementia	1 *			
Hyperkalemia				1
Cardiovascular disease				
Myocardial infarction or cardiac arrest		1		1 *
Resistant congestive heart failure or cardiovascular disease				1
Pericarditis				3
Pleuritis				2
Hypertension				
Neuropathy	1	1		
Convulsive disorder		2		
Worsening anemia	1	1		1
Gastrointestinal bleeding		1		1
Non-gastrointestinal bleeding				
Pancreatitis				1
Severe access infection			1	
Surgical	1 *			
Nonspecified				
Patient preference	1	1	—	1
Totals	5	12	2	19

*Died.

Treatment duration appeared to contribute somewhat to morbidity, since Group III had more hospitalization than Group I, and Group IV had more than Group II. Fluid removal is limited by the duration of dialysis treatment. Although there are marginal effects suggesting that short-duration therapy may be inferior to longer-duration therapy, these effects are minor when compared with the effects of TAC_{urea}. Interpreting the contribution of dialysis TIME to morbidity, however, is made more difficult by the observation that TAC_{urea} was slightly higher in the two short-TIME groups than it was in the two longer-TIME groups. Furthermore, we cannot make inferences about the effect of treatment times that exceed the limits of those employed in this study (six hours or two hours). These periods were chosen because a consensus of medical opinion (among physicians involved in the study as well as advisory physicians) had suggested that they represented the upper and lower bounds of clinically acceptable therapy. Finally, TIME may contribute to medical abnormalities not analyzed in this study, and our comments are restricted to morbidity as reported here.

These data suggest that patients dialyzed according to prescriptions resembling those in Group II and Group IV may have a greater risk of hospitalization

Table 4. Analysis of Time until First Hospitalization.

Group and Factor Analyzed *	Total No. of Patient-Weeks	No. of First Hospitalizations	Expected No. †	Observed No./ Expected No.
I	1394.5	4	12.95	0.31
II	732.9	11	6.77	1.62
III	1529.3	11	20.37	0.54
IV	698.3	22	7.95	3.09
BUN		P<<0.0001		
TIME		P = 0.06		
Interaction		P>0.5		

*The analysis was controlled for hospitalization during control phase, base-line medical risk, and exposure time.

†The expected value represents the number of hospitalizations that would occur in each group if hospitalizations were distributed between groups by chance alone. The expected values are not exactly proportional to exposure time (patient-weeks) because they are adjusted for the covariates listed above.

and medical complications than patients treated by prescriptions similar to those in Groups I and III. Nonetheless, many patients in Group II or Group IV remained non-hospitalized and seemed to tolerate the therapy. Patients receiving these therapies, however, experienced more medical complications as a group.

One cannot infer from these results that one need only maintain BUN at a relatively low level to reduce risk. Dietary intake of protein was not restricted in these patients. Therefore, patients in whom dietary protein is restricted by therapeutic prescription or who reduce protein intake spontaneously, perhaps because of relative underdialysis,[23] are not comparable to the patients described here. In such cases, the concentration of urea nitrogen is reduced by diminished generation of urea. Indeed, undernourished patients may also have a greater medical risk.[25]

Given an adequate intake of nutrients, the salient differences between the low and the high-BUN prescriptions were due primarily to differences in the efficiency of urea removal. In other words, the dialyzer urea clearances prescribed in Group I and Group III were substantially higher than those prescribed in Groups II and IV, in order to achieve more efficient urea removal and lower urea nitrogen concentrations at comparable dialysis times.

Table 5. Primary Reasons for All Hospitalizations.

Diagnosis	Group			
	I	II	III	IV
	no. of patients			
Congestive heart failure and miscellaneous cardiac disease	1	2	3	5
Myocardial infarction and angina			1	3
Pericarditis			2	1
Hypertension	1			2
Upper-respiratory-tract infection/ pneumonia				4
Pancreatitis/gall-bladder disease		2		2
Lower gastrointestinal bleeding				2
Miscellaneous gastrointestinal disorder		3	1	1
Dementia	1			
Seizure		1		
Bone disease		2	1	1
Hyperkalemia				2
Anemia (symptomatic)	1	2	3	1
Miscellaneous bleeding		1		1
Fever of unknown origin/infection		1	2	4
Miscellaneous medical reasons		4	4	4
Nerve compression			1	
Totals	4	18	18	33

Physicians may reasonably be concerned about how best to select the most practical combination of dialyzer clearance and dialysis time to reduce the medical risk to a reasonable minimum for a particular patient. These data do not address that issue and such discussions await further analysis. Nonetheless, these results suggest that the clearance–time combination should be selected to maintain BUN in the range in Groups I and II or lower if one confirms that the patient's diet is adequate.

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MEDICAL PROGRESS

BIOCHEMICAL GENETICS OF NEUROLOGIC DISEASE

ROGER N. ROSENBERG, M.D.

THERE have been major advances in the biochemical genetics of inherited neurologic disease during the past decade. The molecular basis for the pathogenesis of the sphingolipidoses,[1] the mucopolysaccharidoses,[2,3] the glycogenoses,[4] and the hereditary aminoacidopathies[5] represent the most notable achievements. Additional important new developments include the finding of biochemical defects in several inherited ataxias,[6-9] linkage to the HLA complex in patients with multiple sclerosis and myasthenia gravis,[10-12] and the identification of variation in clinical features and corresponding molecular defects due to allelic and nonallelic mutations.[13,14] Reports on cell-surface-membrane and cytoskeletal defects in several major genetic disorders,[15-32] abnormalities in nerve-growth factor,[33-35] and familial involvement by slow, latent infectious agents[36,37] have also provided exciting new observations into the molecular bases of several important diseases. With the knowledge of molecular markers of disease, in utero monitoring of pregnancies at risk and prenatal diagnosis of several lethal disorders have been achieved.[38-40] Several innovative and promising methods of treatment have been introduced.[41-47] Specific genetic counseling of persons at risk with dominantly inherited disease may become a reality, based on two-dimensional gel-protein patterns,[7,10] DNA hybridization and polymorphism analyses,[48] and gene-mapping studies suggesting potential elimination of disease.[49] It is now clear that the preceding revolution in molecular biology, beginning in 1953 with the description of the structure of DNA by Watson and Crick and continuing through the deciphering of the genetic code by Nirenberg et al. between 1961 and 1966, has entered the arena of molecular neurogenetics. A new genetics based on these technologies is being developed that will explain (it is hoped) most genetic neurologic disease at the molecular level leading to clinical improvement, cure, or prevention of disease. To elucidate properly the progress made in the biochemical genetics of the sphingolipidoses, mucopolysaccharidoses, and glycogenoses within the past decade, this review will describe the associated biochemical defects in relation to each clinical disorder. It has become clear that the autosomal-recessive and X-linked recessive diseases are enzyme-defect disorders, in contrast to the autosomal-dominant disorders, in which the molecular mechanism remains unknown or perhaps is due to structural or receptor-membrane defects. These enzyme defects are described with some care in this review in order to illustrate further the potential presence of allelic and nonallelic mutations involving a given enzyme or biochemical pathway in a given clinical syndrome, to show the degree of possible genetic heterogeneity.[13] Genetic variation in recessively and dominantly inherited diseases is emerging as an important factor. A series of different mutations involving the same enzyme or pathway can produce strikingly different phenotypes; conversely, an inherited clinical phenotype can be due to several different nonallelic genotypes.[13,14]

From the Department of Neurology, University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, TX 75325, where reprint requests should be addressed.

LYSOSOMAL STORAGE DISEASES

Sphingolipidoses

In a Medical Progress article for the *Journal* in 1966, Brady reviewed his important concept that the sphingolipidoses were due to enzymatic defects in the degradation of the sphingolipid; he cited his supporting findings in Gaucher's disease and Niemann–Pick disease and predicted the potential enzyme defects in Tay–Sachs disease and Fabry's disease.[50] In a brief period from 1965 to 1975, Brady and his colleagues deciphered the enzyme defects of most of the 10 major

Abbreviations Used:

BH_4	Tetrahydropteridin
DHPR	Dihydropteridin reductase
L-dopa	L-Dihydroxyphenylalanine
Hex-A (B, S)	Hexosaminidase A (B, S)
5-HT	5-Hydroxytryptophan
PH	Phenylalanine hydroxylase