

Table 5. Results obtained by AMINE for the four "unknown" amines.

Amine (prefix only)	Conditions		Solutions (prefix only)	Rank
	DELTA (ppm)	Tallies used?		
N-(3-methylbutyl)-1,5-dimethylhexyl	1.5	no	N-(3-methylbutyl)-1,5-dimethylhexyl	-
N-(3-methylbutyl)-2-ethylhexyl	1.5	no	N-(3-methylbutyl)-2-ethylhexyl	-
N-heptyl-N-(3-methylbutyl)-2-ethylhexyl	1.5	yes	N-heptyl-N-(3-methylbutyl)-2-ethylhexyl	1 (tied)
			N-pentyl-N-(3-methylbutyl)-2-ethylhexyl	1 (tied)
N-pentyl-N-(3,3-dimethylbutyl)- 3,5,5-trimethylhexyl	2.25 ^a	yes	2-ethyl-1,5,5,7,7-pentamethyl-1-(2,2-dimethylpropyl)octyl	1
			N-pentyl-N-(3,3-dimethylbutyl)-3,5,5-trimethylhexyl	2 (tied)
			N,N-di(<u>tert</u> -butyl)-2-methyl-2-(2,2-dimethylpropyl)hexyl	2 (tied)
			N- <u>tert</u> -butyl-1,1,3-trimethyl-3-(2,2-dimethylpropyl)octyl	2 (tied)
			2-ethyl-1,1,5,7,7-pentamethyl-5-(2,2-dimethylpropyl)octyl	2 (tied)

a) With DELTA = 1.5 ppm, no structures were found for this amine.

Figure captions

- Figure 1. A schematic illustration of R, the alkyl chain-end to be tested by the PRUNER. The group X contains the Nitrogen atom, along with any carbons and hydrogens not included in R.
- Figure 2. The hierarchy of pre-tests used by the PRUNER. A "?" attached to an atom indicates that the neighbors of that atom are unknown at testing time.
- Figure 3. A case in which \bar{r} and \bar{o} do not match when $n = N_c$, even though the simple test is passed.
- Figure 4. Sample output from program AMINE (PDP-10 version). The solution structure is written in polish-prefix notation as described in Reference 3a.

Figure 1

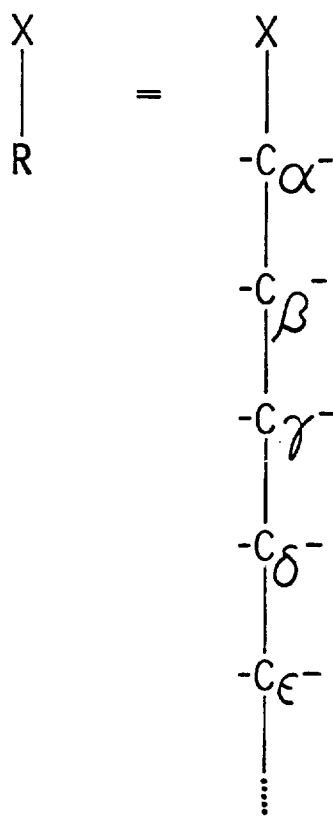


Figure 2.

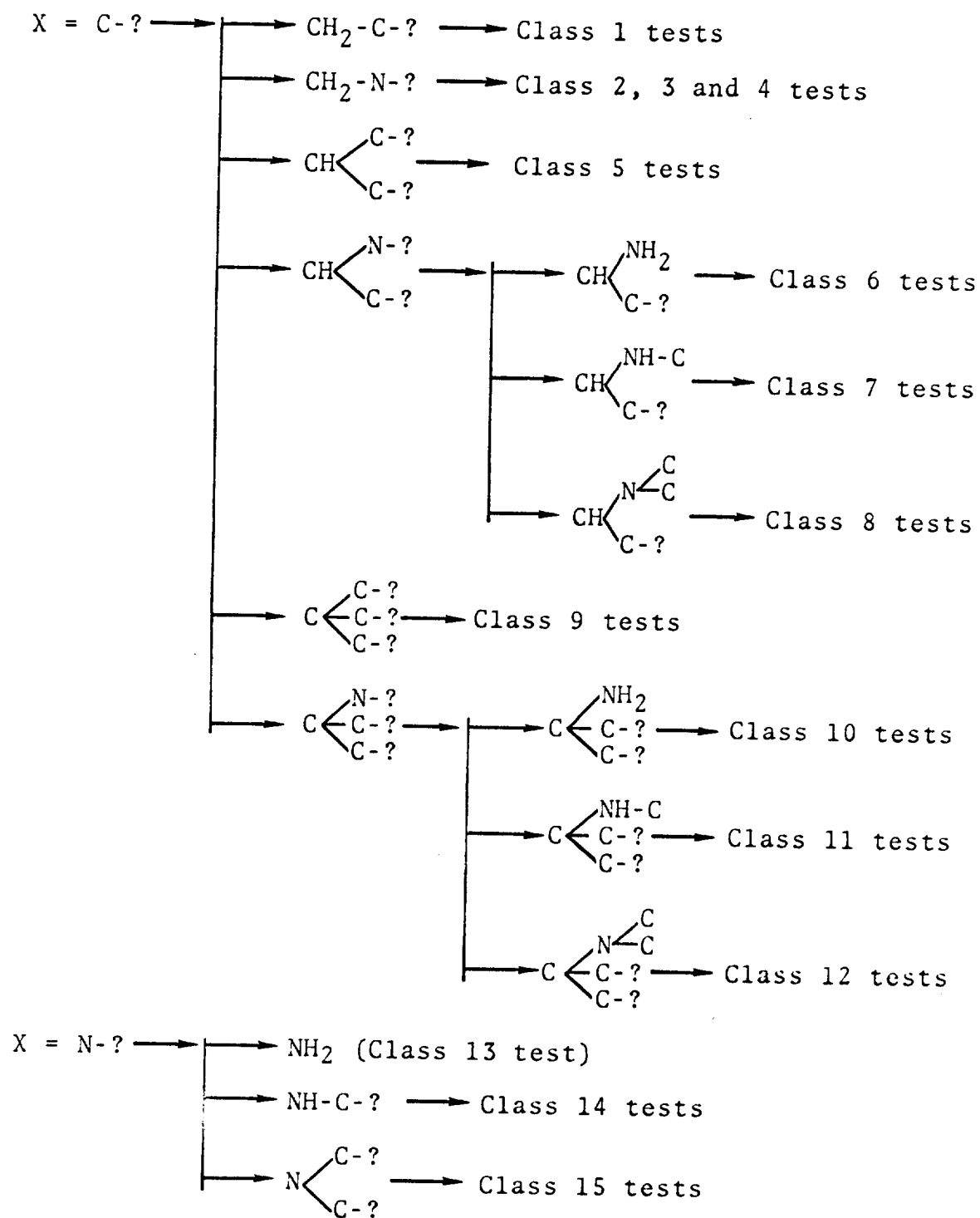
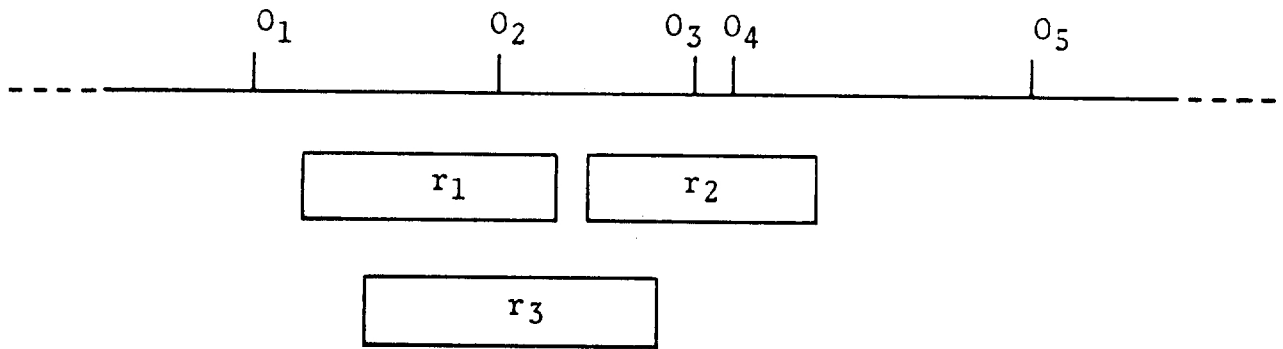


Figure 3.



CASE TITLE: N-ETYLDIPENTYLAMINE
THE AMINE HAS 12 CARBONS
GOODNESS-OF-FIT CRITERION IS 1.500
STANDARD IS TMS
INPUT SHIFTS: 54.00 27.80 30.10 23.00 14.30 47.80 12.50

SOLUTION STRUCTURES:

N...C.C.C.C.CC.C.C.C.CC.C
SHIFTS: 54.299 27.881 30.239 22.960 14.210 54.299
27.881 30.239 22.960 14.210 47.667 12.868
DELMIN = 0.37

CASE FINISHED. PROCESSING TIME (IN SEC.) WAS 9.711

Figure 4.

12.4

SIGNIFICANCE

SIGNIFICANCE

Because of the interdisciplinary character of this research, it has a significant impact in medicine, organic chemistry, and computer science. GC/MS has become one of the most powerful techniques available to the organic and biochemist. The potential applications of these techniques in medical research and in the clinic have just begun to be explored. These techniques are of unique importance to medical science since they alone of the current physical methods have sufficient sensitivity and analytical precision to study human biochemistry at the molecular level. Computer automation of these techniques, both at the instrumentation and interpretive levels, would permit the rapid, exhaustive analysis of body fluids across large populations of individuals in various medical contexts and may provide new discoveries important to public health.

In our study of errors of metabolism, accurate diagnosis of the accumulated metabolite provides insight into the biochemical pathogenesis and into therapeutic approaches to the control of such errors. In the case of inherited errors, accurate diagnosis allows reference to published data on the mode of inheritance and, thus, expresses the recurrence risk for genetic counseling purposes. The GC/MS system, with its potential for identification of any metabolites, provides the diagnostic accuracy necessary for a clinical program. GC/MS also provides the methodology for detecting previously unrecognized metabolic errors.

From the point of view of computer science, mass spectrometry is an advantageous environment in which to investigate the concepts necessary for the emulation of lower-level cognitive and manipulative functions as well as for the study of various forms of knowledge representation and automatic theory formation. These concepts will be common in some form to all "intelligent" systems and must be more fully developed from their present primitive state. Mass spectrometry is ideal as a milieu for this research in that it has tremendous practical importance to medicine, is sufficiently complex to challenge the human intellect, and is structured to an extent amenable to computer program formulation within the current state-of-the-art.

COLLABORATIVE ARRANGEMENTS

COLLABORATIVE ARRANGEMENTS

This project is an interdisciplinary research effort involving day-to-day collaboration between Professor J. Lederberg (Department of Genetics), Professor C. Djerassi (Department of Chemistry), Professor E. Feigenbaum (Department of Computer Science), Professor H. Cann (Department of Pediatrics), Dr. B. Buchanan (Computer Science), Dr. A. Duffield (Genetics), Dr. D. Smith (Chemistry), Dr. N. Sridharan (Computer Science), Dr. S. Hammerum (Chemistry), and the Instrumentation Research Laboratory of the Department of Genetics. We are also soliciting additional participation of clinical research interests of the Departments of Medicine and Psychiatry as well as other members of the Department of Genetics (Professors Cavalli-Sforza and Herzenberg). The proximity of these people and facilities in a medical environment offers a highly unique opportunity for collaborative interaction.

FACILITIES AVAILABLE

FACILITIES AVAILABLE

We will derive much of the clinically significant material for analysis from patients in the Premature Research Center and the Clinical Research Center of the Department of Pediatrics at Stanford. Analyses will be performed on existing gas chromatograph and mass spectrometer instrumentation. We have available a GC-coupled Finnigan 1015 quadrupole instrument in the Department of Genetics and a GC-coupled Varian-MAT 711 instrument in the Department of Chemistry. Also available in the Department of Chemistry are MS-9 and Varian-MAT CH-4 instruments.

We will derive our computing resources from existing PDP-11/20 mini-computer systems which interface the mass spectrometer instruments as well as from the ACME follow-on 370/158 computer at Stanford for data reduction and graphics support. Artificial intelligence program development will be carried out on the Stanford Computation Center IBM 360/67 and machines available over the ARPA computer network. GC/MS data will be interfaced to these programs through standard communication links.

HUMAN SUBJECTS

HUMAN SUBJECTS

As a part of this research project, GC/MS analysis techniques will be applied to human body fluids in collaboration with clinical investigators and blood and urine specimens will be collected from human subjects. Collection of VOIDED URINE SPECIMENS presents no risk to the patient. Collection of 5-10 ml of blood by venepuncture is a procedure attended by minimal risk; infection is a remote possibility, especially from deep venepuncture (e.g. femoral tap). However, superficial veins are usually used in children, and even infants. It is only the occasional infant that requires a femoral tap and this procedure would be deferred for this project unless the specimen was essential for diagnosis.

BUDGETS AND JUSTIFICATION

In the following budget estimates, the abbreviations listed below are used to denote departmental affiliation or professional specialty:

G - Genetics

CS - Computer Science

Ch - Chemistry

E - Electrical Engineering

BUDGET - PART A

APPLICATIONS OF ARTIFICIAL INTELLIGENCE
TO MASS SPECTROMETRY

SUBSTITUTE DETAILED BUDGET FOR FIRST 12-MONTH PERIOD		PERIOD COVERED		GRANT NUMBER
		FROM 5/1/74	THROUGH 4/30/75	
1. PERSONNEL <i>(List all personnel engaged on project)</i>			TIME OR EFFORT %/HRS.	AMOUNT REQUESTED <i>(Omit cents)</i> TOTAL
NAME <i>(Last, first, initial)</i>	G	TITLE OF POSITION		
Lederberg, Joshua	G	Principal Investigator or Program Director	4	PART A
Feigenbaum, Edward A (1)	CS	Co-Principal Invest.	10	
Buchanan, Bruce G. (1,2)	CS	Associate Invest.	50	
Duffield, Alan	Ch	Associate Invest.	25	
Smith, Dennis	Ch	Research Associate	100	
Hammerum, Steen	Ch	Research Associate	50	
Sridharan, Natesa	CS	Research Associate	50	
Reiss, Steve	CS	Computer Programmer	50	
Hjelmeland, Larry	CS	Research Assistant	100	
Masinter, Larry	CS	Research Assistant	50	
Stefik, Mark	CS	Research Assistant	50	
Wharton, Kathy		Admin. Assistant	25	
Larson, Dee		Secretary	25	
(1) See Budget Notes				
(2) In first year only 9/1/74-4/30/75 covered				
TOTAL →				\$ 80,624
2. CONSULTANT COSTS <i>(Include Fees and Travel)</i>				\$ 1,100
3. EQUIPMENT <i>(Itemize)</i>				-
4. SUPPLIES Office supplies				350
5. STAFF TRAVEL <i>(See Instructions)</i>				\$ 1,400
a. DOMESTIC				\$
b. FOREIGN				\$
6. PATIENT COSTS <i>(Separate Inpatient and Outpatient)</i>				\$ -
7. ALTERATIONS AND RENOVATIONS				\$ -
8. OTHER EXPENSES <i>(Itemize per instructions)</i>				
Telephone, postage, etc. \$ 200				
Publication costs 700				
Computer terminal rent 3,200				
Computer usage costs 36,000				
				\$ 40,100
9. Subtotal - Items 1 thru 8 →				\$ 123,574
FOR TRAINING GRANTS ONLY	10. TRAINEE EXPENSES <i>(See Instructions)</i>			
	a. STIPENDS	PREDOCTORAL	No. Proposed _____	\$
		POSTDOCTORAL	No. Proposed _____	\$
		OTHER <i>(Specify)</i>	No. Proposed _____	\$
		DEPENDENCY ALLOWANCE		\$
	TOTAL \$TIPEND EXPENSES →			\$
	b. TUITION AND FEES			\$
	c. TRAINEE TRAVEL <i>(Describe)</i>			\$
	11. Subtotal - Trainee Expenses →			\$
12. TOTAL DIRECT COST <i>(Add Subtotals, Items 9 and 11, and enter on Page 1)</i> →				\$ 123,574

**BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED FROM PUBLIC HEALTH SERVICE
DIRECT COSTS ONLY (Omit Cents)**

DESCRIPTION	1ST PERIOD (SAME AS DE- TAILED BUDGET)	ADDITIONAL YEARS SUPPORT REQUESTED <i>(This application only)</i>					
		2ND YEAR	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR	7TH YEAR
PERSONNEL COSTS	80,624	95,175	100,320				
CONSULTANT COSTS <i>(Include fees, travel, etc.)</i>	1,100	1,200	1,300				
EQUIPMENT	-	-	-				
SUPPLIES	350	400	450				
TRAVEL	DOMESTIC	1,400	1,600	1,800			
	FOREIGN						
PATIENT COSTS	-	-	-				
ALTERATIONS AND RENOVATIONS	-	-	-				
OTHER EXPENSES	40,100	45,450	50,000				
TOTAL DIRECT COSTS	123,574	143,825	153,870				
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD <i>(Enter on Page 1, Item 4)</i> →					\$ 421,269		

REMARKS: *Justify all costs for the first year for which the need may not be obvious. For future years, justify equipment costs, as well as any significant increases in any other category. If a recurring annual increase in personnel costs is requested, give percentage. (Use continuation page if needed.)*

See attached budget justification notes.

BUDGET - PARTS B (i) AND B (ii)

MASS SPECTROMETER DATA SYSTEM DEVELOPMENT

AND

ANALYSIS OF THE CHEMICAL CONSTITUENTS OF BODY FLUIDS

SUBSTITUTE		PERIOD COVERED		GRANT NUMBER
DETAILED BUDGET FOR FIRST 12-MONTH PERIOD		FROM	THROUGH	
		5/1/74	4/30/75	
1. PERSONNEL (List all personnel engaged on project)				
NAME (Last, first, initial)	TITLE OF POSITION	TIME OR EFFORT %/HRS.	AMOUNT REQUESTED (Omit cents)	
			TOTAL	
Lederberg, Joshua	G Principal Investigator or Program Director	3	PART B (i) and (ii)	
Duffield, Alan	Ch Associate Investig.	25		
Pereira, Wilfred	Ch Research Associate	50		
Summons, Roger	Ch Post Doctoral Fellow	100		
Rindfleisch, Thomas	E Research Associate	100		
Veizades, Nicholas	E Research Engineer	100		
Reynolds, Walter	E Research Engineer	20		
Tucker, Robert	CS Computer Programmer	75		
Wegmann, Annemarie	Ch Sr. Research Assist.	100		
Steed, Ernest	E Research Engineer	10		
Pearson, Dale	E Electronics Tech.	60		
DeFrancisci, Richard	Machinist	20		
Allan, Muriel	Secretary	25		
TOTAL			\$ 139,830	
2. CONSULTANT COSTS (Include Fees and Travel)				
			\$ -	
3. EQUIPMENT (Itemize)				
Computer Terminal			\$ 3,000 *	
4. SUPPLIES Office supplies-\$750; chemicals, glassware, and lab apparatus-\$2,500; GC supplies (gases, phases, columns, etc.)-\$950; dry ice and liq. nitrogen-\$1,500; electronic supplies and parts-\$3,500; GC/MS data recording media-\$2,100; mini-computer supplies-\$1,500; mass spec. repairs and parts-\$7,600				
			\$ 20,400	
5. STAFF TRAVEL (See Instructions)				
a. DOMESTIC 1 east coast (\$500); 1 mid-west (\$350); 1 west coast (\$150)			\$ 1,000	
b. FOREIGN			\$ -	
6. PATIENT COSTS (Separate Inpatient and Outpatient)				
			\$ -	
7. ALTERATIONS AND RENOVATIONS				
Mass spectrometer laboratory air conditioning and power modifications			\$ 2,500	
8. OTHER EXPENSES (Itemize per instructions)				
Telephone and data communications - \$1,200; Publication costs - \$1,000; Mini-computer maintenance contract - \$4,600; computing costs from ACME follow-on - \$64,000			\$ 70,800	
9. Subtotal - Items 1 thru 8			\$ 237,530	
FOR TRAINING GRANTS ONLY	10. TRAINEE EXPENSES (See Instructions)			
	a. STIPENDS	PREDOCTORAL	No. Proposed _____	\$ _____
		POSTDOCTORAL	No. Proposed _____	\$ _____
		OTHER (Specify)	No. Proposed _____	\$ _____
		DEPENDENCY ALLOWANCE		\$ _____
	TOTAL \$TIPEND EXPENSES			\$ _____
b. TUITION AND FEES				\$ _____
c. TRAINEE TRAVEL (Describe)				\$ _____
11. Subtotal - Trainee Expenses				\$ _____
12. TOTAL DIRECT COST (Add Subtotals, Items 9 and 11, and enter on Page 1)			\$ 237,530	

**BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED FROM PUBLIC HEALTH SERVICE
DIRECT COSTS ONLY (Omit Cents)**

DESCRIPTION	1ST PERIOD (SAME AS DE- TAILED BUDGET)	ADDITIONAL YEARS SUPPORT REQUESTED <i>(This application only)</i>					
		2ND YEAR	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR	7TH YEAR
PERSONNEL COSTS	139,830	148,066	156,775				
CONSULTANT COSTS <i>(Include fees, travel, etc.)</i>	-	-	-				
EQUIPMENT	3,000	3,000	3,000				
SUPPLIES	20,400	21,050	22,250				
TRAVEL	DOMESTIC	1,000	1,000	1,000			
	FOREIGN						
PATIENT COSTS	-	-	-				
ALTERATIONS AND RENOVATIONS	2,500	-	-				
OTHER EXPENSES	70,800	75,000	79,500				
TOTAL DIRECT COSTS	237,530	248,116	262,525				
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD <i>(Enter on Page 1, Item 4)</i> →					\$ 748,171		

REMARKS: *Justify all costs for the first year for which the need may not be obvious. For future years, justify equipment costs, as well as any significant increases in any other category. If a recurring annual increase in personnel costs is requested, give percentage. (Use continuation page if needed.)*

See attached budget justification.

BUDGET - PART C

EXTENSION OF THE THEORY OF
MASS SPECTROMETRY BY COMPUTER

SUBSTITUTE DETAILED BUDGET FOR FIRST 12-MONTH PERIOD		PERIOD COVERED		GRANT NUMBER	
		FROM 5/1/74	THROUGH 4/30/75		
1. PERSONNEL <i>(List all personnel engaged on project)</i>		TIME OR EFFORT	AMOUNT REQUESTED <i>(Omit cents)</i>		
NAME <i>(Last, first, initial)</i>	TITLE OF POSITION	%/HRS.	TOTAL		
Lederberg, Joshua	G Principal Investigator or Program Director	3	PART C		
Feigenbaum, Edward A. (1)	CS Co-Principal Invest.	10			
Buchanan, Bruce G. (1,2)	CS Associate Invest.	50			
Sridharan, Natesa	CS Research Associate	50			
Hammerum, Steen	Ch Research Associate	50			
White, William	CS Computer Programmer	50			
Farrell, Carl	CS Research Assistant	100			
Wharton, Kathy	Admin. Assistant	25			
Larson, Dee	Secretary	25			
(1) See budget notes					
(2) Covers 9/1/74-4/30/75 in year 1					
TOTAL →			\$ 48,521		
2. CONSULTANT COSTS <i>(Include Fees and Travel)</i>			\$ -		
3. EQUIPMENT <i>(Itemize)</i>			\$ -		
4. SUPPLIES			\$ 350		
5. STAFF TRAVEL <i>(See Instructions)</i>	a. DOMESTIC		\$ 1,400		
	b. FOREIGN		\$ -		
6. PATIENT COSTS <i>(Separate Inpatient and Outpatient)</i>			\$ -		
7. ALTERATIONS AND RENOVATIONS			\$ -		
8. OTHER EXPENSES <i>(Itemize per instructions)</i>					
Telephone, postage, etc. \$ 200					
Publication costs 700					
Computer terminal rental 1,600					
Computer usage 21,000					
			\$ 23,500		
9. Subtotal - Items 1 thru 8 →			\$ 73,771		
FOR TRAINING GRANTS ONLY	10. TRAINEE EXPENSES <i>(See Instructions)</i>				
	a. STIPENDS	PREDOCTORAL	No. Proposed _____	\$	
		POSTDOCTORAL	No. Proposed _____	\$	
		OTHER <i>(Specify)</i>	No. Proposed _____	\$	
	DEPENDENCY ALLOWANCE			\$	
TOTAL \$TIPEND EXPENSES →			\$		
b. TUITION AND FEES			\$		
c. TRAINEE TRAVEL <i>(Describe)</i>			\$		
11. Subtotal - Trainee Expenses →			\$		
12. TOTAL DIRECT COST <i>(Add Subtotals, Items 9 and 11, and enter on Page 1)</i>			\$ 73,771		

SECTION II - PRIVILEGED COMMUNICATION

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED FROM PUBLIC HEALTH SERVICE DIRECT COSTS ONLY (Omit Cents)							
DESCRIPTION		1ST PERIOD (SAME AS DE TAILED BUDGET)	ADDITIONAL YEARS SUPPORT REQUESTED (<i>This application only</i>)				
			2ND YEAR	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR
PERSONNEL COSTS		48,521	61,194	64,655			
CONSULTANT COSTS (Include fees, travel, etc.)		-	-	-			
EQUIPMENT		-	-	-			
SUPPLIES		350	400	450			
TRAVEL	DOMESTIC	1,400	1,600	1,800			
	FOREIGN						
PATIENT COSTS		-	-	-			
ALTERATIONS AND RENOVATIONS		-	-	-			
OTHER EXPENSES		23,500	27,650	30,450			
TOTAL DIRECT COSTS		73,771	90,844	97,355			
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (<i>Enter on Page 1, Item 4</i>) →					\$ 261,970		
<p>REMARKS: <i>Justify all costs for the first year for which the need may not be obvious. For future years, justify equipment costs, as well as any significant increases in any other category. If a recurring annual increase in personnel costs is requested, give percentage. (Use continuation page if needed.)</i></p> <p>See attached budget justification notes.</p>							