10. Morton NE, MacKinney AA, Kosower N, Schilling RF, Gray MP. Genetics of spherocytosis. Am J Hum Genet 1962; 14: 170-184.
11. Becker PS, Lux SE. Disorders of the red cell membrane. In: Hematology of Infancy and Childhood. 4th ed. Philadelphia: W.B. Saunders, 1992; 1: 529-633.
12. Bucx MJL, Breed WPM, Hoffmann JJML. Comparison of acidified glycerol lysis test, Pink test and osmotic fragility test in hereditary spherocytosis: effect of incubation. Eur J Haematol 1988; 40: 227-231.
13. Hanspal M, Yoon S-H, Yu H, Hanspal JS, Lambert S, Palek J, Prchal JT. Molecular basis of spectrin and ankyrin deficiencies in severe hereditary spherocytosis: Evidence implicating a primary defect of ankyrin. Blood 1991; 77: 165-173.
14. Jarolim P, Ruff P, Coetzer TL, Prchal JT, Ballas SK, Poon M-C, Brabec V, Palek. A subset of patients with dominantly inherited hereditary spherocytosis has a marked deficiency of the band 3 protein. Blood 1990; 76: 37a (suppl 1) (abstr).
15. Bouhassira EE, Schwartz RS, Yawata Y, Ata K, Kanzaki A, Qiu JJ-H, Nagel RL, Rybicki AC. An alanine-to-threonine substitution in protein 4.2 cDNA associated with a Japanese form of hereditary hemolytic anemia (protein 4.2^{NIPPON}). Blood 1992; 79: 1846-1854.
16. Van Zwieten R, Bolscher B, Veerman AJP, Hoffmann JJ, Roos D. Bepaling van het spectrinegehalte in erytrocyten: een belangrijk hulpmiddel bij de diagnostiek van Hereditaire Sferocytose. Ned Tijdschr Geneeskd 1995; 139: 2256-2261.
17. Agre P, Casella JF, Zinkham WH, McMillan C, Bennett V. Partial deficiency of erytrocyte spectrin in hereditary spherocytosis. Nature 1985; 314: 380-383.
18. Eber SW, Ambrust R, Schröter W. Variable clinical severity of hereditary spherocytosis: Relation to erytrocytic spectrin concentration, osmotic fragility, and autohemolysis. J Pediatrics 1990; 117: 409-416.

Summary

Roos D. Molecular diagnostics of erythrocytic cytoskeleton disorders. Ned Tijdschr Klin Chem 1996; 21: 120-126.
For the stability of the red blood cell, the integrity of the spectrin-actin network as well as the connection of this cytoskeleton to the plasma membrane is essential. Mutations that weaken the cytoskeleton cause elliptocyte formation and decreased survival of the erythrocytes, a condition known as Hereditary Elliptocytosis. These mutations are found primarily in α- and ß-spectrin, and affect the head-tail coupling of these structural erythrocyte proteins. Permanent cell deformation will then occur. Mutations that weaken the interaction between the plasma membrane and the cytoskeleton lead to formation and loss of phospholipid microvesicles, thus causing formation of spherocytes. The molecular origin of this condition of Hereditary Spherocytosis is strongly heterogeneous: mutations in α- or ß-spectrin or in ankyrin can lead to decreased expression of spectrin in the cell, thus inducing the disease. Determination of the erytrocyte spectrin content is a reliable test for the diagnosis of Hereditary Spherocytosis, with only few patients being missed.
Key-words: Hereditary Spherocytosis, Hereditary Elliptocytosis, Hereditary Pyropoikilocytosis, spectrin, red blood cells, cytoskeleton, anemia.

Ned Tijdschr Klin Chem 1996; 21: 126-131

Computer-aided parenteral nutrition in intensive care: the role of the clinical chemist in the teaching and solution of the problem

A. JABOR[1], A. KAZDA[2] and P. WAGNER[3]

Clinical chemists and pharmacists are - among other specialists - members of nutritional support teams in many hospitals throughout the world. We describe a multilevel system for computer-aided parenteral nutrition. The aim of the system is to support the work of the clinical chemist in nutritional support teams, and to serve as an educational tool. Common knowledge is transformed into supporting programs and educational systems within one logical frame. The problem of computer-aided nutrition is structured into several levels, the results of which are supervised by medically educated clinical chemists serving as a human interface. The first level of the system comprises the computer-assisted interpretation of laboratory data in the areas with complicated pathophysiology. At the second level, the computer-aided proposal of nutritional components is modelled, and the result is checked by the physician. Then the automatic system based on the SIMPLEX method converts the proposal of nutritional components into the optimal set of nutritional products, i.e. computer-modelled optimal prescription. This step is again reviewed (and/or corrected, if necessary) by the physician. The result of the final level is time-specification for the application of the nutritional products (flasks or bags). Every level is supplied with an educational support system, in which all steps are properly described and elucidated. The system is incorporated into the information system of intensive care units.

Keywords: computer-aided nutrition; goal programming; education; computer-aided interpretation

Department of clinical biochemistry, Hospital Kladno[1], Kladno, Czech Republic; Chair of clinical biochemistry, Postgraduate medical school[2], Prague, Czech Republic and Department of clinical biochemistry[3], University Hospital Bulovka, Prague, Czech Republic

Address Correspondence to: Dr. Antonín Jabor, Department of clinical biochemistry, Hospital Kladno, CZ-27259 Kladno, Czech Republic
Received: 04.10.95

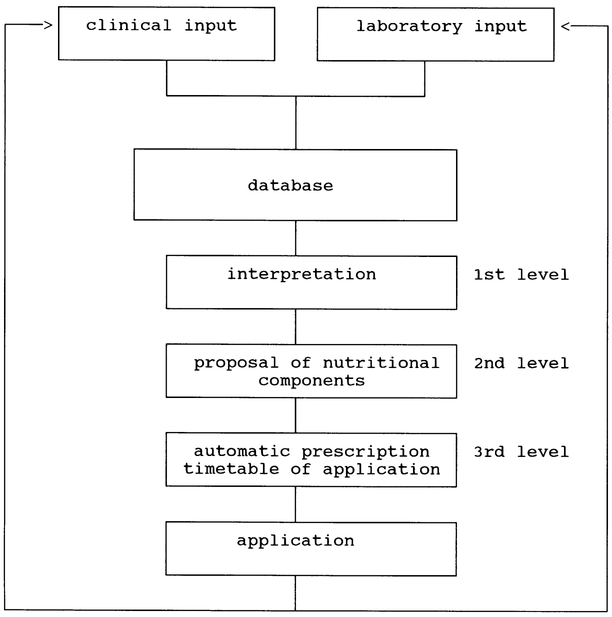


Figure 1. Schematic diagram of nutritional support system with three described levels of supporting system.

Medically educated clinical chemists are frequently members of nutritional support teams. They are, for example, responsible for laboratory data interpretation, assessment of the metabolic (and nutritional) status, calculation of metabolic balances and other important data processing, proposals of nutritional components with respect to the disease and laboratory results, control of applications (speed limits, interactions), recognition of nutritional effects on metabolic situations, and selection of suitable laboratory data for monitoring and evaluation of feedbacks. Such a complex process is, however, time-consuming, and can lead to serious errors in manual sequential calculations, even if pocket calculators are used. We therefore decided to develop a computer system to facilitate the work of the clinical chemist in the nutritional team. The aim of this paper is to describe the computer-aided system for parenteral nutrition. The system was developed over an 8-year period, and is implemented and used in the information system of intensive care units in more than 30 hospitals in the Czech Republic and in Slovakia.

Description of the system

The philosophy of the system enables the user to interact at several levels. Particular outputs, after a check by the physician, are accepted, rejected or modified. Any problem solved automatically by the computer may be solved manually by the physician, without computer support, but this naturally makes a significant time demand.

The algorithmic approach was chosen for the interpretative modules and nutritional proposals, while prescription of nutritional products is based on goal programming. Special emphasis was placed on educational elements.

Computer-assisted interpretation

The scope of laboratory tests used in intensive care is widening, and clinicians are often overloaded with laboratory data. However, a significant amount of clinical data is necessary for decision-making in a particular clinical situation. Both types of data are essential for computer-aided parenteral nutrition. We structured the problem into several levels (figure 1). Clinical and laboratory data are stored in the database. If appropriate, the user can use the computer-aided interpretative modules. Computer-assisted interpretation of laboratory data is suitable in areas with complicated pathophysiology, e.g. water and salt disturbances, acid-base disorders, oxygen status, renal function, metabolic balances or cardiovascular function (1-6). As this part of the system is based on an algorithmic approach, the knowledge is transformed into the form of a decision tree.

Acid-base evaluation. Using the principle of independent and dependent acid-base variables, where the role of strong ions and non-volatile weak acids is emphasized as a logical frame, we received a suitable background for the therapy (4,7,8). From this point of view, the control of independent acid-base variables forms the main homeostatic mechanism, the disturbance in independent variables leads to acid-base disorder, and the manipulation of independent acid-base variables is the only logical treatment of acid-base disturbances.

Water and ions. When the double chart proposed by Siggaard-Andersen is used as a logical frame for water, sodium and potassium evaluation, the system is sufficiently sophisticated, and can be used both for teaching and for therapeutical calculations (9,10). More laboratory, and especially clinical, data (human interface) are, however, necessary for the nutritional proposal of water and ions (see later).

Metabolic balances. Metabolic balances are traditionally the most frequently used modules for nutritional support. The use of a computer accelerates the calculations, and makes possible the graphical presentation of data (4,11). The metabolic situation of the patient is evaluated more precisely, and the clinical input for the next step, i.e. the computer-aided nutritional proposal, is thus more accurate.

Table 1. Advantages and disadvantages of "traditional" and individual nutritional approach

	traditional	individual
Advantage	simple and well-defined regimens	meets individual demands of the patient in particular clinical situations
	scope of products meets the criteria of regimens	focused on nutritional components
Disadvantage	priority is given to nutritional product	lack of suitable products for individual planning
	schematic and generalized	time-consuming and difficult proposals

Table 2. Input parameters for key modules of nutritional proposal system

Type	Input parameter	Program modules Na	K	P	Mg	H_2O	TE	N
Somatic	body weight	+	+	+	+	+	+	+
	body height					+	+	+
	sex	+	+	+	+	+	+	+
	age					+	+	+
	weight excess	(+)				(+)		
Losses	water	+	+			+		
	sodium	+						
	potassium		+					
Serum, blood	sodium	+						
	potassium		+					
	phosphorus			+				
	magnesium				+			
	creatinine							+
	pH		+					
Clinical	hydration	+				+		
	catabolism					+	+	
	temperature					+	+	
	ARDS					+		
	acute/chronic	+						
	renal failure					+		
Other	catabolic N		+				+	
	intake of N		+					
	nebulisation					+		

TE: total energy; N: nitrogen; ARDS: acute respiratory distress syndrome: +: used; (+): may be used

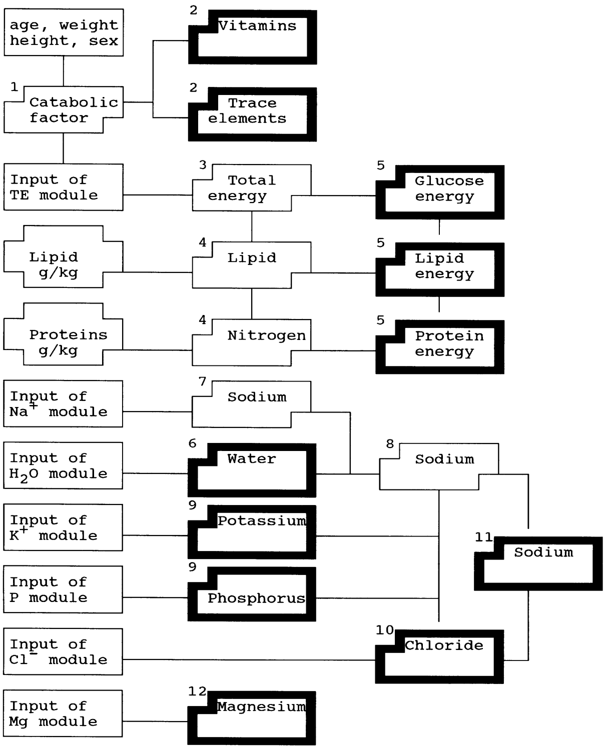
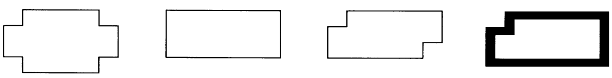


Figure 2. Flow chart of the automatic nutritional proposal. TE: total energy. Numbers 1-12 in the upper left corner of some boxes indicate the respective algorithmic procedures and modules described in the text (section Computer-aided proposal).



Physician's input	Input data (laboratory & clinical) (table 2)	Preliminary proposal (before control)	Final proposal

Renal function. We developed a special module for the evaluation of renal function (4,6,11). This module makes all necessary calculations, and generates two sets of comments, with different aims: one for explanation (less extensive) and one for education (more detailed).

Computer-aided proposal

There have been many attempts to facilitate the work of the expert in nutritional support (4,12-15). There are, in fact, two approaches for the realization of defined nutrition. The first one, more common and traditional, uses defined regimens in defined clinical settings, with the support of a broad scope of available commercial nutritional products. The other one meets individual demands of the patient. The advantages and disadvantages of both approaches are listed in table 1.

Our system (figure 1, 2nd level) is focused on the individual approach. In other words, we switched from a "regimen/product" system to an "individual demand/individual mixture" system. The algorithmic approach was chosen as in the case of interpretive reporting (4,11). The general algorithm consists of 12 procedures and modules (figure 2). Input parameters are listed in table 2.

The procedures and modules are as follows:

1. Selection/calculation of the catabolic factor

The term "catabolic factor" is used for the factor of energy demand, i.e. it is used for the assessment of energy intake with respect to the clinical and technical possibility of nutritional realization. It does not represent the factor of energy output as a result of indirect calorimetry. The catabolic factor is either selected from the "clinical" table or calculated with respect to clinical conditions. The user is supposed to be an "educated user", with appropriate knowledge of the background of this step.

2. Final proposal of trace elements and vitamins
This step is performed using the catabolic factor and body weight. A series of equations is defined for every trace element and vitamin. The proposed dose consists of recommended, upper and lower limits.

3. Preliminary proposal of total energy (TE)
Calculation of TE is based on the catabolic factor and input variables listed in Table 2. Catabolic nitrogen is used for necessary corrections, either in hypercatabolism or malnutrition.

4. Preliminary proposal of lipid energy and nitrogen
Proposal of lipid intake is based on physician's input parameter (recommended grams of lipid per kg body weight). Priority is given to the ratio of saccharide energy to lipid energy, and the ratio of non-protein energy to nitrogen. Serum triglycerides serve as the feedback element.
The proposal of nitrogen is semi-automatic. The physician's input variable (recommended intake of proteins per 1 kg of body weight) is of limited priority. The main priority is given to the ratio of non-protein energy to nitrogen. Renal failure is solved as a special case. The relation between infused nitrogen and serum urea serves as the feedback element originally described by the authors (11).

5. Definition/modification of the final proposal of saccharide, lipid and protein energy, modification of corresponding value of total energy and nitrogen.
The proposal of glucose is automatic. Three control mechanisms are used: maximal rate of glucose utilization, ratio of non-protein energy to nitrogen, and ratio of glucose to lipid energy. The proposal of nitrogen and TE is controlled in several steps.

6. Final proposal of water
Extrarenal elimination of water, i.e. immeasurable water loss, metabolic water and other water losses, are calculated in the first step. The dose of water to ensure the target urine volume is proposed in the second step. The term "target" refers to the appropriate volume of water in view of clinical condition and measured diuresis. Clinical input parameters are listed in table 2. Some water is added in the case of dehydration. Clinical consideration is recommended in hyperhydration, where automatic proposal is almost impossible. More than 70 different clinical situations are solved.

7. Preliminary proposal of sodium
The use of Siggaard-Andersen's sodium-potassium double chart must be implemented in therapeutical practice very carefully. A clinical consideration of the patient's state is superior to any calculation. Thirteen areas with different simplified therapeutical actions are key elements of this module. Input variables are listed in table 2. Slow changes in osmolality and quick corrections of extracellular fluid deficits have priority. The proposal consists of a correction dose, to target plasma sodium concentration, and a substitution of sodium losses (4). More than 90 different clinical situations are solved.

8. Modification of the proposal of sodium according to the proposal of water
The amount of proposed sodium and water is harmonized in this step.

9. Final proposal of potassium and phosphorus
The doses consist of a substitution of losses and a correction to target serum concentration.

10. Proposal of chloride
We used the proposed intake of sodium, potassium and phosphorus for the definition of chloride intake. Predominant cations in infused solutions are Na^+ and K^+, whereas predominant anions are phosphate, chloride and HCO_3^-. The other anions are ignored (for the purpose of chloride intake). The ratio of 71% of chloride to the sum of Na^+ and K^+ in infused solutions, i.e. the same as the normal ratio in plasma, i.e. 100/(137+4), will not influence the acid-base situation significantly. A certain acid-base correction can be reached by changing this ratio (4,7,11).

11. Modification of the dose of sodium (if necessary) after the proposal of chloride intake
The amount of sodium and chloride is harmonized in this step.

12. Final proposal of magnesium
The proposed dose consists of the substitution of losses and correction to the target serum concentration.

The algorithms are believed to be able to solve the difficulties of individual approach effectively, and they thus make it possible to meet individual demands with regard to nutritional components (proposal of water, energy, ions, trace elements, etc.). Manual corrections are allowed in every step. Comments with educational features are added to every output. The output - i.e. target demand, lower and upper limits - is supervised, accepted or modified by the physician.

Computer-modelled prescription
In the third level (figure 1), the target demand of nutritional components (proposed intake of water, ions, energy, nitrogen, etc.) is transformed into the optimal set of nutritional products (commercially available) with optimal volumes. The task is as follows. Using the available nutritional product containing the main nutritional components, propose such volumes of suitable products that the summary content of components in selected solutions shows a minimal difference with respect to the target demand. The system is based on goal programming where we selected the

Table 3. The relative frequency of automatic prescription with negligible error (±5%). The first column indicates an output consisting of whole flasks only; the combination of whole flasks and defined volume fractions was allowed for the data given in the second column.

Nutritional component	Relative frequency of suitable prescriptions in %	
	whole flasks only	whole flasks or minimal amount
Water	76	100
Sodium	71	89
Potassium	59	96
Chloride	62	75
Nitrogen	35	98
Total energy	56	94
Glucose	65	90

Table 4. The relative frequency of automatic prescription with acceptable error (±15%). For details see Table 3.

Nutritional component	Relative frequency of suitable prescriptions in %	
	whole flasks only	whole flasks or minimal amount
Water	100	100
Sodium	99	100
Potassium	96	100
Chloride	78	80
Nitrogen	83	98
Total energy	91	100
Glucose	97	100

SIMPLEX method in connection with optimal rounding. Calculations are controlled by suitable parameters in the TABLE OF COMPONENTS and the TABLE OF SOLUTIONS (16).

The table of components is composed of suitable limits and respective penalties for every nutritional component. The table is selected with respect to different clinical situations (renal and liver failure, cardiorespiratory failure, etc.), and central or peripheral vein. Limits are strict or benevolent. For example, limits for potassium are strict in renal failure, meaning that the difference from the target demand should be minimal.

The table of solutions is composed of solutions which are suitable for a specific clinical situation. Further, a penalty can be assigned to the less important or less suitable solution.

We tested the effectiveness of this method in a validation study (11). In this study, the target demand of nutritional components was a result of a metabolic balance study in intensive care patients, i.e. the target for the automatic system was the amount of nutritional components infused in a real clinical situation. In other words, the amount of nutritional component (H_2O, energy, nitrogen, Na, K, Cl in nutritional solutions, prescribed by an experienced physician and really infused) was used as a target demand. The standard table of components with strict limits for water, sodium, nitrogen and potassium, and the standard table of 40 basic solutions suitable for central vein, were respectively selected.

One hundred automatic prescriptions for 7 nutritional components were run in two regimens of the simulation. The first regimen, "WHOLE FLASK", led to the selection of whole flasks only (or whole ampoules). The second regimen, "WHOLE FLASK/MINIMAL AMOUNT", led to the selection of whole flasks (whole ampoules) or defined fractions of whole flasks (i.e. a suitable less economical way, e.g. for pediatric patients).

The difference between the target demand of nutritional component and the amount of nutritional component in the automatically selected (i.e. automatically prescribed) set of commercial nutritional products was chosen as the main study measure. Two criteria were selected:

- "negligible error" of the prescription, i.e. the difference between the target demand of nutritional components and the proposed amount is up to 5 percent
- "acceptable error" of the prescription, i.e. the difference between the target demand of nutritional components and the proposed amount is up to 15 percent.

A total of 700 automatic proposals were tested. Table 3 shows the results of the simulation with the first criterion (negligible error), and table 4 shows the results with the second criterion (acceptable error). The effectiveness of the system was excellent, with 60.1% of the results showing differences of ±5%, and 92.0% of the results showing differences of ±15% (prescription of whole flasks). The system was even more powerful when the defined fractions of whole flasks were allowed. In that case, 91.7% of the results show differences of ±5%, and 96.8% of the results show differences of ±15%.

The SIMPLEX method appeared to be a useful tool with suitable reliability (17). This step is again reviewed (and/or corrected, if necessary) by the physician. The level is completed by a time-specification for the application of the nutrition.

Table 5. The difference between "education/ (patho)physiology" and "nutritional/clinical". Some examples of parameters measured in laboratory, educational models and clinical approach.

measured parameters	education and/or (patho)physiology	nutritional/clinical
serum potassium	calculated deficit of potassium	the amount of potassium given to the patient
carbon dioxide, oxygen	the amount of catabolized substrates measured by indirect calorimetry	the amount of glucose and fat infused
urine urea	catabolic nitrogen	intake of amino acids
serum sodium	calulated deficit of sodium and water	appropriate intake of sodium and water

Educational features

Education of medical students is directed towards (patho)physiology and/or (patho)biochemistry schemes and diagrams, with the aim to teach the principles. Internal logic is subordinated to educational purposes, and the theoretical model may differ from real clinical decision situations.

Examples of significant differences between the "education/(patho)physiology" and "nutritional/clinical" approaches are listed in Table 5. In this table, the second column is based on common educational calculations used in medical literature (4,9-11,18). The third column shows clinical consequences of measured parameters and theoretical models.

The set of input data for teaching models is, however, limited. Nutritional support requires other data, both laboratory and clinical. Powerful automatic systems need more and more data, their internal structure is complicated, their use is time-consuming and their output is sometimes dubious. Such systems behave like black boxes: they arouse suspicion, and physicians often do not trust them.

We feel that computer-aided nutrition, education and common knowledge have to be connected within the same logical frame. The logical background for teaching and the logical principle of computer-aided parenteral nutrition have to be similar.

A suitable aspect of common knowledge covered by the same logical frame is used both for nutritional support programs and for education. The program has to be educational, i.e. it has to be employable for educational purposes, and/or is equipped with educational modules (a help system or expert system). The program may serve as an educational tool indirectly, i.e. the program forces the user to accept the logical frame and a suitable scientific level as a base. The user should be satisfactorily educated. The logical frame with suitable scientific level can be used as a base for therapy, with the aid of a human interface (and can be used for further education as well).

The problem of unsuitable black boxes and an unlimited amount of input data in automatic systems (due to continuously increasing amounts of information in the common knowledge base) can be solved by appropriate structures with a certain autonomy. Such structures are connected by human interface. The role of the human mind is to compare the real situation with schemes, diagrams, experiences and available strategies. With an increasing amount of information on nutritional therapy, the role of computers and artificial intelligence will probably become more important.

Literature

1. Nykänen P, Boran G, Pincé H, Clarke K, Yearworth M, Willems JL, O'Moore R. Interpretative reporting and alarming based on laboratory data. Clin Chim Acta 1993; 222: 37-38.
2. Goldberg M. Computer-assisted diagnosis and teaching of disorders of electrolyte, acid-base and water metabolism. Proc Annu Symp Comput Appl Med Care 1992: 827-828.
3. Skaredoff MN. A computerized system for rapid interpretation of acid-base disorders. Int J Biomed Comp 1986; 18: 229-238
4. Kazda A, Jabor A, Zámecník M, Matek K. Monitoring Acid-Base and Electrolyte Disturbances in Intensive Care. In: Advances in Clinical Chemistry 1989; 27: 201-267.
5. Kaldor G, Rada R. Computerized evaluation of acid-base disorders based on a nine-cell decision matrix. Med Biol Eng Comput 1985; 23: 269-273.
6. Kazda A, Jabor A, Zámecník M. Evaluation of Renal Function - A Computer Programme. Int J Biomed Comput 1989; 24: 79-87.
7. Fencl V, Leith DE. Stewart's quantitative acid-base chemistry: Applications in biology and medicine. Resp Physiol 1993; 91: 1-16.
8. Jabor A, Kazda A. Modelling of Acid-Base Equilibria. Acta Anaest Scand, Suppl. 1995; 107: 119-122.
9. Siggaard-Andersen O, Fogh-Andersen N, Wimberley PD. Sodium and potassium by ion selective electrodes - clinical interpretation. In: Clinical chemistry - an overview. den Boer NC, Heiden C van, Leijnse B and Souverijn JHM (eds). Plenum Press, New York 1989: 303-308.
10. Jabor A, Horácek M. Computerized form of Siggaard-Andersen's double chart. Acta Anaest Scand, Suppl. 1995; 107: 113-117.
11. Jabor A. Information level of the communication between physician and clinical chemist. Thesis, Charles University, Prague 1992. In Czech, English summary.
12. Orta J, Reinards CL. Comparison of handheld computers for nutrition assessment and support. J Am Diet Assoc 1994; 94: 1409-1414.
13. Dobner M, Miksch S, Horn W, Popow C. Ein Expertensystem für die Berechnung der parenteralen Ernahrung von intensiv behandelten Fruh- und Neugeborenen. Wien Klin Wochenschr 1995; 107: 128-132.
14. Skaredoff MN, Westerman C, Hoffman D, Hazes EM, Tomkiel S, Perkes D. Hyperalimentation worksheet. Crit Care Med 1986; 14: 65-66.
15. Vanderveen TW, Groves WE. Computerized system for a nutritional support service. Computer Methods Programs Biomed 1986; 22: 189-197.
16. Jablonsky J, Jabor A. Prescribing of Parenteral Nutrition via Goal Programming. In: Tabucanon M, Chankong V (Eds.): Multiple Criteria Decision Making: Applications in Industry and Service. Asian Institute of Technology, Bangkok, 1989.
17. Jabor A, Kazda A, Vlk T, Jablonsky J. Goal programming and total parenteral nutrition. ESCTAIC 2nd Annual Meeting, Goldegg, September 1991.
18. Eastham RD. A guide to water, electrolyte and acid-base metabolism. Wright, Bristol, 1983.