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Computer-Aided Diagnosis with an Application to Endocrinology

Abstract: An interactive system for computer-assisted medical diagnosis is described. Medical experts are provided with a framework in which to translate the knowledge on which their decisions are based. The technique is based on simulating the physician's own diagnostic process. The approach taken allows consistency and completeness checks to be made, thereby achieving a high degree of reliability. Information related to a given specialty is described in terms of disorder patterns, clinical facts, and logical relationships among the clinical data. Laboratory results are processed by a subsystem which uses physician-supplied rules to establish validity and to interpret the test data with respect to their diagnostic significance. The system incorporates a dynamically generated questionnaire which provides efficient gathering of anamnestic, observational, and other clinical parameters. The physician is prompted for relevant patient data by an algorithm which assures that an almost minimal amount of information is requested. Simulation facilities allow the user to examine clustering phenomena among disorders, and an option is included that traces the logic of any decision taken to exclude candidates for a final diagnosis.

Introduction

Considerable attention has been focused in recent years on computer-aided medical diagnosis. An evaluation of such efforts must be gauged in terms of one's goals and the constraints imposed. Few systems that function in a clinic on an ongoing basis have been implemented. Numerous studies have shown the suitability of a particular mathematical scheme for differential diagnosis. However, these studies have generally been remiss in establishing the relevance of such schemes to problems facing the practicing physician. In most cases the published results deal with a limited number of disorders (15 or less), while realistic situations often involve much larger domains. We believe that the following are among a number of factors that have prevented diagnostic systems from enjoying wider use.

The medical data base There is a widespread assumption that diagnostic value can be derived from a computer system only if it has access to a suitably large and complex data base. As a result the solution of one problem (diagnosis) is made to depend on, and is often dominated by, the need to resolve a different issue (the creation and maintenance of a suitable data base). Any scheme for collecting patient data assumes implicitly that criteria of relevance are known. Thus the existence of a reliable data base implies that a fairly clear picture of a disorder is established; otherwise, enormous amounts of information must be collected for every patient. Yet the medical knowledge specialists bring to their task is a great deal more explicit than any derivable from a data base. On the basis of an understanding of biological and physiological processes, a highly experienced diagnostician is able to describe the general pattern of a disorder and to specify many logically necessary relationships among data.

Insufficient attention to physician needs In a typical diagnostic setting items of information about a patient (the answer to a question, a clinical observation, the result of a laboratory procedure) suggest to the physician one or more hypotheses together with a decision rule. A set of facts brings to mind possible disorders or causes and prompts him to check some other fact next. (We use *fact* as an all-embracing term, rather than *symptom*, *clinical sign*, *observation*, etc.) When the number of disorders is large and the list of facts extensive, a physician's intrinsic limitations rather than his lack of knowledge may lead to error. The utility of a diagnostic aid is enhanced if it permits the physician to confirm or reject his suspicions, provides an efficient algorithm to prompt for relevant data, and maintains as plausible all disorders not explicitly ruled out. These requirements become especially signifi-

cant when such a system must serve a non-expert who often has limited familiarity with less frequent variants of a disorder.

Appropriateness of method One may classify diagnostic programs into two categories: those based on established medical knowledge and experience, and those relying on large samples of diagnosed patients for whom clinical histories have been recorded. The major research efforts have centered on developing techniques for dealing with nondeterministic clinical signs based on a carefully developed data base or on physicians' assessment of probabilities. In medical areas where many disorders are involved and in which rapidly changing developments influence the diagnostic process, this type of approach seems impractical. The use of multivariate discriminate analysis requires very large random samples, while the use of Bayes' decision rules either is based on unrealistic assumptions, such as independence of symptoms and mutually exclusive disorders, or else necessitates a sizable sample space. Furthermore, these methods are not well understood by physicians and do not reflect the process by which they generally interpret clinical and laboratory findings.

Utility For competent physicians time is at a premium, precluding the ability to become familiar with a different technical field. Systems that are meant to be used by physicians should be designed so that they may be learned quickly and are convenient to use. A knowledge-based system that must be modified continually (as a result of developing medical technology) should be straightforward enough so as not to require the assistance of a systems analyst or programmer.

Our effort began with the desire to investigate the use of sequential procedures in medical diagnosis. Our goal is to provide a practical tool which first enables the specialist to describe his knowledge conveniently and which can then assist a non-expert to gather only relevant diagnostic information and provide him with sufficient information at every point to advance the diagnosis. In a number of medical areas one frequently finds a small number of specialists overburdened with patients referred to them by other physicians. The system described here should enable physicians in related medical areas to make decisions previously left to specialists. For example, using the present information base, the system could assist gynecologists in the diagnosis of numerous endocrine-related reproductive problems, and internists in the determination of thyroid malfunctions.

Description

Use of the system involves two phases. In the first phase medical knowledge appropriate to a given field is specified by expert clinicians who translate diagnostically significant aspects into machine input. Physicians are able to identify with the translation rules because these rules reflect deductive processes typical of those used in clinical practice. Particular attention is placed on affording the experts the capability of validating the information supplied. When found acceptable the system is made available to a larger group of non-experts to assist in patient management. In this phase the physician may enter clinical data at will or be prompted for relevant parameters by invoking a dynamic questionnaire. A status report indicates the set of currently potential disorders with information to differentiate further. If laboratory tests are called for, their results are run through a subsystem which interprets the raw data in terms of their diagnostic significance. A patient record is created or updated automatically as required. The emerging data base (in conjunction with any new medical developments) may be used to improve the medical content and thereby in iterative fashion enhance the system's effectiveness.

The system is fully interactive and uses a command structure to coordinate its operation. The user sitting at a terminal determines the sequence and type of commands he wishes to invoke.

A large outpatient clinic engaged in the treatment of endocrine disorders was selected to provide a framework for this study. Because the clinic deals with many patients whose primary complaint is related to infertility, this factor dominated the selection of disorders [1]. This choice of disease category has criteria typical of those for which the system is intended. The field is nicely circumscribed, and considerable experience in diagnostic procedures has been accumulated. Patient management is simplified by virtue of the fact that treatment is on an outpatient basis. Many tests fall naturally into binary categories. The potential number of facts that a patient may present is large, and the diagnostic process (which is frequently stepwise) is lengthy enough to warrant an effort in reducing the time required to arrive at a final diagnosis.

In addition to maintaining a sizable outpatient clinic, the Institute of Endocrinology (Sheba Medical Center, Tel Hashomer, Israel) supports a variety of research projects, a number of which bear directly on the diagnosis and treatment of infertility. Consequently new tests and therapeutic techniques are continually under study. This provides an opportunity to use the system to absorb advances in medical knowledge that influence the description of disorders and consequently of diagnostic strategy.

Constructing the knowledge base

Consider subjects who experience endocrine-related forms of infertility as classified into groups, where each group represents a set of possible variations of a particular disturbance in the hypothalamic-pituitary-ovarian axis. One can describe for every group a number of pat-

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1 TURNERS SYND. 759.514
HAS THE FOLLOWING PATTERN

  HIST
   8  PRIMARY INFERTILITY
   6  PRIMARY AMENORRHEA

  OBSC
 127  INFANTILISM
  46  NO OVARIES
  27  SHORT STATURE
   4  FEMALE APPEARANCE
   2  FEMALE
  44  MUST NOT HAVE ADNEXAL MASS(ES)

  EXIN
 134  CHROMATIN NEG.
 117  ABN SEX CHROMOSOME
  75  EE + MAP POS.
  74  MAP NEG
  54  STREAK OVARY
  30  KARIOTYPE XO
  98  MUST NOT HAVE PITUITARY FOSSA
      DEFECTIVE
 152  MUST NOT HAVE BBT BIPHASIC
 180  MUST NOT HAVE VISUAL FIELDS
      DEFECTIVE
 116  POSSIBLE CARDIOVASC. ANOMALY

  SLAB
 365  SERUM GROWTH HORMONE NORMAL
  12  HIGH LH >30
  10  HIGH FSH > 30
  24  PROBABLE FEMALE HIGH TESTOST. > 2

IMPLIED FACTS

  HIST
  -7  NO SECONDARY AMENORRHEA
  -9  NO SECONDARY INFERTILITY
 -88  NO HIST OF REPEATED ABORTIONS
      IN WIFE
-151  NO PAIN OF BLEEDING SYNCH MENSES
-158  NO SEC. AMENORRH POST PARTUM
-159  NO HIST. OF DELIVERY
-171  NO HIST. OF DELIVERY COMPL.
-174  NO IRREGULAR CYCLES
 203  AMENORRHEA
-209  NO MENSTRUAL BLEEDING
-211  NO IRREGULAR BLEEDING/METRORRHAGI
 219  INFERTILITY REAL > 1.5 YRS.
-223  NO BTB ON ESTROGENS

  OBSC
  -47  NO BLIND VAGINA
 -173  NO PANPITUITARISM

  EXIN
  -31  NO KARIOTYPE XXY
  -32  NO KARIOTYPE XY 46
  -73  NO MAP POS
  -76  NO EE + MAP NEG.
 -135  NO CHROMATIN POS.
 -189  NO KARIOTYPE XX

  SLAB
  -11  NO LOW FSH (0-10)
  -13  NO LOW LH 0-10
 -129  NO HIGH CHORIONIC GONADOTR.>200
 -287  NO FSH ?NORMAL (IN CYCLE RANGE)
 -288  NO LH NORMAL (10-30)
 -290  NO HIGH PROGESTERONE
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Figure 1 Definition and subsequent display of the pattern for a medical disorder.

terns, each of which is expressed as a combination of clinical and laboratory findings representative of a specific variant of the group. The parameters that enter into the definition of these patterns are often linked among themselves. Thus, the occurrence of spontaneous bleeding, or withdrawal bleeding after progesterone, indicates five important findings: 1) the presence of a uterus with endometrium capable of normal response to ovarian steroids; 2) the presence of some endogenous estrogen activity, which in turn indicates 3) the presence of at least minimal ovarian activity and 4) gonadotrophic stimulation sufficient for evoking follicular maturation as well as 5) sufficient hypothalamic GNRH activity for basic pituitary stimulation.

This representative example of clinical reasoning suggests the essential elements required to effect a translation. Four basic components are needed: facts, disorder patterns, relationships among facts, and rules for interpreting laboratory results.

1. Any item of information which can help to differentiate among disorders is termed a medical fact. Each is defined in a free-format text of the expert's choice and is classified in one of five categories, viz., historical (e.g., spontaneous bleeding), observational (presence of uterus), laboratory tests (endogenous estrogen activity), intermediate treatments (response to clomiphene), and special investigations (chromosome analysis, x-rays). Facts referring to the same clinical data may be defined with varying shades of accuracy, as for example a) age > 30, b) age 20–30, c) age < 35, etc. (To make full use of this information, appropriate

logical relations are subsequently defined.) Differing interpretations may be given to the same fact, so that a history of surgical intervention may have one meaning when referred to in a male disorder and a second when encountered in a female disorder.

2. Any condition of diagnostic significance is termed a disorder and is specified in terms of a collection of facts, each having a status in the pattern for the disorder. Facts are stipulated such that their presence or absence is a *sine qua non* for the diagnosis of the disorder, or are labeled as probable. In the latter case these serve as a basis, when combined with the physician's experience, for acceptance or rejection of a hypothesis concerning a potential candidate disorder. Multiple patterns for the same defined disorder may be described. Each pattern is identified by a user-specified name, and the system assigns it a number which is used for all subsequent references. The pattern for a disorder as stipulated may be relatively small. However, the true picture of the disorder is greatly extended by the implications derived from the facts included in its description.
3. The medical knowledge base is extended through a function that permits the specification of inter-fact implications. Most diagnostic systems have assumed (for convenience of mathematical formulation) that clinical signs are independent of one another. This assumption seems excessive, for not only are facts often interdependent but their dependence can be made logically rigid. Specifically one frequently finds that if a clinical fact A is in a given state, another fact B must be in a certain state in the deterministic sense. Each fact in the system is assigned a number and its status within a disorder encoded. Implication can then be specified by pairs of numbers with negative signs indicating logical negation. Since implication is transitive, the system automatically generates chains of implications when they apply, and adds the corresponding reverse implications. The implicative chains are derived by expressing all fundamental implications within a Boolean matrix and applying transitive closure to it [2]. This technique allows rapid determination of inconsistencies. The implications (among other things) provide a check on the internal consistency of the defined disorder patterns. Inconsistencies are brought to the user's attention and the set of implication chains that caused them is displayed for appropriate corrective action.

The following case illustrates the translation of medical data into the system. Consider a set of disorders for which amenorrhea is a relevant symptom (e.g., Turner's syndrome, menopause, endometrial TB, Sheehan's syndrome, etc.). For some of these disorders the pattern must include primary amenorrhea, for others secondary amenorrhea, while for still a third group the requirement is for either primary or secondary amenorrhea (but not both). The solution is to define three facts: a) primary amenorrhea; b) secondary amenorrhea, and c) amenorrhea with the added implications $a \rightarrow c$, $b \rightarrow c$, and $b \rightarrow \sim a$. (The system will generate $\sim c \rightarrow \sim a$, $\sim c \rightarrow \sim b$ and $a \rightarrow \sim b$.) If the physician is uncertain when performing a diagnosis whether to classify the patient as having primary or secondary amenorrhea, he may indicate the less-accurate-fact amenorrhea. The system will remind him, should the situation arise, that in order to refine the diagnosis he may need to establish which type of amenorrhea applies. An attempt to assign both primary and secondary amenorrhea generates a warning of inconsistency, and the assignment is rejected. Figure 1 represents a typical pattern as defined and its extended description with all implications deduced.

All implication chains for a given fact or alternatively all inference chains leading to a fact may be retrieved (see Fig. 2). Relationships among facts are general in the sense that they hold for all disorders defined. We do not permit those which may be peculiar to one or more disorders, because they are infrequent and their inclusion would unnecessarily complicate the physician's task.

4. Laboratory tests introduce an additional nontrivial element into the diagnostic process. The challenge is to properly assess and interpret the "raw" findings, when these are coupled with the relevant data for the specific patient, in order to arrive at their diagnostic significance. The need for a systematic approach arises from the risk of obtaining inconsistent results, the large number of possible combinations that may appear, and the need to take into account borderline situations. (It might also be noted that there is a tendency for a physician to interpret results in a biased fashion based on his intuitions about the patient's condition.)

For each test the clinician defines a complex of rules. Each rule has the form *If* (*e*) l.o. (*e*) l.o. (*e*) $\cdots$ *then* medical interpretation(s), where *e* is a valid mathematical expression that conforms to the syntax of APL and l.o. is one of the standard logical operators $\wedge$, $\vee$, $\nand$, $\nor$, $\sim$. A set of such rules constitutes a full interpretation of the test. The output is one or more facts (as defined earlier) comprising the interpretation (see Fig. 3).

A number of facilities are provided in order to assure that the knowledge base is consistent, accurately reflects the expert's intentions, and is sufficiently detailed to permit efficient use in diagnosis. In effect the system provides tools to permit "debugging" of the medical knowledge by the clinician himself. These aids are described in the section on validation.

```
      WHI 6
ENTER F FOR 6 → ...
AND B FOR .... → 6
F
 PRIMARY AMENORRHEA → NO IRREGULAR CYCLES (6 ¯174)
 PRIMARY AMENORRHEA → NO SEC. AMENORRH POST PARTUM (6 ¯158)
 PRIMARY AMENORRHEA → NO HIST. OF DELIVERY COMPL. (6 ¯171)
 PRIMARY AMENORRHEA → NO HIGH CHORIONIC GONADOTR.>200 (6 ¯129)
 PRIMARY AMENORRHEA → NO HIST OF REPEATED ABORTIONS IN WIFE
  (6 ¯88)
 PRIMARY AMENORRHEA →  AMENORRHEA → NO IRREGULAR CYCLES
  (6 203 ¯174)
 PRIMARY AMENORRHEA →  AMENORRHEA → NO PAIN OF BLEEDING SYNCH
  MENSES (6 203 ¯151)
 PRIMARY AMENORRHEA →  AMENORRHEA → NO MENSTRUAL BLEEDING
  (6 203 ¯209)
 PRIMARY AMENORRHEA →  AMENORRHEA → NO IRREGULAR BLEEDING/
  METRORRHAGI (6 203 ¯211)
 PRIMARY AMENORRHEA →  AMENORRHEA → NO NORMAL MENSTRUATION
  (6 203 ¯225)
 PRIMARY AMENORRHEA →  AMENORRHEA → NO EPIMENORRHEA (6 203 ¯226)
 PRIMARY AMENORRHEA →  AMENORRHEA → NO LONG CYCLES (6 203 ¯227)
 PRIMARY AMENORRHEA →  AMENORRHEA → NO OLIGO-HYPOMENORRHEA
  (6 203 ¯85)
 PRIMARY AMENORRHEA → NO HIST. OF DELIVERY → NO SEC. AMENORRH POST
  PARTUM (6 ¯159 ¯158)
 PRIMARY AMENORRHEA → NO HIST. OF DELIVERY → NO HIST. OF DELIVERY
  COMPL. (6 ¯159 ¯171)
 PRIMARY AMENORRHEA →  PRIMARY INFERTILITY → NO SECONDARY
  INFERTILITY (6 8 ¯9)
 PRIMARY AMENORRHEA →  PRIMARY INFERTILITY → NO HIST. OF DELIVERY
  COMPL. (6 8 ¯171)
 PRIMARY AMENORRHEA →  PRIMARY INFERTILITY → NO HIST. OF REPEATED
  ABORTIONS IN WIFE (6 8 ¯88)
 PRIMARY AMENORRHEA →  PRIMARY INFERTILITY → NO SEC. AMENORRH POST
  PARTUM (6 8 ¯158)
 PRIMARY AMENORRHEA →  PRIMARY INFERTILITY → INFERTILITY REAL >
  1.5 YRS. (6 8 219)
 PRIMARY AMENORRHEA →  PRIMARY INFERTILITY → NO HIST. HYDATIDIFORM
  MOLE (6 8 ¯257)
 PRIMARY AMENORRHEA → NO SECONDARY AMENORRHEA → NO SEC. AMENORRH
  POST PARTUM (6 ¯7 ¯158)
 PRIMARY AMENORRHEA →  AMENORRHEA → NO HYPOMENORRHEA →
  NO MENORRHAGIA (5 203 ¯122 ¯260)
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Figure 2 Implication and inference chains. *F* signals forward and *B* backward chains.

Dynamic questionnaire

Much of the information having diagnostic significance in medicine involves a negligible cost of acquisition, where "cost" is to be measured as some function of time, money, patient risk, and discomfort. Typically, most historical and observational data, whose determination involves either answering a question or performing a routine physical examination, fall into this category. The

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      IF (BASALEVEL≥4)∧(RESPONSELEVEL≤(0.5×BASALEVEL))∧
         (RESPONSELEVEL≤16)∧(AGE>11)
THEN 302  NORMAL 17OHCS SUPPRESSION TO SMALL DOSE DEXAMETHASONE
          TEST

      IF (AGE>11)∧(((BASALEVEL<3)∧(RESPONSELEVEL≥4)∧(RESPONSELEVEL>
         16))∨((BASALEVEL<4)∧(RESPONSELEVEL>5)∧(RESPONSELEVEL≤16)))
THEN 608  BASAL LEVELS FLUCTUATING BETWEEN NORMAL AND LOW
     376  INCONCLUSIVE TEST REGARDING SUPPRESSION OF ADRENAL
          STEROIDS

      IF (AGE>11)∧(BASALEVEL≥13)∧(BASALEVEL≤19)∧(RESPONSELEVEL≤19)
THEN 607  BASAL LEVEL AT BORDERLINE BETWEEN NORMAL AND HIGH
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Figure 3 A set of rules for interpretation of the test. (See text.)

original design involved the use of suitable forms for collecting and entering patient data into the system. The effort involved in designing a good form can be enormous. A group dealing with an application to internal medicine reported spending twenty man-years in developing a suitable document. Notwithstanding the fact that the medical information base is prone to modification, it is virtually impossible to indicate on a printed form a distinction between essential, relevant, and irrelevant data for a particular patient. The physician records the status of facts without knowing *a priori* whether he actually contributed to the diagnostic process. A competent physician would be hard pressed to digest all the medical knowledge relevant at every decision point in the patient management. He cannot be sure which chains of implications will apply, nor does he necessarily realize the full effect that a particular result will have on the reduction of plausible disorders. To be certain that all the effective information is indeed available to a diagnostic program, the user would be forced to record a great deal of superfluous data for every patient. For the same reason it is infeasible to request the physician to specify a decision tree.

One solution is to develop a technique for determining the status only of those clinical data that actually advance the diagnosis, in such a way that the expected costs will be minimized. Because at every point in the patient management all prior facts entered must be taken into account, one generally requires sequential methods to make optimal decisions at each step. In medical areas comprising well over 100 disorders, the computations involved are beyond the power of any currently available computers. However, by using suboptimal procedures, it is possible to achieve quite good selections. To accomplish this task we distinguish between two categories of medical facts: those that have diagnostic significance but involve negligible cost of acquisition and those facts whose determination incurs considerable cost or risk. (Because patients coming to the Institute of Endocrinology may often have had previous treatments elsewhere, we have included several "extra-institutional" results in the first class.)

A reasonable approach is to determine first the status of all facts of the first type, and then to consider facts in the second group. As all data in the first category have small associated cost, a good criterion for selecting the next fact to be examined is to choose the one with the greatest potential for reduction of the set of plausible disorders. Several alternative decision rules were considered and the following algorithm selected: Consider the full set S_k of facts which have yet to be determined (implicitly or explicitly) at the kth stage of the sequential procedure. For each of the facts in S_k determine the effect on reducing the number of remaining disorders if the fact is found to be present or absent. Then choose the fact j according to the following rule:

$$j = \min_{i \in S_k} [K \max (D_i^+, D_i^-) + \min (D_i^+, D_i^-)],$$

where D_i^+ is the number of disorders remaining if fact i is present, and D_i^- the number if it is absent. This rule ensures that among all the worst possible answers the fact with the highest potential for reduction will be chosen. In cases where more than one fact satisfies the first criterion, a second criterion ($\min D_i^+, D_i^-$) will be used to choose among them. As a rule the algorithm is not particularly sensitive to the exact value of the constant K. In our experience a value of $K = 3$ gave the best results. More refined versions using probabilities of outcomes may be

easily incorporated. These probabilities are currently unavailable; hence the present rule, which requires reasonable computation time, was preferred.

The algorithm for sequential selection of clinical facts was implemented within the framework of a dynamic questionnaire. For every clinical sign that may be selected, the system maintains the text of a question whose response determines the status of the fact. (Question texts may be defined by the experts when needed.) On the basis of the data collected for the patient, the system selects the next fact to be determined. The appropriate question text is displayed on the terminal and the physician supplies the answer. The response is translated into the status of the corresponding fact and is stored in the patient record. Any new implications that stem from the response are derived and disorders no longer applicable are excluded. The algorithm is applied to the remaining set of disorders and facts and selects the next question to be asked. This procedure is repeated until no more relevant medical data can be extracted from data in the first category.

The dynamic questionnaire operates on whatever current medical data are defined in the system. The fact to check at any point is determined on the basis of all defined disorder patterns and implications that apply. This scheme, unlike that of other computer-generated questionnaires, is truly dynamic insofar as the physician is not required to specify the branching logic in advance. Changes in medical knowledge are automatically absorbed and reflected in the order and selection of questions posed.

Diagnosis

With the completion of the definition phase the system is made available to nonspecialists for diagnostic assistance. A physician working interactively enters the clinical facts collected from a patient. These facts are entered as positive or negative, depending on whether they have been found to be present or absent. The status of the facts is recorded in a profile vector, which is then expanded by using whatever implicative relations apply. The derivation of all implied data for a fact in a given state is equivalent to selecting a row from an array formed by computing the transitive closure of a bit matrix embodying all implications. If no inconsistencies are found, the new facts are added to the patient medical record. A comparison of the patient profile vector with the set of profiles is performed, and a check is made to determine whether grounds exist for exclusion. Every disorder pattern continues to be a candidate for a final diagnosis unless logically necessary grounds are found for excluding it. The elimination of any candidate is automatic if and only if the status of any fact in the patient is incompatible with its state in the candidate disorder. The elimination of disorders reduces at each step to a set of Boolean operations between the specific patient profile vector, a vector representing implied facts and a matrix of candidate disorders, i.e., those remaining plausible. A tabular matrix lets the physician see the precise effect of the result of a particular test on the diagnostic process. (The system thus encourages the establishment of efficient descriptions of patterns and stimulates the exercise of good diagnostic strategies.)

The physician may elect to invoke the dynamic questionnaire which prompts him for (only) relevant data. Following the answer to each question, the status of the corresponding fact is determined and the appropriate reduction of disorders (if any) effected.

The physician can adapt the questionnaire to his particular style of inquiry. An option exists to group facts into classes and to specify the order in which these categories should be considered in the questioning procedure. Thus, for example, he may decide to consider first dealing with amenorrhea, then to ask about previous pregnancies, history of drugs taken, etc. The system selects questions from the first group and only after all relevant facts that can effect reduction from this group have been examined does it proceed to the next category. It may well happen that certain responses cause all questions in subsequent groups to be redundant. As a case in point, if the patient is primary amenorrheic, questions about previous pregnancies are unnecessary. The system disregards this category and moves on to the next set specified. Grouping questions may have the effect of slightly detracting from the efficiency of the dynamic questionnaire, but this is a small price to pay for providing the user with smooth flowing interviews similar to his own.

At any time the user can halt the questionnaire and invoke any of the other functions performed by the system. He may add facts to the patient's record, query the patient file, request a list of currently possible disorders, change previous answers and then resume the interview. The system keeps track of the currently active patient data in determining the next question to be asked.

An example of the dynamic questionnaire is given in Fig. 4. Prompted by the system the physician specified basic information, such as name, age, sex, and patient's major complaint (2 0 6 = infertility). As a result of the initial data entered, the number of remaining disorders was reduced from 120 to 63. The system then begins the interview. The first question dealing with an anamnestic fact is displayed. Next to each question (in parentheses) is its fact number. Following each answer the system prints the number of remaining disorders (*REM DIS* =) as an aid in observing the progress of the diagnosis. Queries for which responses were unknown are tracked, should the physician optionally request to be reminded of missing information. When all the relevant anamnestic and extra-institutional facts have been collect-

```
NAME?              AAA BBBB
SEX  (M OR F)?     F
AGE?(OR 0)         22
MAJOR COMPLAINT?    206

ANSWER YES NO DONT KNOW REPEAT OR STOP - TO ADD COMMENTS ENTER C
(203) HAS PATIENT HAD A PERIOD WITHIN LAST 3 MONTHS?  [ Y ]
REM DIS = 35
(152) DOES PATIENT HAVE A BIPHASIC BBT? [ N ]
REM DIS = 22
(219) HAS PATIENT FAILED TO ACHIEVE PREGNANCY DESPITE 1.5 YEARS
OF COHABITATION? [ Y ]
REM DIS = 22
(279) WHILE CARRYING NORMAL DAILY LIFE DOES PATIENT FEEL MORE
TIRED THAN BEFORE? [ N ]
REM DIS = 20
(174) DOES PATIENT HAVE IRREGULAR CYCLES (WITH VARIATIONS OF 14-56
DAYS)? [ N ]
REM DIS = 18
(278) DID PATIENT RECEIVE CORTICOSTEROID THERAPY DURING LAST
3 MONTHS? [ N ]
REM DIS = 17
(182) DID PATIENT TAKE TRANQUILIZERS DURING LAST 3 MONTHS AND AT
PRESENT TIME? [ N ]
REM DIS = 16


**** PLEASE EXAMINE PATIENT - PRESS RETURN WHEN READY ****


(265) DOES PATIENT HAVE PINK STRIATE IN ABDOMINAL AREA? [ N ]
REM DIS = 11
(264) DOES PATIENT HAVE A MOON FACE? [ N ]
REM DIS = 11
(14) IS PATIENT'S BODY WEIGHT IN KG. GREATER THAN
(HEIGHT IN CM. MINUS 110)×1.25? [ N ]
REM DIS = 8
(262) DOES PATIENT HAVE ANY EASILY VISIBLE HAIR IN AREAS WHICH
USUALLY ARE HAIRLESS IN FEMALES? [ Y ]
REM DIS = 8
(79) DOES PATIENT HAVE MALE CONFIGURATION OF MUSCLES, FAT, AND
PUBIC HAIR WITH ENLARGED CLITORIS AND FACIAL HIRSUTISM? [ N ]
REM DIS = 5
NO FURTHER REDUCTION POSSIBLE
```

Figure 4 Example of the dynamic questionnaire. (The program prints the brackets and then backspaces to permit response within them.)

ed, the physician is asked to perform a physical examination of the patient, following which the questioning proceeds with observational facts, and continues until no further differential diagnostic (using facts of negligible cost) is possible. In the example this occurred after twelve questions were asked; five possible disorders remained for which differentiation required more expensive tests.

The questionnaire can be operated optionally in an explanatory mode so that the physician is provided with the system's reasoning at every step. In this mode a list of

```
(174) DOES PATIENT HAVE IRREGULAR CYCLES
WITH VARIATIONS OF 14-56 DAYS? **** [Y]
REM DIS = 20
 2 DISORDERS ELIMINATED
NAMES OR NOS?  A
14 CERVICAL STENOSIS CONGENITAL 627.111
68 CERVICAL STENOSIS ACQUIRED  627.511
DO YOU WISH REASONS?  Y
FOR WHICH DISORDER NO(S) (0 = ALL)
□:
      14
14 CERVICAL STENOSIS CONGENITAL 627.111
WAS ELIMINATED BECAUSE
 174 IRREGULAR CYCLES WAS ENTERED
 IRREGULAR CYCLES → NO AMENORRHEA →
 NO CERVIX OCCLUSION AND PATTERN
 INCLUDES
 123 CERVIX OCCLUSION
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Figure 5 Part of the questionnaire when in the explanatory mode.

disorders excluded by his answer is provided. For any such disorder the precise reason for exclusion is given, exposing the system's logic to the user (see Fig. 5).

When the questionnaire has terminated, the system may list the disorders remaining and the facts that can advance the diagnosis (see Fig. 6). A distribution matrix indicates the status of every remaining fact in each potential disorder. The matrix, which includes the effect of all implications, specifies the differential diagnostic power of the undetermined facts. To continue with the previous example, the decision was to check the patient's 17*KS*, which were found to be less than 15; the physician entered fact - 29 (as a result two disorders were excluded). The subsequent matrix showed a clomiphene test as differentially significant. The decision was made to perform the test, which yielded a positive response, and the corresponding fact (169) was entered, resulting in a final diagnosis of anovulation due to feedback disorder.

This example is fairly representative of patient management in this area of endocrinology in the sense that diagnosis and treatment may well be intertwined. Thus the attempt to activate the hypothalamus with clomiphene not only serves to check the hypothesis of feedback disorder, but when successful is regarded as the therapy of choice. In other situations the selection of treatment constitutes the subsequent phase of system use whereby the indicated therapy is a function of specific patient data and the diagnosis made.

In the example cited, the determination to check the level of 17 ketosteroids involved a special laboratory procedure. (For purposes of illustration the results were entered directly.)

In the normal course of events, a date is scheduled to collect and test a urine sample from the patient. The findings are entered into the system and the physician receives the resulting interpretation together with possible indications of inconsistencies with other patient data. If the interpretation is accepted the appropriate fact(s) are absorbed into the patient record and made available to the diagnostic program. A schematic of information flow and main processing functions within the system is given in Fig. 7. Notice that input may come from various sources (e.g., physician, lab technician) and may be initiated either by the system or by the user. The schematic does not cover that part of the system dealing with development of the knowledge base.

Validation

Reliance on the clinician's expertise to provide an information structure based on his knowledge places a burden on him. The system must support this effort by ensuring that definitions are unambiguous and consistent, and that medical data are sufficiently complete and self-contained to be of diagnostic use. In sum this implies the system's capacity to reveal deficiencies in the information structure. In addition to the standard features for selective retrieval of information (as for example a function to specify which facts appear in which disorder) the following features have been included.

1. Each pattern is automatically checked upon entry for the existence of any conflicting facts.
2. A routine verifies the existence of at least one fact which could conceivably differentiate between each pair of disorders defined. Disorder pairs which are not differentiable are flagged. The physician then specifies conditions (through addition or deletion to patterns and/or implication) for distinguishing between each such pair.
3. The dynamic questionnaire may be simulated. The physician selects a disorder to be checked, and a routine simulates the questioning process for a fictional patient presenting the disorder. At each stage the system chooses the answer depending on whether the fact is an exclusion state, random, irrelevant, or probable. It continues until no further differentiation is possible, using data from the first three categories (anamnestic, observation, and extra-institutional), thereby completing a single trial. For each trial statistics are collected, such as the total number of questions asked, the distribution of remaining disorders, and the number of clinical signs yet to be determined. On the basis of this information, the physician is able to check whether a) related disorders appear and b) the disorder simulated is easily differentiable (based for example on the number of questions required). Histograms of the data collected may be useful in improving the medical data. For example, an analysis of remaining disorders and their clustering could reveal the need for amendments to the patterns (see Fig. 8).

```
      DGP
2 POLYCYSTIC OVARIES SYNDROME 256.912
31 ANOVULATION (IDIOPATHIC) 628.011
32 ANOVULATION (ADRENAL ORIGIN) 628.012
33 ANOVULATION (OVARIAN ORIGIN) 628.013
61 ANOVULATION (FEEDBACK DISORDER) 628.014
THERE ARE 13 FACTS LEFT
SLAB = 29 142 156 179 192 193
DYTH = 162 169 170 195 196 197 198
FULL MATRIX? Y OR N (O=EXIT) Y
                                  M  P  N    2   31   32   33   61
SLAB
 29 HIGH 17KS>15                  3  0  2    M    N    M    M    N
142 HIGH 17OH>15                  1  0  2         N    M         N
156 LOW PROGESTERONE < 10         4  0  0         M    M    M    M
179 NORMAL TESTOSTERONE           2  0  0         M              M
192 NORM 17KS (5-14)              2  0  3    N    M    N    N    M
193 NORM 17OH (5-14)              2  0  1         M    N         M
DYTH
162 TESTOST. HIGH AFTER SUPPR.    0  0  2    N                   N
169 CLOMIPHENE POS.               1  0  1         N                   M
170 CLOMIPHENE NEG.               1  0  1         M                   N
195 17KS HIGH AFTER DEXAM. DOSE 2 1  0  2         N    M              N
196 17OH HIGH AFTER DEXAM. DOSE 2 1  0  2         N    M              N
197 17KS HIGH AFTER ESTROGEN SUPPR 0 0 2    N                   N
198 17OH HIGH AFTER ESTROGEN SUPPR 0 0 1                        N

      ENTPF  -29

      DGP
31 ANOVULATION (IDIOPATHIC) 628.011
61 ANOVULATION (FEEDBACK DISORDER) 628.014
THERE ARE 6 FACTS LEFT
SLAB = 156 179 192 193
DYTH = 169 170
FULL MATRIX? Y OR N (O=EXIT)  Y
                                  M  P  N     31    61
SLAB
156 LOW PROGESTERONE < 10         2  0  0      M     M
179 NORMAL TESTOSTERONE           2  0  0      M     M
192 NORM 17KS (5-14)              2  0  0      M     M
193 NORM 17OH (5-14)              2  0  0      M     M
DYTH
169 CLOMIPHENE POS.               1  0  1      N     M
170 CLOMIPHENE NEG.               1  0  1      M     N

      ENTPF 169

      DGP
61 ANOVULATION (FEEDBACK DISORDER) 628.014
DIAGNOSIS COMPLETE-STORE IN FILE?  Y
FOR A PATIENT RECORD TYPE PRTPF
```

Figure 6 Continuation of the diagnostic process.

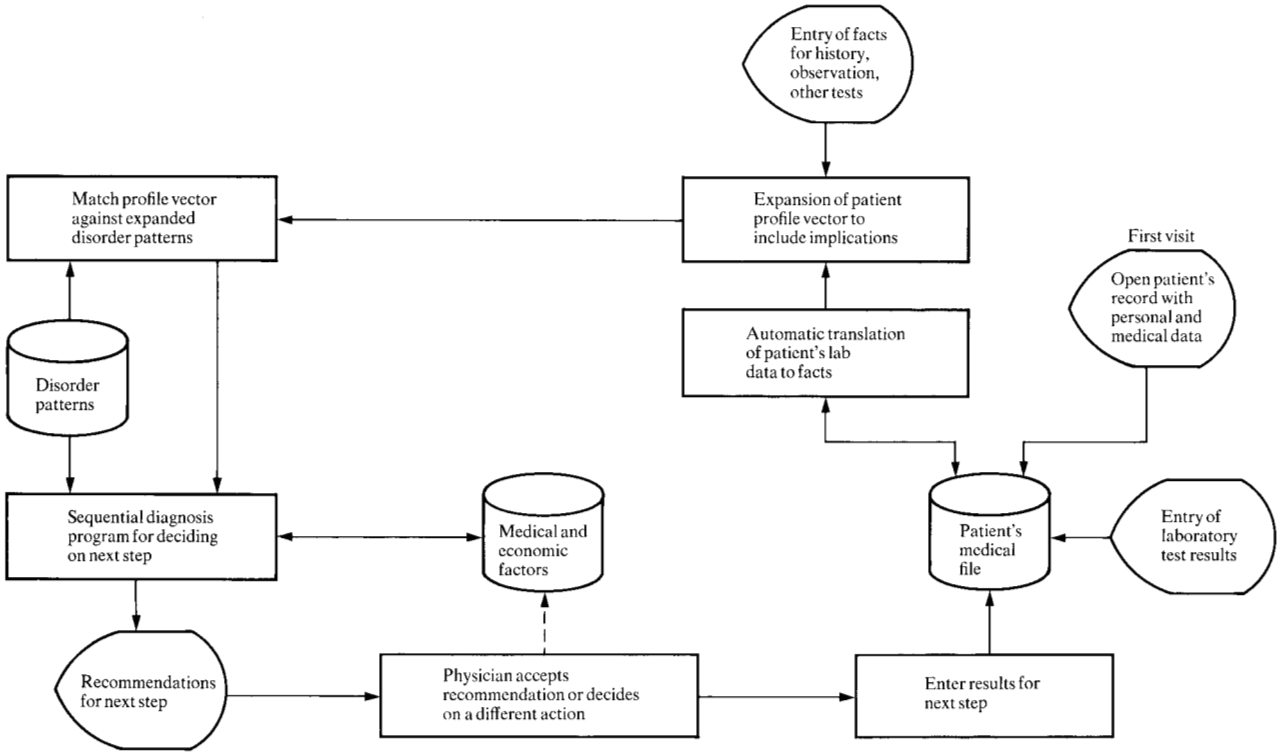

Figure 7 General schematic showing the system functions.

4. In a variation of the aforementioned simulation program the system provides an additional check for validity of medical information. This program assumes that a patient has a given disorder and directs the questioning to the physician who responds with data taken from patients previously diagnosed with the given disorder. The system's resulting diagnosis is checked for validity. (Frequently this routine shows that certain questions typically asked are in fact redundant.)
5. The defined laboratory test has the form of a set of rules—that is, a set of arithmetic logic equations. Flaws in the definition could lead to the following errors: a) A medical condition is neglected; i.e., a certain combination of findings does not respond to any rule. b) A rule is empty in the sense that it does not correspond to any real-life situation. c) Certain laboratory results agree with a set of rules in a way that yields contradictory medical facts. d) The interpretation of some findings is incomplete because it fails to reveal all the clinical implications stored in the data.

An interactive checking device that is easy to use was developed to enable the medical expert to make a comprehensive check of the set of rules by covering all anticipated findings of laboratory tests. The program requests a set of values for each parameter, then responds with all the medical evaluations answering to each possible combination of parameter values. The physician then examines the validity of the conclusions. A set of values that satisfy two or more rules yielding inconsistent interpretations is flagged for correction. A measure of assurance that the set of values chosen for each parameter is indeed comprehensive is obtained by having the program check that each rule was satisfied at least once by the parameter set (see Fig. 9).

These procedures provide a high probability that the majority of cases will be diagnosed correctly by the system. In practice, errors of judgment occurring during operation of the system are corrected by entering comments into a file for subsequent analysis and correction by specialists.

Discussion

The system is problem oriented inasmuch as a patient is first classified according to his major presenting complaint. This initial datum is generally sufficient to establish which of the medical subspecialties defined is relevant. We have provided for a number of possible modes of operation. If a sufficiently large workspace is available,

```
STATISTICS FOR DISORDER 61 ANOVULATION (FEEDBACK DISORDER)
NO. OF TRIALS: 100
                MAX   MIN    AVG    SD
NO. QUESTNS      24    15   18.8    2.12
REMNG DIS        10     3    4.3    1.46
REMNG FACTS      30    13   17.1    4.60
  EXIN            5     2    2.3     .55
  SLAB           15     6    7.8    2.42
  DYTH           13     5    7.1    2.24


TOTL QUESTIONS HIST
NO.    CNT    HIST→
15       5    *****
16      10    **********
17      13    *************
18      17    *****************
19      22    **********************
20      12    ************
21      10    **********
22       5    *****
23       4    ****
24       2    **


ACTUAL DIS HIST
DIS NO CNT  HIST
 2    16    ********
21     3    **
31   100    ****************************************************
32   100    ****************************************************
33    48    ************************
35    24    ************
61   100    ****************************************************
82     1    *
83     1    *
84     6    ***
85     3    **
86     3    **
87     5    ***
88     3    **
89     3    **
91     9    *****
92     9    *****
```

Figure 8 Statistics for 100 simulated patients having disorder "61." Each trial was run until all historical and observational data were exhausted. *Note*: 31 = anovulation (idiopathic); 32 = anovulation (adrenal); and 33 = anovulation (ovarian).

each specialty can be stored separately within its own workspace. When the specific complaint is determined, the appropriate workspace can be loaded. The current implementation uses an alternative scheme. All complaint categories are encompassed in a single information structure residing on files. The system selects the appropriate subset as required. A vector defined globally in the workspace specifies the active disorders to be used for dif-

```
     DEBUGC
ENTER TEST NUMBER 16
ENTER CHECK VALUES
P1: AGE              30
P2: BASALEVEL        10 15 30
P3: RESPONSELEVEL     5 14 25

     P1    P2    P3    FACT     INTERPRETATION
     30    10     5     302     NORMAL 17OHCS SUPPRESSION TO SMALL
                                 DOSE DEXAMETHASONE TEST
                         193     NORMAL. 17OHCS BASAL LEVEL
                         378     BORDERLINE RESPONSE
     30    10    14     303     NO OR INCOMPLETE 17OHCS SUPPRESSION TO
                                 SMALL DOSE DEXAMETHASONE TEST
                         193     NORMAL 17OHCS BASAL LEVEL
     30    10    25     303     NO OR INCOMPLETE 17OHCS SUPPRESSION TO
                                 SMALL DOSE DEXAMETHASONE TEST
                         609     BASAL LEVEL FLUCTUATING BETWEEN NORMAL
                                 AND HIGH
     30    15     5     302     NORMAL 17OHCS SUPPRESSION TO SMALL
                                 DOSE DEXAMETHASONE TEST
                         193     NORMAL 17OHCS BASAL LEVEL
                         607     BASAL LEVEL BORDERLINE BETWEEN NORMAL
                                 AND HIGH
     30    15    14     303     NO OR INCOMPLETE 17OHCS SUPPRESSION TO
                                 SMALL DOSE DEXAMETHASONE TEST
```

Figure 9 Portion of the checkout of laboratory rules.

ferential diagnosis in each specific instance. Thus a physician may focus on a particular class of disorders (e.g., all adrenal-related patterns) by simply initializing this vector.

The inclusion of inter-fact implications has been found to considerably accelerate the diagnostic process. While relatively little information is specified for a patient, the system deduces a large amount of auxiliary data, enabling the set of potential disorders to be reduced more quickly. (Clinicians are sometimes hard pressed to think in terms of exclusion data for patterns; since many of the facts are of the $a \rightarrow \sim b$ type this presents no difficulty.)

The dynamic questionnaire provided a useful measure of the efficacy of the translation scheme. The algorithm chosen was based on an earlier study [3]. We used the questionnaire to simulate over a thousand patients. Beginning with a domain of 100 disorders and over 150 potential facts, we found that an average of less than 20 questions was required to extract all relevant parameters. Yet more significant is the fact that the number of remaining disorders was always less than ten, with an average slightly higher than four. (The simulations deliberately excluded those laboratory and dynamic therapeutic tests where more complex cost functions might affect the decision process.) These figures are small enough for the application of sequential algorithms based on utility functions and probabilistic data.

One could speculate about the extension of logical propositions in expressing relationships in the system. It is of interest to note that in our experience all the medical knowledge could be adequately expressed without the need for such propositions. It has been well said that the less one knows about phenomena the more the need is felt for all kinds of data. Once essential relationships are understood, much of the data is found to be irrelevant or unnecessary.

Diagnosis has sometimes been viewed as a problem in pattern recognition. Each disorder is said to be defined by a set of facts (feature vector) or a series of feature vectors (disorder class). A given feature vector representing a patient's facts is then measured in terms of its distance from each disorder class, and a comparison of distances by some decision rule permits a determination as to which disorders are most likely. We do not, however, respond

to the needs of the nonspecialist when we present the most likely disorders. It is frequently essential that all potential final diagnoses be taken into account and that all facts that can contribute to further differentiation be provided in a suitable form. Clearly, it is possible to arrive at a final diagnosis without specifying a great many of the determining features. By focusing on the widest possible set of facts embracing all relevant disorders, we minimize the chances of misdiagnosis.

Statistical methods for distinguishing among disorders may be used to define patterns based on a data base that includes patient histories. Because such methods are essentially mechanical processes, it is difficult to predict what patterns may result. Physicians are hesitant to accept the results of procedures whose logic (i.e., mathematics) they do not understand. Moreover, it is a truism that statistical results sometimes fail to bring out the logical significance of information gathered (the fact that in a given sample A is always found with B does not permit the conclusion that A implies B). Only the clinician aware of the context and meaning of the medical data can make such a determination.

We believe that a strength of our approach is the formal distinction between raw medical data and its interpretation in the context of disorders, implicative relations, and laboratory tests. The patient's clinical signs are retained separately from conclusions derived from the knowledge base. The iterative process by which the knowledge base is developed is a direct consequence of experience with the system. As an increasing number of real (or fictitious) patients are processed, the medical knowledge becomes more accurate and complete. Apart from its primary goal the system can be extended in a natural way as a tool for medical education.

The approach taken is meant to get around the difficulties discussed above (see Introduction) and should be suitable for medical specialties meeting requirements similar to those encountered in endocrinology, neurology being a good example. Every system for diagnosis depends heavily on domain-dependent characteristics, including the nature and availability of data. The present effort reflects a contention, by now fairly well established, that no single technique is likely to embrace all possible medical applications. At the same time, the degree to which any system is in accord with the physician's own deductions is crucial to its acceptance.

At the present time the system is undergoing field testing at the Sheba Medical Center of Tel Hashomer Hospital. It was written in APL using TSIO (operating under OS/VS2 or OS/MVT) with a workspace of 64K. The system comprises some 75 APL functions, including three highest-level functions for continuous prompting. Twelve functions (commands) for definition are available as well as ten functions for diagnosis and retrieval. The first, and thus far most comprehensive, implementation has been in the area of reproductive endocrinology. This application has been extended to cover a wide range of adrenal and thyroid problems. Over 130 patterns, more than 500 clinical facts and 450 implications have been defined. Some 40 laboratory tests have been included with the emphasis on the pituitary adrenal axis. We estimate that a period of six to nine man-months is typically required to input and reasonably validate the medical knowledge in a specialty of the magnitude described here. Experience has shown that physicians are able to become versatile in using the system in a matter of five to ten hours of terminal time.

Our results to date suggest that it is feasible to create a diagnostic system sufficiently comprehensive to be of real utility. Implementation of such a system deepens the physician's understanding of medical decision making and provides a greater insight into diagnostic criteria.

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