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Computer concepts

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Computerized Consultation System for Selection of Antimicrobial Therapy

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Mycin, a computer-based consultation system which provides to physicians antimicrobial therapy recommendations for patients with bacterial infections, is described.

The consultation program arrives at therapeutic decisions using a built-in knowledge base as well as patient data entered by the physician. The system is capable of explaining its recommendations and answering questions about its reasoning process. The system's knowledge can be updated and corrected easily by infectious disease experts.

At present the system is operational within a research setting; its routine use in a clinical setting will require further evaluation of its reliability and effectiveness.

Key words: Automation, data processing, computers; Antibiotics; Anti-infective agents; Drug information; Patient information; Physicians

The selection of appropriate antimicrobial therapy for a patient having an infectious disease requires the consideration of several variables. Drug efficacy, organism susceptibility, the site and character of the infection, and the patient's clinical status influence the final therapy decision. While the recommended therapy must adequately treat all likely organisms, it is desirable to minimize the possibility of toxic side effects by limiting the number of antimicrobial agents administered. Mycin, a computer-based consultation system, considers these variables and provides physicians with antimicrobial therapy recommendations.

Medical consultation programs such as Mycin are designed to aid the physician in making decisions for particular clinical situations.[1–3] These programs rely on physician input about individual patients together with a store of knowledge contained in large data bases to provide customized diagnosis and treatment. They can also provide rapid computations for complicated dosage adjustments or data comparisons for drug interactions.

Although the use of computer programs in medical situations has been shown to affect clinicians' performance favorably,[4] there is often reluctance on the part of physicians and other medical personnel to use such programs.[5,6] It appears that physicians, in general, will not spend time experimenting with a program unless it satisfies some general requirements.[7] There should be an established need for assistance in its domain of application. The system should be accessible, easy to use and reliable. It should be fast enough to facilitate the physician's task without significantly prolonging the time required to accomplish it. In addition, it should be able to justify its advice so that the physician can accept or reject the recommendations based on an explicitly stated decision-making process.

The Mycin system was designed with these considerations in mind.[8–10] Using techniques from the field of artificial intelligence (the branch of computer science associated with machines that perform tasks normally thought to require human intelligence[11]), Mycin acts as a consultant in infectious disease therapy. It assists the physician in the determination of possible causative organisms and in the selection of appropriate antimicrobial therapy for bacteremias. At the present time the system is operational within a research setting; however, its routine use in a clinical setting will require further evaluation of its reliability and effectiveness.

Infectious Disease Therapy

The area of infectious diseases is particularly well suited for a consultation system. The etiology of infectious diseases can be defined and readily translated into a format necessary for computer appraisal. This is complemented by the availability of specific therapies and the facility and accuracy with which diagnosis and therapy can be evaluated. There is also a recognized need for continuing education in this area,[12–16] as well as for computational assistance with dosage adjustment in renal failure.[17]

One application of Mycin's capabilities occurs in the highly publicized area of unnecessary and inadequate prescribing of antimicrobial agents.[12–15] As recently as March 1976 Ray et al[12] reported a study of the chloramphenicol prescribing habits of physicians who used the drug on 992 ambulatory patients. Upon analysis of diagnosis, the authors concluded that virtually all of the drug was prescribed inappropriately. The etiology of the illnesses was seldom substantiated, with only 1.3% of the patients having cultures made prior to therapy. It is noteworthy that the amount of drug prescribed was insufficient to treat the indicated in-

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fections in almost half of the adults; however, they were still at full risk of idiosyncratic side effects. Several other studies demonstrate irrational use of antimicrobials manifested by failure to consider the possibility of drug interactions and patient allergy, or by errors in dosage and route of administration.[13–15]

Mycin can provide both education and advice. It has the ability to explain the reasoning behind its recommendations for diagnosis and treatment. This allows Mycin to educate the user as well as provide expertise in the therapy of infectious diseases when specialists are unavailable or inaccessible. This educational function is relevant to the recent efforts to educate physicians in the proper use of antimicrobial agents. A self-assessment test was recently developed by the Network for Continuing Medical Education in an effort to improve the diagnosis and treatment of infectious diseases.[16] A mean correct score of only 55% for the 4,513 physicians tested indicates the need for additional education in this area. A significant improvement of 16% in scores after instruction and retesting suggests that instruction can provide beneficial results. In addition to receiving continuing education, physicians are encouraged to seek advice when needed from infectious disease specialists and other consultants.

Mycin's Overall Design

The Mycin system[7–10,18] is composed of three interrelated components as shown in Figure 1. The consultation program arrives at therapeutic decisions using a built-in knowledge base as well as patient data entered by the physician. The explanation program allows Mycin to justify its recommendations and to answer physicians' questions about its reasoning process. This program is available throughout the consultation. Finally, the knowledge acquisition program allows infectious disease experts to update or correct the system's knowledge easily.

Mycin's therapeutic decisions are based on three types of knowledge—dynamic, static factual and judgmental. Dynamic knowledge about the particular patient, such as laboratory data and drug allergies, is entered by the physician and can vary with each clinical situation. Static factual knowledge, such as normal flora, sterile body sites and drug selection preferences for various organisms, is stored in the computer as lists or tables. Judgmental knowledge, which is needed to make decisions and to deduce necessary information from known data, is contained in rules. These rules, numbering over 400, represent the transformation of knowledge from a number of infectious disease experts into semiformal decision-making criteria.

Each rule consists of a premise (a set of preconditions) and an action (a conclusion to be made or an action to be taken). The action will be used in the decision process only if all of the conditions in the premise are true. For example, in rule #035 (Figure 2), in order for Mycin to conclude that the identity of the organism might be Bacteroides, the patient data base must contain the information that the organism is a gram-negative rod able to grow anaerobically. If any of these preconditions is false, the rule does not succeed and Mycin will investigate other rules to conclude the identity of the organism. The strength of a conclusion of a rule is indicated by a number between −1 and 1 (e.g., the .6 in Figure 2). The larger the number, the greater the belief in the conclusion. These numbers, termed certainty factors (c.f.s), are derived from and are related to conditional probabilities, but offer a number of advantages over the traditional formulation. (For a detailed review of the concept, see Shortliffe et al.[9]) For the rule in Figure 2 the evidence is suggestive (.6 out of 1), but not absolutely certain that the identity is Bacteroides. There are many other gram-negative rods able to grow anaerobically which are considered in other rules.

Figure 1. Diagram demonstrating the flow of information within the Mycin system; the light arrows indicate the flow between the three system components and the knowledge sources and the heavy arrows represent physician input and advice

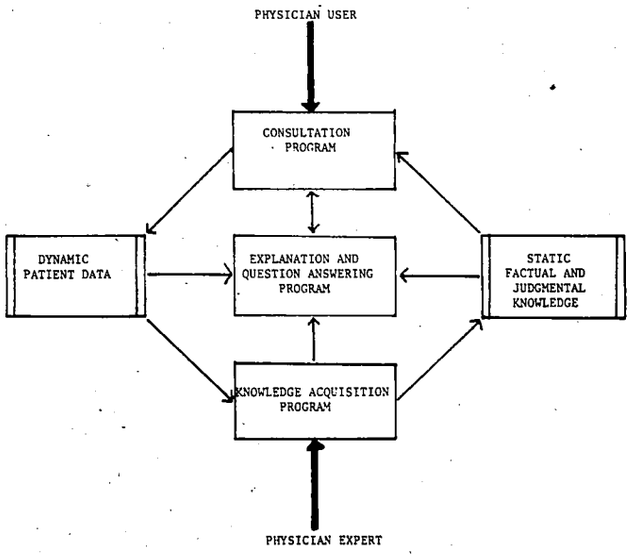

Figure 2. An example of a rule used by Mycin to make decisions or to deduce necessary information from known data; the strength of the conclusion is indicated by the certainty factor (.6)

RULE035

If: 1) The gram stain of the organism is gramneg, and
2) The morphology of the organism is rod, and
3) The aerobicity of the organism is anaerobic

Then: There is suggestive evidence (.6) that the identity of the organism is bacteroides

The Consultation Interaction

The consultation design allows a physician, even one unfamiliar with computers, to interact easily with the system. Each question is phrased in standard English and requires a brief response. If a question is not clear to the physician, it can be rephrased and a list of expected responses can be printed on request. Minor typographical or spelling errors

by the physician are corrected automatically.

A consultation session requires approximately 20 minutes at a computer terminal. During this time the physician will respond to about 60 questions, depending on the complexity of the patient's clinical situation. Following some basic questions regarding the patient's name, age and sex, Mycin begins a discussion of recent infections and cultures. In Figure 3, which presents some initial questions, the words typed by the physician are shown in upper-case letters, are underlined and always follow a double asterisk. All other text is generated by the computer program. Note that in question 7 the physician's typing error on the word BLOOD is automatically corrected. In question 9, the physician indicates that he does not know the identity of the organism. Mycin can accept this incomplete information and will then resort to more detailed questioning to aid in deducing the possible causative organisms (questions 10 and 11). This type of questioning continues until Mycin has obtained all of the patient's clinical or laboratory information which is pertinent for the determination of a therapy recommendation.

Mycin's explanation program allows for justification of advice and for explanations of the motivation for specific questions. Each of Mycin's questions is asked in order to evaluate a condition in a rule being considered. Therefore, the simplest way to understand the reason behind a question is to print the rule under consideration. Question 15 (Figure 4) demonstrates this capability. A physician can further examine the entire chain of reasoning behind a question by using the WHY and HOW commands. By typing WHY, as in question 16, he will receive a detailed explanation from the system as to the type of conclusion it is trying to draw, and how the current rule is applied in this case to establish that conclusion. By repeating the WHY command, the physician can examine the program's reason for seeking the information mentioned. If he would now like to examine how Mycin satisfied the individual conditions mentioned which led to the desired conclusion, the HOW command may be used. This explanation system provides a means for Mycin to become an educational tool, enabling the physician to understand Mycin's medical decision-making processes and also to resolve differences of opinion between the physician and those experts upon whose knowledge the program is based.

After Mycin has used all the rules which could determine the possible identities, it displays its conclusions regarding likely causative organisms (Figure 5). Mycin then asks some

Figure 3. Some initial questions from a consultation session: the physician's responses are in upper-case letters, are underlined and follow a double asterisk (**); all other text is generated by the computer

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                    CULTURE-1

7) From what site was the specimen for CULTURE-1 taken?
**BLOOE
=BLOOD
8) Please give the date and time when this blood culture (CULTURE-1)
   was obtained. (mo/da/yr time)
**5/17/76 1AM
The first significant organism from this blood culture (CULTURE-1)
will be referred to as:

                    ORGANISM-1

9) Enter the identity of ORGANISM-1:
**UNKNOWN
10) Is ORGANISM-1 a rod or coccus (etc.):
**?
What is the morphology of ORGANISM-1?
Expected responses are: ROD COCCUS PLEOMORPHIC SPIRO-
CHETE BUDDING-OVAL-YEAST BRANCHING-FILAMENTS
Enter HELP for list of user options.
**ROD
11) The gram stain of ORGANISM-1:
**GRAMNEG
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Figure 4. A portion of a consultation session demonstrating Mycin's ability to explain its reasoning and to justify its questions; explanations are requested by the RULE, WHY and HOW commands

```
15) Is the patient's illness with ORGANISM-1 a hospital-acquired
    infection?
**RULE

RULE037

If: 1) The gram stain of the organisms is gramneg, and
    2) The morphology of the organism is rod, and
    3) The aerobicity of the organism is facul, and
    4) The infection with the organism was not acquired while the patient was
       hospitalized
Then: 1) There is strongly suggestive evidence (.8) that the category of the
         organism is enterobacteriaceae, and
      2) There is weakly suggestive evidence (.1) that the identity of the
         organism is pseudomonas-aeruginosa
      **NO
      16) Is John Smith a burn patient?
      **WHY
[i.e. WHY is it important to determine whether or not PATIENT-1 has been se-
riously burned?]
[1.0] This will aid in determining the identity of ORGANISM-1.
It has already been established that
    [1.1] the site of CULTURE-1 is blood, and
    [1.2] the gram stain of ORGANISM-1 is gramneg, and
    [1.3] the morphology of ORGANISM-1 is rod
Therefore, if
    [1.4] John Smith has been seriously burned
then
    there is weakly suggestive evidence (.4) that the identity of ORGANISM-1
      is pseudomonas-aeruginosa
    [RULE047]
    [back to question 16 . . . .]
    **HOW 1.3
[i.e. HOW was it established that the morphology of ORGANISM-1 is rod?]
You said so [question 10]
    [back to question 16 . . . .]
    **NO
```

Figure 5. After Mycin decides that the infection is significant, it displays its conclusions regarding likely causative organisms

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My therapy recommendation will be based on the following probable infection(s)
and potential causative organism(s):

INFECTION-1 is PRIMARY BACTEREMIA

(Item 1) PSEUDOMONAS-AERUGINOSA [ORGANISM-1]
(Item 2) E. COLI [ORGANISM-1]
(Item 3) KLEBSIELLA-PNEUMONIAE [ORGANISM-1]
(Item 4) PROTEUS-NON-MIRABILIS [ORGANISM-1]
(Item 5) ENTEROBACTER [ORGANISM-1]
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additional questions to decide the best therapeutic regimen (Figure 6). Using this patient-specific information in combination with sensitivity and efficacy data, Mycin specifies its therapeutic recommendations. The physician then has the option of requesting alternative therapeutic regimens.

If a physician is to accept Mycin's therapeutic advice for his patient, he will require enough information to decide if the treatment is reasonable. At the end of the consultation or at any time during the interaction, the physician may ask Mycin simple questions. These questions may be either specific (about the current consultation) or general (about any of the system's rules, whether used in the current consultation or not). The question-answering session in Figure 7 demonstrates these explanation capabilities. All of Mycin's static factual and judgmental knowledge is accessible through this question-answering program. The user can compare his reasoning process and decisions with Mycin's (e.g., "When do you recommend carbenicillin for Pseudomonas?") as well as learn new information relevant to infectious diseases (e.g., "What are considered to be sterile sites in the body?").[18]

Figure 6. Mycin asks further questions to decide the best therapeutic regimen and then specifies its recommendation

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32) Does John Smith have a clinically significant allergic reaction to any
    antimicrobial agent?
**NO
[Considering GENTAMICIN-AND-CARBENICILLIN for use against INFEC-
  TION-1 . . .]
33) John Smith's weight in kilograms (or (number) POUNDS):
**70

[Rec 1] My preferred therapy recommendation is as follows:
In order to cover for Items (1 2 3 4 5):

Give the following in combination:
1) GENTAMICIN
Dose: 119 mg (1.7 mg/kg) q8h i.v. (or i.m.) for 10 days
Comments: Modify dose in renal failure.
2) CARBENICILLIN
Dose: 2.1 g (30 mg/kg) q2h i.v. for 10 days
Comments: Modify dose in renal failure
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Figure 7. During the questioning-answering session of the consultation, the physicians may ask questions specific to the consultation, and general questions about infectious disease diagnosis and therapy

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                Consultation Specific Questions

**HOW DO YOU KNOW THAT ORGANISM-1 IS PSEUDOMONAS?
I used rule084 to conclude that the identity of ORGANISM-1 is Pseudomonas.
  This gave a cumulative c.f. of (.22). The last question asked before the
  conclusion was made was 22.
I used rule037 to conclude that the identity of ORGANISM-1 is pseudomonas-
  aeruginosa. This gave a cumulative c.f. of (.08). The last question asked
  before the conclusion was made was 21.
**HOW DO YOU KNOW THAT THE SITE OF CULTURE-1 IS BLOOD?
In answer to question 7 you said that the site of culture-1 is blood

                General Questions

**WHAT ARE THE NORMAL FLORA OF THE SKIN?
The normal flora associated with skin are: STAPHYLOCOCCUS-COAG-NEG,
  STAPHYLOCOCCUS-COAG-POS, CORYNEBACTERIUM-NON-DIPH-
  THERIAE
The likely pathogens associated with skin are: STAPHYLOCOCCUS-COAG-
  POS, STREPTOCOCCUS-GROUP-A, STAPHYLOCOCCUS-COAG-NEG
**WHAT DOSAGE OF STREPTOMYCIN DO YOU GENERALLY RECOM-
MEND?
The suggested dosage and route of streptomycin is 7.5 mg/kg q12h i.m. (or
  i.v.)
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Future Goals

Even though Mycin satisfies its original design criteria of accessibility, applicability and justification of recommendations, it is presently not available in a clinical setting. In order to be certain that Mycin's advice is reliable before allowing general use, a formal prospective clinical study of its current performance is being completed.

This study will test Mycin's reliability in the areas of identification of likely organisms and therapy recommendations. Preliminary data suggest that Mycin is not sufficiently reliable when the patient's condition is complicated by additional infections such as endocarditis or pyelonephritis.[9] Therefore, much of our current work is devoted to broadening the system's knowledge of infections. Many new rules dealing with meningitis and venereal diseases have already been written and information on pneumonia and urinary tract infections is being assembled.

The ability to adjust dosage in renal failure is also being developed to improve Mycin's therapeutic recommendations. Presently Mycin's dosage regimens are applicable only to patients with normal renal function. Since many antimicrobial agents are renally excreted and can accumulate to toxic concentrations if the patient has renal insufficiency, it is an important area of clinical concern.

Mycin's educational capabilities are being expanded as well. Currently Mycin can justify its chain of reasoning by presenting the rules being considered as demonstrated in the previous section. However, unless the user has a good background in medicine, he may not understand or remember the underlying concepts that lead to a rule. For example, consider rule #055 in the current system:

If: 1. You are considering tetracycline as therapy, and
    2. The patient is a child.
Then: Tetracycline is a relative contraindication in this patient (.8).

To understand this conclusion, more knowledge is required by the user than is contained within the preconditions of the rule. As one possible solution, Mycin's rule base could include additional rules which could explain the concepts of this judgmental rule at a deeper level. The rule could state that because of chelation between the calcium and tetracycline in the developing teeth of children, discoloration of the teeth could result. The knowledge of the tetracycline-calcium chelation is not required by Mycin to conclude therapy; therefore it is not currently in the system. However, this information would broaden Mycin's educational benefits to the user.

Conclusion

While the actual clinical use of Mycin, or similar programs, may not occur for some time, preliminary research and development have allowed Mycin to be applied to a few diseases for a number of patients. In this limited exposure, we have demonstrated that it is efficient and that it is relatively easy to use. In the next few years it is our intention both to develop further the capabilities mentioned earlier and to make the system as free from error as techniques will allow. To these ends, we view Mycin as a vehicle to provide needed, clinically relevant, pharmacologic information to aid the medical professional.

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Law notes

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Medical Device Amendments of 1976

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The Medical Device Amendments of 1976 are discussed with particular reference to the history of device regulation, classification of devices, performance standards, applications for premarket approval and testing protocols.

Key words: Devices; Laws; Medical Device Amendments of 1976

The Medical Device Amendments of 1976[1] were signed into law on May 28, 1976. This new statutory scheme, an amendment to the Federal Food, Drug and Cosmetic Act,[2] culminates years of efforts to provide controls on medical devices similar to those placed on drugs.

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Background to Current Law

Regulation of medical devices was not authorized until 1938 when the "modern" Food, Drug and Cosmetic Act was enacted into law. Under this law, both drugs and devices[a] were subject to adulteration and misbranding standards[3] and were required to be "safe"[4]; unlike drugs, however, devices were not required to undergo the new drug approval process.[5] Subsequent amendments to the Food and Drug Act provided for increasingly sophisticated and extensive reg-

[a] The Food, Drug and Cosmetic Act contained a definition of "drug" which overlapped somewhat with that of a "device." Section 201(h) of The Medical Device Amendments attempts to eliminate this problem by defining device as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is "(1) recognized in the official *National Formulary,* or the *United States Pharmacopeia,* or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes."