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Development and retrospective evaluation of HEPAXPERT-I: a routinely-used expert system for interpretive analysis of hepatitis A and B serologic findings

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Abstract

HEPAXPERT-I is an expert system that interprets the results of routine serologic tests for infection with hepatitis A or B virus. The tests measure antibody to the hepatitis A virus (anti-HAV), IgM antibody to the hepatitis A virus (IgM anti-HAV), hepatitis A virus (HAV) in the stool, hepatitis B surface antigen (HBsAg) and antibody (anti-HBs), antibody to hepatitis B core antigen (anti-HBc and IgM anti-HBc), and hepatitis B envelope antigen (HBeAg) and antibody (anti-HBe). The knowledge base of HEPAXPERT-I contains 13 IF–THEN rules for hepatitis A and 106 IF–THEN rules for hepatitis B serology. Formally, knowledge acquisition was done by forming a partition of each of the two sets of possible serologic finding patterns that contain patterns of serologic test results, 64 for hepatitis A and 4096 for hepatitis B, respectively. After entering an input pattern of serologic test results in HEPAXPERT-I, a rule pattern matching algorithm based on indexing is internally employed as efficient access method for providing the respective interpretive text. Since 1 September 1989, HEPAXPERT-I has been routinely applied at the Hepatitis Serology Laboratory of the 2nd Department of Gastroenterology and Hepatology at the University of Vienna Medical School (Vienna General Hospital). Beforehand, a retrospective evaluation of the expert system based on 23 368 hepatitis A and 24 071 hepatitis B serology requests was carried out.

Keywords: Medical expert system; Laboratory interpretive system; Hepatitis A and B serology; HEPAXPERT-I

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1. Introduction

Analyzing recent developments in medical computer science and medical artificial intelligence, we largely find agreement that the development of laboratory diagnostic and interpretive systems will lead to clinically useful computer applications that can be applied routinely in laboratories and hospital care [5,6,22]. It is expected that such systems will improve patient care.

Automated hepatitis serologic test interpretation has many of the characteristics of an optimal application domain for clinically acceptable decision tools as are given by Shortliffe and Clancey [31, Chapter 21]. First, there is a demonstrated need for help in the domain and a recognized need for help by the physicians themselves. Second, hepatitis serologic interpretation has a core of knowledge that can be made explicit by a hepatology expert. Third, the domain itself provides a straightforward mechanism for introducing such a system into the daily routine because it can be applied directly in the laboratory performing the tests. And fourth, the computer system maintains the physician's role of the ultimate decision maker because it "only" analyzes and interprets serologic findings and does not attempt to make a final clinical decision.

This paper describes HEPAXPERT-I, a routinely-used expert system for interpretive analysis of single and complex patterns of hepatitis A and B serologic findings. Preliminary descriptions of the HEPAXPERT-I program had been published [1,15]. This paper reports in detail on the medical background of hepatitis A and B serologic testing, the clinical aim of HEPAXPERT-I, the knowledge acquisition process, the knowledge representation scheme, and on some implementation details as well. Moreover, it describes the finally obtained knowledge base for hepatitis A and B serologic test interpretation, the HEPAXPERT-I program package, and the retrospective evaluation study carried out before admitting HEPAXPERT-I to routine usage. Finally, it briefly reports on the present routine application of HEPAXPERT-I at the Hepatitis Serology Laboratory of the 2nd Department for Gastroenterology and Hepatology of the University of Vienna Medical School (Vienna General Hospital).

2. Medical fundamentals

The constellations of serologic parameters which may occur in the course of hepatitis A or B virus infections can be manifold and complex. On the basis of the medical literature [3,7,9,13,19,23,32], a large variety of possible courses of hepatitis A and B virus infections were studied and made explicit for subsequent computer analysis. These courses were then taken as the basis for establishing a complete set of interpretations of all possible constellations of hepatitis A and B serologic findings. The following courses of hepatitis A and B infections were considered: the natural course of hepatitis A infection and possible passive immunization against hepatitis A, four acute and four chronic courses of hepatitis B infections as well as combinations of these courses and, in addition, possible active or passive

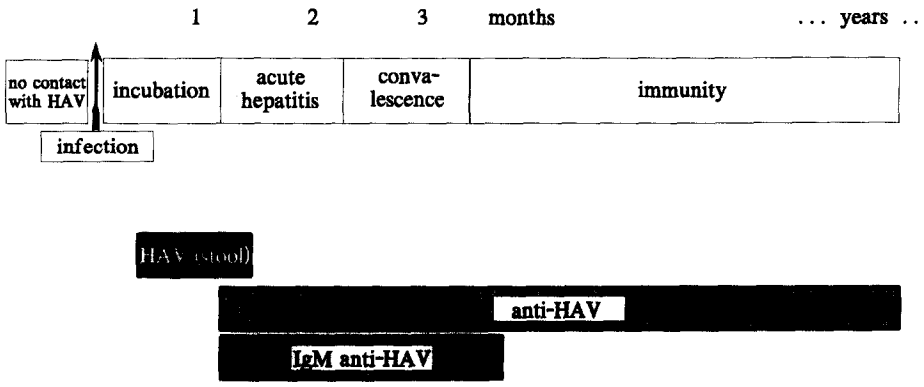

Fig. 1. Typical sequence of immunological events in the course of a natural hepatitis A virus infection.

immunization against hepatitis B. The respective sequences of immunological events in these various courses are discussed in more detail in the following sections.

2.1. Hepatitis A serology

The typical sequence of immunological events in the course of a natural hepatitis A virus infection is shown in Fig. 1.

The incubation period of hepatitis A is short, lasting usually from 2 to 16 weeks. Acute hepatitis A, which may proceed as an icteric or anicteric illness or as a subclinical disease, generally lasts from 2 to 12 weeks. In a protracted form it may persist up to a maximum of about one year, but chronic courses or permanent carriers of the virus are unknown. The patient's stool is already infectious during the incubation period and for about 2 weeks following the onset of the acute disease. Fecal excretion of HAV lasts for a period of 1 to 8 weeks in total. Examinations of the feces for HAV antigen, however, are not easily practicable and for this reason are carried out only rarely. IgM anti-HAV antibody is detectable immediately after the onset of the disease; it is characteristic of acute hepatitis A. The IgM anti-HAV antibody can persist for some months beyond the stages of illness and convalescence, which detracts somewhat from its diagnostic significance. Anti-HAV antibody of the IgG class is usually identifiable for the whole of a patient's life upon restitution following the acute disease and thus characteristic of immunity to the hepatitis virus A. It cannot be serologically differentiated from anti-HAV antibody injected for passive immunization.

2.2. Hepatitis B serology

2.2.1. Acute hepatitis B infection

Four typical sequences of immunological events in the course of an acute hepatitis B infection are depicted in Fig. 2.

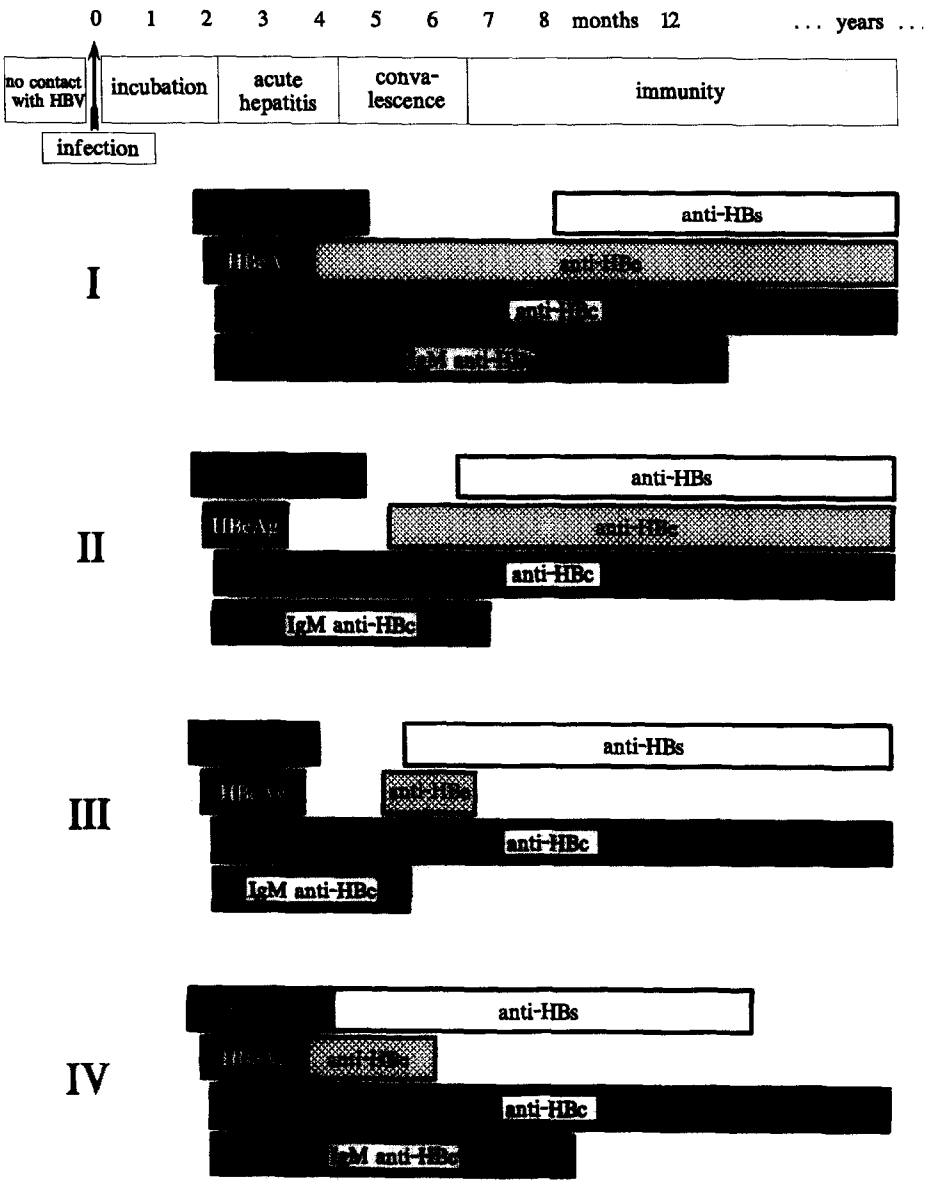

Fig. 2. Four typical sequences of immunological events in the course of an acute hepatitis B infection.

The incubation period of hepatitis B usually lasts from 2 to 4 months, although it may be very short (10 days) or extremely long (9 months). Yet before the outbreak of the acute disease HBs- and HBe-antigen is detectable in the patient's serum. The onset of acute hepatitis B is characterized by the occurrence of

anti-HBc antibody which belongs at first exclusively to the IgM class. From this time on, anti-HBc antibody will be detectable in the patient's serum for the rest of his/her life, no matter whether there is an acute hepatitis B, a form of persisting virus infection, or naturally acquired immunity to HBV without clinical disease. The IgM anti-HBc antibody is detectable not only during acute hepatitis, but sometimes also for considerable lengths of time into the stage of immunity, and furthermore in many phases of chronic hepatitis B virus infection, so that unfortunately the qualitative identification of IgM anti-HBc alone is not sufficient for diagnosing acute hepatitis B. If the disease proceeds without any complications, seroconversion of HBe-antigen will occur within a period of 10 weeks, with anti-HBe antibody appearing in the serum some time after (sequences II and III) or simultaneously with (sequences I and IV) the disappearance of HBe-antigen. Seroconversion of HBs-antigen to anti-HBs antibody follows this event within a period of 6 months after the onset of the disease. In this process we usually find a "window-stage" of several weeks to several months' duration, in which HBsAg is no longer and anti-HBs antibody is not yet detectable (sequences I, II, and III). In some cases the HBeAg and/or HBsAg seroconversions will proceed without any window-stage, so that one serum sample may contain both HBe-antigen and anti-HBe — and/or HBs-antigen and anti-HBs — simultaneously (sequence IV). Anti-HBs and anti-HBe antibodies — together with anti-HBc antibody — can persist for the whole of a patient's life after recovery from acute hepatitis and will be characteristic of the stage of immunity (sequences I and II). In most cases, however, the anti-HBe antibody is less long-lived, and, after years, the anti-HBs antibody may also drop below the level where identification is possible (sequences III and IV). Injection of hepatitis B hyperimmune globulin results in a transitory, active hepatitis B vaccination in a lasting level of anti-HBs antibody in the serum.

2.2.2. Chronic courses of hepatitis B infections

Fig. 3 shows four typical immunological events in the chronic course of hepatitis B infections.

The most significant event indicating a chronic course of hepatitis B is the absence of the HBsAg/anti-HBs seroconversion. If this phenomenon has not occurred within 6 months after the onset of the disease, persistence of the hepatitis B virus infection and the related clinical pictures (asymptomatic HBsAg carrier, chronic hepatitis, cirrhosis, or hepatoma) have to be reckoned with. In the least favorable form of the disease, HBe-antigen and IgM anti-HBc antibody will be detectable in the patient's serum for several years (sequence I). Although the HBeAg/anti-HBe seroconversion is a favorable prognostic sign, even anti-HBe-positive chronic hepatitis may take a severe course (sequence II). If the HBe-antigen phase is relatively short, we will mostly be confronted with the picture of an asymptomatic carrier, in which finally — in the stage of inapparent virus persistence — even HBsAg will no longer be detectable (sequence III). The disappearance of HBe-antigen does not always signal a favorable course of the disease; after a short period of anti-HBe-positive results HBeAg may reoccur and the disease be reactivated (sequence IV).

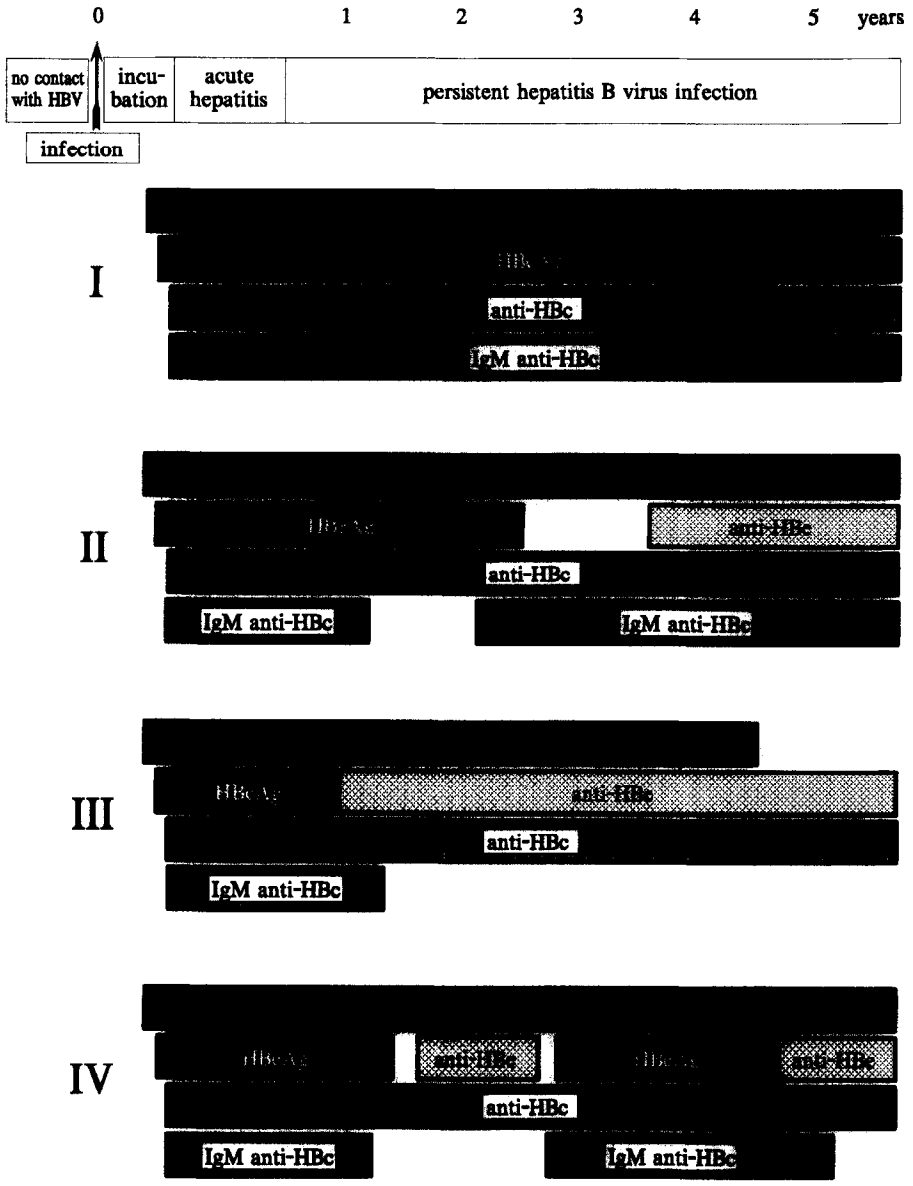

Fig. 3. Four typical sequences of immunological events in the chronic course of a hepatitis B infection.

3. Methods

3.1. General considerations

From the beginning of this project, it was our intention to base the interpretations of the findings solely on routinely performed serologic hepatitis testing, i.e.,

the interpretation should be established without consideration of any additional history data of the patient and without any other biochemical or clinical data. This stands in contrast to the approaches to automated hepatitis serology diagnosis as described in [14,29,30], which use several additional parameters (sex, type of onset of disease, SGPT value, presence or absence of toxic or mechanical liver damage, presence or absence of immunodeficiency, etc.). These additional parameters, however, are usually not available at the laboratory where the serologic tests are being made. We felt that the restriction to those tests that are directly available in the laboratory would be most appropriate for bringing the system into routine laboratory usage.

Furthermore, clinical suspicion of hepatitis infection was not supposed to be a prerequisite for application of HEPAXPERT-I. It should solely interpret the serologic findings obtained, without any prior knowledge on the patient or person from whom the blood sample was taken. Thus not only clinical laboratories, hospital wards and departments, physicians in the hospital or private office but also vaccination institutions, transplantation centres, and blood banks can apply this system in a useful manner because HEPAXPERT-I's serologic test interpretation has universal validity and is not confined to clinical cases of suspected hepatitis alone.

As a result of these considerations, the starting point for automated interpretation of hepatitis serologic findings is qualitative results of the routinely ordered hepatitis A and B antigen and antibody tests (gained by enzyme immunoassays). For hepatitis A serology, the relevant tests are the following: total antibody (anti-HAV), antibody of the IgM fraction (IgM anti-HAV), and detection of hepatitis A virus in stool (HAV), though the latter is rarely ordered and thus a test result is often not available. For hepatitis B serology, the tests are: surface antigen (HBsAg), anti-surface antibody (anti-HBs), anti-core total antibody (anti-HBc), anti-core antibody of the IgM fraction (IgM anti-HBc), envelope antigen (HBeAg), and anti-envelope antibody (anti-HBe). Each of the tests for hepatitis A and B antigens and antibodies can have one of four possible qualitative results: "positive", "negative", "borderline", and "not tested". The following symbols may be used for these results (in the above sequence): "+", "−", "±", and "•".

A further consideration was that the automated interpretation should be based on *one* given pattern of serologic findings only, usually on the pattern of serologic findings most recently issued. Additional consideration of formerly obtained serologic test results would often make the interpretation more specific; however, this will be a subsequent task and is not part of the HEPAXPERT-I system described here. It should be noted that the approaches to automated hepatitis serology diagnosis described in [14,29,30] try to consider the course of time of a viral hepatitis infection. As these programs are either experimental in nature or still in the test stage, a sound evaluation of the different methods applied cannot be presented here.

As a consequence of the above-mentioned considerations — together with some rather obvious requirements such as "the computerized interpretation process should be very 'fast'" and "the knowledge base should be 'clear' and 'easy' to modify" — two methodological approaches to acquire and represent medical

knowledge on hepatitis A and B serologic findings and to apply that knowledge to given test results in an optimal manner were formulated:

- Exhaustive covering of the problem space;
- One-step interpretation process.

First, the system should be able to completely analyze and interpret *any* possibly occurring pattern of serologic findings, even if it occurs extremely rarely, or is contradictory in nature, or consists of nothing but borderline results with insufficient information. Clinically relevant findings, however, should be analyzed and interpreted in detail, including *possible virus exposure, immunity, stage of illness, prognosis,* and *infectiousness*. To determine the number of possible combinations of a given set of findings, combinatorics tells us that a total of m^n combinations has to be considered if m denotes the number of possible results for each test and n stands for the number of tests to be included in our interpretation. Applied to our task, the number of tests is three for hepatitis A serology (anti-HAV, IgM anti-HAV, and HAV in the stool); and six for hepatitis B serology (HBsAg, anti-HBs, anti-HBc, IgM anti-HBc, HBeAg, and anti-HBe). We thus had to create a set of interpretations completely covering the total of 64 ($= 4^3$) patterns for hepatitis A and that of 4096 ($= 4^6$) patterns for hepatitis B serology.

Second, it was expected that *several* patterns of findings can be comprised under *one* interpretation. The interpretive texts should reflect abstracted conclusions of immunological events identifying the possible pathological process in the patient. The level of abstraction (cf., [27, Chapter 17]) should be kept low to achieve: (a) high clearness of the knowledge base; and (b) maximal efficiency of the interpretation process. Soon it turned out that one-level abstraction from findings to interpretations which could be implemented as a one-step interpretation process based on a simple yet efficient rule pattern matching algorithm based on indexing (cf., [4, Chapter 1]; [26, Chapter-3]) was sufficient — although not easily achievable — to build the knowledge base for HEPAXPERT-I.

3.2. Knowledge acquisition

The knowledge acquisition process for HEPAXPERT-I consisted of two essential tasks: (a) the determination of those serologic finding patterns that demand the same interpretive text: this includes the problem of how many different interpretations should be provided; and (b) the formulation of the interpretive texts themselves.

The determination of those different finding patterns that allow identical interpretations was done step by step. By selecting those test results which clearly determine the clinical interpretation, groups of finding patterns could be established that all demand the same interpretive text. As can be seen from Tables 1 and 2, the final result of the knowledge acquisition process consisted in the determination of 17 groups of findings with 13 different interpretations for hepatitis A serology and of 124 groups of findings with 106 different interpretations for hepatitis B serology. The number of groups of findings that had to be established was absolutely unknown at the beginning of the project. It oscillated

Table 1
The complete 17 groups of finding patterns for hepatitis A serologic test interpretation

Group number	Group name	anti-HAV				IgM anti-HAV				HAV (stool)				Inconsistent findings	Rule number
1	AGN				•				•				•	no	1
2	AGU1			±				±	•			±	•	no	2
3	AGU2				•			±				±	•	no	2
4	AGU3				•				•			±		no	2
5	AGI1		−	±		+				+	−	±	•	yes	3
6	AGI2	+					−			+				yes	4
7	AGR1		−				−	±	•		−	±	•	no	5
8	AGR2			±	•		−				−	±	•	no	6
9	AGR3		−					±	•	+				no	7
10	AGR4		−	±	•		−			+				no	7
11	AGR5	+						±	•	+				no	8
12	AGR6	+			•	+				+				no	8
13	AGR7	+			•	+					−	±	•	no	9
14	AGR8	+					−				−	±	•	no	10
15	AGR9	+						±	•		−	±	•	no	11
16	AGR10			±	•			±	•	+				no	12
17	AGR11			±	•			±	•		−			no	13

AGN: no data,
AGU: insufficient data,
AGI: inconsistent findings,
AGR: clinically relevant findings,
where "+" = "positive", "−" = "negative", "±" = "bordeline", and "•" = "not tested".

over a long period of development of HEPAXPERT-I and was finally fixed at the given numbers.

The tables should be read as follows: The established groups of findings are numbered consecutively (column 1); furthermore, a short term name is attached to each of the groups (column 2). The test results for hepatitis A and B serology are given in columns 3-5 and 3-8, respectively. Several test results in one column of a serologic test are connected by "or"; test results of different tests in one row are connected by "and". A column with "inconsistent findings" indicates whether the respective group of finding patterns contains patterns with mutually contradictory findings. This explicit indication of contradictory findings was necessary to prevent the immediate printout of inconsistent test results by the HEPAXPERT-I program (see Section 4.2.). Columns 7 and 10, respectively, headed by "rule number", indicate the respective IF–THEN rule that was established (see Section 3.3) having as conclusion the interpretive text to be issued if the given serologic finding pattern belongs to the respective group of findings that constitutes the premise of the rule.

To define groups of findings, to test them against each other for overlapping finding patterns, and to determine those finding patterns that had not yet been associated with an interpretive text, a comfortable knowledge acquisition system was developed and applied. Using this system, it was easy to make changes in the definition of groups of findings and/or changes in the interpretive texts themselves.

Table 2
Part of the 124 groups of finding patterns for hepatitis B serologic test interpretation

Group number	Group name	HBsAg			anti-HBs			anti-HBc			IgM anti-HBc			HBeAg			anti-HBe			Inconsistent findings	Rule number
1	BGN			●			●			●			●			●			●	no	1
2	BGU1		±			±	●		±	●		±	●		±	●		±	●	no	2
3	BGU2			●		±			±	●		±	●		±	●		±	●	no	2
4	BGU3			●			●		±			±	●		±	●		±	●	no	2
5	BGU4			●			●			●		±			±	●		±	●	no	2
6	BGU5			●			●			●			●		±			±	●	no	2
7	BGU6			●			●			●			●			●		±		no	2
8	BGI1	+		●	+	−	±	●	−	±	+			+	−	±	●	−	±	●	yes	3
9	BGI2		−	±	+	−	±	●	−	±	+				−	±	●	−	±	●	yes	3
10	BGI3		−	±	+	−	±	●	+		●	+	−	±	●	+			+	−	±	●	yes	4
11	BGI4		−	±	+	−	±	●	−	±		−	±	●	+				−	±	●	yes	4
12	BGI5	+			●	+	−	±	●	−	±		−	±	●	+	−	±	●	+			yes	5
13	BGI6		−	±	+	−	±	●	−	±		−	±	●		−	±	●	+			yes	5
14	BGI7		−	±	+	−	±	●	−	±	+			+					−	±	●	yes	6
15	BGI8	+			●	+	−	±	●	−	±	+			+	−	±	●	+				yes	7
16	BGI9		−	±		+	−	±	●	−	±		+			−	±	●		+			yes	7
17	BGI10		−	±		+	−	±	●	−	±			−	±	●	+			+			yes	8
18	BGI11		−	±		+	−	±	●	−	±	+			+					+			yes	9
19	BGR1		−				±	●		±	●			±	●		−	±	●		±	●	no	10
20	BGR2		−			−				±	●			±	●		−	±	●		±	●	no	11
21	BGR3		−				±	●		±	●			±	●		−	±	●	−			no	12
22	BGR4			±	●		±	●		±	●			±	●		−				±	●	no	13
23	BGR5			±	●		±	●		±	●			±	●			±	●	−			no	14
24	BGR6			±	●		±	●		±	●			±	●		−			−			no	15
25	BGR7			±	●	−				±	●			±	●			±	●	−	±	●	no	16
26	BGR8			±	●	−				±	●			±	●		−			−	±	●	no	17
27	BGR9		−				±	●		±	●		−				−	±	●		±	●	no	18
28	BGR10		−			−				±	●		−				−	±	●		±	●	no	19
⋮	⋮		⋮			⋮			⋮				⋮			⋮			⋮			⋮	⋮	⋮
115	BGR97		−			−		+					−				−	±	●	−			no	99
116	BGR98		−	±	●	+				±	●		−				−	±	●	−	±	●	no	100
117	BGR99		−	±	●	+				±	●			±	●		−	±	●	−	±	●	no	101
118	BGR100		−	±	●	+			−				−	±	●		−	±	●	−	±	●	no	102
119	BGR101+				●	+			−	±			−	±	●	+				−	±	●	no	103
120	BGR102+				●	+			+			●	+	−	±	●	+			+	−	±	●	no	103
121	BGR103+					+			−	±			−				−	±	●	−	±	●	no	104
122	BGR104+					+			+			●		−				−	±	●	+	−	±	●	no	104
123	BGR105+					+			−						±	●		−	±	●	−	±	●	no	105
124	BGR106+					+			+		±	●			±	●			±	●	−			no	106

BGN: no data,
BGU: insufficient data,
BGI: inconsistent findings,
BGR: clinically relevant findings,
where "+" = "positive", "−" = "negative", "±" = "borderline", and "●" = "not tested".

3.3. Knowledge representation

Because of the achieved completeness and disjointedness of the established groups of findings, a formal knowledge representation scheme based on the notion of set partition and equivalence classes was established (cf., [20, Chapter 4]). This scheme allows a clear, simple, and concise representation of the medical knowledge base of HEPAXPERT-I in the form of

IF ⟨set of finding patterns⟩ THEN ⟨interpretive text⟩

rules.

Let $\mathcal{F}$ be — separately for hepatitis A and B serology — the set of all possible serologic finding patterns. The cardinality of $\mathcal{F}$ is given by 64 for hepatitis A and 4096 for hepatitis B serology. Now we select a finding pattern $f_i \in \mathcal{F}$ and look for all those finding patterns $f_j \in \mathcal{F}$ that are equivalent to f_i with respect to their interpretations. By doing so, we apply an equivalence relation $f_i \mathbf{R} f_j$, defined on $\mathcal{F}$, and obtain equivalence classes $\mathcal{F}_k$. The intuitive meaning of **R** is "*finding pattern f_i has the same interpretation as finding pattern f_j*". All equivalence classes $\mathcal{F}_k$ form a partition of the set $\mathcal{F}$, i.e., they form a set of nonempty subsets of $\mathcal{F}$, denoted by $\{\mathcal{F}_1, \mathcal{F}_2, \ldots, \mathcal{F}_k, \ldots, \mathcal{F}_n\}$, so that the union of the $\mathcal{F}_k$s is equal to $\mathcal{F}$ and the intersection of $\mathcal{F}_k$ and $\mathcal{F}_l$ is empty for any distinct k and l. The number n of equivalence classes to be distinguished is one of the main results of the knowledge acquisition process. For HEPAXPERT-I, we established 13 different equivalence classes for hepatitis A and 106 for hepatitis B serology.

Thus the results of the knowledge acquisition process may be reformulated in the following way: (a) *each* equivalence class represents a *set* of serologic finding patterns, viz. those demanding the same interpretation; and (b) *each* finding pattern is associated with *one and only one* interpretive text. With respect to the chosen knowledge representation scheme, each equivalence class and its associated interpretation is represented as one IF–THEN rule where the rule premise is composed of those serologic finding patterns which are contained in the equivalence class, and the rule conclusion consists of the respective interpretive text. Thus we obtained 13 rules for hepatitis A and 106 rules for hepatitis B automated serologic test interpretation.

Fig. 4 and 5 show examples of IF–THEN rules of HEPAXPERT-I for the interpretation of hepatitis A and B serologic findings.

3.4. Implementation of the interpretation process

Given medical knowledge in the form of IF–THEN rules whose premises (a) exhaustively cover the problem space and (b) are mutually exclusive, an efficient rule pattern matching algorithm based on indexing could be developed as a fast access method for selecting the applicable rule that provides the appropriate test interpretation (cf., [26, Chapter 1]; [20, Chapter 3]). By applying this method, any input of serologic test results is mapped directly into a one-dimensional array with pointers to the applicable rule and thus the interpretive text can be selected

Rule 8:

IF

anti-HAV	IgM anti-HAV	HAV (stool)
+	± •	+
+ •	+	+

THEN

Positive evidence of hepatitis viruses A in the stool, in combination with the presence of anti-HAV antibodies in the serum, indicates a recent hepatitis A virus infection. Its picture may be that of acute icteric or anicteric hepatitis or of a subclinical disease. The patient's stool is infectious.

Fig. 4. Example of an IF–THEN rule for the interpretation of hepatitis A serologic findings; rule 8 interprets 4 of the possible 64 finding patterns.

immediately. The important advantage of this approach is that instead of searching through the rules, the current state of the problem, i.e., the obtained outcome of the tests, is directly used as an index into the applicable rule and therefore provides optimal performance of accessing the appropriate interpretive text for any given serologic finding.

Rule 8:

IF

HBsAg	anti-HBs	anti-HBc	IgM anti-HBc	HBeAg	anti-HBe
− ±	+ − ± •	− ±	− ± •	+	+

THEN

The findings are inconsistent in several respects as positive evidence of HBe-antigen would have to be associated with positive evidence of HBs-antigen. If, furthermore, anti-HBe antibodies are present, anti-HBc antibodies would have to be identifiable as well. It is recommended to have new material sent in for testing and/or to consult with the head of the laboratory.

Rule 34:

IF

HBsAg	anti-HBs	anti-HBc	IgM anti-HBc	HBeAg	anti-HBe
+	− ± •	+ •	+	± •	− ± •

THEN

Positive evidence of HBs-antigen in combination with a high titre of IgM anti-HBc antibodies indicates the presence of acute hepatitis B. If the IgM anti-HBc titre is low, there may also be a chronic hepatitis B virus infection (chronic hepatitis, cirrhosis, hepatoma). Blood and secretions (saliva, sperm, breast milk) of such patients are to be regarded as infectious.

Fig. 5. Examples of IF–THEN rules for the interpretation of hepatitis B serologic findings; rule 8 interprets 48 and rule 34 interprets 36 of the possible 4096 finding patterns.

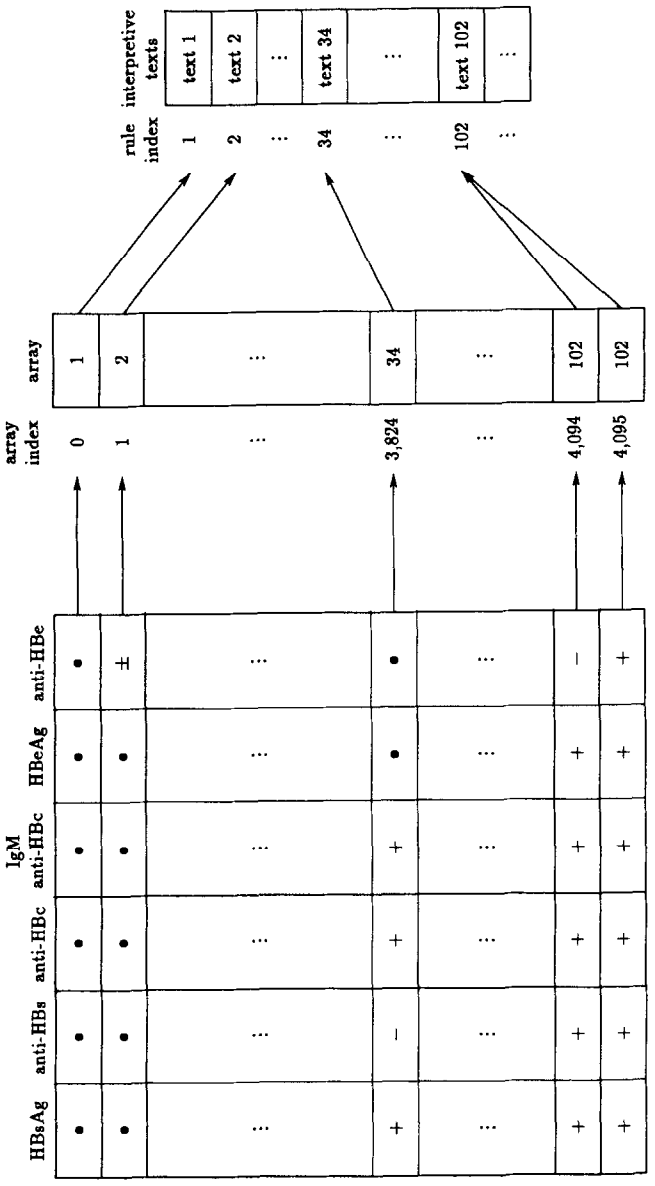

Fig. 6. Implementation of the interpretation process of HEPAXPERT-I as simple rule pattern matching based on indexing.

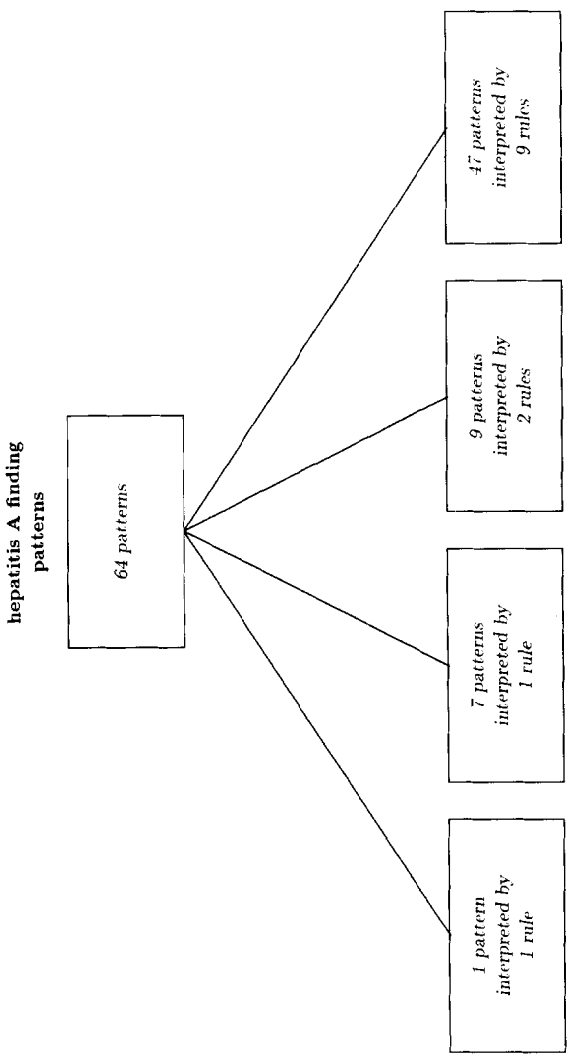

Fig. 7. Survey on the HEPAXPERT-I knowledge base for hepatitis A serologic findings including the categorization of the 64 possible finding patterns into the four natural pattern categories along with the respective number of established rules for interpretation.

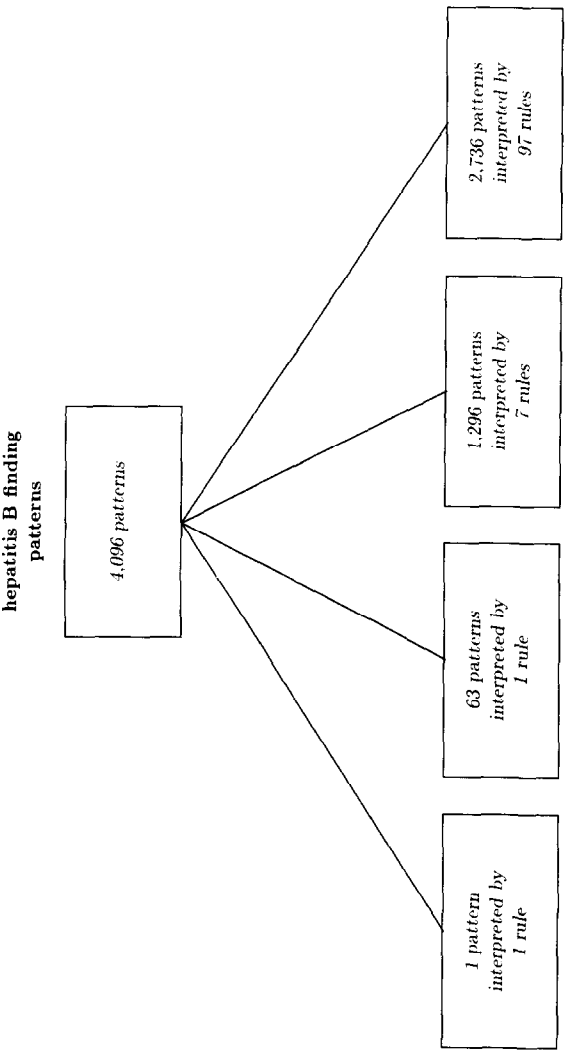

Fig. 8. Survey on the HEPAXPERT-I knowledge base for hepatitis B serologic findings including the categorization of the 4096 possible finding patterns into the four natural pattern categories along with the respective number of established rules for interpretation.

The implemented program is based on the following considerations: Let us define a number system with base 4 where any number is constituted of the quaternary digits 0, 1, 2, 3. These four digits are used to encode the four possible results of the considered serologic tests. We will assign the digits to the test results in the following way: 3 = "positive", 2 = "negative", 1 = "borderline", and 0 = "not tested". Because we deal with three serologic tests for hepatitis A (anti-HAV, IgM anti-HAV, and HAV in the stool) and six tests for hepatitis B (HBsAg, anti-HBs, anti-HBc, IgM anti-HBc, HBeAg, and anti-HBe), we always obtain three-digit sequences for hepatitis A and six-digit sequences for hepatitis B test results. Let us denote these sequences by $(a_1,a_2,a_3)_4$ for hepatitis A and $(b_1,b_2,b_3,b_4,b_5,b_6)_4$ for hepatitis B results. For example, the findings HBsAg = "positive", anti-HBs = "negative", anti-HBc = "positive", IgM anti-HBc = "positive", HBeAg = "not tested", and anti-HBe = "not tested" are encoded by $(323300)_4$.

Given these quaternary numbers in their positional notation we can now calculate their decimal representation. These decimal numbers are then used as indices into a one-dimensional array — this is done separately for hepatitis A and B — that at all index positions contains appropriate pointers to the applicable rules. For indexing hepatitis A rules, the calculation of the polynomial $i = a_1 \cdot 16 + a_2 \cdot 4 + a_3$ yields an index i, $i \in \{0,\ldots,63\}$, into a one-dimensional array of length 64 containing pointers to the appropriate hepatitis A rules. Similarly, by calculating the polynomial $j = b_1 \cdot 1024 + b_2 \cdot 256 + b_3 \cdot 64 + b_4 \cdot 16 + b_5 \cdot 4 + b_6$, we obtain an index j, $j \in \{0,\ldots,4095\}$, into a one-dimensional array of length 4096 containing pointers to the appropriate hepatitis B rules. For example, the sequence $(323300)_4$ yields an index $j = 3824$; the respective index position of the one-dimensional array for hepatitis serology contains rule number 34 whose application provides the correct interpretive text for the given serologic findings (see Rule 34 in Fig. 5). Fig. 6 is intended to illustrate the rule pattern matching process as described above.

The explicit calculation of the two polynomials might be dropped, by using multi-dimensional arrays and initializing them with the respective rule numbers accordingly. We would then need a three- and a six-dimensional array for hepatitis A and B, respectively. However, the calculation of the polynomials stated above was most efficiently done by applying bit shifting. Moreover, not all programming languages allow higher dimensions. (ANS ("standard") FORTRAN, for example, only allows one- to three-dimensional arrays [2].)

3.5. Overview on the HEPAXPERT-I knowledge base

An overview on the obtained knowledge base of HEPAXPERT-I — separate for hepatitis A and B serology — is presented in Figs. 7 and 8. These figures give accounts on the number of rules categorized according to the four natural categories of finding patterns mentioned in Section 3.1. and on the number of finding patterns covered by each of the categories.

3.6. The HEPAXPERT-I program

The HEPAXPERT-I program works in the following way: Serologic results and patient identification data are entered on a standardized screen. If inconsistent finding patterns are entered, the user is informed of the possible incorrectness of the findings before the final results are supplied. It is thus possible to review the findings before they are transmitted to the department that requested them.

As shown in Fig. 9, the reports that the system generates upon request include the name of the laboratory where the test was done, the ward or department in which the results are needed, the patient's identification data (first and last name, maiden name, date of birth, sex, and patient number), the results of the tests, and a detailed analysis of the results, including virus exposure, immunity, stage of illness, prognosis, and infectiousness. The physician providing the specimen for testing has a free choice in requesting individual tests; in addition, the laboratory can issue even findings that are not unambiguously positive or negative, so that it will be possible to interpret incomplete and uncertain results as well as clinically meaningful results.

Information on the laboratory using HEPAXPERT-I (letterhead, name of head of laboratory, etc.) is entered by means of a program, INSTALL, that comes with the HEPAXPERT-I system, and is automatically integrated into each finding report. Another program, TUTOR, teaches new users how to work with HEPAXPERT-I. Technical questions about the use of the system can be answered with the "Help" function. In addition a "Medical fundamentals" function offers information on the fundamentals of the underlying medical theory on which the interpretive decisions of HEPAXPERT-I are based.

3.7. Hard- and software requirements

HEPAXPERT-I was first developed as a prototype system using the expert system shell RULE MASTER 2 [28] and implemented on an IBM compatible PC. This early version is described in [18]. Afterwards, HEPAXPERT-I was completely redesigned and reprogrammed in the programming language C. The implementation details are given in [8]. This version runs under MS-DOS, Version 3.1 or higher on an IBM/PC/XT/AT, a PS/2 system or on any IBM compatible PC hardware with a color graphics or monochrome adapter (CGA, EGA, VGA, HERCULES). The program requires both a 360 KB floppy disk and a hard disk or — as an alternative — a 720 KB or higher storage diskette drive. The minimum RAM storage is 384 KB.

Recently, a mainframe reimplementation of HEPAXPERT-I was completed. HEPAXPERT-I is now also available as CICS transaction under VSE/SP on an IBM 3090 computer. Programming of the software was in PL/I. VSAM files are used to store the HEPAXPERT-I knowledge base. The complete knowledge base can be quickly transferred from the PC to the mainframe by running transfer programs both on the PC side and on the mainframe side. Thus fast update of the HEPAXPERT-I mainframe knowledge base is guaranteed. This version is available to

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HEPATITIS A and B SEROLOGY

sender: Out-patient department, 2nd Gastro

patient: Test Patient Mary born 01/01/1950/f

name at birth: Test Patient ID: 19

date	anti-HAV	IgM anti-HAV	HAV (stool)
09/09/1994	pos		

Antibodies to the hepatitis virus A may occur in three different situations: (a) in the case of a recent hepatitis A virus infection (acute icteric or anicteric hepatitis, subclinical disease, or stage of convalescence from hepatitis), (b) in the case of immunity after an earlier hepatitis A virus infection, or (c) after active vaccination or in the case of passively acquired immunity through injection of gamma globulin.

date	HBsAg	anti-HBs	anti-HBc	IgM anti-HBc	HBeAg	anti-HBe
09/09/1994	pos	pos	neg		neg	neg

The simultaneous occurrence of HBs-antigen and anti-HBs antibodies, with negative anti-HBc antibodies, is a rare event in the natural course of a hepatitis B virus infection. This constellation of findings may be attributed to one of the following causes: (a) circulating HBsAg-anti-HBs immune complexes, (b) hepatitis B virus infection coinciding with a hepatitis B vaccination or injection of HB-hyperimmune globulin, or (c) reinfection with a hepatitis virus B with a different HBsAg subtype. Blood and secretions (saliva, sperm, breast milk) of such patients are to be regarded as infectious.

Vienna, 09/10/1994

W. Horak, M.D. (Head of Laboratory)

Fig. 9. Generated interpretive report of HEPAXPERT-I for a rare pattern of hepatitis B findings.

all medical departments and clinics of Vienna General Hospital which are connected to the medical information system WAMIS [10,11,12,21]. At present, it can be used from more than 260 video display terminals or PS/2 personal computer terminal stations distributed throughout the hospital. The HEPAXPERT-I interpretive reports generated at these terminals can be printed out at the associated printer stations and added to the patient record.

4. Retrospective evaluation of HEPAXPERT-I

In a retrospective study, HEPAXPERT-I was tested with results of hepatitis A and B serologic tests collected by the medical information system WAMIS [10] that runs at the University of Vienna Medical School (Vienna General Hospital). The study was restricted to one laboratory only (Hepatitis Serology Laboratory of the 2nd Department for Gastroenterology and Hepatology). All serologic test results for hepatitis A and B serologic tests were entered into the study obtained between 1977 (when computer recording of test results started in that laboratory) and 31 August 1989 (the day before routine application of HEPAXPERT-I began). This included also serologic findings obtained by radioimmunoassays in former years. In this period, a total of 23368 hepatitis A and 24071 hepatitis B serology requests were issued; the test results obtained were all collected in the central patient data base of WAMIS.

The retrospective study consisted of three steps:

- Analysis and characterization of the hepatitis A and B serologic finding patterns available for evaluation;
- Application of HEPAXPERT-I to all obtained *different* hepatitis A and B finding patterns;
- Evaluation of the generated interpretive reports by the hepatology expert who provided the medical knowledge base of HEPAXPERT-I.

The analysis of the available 23368 finding patterns of hepatitis A serologic tests showed that 'only' 11 *different* finding patterns of a total of 63 possible patterns (the trivial pattern "no data" was eliminated) occurred in this period. This represents a percentage of about 17% among the possible patterns. The most frequent patterns were: (a) a single "positive" anti-HAV test (14360 times); (b) a single "negative" anti-HAV test (8263 times), and (c) a "positive" anti-HAV and a "negative" IgM anti-HAV test (431 times). Rare patterns were all associated with a test for hepatitis A virus in stool (HAV (stool)). Only six times was a "borderline" result (for anti-HAV) determined; a single inconsistent finding pattern with "negative" anti-HAV and "positive" IgM anti-HAV antibodies was found in this set of data.

In a following step, the 11 *different* finding patterns were entered into HEPAXPERT-I and the respective interpretive reports were obtained. By doing so, seven out of the 12 established IF–THEN rules (approximately 58%) were applied. (Rule 1 for the interpretation of "no data" was left out of consideration.) A great disproportionality was noticed with respect to the frequency of application of the different rules. Table 3 gives a survey on how often the respective hepatitis A rules were applied.

The final evaluation of the 11 hepatitis A interpretive reports by the hepatology expert was simple; in all cases the printed interpretive texts reflected the meaning of the given immunological events correctly.

Similarly, the analysis of the available 24071 finding patterns of hepatitis B serologic tests yield a total of 129 *different* finding patterns out of 4095 possible ones (the trivial pattern "no data" was again eliminated). 'Only' a percentage of

Table 3
Retrospective analysis of the frequency of application of the HEPAXPERT-I rules for hepatitis A serologic test interpretation. The given rule numbers may be correlated with the rightmost column in Table 1

Hepatitis A rule number	Frequency of application
rule 11	14360
rule 5	8397
rule 10	432
rule 9	133
rule 6	39
rule 2	6
rule 3	1
7 rules	23368

about 3% among the possible patterns could thus be reached. Some hepatitis B finding patterns occurred extremely often, such as: HBsAg = "negative", anti-HBs = "negative", and anti-HBc = "negative" (14752 times); HBsAg = "negative", anti-HBs = "positive", and anti-HBc = "positive" (3057 times); and HBsAg = "negative", anti-HBs = "positive", and anti-HBc = "negative" (1886 times). These three patterns established a total of approximately 82% of all test results obtained at that laboratory in the given period.

However, 69 *different* finding patterns (more than 53% of the *different* finding patterns found in this test set) occurred only three times or less including some rare patterns such as "positive" tests of HBsAg, anti-HBs, anti-HBc, and HBeAg with "negative" anti-HBe antibody.

Moreover, each of the serologic tests yielded a "borderline" result several times, the total number of "borderline" results being 38.

Furthermore, a total of 19 inconsistent finding patterns were found. Essentially, there were only *two* types of inconsistencies, even though in 11 different combinations: (a) "positive" anti-HBe test with "negative" anti-HBc; and (b) "positive" HBeAg with a "negative" HBsAg test.

In a following step, the obtained 129 *different* finding patterns were entered into HEPAXPERT-I and the respective interpretive reports were analyzed. Sixty-two out of the 105 established hepatitis B rules (approximately 59%) were applied. (Rule 1 interpreting "no data" was again left out of consideration.) Here as well, great disproportionality was noticed concerning the frequency of application of the different rules (see Table 4).

The evaluation of the 129 hepatitis B interpretive reports by the hepatology expert showed that in all cases, HEPAXPERT-I provided the correct interpretation of the given finding patterns. In some cases, retrospective analysis led to some simplifications of HEPAXPERT-I rules.

Those IF–THEN rules for hepatitis A and B serology not triggered by the available laboratory data were not included in this retrospective study. Neverthe-

Table 4
Retrospective analysis of the frequency of application of the HEPAXPERT-I rules for hepatitis B serologic test interpretation. The given rule numbers may be correlated with the rightmost column in Table 2

Hepatitis B rule number	Frequency of application	Hepatitis B rule number	Frequency of application	Hepatitis B rule number	Frequency of application
rule 25	15037	rule 75	21	rule 66	4
rule 94	3202	rule 71	20	rule 89	3
rule 102	1939	rule 11	18	rule 16	3
rule 62	701	rule 43	15	rule 68	3
rule 10	655	rule 78	11	rule 100	2
rule 60	471	rule 101	11	rule 8	2
rule 81	429	rule 53	10	rule 15	2
rule 90	364	rule 4	9	rule 74	1
rule 54	327	rule 80	9	rule 2	1
rule 29	150	rule 5	8	rule 12	1
rule 61	80	rule 19	7	rule 13	1
rule 45	77	rule 34	7	rule 17	1
rule 93	70	rule 63	7	rule 18	1
rule 56	62	rule 99	7	rule 44	1
rule 64	43	rule 30	6	rule 48	1
rule 33	39	rule 55	6	rule 59	1
rule 31	37	rule 58	6	rule 69	1
rule 76	35	rule 36	5	rule 84	1
rule 41	32	rule 72	5	rule 88	1
rule 28	27	rule 21	4	rule 103	1
rule 82	27	rule 49	4		
				62 rules	24071

less, the retrospective evaluation formed a prerequisite for routine application of HEPAXPERT-I, because generally it showed the applicability of the system on the basis of already analyzed cases.

5. Discussion

Automated interpretation of serologic findings of hepatitis A and B by a computer system has been attempted so far — to the best of our knowledge — by the following research groups:

Haux reported in [14] on an experimental program — called EXPERT/VIRUS — an expert system intended to make diagnostic proposals in cases of suspected viral hepatitis. These proposals were primarily provided on the basis of hepatitis serologic findings but also exploited some other clinical and laboratory parameters such as sex and SGPT value of the patient [16]. This experimental program also tried to evaluate the course of a possible viral hepatitis infection. It had been developed by using the expert system shell EXPERT (cf., [33, Chapter 4]).

Another system trying to assist in the interpretation of hepatitis serology was briefly described in [29,30]. Again this system is not only based on serologic findings but also on other clinical and laboratory parameters (acute onset of disease, exclusion of toxic or mechanical liver damage, presence of immunodeficiency, etc.). The duration and time-varying character of the parameters are also taken into account to obtain information on the course of the hepatitis infection. This system had been implemented using the PRO. M.D. shell, a PROLOG program that allows the building of rule-based laboratory expert systems [24]. It was reported in [24] that the application of PRO. M.D. for serologic hepatitis diagnostics comprises about 1200 rules and that it is being verified and validated in a beta test series.

In [25], Pribor describes an application of interpretive reporting of hepatitis diagnostic profiles at a clinical laboratory. He emphasizes the usefulness of microcomputer applications in the laboratory, especially with respect to cost-containment. He concludes that interpretive report writing by computer systems can be extremely rapid, accurate, and economical.

The HEPAXPERT-I system described above has been routinely used at the Hepatitis Serology Laboratory of the 2nd Department for Gastroenterology and Hepatology of the University of Vienna Medical School (Vienna General Hospital) since 1 September 1989. By 15 February 1991 — after 17.5 months of operation — 8505 interpretive reports for 9609 patients were printed and sent out to the departments and private physicians requesting the tests. A first assessment of the impact of HEPAXPERT-I on patient care indicated the following improvements:

- The application of HEPAXPERT-I leads to the avoidance of sending out inconsistent finding patterns as was done several times before HEPAXPERT-I was used routinely.
- Verbal assessment by the physicians requesting serologic tests showed that some of them highly appreciated the availability of extended test interpretations especially in the case of rare patterns of test results. There were no objections by the others.
- Shortly after starting routine operation of HEPAXPERT-I, two transplantation divisions at our hospital extended their requested test patterns after careful analysis of the provided interpretive texts. They noticed that in certain situations the obtained results were not fully conclusive to exclude a hepatitis B infection.

However, an automated system is not free of failure. The most important source of failure in the work with HEPAXPERT-I is an erroneous input of a false positive or false negative serologic test result. This situation may result in the provision of a wrong interpretive text; nevertheless, the clinician is not protected from this type of error either. A second essential source of failure is that the clinical picture deviates from the assumed courses of infection (see Figs. 1–3) which may occur in extraordinary immunological situations [17].

Therefore, in each case, the program's conclusions have to be correlated with the patient's overall clinical picture.

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