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CADIAG: APPROACHES TO COMPUTER-ASSISTED MEDICAL DIAGNOSIS

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Abstract—CADIAG-1 is a medical expert system, based on a symbolic logic representation of medical relationships. Strong relationships such as *confirming, excluding* or *obligatory occurrence* are applied to confirm or exclude diagnoses. Weak relationships are represented by *facultative* and *not confirming* relationships (FN-relationships). Diagnostic hypotheses are established by systematic combination of symptoms showing FN-relationships.

CADIAG-2, a medical expert system based on fuzzy set theory and fuzzy logic, allows detailed specification of medical relationships. Here the diagnostic process also provides confirmed and excluded diagnoses as well as diagnostic hypotheses. Hypotheses are calculated by considering fuzzy relationships between medical entities.

426 cases with rheumatic and 47 cases with pancreatic diseases were tested. For CADIAG-1, the overall accuracy for confirmation and hypothesis generation is calculated with 91.1% for rheumatic diseases and 100% for pancreatic diseases. CADIAG-2 reached an overall accuracy of 93.7% for rheumatic cases and 91.5% for pancreatic cases.

Medical expert system CADIAG-1 CADIAG-2 Medical relationships
Logic Fuzzy sets Rheumatology Pancreatic diseases

1. INTRODUCTION

Medical expert systems draw medical conclusions from patient data by utilizing extended medical knowledge gathered, formalized, and stored in a medical knowledge base. They gain their significance in combining the experience, creativeness, and intuition of a physician with their knowledge-based inferential power.

Medical expert systems take into account an enormous number of diseases that the individual diagnostician cannot simultaneously keep in mind; they can support the physician by displaying rare as well as frequent diseases with the only criterion given that the diagnoses explain the patient's symptom pattern; they can accelerate the diagnostic process by offering proposals for further examinations of the patient in order to confirm or deny diagnostic hypotheses as fast as possible; and they can act as instructional systems for medical students, young physicians, and non-specialists.

The physician examines the patient; he is responsible for the selection of relevant symptoms, signs, test results, findings and their discrimination from unimportant ones; he evaluates symptoms from patient's history and signs of physical and psychological status, and he has to consider that the patient may simulate, dissimulate, aggravate, or diminish; he evaluates lab test results and findings, while being aware that they may be wrong because of technical faults, errors in patient's behaviour before performing the lab tests, or that they may be assigned inadequately to normal or pathological ranges.

Additionally, the physician has to accept an enormous responsibility. For moral and ethical reasons he is undoubtedly fully responsible for the medical decisions that are the outcome of the established man/machine partnership.

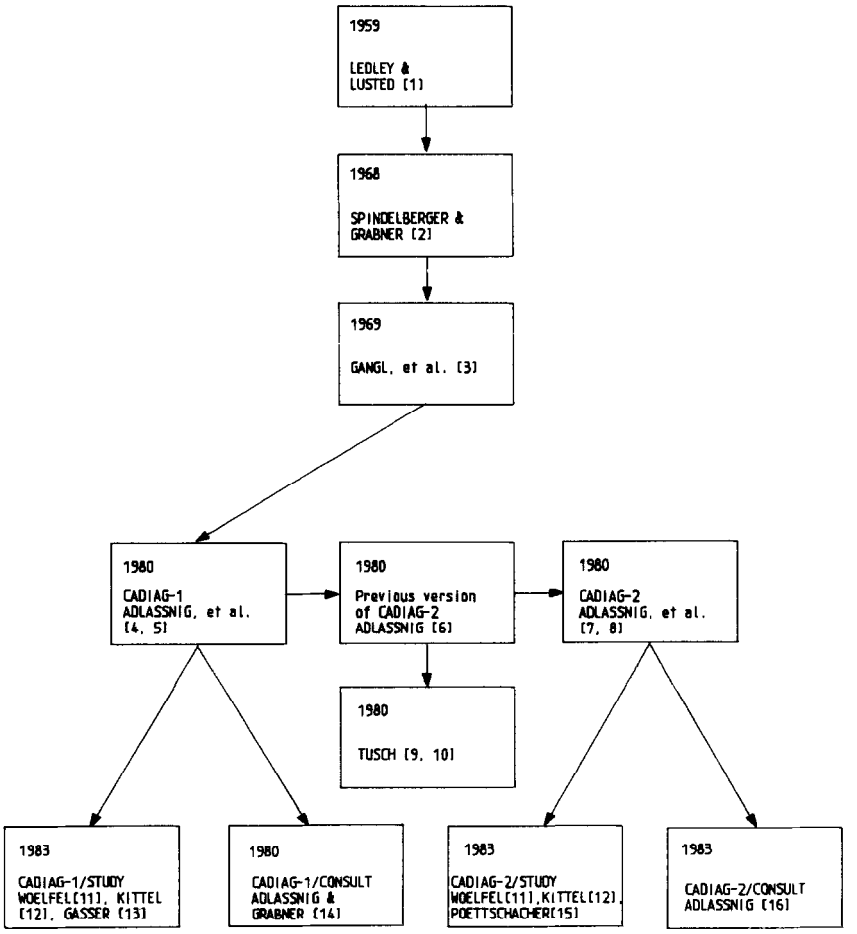

Fig. 1. Line-of-development of CADIAG-1 and CADIAG-2.

CADIAG-1* and CADIAG-2† are the results of intensive collaboration between physicians and computer scientists that has taken place since 1968. Figure 1 presents the line-of-development of these two medical expert systems.

Artificial intelligence methods (see [17–20]) have had a substantial influence on the design of the systems CADIAG-1 and CADIAG-2. Especially the following medical expert systems should be mentioned: CASNET [21, 22], MYCIN [23–25], INTERNIST [26–28], PIP [29], and EXPERT [30, 31].

Further information about medical expert systems are given in excellent surveys by Barr and Feigenbaum [18], Shortliffe, *et al.* [32], Kulikowski [33], Wahlster [34], and Duda and Shortliffe [35].

2. EARLY APPROACH

The concept of symbolic logic introduced to medical diagnosis by Ledley and Lusted in 1959 [1] set the basis for the Boolean logical system developed by Spindelberger and Grabner [2]. This system was intended for internal medicine. It considered two aspects of single symptom‡ disease relationships: (1) necessity of occurrence of a symptom with a disease; (2) sufficiency of occurrence of a symptom for recognizing a disease.

These two aspects were combined and yielded the following six, easy-to-gather, relationships between symptoms and diseases: obligatory and confirming (OC); facultative

* Computer-Assisted DIAGnosis based on symbolic logic.

† Computer-Assisted DIAGnosis based on fuzzy logic.

‡ The term symptom is considered to be synonymous for the terms symptom, sign, lab test, and finding.

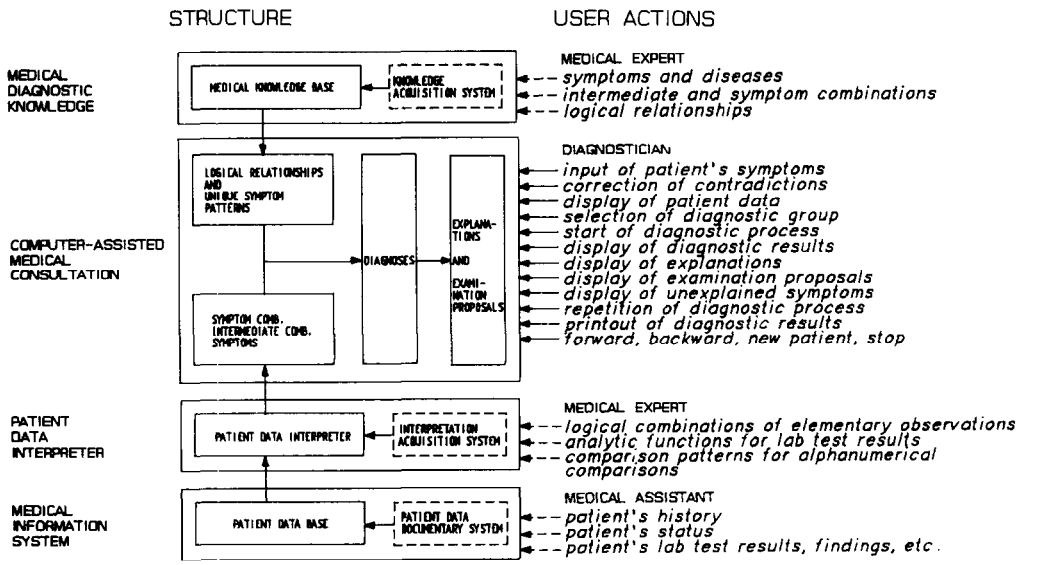

Fig. 2. Structure of CADIAG-1 with connection to a hospital information system (dashed lines mark components effective before starting the individual consultation).

and confirming (FC); obligatory and not confirming (ON); facultative and not confirming (FN); excluding (EX); not known or unspecific (−).

These relationships do not only appear between symptoms and diseases but also between combinations of symptoms and diseases. These combinations were established by using the Boolean connectives of conjunction, disjunction, and negation. Furthermore, the above relationships established among symptoms or among diseases can build up a super–sub relationship scheme for symptoms and a taxonomic scheme for diseases.

Given patient's symptoms, confirmed diagnoses were calculated from present symptoms with confirming relationships. Excluded diagnoses were established from either present symptoms with excluding relationships or absent symptoms with obligatory relationships.

However, definitely confirming, obligatory, or excluding relationships appear relatively seldom in medical science. Knowledge about associations between symptoms and diseases is often uncertain or imprecise. In these cases the physician selected FN-relationships in order to express correlations between symptoms and diseases. These relationships were applied to generate diagnostic hypotheses.

In a preliminary stage, the frequency of FN-relationships to diseases was calculated for every symptom and called degree of ambiguity. The underlying idea was that the lower the degree of ambiguity, the higher the ability of that symptom to discriminate between diseases. Symptoms with a low degree of ambiguity were used to establish unique symptom patterns. They were computed for each disease by systematic combination of five symptoms: those symptoms that show an FN-relationship to the disease in question and have the lowest degrees of ambiguity. At the most, 31 ($2^5 - 1$) unique symptom patterns could be calculated for each disease. If the patient exhibited symptoms that matched unique symptom patterns, unique indications to diseases were provided. These diagnostic indications did not establish strongly confirmed diagnoses, but only diagnostic hypotheses (see also [36]).

Practical applications in hepatology [3, 37] and rheumatology [38] demonstrated the applicability of this method. In [3], Gangl, *et al.* describe an extended hepatological application. The medical knowledge base contained 82 liver diseases, 323 symptoms, signs, lab tests, and findings (patient's history, physical status, laboratory tests, X-ray, histology and biopsy, special tests). By performing 20 test cases, the diagnostic system offered the clinically confirmed diagnoses at least as diagnostic hypotheses.

In [39], Bauer, *et al.* describe an application of the hepatological knowledge base for instructional purposes.

Table 1. Definitions of the logical connectives conjunction, disjunction, and negation for the evaluation of intermediate and symptom combinations in CADIAG-1

	Conjunction				Disjunction				Negation	
$\wedge$	$x_2 = 0$	$x_2 = 1$	$x_2 = -$	$\vee$	$x_2 = 0$	$x_2 = 1$	$x_2 = -$	$\neg$		
$x_1 = 0$	0	0	0	$x_1 = 0$	0	1	-	$x_1 = 0$	1	
$x_1 = 1$	0	1	-	$x_1 = 1$	1	1	1	$x_1 = 1$	0	
$x_1 = -$	0	-	-	$x_1 = -$	-	1	-	$x_1 = -$	-	

3. CADIAG-1

3.1. *Introduction*

Based on the experience gained in the early approach described in the previous section, the diagnostic system was redesigned and named CADIAG-1.

A retrospective study program CADIAG-1/STUDY [11–13] that runs off-line was programmed in PL/1. By performing already diagnosed patients it is used to test the correctness and completeness of the medical knowledge base of CADIAG-1. CADIAG-1/CONSULT [14], based on the same knowledge base but working as an on-line consultation system, was programmed in CICS/VS and PL/1. It is aimed for prospective diagnostic consultation.

The general design of CADIAG-1 is shown in Fig. 2.

During the medical consultation CADIAG-1 has access to a medical knowledge base. The medical diagnostic knowledge has been collected and stored by a knowledge acquisition system.

After starting the consultation process CADIAG-1 offers the physician predefined screens. The physician controls the diagnostic process by his inputs. He can enter patient data into CADIAG-1 or commands for starting the diagnostic process, for displaying diagnostic results, for explaining these results, and for offering proposals for further examinations. CADIAG-1 maintains the actual lists of confirmed and excluded diagnoses, diagnostic hypotheses, and unexplained symptoms.

CADIAG-1 has the ability to work with or without connection to a hospital information system.

In order to acquire patient's symptoms directly, CADIAG-1 can take over symptoms that are put into the system in natural language. The natural language processing algorithm considers synonyms, orthographic variants as well as different flexions of words (see [16]).

If a patient data base of a hospital information system already exists, the automatic transfer of patient data to CADIAG-1 is possible. The transfer is realized by means of a patient data assignment base that includes definitions about the assignment of patient's observations, numerical lab test results, and alphanumerical texts stored in the patient data base to CADIAG-1. The assignments often represent an aggregation of patient data. Patient data collected on a documentary level are concentrated to symptoms on a diagnostic level. But the acting physician has the opportunity to change patient's symptoms on the diagnostic level if there are medical reasons.

The current version of CADIAG-1 has access to the patient data base of the General Vienna Hospital Information System [40, 41].

3.2. *Representation of medical knowledge*

CADIAG-1 considers four medical entities (see also [5, 8, 16]):

symptoms, signs, lab tests, findings (S_i);
diseases, diagnoses (D_j);
intermediate combinations (IC_k);
symptom combinations (SC_l).

Text thesauri contain the appropriate linguistic terms of the medical entities. Each medical entity is named by a preferred term. Synonyms and abbreviations are also stored in

the thesauri in order to provide a broad natural language access to medical entities. A classification number identifies each preferred term.

Every item of information regarded to be relevant for the diagnostic process is considered to be a symptom. Symptoms may be present, absent, or not yet investigated.

Diseases or diagnoses may be present (confirmed), absent (excluded), possible (hypothesis), or not yet considered.

Intermediate combinations have been introduced to model pathophysiological states of the patient. Intermediate combinations are logical combinations of symptoms and/or diseases that act as logical variables. Intermediate combinations can be present, absent, or not yet determinable.

Symptom combinations are logical combinations of symptoms, diseases, and/or intermediate combinations. They are able to confirm or exclude diagnoses. Symptom combinations can also be present, absent, or not yet determinable.

The definitions of the logical connectives for the evaluation of the intermediate combinations and symptom combinations are shown in Table 1, where 0 stands for absent, 1 for present, and –* for not yet evaluated.

CADIAG-1 considers four kinds of relationships:

S_iD_j-relationships;
SC_iD_j-relationships;
S_iS_j-relationships;
D_iD_j-relationships.

The two aspects of relationships already mentioned in section 2 were kept:

obligatory and confirming (OC);
facultative and confirming (FC);
obligatory and not confirming (ON);
facultative and not confirming (FN);
excluding (EX);
not known or unspecific (–).

For SC_iD_j-, S_iS_j-, and D_iD_j-relationships only

OC-relationships;
FC-relationships;
ON-relationships;
EX-relationships;

and "not known or unspecific" are allowed.

Several attempts to formal interpretations of these medical relationships have been made:

IF-THEN-statements [5];
Boolean logical connectives [36];
trivalued logical system of Kleene [5];
semantic network [5];
Boolean matrices [5].

In terms of IF-THEN-statements S_iD_j-relationships are

obligatory and confirming
IF S_i THEN D_j.
and
IF NOT S_i THEN NOT D_j.

facultative and confirming
IF S_i THEN D_j.

obligatory and not confirming
IF NOT S_i THEN NOT D_j.

* – terms the empty set, i.e., symptoms are not yet examined, diseases or diagnoses not yet examined or evaluable. and combinations not yet determinable.

Table 2. Segment of documented symptoms, their relationships and degrees of ambiguity for the rheumatic disease ankylosing spondylitis in CADIAG-1

Ankylosing spondylitis		
Symptoms	Relationships	Degrees of ambiguity
.	.	.
.	.	.
.	.	.
Spine, total, restriction of motion	FN	28
Spine, total, fingertips-to-floor distance > 5 cm	FN	30
Spine, total, respiratory expansion < 4 cm	FN	6
Spine, total, respiratory expansion < 8 cm	FN	6
Spine, cervical, restriction of motion	FN	36
Spine, cervical, tenderness	FN	35
Spine, cervical, hyperlordosis	FN	20
Spine, cervical, decrease of lordosis	FN	18
Spine, thoracic, restriction of motion	FN	31
Spine, thoracic, tenderness	FN	34
Spine, thoracic, hyperkyphosis	FN	18
Spine, thoracic, decrease of kyphosis	FN	16
Spine, lumbar, restriction of motion	FN	37
Spine, lumbar, range of motion according to Schober < 4 cm	FN	13
Spine, lumbar, tenderness	FN	40
Spine, lumbar, hyperlordosis	FN	20
Spine, lumbar, decrease of lordosis	FN	23
Spine, sacroiliac joint, tenderness	FN	10
Spine, sacroiliac joint, Mennell's sign, positive	FN	8
Spine, muscle, tenderness	FN	31
Spine, muscle, paravertebral spasm	FN	30
Spine, muscle, myogelosis	FN	24
.	.	.
.	.	.
.	.	.
X-ray, spine, cervical, restriction of motion	FN	24
X-ray, spine, thoracic, restriction of motion	FN	22
X-ray, spine, calcification of longitudinal ligament	FN	8
X-ray, spine, ankylosis, small vertebral joints	FN	7
X-ray, spine, ankylosis, costotransversal joints	FN	6
X-ray, spine, ankylosis, symphysis	FN	2
.	.	.
.	.	.
.	.	.
X-ray, spine, spondylitis	FN	6
X-ray, spine, arthritis of sacroiliacal joints	FN	8
X-ray, spine, bamboo-spine	FN	5

facultative and not confirming
IF S_i THEN D_j WITH UNSPECIFIED DEGREE x, WHERE $0 < x < 1$.

excluding
IF S_i THEN NOT D_j.

A further formal interpretation of the above-mentioned medical relationships was proposed by Barachini [42]. The relationships are presented in terms of first-order predicate calculus. For S_iD_j-relationships this interpretation yields

$$S_i \text{ OC } D_j \triangleq \forall p[S_i(p) \Leftrightarrow D_j(p)] \wedge \exists p[S_i(p) \wedge D_j(p)]$$

$$S_i \text{ FC } D_j \triangleq \forall p[S_i(p) \Rightarrow D_j(p)] \wedge \neg \forall p[D_j(p) \Rightarrow S_i(p)] \wedge \exists p[S_i(p) \wedge D_j(p)]$$

$$S_i \text{ ON } D_i \triangleq \forall p[D_j(p) \Rightarrow S_i(p)] \wedge \neg \forall p[S_i(p) \Rightarrow D_j(p)] \wedge \exists p[S_i(p) \wedge D_j(p)]$$

$$S_i \text{ FN } D_j \triangleq \neg \forall p[S_i(p) \Rightarrow D_j(p)] \wedge \neg \forall p[D_j(p) \Rightarrow S_i(p)] \wedge \exists p[S_i(p) \wedge D_j(p)]$$

$$S_i \text{ EX } D_j \triangleq \forall p[S_i(p) \Rightarrow \neg D_j(p)] \wedge \exists p[S_i(p) \wedge \neg D_j(p)] \wedge \exists p[D_j(p) \wedge \neg S_i(p)].$$

This interpretation made the medical inference engine KONSDED possible. KONSDED was built primarily in order to check the internal, medical consistency of the knowledge base of CADIAG-1 and secondly to derive possible new medical relationships

Table 3. Unique symptom pattern calculated for ankylosing spondylitis (C = combination)

		C
1	X-ray, spine, bamboo-spine	*
2	Spine, total, respiratory expansion <8 cm	*

from already collected ones. The established inference engine is successful. It is capable of searching valid derivations from given premises. The general form is

$$(\varepsilon_1\ \rho_1\ \varepsilon_2) \wedge (\varepsilon_2\ \rho_2\ \varepsilon_3) \wedge \ldots \wedge (\varepsilon_{n-1}\ \rho_{n-1}\ \varepsilon_n) \overset{?}{\rightarrow} (\varepsilon_1\ \rho_n\ \varepsilon_n)$$

where ε_i stands for a symptom or a disease and ρ_i for any relationship defined in CADIAG-1, i.e. for OC, FC, ON, FN or EX. So far, KONSDED has indicated about 20 inconsistencies in the medical knowledge base (thinking errors and documentation mistakes) and several hundred proposals for new relationships (but only a few dozen of those have been used; the remaining longer part of proposals turned out to be redundant, e.g. the onset in childhood being *obligatory* for juvenile diseases, onset in adulthood is necessarily *excluding* for these diseases).

For generating diagnostic hypotheses, the concept of precalculating unique symptom patterns already explained in Section 2 is applied in an extended form in CADIAG-1. Now not only five symptoms but ten symptoms with the lowest degrees of ambiguity and FN-relationships to the disease in question are used to calculate unique symptom patterns to diseases [at the most 1023 $(2^{10} - 1)$].

Schwarz in [43] did an extended investigation of the usefulness of unique symptom patterns and their applicability generating diagnostic hypotheses. Schwarz found that between 40 and 60% of the calculated symptom patterns were unique for one disease, i.e. that about 500 combinations of the ten selected symptoms turned out to be unique for the disease under consideration. This great number of unique symptom patterns is very suitable for generating hypotheses. But from the physician's point of view, the calculated unique symptom patterns were found to be very arbitrary. Reasons for that are:

(a) incompleteness of medical knowledge considered until now;

(b) difficulties in managing the documentation of diseases that are hierarchically structured [e.g. rheumatoid arthritis (fully documented), Sjögren's disease (partly documented), pancreatitis (not documented), acute and chronic pancreatitis (both fully documented)].

It could also be shown that the larger the number of documented diseases, the smaller the number of unique symptom patterns.

Table 2 shows a segment of the documented symptoms and their relationships to a rheumatic disease and Table 3 a unique symptom pattern for that disease.

3.3. *Diagnostic process*

The diagnostic process of CADIAG-1 is shown in Fig. 3.

Given a certain symptom pattern, confirmed and excluded diagnoses, diagnostic hypotheses, and possible diagnoses are established.

Confirmed diagnoses are obtained if one of the following conditions is true:

symptoms present at the patient with OC- or FC-relationships to diseases;
symptom combinations present at the patient with OC- or FC-relationships to diseases;
already confirmed diseases that are sub-terms of other diseases.

Excluded diagnoses, on the other hand, are received by the following:

symptoms present at the patient with EX-relationships to diseases;
symptom combinations present at the patient with EX-relationships to diseases;
already confirmed diseases with EX-relationships to other diseases;
symptoms absent at the patient with OC- or ON-relationships to diseases;

Table 4. Number of medical entities and medical relationships in the groups of rheumatic (R) and pancreatic (P) diseases in CADIAG-1

Medical entities	R	P
Symptoms	1282	276
Diseases	192	10
Intermediate combinations	63	0
Symptom combinations	39	0
Symptom/disease relationships	**R**	**P**
OC	10	0
FC	63	2
ON	93	0
FN	15788	569
EX	317	0
Symptom combination/disease relationships	**R**	**P**
OC	1	0
FC	18	0
ON	13	0
EX	0	0
Symptom/symptom relationships	**R**	**P**
OC	0	0
FC	139	22
ON	139	22
EX	178	54
Disease/disease relationships	**R**	**P**
OC	0	0
FC	317	0
ON	317	0
EX	1132	0

symptom combinations absent at the patient with OC- or ON-relationships to diseases; already excluded diseases that are super-terms of other diseases.

Diagnostic hypotheses are calculated by means of unique symptom patterns matching symptoms observed on the patient.

Possible diagnoses are made on the basis of preferential symptoms exhibited by the patient and selected as such by the diagnostician. The concept of preferential symptoms gives the physician the opportunity to propagate the diagnostic process in different directions and thus to broaden the diagnostic field. Preferential symptoms generate all diagnoses as possible diagnoses to which they possess FN-relationships. It is advisable to select only symptoms as preferential symptoms which seem to have a certain importance—mostly those showing low degrees of ambiguity.

Unexplained symptoms of the patient under consideration are symptoms having relationships to neither confirmed diagnoses, diagnostic hypotheses nor possible diagnoses. The selection of unexplained symptoms as preferential symptoms generates possible diagnoses and helps the diagnostician to explain all the patient's complaints. The repetition of the diagnostic process with unexplained symptoms offers a second possibility to explain every symptom of the patient.

Extended explanations of the diagnostic results are given to the physician. This makes the diagnostic process comprehensible and supports trust in the computer-generated outcome.

Proposals for a patient's further examination in order to confirm or exclude diagnostic hypotheses or possible diagnoses are offered by CADIAG-1. They allow an iterative diagnostic process and enable the physician to confirm or exclude diagnoses step by step. Thus, it is precisely advised which examinations to perform next. This fact can be seen as an educational tool to optimize the examinations necessary and sufficient to perform.

3.4. *Results*

Until now two different diagnostic groups have been tested in CADIAG-1. The extent of

Table 5. CADIAG-1 results of 426 clinically confirmed rheumatic cases

Clinical diagnosis	Number of cases	Clinical diagnosis compared with CADIAG-1 diagnosis					
		Confirmed	Hypothesis	Possible	Confirmed or hypothesis or possible	Excluded	Not generated
Rheumatoid arthritis	282	229	32	19	280 (99.3%)	0	2
Gout	54	12	13	9	34 (63.0%)	0	20
Ankylosing spondylitis	34	30	1	2	33 (97.0%)	0	1
Psoriatic arthritis	26	0	10	9	19 (73.1%)	5	2
Sjögren's disease	13	7	2	3	12 (92.3%)	0	1
Systemic lupus erythematosus	7	1	1	5	7 (100.0%)	0	0
Reiter's disease	5	0	0	0	0 (0%)	3	2
Scleroderma	5	0	1	2	3 (60.0%)	1	1
Total	426 (100.0%)	279 (65.5%)	60 (14.1%)	49 (11.5%)	388 (91.1%)	9 (2.1%)	29 (6.8%)

Table 6. CADIAG-1 results of 47 clinically confirmed pancreatic cases

Clinical diagnosis	Number of cases	Clinical diagnosis compared with CADIAG-1 diagnosis					
		Confirmed	Hypothesis	Possible	Confirmed or hypothesis or possible	Excluded	Not generated
Pancreatic cancer	22	3	18	1	22 (100.0%)	0	0
Chronic pancreatitis	10	0	9	1	10 (100.0%)	0	0
Acute pancreatitis	5	0	4	1	5 (100.0%)	0	0
Pancreatic pseudocyst and chronic pancreatitis	4	0	4 (both)	0	4 (100.0%)	0	0
Pancreatic pseudocyst and acute pancreatitis	2	0	2 (both)	0	2 (100.0%)	0	0
Zollinger–Ellison syndrome	3	0	3	0	3 (100.0%)	0	0
Insulinoma	1	0	1	0	1 (100.0%)	0	0
Total	47 (100.0%)	3 (6.4%)	41 (87.2%)	3 (6.4%)	47 (100.0%)	0 (0%)	0 (0%)

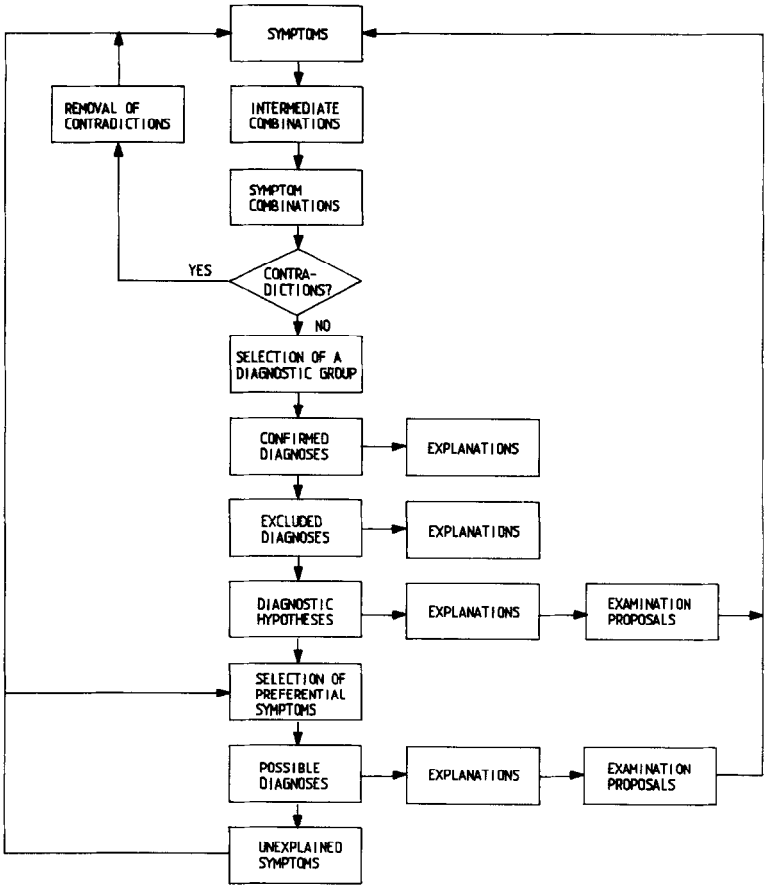

Fig. 3. Diagnostic process of CADIAG-1.

the medical documentation in these two groups is shown in Table 4.

Four hundred and twenty-six cases from a rheumatological hospital were tested. About 800 symptoms, signs, test results, and findings (among them about 100 present and about 700 absent) were available for each case. The results of the 426 cases are shown in Table 5.

Forty-seven cases with pancreatic diseases from a university clinic were tested. About 200 symptoms, signs, test results, and findings (among them about 30 present and 170 absent) were available for each case. The results are shown in Table 6.

Reasons for failure in diagnosing rheumatic diseases with CADIAG-1 were as follows:

(a) some cases do not represent the first hospitalization of the patient but a check-up stay;
(b) histories of therapy that lead to improved clinical patterns and normalized lab test results;
(c) early or stabilized stages of diseases under consideration;
(d) uncertain or incomplete patients' histories;
(e) lack of X-ray documentation;
(f) incomplete consideration of patients' age that often has a strong influence in the differentiation between normal and pathological signs.

4. PREVIOUS VERSION OF CADIAG-2

Assertions about relationships between medical entities often contain terms like almost always, typically, frequently, strong, not always, often, rare, from 40 to 76%, etc. (see [44–47]). In CADIAG-1, these soft relationships are encoded as FN-relationships. By doing this, one avoids problems having their cause in:

(a) figures of relationships not known (medical studies have not yet been carried out or they brought different results);
(b) figures of relationships changing in time (e.g. seasonal changes for influenza, heart disorders, etc.);
(c) figures of relationships changing by place (countries, towns, villages, urban districts and hospitals show often different figures because of different biological, social, and economical circumstances);
(d) co-occurrence of diseases (the usual case in internal medicine) and symptomatic therapy (performing therapeutic actions before establishing the medical diagnosis) changing the symptom pattern of the patient and make the appearances of the nosological textbook descriptions of diseases improbable;
(e) different medical schools having different concepts of diseases.

But, on the other hand, a clear distinction between soft relationships can very often be found. For instance, there is an obvious difference between "high temperature often occurs with acute pancreatitis" and "strongly increased amylase in serum or urine is almost confirming acute pancreatitis", but both assertions are encoded as FN-relationships in CADIAG-1. Naturally, a medical expert values these relationships differently when making his diagnosis.

Starting from this consideration a useful tool to formalize soft expressions was found in the theory of fuzzy sets. Fuzzy set theory developed by Zadeh in 1965 [48] (see also [49, 50]) with its ability of defining inexact medical entities as fuzzy sets, with its linguistic approach [51] providing an excellent approximation to medical texts as well as its power of approximate reasoning [52, 53] seems to be perfectly appropriate for designing and developing medical expert systems.

Reviews of fuzzy approaches to medical decision making are given in [16] and [54].

An early attempt to computer-assisted medical diagnosis using fuzzy set theory that can be considered as a preliminary version of CADIAG-2 was published in [6]. It is based on two relationships between symptoms and diseases already known from CADIAG-1: (1) frequency of occurrence of symptoms with diseases; (2) strength of confirmation of symptoms for diseases.

Frequency of occurrence and strength of confirmation are considered to be linguistic variables (see Bellman and Zadeh [53]). These linguistic variables can take the following linguistic values:

always;
almost always;
very very often;
very often;
rather often;
more or less often;
unknown*;
more or less seldom;
rather seldom;
very seldom;
very very seldom;
almost never;
never.

Single symptom/disease indications can be calculated from the occurrence and confirmation relationships. Examples of fuzzy subsets used to determine single symptom/disease relationships are:

strong
weak.

* Instead of "unknown" as used in [6] "medium" would be more appropriate.

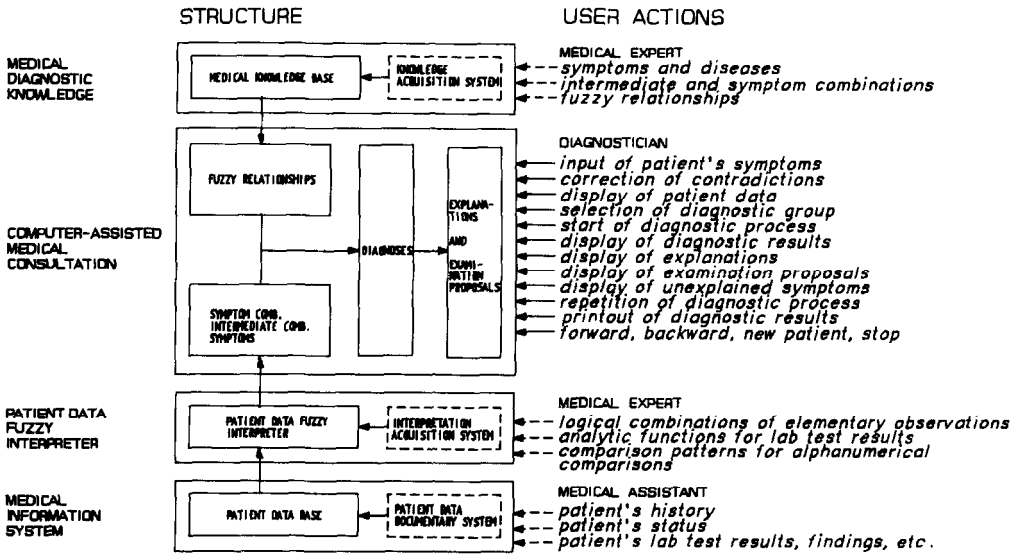

Fig. 4. Structure of CADIAG-2 with connection to a medical information system (dashed lines mark components effective before starting the individual consultation).

Finally one obtains total indications for a disease from the patient's symptom pattern by consolidating the single symptom/disease indications.

Tusch [9, 10] uses this model in a slightly modified form for the cranial computer tomography. The application considers five tumor diagnoses: malignomata, semimalignomata, metastases, malformation tumors and benignomata. Twenty-five symptoms gathered by seven different examinations describe each case: number of foci, structure of foci (native), edemata, localisation of edemata, form and position of ventricles, sulci and cisterns. The symptoms are dichotomous, with "symptom present" and "symptom absent/not investigated" as the two distinct values. Tusch examines different algorithms in order to calculate total indications of the patient's symptom pattern to diseases. The efficiency of the procedures lies between 55 and 76% compared to physicians' diagnoses. Eight hundred and two tumor diagnoses were used to perform this calculation. The symptom/disease occurrence and confirmation relationships have been documented linguistically by a neuroradiologist.

5. CADIAG-2

5.1. *Introduction*

In the final version of CADIAG-2, the compositional rule of inference proposed by Zadeh [52] and introduced in medical diagnosis by Sanchez [55, 56] has been selected to calculate the membership grades of patients to diseases. The relationships between symptoms and diseases are described by occurrence and confirmation values of either linguistic, statistical, or judgmental origin. Furthermore, complex combinations of symptoms that can be evaluated by means of fuzzy logical connectives show relationships to diseases.

The inference mechanism has been embedded both in a retrospective study program CADIAG-2/STUDY [11, 12, 15] and in a prospective consultation program CADIAG-2/CONSULT [16]. CADIAG-2/STUDY was programmed in PL/1 and CADIAG-2/CONSULT in CICS/VS and PL/1. Figure 4 shows the general structure of CADIAG-2.

5.2. *Representation of medical knowledge*

In CADIAG-2, symptoms S_i are not only present or absent. They take their values μ_{S_i} in $[0, 1] \cup -$. The values μ_{S_i} indicate the degrees of membership of symptoms S_i to patients P_q. The essential advantage of this formal approach is the possible representation of borderline symptom values. A detailed interpretation of symptom fuzzy values μ_{S_i} is shown in Table 7.

Table 7. Interpretation of symptom fuzzy values μ_{S_i}

Fuzzy values μ_{S_i}	Interpretation
$0.00 = \mu_{S_i}$	S_i is definitely absent at P_q.
$0.00 < \mu_{S_i} < 1.00$	S_i is partly present at P_q. P_q shows S_i to a certain degree. S_i lies between the normal and pathological range.
$\mu_{S_i} = 1.00$	S_i is definitely present at P_q.
$\mu_{S_i} = -$	S_i has not been examined at P_q yet.

Table 8. Interpretation of disease fuzzy values μ_{D_j}

Fuzzy values μ_{D_j}	Interpretation
$0.00 = \mu_{D_j}$	D_j can definitely not be the cause of P_q's complaints. There are criteria that exclude D_j as diagnosis.
$0.00 < \mu_{D_j} < 1.00$	D_j has to be considered as a possibility to explain P_q's disorders. D_j is regarded as diagnostic hypothesis.
$\mu_{D_j} = 1.00$	D_j is definitely present at P_q. D_j is a confirmed diagnosis.
$\mu_{D_j} = -$	No criterion pro or contra D_j can be found.

Table 9. Interpretation of intermediate combination fuzzy values μ_{IC_k} and symptom combination fuzzy values μ_{SC_l}

Fuzzy values μ_{IC_k} and μ_{SC_l}	Interpretation
$0.00 = \mu_{IC_k}$ or μ_{SC_l}	IC_k or SC_l are definitely not fulfilled at P_q. IC_k or SC_l are absent.
$0.00 < \mu_{IC_k}$ or $\mu_{SC_l} < 1.00$	IC_k or SC_l are partly present at P_q. P_q shows IC_k or SC_l to a certain degree.
μ_{IC_k} or $\mu_{SC_l} = 1.00$	IC_k or SC_l are definitely fulfilled at P_q. IC_k or SC_l are present.
μ_{IC_k} or $\mu_{SC_l} = --$	IC_k or SC_l cannot be determined because of symptoms, diseases, or intermediate combinations not yet examined or determinable.

Table 10. Definitions of the fuzzy logical connectives conjunction, disjunction, and negation for the evaluation of intermediate and symptom combinations in CADIAG-2

	Conjunction			Disjunction			Negation	
$\wedge$	$x_2 \varepsilon [0, 1]$	$x_2 = -$	$\vee$	$x_2 \varepsilon [0, 1]$	$x_2 = -$	$\neg$		
$x_1 \varepsilon [0, 1]$	$\mathrm{MIN}(x_1, x_2)$	-	$x_1 \varepsilon [0, 1]$	$\mathrm{MAX}(x_1, x_2)$	x_1	$x_1 \varepsilon [0, 1]$	$1 - x_1$	
$x_1 = -$	-	-	$x_1 = -$	x_2	-	$x_1 = -$	-	

Table 11. Linguistic fuzzy values and their numerical representatives for frequency of occurrence and strength of confirmation

Frequency of occurrence O		Strength of confirmation C	
Value λ_O	Representative μ_O	Value λ_C	Representative μ_C
Always	1.00	Always	1.00
Almost always	0.99	Almost always	0.99
Very often	0.90	Very strong	0.90
Often	0.75	Strong	0.75
Medium	0.50	Medium	0.50
Seldom	0.25	Weak	0.25
Very seldom	0.10	Very weak	0.10
Almost never	0.01	Almost never	0.01
Never	0.00	Never	0.00

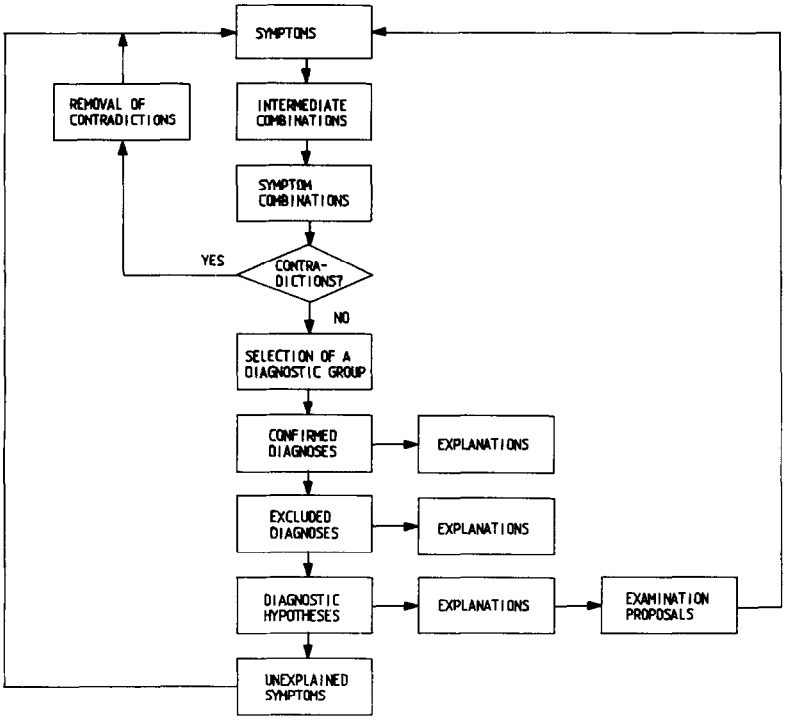

Fig. 5. Diagnostic process of CADIAG-2.

Diseases or diagnoses are treated in a similar way (see Table 8).

Intermediate and symptom combinations can also have fuzzy logical values (see Table 9). They contain symptoms, diseases and, in case of symptom combinations, if necessary, intermediate combinations, as fuzzy logical variables. The appropriate fuzzy logical connectives are presented in Table 10.

As in CADIAG-1, four kinds of relationships are considered:

S_iD_j-relationships;
SC_lD_j-relationships;
S_iS_j-relationships;
D_iD_j-relationships.

Every single relationship is characterized by two aspects: (1) frequency of occurrence (O); (2) strength of confirmation (C).

Interpretation as IF-THEN statements yields relationship rules with associated relationship tupels. The general form is

IF (antecedent) THEN (consequent) WITH (O, C).

The relationship tupels (O, C) contain numerical and/or linguistic fuzzy values (see also [57]) μ_0 and/or λ_0, and/or μ_c and/or λ_c. The linguistic values λ_0 and λ_c cover fuzzy intervals. Reasonable numerical representatives for λ_0 and λ_c were chosen to simplify fuzzy inferences. Table 11 shows the linguistic terms and their numerical representatives to describe the frequency of occurrence and the strength of confirmation of one medical entity for another.

Table 12, analogously to Table 2, shows a segment of documented symptoms and their frequency of occurrence and strength of confirmation to the rheumatic disease ankylosing spondylitis.

5.3. *Diagnostic process*

The diagnostic process of CADIAG-2 is shown in Fig. 5.

Table 12. Segment of documented symptoms and their relationships for the rheumatic disease ankylosing spondylitis in CADIAG-2

Ankylosing spondylitis		
Symptoms	Frequency of occurrence	Strength of confirmation
.	.	.
.	.	.
.	.	.
Spine, total, restriction of motion	0.50	0.20
Spine, total, fingertips-to-floor distance > 5 cm	0.90	0.20
Spine, total, respiratory expansion < 4 cm	0.30	0.80
Spine, total, respiratory expansion < 8 cm	0.50	0.60
Spine, cervical, restriction of motion	0.60	0.20
Spine, cervical, tenderness	0.50	0.20
Spine, cervical, hyperlordosis	0.20	0.10
Spine, cervical, decrease of lordosis	0.30	0.20
Spine, thoracic, restriction of motion	0.30	0.60
Spine, thoracic, tenderness	0.30	0.30
Spine, thoracic, hyperkyphosis	0.30	0.30
Spine, thoracic, decrease of kyphosis	0.20	0.20
Spine, lumbar, restriction of motion	0.80	0.20
Spine, lumbar, range of motion according to Schober < 4 cm	0.40	0.40
Spine, lumbar, tenderness	0.40	0.10
Spine, lumbar, hyperlordosis	0.20	0.10
Spine, lumbar, decrease of lordosis	0.30	0.10
Spine, sacroiliac joint, tenderness	0.30	0.60
Spine, sacroiliac joint, Mennell's sign, positive	0.30	0.80
Spine, muscle, tenderness	0.40	0.20
Spine, muscle, paravertebral spasm	0.40	0.20
Spine, muscle, myogelosis	0.40	0.20
.	.	.
.	.	.
.	.	.
X-ray, spine, cervical, restriction of motion	0.60	0.20
X-ray, spine, thoracic, restriction of motion	0.30	0.50
X-ray, spine, calcification of longitudinal ligament	0.30	0.60
X-ray, spine, ankylosis, small vertebral joints	0.70	0.85
X-ray, spine, ankylosis, costotransversal joints	0.20	0.70
X-ray, spine, ankylosis, symphysis	0.10	0.50
.	.	.
.	.	.
.	.	.
X-ray, spine, spondylitis	0.80	0.80
X-ray, spine, arthritis of sacroiliacal joints	0.95	0.80
X-ray, spine, bamboo-spine	0.20	0.90

After presenting symptoms to CADIAG-2, possible intermediate and symptom combinations present are computed. Detailed checks for contradictions in the presented symptom pattern and the computed patterns of intermediate and symptom combinations are performed. In case of contradictions they can be removed by the physician who works with CADIAG-2. Afterwards, a differential diagnostic group can be chosen.

Then, confirmed diagnoses are determined. The criteria for obtaining confirmed diagnoses are as follows:

symptoms fully present at the patient with always-confirming relationships to diseases;
symptom combinations fully present at the patient with always-confirming relationships to diseases;
already confirmed diseases that are sub-terms of other diseases and therefore have always-confirming relationships to the super-terms.

Excluded diagnoses are received if one of the following criterion is true:

symptoms fully present at the patient with excluding* relationships to diseases;

* "excluding" is interpreted as a relationship "never-occurring" and "never-confirming".

Table 13. Number of medical entities and medical relationships for frequency of occurrence (O) and strength of confirmation (C) in the groups of rheumatic (R) and pancreatic (P) diseases in CADIAG-2

Medical entities	R	P
Symptoms	1282	276
Diseases	192	10
Intermediate combinations	63	0
Symptom combinations	39	0

Symptom/disease relationships	R		P	
	O	C	O	C
Always	103	73	0	2
Almost always	4	0	2	0
Very often or very strong	76	6	57	11
Often or strong	210	16	77	13
Medium	733	125	168	31
Seldom or weak	823	501	97	20
Very seldom or very weak	1158	1374	144	173
Almost never	548	1496	23	195
Never	317	342	0	0

Symptom combination/disease relationships	R		P	
	O	C	O	C
Always	14	19	0	0
Almost always	0	0	0	0
Very often or very strong	0	4	0	0
Often or strong	0	4	0	0
Medium	0	0	0	0
Seldom or weak	0	0	0	0
Very seldom or very weak	0	0	0	0
Almost never	0	0	0	0
Never	0	0	0	0

Symptom/symptom relationships		R	P
O	C		
Always	Always	0	0
Unknown	Always	139	22
Always	Unknown	139	22
Never	Never	178	54

Disease/disease relationships		R	P
O	C		
Always	Always	0	0
Unknown	Always	317	0
Always	Unknown	317	0
Never	Never	1132	0

symptom combinations fully present at the patient with excluding relationships to diseases;

already confirmed diseases with excluding relationships to diseases;

symptoms definitely absent at the patient with always-occurring relationships to diseases;

symptom combinations definitely absent at the patient with always-occurring relationships to diseases;

already excluded diseases that are super-terms of other diseases and therefore have an always-occurring relationship to the sub-terms.

Diagnostic hypotheses are obtained by considering the following criteria:

Fuzzy values μ_{D_j} with $\varepsilon \leqq \mu_{D_j} \leqq 0.99$ where ε is the lower boundary, e.g. 0.10, and μ_{D_j} is calculated by max–min compositions composing

patient's symptom fuzzy values μ_{S_i} and strength of confirmation values μ_c from symptoms S_i to diseases D_j;

Table 14. CADIAG-2 results of 426 clinically confirmed rheumatic cases

Clinical diagnosis	Number of cases	Clinical diagnosis compared with CADIAG-2 diagnosis				
		Confirmed	Hypothesis	Confirmed or hypothesis	Excluded	Not generated
Rheumatoid arthritis	282	224	58	282 (100.0%)	0	0
Gout	54	12	28	40 (74.1%)	0	14
Ankylosing spondylitis	34	30	4	34 (100.0%)	0	0
Psoriatic arthritis	26	0	21	21 (80.8%)	5	0
Sjögren's disease	13	7	6	13 (100.0%)	0	0
Systemic lupus erythematosus	7	1	6	7 (100.0%)	0	0
Reiter's disease	5	0	0	0 (0%)	3	2
Scleroderma	5	0	2	2 (40.0%)	1	2
Total	426 (100.0%)	274 (64.3%)	125 (29.3%)	399 (93.7%)	9 (2.1%)	18 (4.2%)

Table 15. CADIAG-2 results of 47 clinically confirmed pancreatic cases

Clinical diagnosis	Number of cases	Clinical diagnosis compared with CADIAG-2 diagnosis				
		Confirmed	Hypothesis	Confirmed or hypothesis	Excluded	Not generated
Pancreatic cancer	22	3	17	20 (90.1%)	0	2
Chronic pancreatitis	10	0	9	9 (90.0%)	0	1
Acute pancreatitis	5	0	4	4 (80.0%)	0	1
Pancreatic pseudocyst and chronic pancreatitis	4	0	4 (both)	4 (100.0%)	0	0
Pancreatic pseudocyst and acute pancreatitis	2	0	2 (both)	2 (100.0%)	0	0
Zollinger–Ellison syndrome	3	0	3	3 (100.0%)	0	0
Insulinoma	1	0	1	1 (100.0%)	0	0
Total	47 (100.0%)	3 (6.4%)	40 (85.1%)	43 (91.5%)	0 (0%)	4 (8.5%)

patient's symptom combination fuzzy values μ_{SC_i} and strength of confirmation values μ_c from symptom combinations SC_i to diseases D_j;

patient's disease fuzzy values μ_{D_j} and strength of confirmation values μ_c from sub-diseases already established as confirmed diagnosis or diagnostic hypothesis to super-terms.

Unexplained symptoms, detailed explanations of the diagnostic results, and proposals for further examination of the patient are indicated in a way similar to that of CADIAG-1.

An additional feature is built into the explanation procedure of diagnostic hypotheses. Because the value μ_{D_j} calculated by a max–min composition is independent of the number of symptoms or symptom combinations that can be applied for D_j, a heuristic point number is counted that takes into account the number of symptoms or symptom combinations supporting the hypothesis.

5.4. *Results*

The extent of the medical documentation of rheumatic and pancreatic diseases in CADIAG-2 is shown in Table 13.

The rheumatic and pancreatic cases described in section 3.4 were also tested with CADIAG-2. The results are shown in Tables 14 and 15.

Reasons for failure in diagnosing rheumatic diseases are in general the same as mentioned in Section 3.4.

Reasons for failures occurring in diagnostic results for pancreatic diseases are:

(a) difficult differentiation between acute and chronic pancreatitis;
(b) difficult differentiation between acute or chronic pancreatitis and pancreatic cancer.

Essential advantages of CADIAG-2 in contrast to CADIAG-1 are:

(a) the possibility of representing the continuous transition from normal to pathological ranges, which is closer to biological variety than using sharp boundaries;
(b) the detailed description of medical relationships by frequency of occurrence and strength of confirmation;
(c) the extended application of symptom combinations that can have soft relationships to diseases;
(d) the use of a heuristic point number, which plays an important part in reasoning a diagnostic hypothesis (see also [58]).

In general, it can be claimed that CADIAG-2 is quite capable of handling those aspects which are not only strongly characterizing medical knowledge but also real world knowledge such as:

(a) incompleteness of knowledge;
(b) uncertainty of knowledge;
(c) inconsistency of knowledge (see also [59]).

SUMMARY

Since 1968, teamwork between physicians and computer scientists has led to the development of the medical expert systems CADIAG-1 and CADIAG-2. Both systems are general medical expert systems. They are directly connected with the hospital information system of the University of Vienna Medical School.

CADIAG-1 and CADIAG-2 have been successfully tested in rheumatology and gastroenterology with about 470 hospital cases. The overall accuracy for confirmation and hypotheses generation was calculated with about 90%.

The tests are not yet finished because of the extended medical knowledge bases containing about 200 diseases where about 1500 symptoms, signs, test results, and findings are considered.

Special emphasis with establishing CADIAG-1 and CADIAG-2 was given to rare diseases, which the individual physician may not keep in consideration, as well as to detailed reasonings of proposed or excluded diagnoses, low cost plans for further investigations on the patient, and pathological signs not yet explained by the diagnostic results. The results

obtained until now support the opinion that just these facts establish a real aid for the human diagnostician.

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