THE USE OF MICROCOMPUTERS IN OPHTHALMIC DIAGNOSIS AND MANAGEMENT WITH SPECIAL REFERENCE TO DYSTHYROID EYE DISEASE

Volume 1

BY

Mamdouh Hassan Zeini

M.B.BCh.,D.O.M.S.,D.G.S.

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MEMORANDUM

The work described in this thesis is based upon the results of research conducted in the Tennent Institute of Ophthalmology, the Western Infirmary, Glasgow, and the Signal Processing Division of the Electrical and Electronics Department of Strathclyde University, Glasgow, between January, 1986 and May, 1989.

The protocol of the experimental studies was devised by the author, who carried out all the studies apart form those which are appropriately acknowledged either in the acknowledgment overleaf or in the text. Where assistance was provided in the techniques employed, this too is acknowledged.

Supervision was provided by Professor W. S. Foulds and Dr. G. N. Dutton.

The text of this thesis was written solely by the author.

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PREFACE

This thesis reports the first of a two-stage project for the development of an integrated microcomputer-based 'clinic automation system' for which the author has recruited the help of the Electrical and Electronic Department of Strathclyde University. The potential of the application and adaptation of computing techniques in solving clinical problems related to ophthalmic diagnosis and management are investigated.

This thesis is intended to broaden the perspective of clinicians who are interested in Graves' ophthalmopathy, and computer scientists interested in medical computing. The author has endeavoured throughout the thesis to present information related to different disciplines in a manner readily understandable to the reader not well versed in that discipline.

Chapter 1 is written primarily for clinicians who may not be familiar with computers. It provides a simplified introduction to computers and their medical applications.

Chapters 2 and 3 furnish the background knowledge concerning the clinical problem of dysthyroid eye disease.

In Chapter 4 the need for further research in both thyroid ophthalmopathy and medical computing was identified and the objectives of the present study were defined.

The reader will find a detailed account of a long-term study of a series of thyroid ophthalmopathy patients in Chapter 5. Statistical analyses were employed on the collected data appertaining to 'patients' rather than 'orbits' except when comparing the initial and 'final' values of the parameters related to each individual eye (e.g., lid retraction, exophthalmos, visual acuity, intraocular pressure). For such parameters, analysis was applied separately on right and left eye data (no significant statistical difference was found between right and left eyes for those parameters). With regard to clinical parameters such as exophthalmometric reading, expert statistician advice confirmed that, in the context of com-

paring the initial and 'final' values, obtaining control values would not add to the validity of the statistical results and therefore was not required. It is worth noting that Graves' ophthalmopathy, dysthyroid eye disease, thyroid opthalmopathy, Graves' orbitopathy, and thyroid orbitopathy are used interchangeably throughout this thesis.

Detailed descriptions of the development of computer-based systems for testing 'temporal visual acuity' and for automatically digitising and interpreting ophthalmic charts are found in chapters 6 and 7 respectively.

Details of the design and development of a thyroid eye disease expert system are provided in Chapter 8. Testing and validation of this prototype showed that it gives consistent inferences and highly accurate conclusions. This high degree of accuracy resulted from using historical patient data in the evaluation of the performance of the system. This is valid as an indication of the integrity of the programme. However, it is expected that the accuracy will be less on using the system for a different group of patients. This warrants a separate study.

It is hoped that this work will be of interest to ophthalmologists, endocrinologists, and computer scientists.

SUMMARY

The fundamental cause of Graves' ophthalmopathy remains unknown and the optimum management protocol is controversial. This disorder is taken as an example to study some aspects of the use of microcomputer techniques in ophthalmic diagnosis and management.

A simplified introduction on computers and their applications in medicine and a literature review of the pathology, clinical presentations, classifications, patient assessment, and various treatment modalities are presented. The various problem areas and the need for further research to study the long-term effects of thyroid ophthalmopathy were identified. A protocol for the study of examples of the use of microcomputers in assessment of patients, in interpretation of clinical data and in medical decision support systems was devised.

The results of a prospective review of the long-term (mean follow-up time 10 years) effects of thyroid ophthalmopathy in 224 patients, the largest proportion of whom were hyperthyroid at presentation, are presented. Fewer males developed severe ophthalmopathy, but when they did, this tended to occur more rapidly than in females. Patients were grouped into 'mild' and 'severe' categories.

The sensitivity, specificity and predictive value of 25 parameters (at presentation) in making the diagnosis of ophthalmopathy, and in predicting its course were calculated. Risk factors were identified and two linear discriminant analysis equations, based on the combined effect of sets of independent variables, were computed to predict the severity of the disease and the requirement for orbital decompression. The exophthalmometric reading was found to be the most important predictor followed by 'thyroid status', then the magnitude of ocular motility disorder and finally, the time from the onset of thyroid dysfunction to the onset of ophthalmopathy. Based on those four parameters the model gives a 74% correct classification of patients into 'mild' or 'severe' subgroups. The second model, based on 17 parameters, achieves an 81% correct prediction of the necessity for surgical decompression. The results reported emphasise the potential sight threatening nature of thyroid ophthalmopathy and indicate that corneal ulceration can be as serious as optic nerve compression and may warrant orbital decompression especially in the presence of marked proptosis.

Three computer systems were developed. TEMPRAC, a microcomputer-based system for clinical assessment of 'temporal visual acuity' based on Snellen optotypes is described. The most accurately repeatable optotype for normal individuals was 6/9. The test is sensitive in detecting small uncorrected errors of refraction which may not affect the Snellen acuity. 'Temporal acuity' was found to be affected in eyes with retrobulbar neuritis compared with the fellow unaffected eye although each eye can achieve the same Snellen visual acuity. A universal automated chart reading microcomputer system which extracts the plotted information from a range of ophthalmic charts for subsequent scoring and quantification and a novel combination of graphics and image processing algorithms is described.

A disease-specific expert system prototype called TEDEX, which gives advice on the diagnosis and management of thyroid ophthalmopathy, has been developed. The results obtained from the long-term study of dysthyroid eye disease constituted the foundations of the knowledge base for TEDEX.

An overview of the application of artificial intelligence techniques in medicine and representative examples of various approaches of computer-based medical decision aids is provided. A detailed account of building and testing TEDEX prototype is presented to characterise a methodology which led to the achievement of the desired goals in the time available. No standard methodology for designing and building medical expert systems is currently available. Therefore, the methodology presented could be followed in the development of similar systems in other domains. The thesis concludes with successes and limitations of the techniques employed, and an outline of suggestions for future research.

ABBREVIATIONS

AMP	Adenosine monophosphate
CGA	Colour graphics adaptor
Ci	Curies
cm	centimetres
CSR	Central serous retinopathy
EGA	Enhanced graphics adapter
EPS	Exophthalmos-producing substance
KB	Kilobytes
Kg	Kilograms
LATS	Long-acting thyroid stimulator
MB	Megabytes
MHz	Mega Hertz
mm	millimeter
mm. Hg.	millimeters of mercury
msec	milliseconds
PBI	Protein-bound iodine
Rad	Rads
T3	Triiodothyronine
T4	Tetraiodothyronine (Thyroxine)
TBG	Thyroxine-binding globulin
TBPA	Thyroid-binding prealbumin
TEDEX	Thyroid eye disease expert system
TEMPRAC	'Temporal visual acuity' testing system
TRH	Thyrotropine-releasing hormone
TSH	Thyroid-stimulating hormone
STD	Standard deviation

Algorithm

A step-by-step procedure that guarantees a correct outcome. To develop a conventional computer programme, the programmer specifies the algorithm which the programme will follow.

Artificial intelligence

A sub-field of computer science concerned with the concepts and methods of symbolic inference by a computer and the symbolic representation of the knowledge to be used in making inferences. A field aimed at pursuing the possibility that a computer can be made to 'behave' in ways which humans recognise as 'intelligent' behaviour in each other. Artificial intelligence is an academic discipline, not a product, its research aims at improving what computer techniques can offer.

Backtracking

The process of backing up through a sequence of inferences in order to try a different path. Planning problems typically require backtracking strategies which allow a system to try one plan after another until the system finds a path that has no unacceptable outcome.

Breadth-first search

A control strategy that examines all of the rules or objects on the same level of the hierarchy before examining any of the rules or objects at the next lower level.

Certainty

The degree of confidence one has in a fact or relationship. As used in artificial intelligence, this contrasts with probability, which is the likelihood that an event will occur. There are two types of certainty: the certainty that the expert has in a relationship expressed in a particular rule, and the certainty that the user has when he provides information during a consultation.

Confidence factor

A numerical weight given to a fact or relationship to indicate the confidence one has in the fact or relationship. Most rule-based systems use confidence factors rather than probabilities.

Control strategy

The method used by the inference engine to determine the order in which reasoning occurs.

Domain

A subject matter area or problem-solving task. Existing systems only provide 'good' advice when they are used to assist users in solving problems which lie within very narrowly defined domains.

Experiential knowledge

Knowledge gained from hands-on experience. This typically consists of specific facts and rules-of-thumb (surface knowledge). This is in contrast with 'deep knowledge' of formal principles or theories.

Frame

A knowledge representation scheme which associates an object with a collection of features (e.g., facts, rules, values). Each feature is stored in a slot. A frame is the set of slots related to a specific object.

Inference

The process by which new facts are derived from established facts.

Inference engine

Is the portion of an expert system which contains the inference and control strategies. When an inference engine is separated from a knowledge base, it is, in effect, an expert system building tool.

Interface

The link between a computer programme and the outside world. A single programme may have several interfaces.

Knowledge

An integrated collection of facts and relationships which, when exercised, produces competent performance.

Knowledge acquisition

The process of locating, collecting, and refining knowledge. The person undertaking the knowledge acquisition must convert the acquired knowledge into a form which can be used by a computer programme.

Knowledge representation

The method used to encode and store facts and relationships in a knowledge base. Semantic networks, facts, rules, objects, and frames are all methods of knowledge representation.

LISP machines

Are 32-bit computer systems which are used by expert systems developers. They are currently very expensive machines.

Maintenance of an expert system

Unlike conventional computer software which is only infrequently updated, expert systems by their nature are very easy to modify. Most expert systems which are currently in use are constantly being improved by the addition of new rules.

Semantic

Refers to the meaning of an expression. It is often contrasted with syntactic, which refers to the formal pattern of the expression. Computers are good at establishing that the correct syntax is being used; programmers have a great deal of trouble programming them to establish the semantic content of an expression.

Semantic networks

A type of knowledge representation that formalises objects and values as nodes, and connects the nodes with links which indicate the relationship between the various nodes.

Tools

As used in this thesis, tools are computer software packages that simplify the effort involved in building an expert system.

Uncertainty

In the context of expert systems, uncertainty refers to a value which cannot be determined during consultation. Most expert systems allow the user to indicate that he does not know the answer. In this case the system uses its other rules to try to establish the value by other means or relies on default values.

PART I.

GENERAL INTRODUCTION

CHAPTER 1.

THE COMPUTER

1.1. INTRODUCTION:

Computers and microprocessors are used in virtually every aspect of modern medicine. In General Practice, computerisation of patients' notes promises to revolutionise the delivery of health care, especially with regard to preventive medicine. By applying computer techniques to medical decision making it is possible to improve diagnostic and therapeutic accuracy, with improved cost efficiency as an added advantage. The development of expert systems has also advanced our understanding of the nature of medical knowledge and of the decision-making process itself. A wide range of medical databases is now accessible to any doctor equipped with a personal computer and a modem link to the telephone network. Powerful new non-invasive diagnostic instruments, including CT scanners, MRI, and ultrasonic imaging, are based on computers. Computers are used widely in medical research, both for the acquisition and analysis of data. Computerisation has greatly increased the efficiency and the scope of clinical laboratory procedures and advanced analytical instruments. The interpretation of diagnostic tests like the ECG, and monitoring of patients in intensive care have also been improved by careful application of computer technology.

Detailed discussions of certain areas of medicine, where computers have either been shown to be of value in the past or promise as such for the future, are found in the comprehensive reviews by Norris *et al.* (1985), Ellis (1987) and Chard (1988).

1.2. COMPUTER TECHNOLOGY:

The foundations of modern computing were established by the work of Allan Turing in the 1930s, and John von Neumann in the 1940s. Turing presented an abstract design of a computer that could solve any problem provided that it was presented in the form of a series of symbols on an infinite strip of paper tape. Von Neumann on the other hand, suggested a more practical way of constructing a computer, and proposed the idea of an electronic computer controlled by a series of instructions, the 'programme'. This important identification of two separate components - the computer (the 'hardware') and the programme (the 'software') - currently forms the fundamental basis of computer design.

Early computers were room-sized, expensive to operate, and generated a large amount of heat because their logic circuits were constructed exclusively from thermionic valves. In 1948 a further practical step in the development of modern computers was taken by the invention of the transistor. The transistor is small, reliable, and uses comparatively little power (Garetz, 1985).

In 1959, a further advance was made when it became possible to put more than one transistor on the same substrate material (i.e. an integrated circuit, or IC). By 1980, 100,000 transistors occupied the same area previously taken up by one transistor. Since computing power is largely determined by the number of logical operations performed in a given time span, the more transistors available to act as logic components the greater the intrinsic computing power of a chip (Meindl *et al.*, 1981).

Chip technology progressed to the development of IC in which transistors and other components were combined in a single package. Such chips became the backbone of most logic circuits in the large mainframe computers produced in the 1960s. In 1971, the Intel 4004 chip, measuring a few centimeters square was introduced into the semiconductor market. The 4004 chip changed the tradition, by providing 1,900 transistors-worth of data processing capability in a single chip (Garetz, 1985).

Since the early 1970s, the development of microprocessors and related chips has rapidly progressed. The capacity of microprocessors to perform calculations quickly, accurately and cheaply has led to their incorporation in a host of equipment designed where some degree of data processing is required for consumer use. The same qualities of the microprocessor have led to its increasingly diverse application in medicine. Indeed, developments in chip technology have largely determined the growth of certain diagnostic areas. For example, without the computing power of advanced microprocessors the CT scanner would take far too long to perform the mathematical calculations needed to reconstruct tomographic images.

1.2.1. Limitations:

There are limits to the number of transistors that can be packed into a given space in order to produce greater computing power. Close packing also leads to increased heat production.

Von Neumann's system of computing based on a series of programmed instructions is impractical for multiple calculations. For example a single fourth generation CT image requires 10^9 calculations . A single programme would take many hours. Parallel processing in which multiple portions of a complex programme are simultaneously handled has therefore been developed, thus dramatically shortened the processing time to minutes or seconds.

At present microprocessor technology is more than adequate for the majority of tasks in medicine, whether this be non-specialist applications like word processing and accounting, or in the specialised areas such as general practice computing systems for diagnosis and patient management.

1.3. THE HARDWARE:

Current microcomputers are characterised by their flexibility and wide range of input and output. Sources of data can be as diverse as the electrical signal coming from ECG leads, the characters typed on a keyboard, the probabilities from a disease database, the intensity levels from a digitised X-ray film or the signals from a fœtal monitor. The output of data processing can be equally varied (e.g. the display of a text on a monitor screen, the adjustment of a valve to alter a drug infusion rate, or the sounding of an alarm to warn staff of a patient in asystole).

The microprocessor comprises digital logic circuits which operate on the basis of binary arithmetic. The digits 0 and 1 are termed binary digits or 'bits'. Data is communicated in 'bytes' which consist of eight 'bits' each.

The first affordable personal computer which appeared in the 1970s required the user to both enter data and read results in terms of these row binary

values, but market pressures soon led to the development of more user friendly machines with keyboard entry systems.

A programme is a sequential list of instructions. This list has to be sorted in a form which is readily accessible to the processor. This element of computer hardware is called 'memory'. Memory ICs are capable of storing many thousands of bytes of data in a complex array of microscopic, bit-sized memory 'cells' where an empty cells denotes the value '0' and a full cell equals '1'. Memory is also required for storing the data received from inputs until the processor is ready to make use of it. Similarly, data from the processor is often stored in memory before being sent to a display device.

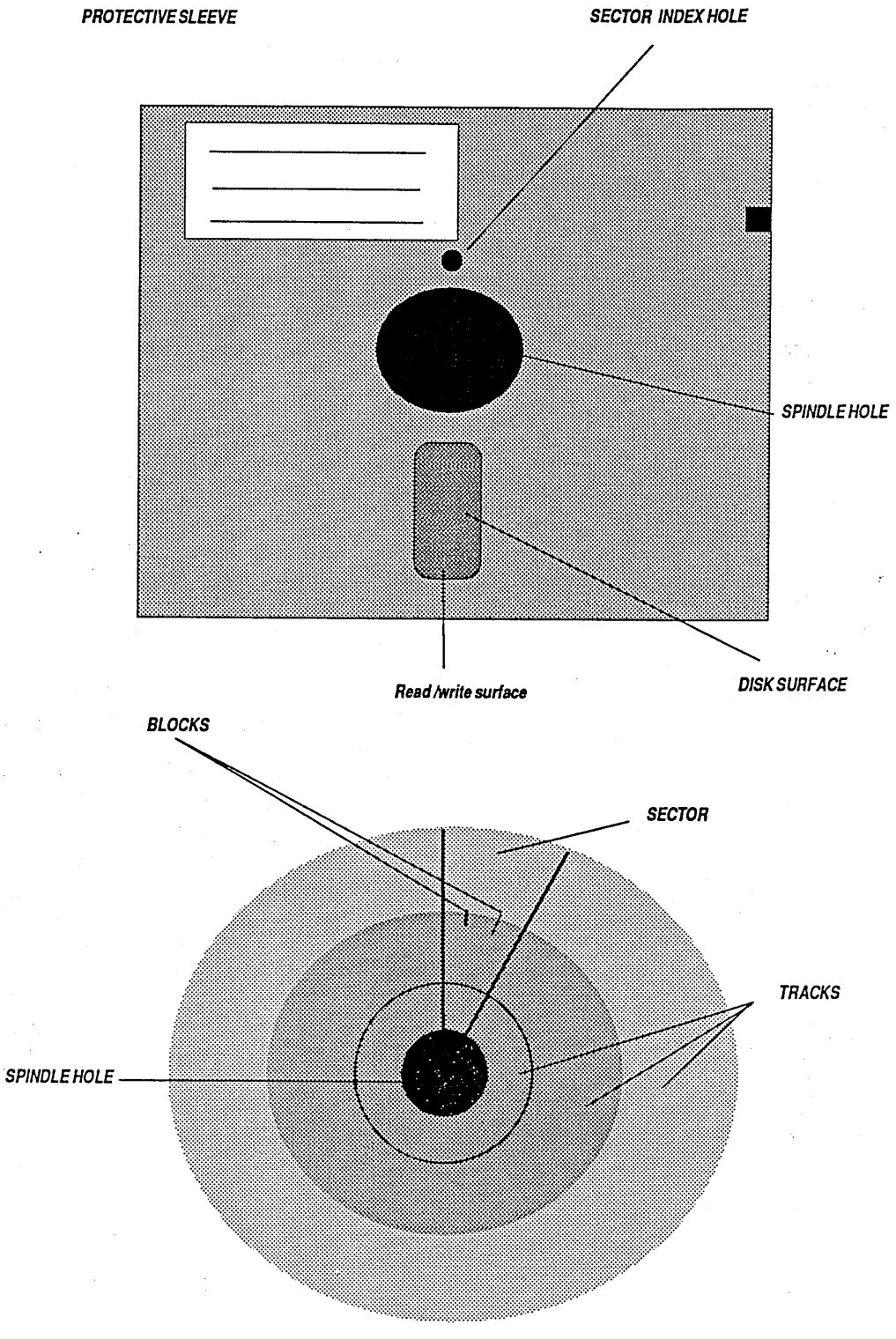
1.3.1. Microprocessors:

Microprocessors play the main role in any computer. Their specifications provide important points of comparison between different machines. Two particular attributes are taken as indications of performance: First the width (in bits) of processing data handling; and second, the speed by which the processor carries out instructions on these data (the so-called clock rate). This last feature derives from a quartz crystal clock which is built into each computer to provide a time-base for its activities.

From the early beginning of the 4004 processor to the latest parallel processing chips, the goal of processor design has been to achieve fast rates of handling data. In computationally intensive areas like medical image processing the advantages of increased speed are obvious. The rapid MRI and CT reconstruction times possible with the new 32-bit processors make such equipment more economically viable.

1.3.2. Memory:

Different types of memory have been produced to serve particular purposes. The two principal varieties are the **R**ead **O**nly **M**emory (ROM) and **R**andom **A**ccess **M**emory (RAM). ROM is so termed because the processor can 'read' the data stored in its memory cells but cannot 'write' data into it. Traditionally, ROM has been used to store programmes that are fundamental to the operation of the computer rather than being specific to a particular task.



The magnetic media after removal of the protective sleeve

Figure 1.1
The floppy disk

RAM differs from ROM in two important aspects. Firstly, the processor is able to use RAM as work space for programme storage and data manipulation because it can be written to as well as read from. Secondly, RAM needs a constant power source in order to retain the contents of its memory cells. Switching the computer off destroys any stored programme or data.

1.3.3. Storage:

The first form of storage which became widely available to the general microcomputer user was the cassette tape. This method suffers from a number of disadvantages. First, it is difficult to locate the start of a programme in the middle of a data cassette. Second, the combination of the slow cassette speed and the slow conversion rate of binary data seriously limits the speed at which the data can be transferred to and from the cassette. From the point of view of medical computing, therefore, such systems would be inappropriate.

The floppy disk became generally available for use with microcomputers in the late 1970s. As with cassette tape, the basic medium is magnetic. However, unlike tapes, the magnetic material is coated onto a plastic disc enclosed in a protective envelope (Figure 1.1). The floppy disk is inserted into a suitable disk drive and rotated at high speed. A head scans across the surface of the disk to perform the read or write functions. When a programme or data is stored on a disk, various coordinates are also stored in a 'directory' on the outermost edge. The next time the computer is instructed to retrieve the data, the directory automatically provides the computer with the necessary information about the location of the data on the disk. As a result, the process of finding a programme and loading it into the computer may be as much as one hundred times faster than the equivalent operation performed with cassette storage.

An alternative to the floppy disk is the 'hard disk'. Although the principle of data storage is the same as its counterpart, the hard disk is designed with the disk as an inseparable and permanently sealed part of the drive mechanism. The hard disk is also a good way of storing data that has to be accessed quickly or updated at frequent intervals as well as providing space for the storage of a large number of programmes. The chief medical use of the hard disk is for storing patient records.

Other forms of storage are under intensive development. The finite size of magnetic particles and the limitations of magnetic recording techniques places an upper limit on the storage density that can be achieved. New forms of storage are making use of the precision of the laser to read and write data. One version of the technology which appeared at the time of writing is the so-called WORM disk (**W**rite **O**nce **R**ead **M**any). The WORM disk stores data as a series of microscopic pits burned into a surface of a tellurium-coated disk by a small laser. Once stored in this manner, the data can be read by the laser, but it cannot be erased. Given a storage capacity of at least 200 Mega bytes such disks may have a role in medical archiving.

A more permanent form of high-capacity storage is the CD-ROM. Physically identical to the audio **C**ompact **D**isk, the CD-ROM is a 12 cm plastic disk read by laser in a special CD player that outputs data rather than audio signals. Since each CD can store as much as 550 Mega bytes of data, the medium offers the possibility of cheap archives for medical data that can be accessed by anyone with a personal computer. The drawback with a CD-ROM is that, like conventional ROMs, data can only be read from the CD not written onto it. However, a number of companies are developing optical storage media with both read and write capabilities. The main use of the CD-ROM is likely to be in the field of large databases.

1.3.4. Inputs and outputs:

The inputs and outputs of the computer have a major part to play in determining its flexibility. All computers have some form of video output for displaying text and graphics on a screen.

One limitation of video technology is the cathode ray tube. An obvious disadvantage of the conventional tube is its length. A second drawback is its considerable power consumption. One solution which has found increasing support and development is **L**iquid **C**rystal **D**isplay (LCD). An increasing number of portable computers are being produced with displays in a 'flip-top-lid'. Other display technologies are also under active development, including plasma displays and electro-luminescent panels. Although both these alternatives improve on the LCD's visibility, power consumption is a problem, making battery power impractical.

The computer keyboard is the most commonly used input device on any microcomputer. Standard computer codes have been developed to represent each keyboard character, since there is no direct binary equivalent of a letter or a number. The most popular of these is the **A**merican **S**tandard **C**ode for **I**nformation **I**nterchange or 'ASCII'. This assigns a decimal number to each character which the computer then converts to its binary equivalent, thereby interpreting a particular command (RETURN for instance) or character entered from the keyboard.

The keyboard is not an ideal input device and remains the major barrier that prevents many users with poor keyboard skills from using computers in the most effective way. This is particularly true if, for example, a paramedical expert system or a waiting room advice programme is being used by someone who has never touched a keyboard before.

Substitutes for the keyboard have been developed. One idea is the touch-screen whereby the user simply points to areas on the screen, an infrared beam detects the relevant spot and acts accordingly to register the choice with whatever programme is being run by the computer. Its disadvantages include the relatively high cost and the limited resolution of finger pointing. The most popular data input technique at the time of writing is known by the acronym 'WIMPs' standing for **W**indows, **I**cons, **M**ice, and **P**ointers. like the touch-screen the basic intention of WIMPs is to simplify computer use for the average user. The technique is based on the use of a hand-operated input device 'the mouse' to select from various options displayed on the screen as pictures 'the icons'. Thus, one picture might be of the eye for the visual system examination, another of the heart to indicate cardiovascular system findings. The mouse is simply an interface for turning movements of the hand on the desktop into x, y coordinates that are used to move an on-screen pointer between the various icon options.

1.3.5. Printers:

The printer is probably the most useful of all microcomputer peripherals. The modern printer has no direct connection with a keyboard, but receives data from the computer. These data are usually presented as a series of ASCII codes, which are turned into their corresponding printed characters.

The most popular form of printer is the 'dot-matrix' printer. For high quality printing, the choice lies between a daisywheel printer or laser printing technology. The daisywheel printer is slower than the dot-matrix printer but is of high quality. Laser printers are essentially an adaptation of photocopier technology. The laser 'writes' text and graphics onto the surface of a photosensitive drum, which attracts pigment 'toner' to the exposed areas and then deposits this onto paper. It has the advantages of high speed and quality with low noise, but it is relatively expensive. Laser printing is an obvious candidate for general practice or clinic and ward use.

1.3.6. Communications:

One of the major features of the microcomputer is its facility to integrate data from a variety of sources. It can be linked to additional computers in the same building or to distant databases. The simplest link that can be made between one computer and another at a distance is to use an 'acoustic coupler'. This item of hardware converts data into audible tones. The main drawbacks of this method are its very limited speed (30 characters per second) and the lack of reliability when competing with noise on the line.

A more satisfactory way of sending data down telephone lines is to use a device called a 'Modem'. The term modem comes from the fact that the device first modulates data with a tone to transmit it, and then reverses the process at the receiving end, and thus demodulates the data.

Although the manner in which data is transmitted is essentially similar to an acoustic coupler, the major difference is that the modem is connected directly to the telephone system, and is therefore both more reliable than the acoustic coupler and has an increased transmission rate.

Some form of local communication system can be provided wherever data have to be shared amongst a number of users so that the individual computers can access the central hard disk, or output data to a single printer.

Two short distance communication systems have been developed. The 'multi-user' system was developed in the 1960s mainly for business use, and

comprises a number of terminals connected to a central processing unit and storage facilities. This sort of system is common in business as well as in hospitals with computerised administration facilities. The main problem with this approach is that users may have to wait their turn in the processing queue when there are many processing requests from the terminals.

A more recent development is the Local Area Network (LAN) system. This uses conventional microcomputers as 'intelligent terminals', with interconnected cables providing high speed transfer of data between one computer and another with a central data store. Special LAN controller chips have been developed which enable even different microcomputers to be coupled together in a network. Computers in a LAN operate at virtually the speed they would on their own because each terminal retains its own processing functions. An apparent decrease in speed may be observed only when two or more computers are being used to access a hard disk at the same time. Since each computer has its own floppy disk drive, users also have the option of running their own computers outside the network, this is impossible with the multi-user system.

1.4. THE SOFTWARE:

Software refers to the instructions required to apply the technology of the hardware to a particular purpose. 'Good' software should provide an efficient interface between the user, the computer, and the application.

Pioneer computer programmers in the early 1970's used to programme with the computer's own language by using the so-called 'machine code' which comprises the basic instructions that the processor requires to carry out a particular data manipulation. A special programmers aid called 'assembly language' was devised to enable the programmer to construct a programme in a mnemonic shorthand which was then assembled automatically into a final sequence of 'low level' machine code for use by the processor. An assembly language programme was easier to write and to eradicate errors (debug) than its pure machine code equivalent. One of the advantages of programming in either machine code or assembly language is that programmes run very fast. In situations where speed is critical, for example updating the screen display of an ECG monitor or the response to a change in blood pressure, the fact that the programme is written in machine code or assembly language (low level language) may be important. On

the other hand, as the processors have themselves become faster and more powerful, shortening the last cycle of a programme has become less important, and many time-critical programmes for modern 16-bit microcomputers may in fact be written in other (high level) languages.

1.4.1. Programming languages:

A large number of 'high level' languages are now available. This is the result of differences in programmers attitudes over several decades of developments in computing.

'BASIC' is the computer equivalent of English language which stands for '**B**eginners **A**ll-purpose **S**ymbolic **I**nstruction **C**ode'. Although 'BASIC' is easy to learn, it is relatively slow and lacks a feature called 'structure', so that it is difficult for someone reading the programme to understand its operation. This makes debugging more difficult.

Many high level languages have been designed for particular programming environments and application. FORTRAN (**FOR**mula **TRAN**slation) is one of the old programming languages and was designed primarily for engineering and scientific applications.

A number of high level languages have been developed for application in artificial intelligence, and therefore find use in the construction of medical expert systems. Examples include PROLOG (**PRO**graming in **LOG**ic) and LISP (**LIS**t **P**rocessing language). Other important languages are PASCAL, C, LOGO and ADA.

1.4.2. Operating systems:

An essential piece of computer software is a programme called the operating system. This programme brings the electronics of the computer into useful function. It allows a user to type at the keyboard, store and recall data from disk, and create programmes. Often this programme is totally 'transparent' to the user. A very popular operating system for microcomputers is the **D**isk **O**perating **S**ystem 'DOS' (Appendix A). Some particular software packages run only under a specific operating system. The standard operating systems, like DOS, have large libraries of commercially available software that will run under them.

1.5. MACHINE SELECTION:

Computers are described as 'mainframe', 'superminis', and 'minis' amongst other names. No absolute definition of these terms exists. All these names indicate some sort of size relating both to the physical volume of the machine and the amount of computational power it can generate. The terminology is further complicated by advances in the design technology which reduce the power of a mainframe into the volume of a minicomputer (Norris *et al.*, 1985).

One of the most noticeable characteristics of different sized computers is the number of users that can use the machine simultaneously. A mainframe can support about 200 users, a mini, 4-40, and a micro, usually only one.

Moreover, the volume of data which each of them can store may differ. A mainframe can typically store vastly more than a mini which in turn can store more than a micro. Roughly one to twenty megabytes for a micro, five to two hundred megabytes for a mini and many thousands megabytes for a mainframe. Each of the machine types can be used profitably in health care, but only within the limits of their design.

A fourth consideration before a machine type is selected might be called the special features of the machine. Mainframes, especially if sited at the local university, have a wealth of software available within them. Minis and some micros are very flexible in their hardware configuration making the solution of certain problems much simpler. A special feature, unique to the micro, is the ability to produce complex graphical pictures on the screen often in colour, cheaply and easily. This feature is very valuable for patient testing and interviewing, and for computer aided education.

1.6. ADVANTAGES AND DISADVANTAGES OF MICROCOMPUTERS:

There is a move away from large computer installations to small desk-sized systems. This partly reflects technical developments which have permitted the reduction in the size of the computer. It also reflects changes in attitudes whereby the computer has become a tool used directly by the consumer. Advantages and disadvantages of microcomputers were discussed by Norris *et al.*, (1985) and Table 1.1 summarises the main points.

Advantages and disadvantages of microcomputers:

Advantages:

- Physical size, small
- Information storage
- Low running cost
- Reliability
- Flexibility
- Confidentiality and security
- Improving assessment
- Saving time
- Ease of operation
- Wide range of applications
- Increased scope
- Good backup provision
- Liaison with other departments
- Low software costs
- Large storage volume

Disadvantages

- Devising programmes, not easy
- Limitations of disks
- Patient comprehension, might be difficult
- Extra work and staff is needed
- Testing of programmes, time consuming
- Effect on staff and management

Table 1.1

The physical size of a computer can be important. Also the portability and the ease by which the device can be moved. Size is also relevant with regard to information storage. A large quantity of paper can be reduced to a small number of floppy disks only 5.25 or 3.5 inches across. Both patient records and research data can accumulate and occupy a great deal of space. When translated into magnetic patterns on disk their physical volume is very much reduced.

The capital cost of equipment, the running expenses and the recurring cost is another aspect. Small machines based on modern electronics are reasonably priced, highly reliable and the cost of machine breakdown and maintenance is greatly reduced.

Microcomputers are flexible instruments, the user can determine exactly what the computer will do, when it will do it and where the computer will be located. They present no problems of privacy. Confidential information can be kept in a safe place, the use of passwords is also available in some programmes.

Microcomputers are straightforward to operate and are not easily damaged. A wide range of applications is available. Liaison with other departments and clinics, reduces software cost and large storage volume.

On the other hand, there are also some disadvantages. Microcomputers need a software programme to run any particular application; this programme might be available commercially or must be written especially for a specific purpose. Devising and writing programmes requires considerable training and usually these take a long time to be operational.

Microcomputer memory and storage devices have their limitations. They can be appreciably slower than bigger machines when searching through thousands of records.

In conclusion, most microcomputers are small, portable, cheap and reliable. They are inherently flexible and offer security and privacy. They have utility for patient assessment and interviewing. Their speed of operation and memory capacity are adequate for many clinical applications. However, their limitations must be recognised.

Medical applications of computers - Administration.

Financial management of health-care

- Billing systems.
- Payroll.
- Accounts.

Patient registers and indices

Stores and supplies

Pharmacy

- Providing a data base of drug information.
- Calculation of dosage.
- Writing prescriptions.
- Providing a data base of poison information.
- Printing labels and instructions.
- Pricing and charging of prescriptions.
- Provision of a complete record of each task.
- Monitoring of patient compliance.
- Monitoring of prescribing practice.

Patient appointment system.

Staff time table.

Scheduling of facilities.

Ambulance scheduling.

Manpower information.

Management forecasting.

Table 1.2

Examples of administrative health-care functions which are suitable for computer system applications.

1.7. THE USE OF COMPUTERS IN MEDICAL ADMINISTRATION:

Administration comprises taking resources (manpower, equipment, building, money, etc.) and transforming them into patient care. The challenge of management is to assemble individual simple steps into vast and complex structures. The inherent facility of computers to provide a total picture at any given time is one of the features of computing which is essential to the management process. Table 1.2 shows a summary of the areas in which computerisation is taking place.

1.8. COMPUTERS AS PART OF MEDICAL EQUIPMENT:

Computers form an integral part of a wide variety of electronic equipment used in both clinical diagnosis and therapy. These applications can be grouped on the basis of the type of signal which is processed by various equipment (Chard, 1988) (Table 1.3).

Medical imaging is one of the areas where computer-based machines uses digitised images in the most effective way (Table 1.4). Computers can improve the basic quality of a digitised image in a number of ways (e.g. enhancement, noise reduction, restoration and image compression). Storage and distribution of computerised images, three dimensional imaging and automatic interpretation of images are growing and promising fields of application.

1.9. COMPUTERS FOR CLINICAL DATA COLLECTION:

The use of computers for the collection, storage and retrieval of patient data has so many advantages over traditional systems that it is likely they will substantially replace written records and represent one of the most rapidly growing activities in clinical medicine. This approach has many advantages (Table 1.5) and, of course, some disadvantages (Table 1.6). However, most of the disadvantages are generally theoretical.

1.10. MEDICAL EDUCATION:

The most significant advantage of the use of computers in education is that they go some way towards converting passive into active systems. This is

Temperature	
	Thermometers.
	Thermocouples.
	Liquid crystals.
	Thermography.
Displacement	
	Strain gauges.
	Induction coils.
	Ultrasound.
	Doppler ultrasound.
	Forces.
Pressure	
	Occlusive cuffs.
	Tonometry.
	Catheter-tip transducer.
Flow	
	Electromagnetic flowmeters.
	Ultrasound.
Electrochemical forces	
	Ion-specific.
	PH and dissolved gas electrodes.
Light	
	Photon detectors.
Bioelectric potentials	
	Electrocardiographs.
	Electroencephalographs
	Electromyographs
	Electrooculographs
	Electroretinographs.

Table 1.3

Some forms of energy which provide input signals to computerised medical equipment.

Medical applications of computers - Imaging.
Classical radiology.
CT scans.
Nuclear medicine.
Contrast radiology.
MRI.
Ultrasound.
Thermography.
Cytology and histology.

Table 1.4

Examples of imaging systems which may use digital techniques.

Medical applications of computers - Data collection.

Legibility and organisation of clinical records
Standardisation
No omissions
Saving on skilled staff
Widespread availability of information
No loss of information
Ancillary checks
Direct input of data by patient
Convenient document preparation
Medicolegal aspect

Table 1.5

Advantages of computerised data collection.

Loss of doctor-patient relationship
Loss of confidentiality
Hardware and software breakdown
Limitations of access
High cost
Problems of system design
Conversion of existing records

Table 1.6

Disadvantages of computerised data collection

achieved by providing 'intelligent interaction' between the pupil and the machine. 'Active' education is delivered by a human teacher to a single student or a small group. On the other hand 'passive' education is delivered by a teacher presenting a formal lecture to a large group of students or by 'inanimate' media such as a book. 'Interaction' is the key contribution which a computer can bring to education.

There are two further contributions. Firstly, the facility of the computer to hold vast amounts of indexed information. Therefore, the machine can move far more rapidly and effectively between various aspects of a subject. Secondly, the facility to provide a simulation of a physiological or pathological situation, and then to modify the model according to the action taken by the student.

CHAPTER 2.

THYROID DYSFUNCTION AND OPHTHALMOPATHY

2.1. INTRODUCTION:

Graves' disease is defined by McKenzie (1968) as:

> "a multisystem disorder of unknown ætiology, characterised by one or more of three clinical entities (1) hyperthyroidism associated with diffuse hyperplasia of thyroid gland, (2) infiltrative ophthalmopathy, and (3) infiltrative dermopathy (localised pretibial myxœdema)."

Not all patients with Graves' disease exhibit the full spectrum of manifestations. Hyperthyroidism is by far the most common overt manifestation. Pretibial dermopathy is rarely seen in the absence of overt ophthalmopathy. Thyroid acropachy, the rarest expression of Graves' disease, is found only in patients who also have thyroid, eye, and skin manifestations of Graves' disease (Gorman, 1984).

The fundamental cause of Graves' disease remains unknown. However, there is general agreement that the hyperthyroidism of Graves' disease is caused by a family of thyroid-stimulating immunoglobulins which are stimulatory antibodies directed toward the TSH receptors (Volpé, 1981). What evokes the production of antibodies remains an enigma.

Although many patients with 'dysthyroid' eye disease are clinically euthyroid most demonstrate subtle disturbance of thyroid regulation or function (Werner, 1955). Moreover, hyperthyroidism and thyroid ophthalmopathy commonly occur in close succession (Gorman, 1983). These diseases may therefore have a common ætiology, however, the occurrence of one disease in the absence of the other is suggestive of either varying tissue susceptibility or a less direct pathogenetic linkage.

Current treatment of hyperthyroidism comprises the reduction or elimination of thyroid bulk or activity by surgery, radioiodine or antithyroid drugs. None of these regimes, however, is directed against the presumed pathogenesis of autoimmune stimulation (Gorman, 1983).

Synthesis of thyroid hormones:

- Iodide is trapped by the thyroid gland and oxidised - becomes Iodine.
- One or two molecules of Iodine are incorporated into Tyrosine to form Monoiodotyrosine or Diiodotyrosine.
- One molecule each of Monoiodotyrosine and Diiodotyrosine couple to form Triiodothyronine (T3).

or

- Two molecules of Diiodothyronine couple to form Tetraiodothyronine (Thyroxine or T4).
- Thyroxine is then stored as part of a molecule of Thyroglobulin (contained as colloid in thyroid follicles) until released by proteolysis.

Table 2.1

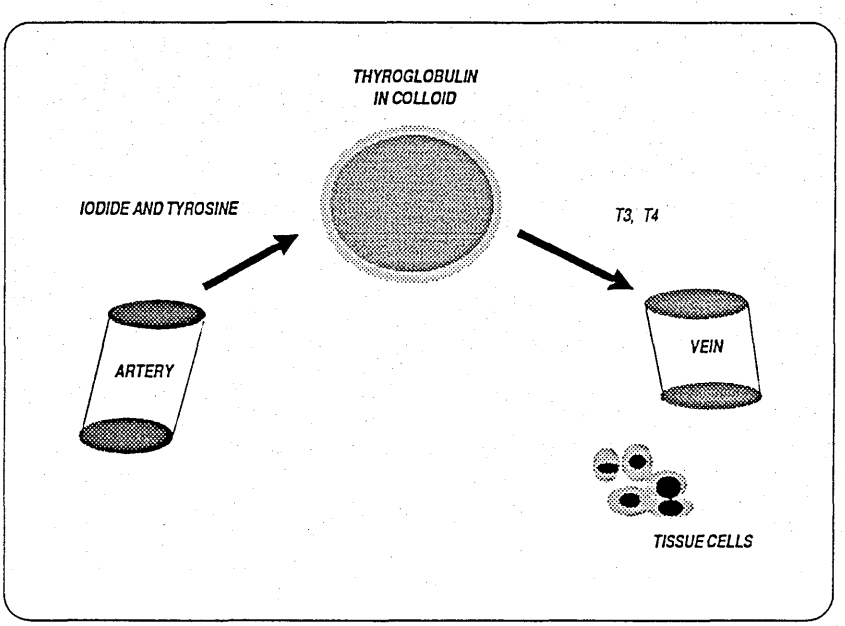


Figure 2.1

Iodine trapped by the thyroid is incorporated into tyrosine in thyroglobulin at the luminal surface of the follicular cell.

2.2. THYROID PHYSIOLOGY AND REGULATION:

2.2.1. Thyroid physiology:

The thyroid gland concentrates dietary iodine which is absorbed throughout the intestinal tract. In the gland the iodine is concentrated 30-fold, oxidised, and attached to tyrosine molecules on thyroglobulin in the thyroid follicle (Figure 2.1). The coupling of monoiodotyrosine with diiodotyrosine produces triiodothyronine (T3) (Table 2.1). When two diiodotyrosine molecules couple, the product is tetraiodothyronine (thyroxine; T4) (Figure 2.2). Antithyroid drugs, for example methimazole and propylthiouracil, act by inhibiting the oxidation, iodination and coupling steps. In addition propylthiouracil acts peripherally to impair T4 to T3 conversion (Brennan and Gorman, 1984).

2.2.2. Thyroid Hormone metabolism:

T3 and T4 in the circulation are almost entirely bound to transport proteins (TBG, TBPA and Albumin), which serve to control the volume of distribution. TBG has a high affinity and is the major T4 and T3 binding protein. Despite a much larger capacity of albumin for T4 and T3, very low affinity results in little T4 and T3 being bound to this protein (Lutz *et al.*, 1972; Refetoff, 1979).

Protein bound thyroid hormone is functionally inactive, whilst free hormone, which comprises less than 0.1% of the total (Sterling and Brenner, 1966), mediates its effect by intra-cellular activity in peripheral tissues (Spaulding and Utiger, 1981). Large variations in protein bound thyroid hormone may then occur without change in metabolic status.

In the peripheral tissues, much of the T4 secreted by the thyroid is monodeaminated to T3 (Schimmel, 1977), which is the more physiologically active form of the hormone. Thyroid hormone effects are brought about, at least in part, by binding of T3 to nuclear receptors in a tissue cells. The systemic manifestations of excessive free T4 and free T3 levels are also illustrated in Figure 2.3.

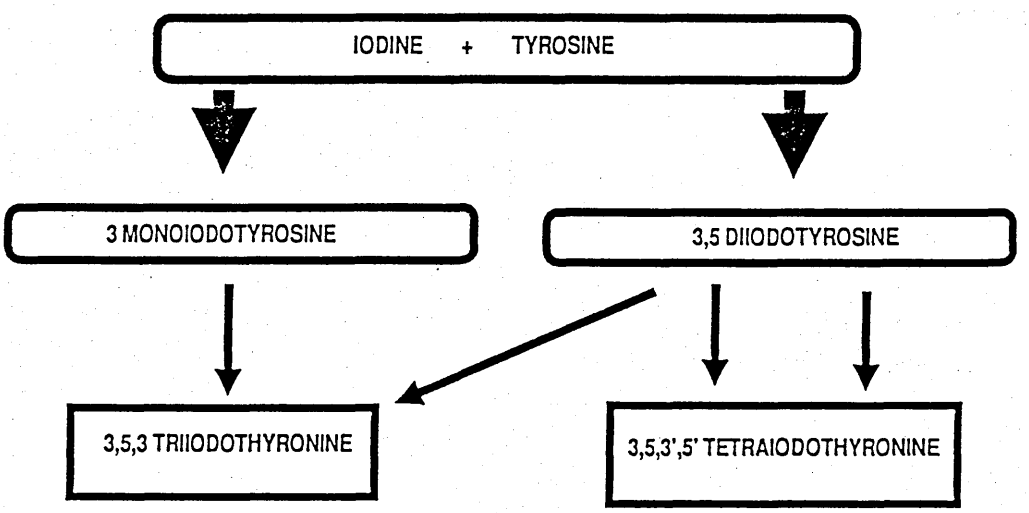


Figure 2.2
Iodine coupling and synthesis of thyroid hormones

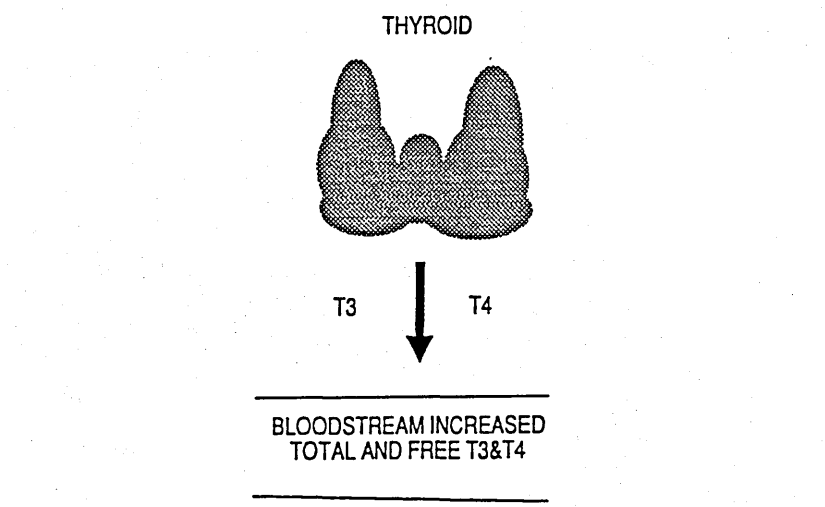


Figure 2.3
Effects of increased production of T4 and T4

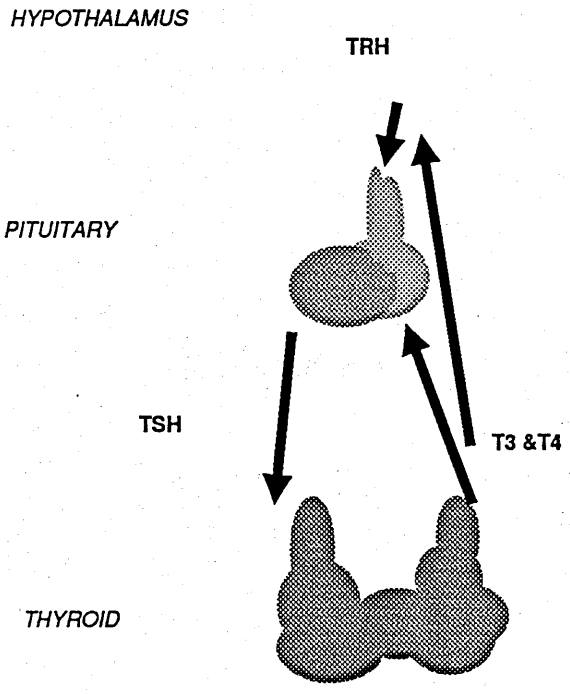


Figure 2.4

Pathways of thyroid gland function regulation

2.2.3. Thyroid gland regulation:

Figure 2.4 summarises the pathways of thyroid gland regulation which ostensibly comprise two negative feedback loops which modulate the output of the hypothalamus and the pituitary.

2.3. THYROID REGULATION IN DISEASE:

2.3.1. Regulation in Graves' disease:

In Graves' disease and other autoimmune thyroid diseases a variety of autoantibodies has been identified. They are directed against membrane and colloid thyroid antigens (Volpé, 1984). Among these, are a group of autoantibodies termed thyroid-stimulating immunoglobulins which have in common the property of binding to or near the TSH receptors. These immunoglobulins initiate a series of stimulatory steps, otherwise normally set in action by TSH production which is tightly regulated by the level of thyroid hormones in the circulation (Figure 2.4). In thyrotoxic Graves' disease, the unregulated continuing production of a potent thyroid stimulator results in inappropriately high levels of T4 and T3 in blood and peripheral tissues, causing the consequences delineated in Figure 2.3. Serum TSH levels are usually undetectable because of negative feedback by T4 and T3. The normal gland, faced with high serum concentrations of T3, inhibits iodine uptake into the gland completely. By contrast, in Graves' disease the thyroid, acting independently of TSH, continues to trap iodine and to release T4 and T3 into the circulation. This principle underlies the T3 suppression test (Werner and Spooner, 1955).

2.3.2. Lymphocytic thyroiditis:

Both Graves' disease and lymphocytic thyroiditis are considered autoimmune thyroid diseases. The main distinction between them may be the population of antibodies directed towards the thyroid. If the family of antibodies produced is predominantly stimulatory, hyperthyroidism may result, whereas if the antibodies are mainly inhibitory or cytotoxic in type Hashimoto's lymphocytic thyroiditis may result (Davies and De Bernardo, 1983). Some patients have both stimulatory and inhibitory antibodies, and the thyroid function may be hypothyroid or balanced in the normal range but is characteristically nonsuppressible

(Wyse *et al.*, 1968). Such patients may histologically exhibit lymphocytic (Hashimoto's) thyroiditis, whereas their eye findings are characteristic of Graves' disease.

2.3.3. Thyroid-stimulating immunoglobulins:

There is no direct immunoassay for thyroid-stimulating immunoglobulins in blood. Their presence can be inferred from the results of the TRH stimulation test or the T3 suppression test (both of which are not specific) and the temporary positive therapeutic effect of plasmapheresis. No direct assay of thyroid-stimulating immunoglobulins has yet been developed. Assays which are based on the ability of thyroid stimulating immunoglobulins to displace ^{125}I-labelled TSH from its receptors on thyroid cells (TSH displacement assay), or those which assess the amount of cyclic AMP generated in thyroid cell monolayers of thyroid slices when they are exposed to serum containing thyroid-stimulating immunoglobulins (cyclic AMP generation assays) provide indices of thyroid stimulating immunoglobulin antibody levels (Brennan and Gorman, 1984).

2.4. DYSTHYROID EYE DISEASE AND THYROID DYSFUNCTION:

About 80% of patients with dysthyroid ophthalmopathy have associated hyperthyroidism, 10% have Hashimoto's thyroiditis or primary hypothyroidism and the other 10% have no demonstrable thyroid disease. Their ophthalmopathy is called euthyroid Graves' disease or ophthalmic Graves' disease (Wall, 1984). On the other hand, the true prevalence of ophthalmopathy in dysthyroid patients is unknown. It depends on the diagnostic criteria when examining the patients (Gorman, 1984). Clinically obvious infiltrative ophthalmopathy is seen in 3-5 % of the hyperthyroid group (Hamilton, *et al.*, 1960), but, by careful study, evidence of subtle ophthalmopathy has been found in most if not all patients with diffuse toxic goitre (Amino, *et al.*, 1980; Tamai *et al.*, 1980; Gamblin, *et al.*, 1983).

CHAPTER 3.

DYSTHYROID EYE DISEASE

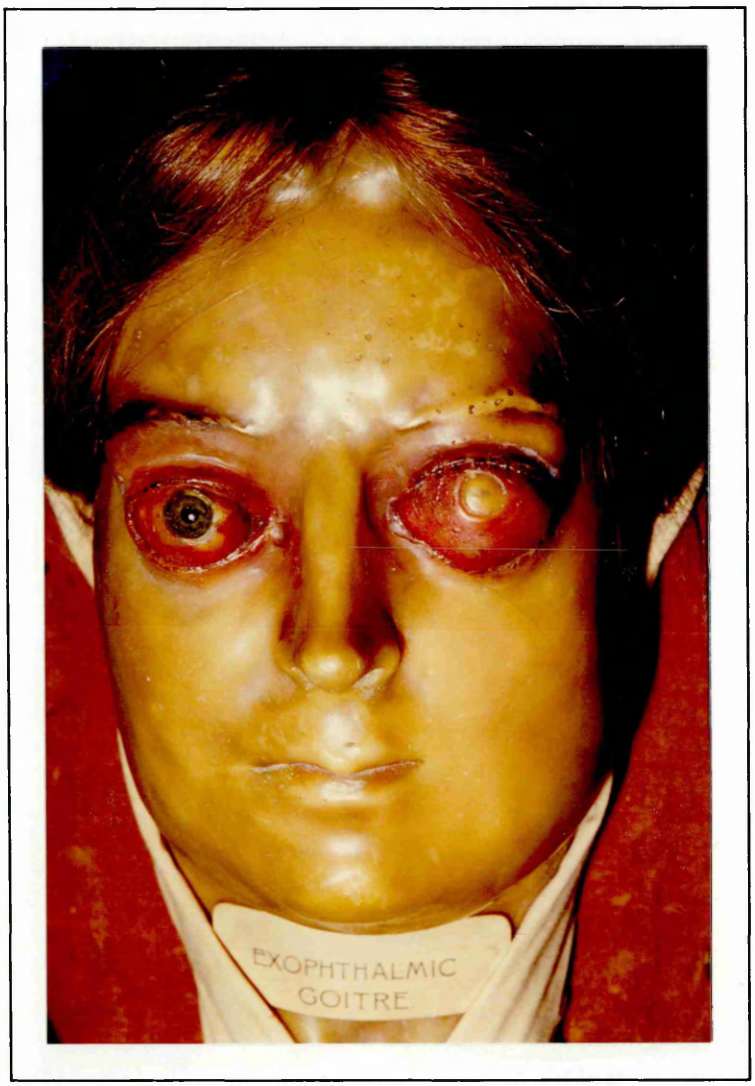


Plate 3.1

Clinical manifestations of dysthyroid ophthalmopathy.

(Photograph of a wax model from the historical collection of the Tennent Institute of Ophthalmology, Glasgow.)

Courtesy Professor W. S. Foulds

3.1. INTRODUCTION:

One of the most enigmatic syndromes in ophthalmology is the variable exophthalmos associated with dysthyroid eye disease. Despite many years of investigation the pathogenesis of this disorder remains obscure and treatment empirical.

Thyroid ophthalmopathy commonly presents as bilateral eye disease characterised by signs of conjunctival, episcleral and eyelid inflammation and vascular congestion, associated with eyelid retraction, proptosis, and extraocular muscle dysfunction (Plate 3.1). These features may be present in varying combinations and may change during the course of the disease. Remissions and exacerbations characterise the disease process. Such signs, when coupled with abnormalities of thyroid function or regulation, leave little question concerning the clinical diagnosis. Not all patients present with the full constellation of symptoms and signs. The eye signs may be subtle or unilateral, or may present without a clearly demonstrable abnormality of thyroid function. Furthermore, a number of vascular, inflammatory, and neoplastic disorders may closely mimic dysthyroid eye disease (Hay, 1984).

Although no single eye finding is pathognomonic, certain patterns can be considered diagnostic of Graves' disease and ostensibly exclude other disorders in the differential diagnosis.

3.2. HISTORY:

Table 3.1 provides a brief historical review of dysthyroid eye disease. The association of eye disease and goitre has been recognised since the twelfth century (Parry, 1825). In the 1780s a physician from Bath, Dr. Caleb Parry, recorded a comprehensive description of exophthalmos associated with goitre. The work of Parry, Robert Graves (1835) and Carl von Basedow (1840, 1848) provides the focus on the triad of hyperthyroidism, diffuse nodular goiter, and ophthalmopathy.

Graves' name is predominantly associated with the syndrome, and has been generally accepted throughout the English-speaking world. The condition is frequently termed Basedow's disease in German literature. Parry's observa-

AUTHORS	YEAR	CONTRIBUTION
Flajani	1802	Described three cases of goitre and cardiac palpitation without associating the two in a symptom complex.
Parry	1825	Gave a detailed clinical description of 13 cases of goitre associated with tachycardia, in one of which, seen in 1786, protrusion of the eyes was described.
Graves	1835	Described a case of an enlargement of the thyroid, palpitation and protrusion of the eyes.
Basedow	1840-1848	Wrote two notable papers describing exophthalmos as due to hypertrophy of the orbital tissues caused by disordered circulation. Discussed exophthalmos, goitre, and tachycardia.
Cooper	1849	Gave a detailed clinical account describing the staring appearance and associating it with exophthalmos, goitre, palpitation and anæmia.
Neumann; Warner; Bristowe	1853; 1883; 1886	Were first to remark that extraocular muscle paresis is an early and prominent feature in patients with normal or subnormal thyroid activity.
Rehn; Mœbius	1884; 1887	Were the first to point out to hyperthyroid as an essential cause of the exophthalmos.
Mœbius	1891	Reported weakness of skeletal as well as extraocular muscles in patients with hyperthyroidism.
Zimmermann	1929	Recognised a group of patients with hypo- or euthyroidism associated with exophthalmos.
Rosenbaum; Ruedemann	1937; 1937	Introduced the term "malignant exophthalmos" for the group of patients with exophthalmos associated with hypo- or euthyroidism.
Burch; Thomas and Woods; Naffziger	1929;1936;1938	Showed the enormous hypertrophy of extraocular muscles seen during orbital decompression for dysthyroid eye disease.
Rundle and Pochin	1944	Considered that all aspects of dysthyroid eye disease varied only in degree following a definitive cycle depending on pituitary activity and more of less independent of thyroid function.
Leob and Friedman; Smelser	1932;1936	Found that pituitary extracts, particularly that containing the TSH fraction produced exophthalmos in experimental animals.
Means	1945	Classified Graves' disease into three main types. Thyrotoxicosis with ophthalmopathy, without ophthalmopathy and a "hyperophthalmopathic" type associated with hyper-, normal, or hypothyroid function.
Jefferies; Dobyns and Steelman	1949; 1953	Isolated the "exophthalmos-producing substance" (EPS) from extracts of the anterior pituitary.
Adams and Purves; McKenzie	1956; 1960	Identified the association of exophthalmos with the "long-acting thyroid stimulator" (LATS) in the sera of thyroid eye disease patients who have undergone pituitary ablation.
Lemarchand-Buraud *et al.*	1967	Showed that TSH in plasma, estimated by radio-immuno-assay, is not increased in dysthyroid exophthalmos but is usually decreased.

Table 3.1

Summary of historical review

tions had been published posthumously by his son and von Basedow's were published a few years after those of Graves.

The first observers to suggest hyperthyroidism as an essential cause of the exophthalmos were Rehn (1884) and Moebius (1887).

Since the time of these early writings, exophthalmos has been generally accepted as a significant feature of diffuse toxic goitre. However, for many years the incomplete association between the two conditions has been recognised. A group of cases called 'paradoxical exophthalmos' by Zimmerman (1929), in which the exophthalmos tends to be more pronounced and intractable than the relatively mild displacement which is characteristic of thyrotoxicosis, were not associated with thyrotoxicosis. This justified the introduction of the term 'malignant exophthalmos' (Rosenbaum, 1937; Ruedemann, 1937). The phenomenon of extraocular muscle paresis was documented by Moebius (1891) as being unusual. Exophthalmic ophthalmoplegia was reported first by Nuemann (1853) and later by Warner (1883) and Bristowe (1886) as an early and prominent symptom of Graves' disease. Burch (1929), Thomas and Woods (1936), and Naffziger (1933) demonstrated both pathologically and neurosurgically the enormous hypertrophy of extraocular muscles.

Rundle and Pochin (1944) and Means (1945) divided Graves' disease into three main types. Thyrotoxicosis with ophthalmopathy, without ophthalmopathy and a "hyperophthalmopathic" type. The differences in the clinical picture and in pathology suggested to others that there are two main divisions representing two separate clinical entities. The first type has been termed 'thyrotoxic' (Brain, 1943), 'dysthyroid non-congestive' (Chandler, 1950) or 'non-progressive exophthalmos' (Cordes, 1954) and the second 'thyrotropic' (Brain,1943), 'dysthyroid congestive' (Chandler, 1950) or 'progressive exophthalmos (Cordes, 1954).

This diversity of nomenclature, which is partly due to ignorance of the ætiology of the condition, remained until the past decade when the concept of hyperthyroidism being an autoimmune response was proposed (Section 3.4.1).

The control of the secretion of the thyroid gland by the anterior lobe of the pituitary gland and the negative feedback mechanism were discovered early

in the 20th century. The theory that Graves' disease is caused by oversecretion of thyroid stimulating (thyrotropic) hormone (TSH) was immediately suggested (Leob and Friedman, 1932). This theory became more appealing after it has been found that pituitary extracts produced exophthalmos in experimental animals (Smelser, 1936). The isolation of 'exophthalmos producing substance (EPS)' further drew attention to the pituitary (Jefferies, 1949; Dobyns and Steelman, 1953). Some investigators found good correlation between exophthalmos and EPS while others did not. Moreover, in 1967 it was shown that TSH in plasma, estimated by radio-immuno-assay, is not increased in dysthyroid exophthalmos and is usually decreased (Lemarchand-Béraud, Vannotti and Scazziga, 1967).

Adams and Purves (1956) and Adam (1958) were able to show an association between exophthalmos and a protein found in the sera of dysthyroid eye disease patients who had undergone pituitary ablation. This led to the identification of a Long-Acting Thyroid Stimulator (LATS) (McKenzie, 1960) which was subsequently found to be an immunoglobulin (Kriss, Pleshakov and Chien, 1964).

3.3. PATHOLOGY:

3.3.1. Introduction:

The pathological changes which occur in Graves' disease may be widespread, and the changes that occur within the orbit are merely part of a generalised pathological process that also affects the thyroid, thymus, heart, skeletal muscles and subcutaneous tissues. Within these structures pathological changes are similar with respect to cellular infiltrate and œdema but differ in degree from patient to patient. These changes have been reviewed by Kroll and Kuwabara (1966), Riley (1972) and Campbell (1984).

3.3.2. Nature of orbital changes:

Authors have debated over the years and presented conflicting evidence as to the precise nature of the increased volume of tissue within the orbit above its average volume of 26 ml.

Von Basedow (1840) described what he called "hypertrophy of the orbital tissue," especially orbital fat. Many others have also emphasised the increased

amount of fibrofatty tissue. Smelser (1937) considered both water and fat to be responsible for the increased amount of retrobulbar tissue in experimental animals. An increase in the fat content of the orbit was demonstrated in the animals treated with thyrotropic hormone. Other authors emphasised the muscle changes and reported enlargement up to 8 or 10 times normal (Naffziger, 1933; Bouzas, 1980), computed tomography scanning and pathology (Deicker, 1979; Trokel and Jakobiec, 1981), and ultrasound (Werner, Coleman and Franzen, 1974; Hodes and Shoch, 1979) studies have shown that the extraocular muscles primarily contribute to the proptosis and are the primary focus of the disease process.

Rundle and Pochin (1944) performed quantitative analysis studies of the orbital contents of 17 autopsy cases with thyrotoxicosis, with and without eye signs, and found an increase in the amount of "muscle fat". The contents of fat within the muscles was more than double that of tissues in control subjects. This increase in fat was found to be proportional to the volumes of the muscles; that is, the levator palpebrae superioris muscle showed the greatest increase in fat, and the medial rectus muscle showed the least. In a normal control patient, fat formed approximately half the total weight of the tissue. This finding suggests an abnormal deposition of fat because the fat content of muscle is not increased in obesity.

In dysthyroid eye disease the orbital contents appear to the surgeon as glistening and œdematous. The muscles are tan in colour and firm or rubbery in consistency. The microscopic picture of the tissues is a combination of œdema, accumulation of mucin, cellular infiltration, and fibrosis of various degrees. These changes are seen predominantly within the extraocular muscles and the lacrimal gland. They are present to a lesser degree in the fibrofatty tissues.

In the normal person, the eye fills 30% of the orbital volume with the remainder of the orbital contents occupied by retrobulbar and peribulbar structures and is composed chiefly of muscles, fat, nerves, and vessels. The vessels include arterial and venous channels as well as lymphatics. The eye is an extension of the central nervous system and is without lymphatics, but it is important to recognise that lymphatic channels are present within the fat and muscle of orbital tissue (Rusznyak, Foldi and Szabo, 1967). Because fibrofatty tissue elsewhere in the body contains lymphatic channels, there is no reason to presume that the fibrofatty tissue within the orbit should differ. The popular miscon-

ception that lymphatic channels do not exist within the orbit was encouraged in part by the experiments of Patek and Bernicks (1960), who failed to demonstrate the channels. Other investigators have ligated the lymphatic ducts within the necks of dogs and cats as well as the submandibular and deep cervical lymph glands. At autopsy they demonstrated both grossly and microscopically, the presence of œdema of the superficial and deep orbital fascia, fibrofatty tissue, extraocular muscles, and lacrimal gland. Some of the animals had exophthalmos due to orbital œdema (Foldi *et al.*, 1963). Kozma and Gellért (1958) were able to demonstrate experimentally the presence of lymphatic pathways within the extraocular muscles. The fact that lymphangiomas occur in the orbit also supports the concept that lymphatic channels are present within that site (Jones, 1961). Thus a body of evidence supports the presence of orbital lymphatic channels hence providing a pathway for the development of orbital œdema and the infiltration of mononuclear cells in Graves' disease.

3.3.3. Pathological tissue changes:

Five pathological changes within the orbital tissue have been described by Wybar (1957): Increase in fat content, increase in mucin content, increase in water content, fibrosis, and lymphocytic infiltration. The extent to which any or all of these factors contribute to the production of exophthalmos has been debated over the years, but many studies have shown that extraocular muscles are predominantly affected. The seven extraocular muscles are not equally affected by the pathological process, although all of the muscles show histopathological changes to some degree. These changes are most marked in the inferior and medial rectus muscles. In specimens obtained during decompression procedures, the inferior rectus muscle shows the earliest exudate and the earliest fibroblastic proliferation.

In Graves' disease the interstitium of the extraocular muscles shows an infiltration with mononuclear cells and fibroblasts with an admixture of œdema fluid and an accumulation of mucin. These changes are present in the endomysium and perimysium and to a lesser extent in the epimysium. The fibrofatty tissue that surrounds the muscle is involved to a lesser extent, and the tendon is not involved at all.

The cellular infiltrate is composed predominantly of mature lymphocytes with some plasma cells and a few macrophages. The histological picture depends on the stage of the disease. In the early stages the cellular infiltrate is scanty and is both focal and diffuse within the endomysium. Mast cells may be present but are few in number; they are found in a perivascular distribution. As the lymphocytes and plasma cells increase in number, the fibroblasts in the interstitium enlarge and proliferate, and in so doing produce collagen and mucopolysaccharide material. Ludwig, Boas and Soffer (1950), linked the orbital changes to those of localised myxœdema occurring in the skin and demonstrated an increased amount of hexosamine content in the orbits of guinea pigs treated with thyroid stimulating hormone. In humans the localised myxœdema of Graves' disease contains 16 times the normal skin concentration of acid mucopolysaccharides. Accumulation of glycosaminoglycans is a characteristic feature of orbital tissue in humans and most experimental animals with exophthalmos. Normal human retrobulbar connective tissue contains hexosamine in the glycoprotein fraction, with one third in the glycosaminoglycan fraction. These substances were formerly considered to be produced by mast cells, but morphological and experimental evidence shows that they are the product of fibroblasts (Tengroth, 1964; Sisson, 1968). Fibroblasts are stimulated to proliferate and to secrete hyaluronic acid by lymphocytes and lymphocytic products. Sisson (1977) demonstrated the enhanced synthesis of hyaluronic acid by the retrobulbar fibroblasts in response to exposure to lymphocytes and their products. Cell cultures of human fibroblasts also show secretion of hyaluronic acid after exposure to lymphocytes and lymphocytic products. The increased mucin content of the tissues causes increased water-holding property and hence œdema.

As fibroblasts proliferate within the perimysium, bundles of fibers are compressed and atrophy. Fibrous strands within the epimysium may extend into the adjacent sector of the orbital fat. This orbital scarring characterises end stage disease and is associated with severe muscle atrophy and loss of function (Campbell, 1984).

The histological changes described above are also observed within the connective tissue of the lacrimal gland. Fibrosis occurs to a lesser degree than in the extraocular muscles and results in only a mild atrophy of the glandular elements (Wybar, 1957; Campbell, 1984).

3.3.4. Pathological changes of the globe:

The pathological changes that may afflict the globe are secondary and are not specific to Graves' disease. The two important complications are keratitis and disc œdema. The keratitis is caused by exposure and is secondary to proptosis and inadequate protection of the cornea by the eyelids. The tear film quickly evaporates, the cornea dries, and in the most severe cases of proptosis the corneal epithelium changes from the normal five-layered epithelium to one which is keratinised, stratified, and squamous. Ulceration may occur. Inflammatory cells are present within the corneal stroma and may be acute or chronic. New vessels may grow into the corneal stroma from the limbal area. According to Ogura, Wessler and Avioli (1971), if the patient is not treated, panophthalmitis may occur in about 1-2 % of patients, and orbital cellulitis may result.

Disc œdema may result from compression of the vessels to and within the optic nerve. On histological examination the disc head varies in its degree of swelling and shows separation of nerve fibres by œdema fluid. Subretinal fluid may accumulate and is first seen adjacent to the optic disc. The histopathological appearance of the optic disc in Graves' disease is identical to that of papillœdema produced by other causes (Hayreh, 1977; Campbell, 1984).

3.4. PATHOGENESIS:

3.4.1. Autoimmunity and Graves' ophthalmopathy:

Much of the research into the pathogenesis of Graves' ophthalmopathy has focused on its association with hyperthyroidism and the possible role of long-acting thyroid stimulator (LATS) (Mckenzie, 1965; Kriss *et al.*, 1967; Lipman *et al.*, 1967; 1968; Mckenzie and McCullagh, 1968). LATS is an immunoglobulin G (IgG) of lymphoid origin which acts like an antibody directed against some components of the thyroid cell plasma membrane receptors for thyroid-stimulating hormone (TSH). There is no direct evidence for an effect of thyroid hormones or TSH on orbital tissues in Graves' ophthalmopathy.

Present evidence suggests that in Graves' ophthalmopathy autoimmune responses are directed against orbital tissue antigens and do not cross-react with

thyroid antigens. Clinical studies suggest that all patients with ophthalmopathy have some abnormality of eye muscles, whereas not all patients with ophthalmopathy have evidence of thyroid disease. It is not possible at the present time to be certain whether Graves' ophthalmopathy is an integral part of Graves' disease or a separate entity (Kendall-Taylor, Atkinson and Holcombe, 1984).

The eye changes of Graves' disease have been classified by the American Thyroid Association (Section 3.5.2) according to the severity of the changes and the extent of the orbital tissue involvement. There are two main subdivisions: (a) mild ophthalmopathy (lid lag and stare), thought to be due to increased sensitivity of the sympathetic nervous system to catecholamines and attributed to hyperthyroidism *per se;* and (b) severe ophthalmopathy, a distinct autoimmune disorder.

Currently, the diagnosis of Graves' ophthalmopathy is mainly clinical and in difficult cases the diagnosis can be helped by advanced imaging techniques. In their well controlled studies, Zappia, Winkelman and Gay (1971) and Gamblin *et al.* (1983), using raised intraocular pressure on upward gaze as a parameter for eye muscle involvement showed that most patients with Graves' disease have eye muscle disease, and almost all patients with ophthalmopathy have eye muscle involvement. Patients with Hashimoto's thyroiditis also showed a high prevalence of extraocular muscle involvement (Gamblin *et al.*, 1985). Although these findings certainly suggest a close relationship between ophthalmopathy and Graves' disease, they also can be interpreted as providing strong evidence that Graves' hyperthyroidism, Hashimoto's thyroiditis and ophthalmopathy are three separate autoimmune disorders. Clearly the controversy concerning the relationship between ophthalmopathy and thyroid disorders will not be resolved for sometime, particularly as the parameters for ophthalmopathy are not well established. Thus one needs not only a very sensitive and specific clinical test for eye muscle disease, but also specific biochemical test to confirm the diagnosis (Donaldson, Bagshaw and Kriss, 1973).

Wall (1984) has reviewed the theories concerning the pathogenesis of Graves' ophthalmopathy in relation to the recently identified eye muscle autoantigens and their corresponding circulating antibodies. He concluded that although it is becoming clear that Graves' ophthalmopathy is an organ-specific autoimmune disorder with target autoantigen and corresponding circulating

Abridged classification of eye changes in Graves' disease:

Class	Definition
0	No physical signs or symptoms
1	Only signs, no symptoms (signs limited to upper Lid retraction, stare and lid lag)
2	Soft tissue involvement (symptoms and signs)
3	Proptosis
4	Extraocular muscle movement
5	Corneal involvement
6	Sight loss (optic nerve involvement)

Table 3.2

From Warner (1969)

antibodies, more work is necessary to clarify the nature of the antigens and the clinical and pathogenetic significance of the antibodies. Moreover, the likelihood that orbital tissue damage is mediated by T or K cell reactions needs to be studied. The mechanism for the association with thyroid disease is still unexplained. Research is currently being directed towards the identification of cross reacting antibodies and whether they demonstrate cytotoxicity or stimulatory activity.

3.5. CLINICAL PRESENTATIONS:

3.5.1. Introduction:

In this section the current classifications of orbital changes of dysthyroid eye disease are considered and the wide variety of eye and orbital signs which may be seen in this disorder is described. The principles underlying the formulation of a clinical diagnosis and the ophthalmic diseases which may be confused with dysthyroid eye disease are also reviewed.

3.5.2. Classification of orbital changes:

The formal classification of the eye changes of Graves' disease was devised in 1969 by a special committee of the American Thyroid Association. The classification was initially presented in both an abridged and a detailed form. The abridged form summarises the six classes which had been devised, the first letter of the definition of each class constituting the acronym NO SPECS (Table 3.2). The detailed classification (Table 3.3) provides specific criteria for grading the signs within each class and identifies the activity of the orbital process as "active, static, or inactive" (Werner, 1969).

In 1977, the Committee of the American Thyroid Association, published several modifications of the original classification (Werner, 1977). As before, the classification had two forms: The abridged and the detailed. Although the original six classes were retained, changes were made in the criteria for class I and III. It was emphasised that progression of disease need not be sequential between each of the classes. Also, it was noted that the amount of myopia and racial differences should influence the measured normal upper limit of proptosis.

Detailed classification of eye changes of Graves' disease:

Grade	Suggestion for grading
Class 0	No physical signs or symptoms
Class 1	Only signs (signs limited to upper lid retraction, stare with or without lid lag and proptosis). Proptosis associated with Class 1 only (specify difference of 3mm or more between eyes; or progression under observation of 3mm or more, Grade 0 included)
0	Absent (2 mm or less - normal)
a	Minimal (21 - 23 mm)
b	Moderate (24 - 27 mm)
c	Marked (28 mm or more)
Class 2	Soft tissue involvement (symptoms of excessive lacrimation, sandy sensation, retrobulbar discomfort and photophobia, but not diplopia; objective signs as follows:
0	Absent
a	Minimal (œdema of conjunctivae and lids, conjunctival injection, and fullness of lids, often with orbital fat extrusion, palpable lacrimal glands, or swollen extraocular muscle palpable laterally beneath lower lids)
b	Moderate (Above plus chemosis, lagophthalmos, lid fullness)
c	Marked
Class 3	Proptosis associated with Classes 2-6 only (specify if inequality of 3mm or more between eyes, of if progression of 3mm or more under observation)
0	Absent (20 mm or less)
a	Minimal (21 - 23 mm)
b	Moderate (24 - 27 mm)
c	Marked (28 mm or more)
Class 4	Extrocular muscle involvement (usually with diplopia)

0	Absent
a	Minimal (limitation of motion evident at extreme gaze in one or more directions)
b	Moderate (evident restriction of motion without fixation of position)
c	Marked (fixation of position of a globe or globes)
Class 5	Corneal involvement (primarily due to lagophthalmos)
0	Absent
a	Minimal (stippling of cornea)
b	Moderate (ulceration)
c	Marked (clouding, necrosis, perforation)
Class 6	Sight loss (dure to optic nerve involvement)
0	Absent
a	Minimal (disc pallor or choking, or visual field defect; vision 20/20-20/60)
b	Moderate (disc pallor or choking or visual field defect; vision 20/70-20/200)
c	Marked (blindness, i.e., failure to perceive light; vision less than 20/200)

Table 3.3

Werner (1969)

Van Dyk (1981) suggested a further modification to the American Thyroid Association classification which, he hoped, would permit "greater clinical specificity" in the description of patients with dysthyroid eye disease. He advised the return of criteria for grading patients in class II soft tissue involvement and argued that symptoms be excluded from the definition. His proposed modification to the detailed classification of class II orbital changes comprised six soft tissue signs, the first letter of each forming the acronym RELIEF (Section 3.5.4.).

Resistance to retrodisplacement of eye

Œdema of conjunctiva/caruncle

Lacrimal gland enlargement

Injection of conjunctiva, focal or diffuse

Œdema of the eyelids

Fullness of the eyelids

Feldon and Unsold (1982) described a simple classification of Graves' ophthalmopathy based entirely on evaluation of seven clinical signs: Proptosis, lid retraction, lid lag, horizontal oculomotor dysfunction, optic nerve involvement, and periorbital œdema. These signs were judged as mild, moderate, or severe based on "strict semi-quantitative clinical criteria", and the patients in their studies were said to be "categorised easily" into three classes on the bases of overall clinical severity of disease.

The ophthalmopathy index suggested by Donaldson *et al.* (1973) is calculated by adding total points for each of four ocular signs: proptosis, motility restriction, keratitis and soft-tissue swelling and injection (Table 3.4).

The Werner classification of the American Thyroid Association falls short of clinical usefulness in ophthalmic practice. It is complicated and does not rep-

Method for calculating the ophthalmopathy index:

Class	Involvement category
2	Soft tissue
3	Proptosis‡
4	Extraocular muscle
5	Cornea
6	Sight loss

Minimal = 1

Moderate = 2

Marked = 3

‡ *For proptosis, Hertel exophthalmometer readings were scored as follows:*

minimal (20-23mm) = 1

moderate (>23-27mm) = 2

marked (<27mm) = 3

Table 3.4

Adapted from Donaldson et al. (1973)

resent a progressive continuum form the class 0 to class 6. The ophthalmopathy index suggested by Donaldson *et al.* (1973) proved to be useful for classifying patients with optic neuropathy and forms the basis of patient evaluation in several recent studies (Grauthoff, Wuttke and Frommhold, 1980; Pinchera *et al.* 1984; Glinoer *et al.*, 1986).

3.5.3. Involvement of the eyelids:

In class I of the American Thyroid Association classification, patients with Graves' ophthalmopathy have eye signs limited to upper lid retraction, stare, and lid lag. These signs, although considered little more than a cosmetic blemish by Werner (1978) may provide a major source of concern and anxiety to the affected patient. In class I involvement the patient has a characteristic 'startled' or 'staring' appearance because the upper eyelid on one or both sides is elevated, thereby exposing the superior corneoscleral limbus. When the eyes pursue a slowly downward-moving target, the lid lags behind. The presence of both lid retraction and lid lag, even when subtle, is considered highly suggestive of Graves' ophthalmopathy, but is by no means pathognomonic. Retraction of the upper lids has been described as the most characteristic ocular sign of Graves' disease (Day, 1978), and is said to occur in at least 50% of cases with ophthalmopathy.

For years, excessive sympathetic nervous system activity was uncritically accepted as the mechanism responsible for lid retraction in Graves' disease. Retraction was attributed principally to overstimulation of Müller's muscle. Evidence for sympathetic overactivity was inferred from the knowledge that propranolol, when used systemically, could produce a ptotic effect on the upper lid, and that the topical administration of postganglionic blocker guanethidine resulted in a significant lowering of the retracted eyelid in the majority of thyrotoxic patients with eyelid retraction (Hodes, Frazee and Szmyd, 1979).

However, recently it has been clinically observed that there are many instances of eyelid retraction for which the sympathetic overactivity theory is an inadequate explanation. These include: (a) the retraction is not abolished by cervical sympathectomy; (b) many retracted eyelids fail to drop to normal with guanethidine; (c) eyelid retraction may be present in the euthyroid or hyporthyroid patients; and that the retraction persists with sleep, general anæthesia, and retrobulbar anæthesia (Hay, 1984). The fact that unilateral lid retraction is so

common makes sympathetic overactivity extremely unlikely. Also, if the lashes or lid margin are grasped and an attempt is made to draw the retracted lid downward, resistance is often encountered, another observation suggesting a mechanical restriction of the levator muscle rather than excess sympathetic tone.

On the bases of the results of high-resolution ultrasonic (Shammas, Minckler, and Ogden, 1980) and computed tomographic scans (Trokel and Jakobiec, 1981) of the orbit, it is being increasingly recognised that dysthyroid eye disease is a diffuse process resulting in a panmyositis affecting all muscles of the orbit. From these findings it can be inferred that the same process of inflammation, thickening, and ultimate fibrosis which affects the recti and oblique muscles in class IV, involves also the levator and Müller's muscle in the upper eyelid. This causes restricted movement and contracture which result in a pharmacologically irreversible elevation of the upper eyelid (Hodes *et al.*, 1979). Such a mechanism would provide a more acceptable explanation than sympathetic overactivity for the fairly frequent finding of eyelid retraction in those euthyroid patients who present with no thyrotoxic history or those who develop eye signs many years after successful ablation therapy for hyperthyroidism.

3.5.4. Soft tissue involvement:

Classes II-VI of the American Thyroid Association classification represent the severe eye changes with a potentially serious prognosis, formerly called 'infiltrative', 'progressive' or 'malignant' (Werner, 1969). Patients who fall within this overall category, are characterised by consistent enlargement of the extraocular muscles, resulting in an increase in orbital contents, and an increase in orbital pressure.

The œdema resulting from the swollen extraocular muscles and their increased water-holding property due to the higher concentration of glycoseaminoglycans (Section 3.3.3), coupled with the increased orbital pressure, probably causes a slowing down of removal of the fluid in the interstitial space. Venous stasis, resulting from compression of apical veins by enlarged muscles, also probably contributes to this process (Trokel and Jakobiec, 1981).

Class II symptoms were described as excessive lacrimation, a 'sandy' sensation, retrobulbar discomfort, and photophobia. Relevant signs include œdema

of the conjunctiva and lids, conjunctival injection, fullness of the eyelids often with orbital fat extrusion, palpable lacrimal glands, and swollen extraocular muscles palpable laterally beneath the lower lid. In Van Dyk's opinion, the inclusion of symptoms in class II was a mistake (van Dyk, 1981). In his proposed modification (Section 3.5.2), criteria for inclusion were limited to six signs remembered by the acronym RELIEF. These are described in detail below:

Resistance to retrodisplacement of the eyes into the orbit results because the orbit is infiltrated and œdematous. In contrast to the normal orbit, which allows about 5 millimeters of backward displacement of the eye, the orbit involved by Graves' disease process provides variable resistance to retrodisplacement of the globe.

Œdema of the conjunctiva and the caruncle, may be represented only by a new fold of redundant conjunctiva hanging over the mucocutaneous junction of the lower lid. However, with more marked involvement, there may be frank prolapse of the conjunctiva across the lower lid, a prolapse in which the caruncle usually participates.

Lacrimal gland enlargement may rarely be palpable, but more often is seen as a contrast-enhancing supero-lateral mass on orbital CT scan. Infiltration of the gland causes enlargement, which is made more prominent by the gland's involvement in the generalised anterior movement of the orbital structures.

Injection of the conjunctiva may occur in the presence or absence of chemosis. When conjunctival œdema is minimal, an intense focal hyperæmia may be seen outlining and overlying the swollen horizontal rectus muscles, sometimes extending anterior to the insertion of the tendon towards the limbus. When gross chemosis is present the conjunctivae are diffusely hyperæmic and the presence at the lateral canthus of large, tortuous, purplish vascular loops with overlying chemosis is considered highly characteristic of dysthyroid ophthalmopathy (Gorman, 1978).

Œdema and Fullness of lids may occur separately, but sometimes the signs are not precisely separable. It is probable that eyelid fullness is caused by

œdema, infiltration or fat extrusion behind the orbital septum, whereas lid œdema reflects fluid anterior to the septum, just under the skin and orbicularis muscle (Van Dyk, 1981).

3.5.5. Proptosis:

In Graves' disease swelling, infiltration, and later fibrosis and eventual muscle contracture within the unyielding confines of the bony orbit tend to push the eye forward (Gorman, 1983).

In the 1977 modification of American Thyroid Association classification, patients with exophthalmometry reading up to 22 mm (2 mm above Caucasian normal) were placed in class I; those with readings in excess of 22 mm, even without symptoms, were placed in class III. It was recognised that for Japanese and black Americans the upper normal values for exophthalmometry reading were, respectively, 18 and 22 mm. Because of these ethnic variations in the proptosis baseline, the grading (a, b, or c) for class III has been changed from being based on the actual millimeters of forward protrusion of the eye to a grade based on the extent to which the proptosis reading exceeds normal (Werner, 1969; 1977).

It has been estimated that about 20 - 25% of patients with Graves' disease develop proptosis. Eye findings are typically bilateral, although the severity of involvement may differ significantly between the two eyes (Duke-Elder and MacFaul, 1974; De Santo, 1980). Occasionally patients present with unilateral signs and symptoms. However, in Graves' disease an asymmetry in exophthalmos rarely exceeds 6 mm (Hall *et al.*, 1970).

Graves' ophthalmopathy can account for 15-28% of all cases of unilateral exophthalmos (Gorman, 1978). In spite of what may seem to be a unilateral process, pathological involvement of the intraorbital contents does occur bilaterally, and this can be confirmed by ultrasonography or computed tomography (Sections 3.4.1 and 3.5.3). It is this bilateral involvement that provides an important clinical clue for differentiating apparent unilateral Graves' ophthalmopathy from an orbital mass lesion.

3.5.6. Extraocular muscle involvement:

Based on a study in which over 200 orbits of patients of Graves's disease were scanned by high-resolution CT, Trokel and Jakobiec (1981) concluded that the extraocular muscles comprised the most consistently involved focus of disease in Graves' orbitopathy, an observation which has been substantiated by histopathological evaluation of both biopsy and autopsy tissue.

Clinically and radiologically, the range of abnormality varies from minimal enlargement of a few muscles in patients with class I disease to enormous enlargement of multiple muscles in class IV disease. In the initial stages of disease the enlarged muscles maintain the ability to contract and relax, but later they become fibrotic and are unable to relax. These fibrotic extraocular muscles restrict mobility by a 'tethering' action and give rise to an apparent underaction of the antagonist muscle. In severe and massive involvement of muscles, the ability to contract may be lost and the resultant restriction in motion may eventually result in class IVc changes with fixation of the position of the globe (Trokel and Jakobiec, 1981).

Patients with clinically significant extraocular muscle involvement usually complain of intermittent or slowly progressive vertical or oblique diplopia. Occasionally, especially during acutely active inflammatory phases, they may complain of a mild painful 'pulling' sensation on attempted upgaze. As inflammation subsides, the ophthalmoplegia is usually not accompanied by pain, except perhaps for a foreign body sensation. Proptosis at this stage is variable, and minimal amounts of proptosis (class II) may coexist with marked limitation of ocular motility. A middle-aged patient presenting with diplopia of gradual onset or double vision on waking, which gradually becomes controlled after a period of minutes but then returns again during the day if the patient becomes tired, or sometimes following a single alcohol drink, is typical of dysthyroid ophthalmopathy (Fells *et al.*, 1988).

The four recti muscles are particularly involved in the restrictive process. Clinical involvement is most common in the inferior rectus (60-70%), less frequent in the medial rectus (25%), and uncommon (10%) in the superior rectus. The lateral recti are seldom involved (Dyer, 1976). Quantification of extraocular

muscle enlargement by CT scanning has recently allowed the demonstration of a regular increase in total muscle volume with increasing ophthalmopathy. Although in a study of 8 patients with variably severe Graves' ophthalmopathy inferior rectus enlargement was apparent in all patients; only medial and lateral rectus muscle volumes increased in proportion to the severity of the clinical disease. Feldon and Weiner (1982) found a linear relationship between worsening ophthalmopathy (judged by multiple clinical signs) and both horizontal and total extraocular muscle volumes.

It is generally agreed that inferior extraocular muscles suffer more severe involvement than the others. Hodes *et al.* (1979) suggested three possible explanations for the observed inferior muscle dominance in the restrictive process. First, they suggested that because twice as many muscles, with far more complex actions, are involved in vertical eye movements than in horizontal eye movements, one might anticipate, based on numbers alone, a predominance of vertical muscle symptomatology. Second, unlike the horizontal muscles, the vertical muscles are paired and cross one another in the orbit. The inferior crossing is possibly more prone to reactive adhesions because unlike the superior crossing which occurs between a muscle and a tendon, the inferior one occurs between two muscles with a consequent large area of surface contact. Finally, they pointed out that horizontal fusional versions are considerably greater than vertical fusional versions, thereby allowing an individual to compensate for larger deficits in horizontal eye movements.

The restrictive extraocular muscle involvement of Graves' ophthalmopathy should be differentiated from other neurological entities, e.g., neurogenic palsy and myasthenia gravis, which may complicate thyrotoxicosis. The forced duction test is indispensable. The presence of a positive test implying restrictive phenomena, is almost diagnostic of orbital disease and usually excludes neurogenic disease except in those cases of long-standing ocular deviation where there may be secondary muscular contracture.

When a patient with extraocular muscle involvement turns his eyes upward, restrictive tethering of the enlarged extraocular muscles, especially the inferior recti, pressing against the globe raises the intraocular pressure. Thus, the measurement of intraocular pressure by applanation tonometry may be helpful clinically in establishing bilateral orbital involvement in those patients who pres-

ent initially with unilateral proptosis, a concept which is further discussed in Section 3.8.7.

3.5.7. Corneal involvement:

Corneal exposure has been ascribed to upper lid retraction, exophthalmos, lagophthalmos, inability to elevate the eyes and a decreased blink rate (Day, 1978; Werner, 1978). Different factors, potentially associated with corneal exposure in Graves' disease, were evaluated to determine which ones were associated with ocular surface damage. Analysis revealed that only increased palpebral fissure width and increased blink rate were significant predictors of ocular surface damage, as demonstrated by rose Bengal. None of the other factors generally considered important in corneal exposure (exophthalmos, lid lag and lagophthalmos) was significantly correlated with ocular surface damage. It is therefore possible that increased palpebral fissure width accelerates tear film evaporation, allowing an increase in tear film osmolarity with resultant ocular surface damage. A secondary increase in blink rate may occur (Gilbard and Farris, 1983).

Patients with corneal involvement and ocular surface symptoms may complain of excess tearing, a gritty or sandy sensation, burning, or a foreign body sensation. In the American Thyroid Association classification, minimal involvement is characterised as mild by superficial punctate keratopathy, moderate by corneal ulceration, and marked by clouding, necrosis, or perforation. When ulcers occur, they are usually located in the central cornea, and if they become secondarily infected, globe perforation may occur with resultant loss of the eye (Day, 1978).

3.5.8. Optic nerve involvement:

Visual loss due to optic neuropathy is infrequent in Graves' ophthalmopathy (Day, 1978; Kennerdel *et al.*, 1981). When present in one or both eyes, it may result in a progressive decrease in visual acuity, impairment in colour vision, an afferent pupillary defect, optic disc congestion or atrophy, and visual field defects (Kennerdel *et al.*, 1981).

In 1933, Naffziger first suggested that optic neuropathy in Graves' disease could be caused by compression of the optic nerve at the orbital apex, where

the swollen muscle bellies of extraocular muscles converge at the annulus of Zinn. Recently the ability of high-resolution CT scanners to resolve structures at the orbital apex has confirmed that dysthyroid optic neuropathy is consistently associated with substantially enlarged extraocular muscles at the apex of the orbit in tight juxtaposition to the optic nerve (Trokel and Jakobiec, 1981). The consequent apical compression may result in optic neuropathy by direct pressure on the nerve or its blood supply (Kennerdel *et al.*, 1981). The results of fluorescein angiography and orbital venography in 20 patients with optic nerve compression suggest that increased intraorbital pressure exerts a profound effect on visual function through interference with first the orbital and then, later, the ocular circulation (Cant and Wilson, 1974).

In most patients with optic nerve compression the involvement is bilateral, although the two eyes may not necessarily be affected simultaneously or to the same degree. In 24-31% of cases the presentation is limited to one eye (Day and Carroll, 1962; Kennerdel *et al.*, 1981). Congestive signs and symptoms almost always precede visual loss, which may be gradual or rapidly progressive. On ophthalmoscopic examination the optic discs appear normal in 40% whereas in about one third hyperæmia or frank papillœdema may be seen. In neglected cases with irreversible visual loss, optic atrophy with pallor may be present (Kennerdel *et al.*, 1981). Chorioretinal folds may be an additional fundoscopic finding. The appearance of the optic disc, unless optic atrophy is severe, does not correlate with visual acuity nor does it predict the potential for recovery of vision with treatment.

Visual symptoms of dysthyroid optic neuropathy are often variable and inconsistent, ranging from a normal corrected visual acuity of 6/6 (class VIa) to a sharp decrease to an acuity of 6/60 (class VIc). Colour vision as tested with Ishihara pseudoisochromatic plates or Farnsworth-Munsell 100-Hue test, may be normal, but in the majority of patients is affected to a variable extent. The axial position of the globe as measured by Hertel exophthalmometer, can vary from a minimum of 18 mm (class I) to a maximum of 30 mm (class III). Afferent pupillary responses are found to be defective in most cases of dysthyroid optic neuropathy, but in a minority they are retained. The most consistent finding in dysthyroid optic neuropathy patients is a change in the visual field (Werner, 1969; Kennerdel *et al.*, 1981).

In a large series of patients with dysthyroid optic neuropathy, Trobe found central scotomata in 94%, arcuate or ultitudenal defects in the inferior or superior field in 72%, and a generalised constriction of the field in 25% of patients. The most common perimetric finding was a combination of a central scotoma (with reduced acuity) and an inferior arcuate nerve fibre bundle defect (Trobe, 1981; Sergott and Glaser, 1981).

3.6. ASSESSMENT OF SYSTEMIC CONDITION:

Assessment of thyroid status and the overall clinical evaluation of the patient is essential for confirmation of the diagnosis, detection of associated conditions and planning of future management especially if surgery or systemic steroids are needed.

3.6.1. Systemic diseases with orbital involvement:

A variety of systemic diseases, including lymphoma, sarcoidosis, amyloidosis, and vasculitis, may involve the orbit and present with symptoms and signs similar to those of dysthyroid eye disease. Certain clinical clues are helpful in distinguishing these diseases from Graves' ophthalmopathy. Lymphoma has a predilection for the trochlear area and should be suspected when palpation of the supero-nasal aspect of the orbit reveals nodular areas. The presence of paraorbital disease involving the lacrimal excretory system, upper eyelid, and forehead should also raise the suspicion of lymphoma. Bilateral involvement with lymphoma does occur. When lymphoma is suspected, a biopsy is indicated for confirmation and histological classification (Henderson, 1980).

Sarcoidosis and amyloidosis may involve the orbit and may resemble dysthyroid eye disease because of their variable manifestations. Sarcoid nodules and amyloid deposits can produce proptosis and may result in extraocular muscle enlargement which becomes apparent on CT scanning. Involvement of the eyelids may also occur. Sarcoidosis and amyloidosis are suspected when typical involvement of other organ systems is present. A biopsy gives the definitive diagnosis (Waller and Jacobson, 1984).

Wegener's granulomatosis should be strongly suspected in any patient with bilateral orbital inflammation, nasolacrimal duct obstruction, or a saddle

Thyroid function tests commonly used to assess ophthalmopathy:

Test	Method	Comment
Serum total thyroxine (T4)	Radioimmunoassay	Preferred screening test. Results are influenced by altered thyroxine binding, and it is sometimes increased after radiographic contrast administration or during therapy with thyroxine. The test should not be used for patients receiving estrogens, androgens, diphenylhydantoin of salicylates.
Serum free thyroxine (T4)	Radioimmunoassay	Usually reliable indicator of thyroid function when total thyroxine results are modified due to altered thyroxine binding.
Total serum triiodothyronine (T3)	Radioimmunoassay	This test is abnormal in ~5% of thyrotoxic patients in whom total T4 is normal 'T3 thyrotoxicosis'.
Thyroid Binding Globulin (TBG) binding capacity	Electrophoresis	A direct check on the normality of thyroxine-binding proteins. This test is used if the results of total thyroxine are modified by œdema, androgen, salicylate, pregnancy or diphenylhydantoin.
TRH stimulation test	Intravenous injection of 200-400 micrograms TRH	The test is used when serum total T4 and T3 are in the normal range but subtle hyperthyroidism is suspected e.g., 'euthyroid Graves' ophthalmopathy'. No TSH response is consistent with early hyperthyroidism.
Radioiodine uptake	^{131}I 3mCi orally; measure percent of dose in thyroid at 24 hours	This test distinguishes Graves' hyperthyroidism from other causes of increased serum thyroxine.
T3 suppression test	Baseline radioiodine uptake (24 hours), T3 25 micrograms t.i.d. for 7 days, repeat radioiodine uptake	This test can be thought of as a bioassay for circulating non-TSH stimulators of thyroid function. Because of the T3 dose, it is contraindicated in elderly or cardiac patients.
Thyroid Stimulating immunoglobulins	Various methods	This test is positive in 90% of patients with thyrotoxic Graves' disease and in a smaller percentage of those who have 'euthyroid Graves' disease'.

Table 3.5

(Summarised from Brennan and Gorman, 1984)

nose deformity in the presence of systemic findings which include epistaxis, hæmoptysis, hæmaturia, or arthralgia. The diagnosis may be confirmed by a biopsy of the nasal mucosa (Waller and Jacobson, 1984).

3.6.2. Pathogen related orbital inflammatory processes:

In addition to infective sinus disease which can produce signs of orbital vascular congestion and inflammation along with proptosis and painful ophthalmoplegia, a wide variety of viral, bacterial, fungal, and parasitic infections can involve the orbit and may, especially early in their course, be difficult to distinguish from dysthyroid eye disease. The most lethal of these is mucormycosis, which most commonly occurs in diabetics with ketoacidosis or patients who are immunosuppressed. Survival of the patient depends on early diagnosis and aggressive treatment. Infectious mononucleosis, syphilis, trypanosomiasis, schistosomiasis, systicercosis, and echinococcal disease have all been associated with orbital inflammation producing lid œdema, conjunctivitis, proptosis, and eye muscle dysfunction (Waller and Jacobson, 1984).

3.7. ASSESSMENT OF THYROID FUNCTION:

Guidelines for the selection of thyroid tests from the wide variety available are delineated in Table 3.5, each of which is specific to a given purpose. Assuming that the ophthalmologist will be working with an endocrinologist, the first-line tests to order are measurements of serum T4 and T3, a check of abnormal binding (e.g., serum TBG or T3 resin test), and a radioiodine uptake test. Radiographic contrast material and Amiodarone invalidate the uptake test (Burgi *et al.*, 1976). If thyroid hormone levels and ^{131}I uptake are high, the problem is solved. If one or both are normal, thyroid-stimulating immunoglobulins assays, T3 suppression testing, or TRH stimulation testing may be selected before the diagnosis of Graves' disease is excluded. A few patients who have normal levels of thyroid hormone in their blood and histologic changes of lymphocytic thyroiditis in their thyroid gland may show the typical eye findings of Graves' ophthalmopathy (Brennan and Gorman, 1984).

3.8. TECHNIQUES OF EYE EXAMINATION:

Eye examination includes the measurement of best corrected visual acuity, pupillary reactions, ocular motility, confrontation fields, flash light in-

spection of the external eye and adnexae, biomicroscopy of the external eye and the anterior segment, ophthalmoscopic examination and measurements of the intraocular pressure. Special observations which pertain to the Graves' disease patients are described below as reviewed by McCrary III (1983) and Younge (1984).

3.8.1. Visual acuity and pupils:

Hypermetropia may be induced by pressure of swollen orbital tissues on the back of the globe (Cant and Wilson, 1974), often hinted at by relatively poor near vision. Pinhole acuity may help improve the vision in the presence of tear film or corneal abnormalities not corrected by refraction.

Before the pupils are dilated, a relative afferent pupillary defect may be found with careful testing indicating asymmetrical optic nerve compromise. Such a finding may be lacking if both eyes have similar optic neuropathy. Thus, any cause of reduced vision must be determined including refractive errors, abnormal tear film or corneal drying, retinal distortion by choroidal folds, or optic neuropathy.

3.8.2. Ocular motility:

Double vision, which is commonly vertical, need not necessarily be accompanied by proptosis. The limited ocular movements are not due to ocular muscle paresis, but to a restriction of free rotation of the globe by tight rectus muscles. Poor elevation which is least in the abducted position, improves slightly as the eye moves towards elevation in adduction. Increasing difficulty in elevation in this condition is shown by diplopia, maximal in the abducted position, increasing intraocular pressure on attempted up gaze, and in the most severe cases actual retraction of the globe into the orbit on attempted upward movement. Limited abduction due to a tight medial rectus and reduced depression from superior rectus fibrosis are the next most commonly impaired rotations. Orthoptic measurements of the field of binocular fixation and the Hess chart showing the relative ocular movements are taken at regular intervals (Fells *et al.*, 1988).

Eponyms for external eye signs

Eponym	Definition
Ballet's sign	Complete immobility of globe without internal ophthalmoplegia
Boston's sign	Staring appearance
Enroth's sign	Fullness of lids due to œdema
Gifford's sign	Difficulty in everting upper lid
Griffith's sign	Laging of lower lid on upward gaze
Joffroy's sign	Absence of forehead creases on upward gaze
Kocher's sign	Spasmodic increase in lid retraction with intense fixation
Means' globe lag	More rapid movement of lid in upward gaze compared to globe movement
Möbius' sign	Difficulty converging
Rosenbach's sign	Trembling of lids on gentle closure
Sainton's signs	Contraction of frontalis after levator has ceased
Stellwag's sign	Infrequent, incomplete blinking
Suker's signs	Inability to hold fixation in extreme lateral gaze
von Graefe's sign	Lid lag

Table 3.6

Summarised from Younge (1984).

A forced duction test may be useful to assess limitation of eye movements, but this is stressful to a patient with red eyes, swollen lids, and tearing. An alternative is to measure the intraocular pressure in slight downward gaze and then in extreme upward and outward gaze (Section 3.8.7).

3.8.3. Exophthalmometry:

The orbits should be palpated for the resistance to retropulsion of the globe. This may be asymmetrical, depending on the stage of the disorder. Failure of the globe to recede at least 1 mm into the orbit on measurement with exophthalmometer on the patient in a reclining position is also a sign of expanded and incompliant orbital soft tissue. Although exophthalmometry is not an accurate means of measuring exophthalmos, it is a useful procedure when performed with care, especially if repeated on subsequent visits by the same examiner under similar circumstances with the same instrument.

The Hertel exophthalmometer is the preferred instrument because the optics of the mirror system prevent significant error produced by parallax. It is important to fit the reference pieces comfortably and correctly against the lateral orbital rims so that the same horizontal base measurement is used for subsequent recordings.

3.8.4. Eyelids:

One needs to note the width of the palpebral fissure, the position of the upper lid relative to the superior limbus (e.g., 2 mm above), and the presence of lid lag as the patient follows a target into downward gaze.

One occasionally sees ptosis as a manifestation of Graves' disease and myasthenia can accompany this disorder, producing anomalous eye findings. Many eponyms are used for the external eye signs which are varied and often confusing (Table 3.6).

3.8.5. Ophthalmoscopy:

Disc œdema identical in appearance to that of papillœdema secondary to increased intracranial pressure can occur, and this can seriously compromise

vision if left untreated too long. Choroidal folds may result from increased orbital pressure. After reversal of the underlying disorder, these may persist as pigmented lines even though the folds themselves resolve. Such folds are associated with distortion of vision and decreased visual acuity. The clarity of the media may be impaired because of exposure keratopathy. Indirect ophthalmoscopy is indicated in such cases.

3.8.6. Visual fields:

Perimetry is often difficult in patients with thyroid ophthalmopathy, because of the problem of maintaining comfortable straight-ahead gaze and because of the chronic irritation of the exposed globe.

The most common effect of severe dysthyroid eye disease on the visual fields is generalised depression. There may be arcuate defects or, more rarely, paracentral, central scotomata, or an irregular contraction of the field. Enlargement of the blind spot occurs in cases with disc œdema (Kennerdel *et al.*, 1981).

True glaucomatous defects are rare and occur with a similar frequency as the general population (Ching and Perkins, 1967). Nonetheless, it is common to see patients being treated with anti-glaucoma medications largely because the intraocular pressure may be increased even in the straight-ahead position. In slight downward gaze the pressure is more likely to be normal (Section 3.8.7).

Visual field defects are usually seen in conjunction with impaired colour vision, decreased central visual acuity, prolongation in latency of visual evoked potential and, in asymmetrical involvement, a relative afferent pupillary defect. These findings indicate compromise of optic nerve function. Such defects are often reversible after medical or surgical orbital decompression (Ravin, Sisson and Knapp, 1975; Marcocci *et al.*, 1978; Gasser and Flammer, 1986).

Static perimetry may reveal that the whole of the field is depressed. Central values may be depressed in the presence of normal acuity, as they are in all other mild optic neuropathies, e.g., the optic neuritis of multiple sclerosis. As experience with the automated static perimeters develops, these defects may be seen earlier than with a standard kinetic perimetry (Younge, 1984).

3.8.7. Intraocular pressure:

Applanation tonometry using the Perkins or Draeger hand-held tonometer, allows for accurate central applanation when positional changes are being measured (Manor, Kurz and Lewitus, 1974). By careful head positioning, the slit-lamp mounted Goldmann applanation tonometer can be used to measure the intraocular pressure in straight, up and down directions of gaze whilst still applanating the central area of the cornea.

Braily and Eyre (1901) were the first to report cases with hyperthyroidism and exophthalmos who had evidence of glaucoma by palpation. The studies during the first half of the twentieth century were reviewed by Pohjanpelto (1968), who emphasised the lack of agreement on the question of the link between intraocular pressure and thyroid dysfunction and that tonometry had been poorly developed during that period.

Interest in the relation between thyroid function and intraocular pressure was renewed during the 1960's by the study of Mclenachan and Davis (1965) and Beker, Kolker and Ballin (1966).

Other investigators, paying close attention to eye position when performing tonometry, have failed to confirm previously reported findings. Ching and Perkins (1967), found only two cases of glaucoma in a group of 155 patients with thyroid disease. This prevalence is the same for all individuals over 40 years of age (2.0 to 2.4%).

Lyons (1971), Zappia, Winkelman and Gay (1971) and Gamblin *et al.* (1983), have suggested that the measurement of positional intraocular pressure changes may be clinically useful in the detection of orbital involvement in Graves' disease as well as in monitoring the progression of ophthalmopathy.

The presence of intraocular pressure abnormalities in most patients without clinical eye disease is consistent with orbital ultrasonographic (Werner *et al.*, 1974) and CT studies (Enznann, Donaldson and Kriss, 1979) which also indicate frequent subclinical ophthalmopathy. Pressure changes on eye move-

ments correlate well with the severity of ophthalmopathy as suggested by Draeger and Schneider (1975).

It should be recognised that the presence of positional intraocular pressure changes is not specific for Graves' ophthalmopathy. Both orbital myositis and orbital fracture with inferior rectus entrapment have been shown to cause intraocular pressure changes on upgaze (Zappia *et al.*, 1971).

3.9. IMAGING TECHNIQUES FOR THE DIAGNOSIS AND MANAGEMENT OF DYSTHYROID EYE DISEASE:

3.9.1. Ultrasonography of the orbit:

One of the most important uses of diagnostic ultrasonography in the orbit is the demonstration of fat and extraocular muscles changes accompanying active stages of dysthyroid eye disease. The space between the retrobulbar fat and the orbital wall shows generalised widening. The usually echo-free area occupied by the muscles acquires internal tissue echoes from the histological disorganization within the muscles. Additionally, muscles are compressed against the bony orbital wall, thus producing a better reflecting surface and a more defined outer margin of the muscle and orbital walls. The four rectus muscles may be visualised ultrasonographically by scanning both the horizontal and sagittal meridia. Superiorly, where the orbital roof slopes down towards the apex, one often can distinguish the levator muscle from the superior rectus muscle by the tissue plane separating them (Ossoinig, 1984).

The degree of muscle enlargement varies from being subtle to pronounced, depending on the amount of soft tissue œdema from the disease process. Bilateral changes are often evident ultrasonographically, even when the exophthalmos appears clinically to be unilateral. Quantitative measurements of muscle enlargement are of questionable accuracy, depending on which portion of the muscle is measured and whether the beam is perpendicular or oblique to the muscle. Expansion of the retrobulbar fat volume and a slight enlargement of the optic nerve profile frequently accompany the enlarged extraocular muscle seen ultrasonographically in dysthyroid eye disease.

Although ultrasonic findings are highly suggestive of dysthyroid eye disease, they are not pathognomonic for it. Passive congestion of the orbit secondary to arterio-venous anomalies or active inflammation from cellulitis or pseudotumour may produce similar ultrasonographic findings. Enlargement of a single extraocular muscle, with the other appearing nearly normal in size, is characteristic of myositis or pseudotumour involving one muscle (Dallow, 1986)

3.9.2. Computed tomography of the orbit:

Orbital CT is outstanding in identifying the typical myopathy, often in the contralateral unsuspected eye as well (Leib, 1986).

With CT scanning it is possible to define the type and extent of change in the retrobulbar space, to differentiate it from neoplastic, vascular, and inflammatory lesions, to plan and control orbital radiotherapy in active cases, and to plan surgical orbital decompression.

Computation of extraocular muscle volume on CT identifies the population at risk for developing optic neuropathy (Feldon and Weiner, 1982; Feldon, Muramatsu and Weiner, 1984; Feldon *et al.*, 1985). Doubling of the total extraocular muscle volume is correlated with the development of optic neuropathy, and affected muscles may undergo as much as an eightfold increase in volume in severe cases (Haik, Saint-Louis and Smith, 1986).

Recently, one hundred and fifty-two orbits were studied by Hallin and Feldon (1988). Analysis of CT scans was performed, consisting of a quantitative estimation of extraocular muscle volume, mid-orbital extraocular muscle area, mid-orbital medial rectus muscle area and width. They showed that medial rectus muscle width on a mid-orbital slice of CT scan, which can be obtained manually, was found to reliably distinguish between the group that would develop optic neuropathy and the group that would not.

3.9.3. Magnetic Resonance Imaging (MRI):

MRI produces an image based on hydrogen protons (both density and relaxation, T1, T2). Although in this instance the image is derived from both the tissue density of hydrogen protons and its T1 or T2 value, it is possible to derive

images based on fluoride or sodium or other atomic nuclei with odd numbers of protons or neutrons. Thus, it is potentially possible to obtain high-resolution, anatomically correct images of the orbit and to image different biochemical substrates of the orbital tissues. Nuclei other than hydrogen result in images that have a relatively poor signal to noise ratio because of their low abundance in vivo and lower magnetic moment than hydrogen (Isherwood, Pullan and Ritching, 1970; Bottomley *et al.*, 1984).

Imaging of the orbit by MRI has been available only for the last few years. The initial experience has been either that the MRI offers no advantage over CT scanning (Han *et al.*, 1984), or that results are competitive with those of CT images (Mosely, Brant-Zawadzki and Mills, 1983; Hawkes *et al.*, 1983). In these studies a slice thickness of 7-12 mm was imaged. At present, CT is capable of 1.5 mm slice thickness and a resolution of 0.75 by 0.75 mm. For MRI to be equally sensitive, the spatial resolution of the images must be improved by decreasing both pixel size and their slice thickness. The limitation of the low-magnetic field MRI systems is that their inherent signal to noise ratio do not permit thinner sections and finer spatial resolutions without degrading the image quality. To improve the signal to noise ratio, the scan time must be increased to an unacceptable duration.

Zimmerman *et al.* (1985) used a surface coil with a large diameter as a transmitter to produce relatively uniform excitation throughout the image plane. A surface coil with a smaller diameter placed over the orbit acted as the receiver. Using a surface coil increases the signal to noise ratio permitting the use of much smaller pixels. The improvement in signal to noise ratio is a function of bringing the receiver coil closer to the anatomy being scanned, so that MRI signals are derived from tissues within the area of interest whereas only minimal noise is derived from tissues outside this area.

3.9.4. Advantages and limitations of different imaging techniques:

Standardised A-scan ultrasound can often determine the nature of intraocular or intraorbital disease based on microscopic anatomical differences in tissue texture which result in alterations in tissue acoustic reflectivity. CT can often aid in diagnosis based on differences in Roentgen density and anatomical

localisation (Mosely *et al.*, 1983). Both of these techniques, however have significant limitations.

Many disease processes give similar ultrasound appearances, e.g., lymphoma and pseudotumour. CT can be hampered by overlying bone and cannot distinguish between soft-tissue masses, which are radiologically isodense. In addition, CT exposes the patient to substantial doses of x-radiation (Chan and Chukovsky, 1976; Harris and Levene, 1976; Isherwood *et al.*, 1970). However, some surgeons consider that the delineation of bone is an advantage which makes CT more helpful than other imaging techniques in planning surgical orbital decompression.

Magnetic resonance imaging techniques are not hampered by bone since it is a solid structure with low molecular mobility that renders it relatively invisible on MRI images (Zimmerman *et al.*, 1985). Therefore, soft tissues are seen in an unobstructed fashion.

Computer tomography has scan times in the order of 5-10 seconds where surface-coil MRI has scan times of 3-8 minutes with a potential for shorter times. For the present, CT is faster than MRI (Hawkes *et al.*, 1983; Sassani and Osbakken, 1984; Han *et al.*, 1984).

MRI does not expose the patient to ionizing radiation and is safe as employed clinically (Wolff *et al.*, 1980), provided the patient is free from foreign metal and has no cardiac pacemaker, which might inadvertently be turned on or off (Finn *et al.*, 1985). Furthermore, MRI techniques promise not only to distinguish between lesions based on location and tissue structure but also on the basis of metabolic profile (Isherwood *et al.*, 1970; Crooks *et al.*, 1980; Bottomley *et al.*, 1984; Zimmerman *et al.*, 1985). Although these techniques are in their clinical infancy, recent developments indicate that MRI techniques will offer much needed information for improvement of clinical diagnosis and management of patients with thyroid ophthalmopathy (Weiss, Haik and Smith 1986).

3.10. TREATMENT OF DYSTHYROID EYE DISEASE:

A number of medical treatments and surgical procedures have been advocated for dysthyroid eye disease. Although none has proved to be ideal, some do have a definite place in the treatment of certain types of ophthalmopathy. In this section these modalities are presented and discussed to see how they fit into the therapeutic picture.

3.10.1. Guanethidine:

It has been shown that mild to moderate degrees of lid retraction can be ameliorated by local instillation of the adrenergic blocking agent Guanethidine. Cant, Lewis and Harrison (1969) treated 81 patients with upper lid retraction for an average of 54 weeks with either 10, 5, or 2% Guanethidine eye drops. They found the treatment to be effective in almost all cases. Two percent drops were much less effective, and 10% caused eye pain and punctate keratitis. They advised the use of 5% drops instilled into the eyes three times a day. They also found that when treatment was stopped the eyelids of most of the patients returned to their former position. Crombie and Lowson (1967) and Bowden and Rose (1969) reported that in addition to decreasing the lid retraction, instillation of 5% Guanethidine eye drops decreased the proptosis, although others (Gay and Wolkstein, 1966; Cant *et al.*, 1969; Haddad, 1973) have not found any effect on proptosis. A decrease in intraocular pressure in patients so treated has been noted by Crombie and Lawson (1967) and Cartlidge *et al.* (1969).

3.10.2. Oral corticosteroids:

The most frequently used medical treatment for severe thyroid ophthalmopathy is the oral administration of corticosteroids. In 1953, Kinsell, Partridge and Foreman reported improvement in 9 such patients who received large doses of both cortisone and ACTH. In 1955 Brain reported moderate to marked improvement in 8 of 28 patients treated with either cortisone or ACTH, usually in relatively small doses.

In 1966 Werner reported remarkable immediate improvement following the sustained administration of unusually large doses of prednisone (120-140 mg/day) of two patients with advanced changes of Graves' disease. However,

Systemic steroids:	
Hoffenberg	1958
Brown *et al.*	1963
Day	1967
Riley	1972
Mulherin, Temple And Cundey	1972
Aper *et al.*	1975
Freiwald and Gonzalez	1986
Nagayama *et al.*	1987

Table 3.7

Reports which document the immediate beneficial effects of giving large doses of corticosteroids to patients with severe Graves' ophthalmopathy.

he pointed out that this treatment could not be relied on to induce a permanent remission.

Many reports have now appeared which document the immediate beneficial effects of giving large doses of corticosteroids to patients who have severe ophthalmopathy either alone or combined with orbital radiotherapy or immunosuppressive agents. Some of such reports are listed in Table 3.7.

3.10.3. Subconjunctival and intraorbital injection of corticosteroids:

Several workers have reported the beneficial effect of subconjunctival or retrobulbar injection of corticosteroids for the treatment of Graves' ophthalmopathy. Garber (1966) treated 15 patients with such injections using 10-15 mg of methylprednisolone acetate and reported that all patients obtained relief from the symptoms of ocular discomfort, ranging from 'moderate' to 'dramatic', after the first injections. The number of injection varied from two to 18 over time periods ranging from 2 to 24 months. The intervals between injections were lengthened progressively as indicated. The aim of treatment was to maintain improvement until a spontaneous remission of the disease occurred.

Riley (1972) treated 27 patients and reported minor improvements in most patients. Trobe, Glaser and Laflamme (1978) saw no perceptible change in five eyes treated with repeated injections of 60mg of triamcinolone acetonide. They cautioned that such subconjunctival or retrobulbar injections should not be used for a prolonged period because of the risk of causing glaucoma.

On the other hand Haddad (1973) has advocated the injection of steroids into the retrobulbar or subtenon space as a test for the effectiveness of oral steroid therapy.

3.10.4. Plasmapheresis:

The successful use of intensive plasma exchange in the treatment of one patient with severe thyroid ophthalmopathy was originally reported by Dandona *et al.* (1979). Later, the same investigators reported on a total of 7 patients with Graves' ophthalmopathy treated with plasmapheresis: Four were in an acute

stage and responded favourably, while 3 presented with chronic disease and did not respond to treatment (Dandona *et al.*, 1980). Because of possible relapses after plasma exchange, treatment was combined with subsequent administration of immunosuppressive drugs.

Sawers *et al.* (1981) reported improvement in the ophthalmopathy of two patients treated with plasma exchange, prednisolone and cyclophosphamide, and one patient treated with plasma exchange and pednisolone.

Confirmation of the beneficial effects of intensive plasma exchange in severe thyroid ophthalmopathy was shown in a preliminary study by Glinoer *et al.* (1981) and in 1986 the same investigators treated nine patients with severe Graves' ophthalmopathy by intensive plasma exchange, followed by immunosuppression. Each patient was submitted to 4 plasmapheresis sessions over a period of 5 to 8 days. A total of 8.5-10 liters of plasma was removed and replaced by frozen plasma, concentrated albumin solution or stable solutions of plasma proteins. Immunosuppressive therapy with prednisolone (40mg/day) and azathoprine (100mg/day) was administered to all patients from the day following the last plasmapheresis session. The severity of ocular involvement and response to therapy were evaluated clinically by numerical scoring based on the ophthalmopathy index of Donaldson *et al.* (1973). Serum thyroid stimulating immunoglobulin and urinary excretion of glucosaminoglycans were measured immediately before and immediately after plasmapheresis. Plasma exchange was rapidly accompanied by marked clinical improvement in 8 patients. The most marked effects were on soft tissue involvement, proptosis, intraocular pressure, and visual acuity. The ophthalmopathy index decreased from 9.7 (+/- 4.1) to 5.7 (+/- 2.2) ($p<0.001$) after plasmapheresis. Serum thyroid stimulating immunoglobulin levels were initially elevated in 6 patients and remained positive in 3 patients after treatment. Urinary glucosaminoglycans excretion was initially 2 to 12 fold normal levels and was decreased by 60%. After plasmapheresis, patients received immunosuppressive drugs for three to six month. The follow-up period, after withdrawal of drugs, ranged from 5 to 38 months with a median of 17 months. The ocular condition remained stable in 6 patients. Three patients had relapse one year after plasmapheresis; they were treated a second time by plasma exchange with subsequent improvement.

In conclusion, intensive plasma exchange provided prompt and effective improvement in patients with severe progressive Graves' ophthalmopathy. Relapses were responsive to further plasmapheresis therapy. This therapeutic procedure followed by immunosuppression, gives long lasting results.

3.10.5. Immunosuppression:

Because of the suggested autoimmune pathogenesis of the ophthalmopathy of Graves' disease, treatment with immunosuppressive agents has been tried. Burrow *et al.* (1970) treated five patients with azathioprine 2mg/kg/day for periods of 8 to 11 weeks for three patients and for more than 36 weeks for one patient with no improvement in ophthalmopathy.

In 1979 Bigos *et al.* reported some success with the use of cyclophosphamide in three patients. They did not report any side effects from the drug.

Ten patients with severe Graves' ophthalmopathy, resistent to other therapeutic regimens were treated with cyclosporin A over a period of six months. Clinically, nine patients improved, two of them only after addition of corticosteroids. Intraocular pressure on upward gaze decreased in all of these nine patients. In six patients there was a significant decrease in eye muscle thickness under the treatment as determined by computerised tomography. Side effects (e.g., paræsthesia and proteinuria) which were observed under high doses of cyclosporin A disappeared after lowering the dose. It was concluded that this drug appears to be valuable for treatment of severe Graves' ophthalmopathy when previous therapeutic regiments turned out to be unsuccessful (Utech *et al.*, 1985).

Witte *et al.*, (1985) treated 13 patients with severe Graves' ophthalmopathy with cyclosporin A. They concluded that cyclosporin A was not able to stop acute progression of ophthalmopathy in one patient and did not obviate surgical decompression of the orbits in two more patients. There was no measurable effect of treatment on underlying immunological process with regard to thyroid disease. Kvetny *et al.* (1986) studied six patients and also concluded that cyclosporin A has no effect in the treatment of Graves' ophthalmopathy, but rather exerts serious renal effects.

On the other hand, three recent studies showed that cyclosporin A is effective both in terms of improvement of the acute signs and symptoms and in relapse prophylaxis of Graves' ophthalmopathy (Kahaly *et al.*, 1986; Glinoer and Schrooyen, 1987; Utech *et al.*, 1988).

It can be concluded that treatment of thyroid ophthalmopathy with a low dose of cyclosporin A combined with plasmapheresis (Sawers *et al.*, 1981; Glinoer *et al.*, 1986) or orbital radiation (Teoh and Woo, 1987) needs further investigation.

3.10.6. Radiotherapy:

Pituitary irradiation:

External orbital irradiation has been employed sporadically for more than 50 years. The earliest reports (Thomas and Woods, 1936; Mann, 1946) comprised those of isolated cases and were poorly documented. In later series attention was focused on pituitary irradiation when effective therapeutic responses were occasionally noted months after radiotherapy (Dobyns, 1950; Hermann, 1952; Beierwaltes, 1953).

Orbital irradiation:

In 1951 Jones indicated that orbital irradiation was more successful in the treatment of thyroid ophthalmopathy than pituitary irradiation; a finding further supported by Gedda and Lindgren (1954) and Horst, Sautter, and Ulerich (1960). However, in all these early reports documentation of the eye and orbital changes was not standardised. The main doses were delivered using low energy x-ray beams with poor collimation, different field sizes were employed, and the results were disappointing except in those cases in which the posterior portion of the orbit was either deliberately or inadvertently included in the radiation field (Beierwaltes, 1950; 1953; Blahut, Beierwaltes and Lampe, 1963).

In 1973, Donaldson *et al.* reported significant improvement in patients with severe Graves' ophthalmopathy after supervoltage orbital radiotherapy. They reported the use of a well collimated high energy x-ray beam generated by a linear accelerator. Their patients received a total orbital dose of 2000 Rad which was usually calculated at the midline and was given in 10 fractions over a 2 week

period. The beam was angled 5 degrees posteriorly to avoid the lens of the contralateral eye. They reported a good to excellent response in 15 (65%) of 23 patients treated and no serious complications were observed.

In 1975, Ravin *et al.* treated a series of 37 patients. They found that patients with optic nerve involvement have the best response to radiation treatment and suggested this as a primary treatment modality for dysthyroid optic neuropathy. They also concluded that patients with only proptosis probably should not be treated with radiotherapy. Trobe *et al.* (1978) also reported beneficial effects of radiation treatment for dysthyroid optic neuropathy.

Teng *et al.* (1980), studied 20 patients with 'moderately severe' ophthalmopathy due to Graves' disease. Their results were disappointing, about half of the patients showed some improvement, but the benefit was 'not impressive', and in fact were minor and mainly in soft tissues which could not be assessed objectively. Proptosis improved in only 25% of patients and by 2 mm at most. Patients with long-standing ophthalmoplegia, presumably associated with fibrotic extraocular muscles rarely responded. Their overall results were not as good as Donaldson *et al.* (1973), or Covington, Lobes and Saudarsanam (1977), who found good to excellent results in about 65% of their patients. The difference might partly be explained by the fact that their patients had had a longer duration of involvement (the mean duration was more than 3 years), which was also less severe; and none of their patients were suffering from optic neuropathy.

Thus, orbital irradiation may be beneficial in acute ophthalmopathy where there is lymphocytic infiltration of the muscles and orbital tissues, but, it is unlikely to have any effect when this infiltration has been replaced by fat or fibrous tissue. Indeed, as it is clear from the literature, and as one might expect, unsuccessful cases were treated late or as a last resort after failure of other treatment modalities.

Previous reported complications of the orbital irradiation for Graves' ophthalmopathy included: Periorbital and conjunctival œdema, hair loss, erythema, headaches, increased proptosis, diplopia, nausea, and vomiting. These complications had been transient and mild and no permanent sequelae were reported (Ravin *et al.*, 1975; Trobe *et al.*, 1978).

Radiation retinopathy is well known to occur after total dose exceeding 3500 Rad which generally is considered to be the upper limit to safe dosage. Other important variables that need to be considered to avoid complications of radiation include the total elapsed time during the course of the irradiation, and the size and number of radiation fractions (Duke-Elder and MacFaul, 1972).

Sporadic reports of radiation retinopathy after reportedly safe doses of radiotherapy have appeared in the literature. Bagan and Hollenhorst (1979), reported retinal microaneurysms in an eye after only 2000 Rad delivered to a pituitary tumour, and Perrers-Taylor (1965), reported radiation retinopathy after a retinal dose of approximately 1700 Rad. In addition, Tomsak and Smith (1980), reported a case of radiation retinopathy after irradiation of the whole head with 3300 Rad for palliative treatment of metastatic carcinoma.

Mewis, Tang and Salmonsen (1982) described three patients with radiation retinopathy after 2500-3000 Rad for choroidal metastases. These three patients, however, were treated also with chemotherapy for systemic effects, which is known to be associated with an increased risk of ocular damage due to irradiation (Chan and Shukovsky, 1976). Other risk factors include hypertension, diabetes mellitus, collagen vascular disease and large fraction size (Harris and Levene, 1976).

Bagan and Hollenhorst (1979), reported radiation retinopathy and optic atrophy secondary to irradiation after treatment of Graves' ophthalmopathy with high doses of irradiation, but the doses were not stated. The clinical similarities between irradiation and dysthyroid optic neuropathy make it difficult if not impossible to determine which diagnosis is correct in patients with Graves' ophthalmopathy who have had prior orbital irradiation, particularly if the CT scan is equivocal for optic nerve compression at the orbital apex.

Recently, a group of 62 patients treated with orbital irradiation has been reported by Hurbli *et al.* (1985), almost all patients had been on treatment with high doses (60-120mg/day oral prednisone). Those who had no response, incomplete response or transient improvement were treated with radiation. Different radiation sources were used during the course of this study. Most patients received 20 Gy at 2.5 to 3 cm depths (or in the case of bilateral treatments to the mid-plane) in ten daily fractions over 12 to 14 day period. In all but two cases

corticosteroids were decreased and stopped within two weeks of radiation. Four patients required surgical decompression, they did not appear to be significantly different from those who responded favorably to radiation in terms of length of the disease, amount of visual disability, or medication usage. Unfortunately there were no comments on the histopathology of the orbital tissues of these four patients. The first objective sign of response to radiation occurred between two days to two months after the start of the treatment (mean 14 days). The maximum benefit was observed at one to 14 months (mean 5.6 months). External beam irradiation reduced or eliminated signs and symptoms of thyroid ophthalmopathy in approximately 56% of patients. In 74% of those with non-chronic myopathy (34 of 46 cases), motility disturbances were alleviated. As others have noted, radiation was most effective in patient with relatively recent thyroid eye disease with marked soft tissue signs (Kriss *et al.*, 1983; Bartalena *et al.*, 1983). No morbidity with radiation delivered to the orbits in the manner described was observed.

At 20 Gy given in 10 fractions, patients are unlikely to develop significant ocular complications. Vascular retinopathy occurs with significantly higher doses or in patients whose ocular vasculature is compromised from diabetes, other vascular disorders or systemic chemotherapy (Chan and Shukovsky, 1976; Harris and Levene, 1976).

Radiation therapy is useful in the management of some patients of dysthyroid eye disease, particularly those with recent onset of marked tissue signs, proptosis, optic neuropathy or myositis. Radiotherapy may play a role in cases of acute congestive ophthalmopathy, as an alternative to steroid therapy or before contemplating orbital decompression. Radiation therapy was found not to be useful in patients with mild and long-standing noninflammatory thyroid ophthalmopathy (Konishi *et al.*, 1986; Pigeon *et al.*, 1987; Marcocci *et al.*, 1987). More recently the treatment field was limited to the orbit based on the rationale that this disease is a cellular immune-reaction in the extraocular muscles and is not hormonal in origin. Radiation therapy as described above has less morbidity than long-term corticosteroids and does not make subsequent surgical decompression more difficult if this becomes necessary (Hurbli *et al.*, 1985).

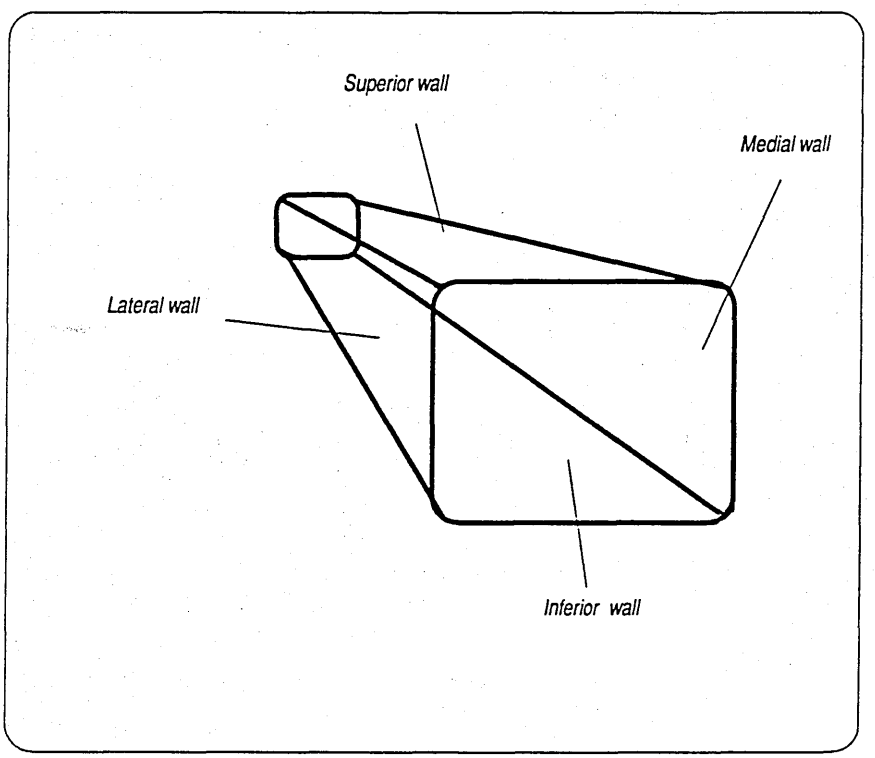


Figure 3.1

Showing the right orbital walls forming a four sided pyramid.

3.10.7. Orbital decompression:

Whenever the pathophysiology of a disease is incompletely understood, treatment tends to be multifaceted and directed toward alleviation of symptoms rather than resolution of the disease. This is true for dysthyroid eye disease.

The ideal treatment would be to identify the process which leads to massive enlargement of the extraocular muscles and periorbital fat, stop the process, and then reverse it. Unfortunately this is not possible at this time. Systemic steroids and radiation therapy do have effects on the process. Surgical decompression of the orbit is usually recommended when the control of thyroid disease, local ophthalmic therapy, and systemic steroids fail.

Orbital decompression is not an ideal treatment. It does nothing to alter the basic process. In fact, the orbital contents are merely displaced rather than reduced. There is consistent alleviation of certain problems, but other problems are created i.e., extraocular muscle imbalance. The concept of decompression is relatively simple. There is too much tissue in a limited space, and either the tissue must be removed or the space enlarged.

The bony orbit can be thought of as a four sided pyramid, in which the apex represents the optic canal and the base the orbital rim. This leaves four walls designated as superior, inferior, medial, and lateral. The superior wall comprises primarily the orbital process of the frontal bone. The lesser and the greater wings of the sphenoid and the zygomatic bone forms the lateral wall. Inferiorly is the maxilla. The medial wall comprises the ethmoid and lacrimal bones (Figure 3.1). Orbital decompression procedures involve the removal of one or more of these walls. This alleviates pressure and creates space to accommodate excess orbital tissue (Harner, 1984).

Indications for decompression fall into three categories: Decreasing visual acuity, deterioration of colour vision, disc œdema and increasing visual field defects. These emergency situations are the unquestioned indications for orbital decompression.

Keratitis, chemosis, diplopia and lid œdema are relative indications for surgery. Early reports dealing with dysthyroid eye disease were not concerned with cosmetic appearance as an indication for surgery. This is an important fact to remember when evaluating results. A series that includes patients operated for cosmetic reasons requires better results and fewer complications.

The operative procedures can be placed into one of three groups: lateral approach, superior approach and inferior approach

The lateral approach:

Lateral approach has been used primarily by ophthalmologists. It is the same surgical approach which Krönlein described in 1888 to remove tumours in the infratemporal fossa and retrobulbar area. The lateral approach requires a skin incision somewhere in the region of the lateral canthus or over the zygomatic arch. Usually a significant portion of the temporalis muscle is removed. The lateral rim and wall of the orbit are removed from anterior to posterior. The bony walls can be removed superiorly across the midline nearly to the ethmoid complex. The inferior wall and approximately half of the medial wall can also be removed by this approach. Generally the decompression is considered to be less than that achieved with the inferior approach even when combined with that of the superior approach. The four wall dissection of Kennerdel and Maroon (1980; 1982) is reported to yield 10-17 mm of recession. Although results are satisfactory, there are some negative aspects of this approach.

Generally, only one side is operated on at a time and some type of external incision is necessary in order to expose the lateral orbital rim. This, combined with the removal of a segment of the lateral orbital rim and temporalis muscle creates a subsequent noticeable change in facial appearance.

The space available with the lateral approach is limited. There are the problems of bleeding, paralysis of the frontalis muscle, and post operative weakness of the lateral rectus muscle.

The superior approach:

The first example is the frontal craniotomy approach described and popularised by a neurosurgeon, Naffziger and Jones (1932) and the second is the pte-

rion approach described by Welti and Offert (1943) and used by a number of surgeons (Rowbotham and Clarke, 1956; Hamby, 1964; Backlund, 1968).

Initially, Naffziger and Jones described the removal of only the superior roof on one side. Later they recognised that the lateral orbital wall should also be removed and that both sides could be decompressed in one procedure. It is important to recognise that this procedure is intracranial but extradural.

The results of this approach are good, vision is stabilised or improved, ocular motility is improved, and the appearance is satisfactory in most cases. The degree of recession varies, but the average (from series in the literature) seems to be around 3 mm (Harner, 1984).

Frontal lobe injury, intracranial hæmorrhage, cerebrospinal fluid rhinorrhea and meningitis are potential problems but in fact are very uncommon. The limited space available for decompression is a much more significant criticism of this procedure. The external incision and deformity secondary to the bone flap can also be distressing.

Another criticism has been post-operative pulsating exophthalmos. However, this did not seem to be a problem from the patient's point of view (MacCarty *et al.*, 1970).

The pterion approach has the same goals as the trans-cranial, i.e., removal of the superior and lateral orbital walls (Welti and Offert, 1943). As in the transfrontal approach, the lateral rim of the orbit is preserved. The scar created by the procedure is inconspicuous and the bony defect well covered by temporalis muscle. The basic results and potential complications are otherwise the same as with the transfrontal procedure, but generally the two sides are operated on at different sessions.

The inferior approach:

Currently the inferior approach is the most widely used and accepted decompression technique. This procedure can be carried out either by a transan-

tral or a transorbital approach. The greatest number of decompressions have been done by otolaryngologists using the transantral rout.

The inferior approach has tremendous appeal because it provides the greatest space for transorbital contents. The concept of transantral orbital decompression is to remove the bony wall between the orbit and the ethmoid and the maxillary sinuses. The technique is described by DeSanto (1984). The ability to preserve or restore vision, improve ocular motility, and enhance appearance is excellent. Potential complications include blindness, cerebrospinal fluid leakage, orbital cellulitis, sinusitis, nasolacrimal duct obstruction and persistent numbness of the face. The advantages are that there is no external incision, no facial deformity, and morbidity is minimal.

The most consistent criticism of the transantral approach has been the relatively high incidence of extraocular muscle imbalance, ptosis of the globe, the need for secondary eye muscle surgery and persistent diplopia.

Transorbital decompression has been criticised first because it utilises a transcutaneous lid incision with scarring and some degree of deformity. Exposure through the inferior fornix combined with lateral canthotomy results in an inconspicuous incision. The medial, inferior, and lateral walls can be approached.

As with all the various approaches the results are quite good. The average recession achieved approaches 6 mm, which is slightly higher than most reports of the transantral procedures. The complications, morbidity, and mortality of this procedure should be the same as with the transantral procedure.

Until 1970, nearly every patient who was surgically decompressed had 'malignant exophthalmos'. By definition they had failing vision, corneal ulcers, ophthalmoplegia, and severe proptosis. Multiple treatment options had been utilised and failed. The goal in these patients was prevention of blindness or possible death. Over the past 10-15 years the success of orbital decompression has lead to significant changes in indications for surgery. This means greater numbers of patients with milder degrees of disease, better results, and fewer complications.

Lateral and superior approaches can achieve reasonable results in the preservation of vision and prevention of corneal ulcers. However, in the milder cases, the cosmetic defects of these procedures are unacceptable. The transantral inferior approach achieves excellent results. It has the logical appeal of greater space for orbital contents, no cosmetic defects, short hospitalisation, and acceptable morbidity and mortality. Even the incidence of diplopia has decreased as the milder cases are treated surgically. Furthermore, the incidence of inadequate decompression via the anterior approach is higher than with the transantral approach. Transantral decompression allows for complete removal of the posterior ethmoidal air cells and successful decompression of the orbital apex (Gorman, Waller and Dyer, 1984). However, many ophthalmologists prefer the anterior approach because the anatomy is more familiar.

It is obvious that consistently successful surgical decompression requires the removal of two walls of the orbit. It now seems that three or more walls can be safely removed when indicated (DeSanto, 1984).

If decompression is indicated it still represents only one stage in the overall rehabilitation of a patient with dysthyroid eye disease. Control of thyroid function, correction of extraocular muscle imbalance, and relief of residual lid retraction require coordinated efforts by several medical and surgical disciplines.

PART II.

EXPERIMENTAL STUDIES

CHAPTER 4.

OBJECTIVES OF THE PRESENT STUDY

4.1. INTRODUCTION:

Microcomputers:

Microcomputers are powerful, flexible, portable and relatively cheap tools. They are easy to operate and have excellent graphics capabilities. Therefore, they can be adapted to solve a wide range of clinical problems.

In the present study, some aspects of the use of microcomputer techniques in ophthalmic diagnosis and management will be investigated. Thyroid ophthalmopathy will be taken as an example in order to demonstrate the application of these techniques.

The clinical problem of thyroid ophthalmopathy:

It is now generally agreed that dysthyroid eye disease is most probably an autoimmune disease affecting primarily the extraocular muscles, with possible roles of pituitary or thyroid hormones in modifying the course of the disease. However, the ætiology and the exact pathophysiology of the immune disturbance are yet to be known.

4.2. THE NEED FOR FURTHER RESEARCH:

The following problem areas had been identified after reviewing thyroid eye disease literature.

(a) Immunology:

The following problems require further research in clinical immunology.

1- There is no direct immunoassay for thyroid-stimulating immunoglobulins. The availability of such test will help in making the diagnosis as well as in following up the patients.

2- A biochemical or immunological test which is specific to thyroid ophthalmopathy is needed.

3- Identification of the ætiological factors and the pathophysiological processes is required.

4- A specific treatment which prevents the immune disturbance or modifies the reaction of the body is required.

(b) Patient management:

The following problems require further research to optimise the techniques which are currently used for making the diagnosis and planning the management of patients. These techniques are empirical in most cases.

The diagnostic problem:

No single clinical or laboratory test is currently available which is sufficiently sensitive or specific to make or confirm the diagnosis of dysthyroid eye disease.

- The natural history of this disorder is not clearly known.
- Current classifications and scoring systems are either complicated and therefore impractical or inadequate. No system is available which helps to predict the prognosis and the disease course.
- Many of the currently used clinical tests are subjective and the majority of them are interpreted qualitatively.

The management problem:

- The number of cases is small.
- The course is variable.
- The follow-up is long.
- No clear guidelines are available regarding the choice of treatment.
- Treatment is nonspecific and directed to the effects rather than the cause of the disease.

Therefore, thyroid ophthalmopathy is an appropriate area for studying the application of microcomputer techniques.

(c) Computing techniques:

The facilities offered by microcomputers have not been fully exploited in the field of clinical ophthalmology. Further research is required which involves

clinicians and computer scientists working closely in solving clinical problems. Three areas were identified which need further investigations:

1- The use of the graphics capabilities of microcomputers in devising new tests and refining existent equipment for patient assessment.

2- The application of image processing techniques in quantifying charted clinical information automatically.

3- The application of artificial intelligence approaches in the diagnosis and management of ophthalmic patients.

4.3. AIMS OF THE PRESENT STUDY:

4.3.1. The long term effects of dysthyroid eye disease:

1- To study the long term effects of thyroid ophthalmopathy.

2- To investigate the relative importance of various clinical signs and symptoms of the disease as well as the investigations for making the diagnosis and planning the management of patients.

3- To identify the risk factors and to devise a technique for predicting the outcome in terms of severity of the course of the disease.

4.3.2. The use of microcomputers in patient assessment:

To provide an example of the uses of microcomputers in assessment of patients which involves:

(1) To devise a microcomputer-based clinical test for the assessment of 'temporal visual acuity' using Snellen optotypes.

(2) To present an account of the process of development of the system and its evaluation.

(3) To provide guidelines regarding the potential clinical applications of this test.

4.3.3. The use of microcomputers in data interpretation:

To provide an example of the use of microcomputers in the interpretation of patient data by devising a universal chart reader which automatically di-

gitises the images of various ophthalmic charts and extracts the charted information and applies various calculations and formulae to score and quantify this information.

4.3.4. Expert system for the diagnosis and management of dysthyroid eye disease:

1- To discuss the various approaches to computer aided medical decision making systems.

2- To provide an example of the use of microcomputers as medical decision support systems by building a 'disease-specific' expert system model which gives advice on the diagnosis and management of dysthyroid eye disease.

3- To provide an account of the methodology followed in the development of the prototype expert system so developed.

4- To investigate the difficulties which may be encountered in building expert system models.

5- To investigate the potential use of expert systems designed to run on microcomputers in clinical ophthalmology.

6- To study the proposed expert system with a view to understanding and investigating the value of expert system programmes in achieving the following aims:

- To investigate the issues involved in designing consultation programmes.
- To investigate the nature of expertise to be formalised.
- To improve the accuracy and reliability of clinical decisions.
- To improve the cost efficiency of tests and therapies.
- To improve understanding of the structure of medical decision making.
- To disseminate rare and costly expertise.

- To integrate the various sources of knowledge.

This thesis reports the first stage of a project to develop a model of an ophthalmic clinic automation system. This project is running jointly with Mr. A. Wail, who is currently a research fellow at the Signal Processing Division of the Electronic and Electrical Department of Strathclyde University. Achieving the above delineated aims will conclude the first stage and establish the foundations for the second stage of the project in which further refinement of the prototype computer systems will take place. These systems will then be integrated so that they will be operated using one universal user interface.

CHAPTER 5.

LONG TERM EFFECTS OF DYSTHYROID EYE DISEASE

5.1. INTRODUCTION:

Current knowledge concerning the long-term outcome of dysthyroid eye disease is limited. Hales and Rundle (1960) carried out a retrospective review of 104 patients with an approximately 15 year follow-up. They presented their results in terms of lid retraction, ophthalmoplegia and exophthalmos and concluded that lid retraction disappears in a large number (60%) of patients so affected. Ophthalmoplegia remained unchanged in approximately two thirds of patients and exophthalmos reaches its peak early in the course of the disease and becomes static near its maximum. The study described in this chapter was carried out in order to gain greater insight into the natural evolution of dysthyroid eye disease and to determine which features at presentation constitute the principal risk factors for the development of adverse complications.

In the early 1960s a prospective review of patients with dysthyroid ophthalmopathy was started in the Tennent Institute of Ophthalmology, Glasgow. A wide range of investigations was carried out upon these patients who have since been followed up in detail over an average of 10 years. The assessment of the long- term effects of this disorder on systemic and ocular structure and function of those patients forms the basis of the information presented in this chapter.

The overall amount of data available comprises 140 pieces of information concerning each of 224 patients. Eight thousand contingency tables have been derived from this information and subsequently evaluated. The accent of this thesis is towards the utilization of computers in ophthalmology and to that end the results presented in this chapter comprise a small proportion of the data available, but they have been carefully selected as those which provide the knowledge base for the computer expert system (subsequently described in Chapter 8).

5.2. PATIENTS AND METHODS:

5.2.1. Patient identification:

All patients who had been entered into the prospective study of dysthyroid eye disease between 1961 and 1983 were identified and traced (Section 5.2.4).

5.2.2. Inclusion criteria:

Patients were included in this study if they met with the following criteria:

(1) Adequate clinical data recorded at the onset of the eye disease (Section 5.2.5).

(2) Comprehensive follow-up data for four or more years.

(3) Evidence of disturbed thyroid function either at presentation or during follow-up.

5.2.3. Patient assessment:

All the case records were examined and data collected (Section 5.2.4). Those patients for whom a comprehensive clinical examination was carried out four or more years after the onset of the disease and who demonstrated no detectable change were deemed to have sufficient data for demonstration of a 'final' outcome. The patients for whom these data were not available were traced and underwent detailed assessment of the features described in Section 5.2.5. The last available clinical data of patients who were deceased was considered 'final'. Those patients who could not be traced and for whom adequate 'final' data was not available were not included in the study.

5.2.4. Data collection:

A list of patient names and/or hospital numbers was prepared from the following sources:

- Ophthalmic photography department: The information available between 1963 and 1987 was used.
- Operating theatre books: These were available for between 1975 and 1987.
- Orthoptic department records: For which data was available between 1969 and 1987.

Plate 5.1

Photocopied Patient information.

The collection of data was carried out during five-hour sessions, five times per week for 12 months. Case records from the following Glasgow hospitals were scrutinised.

- The Western Infirmary,
- Gartnavel General Hospital.
- The Eye Infirmary.

Patient identification was completed using the record office microfilm 'master index' and by examination of microfilm reels and case notes.

Photocopies of the relevant pages of the case notes and the microfilms were made to include the following information:

- Administrative and personal information.
- Relevant clinical notes and letters.
- Visual field charts.
- 100-Hue colour vision test charts.
- Hess charts.
- Orthoptic assessment reports.
- Thyroid biochemistry results.

Plate 5.1 is a photograph of all the photocopied information.

5.2.5. 'Final' assessment of patients:

Patients undergoing routine clinic visits were identified and examined by the author. Those not undergoing follow-up for whom inadequate 'final' follow-up data were available were asked to return for assessment by the author. Eighty six percent of 145 such patients attended.

The protocols of clinical examination and investigations are shown in Figures 5.1 and 5.2.

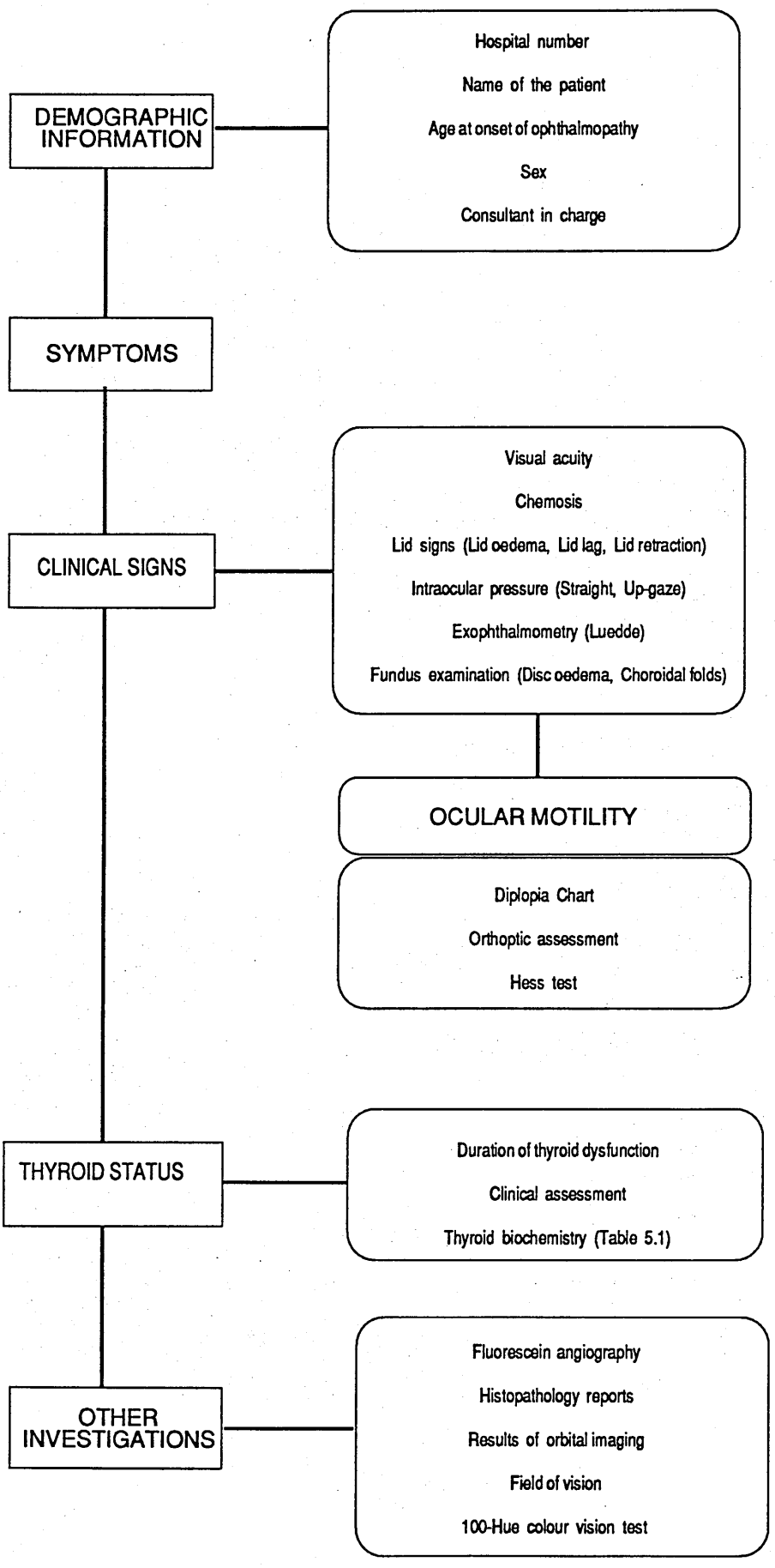


Figure 5.1 Data examined at presentation (for all cases).

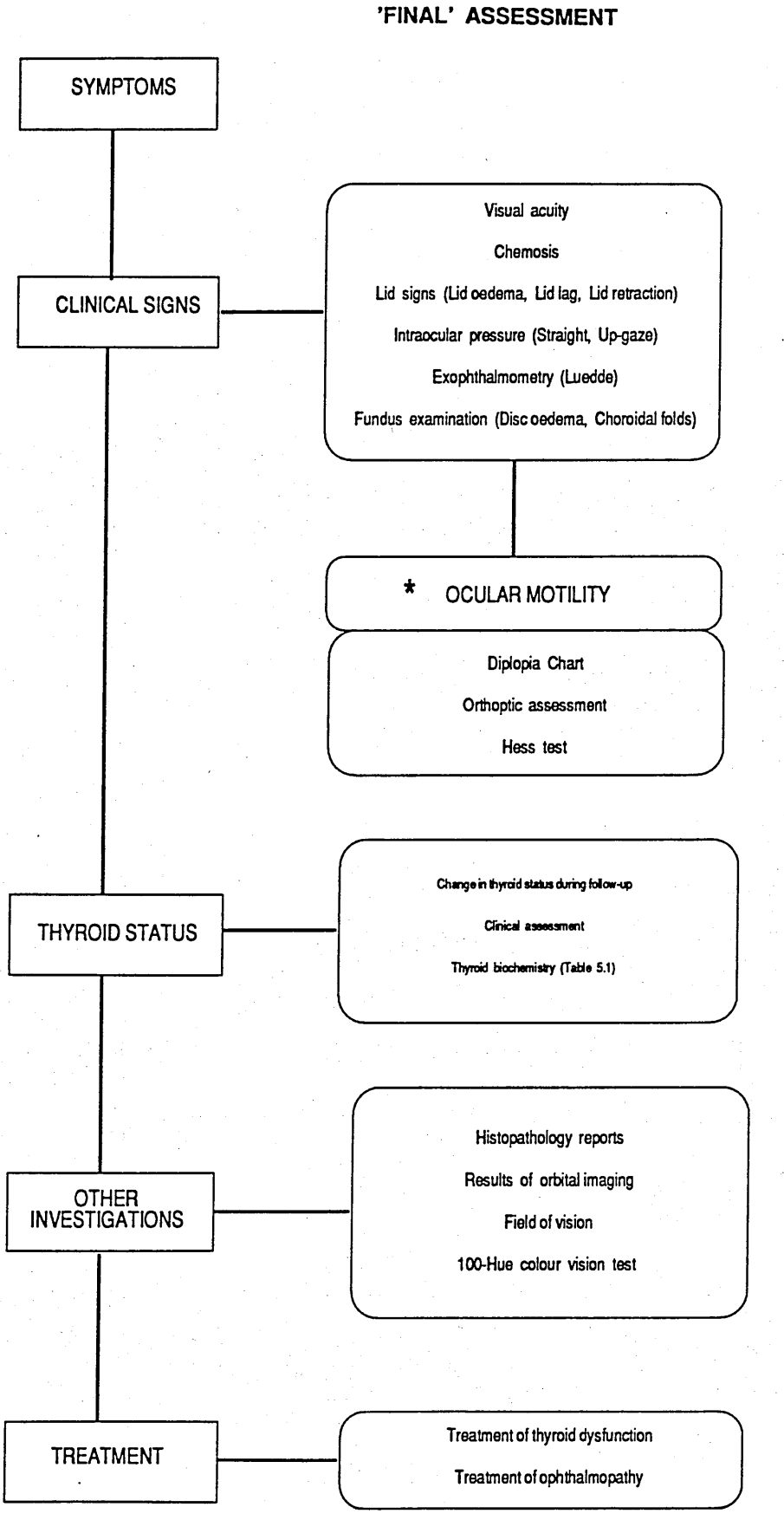


Figure 5.2 Data examined at 'final' assessment for all cases.

* Features examined on 'final' assessment for patients demonstrating disturbance of ocular motility

Examination techniques:

Visual acuity:

The Snellen internally illuminated chart was used to assess the visual acuities of all patients.

Eyelid signs:

Lid lag, lid retraction, lid œdema chemosis and ptosis were qualitatively evaluated and coded into two categories, present or absent (Appendix C1). No attempt at quantification of these parameters was made because this was the only classification used at the time of initial assessment of patients.

Cornea:

Slit lamp examination, for fluorescein and Rose Bengal staining were used to assess the corneal condition and to detect exposure keratitis.

Intraocular pressure:

The Goldmann applanation tonometer mounted on a Haag-Streit slit lamp was used to measure the intraocular pressure. The intraocular pressure was recorded while the patient was looking straight ahead and in extreme upgaze. Applanation of the central part of the cornea on upgaze was ensured by manipulating the patient's head accordingly.

Exophthalmometry:

The Luedde exophthalmometer had been used for initial assessment of the vast majority of patients and therefore was also used for the 'final' examination in order to provide comparable data.

Extraocular muscle function:

A simple diplopia chart was used to document the direction of gaze in which diplopia could be elicited in the clinic. A full orthoptic assessment was also carried out and included the Hess screen test on those patients with detectable motility disorders.

Thyroid function tests:
- Protein-bound iodine.
- Radio-active iodine uptake ratio.
- T3 Resin uptake ratio.
- TSH radio-immuno assay.
- TRH stimulation test.
- Total and free serum T4.
- Total and free serum T3.
- T3 suppression test.
- Thyroid scan.

Table 5.1

Thyroid function tests used in this series. The trend for using individual tests changed with time (e.g., Protein-bound iodine which was the most frequently used test at the outset of the study was gradually replaced by other tests.)

Field of vision:

Kinetic perimetry of the central visual field was carried out using the Tübingen perimeter. Copies of all the field charts were kept for subsequent quantification and analysis (Chapter 7).

Colour vision testing:

The Farnsworth-Munsell 100-Hue test had been used both initially and at follow-up visits. Most of the results were recorded in chart form without the original figures. Photocopies of these charts were also made in preparation for defining the axis and calculating the error score of colour vision impairment (Chapter 7).

Fluorescein angiography:

Fluorescein angiography and orbital venography had been performed upon 20 patients in this series as part of a study of ocular and orbital circulations in 'infiltrative' dysthyroid eye disease by Cant and Wilson (1974). (Thirteen patients showed a delayed arm-retina circulation. Six patients had bilateral and one unilateral papillœdema. One patient had bilateral optic nerve atrophy. Seven patients showed pronounced chorio-retinal folds. The angiograms were repeated 2 months after starting treatment by which time the arm-retina circulation times had returned to the normal range and the optic disc œdema had subsided. Despite the rapid disappearance of optic disc œdema, the chorio-retinal folds were still present 6 months after starting therapy and they resolved only very slowly after this. The study demonstrated that interference with orbital and then, later, ocular circulation occurs as a result of orbital infiltration). It had been decided after the end of the study that fluorescein angiography need not be repeated because little information had been obtained relevant to the management of the patients.

Thyroid status:

For the majority of cases clinical and biochemical assessment (Table 5.1) of thyroid function had been carried out in the endocrinology department at the Gardiner Institute, Glasgow.

Plate 5.2

Table of coded patient data stratified and stored on the computer hard disk.

5.2.6. Data coding:

One hundred and forty parameters of ocular and systemic status were identified for each patient. A coding system was devised to allow all this data to be entered into the computer system and manipulated (Appendix C1).

5.2.7. Data stratification:

Coded data were entered into an IBM/AT microcomputer and stored on its hard disk using SPSS/PC+ V2.00 DATA ENTRY II programme (Appendix C2). This programme allows for conversion of the data file into different file formats suitable for handling by various spread sheet programmes and statistical packages which are capable of running on both mainframe and microcomputers. Plate 5.2 shows the table containing the coded data stored on the computer hard disk.

5.2.8. Data handling:

Statistical Package:

SPSS/PC+ V 2.00 BASE module was the main statistical package for performing descriptive statistics and cross tabulation. SPSS/PC+ ADVANCED STATISTICS was used to implement discriminant function analysis statistics. All the statistical tables were produced using the SPSS/PC+ TABLES module (Appendix C2).

Patient groups:

In this study attention will be focused on the aspects which are directly relevant to making the diagnosis and planning the management of thyroid ophthalmopathy patients. Therefore, the patients were grouped into the following major subcategories:

- 'Mild disease'. This group includes those cases whose management had required only conservative measures and did not involve systemic steroids, orbital radiotherapy or orbital surgical decompression.

- 'Severe disease'. This group includes those cases who had been deemed to be severe enough to necessitate systemic steroids, orbital radiotherapy or orbital surgical decompression or any combination of them.

Plate 5.3

Demonstrating the large size of cross-tabulation results.

During the follow-up period surgical orbital decompression was performed for sight threatening conditions and not for cosmetic reasons in all but one patient.

Statistical techniques:

Summary statistics of all groups were first completed followed by cross tabulation of each possible combination of variables. The printed results came out as a large file of more than eight thousand pages (Plate 5.3). These tables were examined and the most relevant and interesting ones have been included in Appendix C3. Examples of these results are discussed in the following sections.

No significant difference was found between the right and left eyes for any of the 32 parameters studied in this series. Many of these parameters are related to functions which in spite of being performed by each eye individually, are finally dependent on one and the same visual processing system. For such parameter statistical analyses performed apply only to the data appertaining to the right eyes. Right and left eye data were not pooled for any statistical test.

The independent t-test was used to compare means of numeric variables. The linear discriminant function analysis was used for the calculation of risk prediction equations.

5.3. RESULTS:

5.3.1. Population characteristics:

During the time allocated for data collection (12 months) 258 case notes from a total of 408 identified patients were available for examination. Two hundred and twenty four (86.8%) of these patients met with the inclusion criteria (Section 5.2.2).

The population of our series consisted of 174 (78%) females and 50 (22%) males. The distribution of sex in the original list which contains 408 names is 295 (72%) females and 113 (28%) males which does not vary significantly from the overall study group.

Summary of the studied sample:	
Total number of patients identified	**408**
- Females	295
- Males	113
Number of case notes available	**258**
- Appointments sent for re-assessment	179
Dead	7
Moved	3
Did not attend	24
- Number of cases entered into the study	**224**
Males	50
Females	174
Routine follow-up	49
Patients attended for re-assessment	145
Dead (adequate data)	9
Moved (adequate data)	21

Table 5.2

General information and summary of the studied series of patients.

Of the 224 patients, at presentation, the youngest was a 17 year-old girl and the oldest an 86 year-old man. The different age groups at presentation were normally distributed with the mean being 49 years (Figure 5.3). Table 5.2 summarises the main characteristics and findings in this population.

Figure 5.4 shows the distribution of the duration of thyroid dysfunction prior to the onset of ophthalmopathy at the time of presentation (excluding the 49 patients who were euthyroid). The mean duration of thyroid dysfunction was just over 52 months while the mode was 12.

The mean follow-up time for this study is just over 10 years with a standard deviation of 6.

5.3.2. Systemic findings:

Thyroid status:

As expected the largest proportion of patients were hyperthyroid at presentation (46%). However, just over half were either hypothyroid (32%) or euthyroid (22%). All the patients who presented initially as being euthyroid developed thyroid dysfunction during the follow-up period (as this was one of the inclusion criteria). Eventually 15% of patients became hypothyroid and 85% euthyroid with or without thyroid hormone replacement therapy at the time of 'final' assessment.

Treatment of thyroid dysfunction:

In our series 38% had received radioiodine treatment and 43% had had the antithyroid drug carbimazole. Only 19% had undergone partial thyroidectomy prior to presentation with ophthalmopathy.

5.3.3. Severe and mild groups:

Population details:

Of the 224 patients, 167 (75%) were included in the mild group while 57 (25%) met with the criteria for inclusion in the severe group. In the mild group 34 (20.4%) were males with a mean age of 47.7 years and 133 (79.6%) were females with a mean age of 49.1 years. The number of males in the severe group was 16 (28.1%), which constitutes a larger proportion than the mild group and

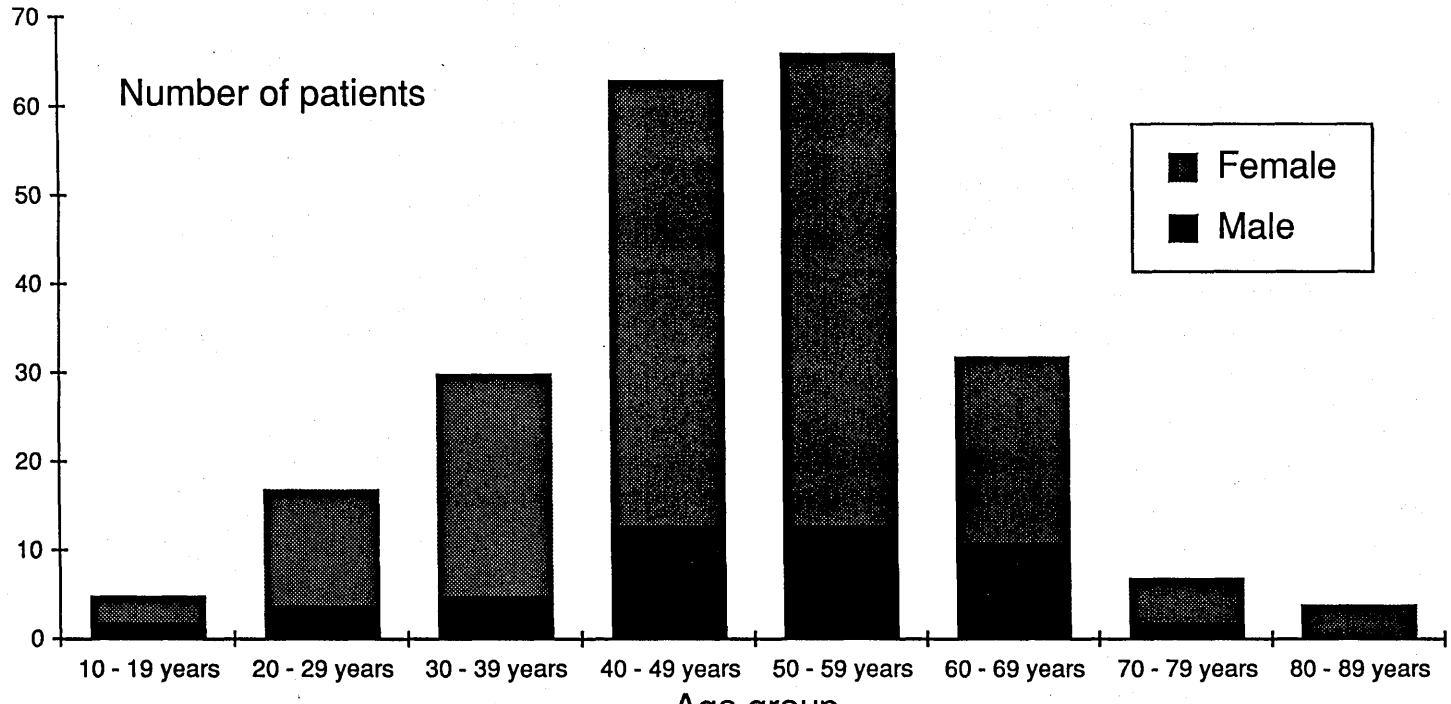


Figure 5.3

Distribution of age groups of males and females in the whole series.

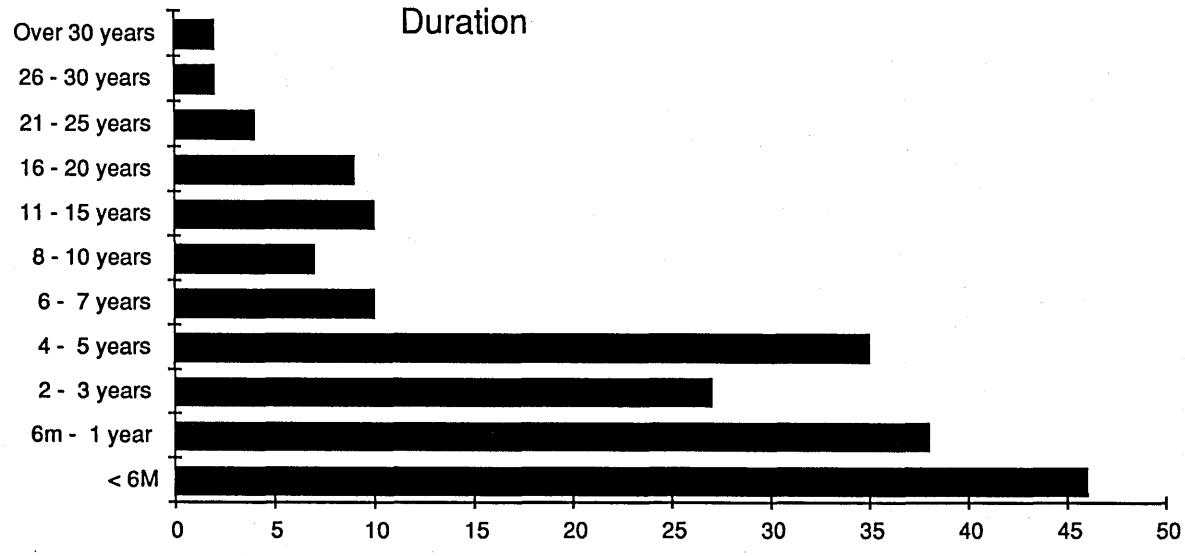


Figure 5.4
Duration of thyroid dysfunction prior to the onset of ophthalmopathy.

the mean age of the males was also about one decade higher at 53.3 years. The number of females was 41 (71.9%) and the mean age was 45.9 years.

Duration of thyroid dysfunction:

In this series the mean time from the date of diagnosis of thyroid dysfunction to the onset of ophthalmopathy for females was 59.4 and 43.3 months for the mild and severe groups respectively ($p<0.314$). The mean duration for males was 21.4 months in the mild and 26.8 months in the severe group ($p<0.727$) These values are not significant, however, the difference between males and females is significant and means that fewer males develop ophthalmopathy but if they do this tend to occur more quickly than in females.

Follow-up period:

The mean follow-up periods for the mild and severe groups were 10.8 and 9.7 years respectively. However, the mean follow-up period for the females (10.5 years) was two years more than that for males (8.2 years). In the mild group the mean follow-up period was 10.8 years for males and 10.6 years for females.

Systemic findings:

Thyroid status:

About a quarter of each of the 'thyroid status' groups (at onset) developed severe ophthalmopathy. Twenty six (25%) of the hyperthyroid patients, 20 (28.2%) of the hypothyroid patients and 11 (22.4%) of the euthyroid patients developed severe disease.

Goitre:

The presence of goitre was documented in 77 (42%) of the 185 patients for whom this sign was sought. Of these, 16 (20.8%) patients developed severe disease. Of the 108 patients who did not have goitre at presentation, 32 (29.6%) patients developed severe disease. On the other hand, one third of the severe disease group and 44.5% of the mild group had had goitre.

On 'final' assessment only 14 (10.9%) patients in the whole group still had goitre. Four of them were in the severe group and 10 in the mild group.

Pretibial dermopathy and thyroid acropachy:

Only 3 (5.9%) patients in the severe group and 4 (2.9%) in the mild group had had pretibial dermopathy, while thyroid acropachy was documented in only one patient who was eventually classified into the severe group.

Thyroid myopathy:

None of the severe group patients had had thyroid myopathy at onset, the two reported cases were among the mild group. However, during the follow-up period, one patient in the severe group developed thyroid myopathy.

Treatment of thyroid dysfunction:

Antithyroid drugs:

At presentation, 87 (43%) patients had had carbimazole treatment for hyperthyroidism. Of these 24 (27.6%) patients developed severe disease. Of the 111 patients who were treated by other means 27 (24.3%) patients developed severe ophthalmopathy.

Radioactive iodine:

Of the 78 patients who were treated with radioactive iodine, 23 (29.5%) developed severe disease while out of 126 patients who did not have this treatment 28 (22.2%) developed severe ophthalmopathy.

Partial thyroidectomy:

Partial thyroidectomy had been carried out for 40 patients before the onset of ophthalmopathy. Of these 11 (27.5%) were eventually placed in the severe group. Out of the 166 patients who did not have surgery, 41 (24.7%) were in the severe group.

Ocular conditions:

Eyelid and conjunctiva:

Fifty (98%) patients in the severe group had lid lag compared to 135 (88.2%) in the mild group. Only one case (2%) of the severe group had no detectable lid lag. Lid retraction was detected in 187 patients of whom 52 (27.8%) were

Mild and severe groups

	Severity of Disease		Row total
	mild	severe	
Cornea R. Normal cornea	138 76.7% 85.7%	42 23.3% 73.7%	180 100.0% 82.6%
Punctate keratitis	21 63.6% 13.0%	12 36.4% 21.1%	33 100.0% 15.1%
Corneal ulceration	1 25.0% .6%	3 75.0% 5.3%	4 100.0% 1.8%
Corneal scarring	1 100.0% .6%		1 100.0% .5%
Column total	161 73.9% 100.0%	57 26.1% 100.0%	218 100.0% 100.0%

TABLE 5.3
The condition of the cornea at onset
in mild and severe groups.

in the severe group. On the other hand only one case in the severe group had no lid retraction.

Lid œdema was documented in 58.8% (30) of the severe group of patients and in only 30.6% (45) of the mild group. Also 40% of those who presented with lid œdema developed severe disease in contrast to 17.1% of those who did not present with lid œdema. Similarly 74.4% of patients who presented with chemosis were in the severe group while only 20.9% of those without chemosis were in this group. Finally, one case only in the mild group presented with ptosis rather than lid retraction.

Cornea:

Table 5.3 shows that 26.4% [n=15] of the severe group presented with corneal involvement while only 14.2% [n=23] of the mild group had corneal abnormalities. Also it can be seen that 23.3% [n=42] of the patients presented with normal corneae developed severe ophthalmopathy later while 36.4% [n=12] of the patients presented with superficial punctate keratopathy and 75% [n=3] of those who presented with corneal ulceration developed severe disease.

Fundus examination:

Five cases presented with disc œdema which obviously placed them into the severe disease group. Only three cases presented with choroidal folds, two of these progressed to severe ophthalmopathy.

Extraocular muscles:

Diplopia was one of the presenting symptoms in 90 patients. In 51 of them diplopia was mild, in 28 patients diplopia was moderate and in 11 patients diplopia was severe (Appendix C1). Table 5.4 demonstrates that 31% [n=16] of the mild diplopia patients, 46% [n=13] of the moderate diplopia patients and only 18% [n=2] of the severe diplopia cases took the severe course. In contrast, only 20% [n=26] of patients who did not have diplopia on presentation developed severe disease.

Tables 5.5 and 5.6, which show the relation between the course of the disease and diplopia at presentation as detected by clinical examination and as assessed by Hess screen testing respectively, establish results which are com-

Mild and severe groups

	Severity of Disease		Row total
	mild	severe	
Symptom of diplopia No diplopia	103 79.8% 63.6%	26 20.2% 45.6%	129 100.0% 58.9%
Mild diplopia	35 68.6% 21.6%	16 31.4% 28.1%	51 100.0% 23.3%
Moderate diplopia	15 53.6% 9.3%	13 46.4% 22.8%	28 100.0% 12.8%
Severe diplopia	9 81.8% 5.6%	2 18.2% 3.5%	11 100.0% 5.0%
Column total	162 74.0% 100.0%	57 26.0% 100.0%	219 100.0% 100.0%

TABLE 5.4
Diplopia as a presenting symptom
in mild and severe ophthalmopathy groups.

Mild and severe groups

	Severity of Disease		Row total
	mild	severe	
Diplopia on examination No diplopia	88 83.0% 55.7%	18 17.0% 31.6%	106 100.0% 49.3%
Up / down	6 54.5% 3.8%	5 45.5% 8.8%	11 100.0% 5.1%
Add / abd	12 48.0% 7.6%	13 52.0% 22.8%	25 100.0% 11.6%
Close to midline	17 73.9% 10.8%	6 26.1% 10.5%	23 100.0% 10.7%
Extreme gaze	35 70.0% 22.2%	15 30.0% 26.3%	50 100.0% 23.3%
Column total	158 73.5% 100.0%	57 26.5% 100.0%	215 100.0% 100.0%

TABLE 5.5
Diplopia elicited on initial examination
in relation to mild and severe groups.

*(**Up/down** = Diplopia on elevation or depression.*

***Add/abd** = Diplopia on adduction or abduction.)*

Mild and severe groups

	Severity of Disease		Row total
	mild	severe	
Ocular motility R. Normal	82 84.5% 52.9%	15 15.5% 26.8%	97 100.0% 46.0%
R. Up gaze	31 79.5% 20.0%	8 20.5% 14.3%	39 100.0% 18.5%
R. Down gaze	1 33.3% .6%	2 66.7% 3.6%	3 100.0% 1.4%
R. Up & Down	8 80.0% 5.2%	2 20.0% 3.6%	10 100.0% 4.7%
R. Add	1 50.0% .6%	1 50.0% 1.8%	2 100.0% .9%
R. Add & Abd	7 53.8% 4.5%	6 46.2% 10.7%	13 100.0% 6.2%
Combination	25 53.2% 16.1%	22 46.8% 39.3%	47 100.0% 22.3%
Column total	155 73.5% 100.0%	56 26.5% 100.0%	211 100.0% 100.0%

TABLE 5.6
Ocular motility (orthoptic assessment) at onset in mild and severe groups.

*(**R. Up gaze** = Restricted up gaze.*

***R. Down gaze** = Restricted down gaze.*

***R. Up & Down** = Restricted up and down gaze.*

***R. Add** = Restricted adduction.*

***R. Add & Abd** = Restricted adduction and abduction, **Combination** = Combination of restrictions.)*

parable to Table 5.4. As expected, by clinical examination more cases of ocular motility disorders (109) were detectd.

The relationship between thyroid and ocular myopathy:

In this series both of the patients who presented initially with thyroid myopathy [n=2] and the patients who developed myopathy later [n=1] all developed extraocular muscle dysfunction.

Intraocular pressure:

The mean intraocular pressure at presentation of the mild group was 16.8 mm. Hg. and the standard deviation was 4, while in the severe group it was 19 mm. Hg. and the standard deviation was also 4. This difference was statistically significant ($p<0.002$). On 'final' assessment both the mild and the severe groups had identical mean intraocular pressures of 16.2 mm. Hg. with standard deviations of 3 ($p<0.937$).

The mean intraocular pressure on upgaze was 22.5 mm. Hg. for the mild group and the standard deviation was 6, while in the severe group it was 25.6 mm. Hg. and the standard deviation was 5 ($p<0.052$). On the 'final' assessment the mild group mean pressure was 21 mm. Hg. and the standard deviation was 5 while in the severe group, the mean was 19.2 mm. Hg. and the standard deviation was 4. This difference was not significant ($p<0.200$).

Furthermore, the number of cases diagnosed as having and who were treated for open angle glaucoma in the whole series was only 5 (2.2%).

Exophthalmometry:

The mean exophthalmometric reading of the severe group (22.9 mm.) was significantly higher than that of the mild group (20.6 mm.)($p<0.0005$). The 'final' outcome for both groups was very close, with readings of 20.6 and 20.5 in mild and severe groups respectively ($p<0.924$).

MILD GROUP

CASE NO.	INITIAL V. ACUITY	'FINAL' V. ACUITY	EXPLANATION OF LOW VISUAL ACUITY
028	2/60	3/60	Strabismic amblyopia
096	6/60	C F	Myopic degeneration
203	C F	C F	Old retinal detachment
009	6/12	C F	Senile cataract
062	6/12	6/60	Senile cataract
197	6/12	6/60	Marked glaucomatous cupping

Table 5.7 Explanation of visual loss in patients of the mild group whose visual acuity was 6/36 or less at presentation or at 'final' assessment.

Treatment of ophthalmopathy:

Of the 57 patients in the severe group 19 (33%) had been treated with systemic steroids only and 18 (32%) had undergone surgical decompression while 20 patients (35%) required both.

Extraocular muscle surgery was carried out for 37% [n=21] of the severe group and for only 5% [n=12] of the patients in the mild group.

Permanent tarsorrhaphy was required for 11% [n=6] of the severe group and for 5% [n=8] of the mild group.

5.3.4. Visual acuity:

Figure 5.5 shows the distribution of the various visual acuity levels of the whole series at presentation. The majority of patients in either the severe or the mild groups had visual acuities of 6/18 or better and the most frequently recorded acuity was 6/6. The same also applies to the distribution of visual acuity at 'final' assessment (Figure 5.6).

Figure 5.7 shows that the majority of patients had 'final' visual acuities which, in general, did not differ from those at the initial assessment. Both mild and severe groups behaved in a similar manner regarding the 'final' visual acuity (Figure 5.8). However, the two cases with the worst 'final' visual outcome were amongst the severe group.

The scattergram of Figure 5.9 shows that the overall visual outcome of patients who underwent orbital decompression and those who were treated with steroids only is nearly the same. However, two cases in the steroid treated subgroup ended up with the worst 'final' visual acuity of the whole series.

Table 5.7 shows that amblyopia, myopic degeneration, and old retinal detachment were the causes of reduced visual acuity at presentation in three patients in the mild group. The 'final' visual acuities of the other three patients were reduced because of senile cataract in two and advanced glaucoma in the third patient.

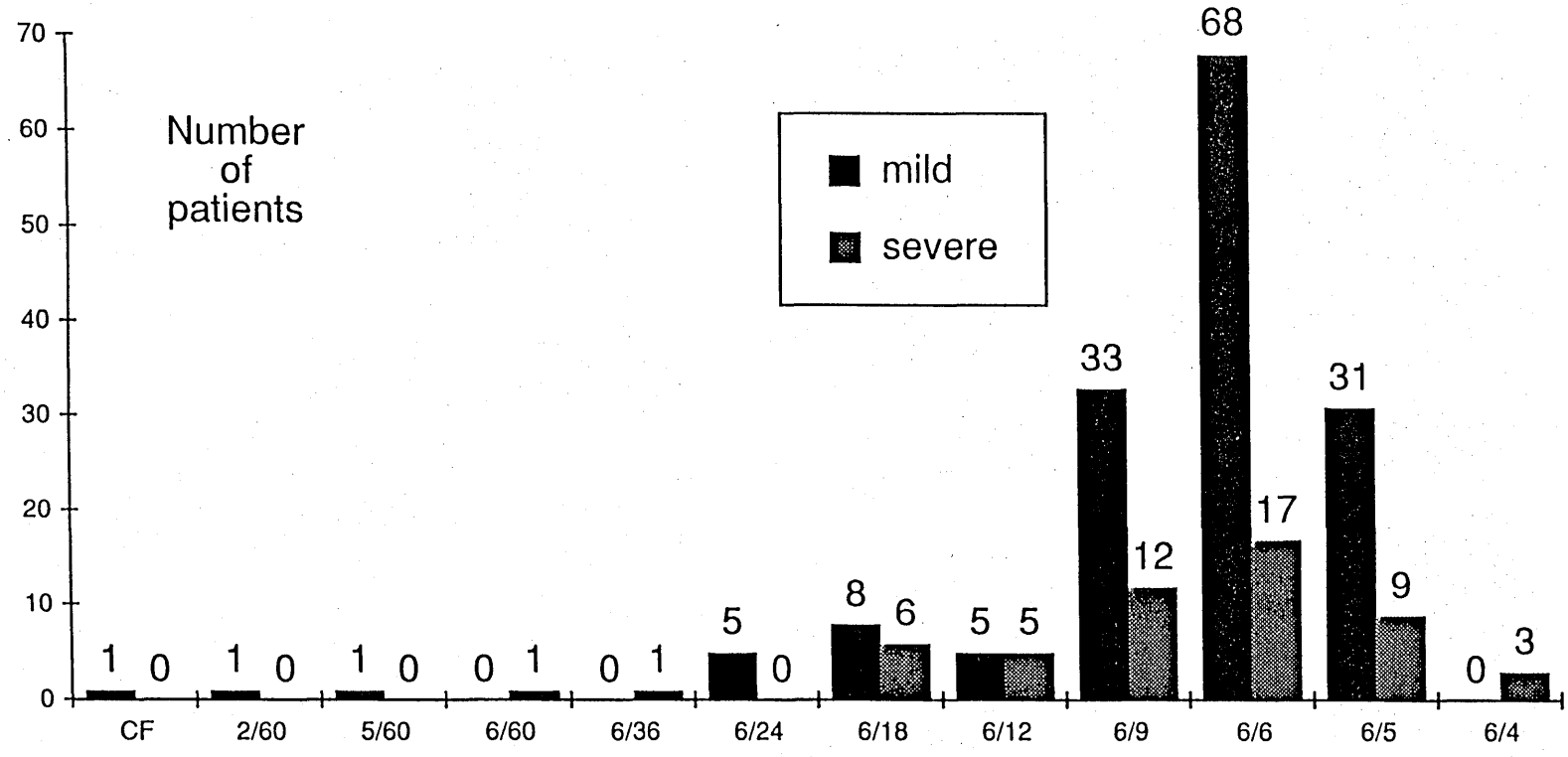
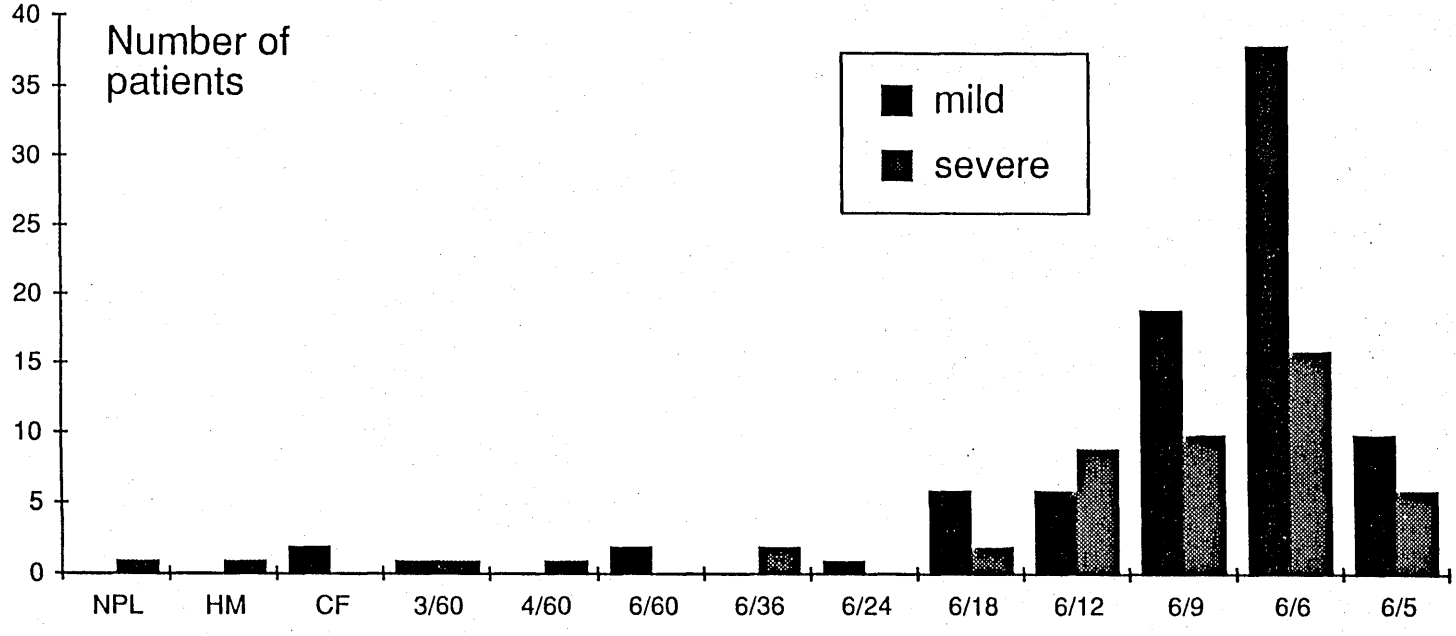


Figure 5.5
Visual acuity at presentation in the mild and severe groups.



Visual acuity

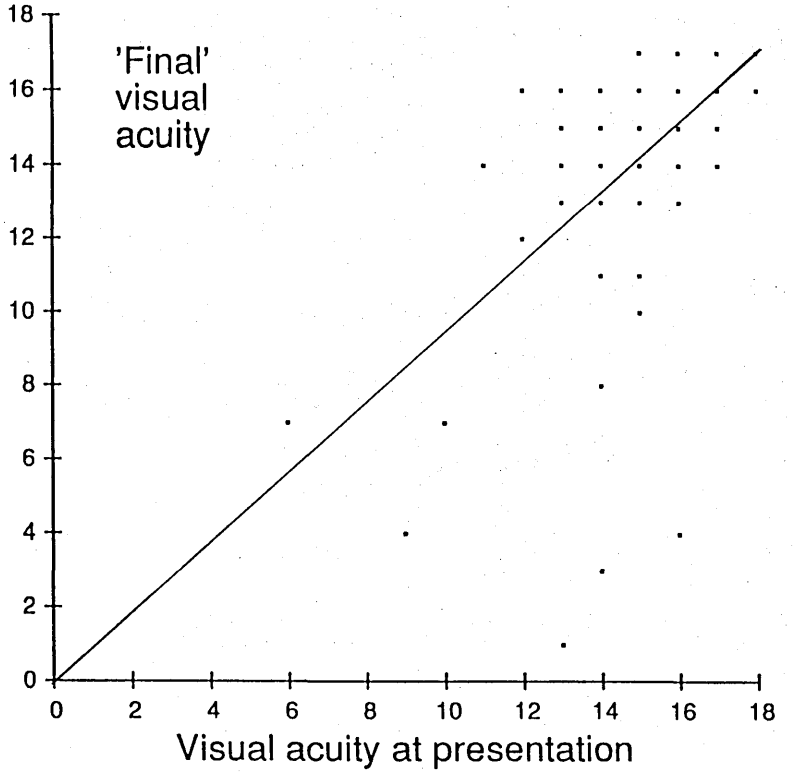
Figure 5.6

'Final' visual acuity of the mild and severe groups.

Figure 5.7

The initial and 'final' visual acuities of the whole series.

01=NPL	**02=PL**	**03=HM**
04=CF	**05=1/60**	**06=2/60**
07=3/60	**08=4/60**	**09=5/60**
10=6/60	**11=6/36**	**12=6/24**
13=6/18	**14=6/12**	**15=6/9**
16=6/6	**17=6/5**	**18=6/4**



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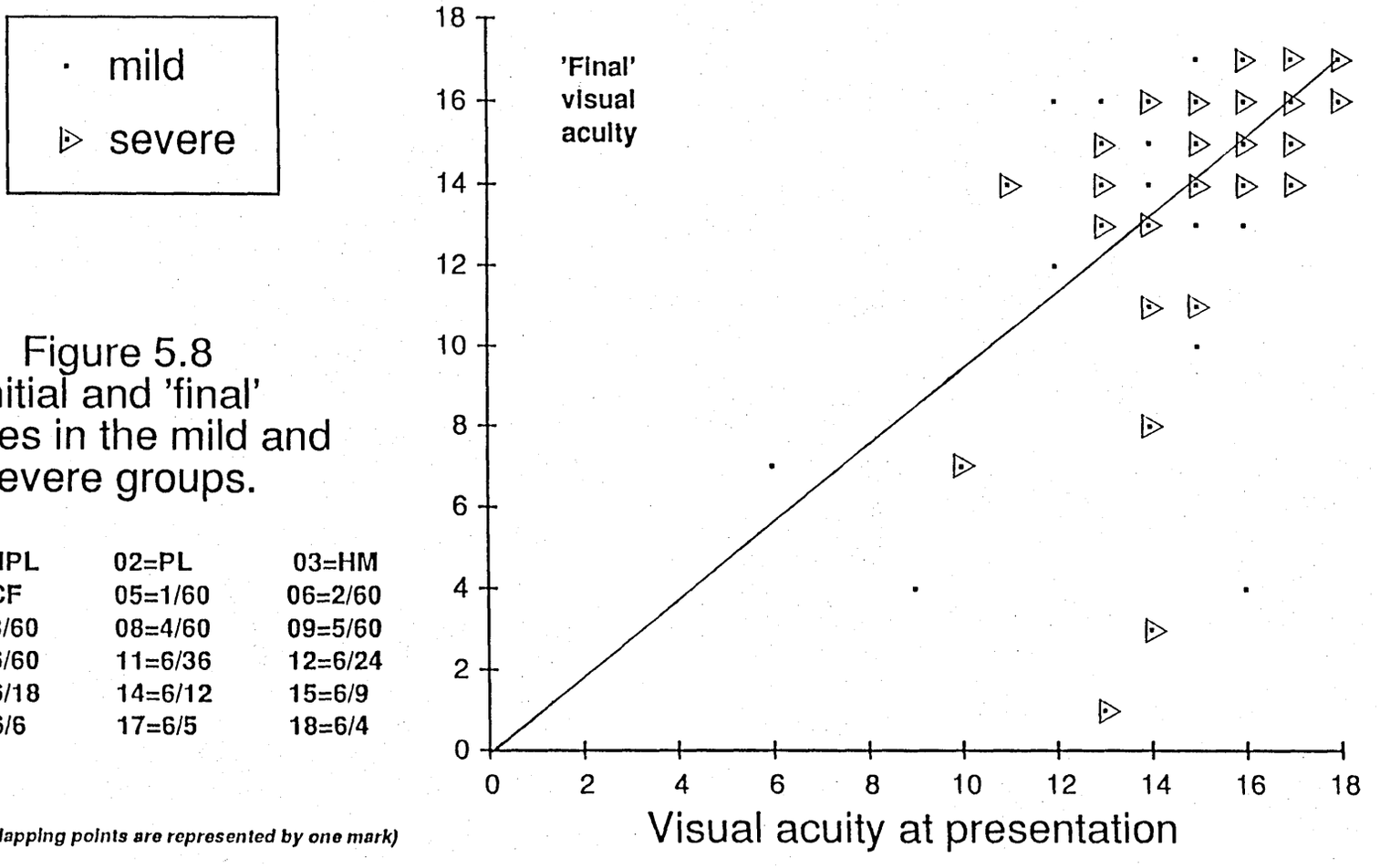


Figure 5.8
Initial and 'final' acuities in the mild and severe groups.

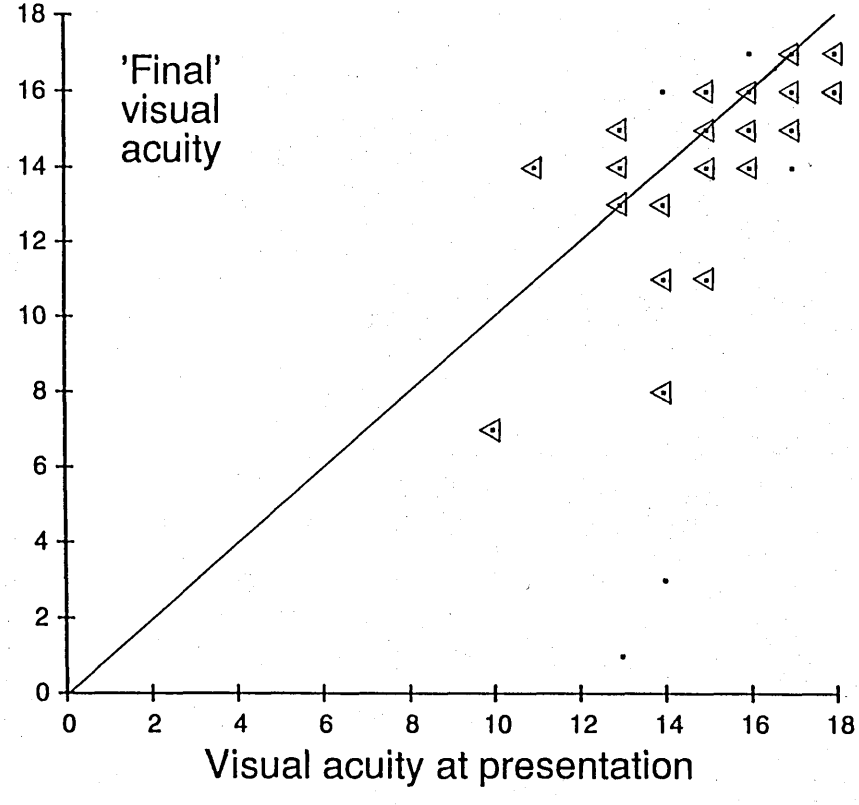
01=NPL	02=PL	03=HM
04=CF	05=1/60	06=2/60
07=3/60	08=4/60	09=5/60
10=6/60	11=6/36	12=6/24
13=6/18	14=6/12	15=6/9
16=6/6	17=6/5	18=6/4

(Overlapping points are represented by one mark)

Figure 5.9

Initial and 'final' visual acuities of the steroid and decompression subgroups.

01=NPL 02=PL 03=HM
04=CF 05=1/60 06=2/60
07=3/60 08=4/60 09=5/60
10=6/60 11=6/36 12=6/24
13=6/18 14=6/12 15=6/9
16=6/6 17=6/5 18=6/4.



· Steroids only

◁ Decompression

(Overlapping points are represented by one mark)

SEVERE GROUP

CASE NO.	INITIAL V. ACUITY	'FINAL' V. ACUITY	EXPLANATION OF LOW VISUAL ACUITY
† 052	6/12	H. M	§ Optic nerve atrophy
† 114	6/18	N. P. L	§ Corneal ulcer - graft - enucleation
‡ 132	6/36	6/12	Choroidal folds - increasing hypermetropia
‡ 181	6/12	6/36	§ Rapid deterioration - emergency decompression
‡ 193	6/12	4/60	§ Reduced vision after decompression
‡ 195	6/60	3/60	Myopic degeneration, aphakia since onset, glacoma - trabeculectomy later
‡ 164	6/12	6/36	§ Reduced vision after decompression

Table 5.8 Explanation of visual loss in patients of the severe group whose visual acuity was 6/36 or less at presentation or at 'final' assessment

† Patients treated with steroids.
‡ Patients treated with orbital surgical decompression.
§ Ophthalmopathy-related visual loss.

In the severe group (Table 5.8), two of the patients who were treated with systemic steroids, and who subsequently lost vision, presented with visual acuities of 6/12 and 6/18. The 'final' visual acuities were 'hand movements' and 'no perception of light' respectively. Optic atrophy was the cause of reduction of vision in the first patient and corneal ulceration in the second.

Of the five patients who were treated with orbital decompression, one showed improvement from 6/36 (accompanied with choroidal folds) at presentation, to 6/12 at 'final' assessment. Three had reduced visual acuity (by more than two lines) immediately following orbital decompression with no recovery afterwards and only one had ocular problems which were not related to dysthyroid ophthalmopathy.

5.3.5. Extraocular muscle surgery:

Of the 33 patients who required extraocular muscle surgery in this series 7 (21.2%) had had no diplopia on presentation, 9 (27.3%) presented with mild, 12 (36.4%) with moderate and 5 (15.2%) with severe diplopia (Table 5.9).

At presentation there was no diplopia in 6 (31.6%) of the 19 patients who were treated with steroids only and in 20 (52.6%) of the 38 patients who required decompression (Table 5.10). Eventually, only 4 (22.2%) of the steroid subgroup and 17 (44.7%) of the decompression subgroup needed extraocular muscle surgery. On 'final' assessment 53% of the patients who underwent orbital decompression were free from diplopia in contrast to 75% for the steroid treated subgroup.

5.3.6. Effect of decompression:

At presentation, the mean intraocular pressures were 17.3 mm. Hg. and 19.8 mm. Hg. in the steroid and the decompression subgroups respectively ($p<0.051$). The 'final' mean pressure of the decompression (15.9 mm. Hg.) was lower than that of the steroid subgroup (17.1 mm. Hg.), but the difference was not statistically significant ($p<0.225$).

The mean exophthalmometric reading of the steroid subgroup was 20.8 mm. and the reading for the decompression subgroup was 23.6 mm at pres-

Muscle surgery

	Symptom of diplopia				Row total
	No diplopia	Mild diplopia	Moderate diplopia	Severe diplopia	
Muscle surgery No	111 68.5% 94.1%	37 22.8% 80.4%	9 5.6% 42.9%	5 3.1% 50.0%	162 100.0% 83.1%
Yes	7 21.2% 5.9%	9 27.3% 19.6%	12 36.4% 57.1%	5 15.2% 50.0%	33 100.0% 16.9%
Column total	118 60.5% 100.0%	46 23.6% 100.0%	21 10.8% 100.0%	10 5.1% 100.0%	195 100.0% 100.0%

Table 5.9

The relationship between diplopia as a presenting symptom and the need for muscle surgery.

Severe group

	Symptom of diplopia				Row total
	No diplopia	Mild diplopia	Moderate diplopia	Severe diplopia	
Steroids only	6 31.6% 23.1%	6 31.6% 37.5%	6 31.6% 46.2%	1 5.3% 50.0%	19 100.0% 33.3%
Surgical decompression	20 52.6% 76.9%	10 26.3% 62.5%	7 18.4% 53.8%	1 2.6% 50.0%	38 100.0% 66.7%
Column total	26 45.6% 100.0%	16 28.1% 100.0%	13 22.8% 100.0%	2 3.5% 100.0%	57 100.0% 100.0%

Table 5.10

Diplopia at presentation in the steroid and the decompression subgroups.

entation ($p<0.016$). Very close mean readings were found on the 'final' assessment of the steroid treated (20.0 mm) and the decompressed (20.8 mm) subgroups ($p<0.681$).

In the severe group 6 patients required permanent tarsorrhaphy 4 of whom had had surgical decompression.

5.3.7. Diagnosis of optic nerve compression:

Optic nerve compression had been diagnosed in 25 of the 57 patients of the severe group. Figure 5.10 shows the relative importance of visual acuity, ophthalmoscopy, field of vision and colour vision testing in detecting patients with optic nerve compression. It also shows that the combination of field loss and colour vision deterioration was the most helpful parameter in making the diagnosis.

Indications for treatment in this group are shown in Figure 5.11. Corneal exposure comes first (23 patients) then optic nerve compression (22 patients). Only one patient in this series was treated for cosmetic reasons as the main indication.

A larger proportion of the decompression subgroup suffered from optic nerve compression [n=15] and from corneal exposure [n=13] than in the steroid subgroup where the number of patients with nerve compression and corneal exposure were 7 and 10 respectively (Figure 5.11).

5.3.8. Efficiency of individual parameters at presentation for the prediction of outcome:

Introduction:

The results presented in the previous sections provide background information about the diagnosis and the 'final' outcome in the various patient groups and subgroups. The efficiency of each individual clinical test or observation in predicting the 'final' outcome will be calculated. This gives some indication as to the importance of each parameter based on the data of the present study. The efficiency (or accuracy) values are one of the essential requirements for building an expert system (Chapter 8).

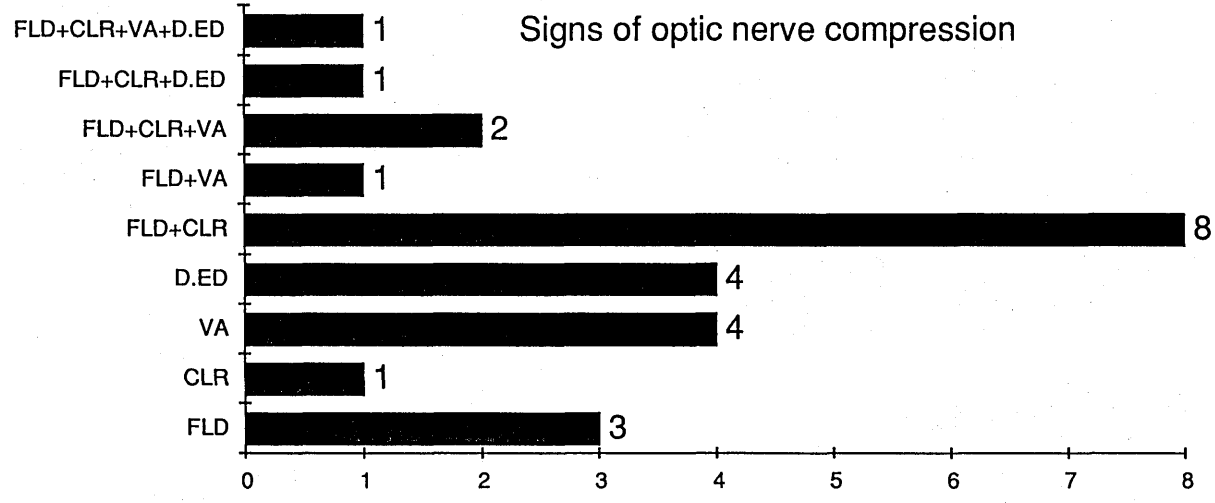


Figure 5.10

Signs and tests used to diagnose optic nerve compression in severe group
[FLD=Field of vision, CLR=Colour vision, D.ED=Disc oedema, VA=Visual acuity]

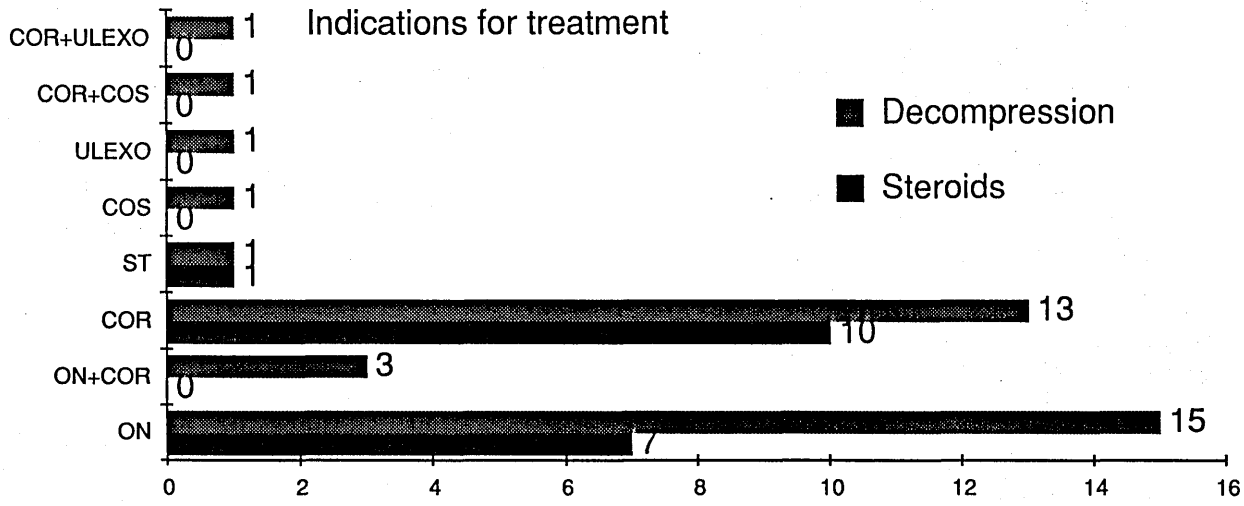


Figure 5.11
The main indications for treatment in the severe group.
[COR=Corneal problem, ULEXO=Unilateral severe exophthalmos,
COS=Cosmetic reason, ST=Soft tissue changes, ON=Optic nerve compression]

Accuracy of different observations:

Parameter	Sensitivity	Specificity	Predictive value
Lid lag	0.93	0.00	0.28
Lid retraction	1.00	0.03	1.00

Table 5.11

Sensitivity, specificity and predictive values of lid lag and lid retraction at presentation in predicting patients who are likely to develop corneal problems.

Definitions and calculations:

The efficiency of any diagnostic test is assessed by determining the rates of true and false positive results and true and false negative results which are defined as follows (Chard, 1988):

- *True positive (TP):* The result is positive in the presence of the clinical abnormality.
- *True negative (TN):* The result is negative in the absence of the clinical abnormality.
- *False positive (FP):* The result is positive in the absence of the clinical abnormality.
- *False negative (FN):* The result is negative in the presence of the clinical abnormality.

Sensitivity is an index of the proportion of all cases of the clinical abnormality correctly identified by the test. *Specificity* is an index of the proportion of all patients in whom the absence of the condition is correctly identified. *Predictive value* is an index of the proportion of all patients who have the condition identified by the test and who actually have the condition (Chard, 1988). The formulae for calculation of these efficiency indices are as follows:

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

$$\text{Specificity} = \frac{TN}{TN+FP}$$

$$\text{Predictive Value} = \frac{TP}{TP+FP}$$

These values have been calculated from the contingency tables (Appendix C3) for the parameters which are relevant to the detection of patients who develop severe disease. This includes identification of patients who are likely to have corneal problems (Table 5.11), those who are likely to run a severe course (Table 5.12) and the prediction of patients who might require surgical orbital decompression or steroid treatment for severe disease (Table 5.13).

Accuracy of different observations:

Parameter	Sensitivity	Specificity	Predictive value
Lid lag	0.98	0.12	0.27
Lid retraction	0.98	0.14	0.28
Lid œdema	0.59	0.69	0.40
Chemosis	0.35	0.86	0.47
Ptosis	0.00	0.99	0.00
Cornea	0.26	0.87	0.40
Disc œdema	0.02	1.00	1.00 *
Choroidal folds	0.04	0.99	0.67 *
Symptom of diplopia	0.54	0.65	0.35
Diplopia on examination	0.68	0.56	0.36
Goitre	0.33	0.56	0.21
Pretibial dermopathy	0.06	0.97	0.43 *
Thyroid acropachy	0.02	0.67	1.00 *
Thyroid myopathy	0.00	0.99	0.00*
Cardiac failure	0.02	0.98	0.25*
Guanethidine	0.38	0.65	0.30
Carbimazole Rx	0.47	0.57	0.27
Propranolol Rx	0.20	0.89	0.28
T4 Rx	0.61	0.48	0.29
T3 Rx	0.18	0.76	0.21
Radioiodine Rx	0.45	0.64	0.29
Partial thyroidectomy	0.21	0.81	0.28
Diabetes	0.04	0.96	0.25*
Hypertension	0.11	0.90	0.29*

Table 5.12

Sensitivity, specificity and predictive values of various clinical parameters for assessment of the severity of thyroid ophthalmopathy (* Five cases or less).

Accuracy of different observations:

Parameter	Sensitivity	Specificity	Predictive value
Lid lag	1.00	0.05	0.66
Lid retraction	1.00	0.05	0.67
Lid œdema	0.64	0.50	0.70
Chemosis	0.39	0.72	0.72
Ptosis	0.00	1.00	0.00
Cornea	0.24	0.68	0.60
Symptom of diplopia	0.47	0.32	0.58
Diplopia on examination	0.63	0.61	0.63
Orthoptic assessment	0.16	0.68	0.89
Disc œdema	0.07	0.89	0.38 *
Choroidal folds	0.05	1.00	1.00 *
Goitre	0.29	0.57	0.62
Pretibial dermopathy	0.05	0.94	0.67 *
Thyroid acropachy	0.03	1.00	1.00 *
Thyroid myopathy	0.00	1.00	0.00*
Cardiac failure	0.03	0.17	0.10*
Guanithidine treatment	0.70	0.61	0.67
Carbimazole Rx	0.43	0.44	0.63
Propranolol Rx	0.21	0.81	0.70
T4 Rx	0.53	0.63	0.75
T3 Rx	0.09	0.63	0.34
Radioiodine Rx	0.46	0.56	0.70
Partial thyroidectomy	0.22	0.81	0.73
Diabetes	0.00	0.82	0.00*
Hypertension	0.11	0.88	0.67*

Table 5.13

Sensitivity, specificity and predictive values of various clinical parameters in predicting patients who are likely to require surgical orbital decompression amongst the severe group (* Five cases of less).

Discriminant analysis techniques:
(1) Independence-based models for unordered categorical data.
(2) Lancaster class model.
(3) Lancaster first-order interaction models for unordered categorical data.
(4) Kernel-based procedures for categorical data.
(5)'Linear and quadratic' discrimination based on normality assumptions.
(6) Linear logistic discrimination.
(7) Loglinear models.
(8) Non-parametric methods on orthogonal series.
(9) Continuous kernel methods.
(10) Location model.
(11) Independent class model.
(12) Latent class model.

Table 5.14

Various available discriminant analysis techniques summarised by Titterington *et al.* (1981)

5.3.9. Risk prediction:

Introduction:

In the previous section the predictive value of each test or clinical observation was calculated individually and the interplay of other variables was not taken into account. It is impossible to make a complete mental picture using these individual efficiency indices and the statistical significance values to make predictions. A technique is required which shows the combined effects of a set of independent variables and the separate effect of each independent variable in relation to the others.

Statistical methods:

Several techniques for discriminant analysis can be applied on complex sets of data. Table 5.14 enumerates some of these techniques. The complexity of data sets in the present study was caused by the inclusion of data which could be regarded as being continuous, binary, or ordered categorical, and the occurrence of missing values.

The performance of six discriminant analysis techniques was compared by Titterington *et al.* (1981) using criteria of prognostic success and reliability. They concluded that, in general, performance varies more with the choice of the set of predictor variables than with that of the discriminant rules. Linear discriminant function analysis was used in the present study.

Linear discriminant function analysis:

This is a statistical technique for deciding into which category of a variable a case is most likely to fall. Individuals in the study are assumed to belong to one or other 'outcome category'. A linear combination of the independent variables is formed and serves as the basis for assigning cases to groups. Thus information contained in multiple independent variables is summarised in a single index.

A discriminant rule is set up to assign an individual to one of the outcome categories. A 'training data set' of individuals whose outcome categories is known is used to construct the discriminant rule. A 'test data set' of individuals

whose outcome categories is also known, is required for the evaluation of the discriminant rule used. Often the training set and the test set are the same. Less biased evaluation can be achieved if a 'leaving-one out' technique is used. This technique involves leaving out each of the cases in turn, calculating the function based on the remaining cases, and then classifying the left-out case. If the sample is large enough separate test and training sets are used (Norusis, 1988).

Variable selection methods:

The two methods used in this analysis are summarised as follows:

1. Stepwise selection:

In this method the first variable included in the analysis has the largest acceptable value for the selection criterion. After the first variable is entered, the value of the criterion is re-evaluated for all variables not in the model, and the variable with the largest acceptable criterion value is entered next. At this point, the variable entered first is re-evaluated to determine whether it meets the removal criterion. If it does, it is removed from the model.

The next step is to examine the variables not in the equation for entry, followed by examination of the variables in the equation for removal. Variables are removed until none remains that meets the removal criterion. Variable selection is terminated when no more variables meet entry or removal criteria.

2. Forced entry method:

In this method all variables are entered simultaneously in the discriminant analysis.

Variable selection criteria:

Several criteria for variable selection are available. This analysis uses minimisation of Wilk's lambda which is the ratio of the within-groups sum of squares to the total sum of squares. Thus, in each step the variable that results in the smallest Wilk's lambda for the discriminant function is selected for entry.

Predictor variables:

1. Exophthalmometry (in mm.)
2. Age (in years)
3. Duration of thyroid dysfunction (in months)
4. Sex
5. Corneal condition
6. Thyroid status
7. Lid œdema
8. Chemosis
9. Ptosis
10. Cornea
11. Disc œdema
12. Choroidal folds
13. Symptom of diplopia
14. Diplopia on examination
15. Goitre
16. Pretibial dermopathy
17. Thyroid acropachy
18. Myopathy
19. Cardiac failure
20. Guanethidine Rx
21. Carbimazole Rx
22. Propranolol Rx
23. T4 Rx
24. T3 Rx
25. Radioiodine Rx
26. Partial thyroidectomy
27. Diabetes
28. Hypertension

Table 5.15

Variables entered for discriminant function analysis.

Outcome categories:

Two discriminant analysis models have been computed. The first predicts the severity of thyroid ophthalmopathy using a stepwise variable entry method. The outcome categories are 'severe disease' and 'mild disease'. The second model predicts the need for orbital surgical decompression using a forced entry method. The outcome categories are 'decompression' and 'no decompression'.

Predictor variables:

The variables which had been judged as candidates for testing were first selected. The initial selection was based on statistical significance, indices of efficiency and clinical impression. Discriminant analysis was then used as an exploratory tool in order to arrive at the set of 'good' predictor variables. Table 5.15 shows the list of the predictor variables which had been finally selected for testing.

The linear discriminant equation:

To calculate the discriminant function score the following equation is used:

$$D = B_0 + B_1X_1 + B_2X_2 + ... + B_pX_p$$

The Xs are the values of the independent variables and the Bs are coefficients estimated from the data. If a linear discriminant function is to distinguish between patients who develop severe disease from those who continue to have only mild disease, the two groups must differ in their D values.

The group centroid is the point corresponding to the mean score of the group on each function. In classifying cases, the predicted group membership is the one whose centroid is closest to the case's discriminant function scores i.e. the D value.

Prediction of disease severity:

Four predictor variables were accepted in the model. These were ***exophthalmometric reading in millimeters, thyroid status*** (Table 5.16), ***diplopia on examination; and duration of thyroid dysfunction in months***, ordered

Discriminant function coefficients:

+ 0.2561361 = Exophthalmos in millimeters (Luedde).

+ 0.2493058 = Diplopia on examination*.

+ 0.6831180 = Thyroid status**.

- 0.0052511 = Duration of thyroid dysfunction (in months).

- 6.8772280 = Constant.

Table 5.16

The coefficients of the four predictor variables of the linear discriminant equation for classifying patients into severe or mild categories.

** = diplopia on examination code: (0 = no diplopia, 2 = in extreme gaze , 3 =on elevation or depression, 4 = on adduction or abduction, 5 = close to midline). ** = thyroid status: (1 = hyperthyroidism, 2 = hypothyroidism, 3 = euthyroidism).*

according to their relative importance in terms of contribution to the overall discriminant function. Including additional variables did not substantially improve prediction. Table 5.16 shows the discriminant function coefficients. The group centroid of the mild cases is (- 0.37366) and of the severe cases is (+ 0.71929). The percent of cases which was correctly classified into mild or severe using this model was 74%.

Orbital decompression risk prediction:

The discriminant function coefficients of this model which predicts patients who are likely to require orbital surgical decompression are listed in Table 5.17. The forced entry variable selection method was used in computing this model. Seventeen independent predictor variables were accepted. Using this model, a correct classification rate of 81% was achieved.

(Appendix C5 contains the full discriminant function analysis computer print out of the two models).

5.4. DISCUSSION:

5.4.1. Population characteristics:

In the present study which had been running for 22 years every effort was made to avoid introduction of any element of bias. The lapse of such a long period would tend to eliminate already elderly patients who had been seen at the outset of the study. Patients had either been discharged, recovered, moved or died. The inclusion criteria were carefully designed to cope with these potential sources of bias inherent in such a long-term prospective study. However, this series can represent only the population of patients typically referred to a research ophthalmic clinic in a teaching hospital.

The female to male ratio is in accordance with that presented in previous series of patients (Mulvany, 1944; Werner, 1971). The disease is four times more common among women than men but in older age groups the sex distribution is equal. The distribution of age among the males and females is almost the same. The rate of onset (in severe cases) is more rapid in males.

Discriminant function coefficients:

+ 0.5723660 = Sex of the patient (1=MALE, 2=FEMALE).
- 0.0353433 = Age of the patient (in years).
- 0.2620977 = Visual acuity.*
+ 0.2562185 = Lid œdema (1=NO, 2=YES).
+ 0.9450156 = Chemosis (1=NO, 2=YES).
- 0.0847337 = Cornea**
+ 0.7151085 = Disc œdema (1=NO, 2=YES).
+ 1.0887400 = Choroidal folds (1=NO, 2=YES).
+ 0.1239730 = IOP straight (mm. Hg.).
- 0.1581213 = Symptom of diplopia***
+ 0.0524721 = Assessment of ocular motility by Hess test . †
+ 0.0388947 = Thyroidectomy (1=NO, 2=YES).
+ 0.1326484 = Radioactive iodine treatment (1=NO, 2=YES).
+ 0.1255362 = Exophthalmos (in millimeters).
+ 0.0014569 = Diplopia on examination. ‡
+ 0.1238457 = Thyroid status. §
+ 0.0025597 = Duration of thyroid dysfunction (in months).
- 3.8321760 = Constant.

Table 5.17

The coefficients of the predictor variables of the linear discriminant equation for identification of patients who are likely to require orbital decompression and those who are not.

*** = Visual acuity:**

01=NPL	02=PL	03=HM
04=CF	05=1/60	06=2/60
07=3/60	08=4/60	09=5/60
10=6/60	11=6/36	12=6/24
13=6/18	14=6/12	15=6/9
16=6/6	7=6/5	18=6/4

**** = Cornea:**

1=NORMAL 2= SUPERFICIAL PUNCTATE KERATITIS 3=ULCER
4=NECROSIS/ PERFORATIO N 5= SCARRING

***** = Symptom of diplopia:**

1=NONE	2=MILD
3=MODERATE	4=SEVERE

† = Hess test:

1=NORMAL	2=RESTRICTED UP-GAZE
3=RESTRICTED DOWN-GAZE	4=RESTRICTED UP & DOWN-GAZE
5=RESTRICTED ADDUCTION	6= RESTRICTED ABDUCTION
7=RESTRICTED ADDUCTION & ABDUCTION	8= COMBINATION OF RESTRICTIONS
9=FIXED EYE	

‡ = Diplopia on examination:

1=ABSENT	2=IN EXTERME GAZE
3=ON ELEVATION/DEPRESSION	4=ON ADDUCTION/ABDUCTION
5=IN EXTREME GAZE	

§ = Thyroid status:

1 = HYPERTHYROIDISM	2 = HYPOTHYROIDISM
3 = EUTHYROIDISM	

The mean duration of thyroid dysfunction before the onset of thyroid ophthalmopathy is 52 months, the standard deviation is 77 and the mode is 12 months. This means that there were a few patients in the group who had had thyroid dysfunction for many years prior to the onset of ophthalmopathy, which skews the data to the right.

5.4.2. Systemic findings:

Thyroid status:

In the present study 49 patients were euthyroid on presentation of whom 69% became hyperthyroid and 31% became hypothyroid. They all did so within a mean period of 10 years. It can therefore be argued that all such patients should be subject to tests of thyroid function for up to 10 years from presentation. However, no valid comparison can be made between our series and other studies of 'euthyroid Graves' ophthalmopathy' because CT scans were not available at presentation of our patients to make the diagnosis. Therefore, the development of abnormal thyroid status at onset or during follow-up was a criterion for inclusion in our study.

Treatment of hyperthyroidism:

It has been the clinical impression of a number of ophthalmologists that the administration of radioiodine treatment may be associated with the onset of dysthyroid eye disease and in particular its severe form. The series described here represents a group of patients who had been referred from various hospitals in the West of Scotland because of their ocular conditions. One cannot draw any conclusions regarding the incidence of ophthalmopathy in different treatment groups from such a selected sample. A knowledge of the proportion of patients who had been offered a particular form of therapy i.e., radioactive iodine, partial thyroidectomy or medical treatment with antithyroid drugs is a first requirement. Furthermore, it is expected that these figures will vary in different endocrinology departments and may change in the same department over years.

However, for the series described, the proportion of patients presenting with severe dysthyroid eye disease following radioiodine treatment was similar to that which had received medical or surgical treatment. Recognising the caveats outlined above, this fails to lend credibility to the popularly held belief that

radioiodine treatment is more liable to produce severe dysthyroid disease than the alternative treatments.

5.4.3. Severe and mild groups:

Classification:

In the present study, patients were categroised into severe and mild outcome groups because the emphasis was on the long-term effects of thyroid ophthalmopathy. Formal classifications (Section 3.5.2) were used only as a guide for devising the coding system (Appendix C1).

Population characteristics:

A quarter of the patients in our series ran a severe course. This clearly demonstrates the potential seriousness of the condition which should be considered, along with chronicity, when discussing the disease and its complications with the patient.

The female to male ratio of the whole group was maintained in the mild group (i.e., 4:1), while in the severe group the ratio was just above 3:1. This ratio is higher than other studies by Mulvany (1944) and Werner (1971) who found an equal sex distribution in the severe group. This difference might be explained, at least in part, by the difference in the classification criteria of patients into mild and severe adopted in different series.

5.4.4. Systemic conditions:

Thyroid dysfunction:

Our results support the views of Gorman (1984) who reported that pretibial dermopathy is rarely seen in the absence of overt ophthalmopathy and that thyroid acropachy, the rarest expression of Graves' disease, is found only in patients who also have had the thyroid, eye, and skin manifestations of Graves' disease. However, in the present study, the number of patients showing these signs is too small to reach definitive conclusions. This is also true for thyroid myopathy and cardiac failure as the presenting manifestation of hyperthyroidism.

Treatment of hyperthyroidism:

The receipt of antithyroid medication or radioactive iodine treatment or having undergone thyroidectomy did not seem to influence the course of the disease. Although, previous radioiodine therapy or thyroidectomy were associated with increased incidence of severe ophthalmopathy, this difference was not statistically significant.

Furthermore, patients whose management included receiving thyroxine or triiodothyronine developed the severe form of ophthalmopathy more frequently compared to those who did not receive hormonal therapy. This is more likely to be due to the endocrinologists tending to prescribe these hormones for patients showing evidence suggesting that their ophthalmopathy might be severe. The rationale is to suppress the production of excess thyrotropic hormone by the pituitary gland.

Ocular condition:

Eyelids:

Lid lag and eyelid retraction are among the most characteristic signs of thyroid ophthalmopathy. Larger proportions of patients with these signs were in the severe group for whom only a very small number did not have them.

Comparing the mild and the severe groups, the sensitivity of both lid lag and lid retraction (at onset) is 0.98 while the specificity is 0.12 and 0.14 and the predictive value is 0.25 and 0.28 for lid lag and lid retraction respectively. These signs are therefore among the most useful clinical signs for making the diagnosis of thyroid ophthalmopathy. However, their value is limited in predicting its course. The present study confirms the observations of McLarty (1973) who reported an incidence of lid retraction of more than 90% in hyperthyroid patients.

Lid œdema (sensitivity 0.59) and chemosis (sensitivity 0.35), at onset, are not as helpful in making the diagnosis as lid retraction and lid lag. However, lid œdema with a specificity of 0.69 and a predictive value of 0.40 and chemosis (specificity 0.86 and predictive value 0.47) are more consistently associated with severe ophthalmopathy and are therefore better predictors of the severity of the disease. These signs give an indication of the severity of soft tissue changes, the

presence of increased orbital pressure and vascular engorgement, which in turn reflect the severity of the condition.

Cornea:

In the present study, the degree of corneal involvement at presentation closely paralleled the severity of ophthalmopathy. It is of course not surprising that severe corneal disease is correlated with the severity of ophthalmopathy because it is one of the indications for treating the patient with systemic steroids or orbital decompression. Our results indicate that corneal disturbances at onset are indicative of the development of severe ophthalmopathy especially if the corneal involvement is in the form of corneal ulceration.

Furthermore, corneal disturbance at onset is not very helpful in making the diagnosis (sensitivity 0.26) but it is among the more specific parameters (specificity 0.87) in predicting the severity of the disease (predictive value 0.40).

The correlation between the degree of corneal disturbance and the severity of the ophthalmopathy is understandable in view of the pathogenesis of corneal involvement in this disease. Five factors are thought to be associated with corneal exposure in thyroid ophthalmopathy, namely, upper lid retraction, exophthalmos, lagophthalmos, inability to elevate the eyes, and a decreased blink rate (Day, 1978; Werner, 1978; Sergott and Glaser, 1981).

Fundus examination:

Disc œdema is pathognomonic of optic nerve compression if the diagnosis of ophthalmopathy is not in question, this explains the high specificity and predictive value (both are 1.00). However, it occurs only in a minority of cases (8.8% [n=5] of severe cases in this series), which also explains the very low sensitivity (0.02).

Choroidal folds were seen in only three patients, two severe and one mild. This number is too small to draw firm conclusions regarding their predictive value.

Extraocular muscles:

Our results indicate that the severity of ocular motility disturbances (at onset) is correlated with the severity of the course of the disease. This is true for the symptom of diplopia (sensitivity 0.54, specificity 0.65, and predictive value 0.35), ocular motility disorders detected on clinical examination (sensitivity 0.68, specificity 0.56, and predictive value 0.36) and orthoptic assessment, including Hess test, (sensitivity 0.73, specificity 0.53, and predictive value 0.53). These values indicate that the presence of ocular motility disturbance is one of the sensitive parameters both in making the diagnosis of ophthalmopathy and in predicting that the disease is likely to follow a severe course.

These results are in full agreement with those of Trokel and Jakobiec (1981). They studied 200 orbits of patients with thyroid ophthalmopathy using high resolution CT scans and concluded that the extraocular muscles are the most consistently involved focus of disease in this disorder. They also concluded that, clinically and radiologically, the range of extraocular muscle abnormality varies from minimal enlargement of a few muscles in mild disease to enormous enlargement of multiple muscles in severe disease. These observations have been substantiated by histopathological evidence of both biopsy and autopsy tissue (Daicker, 1973).

The relation of thyroid and ocular myopathy:

Thyroid myopathy which was documented in 3 patients of this series was also associated with extraocular muscle dysfunction. Very little has been published about thyroid myopathy. Perhaps the number of cases is so small that a satisfactory clinical study is virtually impossible.

Intraocular pressure:

It was established that only 2.2% of the whole series had open angle glaucoma which is the same ratio in the general population (Perkins, 1974). This indicates that intraocular pressure rise detected during the course of the disease probably does not result in an increased incidence of glaucomatous visual loss (Section 3.8.7). These results are in accordance with a previous study by Cheng and Perkins (1967) who studied 155 patients with thyroid ophthalmopathy and found only 2 cases of glaucoma.

Exophthalmometry:

In the present series the severe ophthalmopathy group had a mean exophthalmometric reading of 22.9 mm, at presentation, which is significantly higher than the mean reading of the mild group ($p<0.0005$). At 'final' assessment there was no change in the mean reading of the mild group while the reading of the severe group was 20.5 (STD 4). This is very close to the mild group value. Whether this was due to treatment or could have resulted from no treatment would require a differently designed study which would probably be questionable from the ethical point of view.

Intraocular pressure and exophthalmometry after decompression:

The mean intraocular pressures and exophthalmometric readings, at presentation, were significantly higher in the decompression than in the steroid subgroup. At 'final' assessment, no significant difference was found in intraocular pressure or in exophthalmometric readings between the two groups.

5.4.5. Visual acuity:

A valid statistical analysis is not possible for the present series in which there was a range of affected visual acuity before the onset of the disease or arose during the follow-up. However, it can be concluded that although the overall visual outcome is good, the disease represents a real threat to vision and can result in permanent damage or even loss of the eye.

In this series, 4 patients had a reduction of vision (6/36 or less) due to optic nerve compression and one patient lost his eye due to corneal ulceration and perforation.

Three patients had reduced visual acuity following decompression. One might argue about the safety of surgical decompression. Certainly this procedure has its own risks, however, it can also be argued that reduction of visual acuity after decompression might be related to surgery being performed late in the course of the disease.

5.4.6. Extraocular muscle surgery:

In our series, the proportion of patients whose management required extraocular muscle surgery following orbital decompression was not significantly different from that following systemic steroid treatment. The majority of patients who required extraocular muscle surgery presented initially with diplopia as compared with those who did not.

Harner (1984) stated that "in orbital decompression there is a consistent alleviation of certain problems, but other problems are created, i.e., extraocular muscle imbalance." In a study of 200 patients who had transantral orbital decompression DeSanto (1984) reported that 70% of the total group required extraocular muscle surgery and that even if normal ocular motility existed before decompression, muscle dysfunction was still possible after surgery. However, in our series, there was no significant difference between the decompressed and the steroid treated subgroups in the 'final' ocular motility nor in the proportion of patients requiring extraocular muscle surgery.

5.4.7. Diagnosis of optic nerve compression:

Four parameters were used in making the diagnosis of optic nerve compression in the 25 patients in this series who suffered from this condition. These comprised visual acuity, ophthalmoscopy, field of vision and colour vision testing which were available for all the patients in this subgroup (Figure 5.10). In 12 patients only one test was positive and the diagnosis was made on that basis (Visual acuity drop of more than two lines [n=4], disc œdema [n=4], colour vision deterioration [n=1] and visual field changes [n=3]). In 13 patients the diagnosis was based on a combination of two or more of these tests. The combination of visual field loss and colour vision deterioration was the most helpful amongst other tests.

No single sign or test was found to be positive in all of the patients with optic nerve compression. Furthermore, in 4 of the 5 patients who presented with disc œdema, visual acuity was normal and no changes were detected either in the visual field nor in the colour vision test results. This is in accordance with the findings of Sergott and Glaser (1981) who showed that the appearance of the

optic disc does not correlate with visual acuity nor does it predict the patient's recovery of vision with treatment unless optic atrophy is severe.

Furthermore, the variability of visual acuity in patients with optic nerve compression in the present series is in agreement with previous studies (Werner, 1969; Kennerdel *et al.*, 1981).

Changes in the field of vision were detected in 15 out of the 25 patients with optic nerve compression. This is the most consistent finding in our series. This is also in accordance with the results of other investigators (Cant and Wilson, 1974; Trobe, 1981; Sergott and Glaser, 1981, Kennerdel *et al.*, 1981; Younge, 1984). Further analysis of the field charts of this series in order to study the pattern of field loss will be carried out in the second stage of this project (Chapter 7).

5.4.8. Indications for treatment of patients in the severe group:

Corneal problems and optic nerve compression were on the top of the list of indications for treatment. A larger proportion of patients with optic nerve compression was treated with orbital decompression than with systemic steroids. This can be interpreted as reflecting the policy of the surgeons who tended to consider that decompression is more justifiable in patients with optic nerve compression than with other conditions. It may also indicate that optic nerve compression is simply more steroid resistant because a large number (52.6% [n=20]) of patients who had undergone orbital decompression had a preliminary trial of systemic steroids.

In this series the principal indication for surgical decompression was optic nerve compression whereas corneal pathology was deemed to warrant surgery less frequently. It is recognised that optic nerve compression differs from other indications in the necessity for immediate relief of an ostensibly 'mechanical' problem. It should also be recognised that the results reported are based on a study which started over 20 years ago when current technical and technological advances in orbital surgery and in general anæthesia were not available. However, corneal ulceration was the cause of a disastrous outcome in the only patient who lost his eye in this series despite orbital decompression. Therefore, it should be emphasised that corneal disturbances can be as serious as optic nerve com-

pression and may warrant decompression, especially in the presence of marked exophthalmos.

5.4.9. Risk prediction:

Descriptive statistics and univariate tests of significance provide basic information about the distribution of the variables in this series and help identify some differences among the groups. However, any accurate prediction requires more than such lists of separate prognostic variables. The interrelationships of these variables, and their combined predictive power need to be investigated. In discriminant analysis and other multivariate statistical procedures, the emphasis is on analysing the variables together, not one at a time. By considering the variables simultaneously it is possible to incorporate important information about their relationships.

Linear discriminant function analysis does not require assumptions about the variance of the dependent variable. In fact, it is designed to work with nominal dependent variables. It is a convenient technique for evaluation of the association between large sets of independent variables and a dependent variable (Hedderson, 1987). One of the limitations of the linear discriminant function analysis, however, is that it cannot handle well a dependent variable with a large number of values. Interval variables must be re-coded into a small number of categories, which involves loss of some detailed information (Norusis, 1988).

The two models which have been computed were aimed at fulfilling two different requirements. The first model, which predicts the severity of the disease, needed to be based on the least possible amount of information that gives the best possible accuracy of prediction. This is the reason for the use of the stepwise variable selection method which resulted in only 4 parameters being included in the model.

The second model for prediction of the requirement for orbital decompression was intended for patients who had been first classified into the severe group using the first model. These cases require a complete work-up (history, examination and investigation) before the second model can be used, therefore, reduction of the number of predictors was not as important as in the first model. The forced entry variable selection method was used in the computation of the sec-

ond model to make use of the increase in the predictive value by inclusion of a large number of variables.

Both models were intended to be used in building a thyroid eye disease expert system (Chapter 8) maintaining the highest possible levels of accuracy. Therefore, no attempt has been made to simplify these two models to be suitable for use by a clinician as a kind of scoring system.

In the first model the analysis identified 4 risk factors for the prediction of outcome in terms of the severity of the course. Prediction is based on the clinical findings at the time of presentation of the patient with ophthalmopathy. Exophthalmometric reading was the most important predictor followed by thyroid status then diplopia on examination. The duration of thyroid dysfunction was the fourth and the least important predictor in terms of discrimination between the mild and severe outcome categories. It can be concluded that, at presentation, the greater the exophthalmometric reading, the more likely is the development of severe disease. Euthyroid patients are more likely to run a more severe course than hypothyroid patients who are in turn more at risk than patients who present with ophthalmopathy associated with thyrotoxicosis. Ocular motility disorders at presentation as elicited by clinical examination is another risk factor whose magnitude is correlated with the severity of diplopia. Furthermore, the longer the period from the time of diagnosis of thyroid dysfunction to the onset of ophthalmopathy, the greater the risk of developing severe disease. These risk factors must be used in combination in order to accurately predict the likelihood of a particular patient being classified into the mild or the severe outcome group.

The second model which achieves 81% correct prediction was computed, based on the values of 17 parameters for the prediction of the necessity of surgical orbital decompression. The percentage of cases classified correctly is often taken as an index of the effectiveness of the discriminant function. When evaluating this measure, it is important to compare the observed miss-classification rate to that expected by chance alone. If there are two groups with equal prior probabilities, the expected miss-classification rate is 50%. The rate of correct classification of the first and the second models (74% and 81% respectively) can be regarded as highly satisfactory considering that they are based on clinical parameters only because the new advanced imaging techniques, with their high di-

agnostic value, were not available at the outset of the study and therefore were not included in this series.

The medical literature contains reports of the successful application of discriminant analysis based on an independent models for prediction of outcome in coma patients following head injury (Jennett, Pitts and Murray, 1980; Teasdale *et al.*, 1976; 1981; Titterington *et al.*, 1981) and in prophylaxis of deep vein thrombosis (Crandon *et al.*, 1980), but to the author's knowledge, these risk factors for the potential development of severe optic nerve pathology have not hitherto been described.

5.5. SUMMARY:

The results of a prospective review of the long-term effects of dysthyroid eye disease are presented. The study involved 224 patients (174 females and 50 males) who presented to the Tennent Institute of Ophthalmology, Glasgow, between 1961 and 1983 who were traced and 'finally' reassessed. The age of the patients ranged from 17 to 68 years with a mean of 49 years and the mean follow-up time was 10 years.

Patients were grouped into 'mild subgroup', whose management had required only conservative measures, and 'severe subgroup' who had been deemed to necessitate systemic steroids or orbital surgical decompression. The female to male ratio was 1:4 in the mild group and 1:3 in the severe group. Fewer males developed severe ophthalmopathy, but when they did this tended to occur more quickly than in females.

At presentation, the largest proportion of patients were hyperthyroid. The 49 patients who initially presented with ophthalmopathy associated with normal thyroid function developed thyroid dysfunction within 10 years. The treatment received for thyroid dysfunction did not seem to influence the course of the disease in our series. Thyroid acropachy and pretibial dermopathy were associated with severe disease, but the number of patients was small.

The diagnostic sensitivity of the presence of lid lag and lid retraction at presentation was high but the specificity and the predictive value were low. Lid

œdema and chemosis were less sensitive in making the diagnosis of ophthalmopathy but they were more consistently associated with severe disease (specificity: Lid lag 0.69, chemosis 0.86).

Patients who presented with corneal ulceration were more likely to develop severe disease. Corneal disturbance at presentation was not particularly sensitive but was one of the more specific parameter in predicting severity of the disease (specificity 0.87).

The mean exophthalmometric reading (Luedde) at presentation was 22.9 mm in the severe group, which was significantly higher than that of the mild group (20.6 mm). Similarly, the mean intraocular pressures at presentation both in the straight-ahead and in upgaze were significantly higher in the severe than in the mild group. At 'final' assessment, no difference was found in the exophthalmometric or the intraocular pressure readings of the two groups. Surgical orbital decompression was significantly more effective in reducing both the intraocular pressure and the exophthalmometric readings than systemic steroids. Open angle glaucoma was found in 2.2% of patients at 'final' assessment which matches the proportion in the general population.

The severity of extraocular muscle involvement at the onset of ophthalmopathy was correlated with the severity of the course of the disease (diplopia: Sensitivity 0.54 and specificity 0.65). All the patients who developed thyroid myopathy were also suffering from ocular myopathy, but the number of patients was too small [n=3] to draw any firm conclusions. The majority of patients who required extraocular muscle surgery presented initially with diplopia. Decompression was not associated with a significant increase in the number of patients requiring extraocular muscle surgery; an association which has been noted in other studies.

Reduction of visual acuity (2 or more lines), optic disc œdema, visual field loss, and colour vision deterioration were the parameters used to make the diagnosis in the 25 patients with optic nerve compression. No single test was sufficiently sensitive to be positive in all of these cases. In 13 patients the diagnosis was based on a combination of two or more of these parameters; the most im-

portant of which was field loss combined with colour vision deterioration. Disc œdema was reported in 5 patients and choroidal folds in only three.

Optic nerve compression was the most common indication for surgical decompression followed by corneal ulceration. Decompression was carried out for cosmetic reasons in only one patient in this series. More than half of the patients in the decompression subgroup had a trial of systemic steroids before the operation was contemplated.

The present study emphasises the potential sight threatening nature of thyroid ophthalmopathy. Two patients had marked reduction of visual acuity (to 6/36 or less) due to optic nerve compression and one patient lost his eye due to corneal ulceration and perforation.

A linear discriminant function equation has been computed. The analysis identified 4 risk factors for the prediction of outcome in terms of severity of the course of the disease. Prediction is based on the clinical findings at the time of presentation of the patient with ophthalmopathy. Exophthalmometric reading was the most important predictor followed by thyroid status then diplopia on examination. The duration of thyroid dysfunction was the fourth and the least important predictor in terms of discrimination between the mild and severe outcome categories. It can be inferred that the greater the exophthalmometric reading, at presentation, the more likely is the development of severe disease. Euthyroid patients are more likely to run a severe course than hypothyroid patients who are in turn more at risk than patients who present with ophthalmopathy associated with thyrotoxicosis. Diplopia at presentation as elicited by clinical examination is another risk factor whose severity is correlated with the severity of ophthalmopathy. Finally, the longer the period from the time of diagnosis of thyroid dysfunction to the onset of ophthalmopathy, the greater the risk of developing severe disease. These risk factors must be used in combination in order to accurately predict the likelihood of a particular patient being classified into the mild or the severe outcome group. This model gives a 74% correct classification rate.

A second model which achieves an 81% correct prediction has been computed based on the values of 17 parameters for the prediction of the necessity of surgical orbital decompression.

Both models were intended to be used in building a thyroid eye disease expert system (Chapter 8).

CHAPTER 6.

COMPUTER SYSTEMS FOR PATIENT ASSESSMENT

6.1. INTRODUCTION:

Microcomputers potentially provide a means of assessing a wide range of visual functions. This chapter outlines the development and preliminary assessment of a system which we have devised that imposes temporal constraints on the measurement of visual acuity.

6.1.1. Snellen acuity:

The ability to discriminate the letters of the Snellen chart has provided the mainstay of visual assessment since the last century. This is because the test is accurately reproducible, quick to perform, and provides a relatively sensitive screening test for impairment of visual function. However, a 'normal' visual acuity of 6/6 can be achieved by a person who has extensive pathological damage of the visual apparatus. For example, in the present study of dysthyroid eye disease (Section 5.3), 17 of the 25 patients who had optic nerve compression demonstrated normal visual acuities despite the nerve condition. A test is therefore required which can be rapidly performed, is repeatable and which has a high degree of sensitivity to facilitate the detection of such individuals.

6.1.2. Temporal assessment of visual acuity:

The reciprocal relationship between the luminous flux and the duration of a test flash for the threshold visual function is well known (Bloch, 1885); the longer the exposure, the lower the level of illumination required for detection of a test light as long as flash duration does not exceed a critical duration. The magnitude of critical duration is significantly influenced by the level of adaptation. At higher levels of adaptation, critical duration tends to be shorter and temporal resolution is improved. When the eyes are in a relatively dark adapted state, temporal resolution is decreased but the system can respond to lower stimulus levels. It is suggested that this change in critical duration may reflect the transition from cone receptors in the light adapted state to rod receptors in the dark adapted state (Brown, Phares and Fletcher, 1960; Brown and Black, 1976).

Kahneman and Norman (1964) showed that critical duration is in general shorter when the brightness criterion is employed than when a criterion dependent upon form discrimination is employed. Kahneman (1964) demonstrated the possibility of obtaining rather longer integration times for the resolution of form.

Nachmas (1967) has also reported evidence for longer temporal summation time with fine gratings as compared to coarse gratings.

In an experiment concerned with the possible influence of eye movements on visual acuity Keesey (1960) demonstrated that for a given level of illumination, grating visual acuity increases with increased duration of exposure up to 200 msec. The results were the same when the image was stabilised on the retina as when image movements could occur.

Baron and Westheimer (1973) have reached a similar conclusion based on experiments involved a Landolt C target under photopic conditions of adaptation. They also ruled out any role of pupillary or accommodative fluctuation by employing a small artificial pupil and using a cycloplegic.

Researchers in both psychology and physiology are using an experimental device called tachistoscope. Zusne (1970) reviewed the principle of the variety of available tachistoscopes. All operate on the same basic principle, namely, presenting a visual display for a very brief period of time, usually some fraction of a second. The exact control of time may be accomplished in a number of ways: A gas discharge tube, a specially wired neon lamp or a mechanical device such as large photographic shutters.

No published work of which we are aware provide a system for clinical assessment of temporal acuity based on the widely used Snellen optotypes.

6.2. GENERAL DESCRIPTION OF THE SYSTEM:

The test provides a temporal assessment of visual acuity and has been called TEMPRAC. TEMPRAC assesses the time taken to perceive each level of Snellen visual acuity. The Snellen visual acuity is a measure of the smallest angle which the individual components of a letter of the alphabet must subtend at the eye for that letter to be discriminated when it is presented at maximum contrast. The normal limit of resolution for the eye is 1 minute of arc.

Individuals who have a relatively normal visual acuity in association with pathological damage of the visual system, whether it be the eye, optic nerve, chi-

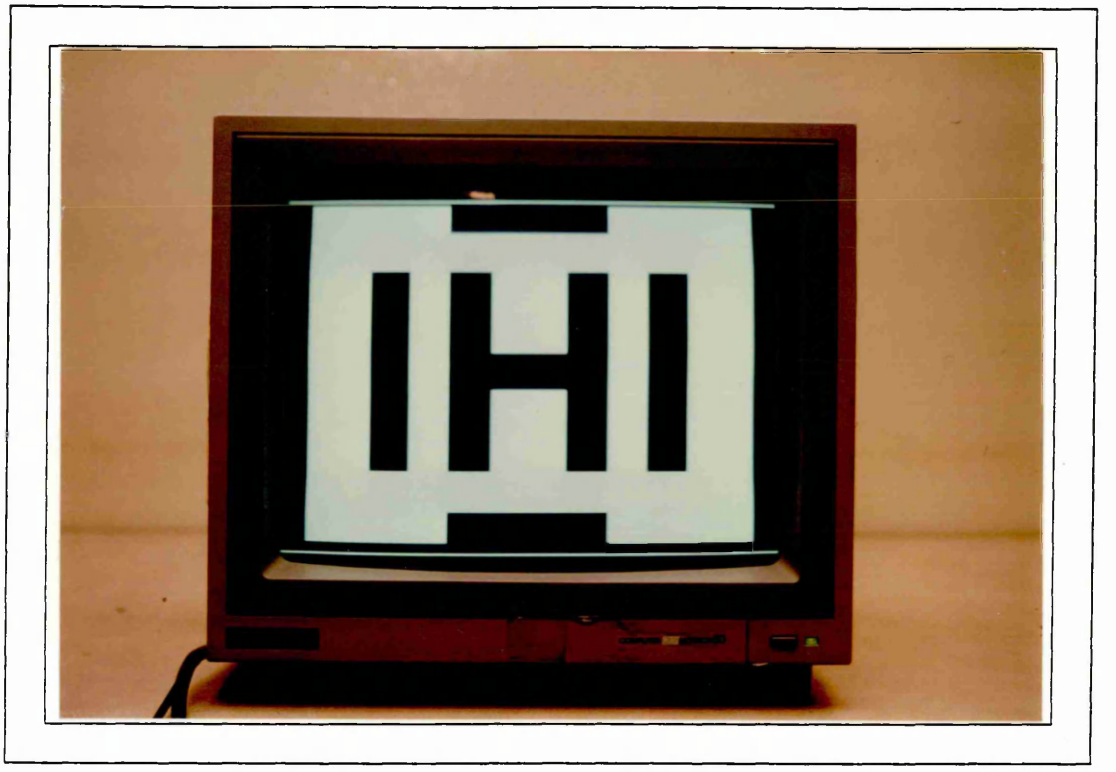


Plate 6.1

Shows the letter H surrounded by confusion bars displayed on a Black/White monitor which is placed 6 meters from the patient.

Plate 6.2

The examiner, the patient, the colour monitor and the keyboard.

asm or optic radiations, may be subjectively aware of visual dysfunction despite a 'normal' acuity. One reason for this is that it takes longer to interpret a visual image and tasks requiring vision thus become more time consuming.

A microcomputer system has been developed, as a prototype, which measures the temporal as well as the spatial aspects of visual acuity. The hardware configuration of the system comprises a 6MHz-IBM AT compatible computer, two monitors, one of which is a non-glare, black/white monitor (providing a maximum contrast black on white image), and a keyboard (Appendix E). The black/white monitor is placed at 6 meters from the person being tested (Plate 6.1). The keyboard and the second monitor are placed on the desk beside the subject and are operated by the examiner (Plate 6.2). The examiner selects a manual or an automatic system.

6.2.1. Testing procedure:

After keying in the personal and administrative information about the patient, a letter of the alphabet with the same dimensions of the 6/60 Snellen optotype is presented on the monitor screen for a short period of time (current minimum 0.01 seconds). The individual being tested is asked to identify that letter. If the letter is not identified, randomly selected letters of the same dimensions are presented for sequentially longer periods, in 0.05 second steps, until a correct identification is made, for example on thee consecutive occasions.

The next letter to be presented corresponds to the ensuing line on a standard Snellen chart. This letter appears for the same maximum duration as the preceding letter, the time is again sequentially increased until accurate identification is reached.

The 'crowding' phenomenon is important in the measurement of Snellen acuity. It is observed when acuity is poor and particularly in children with amblyobia (Parr, 1981). The phenomenon results in easier recognition of letters when presented singly (angular acuity) than when viewed in a row. In tests such as TEMPRAC, angular acuity is recorded and this could overestimate visual performance if confusion bars are not included (Parr, 1981). This has been taken into account and compensated for by surrounding each letter with such bars, the

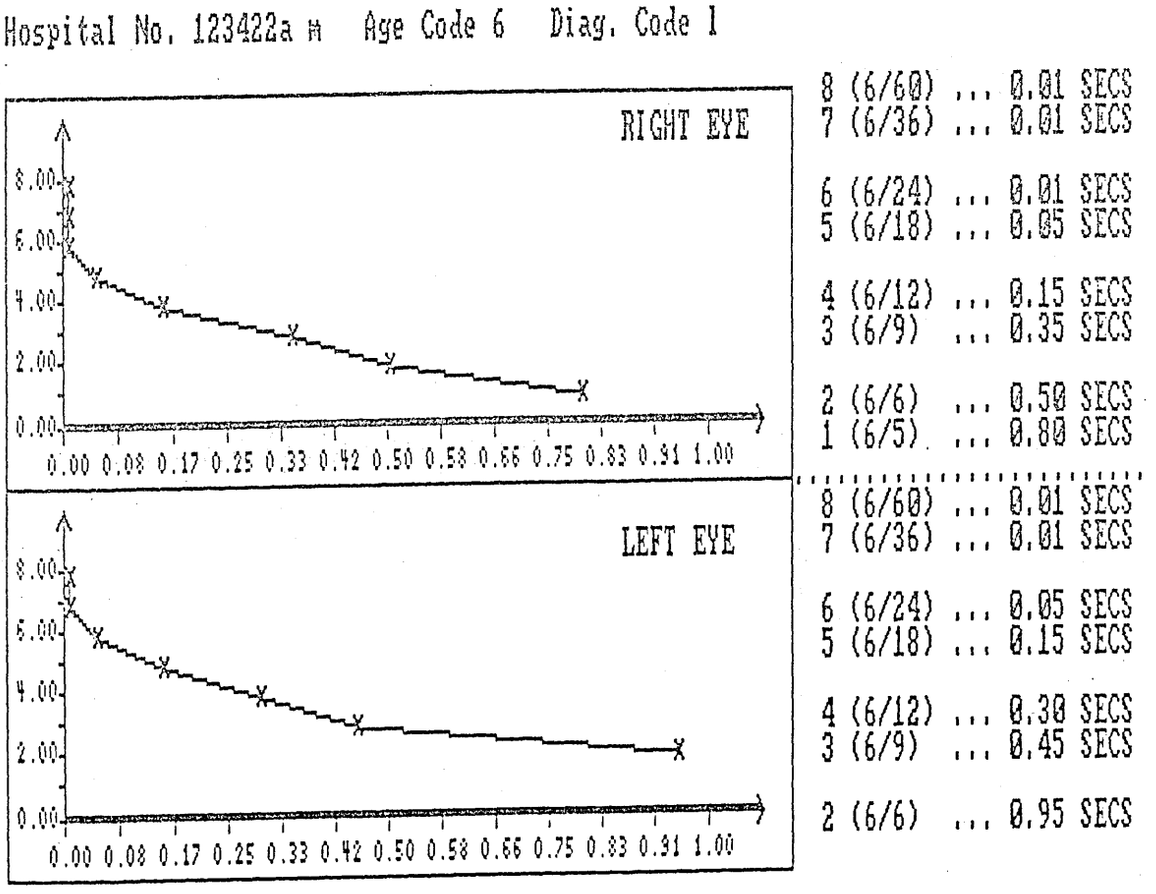


Figure 6.1

A typical print out of TEMPRAC test result in graphical form.

components and separation of which from the optotype, subtend the same angle as the letter components.

The test is terminated when either all the letters have been correctly identified, or when no further letters can be recognised even when shown continuously.

The data accrued from the test can be printed out in graphical or numerical tabular form and are stored on the computer hard disk. A typical print out is shown in Figures 6.1 and 6.2. The interactive screen text is given in Appendix B1.

6.2.2. Software design:

The programme has been written using a Turbo Pascal compiler and a Turbo graphics toolbox (Appendix B2).

Figure 6.3 illustrates the main structure of the software programme. There is a procedure to draw each letter (using DrawLine, DrawSquare procedures). The size and the period of letter presentation are chosen either automatically or manually by the user at the beginning of each consultation session. The 'letters' procedures are invoked randomly using a 'random number generation' procedure. Changing letter dimensions is achieved by using a 'window zoom-out' subroutine. All these procedures and subroutines are facilities offered in the Turbo Pascal Graphics Toolbox (Appendix B2).

In the Turbo Pascal 'letters' procedure, a letter is drawn bit by bit. This is rather a slow process, during which the part of the letter which first appears, "grows" up to full size. What is actually needed is a complete letter that appears for the preset specific period of time. To achieve this, the letter is first drawn in the virtual RAM screen (i.e. in the computer memory). Thus it remains invisible until it is completely drawn at which time the image of the whole letter is moved to the display screen.

* * * * *

HOS.NUM.: 333433

AGE CODE: 3 SEX : m

DIAGNOSIS CODE : t1

VAR CODE : 3 VAL CODE : 4

RIGHT EYE TEST

SIZE	PERIOD	RESULT
8 (6/60)	00.01 SECS	CORRECT
7 (6/36)	00.01 SECS	UNRECOGNIZED
7 (6/36)	00.05 SECS	CORRECT
6 (6/24)	00.05 SECS	UNRECOGNIZED
6 (6/24)	00.10 SECS	UNRECOGNIZED
6 (6/24)	00.15 SECS	CORRECT
5 (6/18)	00.15 SECS	UNRECOGNIZED
5 (6/18)	00.20 SECS	UNRECOGNIZED
5 (6/18)	00.25 SECS	UNRECOGNIZED
5 (6/18)	00.30 SECS	UNRECOGNIZED
5 (6/18)	00.35 SECS	CORRECT
4 (6/12)	00.35 SECS	UNRECOGNIZED
4 (6/12)	00.40 SECS	UNRECOGNIZED
4 (6/12)	00.45 SECS	UNRECOGNIZED
4 (6/12)	00.50 SECS	CORRECT
3 (6/9)	00.50 SECS	UNRECOGNIZED
3 (6/9)	00.55 SECS	UNRECOGNIZED
3 (6/9)	00.60 SECS	UNRECOGNIZED
3 (6/9)	00.65 SECS	CORRECT
2 (6/6)	00.65 SECS	UNRECOGNIZED
2 (6/6)	00.70 SECS	UNRECOGNIZED
2 (6/6)	00.75 SECS	UNRECOGNIZED
2 (6/6)	00.80 SECS	UNRECOGNIZED
2 (6/6)	00.85 SECS	CORRECT
1 (6/5)	00.85 SECS	UNRECOGNIZED
1 (6/5)	00.90 SECS	UNRECOGNIZED

Figure 6.2

A typical print out of TEMPRAC test result in numerical tabular form.

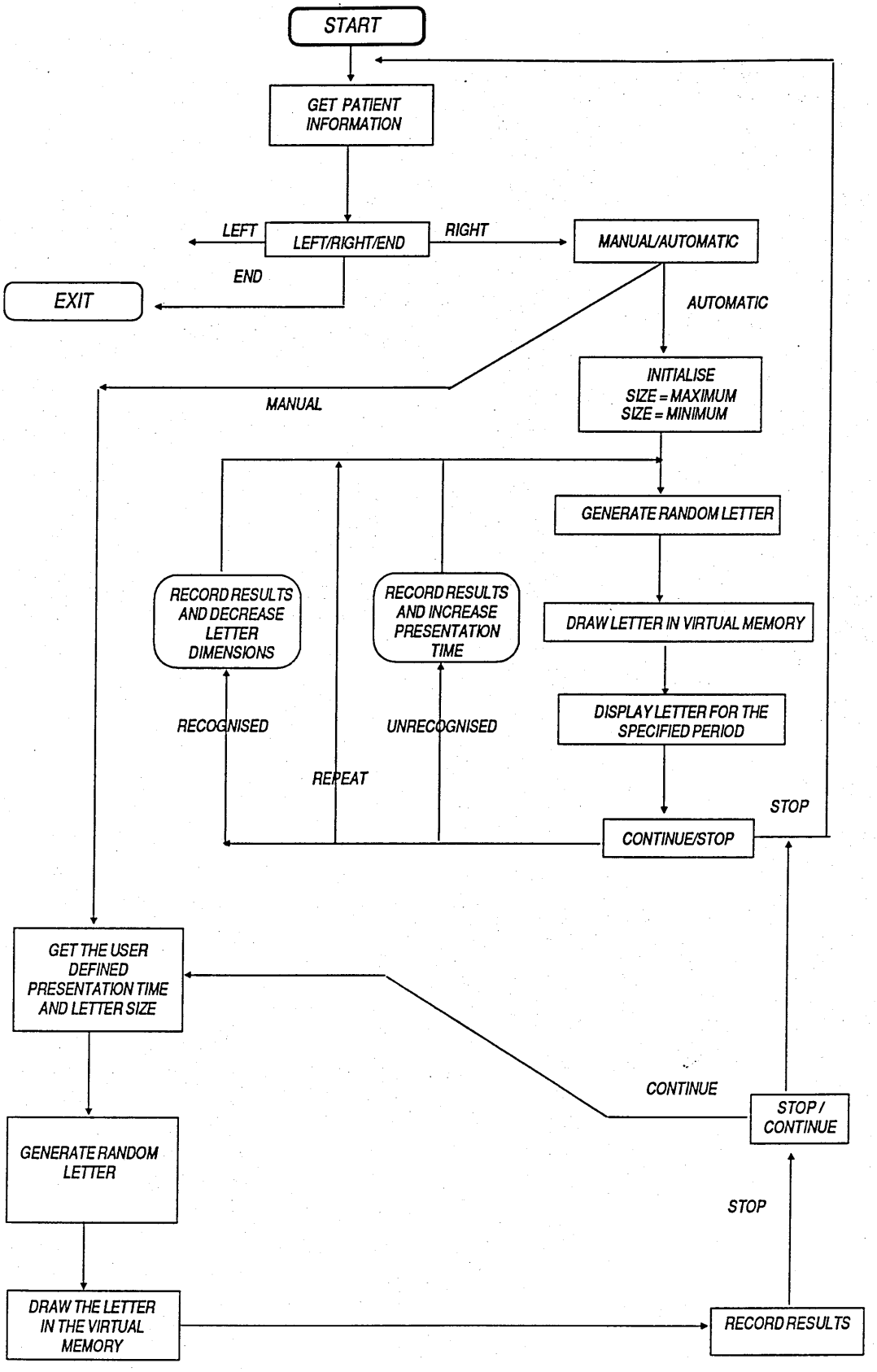


Figure 6.3 Showing the main operations of the TEMPRAC software algorithm.

The control of presentation time is achieved by a 'control loop', where the 'control variable' is the machine's real time obtained using the 'DOS' interrupt function (Appendix A1).

It is important to point out that two of the performance parameters of the system are hardware dependent. Firstly, the accuracy of the letter dimensions at various sizes is related to the display graphics card resolution (pixel dimensions). High resolution cards enables the production of greater dimension accuracy. Secondly, the minimum letter presentation time and the tolerance of successively longer presentation periods are dependent on the speed of the machine used (i.e. the microprocessor type, the clock frequency, and the monitor specifications).

The data acquired from the test are printed in graphical form using the 'polygon' procedure of the Turbo Pascal Graphics Toolbox (Appendix B2). The numerical form is printed or saved as a table and also as a text file in 'comma-delimited' format which ensures direct translation to most of the standard spread sheets, databases, and statistical packages.

A copy of the software program is enclosed on a floppy diskette which can run under MS or PC DOS on any IBM or compatible computer with hardware configuration of colour graphics card (CGA), black/white monochrome monitor and 512 KB RAM as a minimum. Software adjustments are needed if a processor or a clock speed other than Intel 80286-6 MHz is used.

The programme has been written, debugged and calibrated by the joint effort and close collaboration at all stages between the author and Mr. A. W. Ahmed. (programme listing is found in Appendix B3 and programme diskettet in Volume 2, pocket).

6.3. CLINICAL USE OF TEMPRAC:

6.3.1. Patient and methods:

Aims and protocols:

1. Normal volunteers:

Aim:

To determine the range of normal results for different age groups.

Protocol:

100 normal volunteers were examined, they were chosen from:

- Colleagues.
- Friends.
- Patients' relatives and friends.

Test for repeatability:

Aim:

To determine the intra-observer repeatability.

Protocol:

Ten individuals were tested on 8-10 occasions at different times of the day and different days of the week to evaluate the reproducibility of the test results.

Effect of induced errors of refraction:

Aim:

To establish whether errors of refraction affect the results obtained.

Protocol:

Ten patients were tested with the best correction then with a +1.00 diopter sphere, and finally with -1.00 diopter sphere added to their correcting lenses.

2. The assessment of the test following the central retinal dysfunction caused by central serous retinopathy (CSR):

Aim:

To determine whether patients with subtle central pathology, namely, with healed CSR and 'normal' or near-normal visual acuity still demonstrate impairment of temporal processing of image data.

Protocol:

A group of 23 patients who had had central serous retinopathy (CSR) were assessed by Dr. J. Mutlak in a separate study. Temporal visual acuity were tested amongst other investigations to evaluate the long term visual outcome of CSR.

3. The assessment of the test following optic nerve dysfunction due to retrobulbar neuritis:

Aim:

To determine whether patients whose visual acuity returned to 'normal' after they had had unilateral retrobulbar neuritis still demonstrate impairment of temporal processing of image data.

Protocol:

A group of 12 patients who had had unilateral retrobulbar neuritis had the visual function of both eyes assessed by Dr. G. Craig by means of TEMPRAC.

Method of testing:

- Snellen visual acuity was determined using the standard printed test type used in the clinic for examination of all cases.
- Each eye was examined while the other eye was covered.
- Each letter was presented once. If the patient was able to recognise it the next smaller letter was presented for the same period of time.
- If the patient failed to recognise the letter, the test was repeated three times using the same size and time setting.
- The presentation time was increased only if the patient failed to recognise the displayed letters for the third time.

```
Enter Patient Sex (M/F)



                    Diagnosis Codes
-------------------------------------------------------------------------
Normal ---------(N)

Amblyopia ------(A)
Cataract -------(C)
                        (C1) -- Congenital
                        (C2) -- Nuclear Sclerosis
                        (C3) -- PSCLO
Diabetes -------(D)
                        (DN) -- No  retinopathy
                        (DB) -- Background; no visible maculopathy
                        (DP) -- Proliferative; no visible maculopathy
                        (DO) -- Macular oedema
                        (DI) -- Ischaemic maculopathy
                        (DE) -- Exudative maculopathy
Glaucoma [OA] --(G)
                        (G0) -- Ocular hypertension
                        (G1) -- Baring of Blind spot
                        (G2) -- Arcuate scotoma
                        (G3) -- Constriction of part of field to <10 deg
                        (G4) -- Constriction of all field to <10 deg
-------------------------------------------------------------------------
                  Press Any Key


                    Diagnosis Code (cont.)
-------------------------------------------------------------------------
Hypermetropia --(H)
                        (H1) -- 0-5 DS
                        (H2) -- 6-8 DS
                        (H3) -- 9+  DS
Leber ----------(L)
Myopia ---------(M)
                        (M1) -- 0-5  DS
                        (M2) -- 6-10 DS
                        (M3) -- 11 + DS
Optic N / CNS --(O)     ------- (O+number) referring to card file
Retinitis pig --(R)
SMD ------------(S)
                        (S1) -- Dry
                        (S2) -- Exudative
Thyroid --------(T)
                        (T0) -- Normal nerve function
                        (T1) -- Evidence of optic neuropathy

Unclassified ---(U)
-------------------------------------------------------------------------

      Enter Diagnosis Code :
```

Figure 6.4

Coding system used for data entry to TEMPRAC system.

- The test was terminated if the optotype 6/5 was recognised or if no recognition was possible even when the maximum display time was reached (current maximum 0.95 seconds).

Calibration:

- The screen background and room illumination were measured using a photometer and were kept constant all the time by regular measurements and adjustments.
- The test distance was 6 meters.

Diagnostic code:

The coding system which was included in the test to facilitate data entry is shown in Figure 6.4.

Documentation:

The results of the tests were automatically saved onto the hard disk of the computer. Regular backups and hard copies were made for all the collected data.

6.4. RESULTS:

6.4.1. Normal individuals:

The temporal visual acuity was assessed for 118 normal individuals the majority of whom were examined by the author. Their ages ranged from 14 - 79 years (mean age 37 years). Fifty four (45.8%) were females and 64 (54.2%) were males. Figure 6.5 shows the distribution of various age groups of this sample.

The majority (93) of this group were emmetropes, 15 were myopes and only 10 were hypermetropes as shown in Figure 6.6.

The best corrected visual acuity was 6/5 in 92, 6/6 in 17 and 6/9 in 9 individuals of this group.

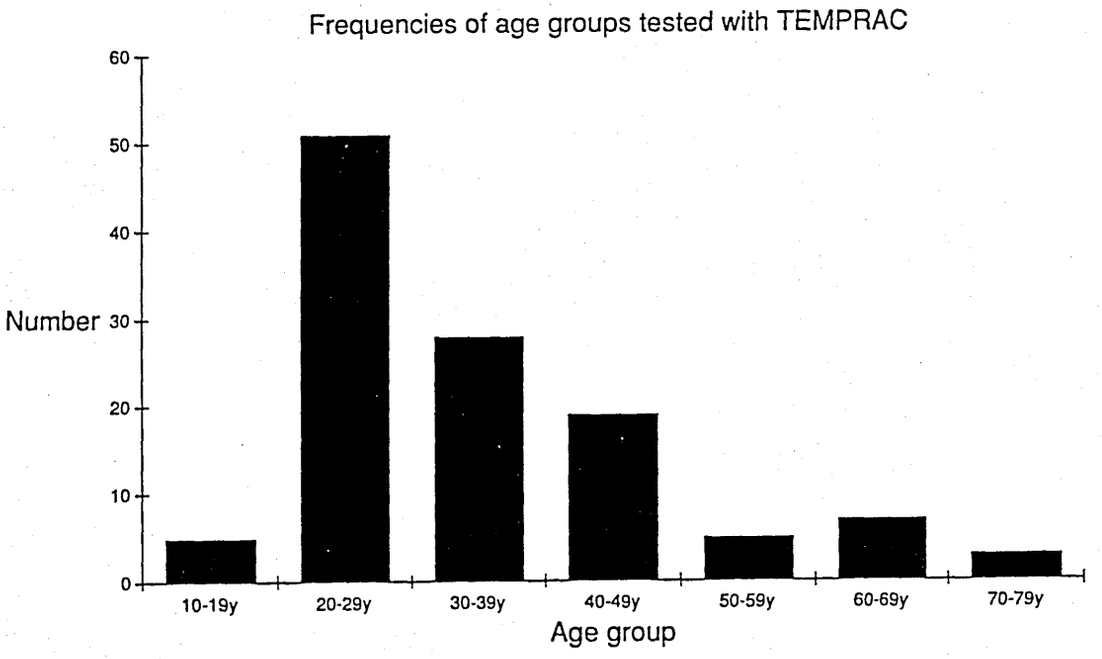

Frequencies of age groups tested with TEMPRAC
Number
60
50
40
30
20
10
0
10-19y
20-29y
30-39y
40-49y
50-59y
60-69y
70-79y
Age group

Figure 6.5

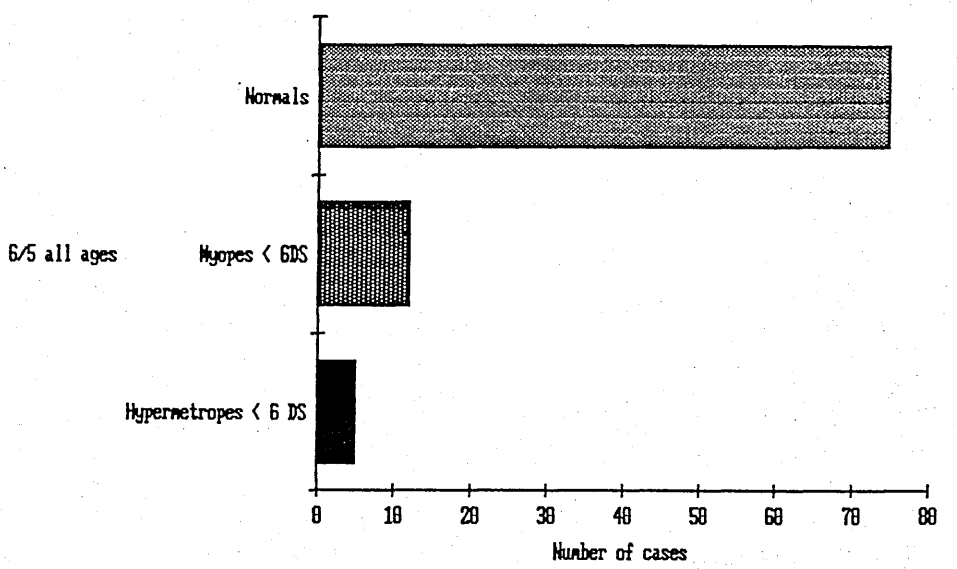


Figure 6.6

Distribution of errors of refraction in the normal group.

No significant statistical difference was found between right and left eyes when the temporal acuity values for each individual optotype were compared. The results from only one eye were randomly selected for statistical analysis for each individual.

A typical test result for a normal individual who achieved 6/60 in 0.010 seconds and 6/5 in 0.150 seconds is shown in Figure 6.7.

Table 6.1 shows the mean temporal acuity values of the whole group of normal individuals. It also shows that the mean time required to recognise the different optotypes steadily increased from 0.010 seconds for the 6/36 to 0.354 for the 6/5 letter. The standard deviation also increased correspondingly. All the values for the 6/60 and 6/36 optotypes were identical.

The frequency distributions of presentation times of the 6/6 and 6/9 optotypes are shown in Figures 6.8 and 6.9 respectively. Table 6.2 shows details of the temporal acuity values for different age groups.

6.4.2. Test repeatability:

Ten normal volunteers were examined repeatedly to assess the reproducibility of the test. The test values were identical for the 6/60, 6/36, 6/24 and 6/18 optotypes. The variability of the test values was within 1% for the 6/12 optotype, 5% for the 6/9 optotype 10% for 6/6 optotype and 18% for the 6/5 optotype. Figure 6.10 shows the 8 test results for one normal volunteer.

6.4.3. Effect of errors of refraction:

Snellen visual acuity did not deteriorate in any individual on adding - 1.00 diopter sphere lens. Creating myopia by placing + 1.00 diopter sphere in front of the eye resulted in deterioration of vision by one line in four out of the 10 tested patients. However, the TEMPRAC test showed that the time required to achieve the same visual acuity was at least doubled when a concave lens is added and more than doubled when the lens was convex (Figure 6.11).

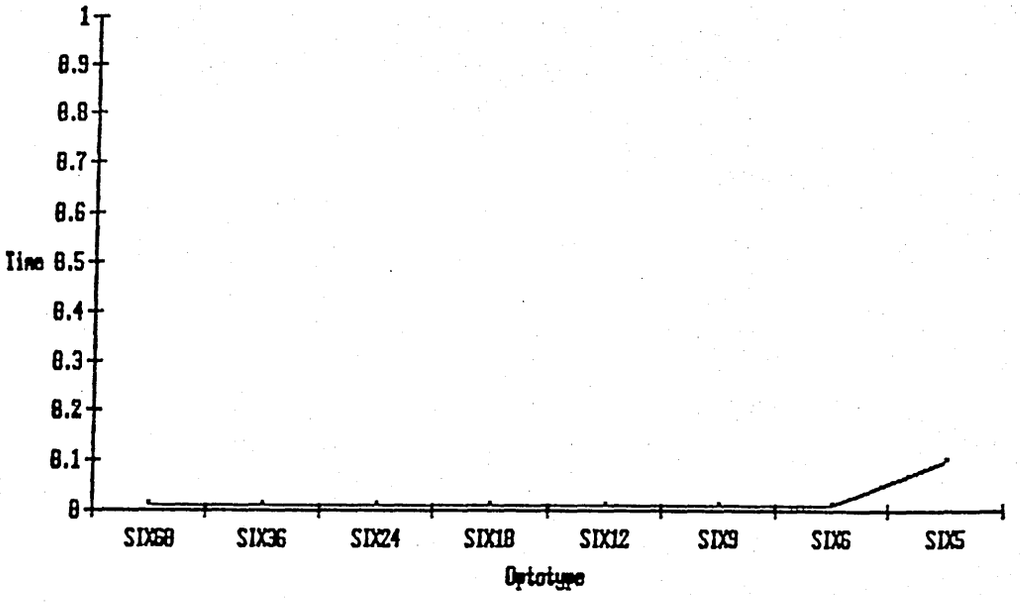


Figure 6.7

A typical test result for a normal individual.

TEMPORAL VISUAL ACUITY

OPTOTYPE	TEMPORAL ACUITY	STANDARD DEVIATION	MIMIMUM VALUE	MAXIMUM VALUE
6/60	0.010	0.000	0.010	0.010
6/36	0.010	0.000	0.010	0.010
6/24	0.012	0.012	0.010	0.100
6/18	0.014	0.033	0.010	0.350
6/12	0.031	0.101	0.010	0.900
6/9	0.080	0.141	0.010	0.900
6/6	0.235	0.224	0.010	0.950
6/5	0.354	0.247	0.050	0.950

TABLE 6.1 The temporal acuity, standard deviation, mimimum and maximum values for the whole group of normal individuals assessed by TEMPRAC.

Tempral Visual Acuity

AGE GROUP	6/5	6/6	6/9	6/12	6/18	6/24
10- - 19 years	0.238 (0.250)	0.134 (0.250)	0.026 (0.022)	0.010 (0.000)	0.010 (0.000)	0.010 (0.000)
20 - 29 years	0.282 (0.208)	0.180 (0.189)	0.040 (0.054)	0.031 (0.125)	0.017 (0.047)	0.012 (0.012)
30 - 39 years	0.412 (0.267)	0.239 (0.211)	0.052 (0.072)	0.016 (0.014)	0.011 (0.007)	0.011 (0.007)
40 - 49 years	0.441 (0.246)	0.284 (0.254)	0.090 (0.173)	0.042 (0.113)	0.019 (0.022)	0.016 (0.020)
50 - 59 years	0.489 (0.257)	0.259 (0.134)	0.132 (0.122)	0.090 (0.151)	0.029 (0.028)	0.019 (0.018)
60 - 69 years	0.350 (0.071)	0.460 (0.272)	0.240 (0.297)	0.038 (0.049)	0.010 (0.000)	0.010 (0.000)
70 - 79 years	0.350 (0.000)	0.200 (0.000)	0.317 (0.225)	0.103 (0.081)	0.010 (0.000)	0.010 (0.000)

TABLE 6.2 The mean time (in seconds) required to achieve verious levels of visual acuity in different age groups of normal individuals.

Standard deviation is shown between brackets.

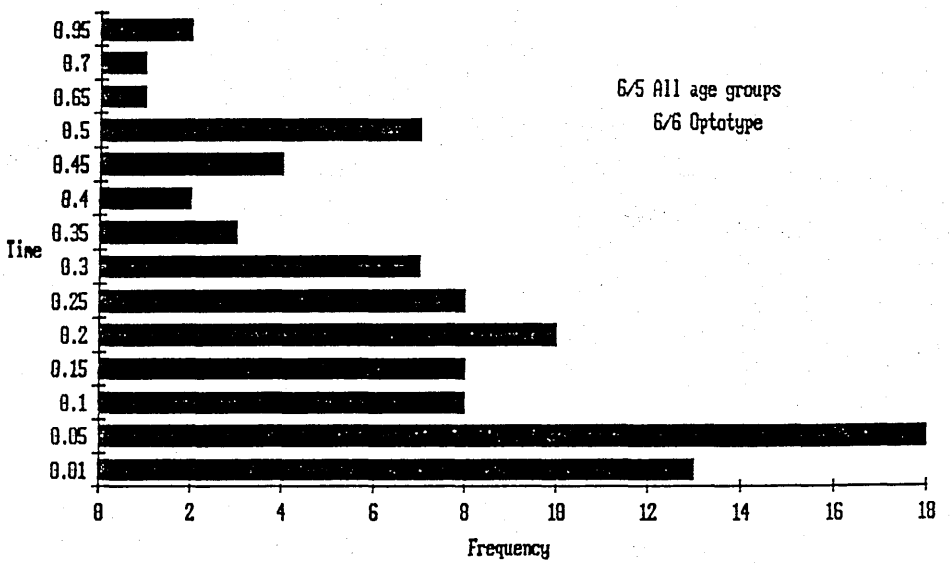


Figure 6.8

Number of normal individuals who achieved 6/5 Snellen acuity in each presentation time category required to recognise 6/6 optotypes.

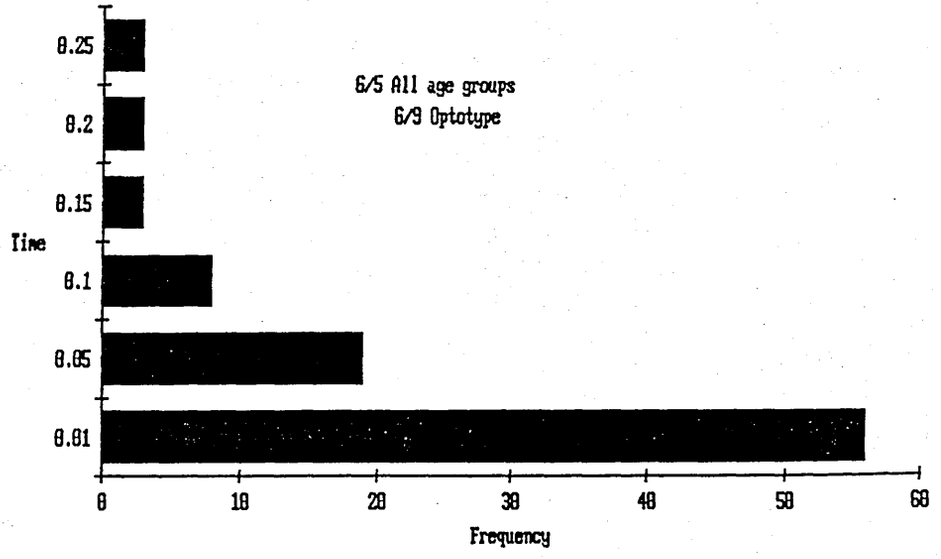


Figure 6.9

Number of normal individuals who achieved 6/5 Snellen acuity in each presentation time category required to recognise 6/9 optotypes.

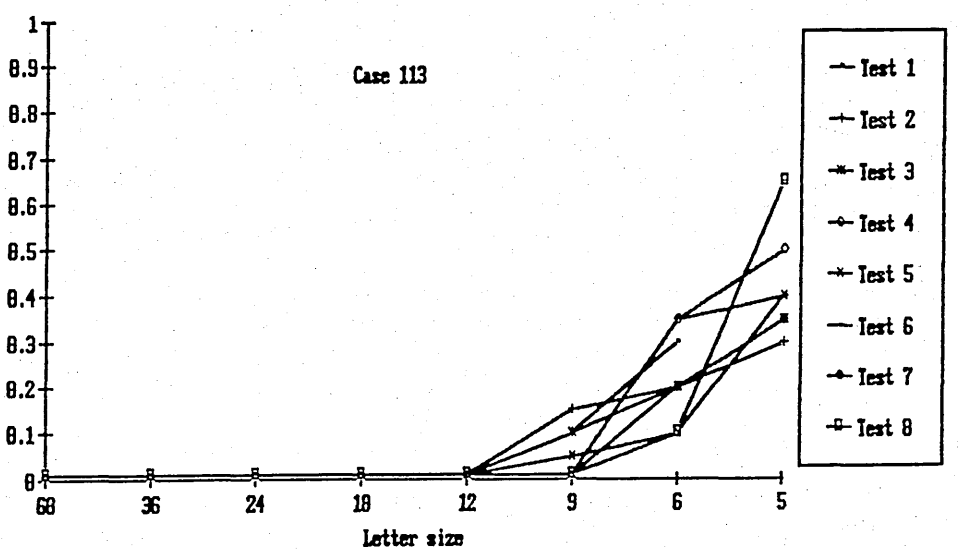


Figure 6.10

Test results of one normal volunteer repeated at 8 different occasions.

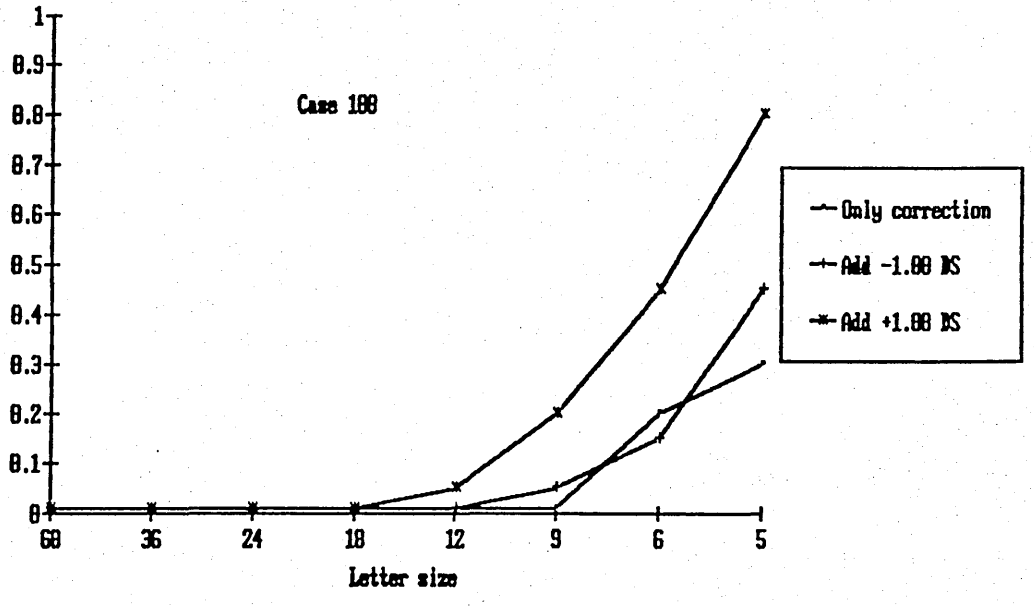


Figure 6.11

The typical effect of induced error of refraction on temporal acuity.

6.4.4. CSR patients:

Twenty three patients who had had CSR were examined. Twenty were men (87%) and three women (15%). The ages of these patients ranged between 26 - 65 years with a mean age of 49 years. The follow-up time ranged between 2 - 14 years with a mean of 7 years.

The 'temporal' visual acuities were compared with those of the control unaffected eyes. Furthermore, findings were compared with age matched normal controls.

Statistical analysis:

Data were analysed by Dr. D. Allan using the facilities of the MINITAB package on the University of Glasgow ICL 3980 mainframe computer. Paired comparisons were made between the performance of the affected eye and its unaffected fellow for temporal visual acuity. The Mann-Whitney confidence interval and Mann-Whitney test were used.

Results:

Temporal acuity curves of all the affected eyes were overlaid as shown in Figure 6.12 and those of the control eyes in Figure 6.13. The overall similarity of these two graphs was confirmed by statistical analysis.

The affected eyes were compared with the unaffected fellow eyes together with 52 normal age matched subjects. No statistical difference was found between eyes with (resolved) CSR and the unaffected eyes of the same patients. Furthermore, the eyes with CSR and the unaffected eyes were compared with age matched normal subjects. However, on individual analysis of each patient, there was a clear difference between the unaffected eye and the eye with CSR (the unaffected eyes did better than the affected eyes) in nine patients.

In a further 6 patients the eye with CSR showed the better performance and in 5 patients there were no clear difference between both eyes. The remaining three patients had had bilateral CSR, in two of them there was no difference between both eyes and in the third there was a clear difference between both

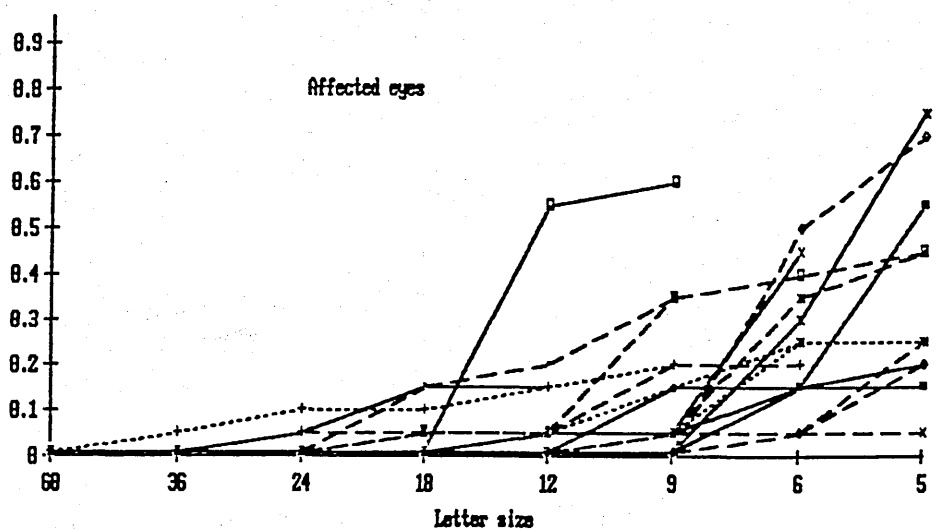


Figure 6.12

Temporal acuities of all eyes affected with CSR.

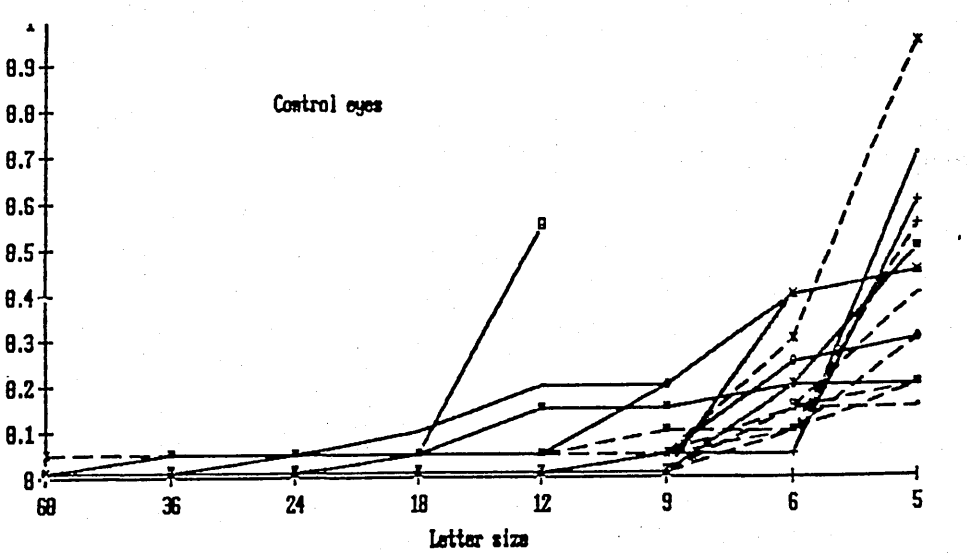


Figure 6.13

Temporal acuities of all the control fellow eyes.

eyes. In this particular case the eye with recurrent attacks of CSR had poorer performances than the other eye which had had no recurrence of the disease.

6.4.5. Retrobulbar neuritis:

The temporal acuities of 12 patients who had had retrobulbar neuritis followed by recovery of their Snellen visual acuity were assessed. In all of these patients the temporal acuity was much worse in the affected eyes compared with the fellow unaffected eyes of the same individual. The time required to recognise even the larger optotypes is increased in the affected eyes although in the majority of these patients (n=10) 6/6 vision was achieved with each eye. The curves shown in Figure 6.14 with the higher curve for the affected eye was characteristic for all cases.

6.5. DISCUSSION:

6.5.1. Normal group:

It can be seen from Table 6.2 that individuals of younger age groups require a shorter time to recognise letters than those of the older age group except for the two oldest age groups. However, the number of patients in these old age groups was small.

The results indicate that, probably the best way to present the test values is by displaying the graph which comprises the values of all the recognised optotypes rather than concentrating on the time needed to achieve the best visual acuity. The system automatically provides this on the screen at the end of the test and the user can choose to print it as well.

Test repeatability:

It can be concluded from the results of assessment of repeatability of the test that the 6/9 optotype is the most accurately repeatable optotype for normal individuals. It is also possible to suggest that the most appropriate optotype for assessing the temporal acuity is two lines before the best achievable Snellen acuity. However, investigation of a larger groups of patients with known visual function disturbances is required to confirm this conclusion.

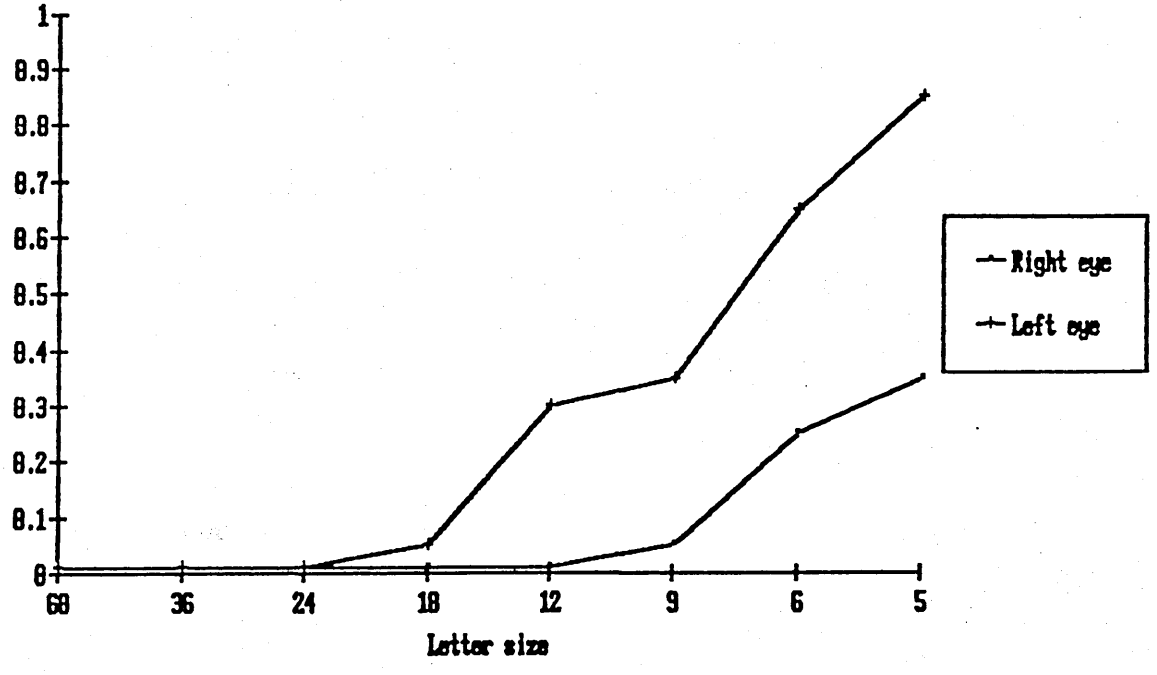


Figure 6.14

A typical result of the test in a patient with left optic neuritis who achieved 6/5 with each eye. The left eye 'temporal acuity' is much worse than the unaffected right eye.

Effect of errors of refraction:

It was of interest to find that one diopter of ametropia resulted in a marked increase in the time required to recognise the optotypes even though it did not affect the Snellen visual acuity. The effect of making the patient myopic was greater perhaps because there is no mechanism to compensate for myopia, in contrast to hypermetropia which can be compensated for by exerting accommodation.

6.5.2. CSR group:

No overall significant difference was found in the temporal acuity of eyes with CSR and the unaffected eyes and between those of age matched controls.

The affected eyes of these patients were found to have decreased macular sensitivity. Failure to demonstrate an abnormality implies that the spatial resolution was not sufficiently impaired to necessitate compensation by means of temporal summation of the data.

The temporal visual acuity of patients with acute CSR may be assessed to be compared later with the temporal acuity after resolution of the disease.

6.5.3. Retrobulbar neuritis group:

The temporal acuity has been found to be affected in eyes with retrobulbar neuritis compared with the fellow unaffected eye although each eye can achieve the same Snellen visual acuity level. This might be of value in making the diagnosis of multiple sclerosis. Further investigation of larger number of patients with both retrobulbar neuritis and other optic nerve conditions is necessary before final conclusions can be made about the value of the test.

6.6. GENERAL DISCUSSION AND FUTURE RESEARCH:

It is recognised that the apparatus described above is custom built with appropriate computer components. Moreover, a similar system could be built in which the translucent component of Snellen chart is transiently illuminated for

specific progressively longer periods in a manner analogous to that provided by the computer programme. Other similar modifications can also be envisaged.

It was expected that some letters can be missed because of lapses in the patient's concentration. The operator can then display another randomly selected letter of the same size and presentation time. Another way that helps the patient to concentrate are two sharp audible beeps which are sent to the computer loudspeaker shortly before each letter is displayed.

The non-linearity of the steps between the different sizes of Snellen chart rows and the error it may introduce in statistical analysis has been discussed by Ridley (1959). Despite this, no attempt was made to change the sizes of the letters used by TEMPRAC. Our intention was to design a system based on the same principles of Snellen chart which has gained world-wide acceptance as the standard visual acuity test. We believe that, by utilising an existing accepted test principle the operator can easily familiarise himself with the new test and the interpretation of the results with the added test parameter is more straightforward to understand. This test fulfils both these requirements and the others mentioned in the introduction to this chapter. It provides a new approach to the study of visual function, particularly in those patients who have apparently normal or mildly impaired visual acuity. It is expected to be more sensitive than Snellen acuity in detecting patients whose visual system compensates for the impairment in spatial analyses by temporal summation of the input data.

It was noted that some of the 14 letters which are presented randomly during the test are easier to recognise while others are more difficult. Sloan (1951) revised the selection of the most suitable type of test object, the specification of the range and gradation of the size of test object required, and standardisation of the brightness of the test object and background and of other variable factors in the test procedures using Snellen optotypes. He concluded that the ideal test object should contain horizontal, oblique, vertical and curved contours such that it can be recognised only when clearly focused.

Hartridge and Owen (1922), Bainster (1927) offered experimental evidence showing that the letters of the Snellen chart are not equal in difficulty. The alphabet and numerals were arranged as follows: (1) Easily recognised - A C L D V O U 7 1 4; (2) intermediate - T P Z I G E F K N W R 6 2 3; and (3) difficult - H

M Y X S Q B 5 8 9. The question of which are best letters to use has given rise to considerable controversy. Hay (1919) suggested that the easiest letter to resolve should be used; Sheard (1921) following the recommendations of the Ophthalmological Section of the American Medical Association, and advised letters of different degrees of difficulty; Hartridge and Owen (1922) recommended letters of medium difficulty, and Bainster (1927) advocated the use of confusion letters such as C D G O Q and H K M N W. Further investigations are required to establish the optimum letters which have the greatest similarity.

This test is based on the Snellen visual acuity test and by adding the temporal dimension it should be more sensitive. Therefore, one of its potential uses is screening which requires high sensitivity although the specificity may be low.

It is clear from the results of the effect of induced errors of refraction that TEMPRAC can only be used on patients who have been correctly refracted. This detracts from the potential use as a screening test as refraction is time consuming. By contrast, however, the results obtained for ametropia indicate that the test may prove very useful as a final subjective guide to optimal refraction.

The results obtained from testing the group of patients with retrobulbar neuritis indicate the potential usefulness of this test in the detection of other optic nerve diseases.

The frequency distribution of the values related to each optotype is shown as half of a normal distribution curve (Figure 6.8 and 6.9). This can be explained by the fact that the current minimum time of presentation is 0.01 seconds. If this time were shorter the curve would be expected to adopt the characteristic normal distribution shape. The sensitivity would also be increased by shorter time presentations for the larger optotypes.

Resolved CSR and retrobulbar neuritis were chosen for the study to evaluate the sensitivity of the test in the detection of both mild retinal and optic nerve pathology. Groups of patients with known minor dysfunction which had not affected Snellen visual acuity were chosen and tested. Thus making comparison of the two groups of results reasonably valid.

CHAPTER 7.

COMPUTER SYSTEMS FOR DATA INTERPRETATION

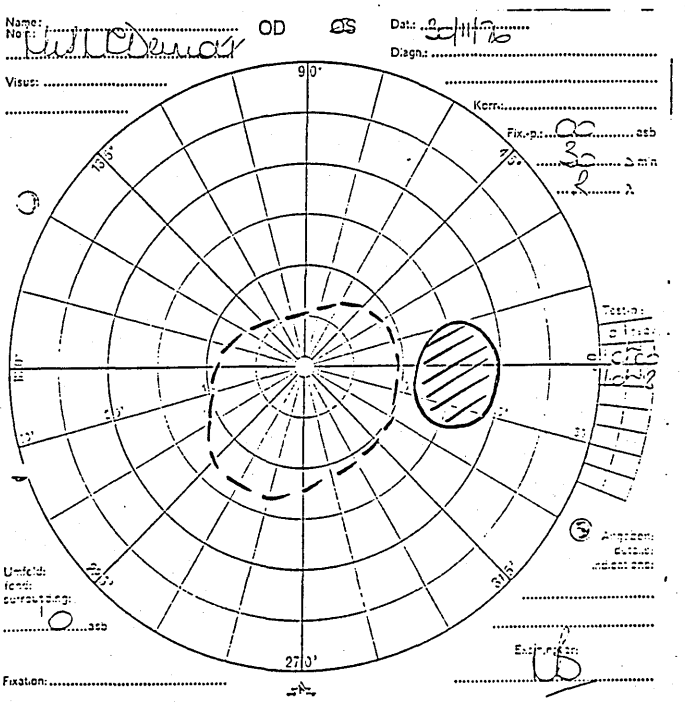


Figure 7.1

The Tübingen kinetic central visual field chart.

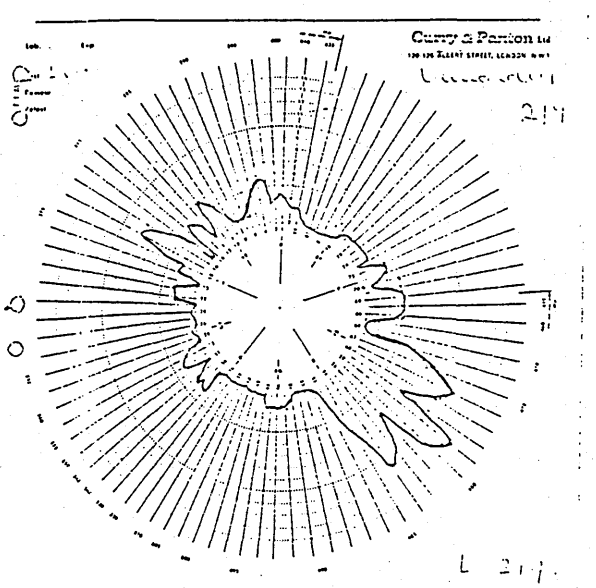


Figure 7.2

The 100-Hue colour vision test chart.

7.1. INTRODUCTION:

A wide range of charts is used in ophthalmic practice in order to document various forms of eye disorder. Those which are relevant to the follow-up of the thyroid ophthalmopathy patient are also the most commonly employed, and comprise the field of vision chart (Figure 7.1) and the 100-Hue colour vision test chart (Figure 7.2). At present, the interpretation of the data presented in these charts is carried out by a skilled clinician who assesses them in a qualitative manner on the basis of his previous experience. This is a time consuming, expensive and unreliable procedure, and one which is clearly a candidate for some form of automation.

There have been some attempts at 'computerising' the data from these charts to allow more detailed and reproducible interpretation (Hart and Becker, 1977; Pe'er, Zajicek and Barzel, 1983; Sponsel *et al.*, 1984; Weleber and Tobler, 1986). However, these methods have required manual digitising techniques for which an operator traces the key features of the chart using a digitising tablet or a mouse device. This process is slow, and prone to errors. Moreover, the manual entry of chart data becomes difficult and sometimes impractical when employed with crowded charts containing many important features.

A technique is required which allows automatic digitisation of the above forms of chart. It must be fast and reliable and provide a system in which the digitised image can be processed by a microcomputer to extract and quantify the information presented.

Such a system is currently being developed as part of an ophthalmic clinic automation project which is running in collaboration with Mr. A. W. Ahmed, who is currently a research fellow at the Signal Processing Division of the Electric and Electronic Department of Strathclyde University.

In this chapter the main features of the system are presented. In this early stage of the project details can only be presented in relation to the steps taken for quantification of the central 30 degree visual field charts plotted by the Tübingen perimeter.

7.1.1. Definitions:

Image: As used in this thesis, the term image refers to the series of values representing the brightness and colour at every given point. These points are called picture elements or pixels (Sheldon, 1987).

Digital image: Is a matrix whose coordinates (row and column indices) identify points in the image and the corresponding matrix element value identifies the grey level or colour at that point (Dawson, 1987).

Image processing: Is the science of modifying and analysing pictures.

Image processing algorithms: Are step by step procedures for performing image processing operations (Sheldon, 1987).

Digitisers: A digitiser is an input device which converts an image into a numerical representation suitable for processing by a digital computer. Among the commonly used digitising devices are, graphics tablets, flat bed automatic scanners, and television cameras.

7.1.2. Field quantification methods:

Sponsel (1985) reviewed visual field scoring methods and suggested a scoring system on a 0-100 scale regardless of the technique of measurement or quantification. This method is easily intelligible by the clinician and is the method adopted in our system.

A comprehensive appraisal of the various quantification approaches has also been given by Sponsel (1985). Three of these methods which are employed in our system are summarised as follows:

Simple area calculation:

'Simple area' is the area enclosed by a given isopter. Hart and Becker (1977) were the first to employ electronic digitising graphics tablet for quantifying

visual fields. They expressed their results in terms of 'degree squared'. Williams (1983) used a similar method, expressing area in terms of 'square millimeters' on the perimetric paper. This technique is applicable to recorded charts of all sizes. However, its major disadvantage is the absence of any central or functional weighting. In our system the field is quantified by calculation of this area as a percentage of normal maximum using a scale of 0-100.

Radial summation system:

The field score calculated in 'radial units' is the sum of the lengths of the twenty four 15 degree radial lines which transect the centre of the visual field (Sponsel *et al.*, 1983)

The length of lines passing through a scotoma or indentation in the field is therefore easily subtracted from the length of each line at its outermost limits. A scotoma near the macula will be crossed by more radial lines than an equivalently sized defect near the periphery, and this difference is reflected in the scoring, which can therefore be considered to be relatively 'functionally weighted' to central vision. This approach allows all the recorded perimetric information to be used (i.e., points on the 15 degree radial lines) without interpolation of lines or areas. A further characteristic of this system is that it can be applied to charts of any size, since the concentric isopter grid with its 5 degree intervals is used as the basis for determining the 'length' of each radial line recorded.

Esterman grid:

The Esterman grid is a plastic overlay which when placed over a Goldmann visual field chart divides it into 100 unequal areas (Esterman, 1968), each of which represents approximately 1% of the functional visual area (as deduced by its designer). In general, the central field is deemed more important (and therefore has smaller grid sections) than the periphery, and the inferior field of greater functional value than the superior field. This scoring system was designed as a general tool for quantifying the extent of visual disability in medicolegal terms. The classical grid is designed for a 0.5 degree white target and this has to be taken into account to derive equivalent grids in relation to smaller and dimmer or larger and brighter targets.

Plate 7.1

The hardware of the image processing system used for the development of the chart reading programme.

The 'Solid angle' approach:

Another approach suggested by Weleber and Tobler (1986), converts the field area into the solid angle subtended by the seeing region of the visual field minus the solid angle of any scotomata with the same test target within that isopter. The most commonly applied measure of solid angle is the steradian, which is the three-dimensional counterpart of the two-dimensional degree. The steradian is that solid angle where the surface area on the sphere equals the square of the radius. They also suggested a method for determining the solid angle of the kinetic perimetric visual field by transferring the sampling points for an isopter of a given test size and brightness onto the surface of a sphere and determining the area of the polygon so created. The solid angle in steradians, is then proportional to this area and is calculated using the following formula:

$$\text{Solid angle} = \text{Surface area} / (\text{radius})^2.$$

This method gives a better estimation of the visual field as mapped on the inner surface of the perimeter but there still exist distortions in the representation of the visual field with regard to retinal eccentricity and functional weighting.

7.2. SYSTEMS AND METHODS:

7.2.1. Hardware configuration:

A simple image processing system (Plate 7.1) (which consisted of an image acquisition device [digitiser], an image memory [Display card], a microcomputer and a display device [monitor] was assembled (Figure 7.3). The details of these components are shown in Table 7.1.

A Cannon scanner was used for image acquisition. Various scanning techniques may be employed in different scanner designs. The method used in the Cannon scanner is based on focusing the 'flood-illuminated' chart by a system of mirrors and lenses onto a linear photosensitive silicon device called a 'Charge coupled device'. Charges accumulate in proportion with the light flux while light is incident on this device. These charges are transmitted, amplified and eventually converted from analogue to digital form (Stamps, 1982). The Cannon flat bed scanner takes only 12 seconds to digitize an A4 page at maximum

Automatic Chart Reader:

Digitiser

Cannon IX 12 Scanner

Cannon IX Scanner Interface

Computer:

IBM PC/ at Microcomputer

640 KB RAM

84 Hard Disk Storage

Display device:

NEC Multiscan Colour Monitor (Resolution 800X560)

ATI EGA-Wonder Automatic switching Display Card with 256 KB image Memory

Table 7.1

Hardware configuration of the image processing system.

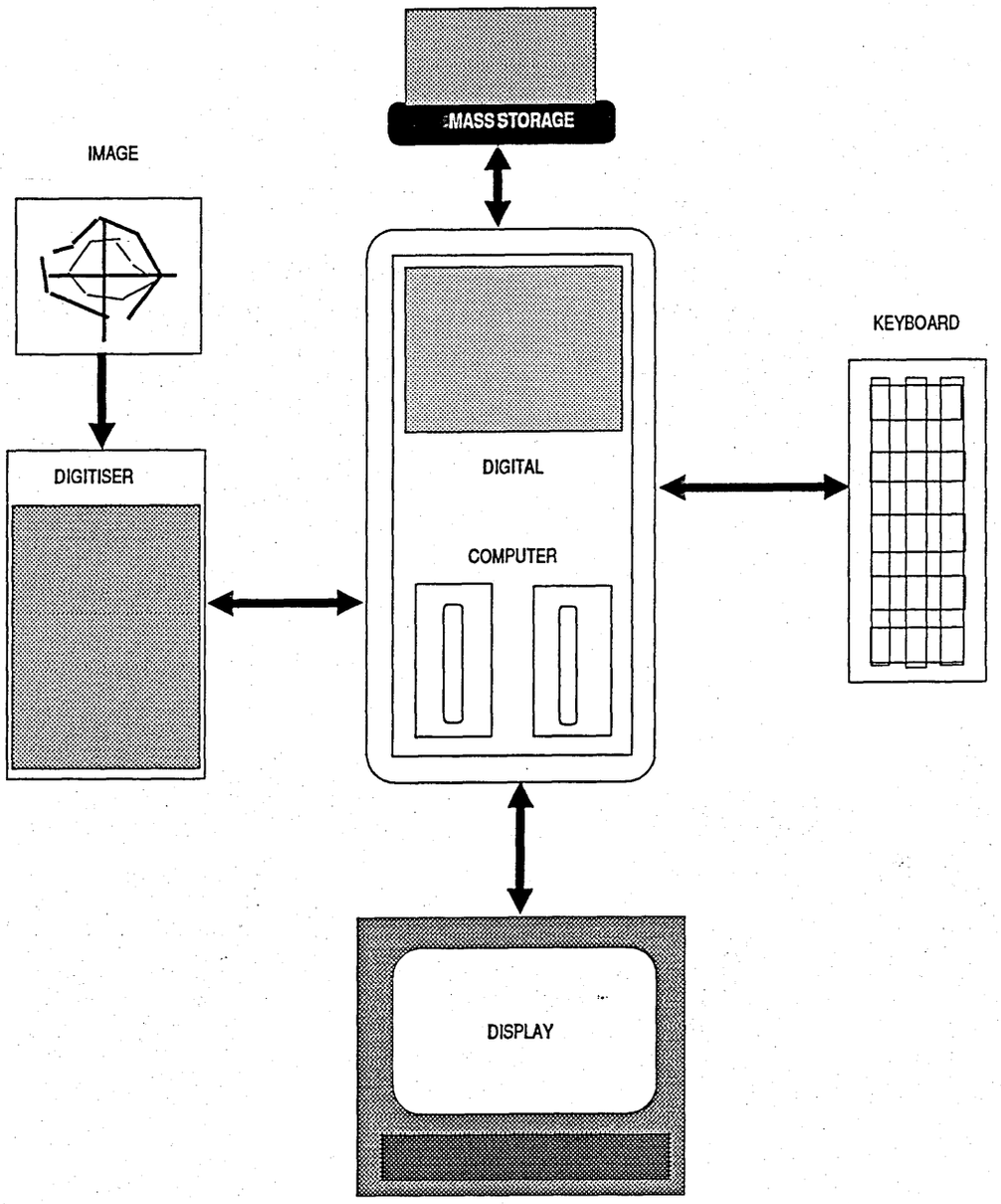


Figure 7.3

Hardware configuration of the chart reading system.

resolution of 300 DPI (Dots Per Inch) which is equal to 90,000 dot per square inch (Dallas, 1988).

The computer processes the pixel data in the image memory and makes the required calculations. The function of the display unit in this system is to convert the numerical arrays stored in the computer memory back into spatially organised image intensities, i.e., a from suitable for simple interpretation.

7.2.2. Software design:

Software tools:

1. Turbo C, Version 2.0: This is a version of the C programming language which is a powerful structured language characterised by having the flexibility required to write graphics and image processing subroutines.

2- Halo-88 Graphics developers toolbox: Is a graphics library which is written in the C language. The use of such tools saves time by offering ready-made sub-routines which can be included into a computer programme.

Major features of the algorithm:

Figure 7.4 summarises the procedures that make up the software algorithm, which is described as follows:

1. Scanning:

The scanning or 'image capturing' procedure is software controlled and is fully automated in this system. Software device drivers and subroutine which are supplied with the scanner and those which are included in the Halo-88 library, control the mechanical operation and select one of the three grey level choices provided by the Cannon scanner. These drivers have been integrated into our system.

2. Re-sizing:

The scanned image which is sent to the computer is so highly magnified that one typed letter fills the whole screen. The first step is to reduce its size and to adjust the aspect ratio (which is the ratio between the number of pixels in the vertical and the horizontal axes) according to the display device characteristics so that the image fits the screen keeping its original proportions.

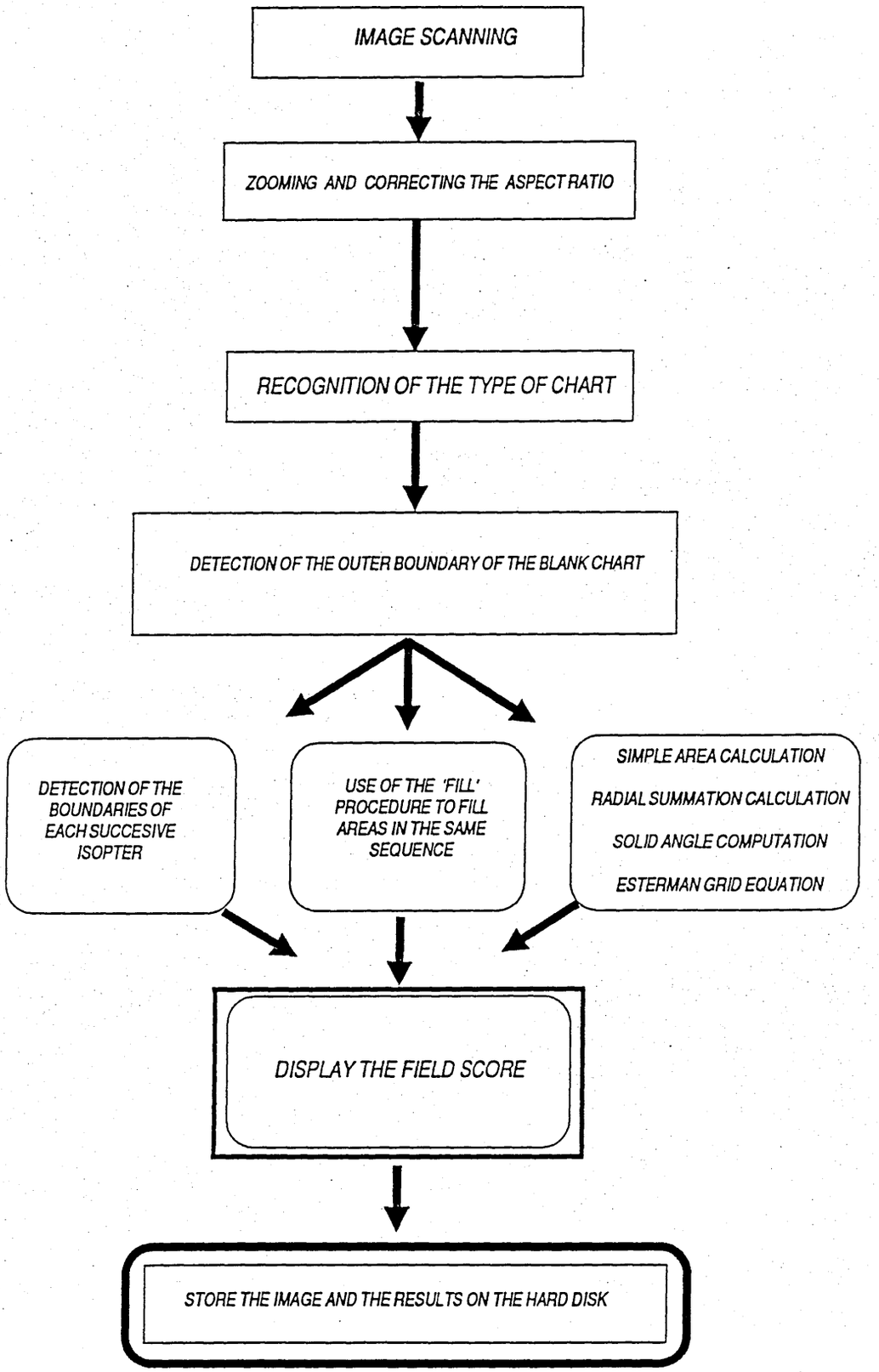


Figure 7.4 Algorithm for visual field chart reading and scoring using the image processing system based on Cannon automatic scanner.

3. Recognition:

The programme then detects the external general features of the image which characterises the type of chart. This process will be completed at the final stages of the development when an expert system is linked to this programme for pattern matching processes to be carried out (high level image processing algorithm).

4. Orientation:

A 'paint' with a certain colour value then 'floods' the whole chart area outside the outer circular boundary of the blank chart. A 'fast area-fill' subroutine is used for this purpose. The system then defines the centre of this circle which is also the centre of the field chart.

5. Information extraction:

The chart is divided into four equal areas by horizontal and vertical lines passing through its centre. The foreground of the lower left area is then given a colour value which is different from the rest of the chart. This area is then rotated through 180 degrees and overlaid onto a copy of the upper right area. All symmetrical overlapping pixels (e.g., grid lines, scale markings) are cancelled. This subtraction procedure leaves the plotted information and some other scattered 'asymmetrical' marks and numbers. Another algorithms has been written which removes any group of pixels which are not in continuity with a plotted line. An extrapolation algorithm fills any gap and completes any missing sections of the plotted information. Finally, what remains is the plotted data with no background noise constituting the 'output image'. Information vectors describing the output image are then saved on the computer hard disk for storage and further processing. This process is repeated for the other three sectors using the odd symmetry principle (Section 7.4). This allows subtraction of one fourth of any circular area from any of the other three quarters maintaining full symmetry provided that it is rotated through the correct angle.

6. Calculations:

Area calculation and application of the scoring systems are applied on the information vectors of the output image using the four quantification approaches described in Section 7.1.2.

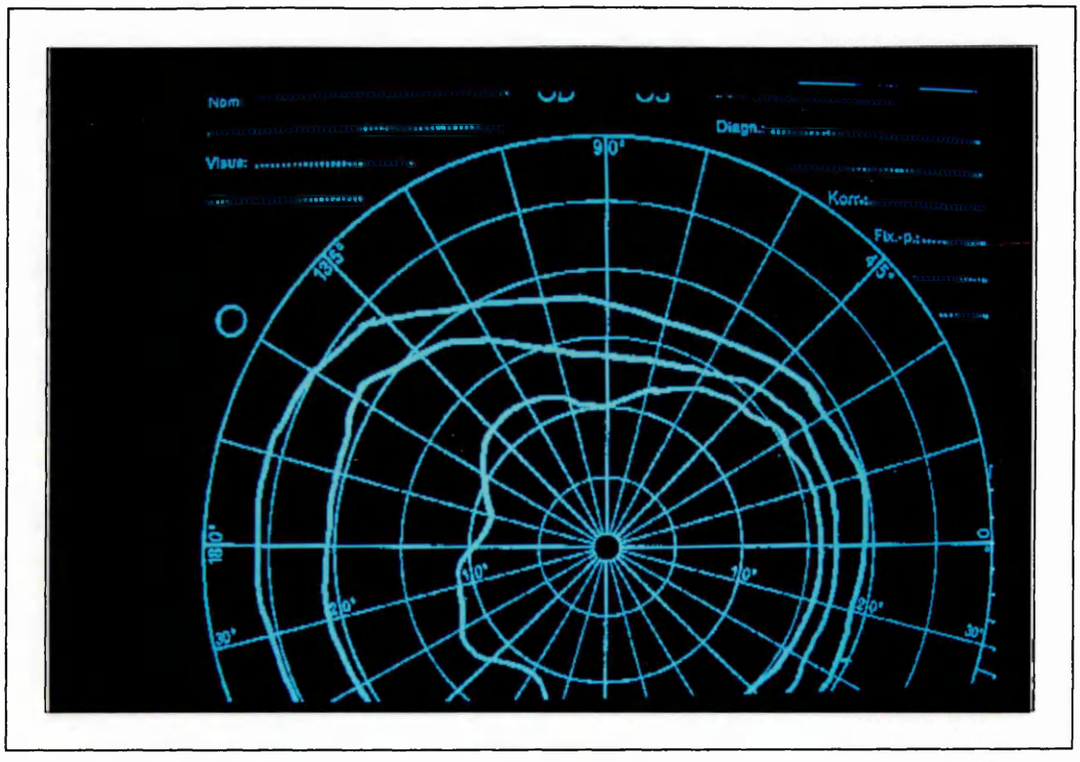


Plate 7.2

The first stage in the process of scanning.

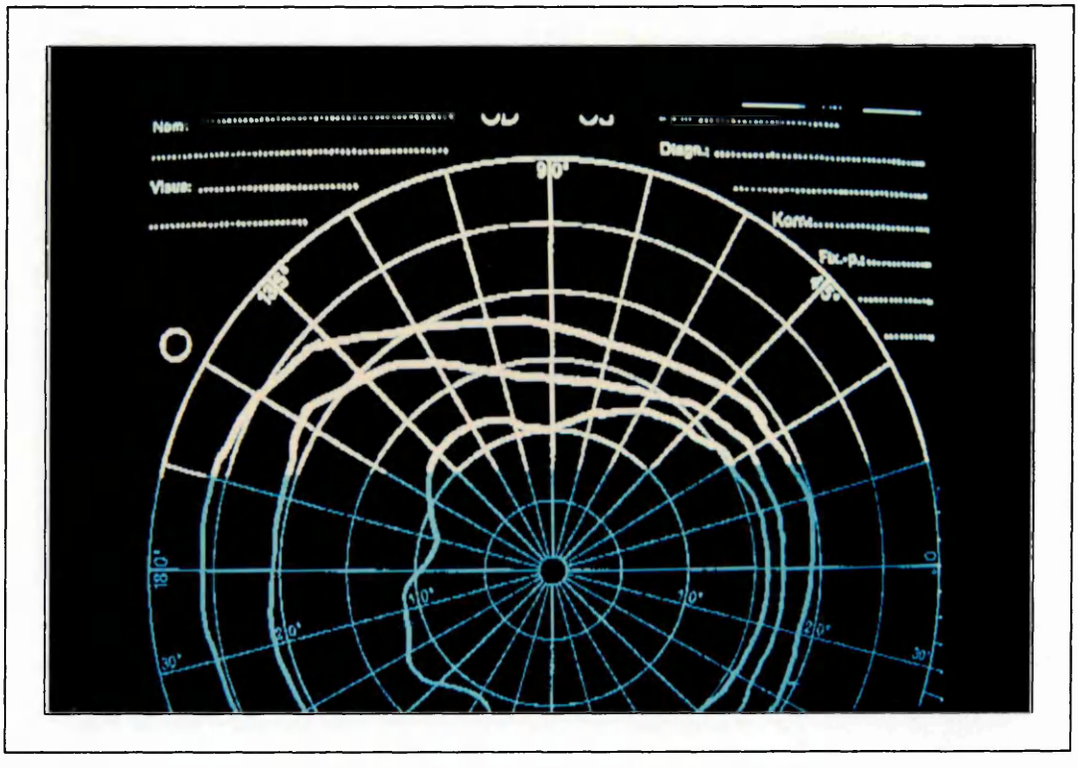


Plate 7.3

Showing the screen half-way through the final stage of digitisation.

7.3. RESULTS:

Five of the six steps of the algorithm described above have been completed at the time of writing; namely, scanning, re-sizing, recognition, orientation and information extraction. These processes take place in the computer and the graphics memories. During normal operation, they are invisible to the user. Screen displays (Plates 7.2 through 7.8) are presented to demonstrate the principal operations of the algorithm and the progress made so far in this project. A demonstration disk is enclosed (Volume 2, pocket) which more effectively shows the dynamics of the described steps (Programme listing is found in Appendix B4).

7.4. DISCUSSION:

Several methods have been described for using a digitising tablet and a computer in quantification and scoring of charted information (Hart and Becker, 1977; Sponsel *et al.*, 1984; Sponsel, 1985; Weleber and Tobler, 1986). The disadvantages of these methods of data entry are that they are time consuming and that there is a high risk of error. Moreover, these techniques are only suitable for entry of data concerning the visual field and it is not practicable to enter all the points of a 100-Hue chart as the likelihood of error is too great.

The new approach described overcomes this problem by using low level and high level image processing algorithms to directly process the raw chart image. These new techniques operate on the binary image of the medical chart obtained from a scanning device.

Direct digital image subtraction:

The most straightforward approach to the extraction of information plotted on a chart is by using the conventional 'digital subtraction technique' which is used in diagnostic radiology. In essence, a stored image of the blank chart is superimposed on the image of the plotted chart allowing the overlapping pixels to cancel each other leaving only the plotted information. There are however several disadvantages which make this approach inappropriate for application on microcomputers. The major difficulties and disadvantages are:

1- The computer must deal with three complete images simultaneously. These are the image of the blank chart, the image of the plotted chart and the output image (after subtraction is completed). This requires large

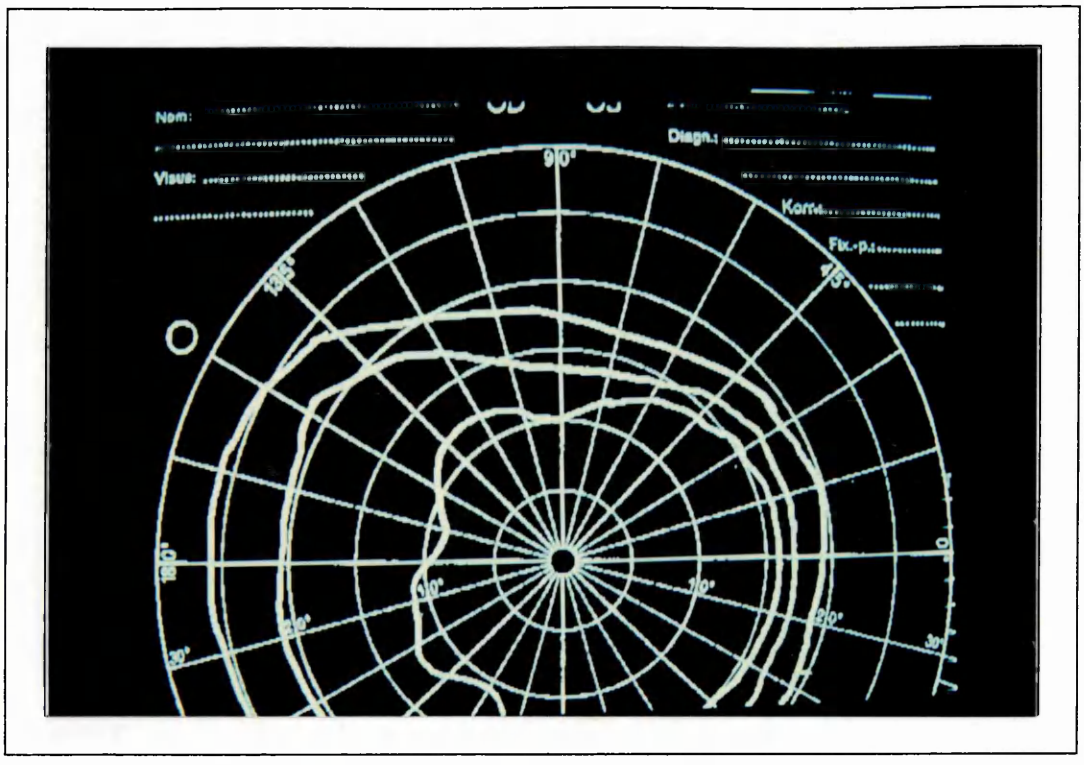


Plate 7.4

The monitor screen at completion of digitisation.

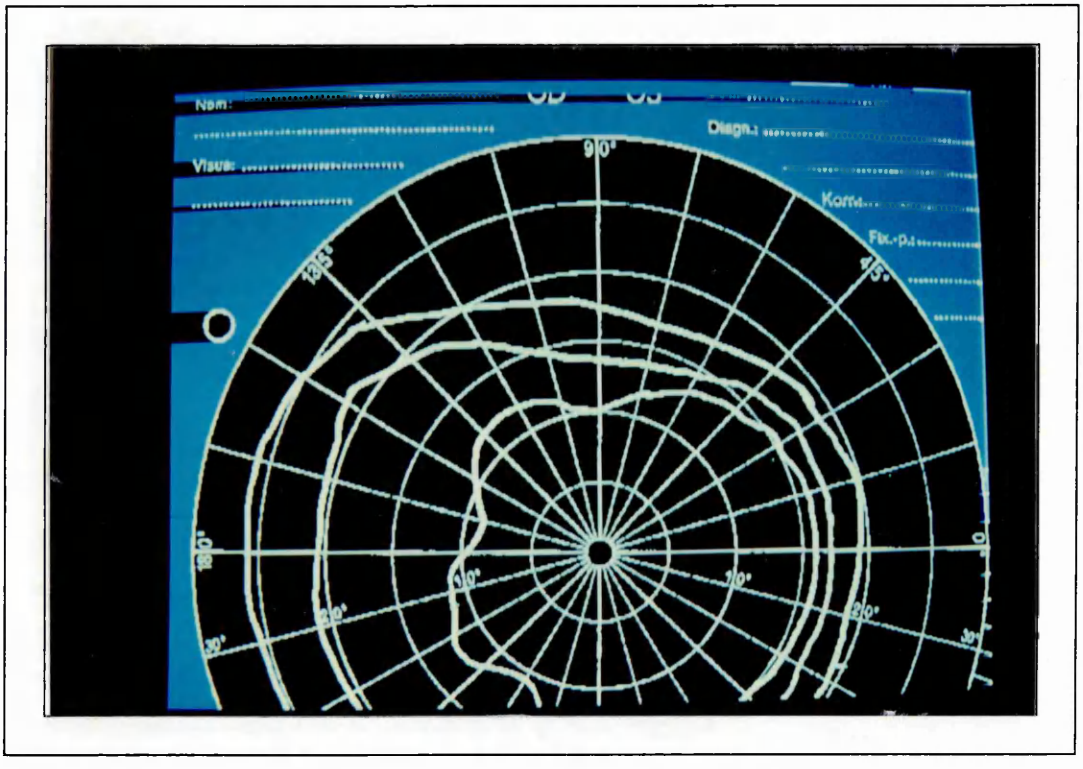


Plate 7.5

Showing the 'flooding' of the areas outside the circular chart using blue 'paint'.

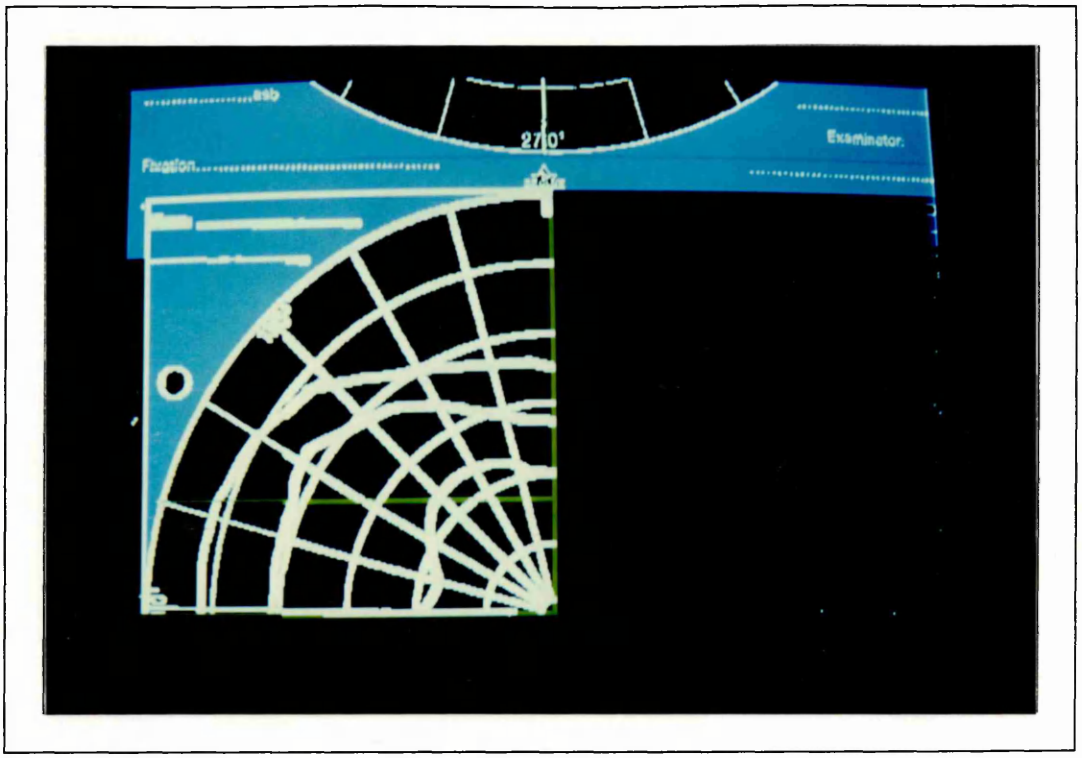


Plate 7.6

Showing a copy of the upper right quadrant of the chart which is to be subtracted from the lower left quadrant.

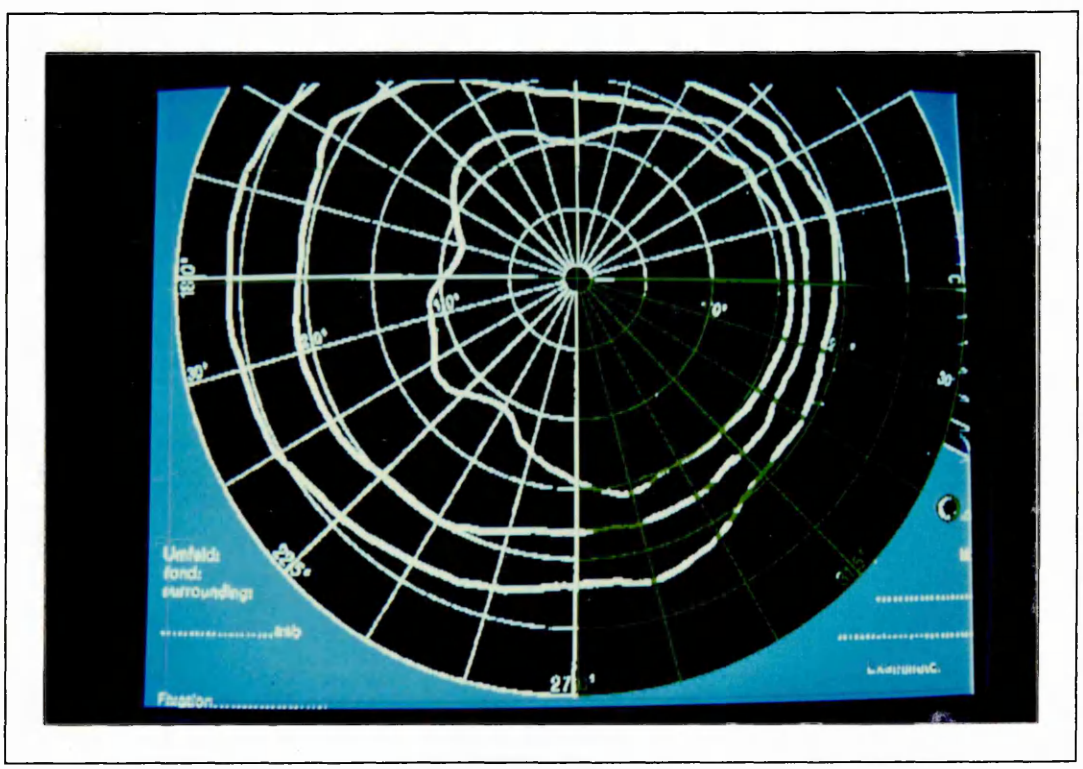


Plate 7.7

This display shows that subtraction is completed, the circular chart grid has been removed and only some marks are left in addition to the charted information.

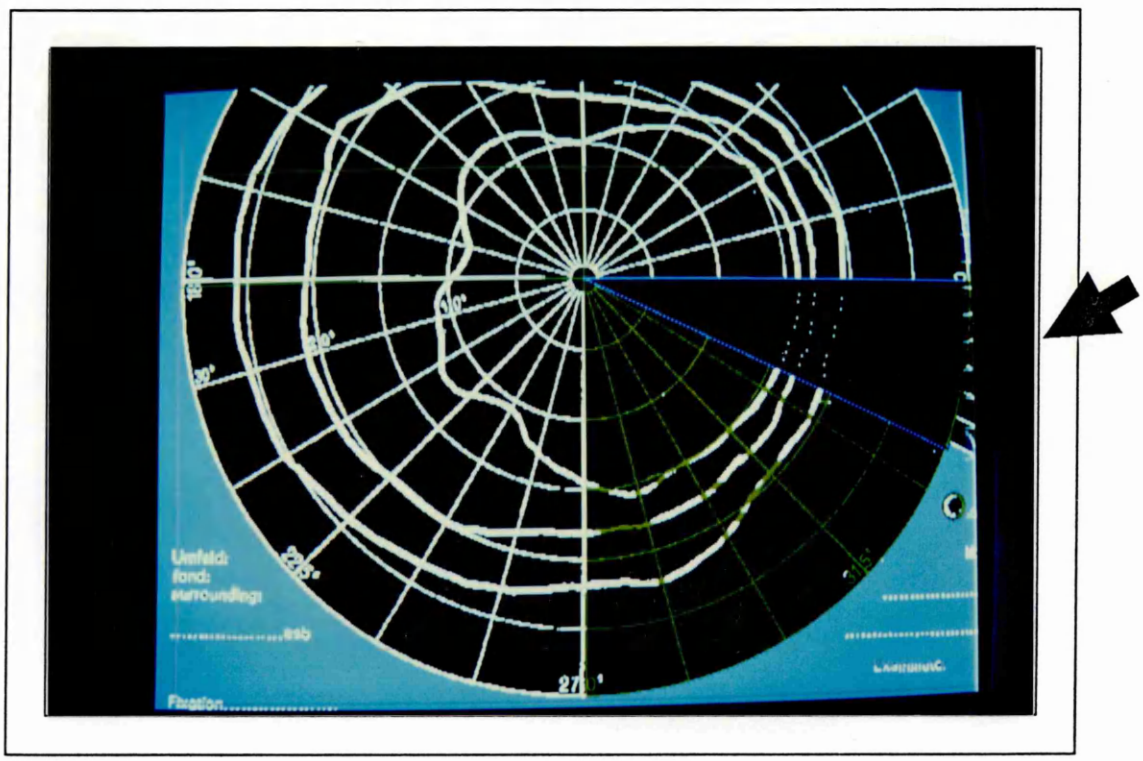


Plate 7.8

Demonstrates various stages of information extraction and background noise removal. The arrow points to a sector containing the charted information only.

graphics and working computer memories to accommodate the high resolution images of such crowded charts. Sufficient memory space is only available in dedicated expensive high resolution image processing work stations.

2- Perfect alignment of the blank and plotted chart images is essential for successful subtraction. This can not be guaranteed in an automated system.

3- The sizes of the blank and plotted charts must be exactly the same for the technique to be successful. This means that photocopied charts will not be suitable if there is even a small reduction or enlargement of the original size. Although image processing techniques (e.g. 'tie points spacial relocation' and geometric transformation) may solve this problem by 'stretching' or 'shrinking' the plotted chart to match the size of the blank chart, these techniques require vast number of calculations and therefore are unacceptably slow (Green and van Nostrand, 1983).

Odd symmetry subtraction:

This technique is based on the fact that the majority of medical blank charts are circular and symmetrical around the horizontal axis. Biological data plotted on these charts is unlikely to be completely symmetrical and even more unlikely if comparisons are made on the basis of 'odd symmetry', i.e., the lower left quarter is compared with the upper right area of the chart. Subtraction of the upper lower data from the upper data effectively removes the blank chart data and leaves the plotted data for analysis and interpretation.

This approach had been devised and employed in our system because it has many advantages over the conventional direct method which can be outlined as follows:

1- Only the image of the plotted chart is required to be loaded into the memory which makes it possible to use any of the popular, reasonably priced EGA-based general purpose microcomputers connected to a suitable scanner to run the programme.

2- Problems regarding alignment, orientation or centering are completely avoided when this approach is employed.

3- By applying this technique it was possible to write a universal chart reading algorithm which extracts the plotted information from a wide range of

charts. The size of the chart, which is taken into account when applying the calculations regarding quantification and scoring, has no influence on the effectivity of the algorithm in extracting the plotted data as long as the chart does not exceed the dimensions of the scanner. It is therefore possible to use photocopies or charts plotted using different types of equipment.

However, there are some difficulties and limitations of the odd symmetry digital subtraction approach which can be summarised as follows:

(1) Subtraction may be applied on some sectors of the plotted information if they fall on one of the blank chart grid lines. A separate interpolation algorithm had to be written to fill in any gaps found between plotted line ends. This can fill a gap as large as half of a circle.

(2) Some unwanted asymmetric information remains after subtraction (e.g., numbers and marks). These are removed using another algorithm which removes any collection of pixels which is not in continuity with a line.

(3) The only limitations which are yet to be overcome arise when the plotted data is in the form of a perfect circle concentric with the chart grid or when larger than half of a circle overlaps one of the circular grid lines. However, it is highly unlikely to come across such a chart in practice.

With such a system it will be possible to carry out automatic, accurate and fast digitisation and analysis of the kinetic visual field and 100-Hue charts. In addition the facilities will be available to digitise any other charts and diagrams related to the ophthalmic patient such as the field of binocular single vision, and the autoclave temperature and pressure charts. Furthermore, a wide range of charts used outside the medical field such as barometer, tachometer, and refrigerator circular charts may also be read using the same principle. This in turn will allow immediate storage and retrieval of information, and analysis and quantification of the complex data presented in such two dimensional charts.

To the best of our knowledge no automated chart reading devices are currently available and this is the first such system to be designed exploiting the concept of odd symmetry in processing a circular image.

This work, which took five and half months to reach this stage, has resulted in the development of a novel class of efficient segmentation algorithm that

employs a fast area-fill method to detect object boundaries. The first stage involves a noise removal and thresholding operation to clean the image for the subsequent algorithms. These algorithms are the key to the diagnostic process and provide a means of extracting the desired features from the background noise (e.g., patient name and data, grid lines and scale marks)

This programme will allow a meaningful scoring system to be accorded to the charts which will, in the long-term, improve the management of patients who require repeated evaluation in order to detect whether significant change in visual function has taken place. This would include, for example, patients with primary open angle glaucoma and those with chronic dysthyroid eye disease. Moreover, this technique will greatly facilitate the conduction of studies in which the effects of treatment are being evaluated.

CHAPTER 8.

EXPERT SYSTEM FOR THE MANAGEMENT OF DYSTHYROID EYE DISEASE

8.1. INTRODUCTION:

An expert system has been defined as the "embodiment within a computer, of knowledge from an expert skill in such a form that the system can offer intelligent advice or take an intelligent decision" (Chard, 1988). It can be distinguished from other kinds of artificial intelligence techniques in that it deals with subject matters with realistic complexity that normally require a considerable amount of human expertise. It must exhibit high performance in terms of speed and reliability in order to be a useful tool. It must also be capable of explaining and justifying solutions and recommendations in order to convince the user that its reasoning is correct.

Human experts in any field are frequently in great demand and are therefore, usually in short supply. An expert system contains the knowledge about a particular field thus assisting human experts in providing information to people who do not have direct access to an expert in that particular field.

The most obvious reasons for building an expert system are dissemination of rare and costly expertise, and the more effective use of the human expert. Other reasons go beyond these productivity considerations. From a scientific point of view, the most important reason is the formalization and clarification of knowledge that results from having the human expert make his reasoning explicit.

Medical expert systems take in diverse areas such as patient-monitoring systems, x-ray and ultrasound imaging systems, and prosthetic devices. The present thesis restricts the topic to systems concerned primarily with diagnosis and therapy.

8.2. OVERVIEW:

In the early 1960s researchers in artificial intelligence had focused on problem solving in game playing, image recognition, speech understanding, and language understanding (Feigenbaum and Fieldman, 1963). During this period some general problem solving principles were formalised. However, it was discovered that most of the difficulty in achieving intelligent computer performance was in collecting and storing a large knowledge base of facts specific to the prob-

lem area. This result was confirmed by the success of a few large programmes in scientific and mathematical areas. At that time, the explosion in medical knowledge was forcing physicians to specialise increasingly. Medicine was therefore an appropriate field in which to apply the developing knowledge-based techniques (Clancey and Shortliffe, 1984).

Large domain-specific problem solving systems came to be known as 'consultation programs', because they fitted the image of an expert specialist who is asked to provide advice about a difficult problem. In medicine, the 'problem' would typically be a patient with an illness to be diagnosed. By the late 1970s these programs became known as 'expert systems'.

The early efforts in developing the major systems in the late 1970s namely, PIP, CASNET, MYCIN, and INTERNIST (Section 8.5) resulted in the production of prototypes directed at two research areas: Firstly, the issues involved in designing consultation programmes (e.g., acceptability to the end user) and secondly, the nature of expertise to be formalised (e.g., integration of factual and judgemental knowledge).

Over the past 10 years various research groups in artificial intelligence have built highly specialised systems containing the expertise needed to solve such problems as medical diagnosis and treatment, chemical structure analysis, geological exploration, computer configuration selection, and computer fault diagnosis. Such systems have been comprehensively reviewed by Duda, Gasching and Hart (1979), Barra and Feigenbaum (1981), Weiss and Kulikowski (1984), Engelbrecht and Rothemund (1987) and Ellis (1987).

8.3. MOTIVATION FOR BUILDING A MEDICAL EXPERT SYSTEM:

The primary care physician who first sees the patient has many tests available with a wide range of costs (both financial and physical) and potential benefits (i.e., arrival at a correct diagnosis or optimal therapeutic management). Even the experts in a specialised field may reach very different decisions regarding the management of a specific case. Furthermore, medical students usually learn about decision making in an unstructured way, largely through observing and emulating the thought process they perceive to be used by their clinical

supervisors (Kassirer and Gorry, 1978). Clancey and Shortliffe (1984) have summarised the reasons for introducing medical expert systems as follows:

1. To improve the accuracy of clinical diagnosis through approaches which are systematic, complete, and able to integrate data from diverse sources.
2. To improve the reliability of clinical decisions by avoiding unwanted influences of similar but not identical cases and by making the criteria for decision explicit and hence reproducible.
3. To improve the cost efficiency of tests and therapies by balancing the expenses of time, inconvenience, or funds against benefits and risks of definitive actions.
4. To improve understanding of the structure of medical knowledge.
5. To improve understanding of clinical decision making, in order to improve medical teaching and to make computer programmes more effective and easier to understand.
6. To disseminate rare and costly expertise.

8.4. COMPUTER-BASED CLINICAL DECISION AIDS:

The applications of formal methods of decision making have concentrated on problems of diagnostic reasoning, whilst decision-analysis techniques have been applied to treatment-selection problems. Table 8.1 summarises the sequence in which different techniques have been introduced.

An exhaustive review of computer-aided diagnosis will not be attempted because the field is vast and only representative examples based on simplified classification of the topic are presented (Table 8.2).

8.4.1. Clinical algorithms:

Clinical algorithms, or protocols, are flow charts to which a diagnostician or therapist can refer when deciding how to manage a patient with a specific clinical problem. Such protocols usually allow decisions to be made by carefully following a simple branching logic. They contain built-in safeguards whereby referral to experts is recommended if a case is unusually complex. The value of such a protocol depends on the infrequency with which such referrals are made,

Medical decision making:

Mid-1940s	Statistical hypothesis-testing methods: Mostly for screening and radiology, computations by calculator.	Yerushalmy, 1947
1954	Logic scheme: For matching, symptoms to diagnoses, slide rule or Cards used for sorting and matching.	Nash, 1954
1958	Statistical and logical techniques combined: Computers introduced.	Lipkin & Hardy, 1958
1960	Bayesian and discriminant methods	Ledley & Lusted, 1959
1968	Sequential Bayesian methods and decision-theory approaches: Applied to treatment selection.	McNeil *et al.*, 1975
1970	Information-processing models for diagnosis.	Wortman, 1972
1971	Knowledge-based artificial intelligence systems	Kulikowski & Weiss, 1971; Pople *et al.*, 1975; Shortliffe, 1976

Table 8.1

Evolution of methods of medical decision making

Computer-based medical decision aids:
(1) Clinical algorithms.
(2) Data bank analysis.
(3) Mathematical models.
(4) Statistical pattern recognition.
(5) Bayesian statistical approaches.
(6) Decision theory approaches.
(7) Symbolic reasoning approaches.

Table 8.2

A simplified classification of the computer-based medical decision making approaches.

so it is important to design algorithms that reflect an appropriate balance between safety and efficiency (Weiss and Kulikowski, 1984; Shortliffe, Buchanan and Feigenbaum, 1984; Chard, 1988). The systematic approach to eyelid surgery (Collin, 1983) and the work of Khir (1985) who presented an algorithm which establishes a functional and ætiological diagnosis and gives brief notes on the appropriate treatment of thyrotoxicosis, represent examples of this approach.

However, the role of the computer in such applications has been limited. Since algorithmic logic is generally simple and can often be represented on a single sheet of paper, the advantage of an automated approach over a manual system has not been clearly demonstrated (Vickery, 1974).

Although clinical algorithms are amongst the most widespread and accepted method of the decision aids described in this section, the simplicity of their logic makes it clear why the technique cannot be effectively applied in most medical domains. Decision points in the algorithms are generally binary. Thus the difficult decision tasks are left to experts, and there is generally no formal algorithms for managing the case from that point on.

There are two other major problems with clinical algorithms. Firstly, each binary decision depends on the sensitivity of the test which brought about that decision being 100% - no such test exists, therefore the wrong pathway may be followed especially when there are multiple steps. Secondly, the determination of the sequence of an algorithm is to a certain extent arbitrary. Ideally tests of high sensitivity are used first and those of high specificity last. If the sequence is chosen inappropriately, inaccuracies will ensue.

8.4.2. Data bank analysis:

There have been several recent attempts to create programmes that could provide analyses of the information stored in a computer data bank. Some early systems had retrieval modules that identified all patient records matching a Boolean combination of description (Boolean algebra proposed by George Boole (1854) for describing logic in mathematical terms). However, further analysis of these records for decision-making purposes was left to the investigator.

Systems for data bank analysis depend on the development of a complete and accurate medical record system. Once such a system is developed, a number of additional capabilities can be provided: Correlation amongst variables can be calculated, prognostic indicators can be measured and the responses to various therapies can be compared.

Physicians faced with a complex management decision can look to such a system for assistance in identifying patients who had similar clinical problems in the past and can then see how those patients responded to various therapies. A clinical investigator who keeps the records of his study patients on such a system can use the programme's statistical capabilities for data analysis.

The HELP system (Warner, Olmsted and Rutherford, 1972a; Warner *et al.*, 1974; Warner, 1978) is an example of one of the most successful projects in this category.

Data bank analysis systems have powerful capabilities to offer to individual clinical decision makers. Furthermore, medical computing researchers recognise the potential value of large data banks in supporting many of the other decision-making approaches discussed in subsequent sections. The following are important additional issues regarding data bank systems (Shortliffe, Buchanan and Feigenbaum, 1979):

1. Data acquisition remains a major problem. Many systems have avoided direct physician-computer interaction but have then been faced with the expense and errors of transcription.

2. Analysis of data in the system can be complicated by missing values, outlying values, and poor reproducibility of data over time and amongst physicians. Conversely, the system can itself be used to identify questionable values of tests or observations.

3. The space requirements for data storage can be large since the decision aids require a comprehensive medical record system as a basic component.

Slamecka *et al.* (1977) have distinguished between structured and empirical approaches to clinical consulting systems, pointing out that data banks provide a largely empirical basis for advice whereas structured approaches rely on judgemental knowledge elicited from literature or from experts. However, it is

important to note that judgemental knowledge is itself based on empirical information. Even an expert's intuitions are based on observations and 'data collection' over years of experience. Thus one might argue that large, complete, and flexible data banks could form the basis for large amounts of judgemental knowledge that we currently have to obtain from other sources.

8.4.3. Mathematical models:

Pathophysiological processes can be well described by mathematical formulae in a limited number of clinical problem areas. Such domains have lent themselves readily to the development of computer-based decision aids since the issues are generally well defined. The techniques used by such programmes tend to reflect the details of individual applications, the most distinguished of which have been in pharmacokinetics (Jelliffe *et al.*, 1970) and acid-base/electrolyte disorders (Menn *et al.*, 1973).

The major strength of mathematical models is their ability to capture mathematically sound relationships in concise and efficient computer programmes. However, the major limitation is that few areas of medicine are amenable to firm, quantitative description. Mathematical models have limited applicability at present because the accuracy of the results depends on correct identification of relevant parameters, the precision and certainty of the relationships among them, and the appropriateness of the techniques for measuring them.

8.4.4. Statistical pattern-matching:

This general methodology includes a variety of techniques used to extract characteristic measurements (the features) and to find and refine the pattern classifier. Linear regression analysis, cluster analysis and discriminant function analysis are the most commonly employed techniques.

Pattern recognition techniques are used for determining prognosis or predicting disease duration and outcome. These techniques have been applied to a variety of medical domains, such as image processing and signal analysis, in addition to computer-assisted diagnosis.

In order to find the diagnostic pattern, or discriminant function, the method requires a 'training' set of cases for which the correct classification (e.g., diagnosis or outcome category) is already known, as well as reliable values for their measured features (Section 5.3.9).

The number of reported medical applications for pattern-recognition techniques is large, but there are also numerous problems associated with this approach. The most obvious difficulties are choosing the set of features in the first place, collecting reliable measurements on a large sample, and verifying the initial classification among the 'training' set of data. Current techniques are inadequate for problems in which trends or movement of features are important characteristics of the categories.

Various forms of discriminant analysis approaches have been described (Section 5.3.9) and the topic can be confusing for the non-mathematician (Norusis, 1988). However, the choice of approach has been shown to make little difference to the eventual clinical results (Titterington *et al.*, 1981).

Pattern recognition techniques are often misapplied in medical domains in which the assumptions essential for the validity of the chosen statistical techniques are violated (Weiss and Kulikowski, 1984; Shortliffe *et al.*, 1984; Chard, 1988).

8.4.5. Bayesian statistical approaches:

The theoretical basis of this approach was described by Thomas Bayes in the eighteenth century. In essence Bayes' theorem presents all the knowledge related to a problem as a set of probabilities and combines the prior probabilities of various input variables in order to reach a posterior probability or conclusion (Weiss and Kulikowski, 1984; Shortliffe *et al.*, 1984).

Bayes' theorem can be used to calculate the probability of various diagnoses given the clinical features of a particular patient.

The equation for Bayes' theorem can be described in various forms, one of which is as follows (Chard, 1988):

$$P(D:CF) = \frac{P(CF:D)P(D)}{P(CF:D)P(D)+P(CF:notD)P(notD)}$$

Where P is probability, D is diagnosis, and CF is a set of clinical features. Thus the expression on the left, P(D:CF), is equivalent to 'the probability P of diagnosis D given the set of features CF. On the right, P(D) and P(notD) represent the prior probabilities of the diagnosis and its alternatives.

In a clinical situation there would be a number of possible diagnoses and a number of clinical features. A separate calculation is performed in respect of each diagnosis. In other words, with regard to its diagnostic application Bayes' theorem requires three sets of data for each condition which may present, the comprehensive differential diagnosis, the order of likelihood of each diagnosis (or conditional probabilities) and the investigation (or set of investigations) which establishes each diagnosis. Exclusion of the first diagnosis on the list immediately updates the diagnostic likelihood of the next diagnosis. This constitutes the *a priori* probability. Negative investigation results for the common diagnosis therefore update the probability of the unusual diagnosis.

More work has been done on Bayesian approach to computer-based medical decision making than on any of the other methodologies which have been discussed. The process of drawing conclusions of practical certainty from multiple pieces of information, each of which is uncertain in its own right, is an almost perfect description of much of clinical medicine (Macartney, 1987). In several domains the technique has been shown to be exceedingly accurate, but there are also several limitations to the approach.

Among the most commonly recognised problems with the use of a Bayesian approach is the large amount of data required to determine all the conditional probabilities needed for the rigorous application of the formula. A variety of additional assumptions must be made, for example, the diseases under consideration are assumed to be mutually exclusive and exhaustive (i.e., the patient is assumed to have only one of the diseases listed); the clinical observations are assumed to be conditionally independent for a given disease; and the incidence of a symptom of a disease is assumed to be stationary (i.e., the model generally does not allow for change in a disease pattern over time).

During the study of deDombal's abdominal pain programme (Section 8.5.1), which is based on Bayesian probability theory, the computer generated diagnoses were simply saved and later compared with the diagnoses reached by the attending clinicians and with the ultimate diagnosis verified at surgery or through appropriate tests. Although the clinicians reached the correct diagnosis in 65-80% of the 304 cases studied (with accuracy depending on the individual's training and experience), the programme was correct in 91.8% of cases (deDombal *et al.*, 1972).

Even when diagnostic performance is excellent, such as in deDombal's approach to abdominal pain evaluation, clinical implementation and system acceptance will generally be difficult (Shortliffe *et al.*, 1984). So, in general, a purely Bayesian approach can constrain problem formulation so as to make a particular application unrealistic and hence unworkable.

8.4.6. Decision theory approaches:

Decision analysis is a process by which numerical values are assigned to choices and probabilities in order to break down the processes by which decisions are made or should be made in the form of a decision network. The following topics are among the central issues in the field (Ginsberg, 1972; Shortliffe *et al.*, 1984):

1. The decision tree: The decision-making process can be seen as a sequence of steps in which the clinician selects a path through a network of plausible events and actions. Nodes in this tree-shaped network are of two kinds: decision nodes, where the clinician must choose from a set of actions (e.g., choice to perform a test), and chance nodes, where the outcome is not directly controlled by the clinician but is a probabilistic response of the patient to some action taken (e.g., occurrence or non-occurrence of complications). By analysing a difficult decision process before taking any action, it may be possible to delineate in advance all relevant chance and decision nodes, all plausible outcomes and the paths by which these outcomes might be reached. Data may exist to allow specific probabilities to be associated with each chance node in the tree.

2. Expected values of various outcomes: In actual practice physicians make sequential decisions based on more than the probabilities associated with the chance nodes that follow. Thus anticipated 'cost' (financial expenditure, complications, discomfort or patient preference) can be associated

with the decision nodes. Using the probabilities at chance nodes, the cost at decision nodes, and the values 'of the various outcomes', and the 'expected values' for each pathway through the tree (and in turn each node) can be calculated.

3. Test evaluation: The tests that lie at decision nodes are central to clinical decision analysis, therefore it is crucial to know the predictive value of tests that are available. This leads to considerations of test sensitivity, specificity (Section 5.3.8) and disease prevalence (McNeil and Adelstein, 1977; Komaroff, 1979).

Computer implementations of clinical decision analysis have appeared with increasing frequency since the mid-1960s. Gorry and associates developed one of the most successful programmes in this category for the management of acute renal failure (Gorry and Burrnet, 1968; Gorry *et al.*, 1973). The investigators recognised the need to incorporate a means of balancing the dangers and discomfort of a procedure against the value of the information that can be gained.

Perhaps the most difficult problem with the decision theory approach is the assignment of numerical values to a human life or for example a day of health (Warner, 1978). Overlapping or coincident diseases are also not adequately considered, unless they are specifically included in the analysis, and the Bayesian foundation for many of the calculations still assumes mutually exclusive and exhaustive disease categories. The problem of symptom conditional dependence still remains, and there is no easy way to include knowledge regarding the time course of disease. Kassirer and Gorry (1978) point out that the acute renal failure programme was incapable of recognising circumstances in which two or more actions should be carried out concurrently.

8.4.7. Symbolic reasoning approaches:

Computers originally were designed specifically to process numbers. Humans however, tend to think symbolically rather than numerically. Human intelligence seems to be based, in part, on the mental ability to manipulate symbols rather than just numbers.

Computer architecture readily lends itself to algorithmic approach. Many human reasoning processes however, tend to be non-algorithmic, i.e. human

mental activities consist of more than just following logical step-by-step approach.

Large number of artificial intelligence research continues to be devoted to symbolic and non-algorithmic programming techniques in an attempt to emulate more closely human reasoning processes with a computer.

In contrast to numerical calculation programmes, whose power is derived from the analytical equations used, symbolic programmes gain their power from qualitative and experiential judgements codified in heuristics. A heuristic is a 'rule of thumb' which applies to a certain situation to suggest how to proceed without the need to re-think the problem completely every time similar or analogous situation is encountered. Heuristics focus the attention of the reasoning programme on parts of the problem that appears most critical and parts of the knowledge base that seem most relevant. They also guide the application of the domain knowledge to an individual case by deleting items from consideration as well as focusing on other items. The result is that these programmes pursue a line of reasoning, as opposed to following a sequence of steps in a calculation.

It was the landmark paper by Gorry *et al.* (1973) that first critically analysed the hitherto conventional approaches to computer-based clinical decision making and outlined his reasons for turning to the newer symbolic techniques. He used the acute renal failure programme as an example of the problems which arise when decision analysis is used alone (Gorry *et al.*, 1973). His conclusions from these observations include the following points:

1. Clinical judgement is based less on detailed knowledge of pathophysiology than it is on gross 'chunks' of knowledge along with a good deal of detailed experience from which rules of thumb are derived.

2. Clinicians know facts, of course, but their knowledge is also largely judgemental. The rules they learn allow them to focus attention and generate hypotheses quickly. Such heuristics permit them to avoid detailed research through the entire problem aspects and to take 'short cuts' based on previous experience.

3. Clinicians recognise levels of belief or certainty associated with many of the rules they use but they do not routinely quantitate or use their certainty concepts in any formal statistical manner.

Symbolic reasoning is therefore knowledge based but the 'chunks' of knowledge are not just composed of factual data but comprise knowledge of patterns, associations and sequences of events and actions for which the outcome may be predicted with reasonable accuracy based on previous experience.

Based on observations such as those above, Gorry identified at least three important problems for investigation:

a. Medical concepts: Clinical decision aids traditionally had no true 'understanding' of medicine. Although explicit decision trees have given the decision theory programmes a greater 'sense' of the pertinent associations, medical knowledge and the heuristics for problem solving in the field had never been explicitly represented or used. So-called common sense, was often clearly lacking when the programmes failed and this was often what most alienated potential physician users.

b. Conversational capabilities: Gorry argued that further research in the development of computer-based linguistic capabilities was crucial both for capturing knowledge from collaborating experts and for communication with physician users.

c. Explanation: Diagnostic programmes had seldom emphasised the importance of the ability to explain the basis for their decisions in terms understandable to physicians. System acceptability was therefore inevitably limited; the physician would have no basis for deciding whether to accept the programme's advice, and might therefore resent what could be perceived as an attempt to dictate the practice of medicine.

It was perhaps inevitable that some medical researchers would turn to the artificial intelligence field for new methodologies because of the limitations of the older techniques . Major research areas in artificial intelligence include knowledge representation, heuristic search, natural language understanding and generation, models of thought processes and neural computing (Wolfgram, Dear and Galbraith, 1987; Eckniller and Malsberg, 1988; Recce and Treleaven, 1988) - all topics clearly relevant to the problems discussed above. For artificial

intelligence researchers the question of how best to manage uncertainty in medical reasoning remains a central issue.

Whereas the computations used by the other approaches mostly involve straightforward application of well-developed computing techniques, artificial intelligence methods are largely experimental. New approaches to knowledge representation, language understanding, heuristic search, and the other symbolic reasoning problems mentioned above are still needed.

The techniques of artificial intelligence provide a way to respond to many of Gorry's observations regarding the three major inadequacies of earlier approaches described above: (1) medical artificial intelligence programmes all stress the representation of medical knowledge and an 'understanding' of the underlying concepts; (2) many of them have conversational capabilities which are based on language processing research; and (3) explanation capabilities have been a primary focus of systems such as MYCIN (Section 8.5.5).

This overview of the computer-based clinical decision aids has shown that there are two recurring questions. Firstly, how can systems designed to reach better and more reliable decisions in a broad range of applications? And secondly, how can we more effectively encourage the use of such systems by physicians or other intended users?

8.5. EXAMPLES OF MEDICAL EXPERT SYSTEMS:

8.5.1. The deDombal system for abdominal pain:

Since the late 1960s, deDombal and associates at the University of Leeds, England, had been studying the diagnostic process and developing computer-based decision aids using Bayesian probability theory. Their area of investigation has been gastrointestinal diseases (deDombal *et al.*, 1972). The programme was designed for the evaluation of cases of abdominal pain of less than one week's duration presenting at a hospital emergency department. The information from each patient was compared, using a Bayesian probabilistic analysis, with reference data derived from 6000 patients in 13 countries, with the addition of a more recent analysis of dyspepsia (Horrock and deDombal, 1975) and gastric carcinoma (Zoltie *et al.*, 1977).

The system was evaluated in eight centres with more than 250 participating doctors and 16,737 patients. Initial diagnostic accuracy rose from 45.6% to 65.3%. The rate of negative laparotomies fell by half, as did the rate of perforation in patients with appendicitis. Serious management errors fell from 0.9% to 0.2%, and mortality by 22 percent (Adams *et al.*, 1986).

8.5.2. CASNET/GLAUCOMA:

CASNET/GLAUCOMA is a model-based expert system which has been developed during the mid 1970s. It gives advice on diagnosis and treatment of glaucoma.

This system is based on causal associational network (CASNET) models of disease. A CASNET model consists of three main components: Patient clinical features, pathophysiological states, and disease classification.

As observations are recorded, they are associated with causally related network that summarises the mechanism of disease.

Strategies of specific treatment selection are guided by the individual pattern of observations and diagnostic conclusions as well as by the disease classification itself.

CASNET/GLAUCOMA demonstrated that there are areas of medicine in which explicit model representations permit powerful reasoning strategies that go beyond simple matching of treatment with disease. The CASNET model of glaucoma helped to provide consultation for complex clinical cases, including those involving long histories and multiple follow-up visits. For some situations it provided alternative opinions derived from different consultants. The programme was developed and tested jointly by a national network of investigators linked to Stanford University computer in the USA (Kulikowski and Weiss, 1971; Weiss, 1974).

8.5.3. INTERNIST:

INTERNIST is one of the best-known expert systems. It is an experimental computer-based diagnostic consultant for general internal medicine developed by Pople, Myers and Miller (1975).

The investigators decided to consider the entire field of internal medicine rather than selecting a small subspeciality in medicine for the programme. This necessarily requires approaches that quickly narrow the search space for possible disease and also permit case analysis in which two or more diseases may coexist and interact. It differs from other expert system programmes in the generality of its approach and in the size and diversity of its knowledge base. The knowledge base was developed over several years. Major and minor manifestations and weights that link each finding with the diseases in which they can occur were identified. Knowledge concerning 575 diseases and more than 4000 individual manifestations of disease (demographic, history, symptoms, physical signs and laboratory data) were included. The resulting scoring scheme proved to be capable of guiding effective diagnostic reasoning (Pople *et al.*, 1975; Pople, 1975; Oleson, 1977).

8.5.4. PIP (Present Illness Programme):

PIP is a computer programme designed to investigate the present illness of a patient with œdema. It has a goal-oriented control strategy. Its data base has been organised into associative memory in which clusters of closely related facts about disease and clinical states are stored in a fashion analogous to a richly cross-referenced encyclopædia. These groups of facts, called 'frames', are further organised into a network.

When the programme is presented with a clinical problem (i.e., chief complaint) it generates hypotheses about the case by moving frames from the long-term (associative) memory into the short-term memory where the frames interact with the patient data. The computer characterises each finding into details, seeks relevant advice from associative memory, and tests the hypotheses.

As new facts are obtained, additional hypotheses may be generated. As questioning proceeds, all hypotheses under consideration are repetitively tested and scored to measure the 'goodness of fit'.

At the termination of questioning, the accepted hypotheses are listed and the other hypotheses are rank ordered on the basis of the final score calculated for each. The programme was initially tested with a series of exemplary cases, and the 'present illness' diagnosed by the computer was compared with those concluded by the clinicians in their group. Discrepant behaviour on the part of the programme was taken as a stimulus for further refinement. Corresponding refinements were then made in the programme, and the process of testing and revision was repeated until the programme's behaviour closely resembled that of the clinicians (Pauker *et al.* 1976).

8.5.5. MYCIN:

MYCIN is an expert system developed to advise physicians and medical students on the appropriate treatment of infections. It selects antimicrobial therapy for patients with severe infections. The programme uses knowledge obtained from infectious disease specialists. This knowledge was captured in the form of heuristics or (rules of thumb) that relate microbiological data and clinical signs and symptoms to possible pathogenetic organisms.

MYCIN knowledge is expressed principally in a number of rules of deduction in the form of:

IF	condition (ANTECEDENT)
THEN	conclusion (CONSEQUENT)

The deduction forms an AND/OR tree with a certainty factor assigned to each rule. This factor is a number between 0 and 1. With each fact in the data base is a 'measure of belief' and a 'measure of disbelief', both of which are also numbers between 0 and 1 (Shortliffe and Buchanan, 1975).

Evaluation of the programme has shown that the performance of the system approaches that of a specialist in the two areas of bacteræmia and meningitis for which the knowledge base had been developed (Yu *et al.*, 1979a, 1979b).

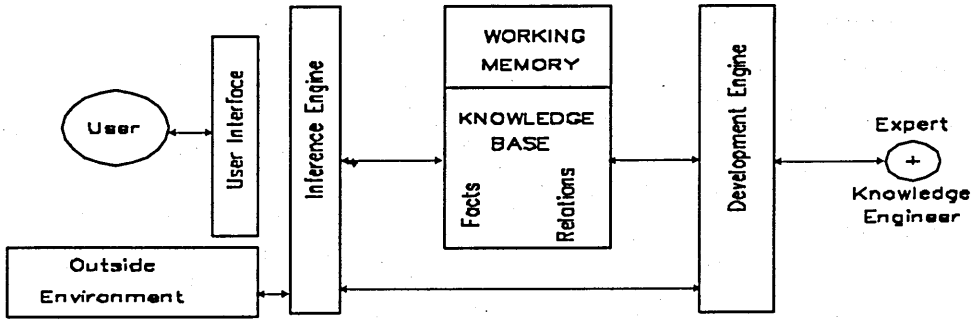


Figure 8.1 Expert System Components

8.6. COMPONENTS OF AN EXPERT SYSTEM:

In general, an expert system consists of four major components: (a) a knowledge base on a specific topic (domain-specific), (b) an inference engine, (c) a communication interface; and (d) a development engine. Figure 8.1 demonstrates these components and their interrelations.

8.6.1. Knowledge base:

The knowledge base is the stored collection of facts on a particular subject and the hundreds or thousands of if-then (situation/action) rules by which the facts relate. The base includes rules provided by a group of experts in that field and thousands of facts and heuristics, as well as judgments, intuitions, and experiences.

The knowledge base differs from a traditional data base. A data base is a collection of related or unrelated facts. A knowledge base, on the other hand, not only contains static data as in the data base, but also contains relational information.

Another component of the knowledge base is working memory. Working memory is used only during processing and is the resident space for information manipulation.

To create a knowledge base, special designers called knowledge engineers, familiar with expert system methods, spend months working with the human experts to extract and structure the facts, rules, and knowledge. After the knowledge base is developed, the inference engine will be able to 'investigate' that base.

8.6.2. Inference engine:

An inference engine is the programme that allows the computer to 'intelligently' apply the facts and information to a particular problem. It retrieves and manipulates the facts and rules, deciding in which order to make connections, associations, and inferences.

8.6.3. Communication interface:

Various forms of interface are used in the creation and operation of an expert system. Interfaces include terminals, graphical representations, multiple character windows, and multiple graphics windows. These interfaces operate in three situations. The first is where the user wants answers to problems. The second situation is where the knowledge engineer wants to improve or increase the knowledge of the system. The third situation is where the user is a student who needs to learn form the knowledge base.

8.6.4. Development engine:

The development engine, also called an editor or knowledge acquisition subsystem, is vital in the creation of the expert system in that it allows the knowledge engineer to create, modify, add or delete information from the knowledge base.

8.7. THE PROCESS OF BUILDING MEDICAL EXPERT SYSTEMS:

8.7.1. Knowledge acquisition:

The general motivations for building expert systems discussed in Section 8.3 apply to any system of this type, but when a specific model of reasoning is built, the reasons have to be much more precise. An expert model is constructed to solve a specific class of problems and to give advice on their solution.

A human expert has to provide the builder of an expert reasoning model with different types of information. This includes personal experience of past problems solved, expertise of methods for solving the problems and knowledge about the reasons for choosing the methods used. The expert model designer groups knowledge of the right class and degree of specificity to solve the problem.

Expert knowledge is generally represented as a modular collection of rules with relatively well established and agreed-upon conclusions. This is a key

factor for the success of those expert systems in everyday use (Weiss and Kulikowski, 1984; Quinlan *et al.*, 1987).

8.7.2. Choice of computer representation:

The choice of computer representation must be based upon two attributes: Power to express the expert knowledge and simplicity to describe, update and explain the knowledge in the model.

There is often a compromise between the ease of representing knowledge in a computer and the richness in the structure of possible semantic relations that may be described in an expert system's framework. For instance, a system which represents cause-and-effect relationship of certain events may be more powerful but it will generally be more difficult to encode.

Another important issue in choosing representation should be the ease with which knowledge can be changed and updated. Flexibility is essential, particularly in the early stages of building the model. In fact, lack of flexibility was one of the most important defects of many of the early artificial intelligence systems, which used complex descriptive frameworks (Weiss and Kulikowski, 1984).

An expert usually has many judgemental or empirical rules according to which the evidence supports a conclusion or hypothesis, but with less than absolute certainty. In these cases, numerical values are associated with each rule to indicate the degree of confidence which can be placed in the hypothesis or conclusion which follows from the evidence provided.

8.7.3. Choice of control strategies:

The control strategy decides the order in which rules should be applied. One of the simplest strategies is to scan through the rules until one is found whose antecedents match assertions in the data base. When the rule is applied the knowledge base is updated and the scanning resumes. This process continues until either a goal state is reached or no applicable rules are found. This is known as a data-driven control strategy because the behaviour of the system is a direct response to the facts about the problem which have been entered into

the data base. This strategy is also known as forward-chaining or antecedent reasoning.

Another strategy is to select a goal to be achieved and to scan the rules to find those whose consequent actions can achieve the goal. Each such rule is tried in turn. If the antecedents for a rule match existing facts in the data base, the rule is applied and the problem solved. If an unmatched antecedent is encountered, arranging conditions to match that antecedent becomes a new subgoal, and the same procedure is applied repeatedly. If there are no rules to establish the new subgoal, the programme asks the user for the necessary facts and enters them in the data base. The behaviour of such a system is governed by the goals which the system is trying to achieve. This strategy is known as goal-driven, backward-chaining or consequent reasoning.

It is possible to use other control strategies that combine elements of data-driven and goal-driven techniques.

8.7.4. Expert systems building tools:

Various types of tools may be used for building expert systems. A true split between these types cannot be made since the borders between them are vague and subjective.

Although it may be possible to write many expert system programmes in any programming language, certain languages are designed to execute certain kinds of programmes with maximum efficiency.

Representation languages:

Representation languages such as PROLOG and LISP are designed to deal with knowledge and to exploit the power of the computer in processing rules rather than numbers. They offer less freedom to the user than normal programing languages. The largest disadvantage of these languages is the fixed control strategy. It is impossible to choose a control strategy depending on the problem. Also the methods to represent knowledge are less advanced. Since these languages can easily be extended they allow the programmer to build constructs tailored to their specific needs. (General purpose programming languages such as

BASIC, PASCAL and the C language (Section 1.4.1.), do not separate knowledge from the reasoning process, they represent knowledge inadequately except for the most simple kind of problems which practically do not require artificial intelligence programming in the first place; and they produce programmes which are very inflexible, any modification means rewriting large parts if not all of the programme. In general, the languages devised for other purposes have not proven to be especially effective for writing artificial intelligence programmes).

Expert systems shells:

One of the most important outcomes of research in expert systems has been the framework computer programmes which provide inference engine and syntaxes for knowledge, but which contain no problem-specific knowledge themselves (Figure 8.2). Such framework programmes, now commercially available, are called expert system shells.

In empty shells there are a limited number of knowledge representations available. The knowledge engineer is therefore not completely free in the way the knowledge is structured. However, a number of facilities which are not available in other tools, are available in these shells. The most important advantage of using a shell is the considerable time saved in the process of building an expert system because the inference engine and the control strategy mechanisms are built into it.

Environments:

Environments are powerful and flexible programmes designed to develop expert systems. They are usually running on specially designed computers (LISP machines) with fast processors and advanced, interactive, user-friendly graphics interfaces. Some of the latest environments run on microcomputers. These environments can probably succeed where shells cannot achieve the desired results.

Environments are generally more advanced than shells and shells are more advanced than representation languages (van Koppen, 1986; Grigoriu, 1986; SAVOIR technical description booklet, 1986).

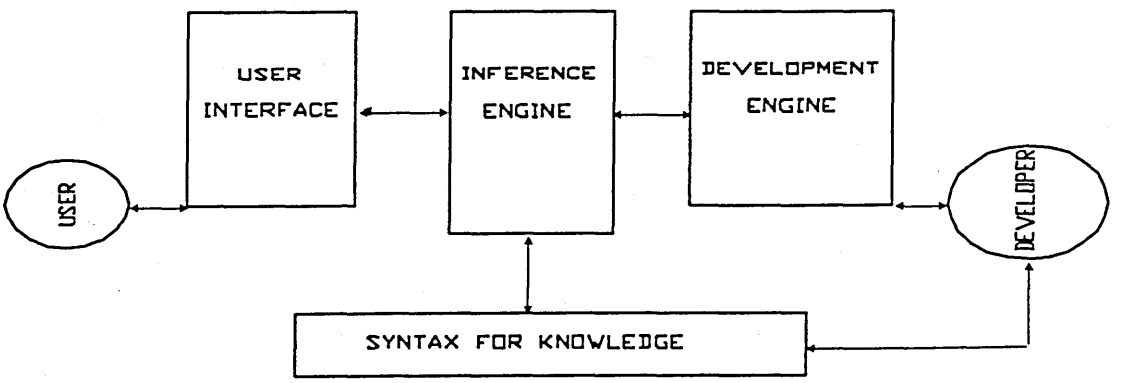


Figure 8.2 Expert system shell

8.8. PARAMETERS FOR ASSESSMENT OF EXPERT SYSTEMS:

The barriers to successful implementation of computer-based diagnostic systems have been analysed on several occasions (Starsman and Robenson, 1972; Friedman and Gustafson, 1977). In assessing programmes from the point of view of its intended user, it is pertinent to examine several parameters that affect the success and scope of a particular system. Unfortunately, the medical computing literature has few descriptions of systems for which all the following questions have been addressed:

1. How accurate is the expert system?
2. What is the nature of the knowledge in the system and how it is generated or acquired?
3. How is the clinical knowledge represented, and how does it facilitate the performance goals of the system described?
4. How are knowledge and clinical data used, and how does this impact on the system performance?
5. Is the system acceptable to the user for whom it is intended?
6. Is the interface with the user adequate?
7. Does the system function outside the research setting and is it suitable for dissemination?
8. What are the limitations of the approach?

The accuracy of any diagnostic expert system is assessed by determining the rate of both true and false positive, and true and false negative results. From these, the sensitivity, specificity, and predictive values are calculated (Section 5.3.8). These values are calculated in relation to a given diagnosis and compared with the figures derived from the conclusions reached by an expert given the same information (Chard, 1988).

The system must demonstrate that it is useful and must confer some advantages not available from the human expert. Speed and cost are other practical factors which may be looked for in the system. The system must also reflect widely accepted views on a topic, not the views of one particular designer. Trans-

ferability of the system should be considered in the design if it is intended to be used in an environment other than that where it has been developed.

Reggia and Tuhrim (1985) have reviewed the studies which compare the performance of medical expert systems with different knowledge representation techniques and concluded that they are similar. Their advice was that methods should be chosen according to the specific problem. For example, if there are several well-documented groups of rules, a knowledge base of a production rule system can be used with little modification of the original rules. Similarly, there are problems which demand probabilistic solution of the Bayesian type. Systems which combine a number of different approaches probably provide the optimum solution.

8.9. REASONS FOR BUILDING A DYSTHYROID EYE DISEASE EXPERT SYSTEM:

Expert system building tools have reached an acceptable stage of development and many lessons have been learned from pioneering work over the last two decades. Building useful medical expert systems for use in the clinical environment is now possible.

Further improvements in the techniques for developing medical expert systems are desirable. This can only be achieved if many clinicians are encouraged to help design, to use and to criticise such systems.

Early expert systems were built to run on mainframe, minicomputers or dedicated workstations. For obvious reasons this has limited their use. With the steady increase in the use of microcomputers in the medical profession, they can be seen as the most practical way to popularise expert system programmes amongst clinicians.

Dysthyroid eye disease is an appropriate area for expert systems application because:

1- The disorder is uncommon.

2- Its course is variable.

Specifications of TEDEX:

Comprehensive data base and coverage.

High quality.

Flexibility.

Reliability.

Modular design.

Low cost.

Run on microcomputer.

Disease specific.

Use multiple control strategies.

Multiple knowledge formalization techniques.

Provide explanations and justifications.

Based on:

- Long term study of thyroid ophthalmopathy.
- World literature.

User friendly interface.

Table 8.3

Specifications of the required thyroid eye disease expert system.

3- The outcome is unpredictable.

4- Management is uncertain.

5- There is a large number of diagnostic and management parameters.

6- Treatment is currently empirical in most cases.

8.10. SYSTEMS AND METHODS:

8.10.1. Protocol:

System specifications:

The proposed expert system has been called TEDEX (**T**hyroid **E**ye **D**isease **EX**pert). It should be designed to satisfy the requirements summarised in Table 8.3. It should cover all major aspects of the diagnosis and management problems of thyroid ophthalmopathy. The quality of advice should approach expert standards and the system should demonstrate stability and reliability under various consultation conditions.

The initial cost of expert system building as well as the cost of maintenance and updating in terms of hardware, software, development time, and manpower must be acceptable. Running the system on personal computers satisfies most of these requirements. In addition, it ensures the availability of the system to the large number of clinicians who have already been or are likely to become microcomputer users.

The system should be designed as a 'disease specific expert system' i.e., capable of dealing with a specific group of patients who have been initially diagnosed as suffering from thyroid ophthalmopathy. It is not intended to handle other ophthalmic problems or to provide comprehensive lists of differential diagnoses.

Powerful and flexible expert system building tools are required to design a knowledge base in which combinations of different control strategies and various knowledge formalisation techniques are possible. Forward chaining strategies may be used in one part of a module and backward chaining

strategies in another part, directed only by considerations related to the appropriateness of application of each strategy.

Explanation and amplification of questions and clarification of the responses required during the user/system dialogue should be built into the system. The system should also exhibit the capability of justifying its decisions and suggestions.

Although the user interface is not intended to be designed according to the commercial standards, it is necessary to be in agreement with the following conditions:

- Sufficiently user-friendly to be acceptable by the clinician.
- Questions and instructions must be short and clear.
- Phrasing and sequence of history taking dialogue must comply with the conventions adopted by ophthalmologists.
- A parsimonious balance should be achieved between the speed and completeness of consultation sessions.

The knowledge base for the system comprises the results of the long term study of thyroid ophthalmopathy (Chapter 5) and the world literature in the areas which have not been covered by our own study.

Testing procedure:

The performance of the programme is to be tested after validation of its rules. Testing should include:

- Patient data of exemplary cases (for whom the outcome was known) are to be entered into the system and the conclusions obtained are compared with an independently obtained expert opinion and the known outcome.
- Questionnaire for a panel of consultants is to be designed for evaluation of the performance of the system.

The system is considered to be a prototype until repeated cycles of testing and refinement are complete. This should be done while the system is being

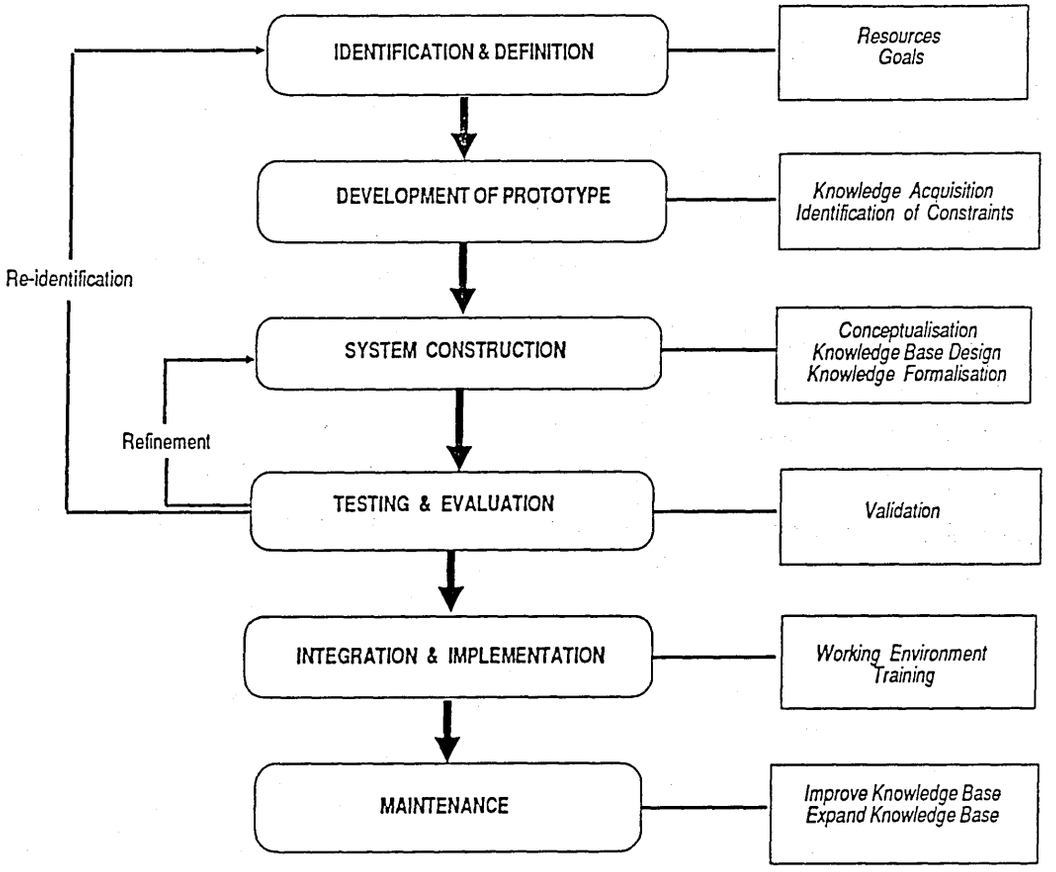


Figure 8.3 Stages of building an expert system

used by various intended users (e.g., ophthalmologists in orbital clinics, general ophthalmologists, endocrinologists and general practitioners). It takes several years of usage of the system before this final stage is reached.

TEDEX development team:

TEDEX development team comprised the author and Mr. A. Wail, who is currently a research fellow at the Signal Processing Division of the Electrical and Electronic Department of Strathclyde University. The process essentially requires prolonged sessions for all of the stages of system development.

Stages of building TEDEX:

Figure 8.3 outlines the steps which have to be followed in the process of building the different modules of TEDEX. Basically the main stages comprise the definition and evaluation of the problem, the development of a simplified prototype, the construction of the system and finally the testing and evaluation stages. Integration of the expert system into the clinical environment, documentation and coordination of user training are advanced stages. In addition, maintenance of the system by improving or expanding its knowledge base takes years to be accomplished.

8.10.2. Preparatory phase:

Programming courses:

The author attended a six weeks course for programming in BASIC and a similar course for 'Learning to programme in Pascal' (Section 1.4.1) in order to become familiar with the concepts and techniques of microcomputer programming.

8.10.3. Problem identification and evaluation:

1- Our objective was to build a disease specific expert system which gives advice about the diagnosis and management of dysthyroid eye disease patients and performs the following functions:

- Confirmation of the diagnosis of dysthyroid eye disease.
- Assessment of the severity of the condition.
- Identification of high risk patients.

Hardware requirements:

Minimum configuration:

IBM PC AT or XT or compatible microcomputer.

EGA or Hercules graphics adaptor.

Monochrome or EGA colour monitor.

Dot matrix printer.

512 KB RAM.

Two floppy disk drives (Hard disk is recommended).

Hardware used for system development:

IBM PC/AT (80286 processor/6.4 MHz).

EGA Wonder Display adaptor.

NEC Multisync colour monitor.

Fujitsu DPL-124, 18-pin dot matrix printer.

640 KB RAM.

Math coprocessor (80287/6.4 MHz).

84 MB Hard disk storage.

Table 8.4

Minimum hardware configuration required to run TEDEX and details of the system used for its development.

- Suggestion of a suitable management plan.
- Evaluation of the significance of any change in the condition of the patient at the time of follow-up visits.
- Provide a new management plan according to changes in patient condition.
- Provide an explanation and justification of its conclusions whenever requested by the user.

2- The problem is sufficiently well defined and reasonably circumscribed. The potential sources of expertise are available.

3- The domain is representable, i.e. can be modelled in a computer knowledge data structure.

4- The data required to be entered into the expert system for analysis are reliable, available, and complete.

5- The domain knowledge is: Heuristic, judgemental, experiential, specific, or descriptive, i.e., it is symbolic and not data intensive.

6- The intended users of the system are general ophthalmologists, endocrinologists, general practitioners and perhaps, at a later stage, medical students.

7- The project effort (duration, time and cost) is within the acceptable range allowed for our study.

8- Identification of appropriate hardware and software tools:

The microcomputer used to conduct this study and the minimum configuration required to run the expert system programme are listed in Table 8.4.

A list of the required software features was prepared. The SAVOIR expert system shell (Appendix D1) was deemed to be the most appropriate tool to develop TEDEX after careful consideration of the criteria summarised in Table 8.5.

Software tool requirements:
Run on IBM XT/AT or compatible under MS/DOS.
Consistent run time response/seconds.
Interfaced with local or integrated data base.
Interfaced to other application programmes.
U.K. support for software maintenance.
Implemented knowledge base easily intelligible to the expert.
Reasoning process easily explainable to the user.
Screen interface reasonably controllable by the developer.
Report generation facility available.
Inference strategy controllable by the knowledge engineer.

Table 8.5

The required specifications of expert system development software tools.

Data requirement:

List of possible questions:

Administrative information	Personal data.
Clinical history.	Clinical findings.
Investigations.	User choice of treatment options.
Choice of output device.	Treatment contraindication.

List of possible clinical findings:

Structure	Function

List of possible requested investigations:

Visual field	Optic nerve function
Extraocular muscles	100-Hue colour vision test
X-ray	Hess screen test
MRI	Orbital ultrasound
CT scan	Thyroid function tests

List of possible diagnoses:

Not thyroid ophthalmopathy	Possible associated disease
Normal eyelid	Eyelid retraction
Lid œdema	Normal cornea
Superficial punctate keratopathy	Corneal ulcer
Corneal necrosis or perforation	Normal extraocular muscles
Extraocular muscle involvement	No optic nerve involvement
Suspected optic nerve compression	Definite optic nerve compression

List of possible treatment options:

Artificial tears	Corneal ulcer treatment
Prisms	Occlusion
Extraocular muscle surgery	Lid lengthening procedure
Temporary tarsorrhaphy	Permanent tarsorrhaphy
Systemic steroids	Orbital radiotherapy
Cyclosporin A	Surgical orbital decompression
Plasmapheresis	Retrobulbar steroid injection

List of possible suggested actions:

Emergency admission	Appointment in 6-8 months
Appointment in 3-5 months	Next appointment in two weeks
Refer to orbital surgeon	Refer to Endocrinologist

List of possible explanations.

Statistics:

Discriminant function analysis equations	Statistical significance
Sensitivity, specificity and predictive value of various parameters.	

List of rules:

The study of thyroid ophthalmopathy (Chapter5)	World literature.

Table 8.6

Selected examples of the data lists compiled for development of TEDEX knowledge base.

8.10.4. Development of TEDEX prototype:

Studying the Shell:

The first step after choosing SAVOIR was to study the technical manual as well as to run, practice and experiment with the sample programmes supplied with the shell before starting to use it.

Conceptualistion and formalisation:

The delineation of the components of each problem with regard to essential data, the hypotheses employed and the intermediate measuring concepts (or scores) was first required. The manner in which these concepts determine the implementation of the programme was then studied and defined.

Data requirements:

An outline of the main items of the lists of all the required data is shown in Table 8.6. This comprises questions, clinical findings, diagnoses, investigations, treatment options, suggested actions, error messages and various question-related amplifications and explanations.

Knowledge acquisition:

Although knowledge acquisition is always a formidable task, there has been no great difficulties in our case. The familiarity of the author with computing concepts and techniques considerably expanded the common area shared by the second member of the expert system building team. The author initially prepared a written report delineating the main features of the problems and the expected solutions. This constituted the basis for the first simplified prototype of TEDEX. Subsequently, modifications, expansion and refinement of this prototype was achieved during repeated discussions of each individual module. These meetings constituted the principal knowledge acquisition technique and there was no practical need for any of the formal techniques such as 'structured' or 'unstructured' interviews, 'verbal protocols' or questionnaires which are usually necessary in this stage.

Preliminary knowledge:

The following initial objectives were achieved:

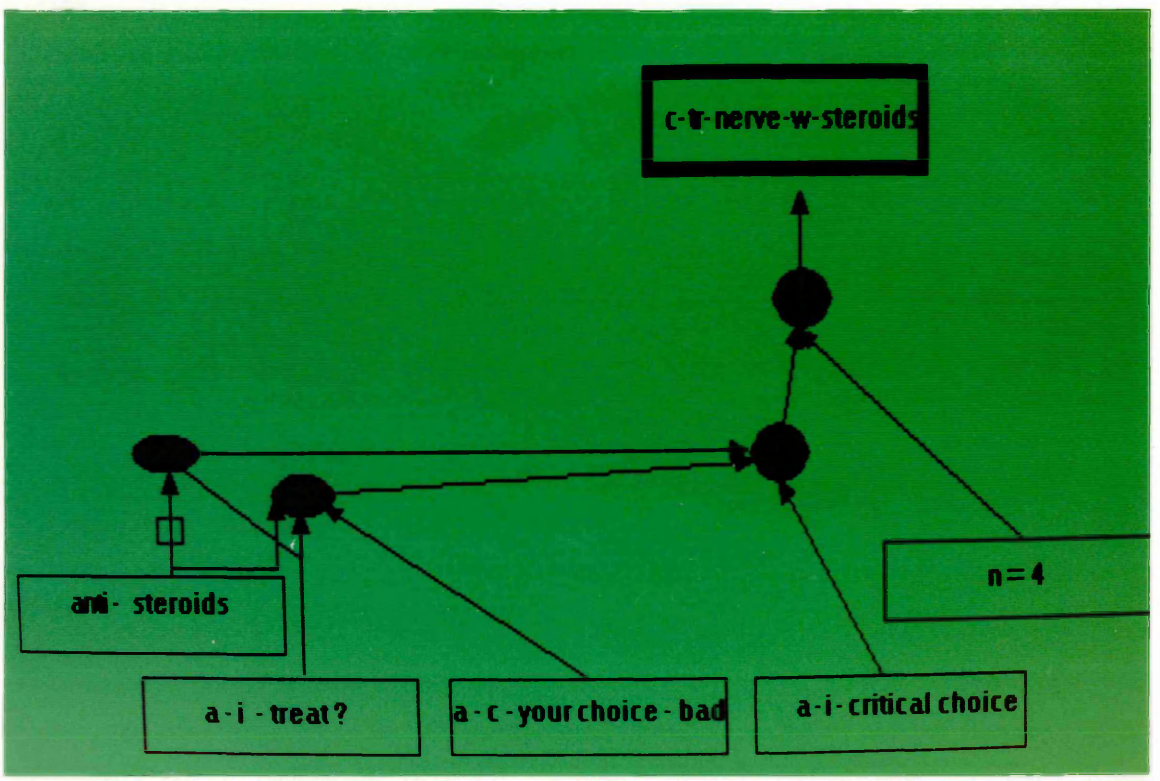


Plate 8.1

Part of the TEDEX semantic network.

- Identification of the basic terms and concepts.
- Identification of typical inputs and outputs of the system.
- Identification of typical solutions or classes of solution.
- Identification of strategies for handling problems and of forming control strategies for initial implementation of the system.

Once sufficient information had been gathered and the team had good understanding of the different aspects of the application and the problem-solving structure, a short, preliminary prototype programme was written in SAVOIR code. Running and experimenting with the compiled programme was essential to determine the detailed knowledge required for building the complete prototype.

Semantic network design:

A semantic network representation of TEDEX was then designed. A semantic network is a collection of nodes linked together by various relationships which are shown graphically. The nodes represent concepts, situations or any other variable. This network had to be very detailed, showing the inputs, problem solving processes and outputs. A sample of this tree is shown in Plate 8.1.

Detailed knowledge acquisition:

The objective of detailed knowledge acquisition was to gain the specific information summarised in Table 8.7. The detailed rules that represent the knowledge were gradually formulated and refined by combining and reorganising the knowledge within the preliminary prototype.

The results of the dysthyroid eye disease study (Chapter 5) constituted the major component of the knowledge base. This comprised all the tables in Appendix C3, efficiency values of the individual predictor variables (Tables 5.12 and 5.13), the inferences based on the data of the study (Sections 5.4 and 5.5) and the linear discriminant function analysis equations (Tables 5.16 and 5.17).

Detailed knowledge acquisition.

- Identification of relationships between various data and rules.
- Identification of the hierarchy of rules, what rules are intermediate, and what rules lead directly to conclusions.
- Judging the relative validity and importance of data.
- Judging the certainty of data and the relative probabilities regarding assumptions, strategies and conclusions.
- Judging the priorities and order of performing different functions.
- Determining how conflicts between rules and conclusions are resolved.
- Recognition of alternative paths and strategies for problem solving.
- Determination of shortcuts in reasoning and the conditions under which they are used.
- Detailing responses to both expected and unexpected outcomes.
- Determination of 'strength of belief' in different rules, outcomes and data.
- Understanding the input requirements of different goals and sub-goals.

Table 8.7

Objective of the detailed knowledge acquisition stage.

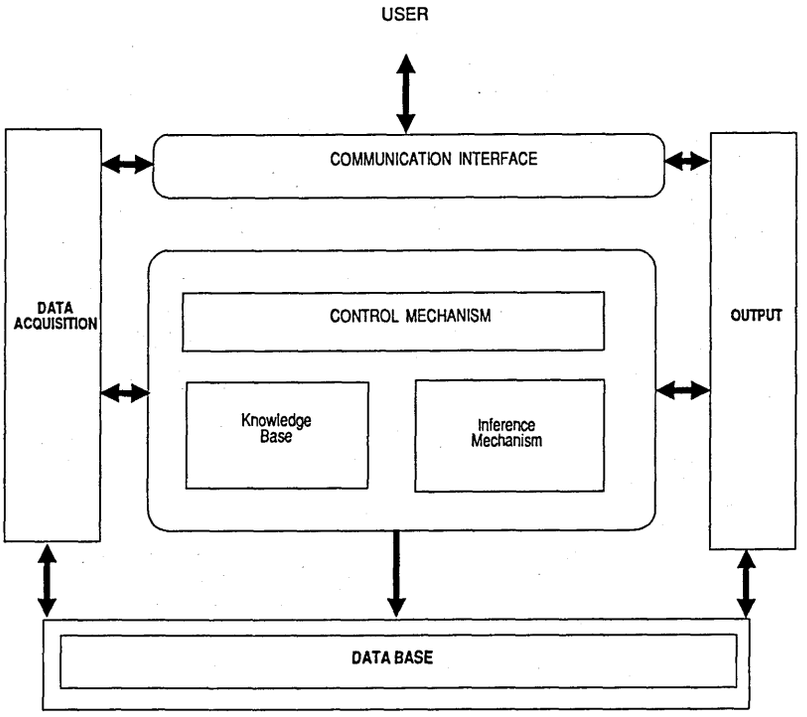


Figure 8.4 TEDEX Components

Knowledge base design:

Modularity:

TEDEX is designed in a modular form so that it meets with the above specifications (Section 8.10.1), it ensures easy expendability and maintainability and it facilitates testing and validation of each individual module before the final assembly of the programme. Figure 8.4 shows the principal components of TEDEX and Figure 8.5 shows the various modules of the system.

Data acquisition module:

When the data acquisition module (Figure 8.6) is activated, on-line data can be obtained by direct interaction with the user. The potential is available for direct data acquisition from an external source. TEMPRAC (Chapter 6), computerised visual field testing equipment, automatic chart reader (Chapter 7), automated 100-Hue colour vision test or laboratory computers are examples of the data sources which could be linked to the system. This option has been kept open by designing 50 empty slots into the system. Future addition of these facilities will be possible with a minimal amount of programming effort.

Another form of data acquisition occurs at the beginning of a follow-up visit. All the data acquired during the previous consultation are automatically retrieved from the data base and loaded by this module into the computer RAM. The data can then be updated or amended.

Data validation and interpretation module:

Data validation and interpretation module (Figure 8.7) detects any data entry error, displays an error message and prompts the user to retype his response. This process is repeated until the correct response is entered. Only appropriate responses will be interpreted (scored).

This module also monitors the change of data over time. It evaluates and scores the change before the information is used by the diagnosis module.

Diagnosis module:

The diagnosis module has four main goals: To confirm or refute the diagnosis of thyroid ophthalmopathy, to detect possible associated disease and to

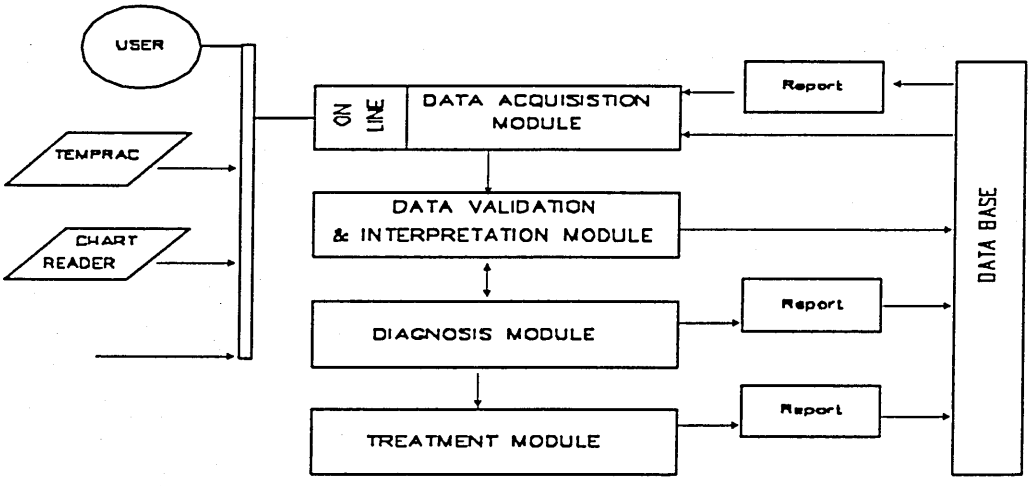


Figure 8.5 TEDEX Modules

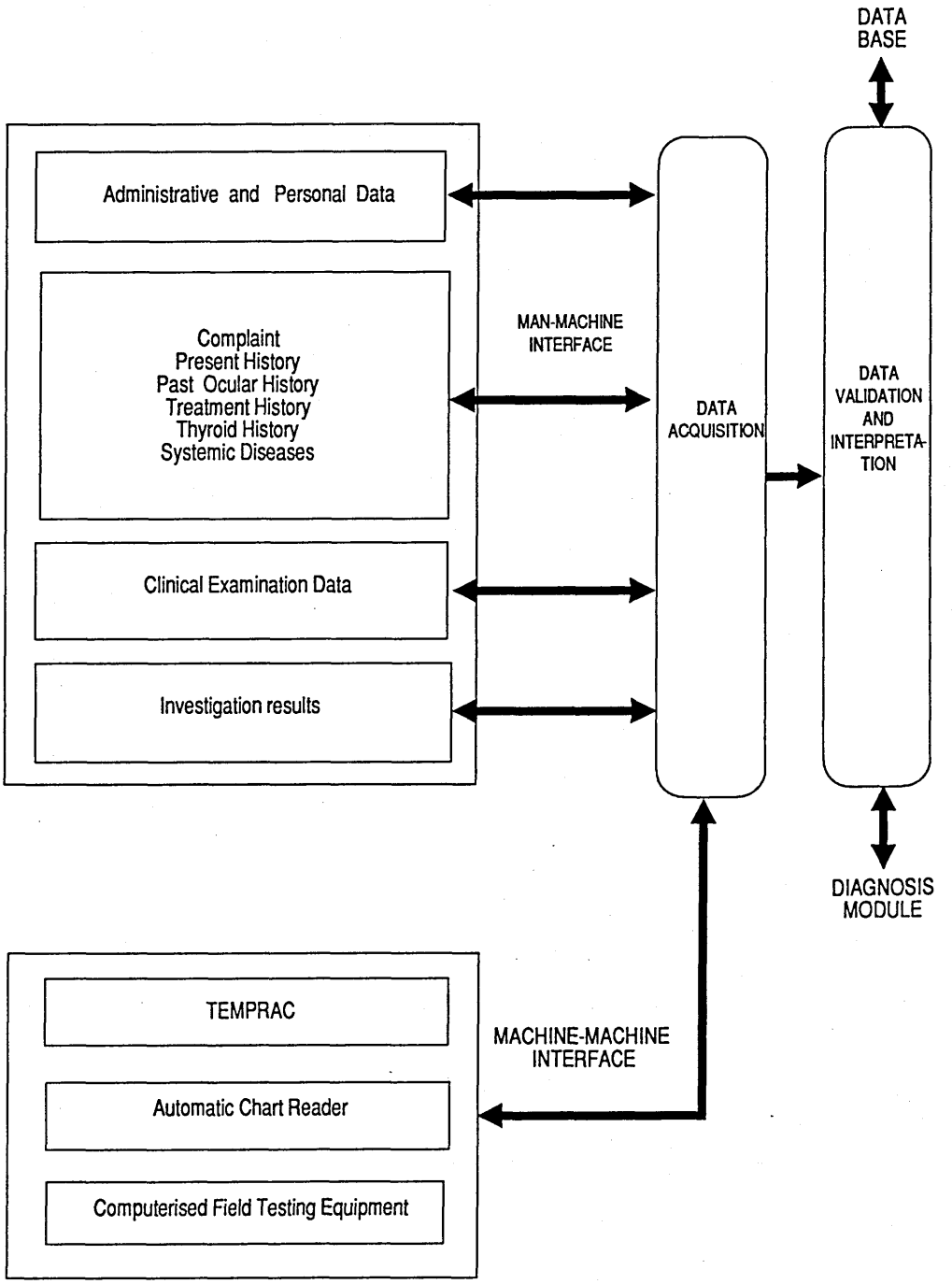


Figure 8.6 Data acquisition module

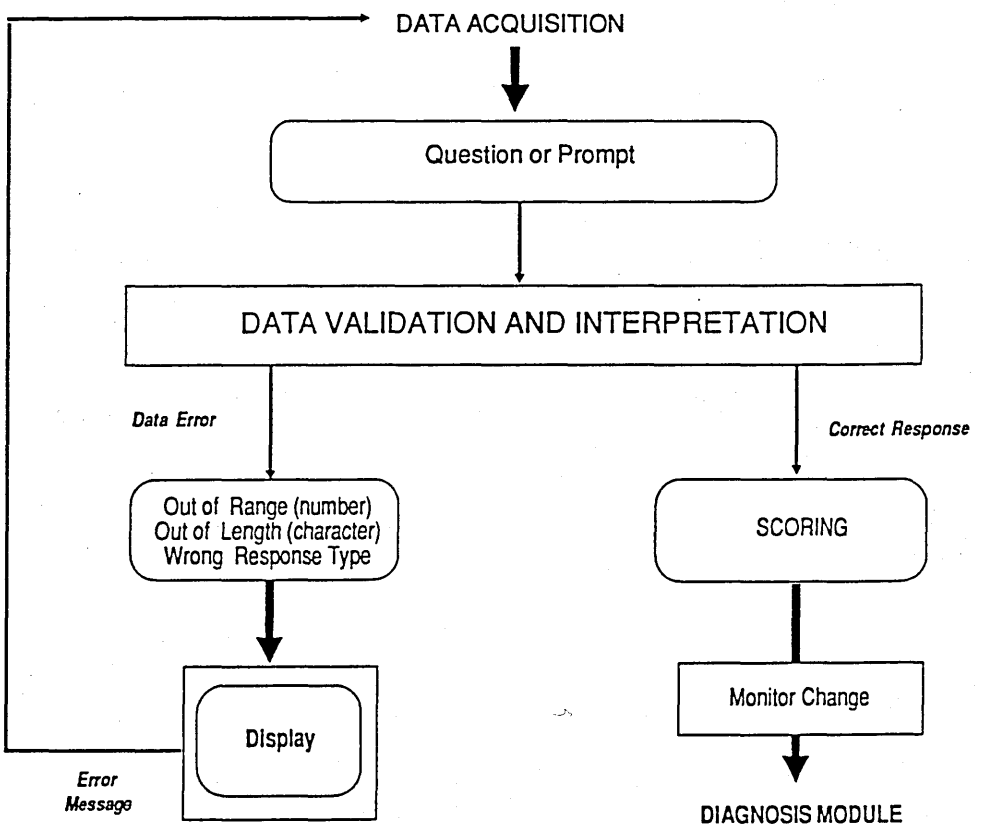


Figure 8.7 Data validation and interpretation module strategy

evaluate the risk of developing severe ophthalmopathy in a particular patient (Figure 8.8).

Components of Diagnosis module:

Six main components (Figure 8.9) comprise the core of the diagnosis module. The structure and function of the eyelids, cornea, optic nerve and extraocular muscles and the degree of soft tissue involvement are evaluated in addition to the calculation of risk score.

Each component handles the validated relevant group of data (e.g., History data, clinical examination findings and test results). Intermediate diagnosis (or score) is determined. When the 'final' diagnosis is accomplished the proper management plan is chosen. After the appropriate report is displayed, the relevant data and scores are stored into the database. Subsequently, the other components are similarly investigated (Figure 8.10).

Diagnosis reasoning strategies:

In breaking down the various types of reasoning involved in building this module, we identified several kinds of reasoning sub-problems (Figure 8.11):

1. Given some pattern of symptoms, signs, and test results, infer the possible diagnosis (data driven reasoning strategy) and the degree of certainty which can be assigned to this diagnosis.

2. Given this same pattern of data, other findings should be obtained to improve certainty about the diagnosis (goal driven reasoning strategy).

3. After a diagnosis is provisionally established, discrepant, unexpected or incompatible findings are detected and conflict (e.g., if more than one rule is applicable to a situation) is resolved.

4. Deciding how and when does the system move from a provisional diagnosis to a more conclusive one based on results of further confirmatory investigations.

5. Given that a diagnosis has been established, how does the system proceed to choose a treatment, and which treatment option is to be chosen in urgent situations without having to wait for test results?

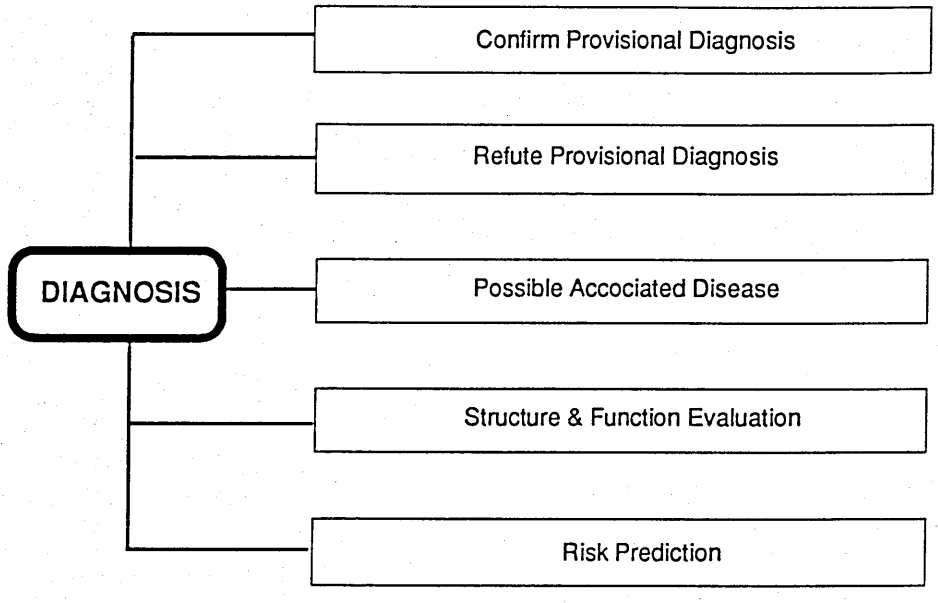


Figure 8.8 Diagnosis module objectives

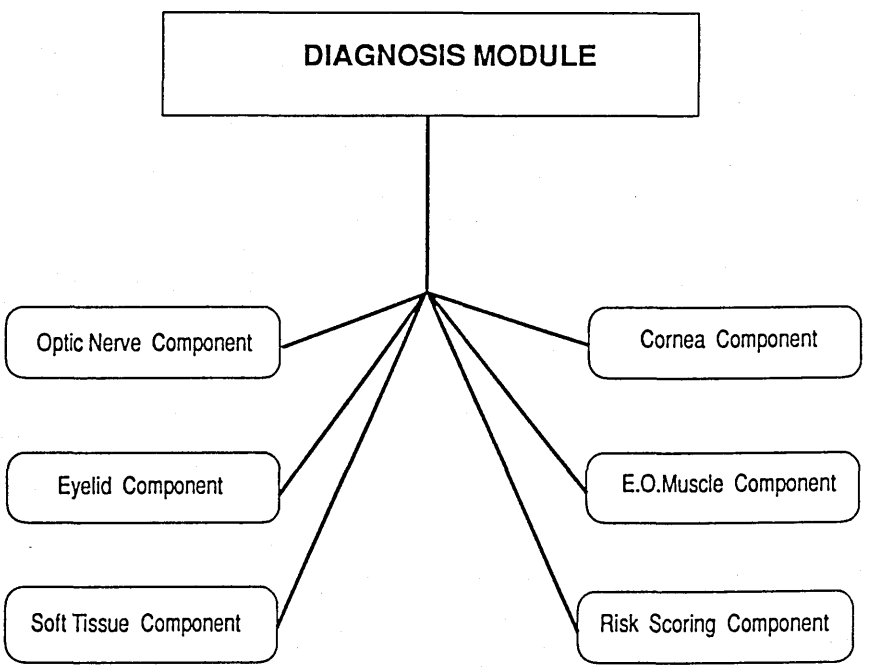


Figure 8.9 Diagnosis module components

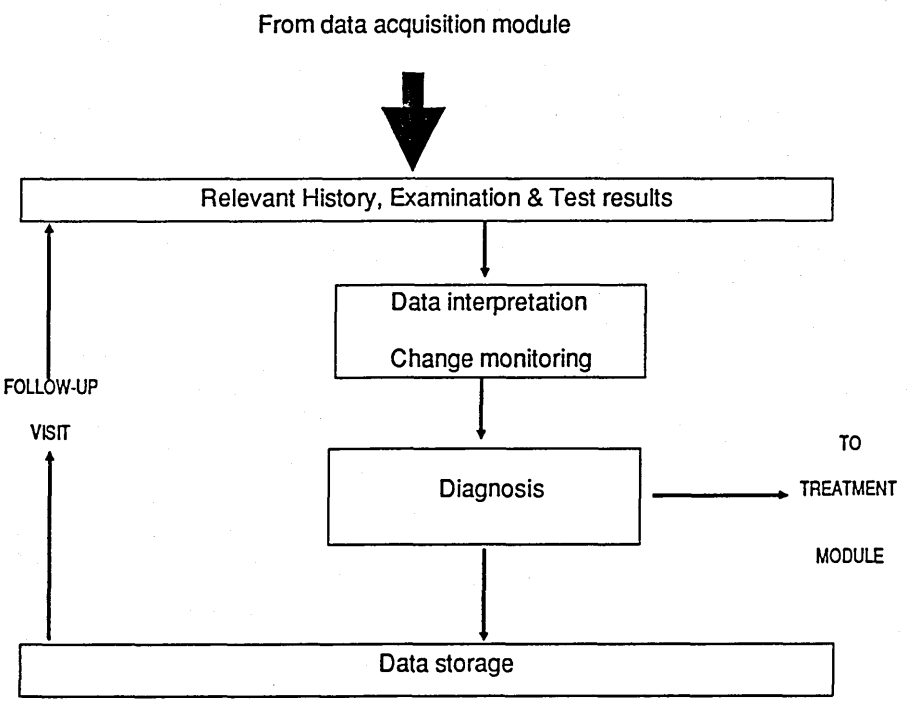


Figure 8.10 Algorithm For Individual Components Of The Diagnosis Module

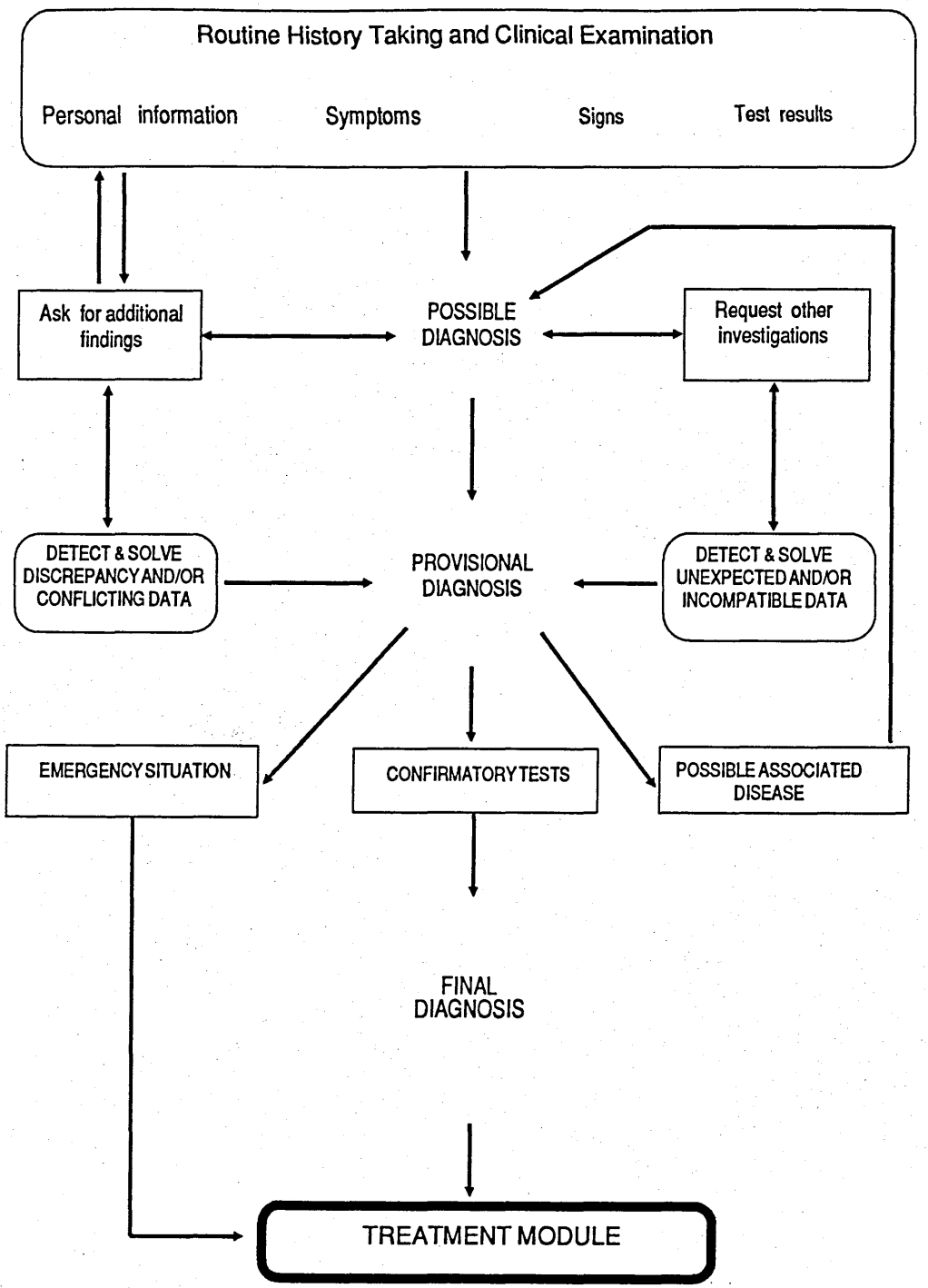


Figure 8.11 Diagnosis Module Strategy

Coding and scoring systems:

The same system used for coding the data of dysthyroid eye disease study (Appendix C1) was applied on the corresponding parameters included in this programme. A uniform simple grading system which assigns one value (score) to each division on the scales of severity and certainty was devised as follows:

1= Normal	or	(=/< 0.25	certainty value)
2= Mild	or	(0.25-0.50	certainty value)
3= Moderate	or	(0.50-0.75	certainty value)
4= Severe	or	(>0.75	certainty value)

This scoring scheme has been adapted from the scheme used in INTERNIST (Section 8.5.3) which proved to be capable of guiding effective diagnostic reasoning (Pople, 1975; Pople *et al.*, 1975; Oleson, 1977).

In situations where the user is required to answer any question using such grading system, explanation of the scores and any of its modifications are displayed in association with the question.

The above grading system is applied so that the intermediate diagnosis of a particular patient is represented as a pattern composed of a combination of the scores of the condition of soft tissue (S), the cornea (C), the extraocular muscles (M), the optic nerve (N), the eye lid (L) and the degree of proptosis (P). The risk score (R) is expressed as probability which ranges from 0 to 100. The pattern might be as follows:

S 2, C 3, M 1, N 2, L 2, P 4, (R 85)

Which means that this patient has mild soft tissue changes (S2), corneal ulceration (C3), no extraocular muscle imbalance (M1), suspected optic nerve compression with a certainty between 25 and 50 % (N2), mild lid retraction (L2), and severe proptosis of 6mm or more above the average normal value 'considering the race and refraction of the patient' (P4). The risk of running a severe course is 85% (R85). This diagnosis is considered as 'final' when all the questions regarding confirmatory investigations are completed.

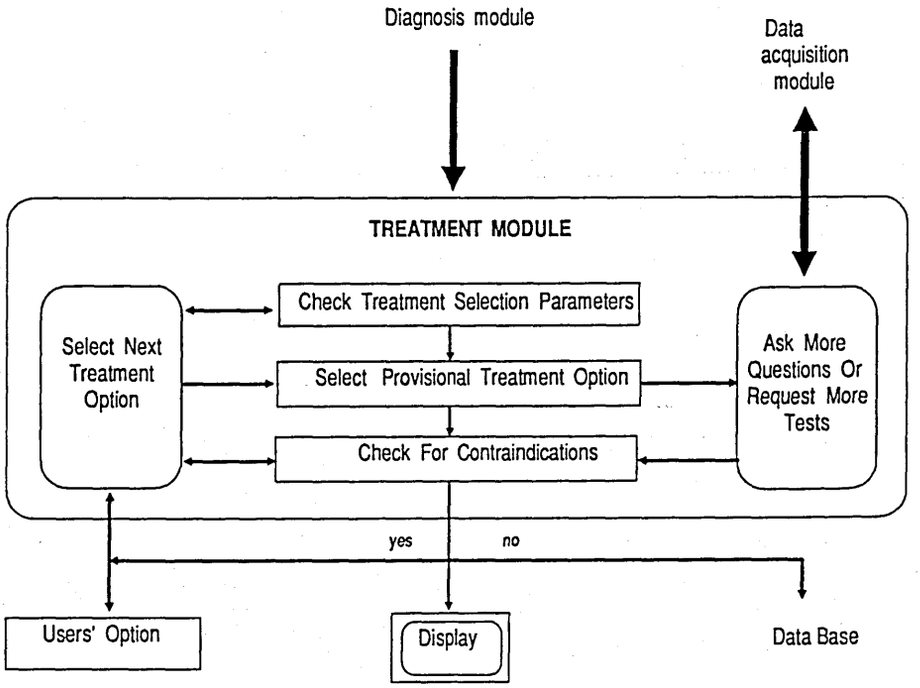


Figure 8.12 Treatment Module Strategy

Treatment module strategies:

On reaching a 'final' diagnosis, the treatment module (Figure 8.12) is activated. This module examines the treatment option selection parameters. These are sets of rules relating treatment options to the following variables:

(a) personal information,

(b) structure and function of different ocular tissues,

(c) thyroid status,

(d) treatment history,

(e) combination of diagnoses (i.e., pattern), and

(f) history of systemic diseases.

These rules predetermine the order of option selection and investigate the possibility of relative or absolute contra-indications for each treatment option.

Once an option has been selected, the data acquisition module is reactivated to ask more questions or request more investigations relevant to possible contra-indications for this particular treatment option. If the selected option is found to be contraindicated, the second 'best' option is chosen and another set of questions may be asked. A selected option is considered to be 'final' if no contra-indications are found and the user accepts the choice, or if the user accepts a choice despite the presence of contra-indications (overriding the system).

Knowledge representation:

A hybrid of four knowledge representation approaches was used to develop the knowledge base. Firstly, the semantic network (Plate 8.1), which is the most general representational structure, served as the basis for other knowledge representations. Secondly, the production rules approach, which is the technique used most extensively in the system. The following is an example of one of the rules used in TEDEX:

"IF	there is evidence of optic nerve compression
AND	the patient has had orbital radiotherapy in the past
THEN	the option of orbital radiotherapy should not be offered."

The rule is 'activated' when all of the conditions (antecedents) are satisfied by the current situation. The production rule is 'fired' or executed when the action (consequent) is performed. The inference engine is responsible for controlling the activity of the production rules through cycles of matching, conflict resolution and action.

The third knowledge representation approach is 'Predicate Calculus' (or logic programming). Predicates describe the relationship or make a statement about the variables under consideration. They produce a simple way of determining the truth or fallacy of a statement. Some of the predicates which are commonly used in TEDEX are:

AND, OR, NOT, IMPLIES, EQUIVALENT, BESTOF, WORSEOF

The fourth representation comprises a pattern matching approach where each of the various combinations of clinical features of thyroid ophthalmopathy forms a particular pattern which requires a specific management plan.

Problem solving strategies:

Search strategies:

TEDEX follows a 'Breadth-First Blind Search' strategy in the first part of the consultation session which is concerned with the establishment of a data base (e.g., personal information, history and clinical findings). This involves examining the first steps in all paths available. If an answer is found, the next step is searched, if not, the appropriate question is displayed requesting the user to enter the answer.

A 'Hill-Climbing' heuristic search strategy is followed in the other parts of the programme. A search is initiated downward along a given path until an answer is found or a dead end is reached. If a dead end is reached, the search will backtrack to the first alternative path and repeat the procedure.

Control strategies:

Once the search strategies had been established, it was realised that different situations require different control strategies for deciding which procedure to apply and where to apply it.

A 'Bidirectional' reasoning strategy was chosen. This involves going both forward and backward through the knowledge base during a session. To begin a session, the inference engine starts by following forward chaining strategy, i.e., driven by the acquired data. As the inference engine traverses through the knowledge base, it has the choice of proceeding forward or backward at each decision node. Heuristic algorithms have been implemented into the system in order to determine these choices at various nodes.

'Monotonic reasoning', which is straightforward, repetitive procedural technique has been applied to the history taking part of the data acquisition module.

The 'Certainty factors' which have been associated with reasoning paths of TEDEX fall into one of the following categories:

1- Certainty: The proposition statement (question or variable) may be either true (a value of 1) or false (a value of 0). A value of zero will automatically halt the continuation of solving the problem along this solution path and will proceed to a different path.

2- Confidence: This indicates a value ranging from -1 to +1. These factors do not imply absolute truth or falseness, but rather imply the strength or weakness of the proposition. A zero implies no tendency toward the response being true or false, but maintains neutrality. A value of 1 indicates an absolute truth, whereas a value of -1 is indicative of absolute falseness.

3- Probability: The proposition may have a probability of occurrence which ranges from 0 to 100. A value of 100 implies the maximum probability that the proposition will be true or will occur. A value of 75 may imply a 75% chance of the proposition occurring and a 25% chance of it not occurring.

Another technique used to enhance the efficiency of the search is 'Abstraction'. The computer should abstract the information to a higher level before deciding whether it is relevant or not. This is done by means of forward and backward chaining. The goal of abstraction is to quickly and efficiently find a solution path. For example in the diagnosis module this technique is employed to reduce the amount of detailed information acquired by the system to 7 intermediate diagnoses or scores forming a diagnostic pattern.

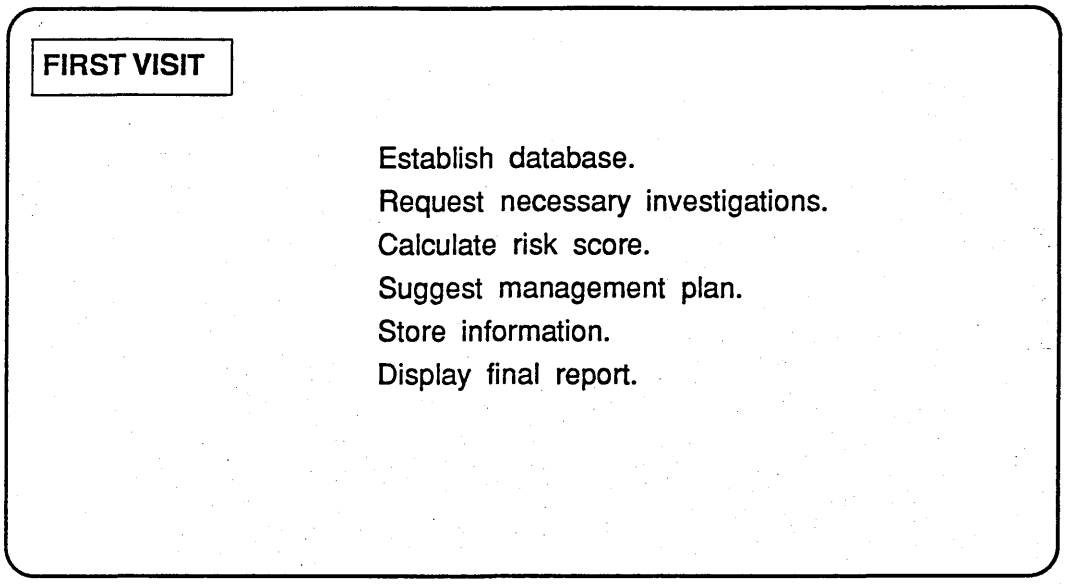


Figure 8.13 First visit objectives.

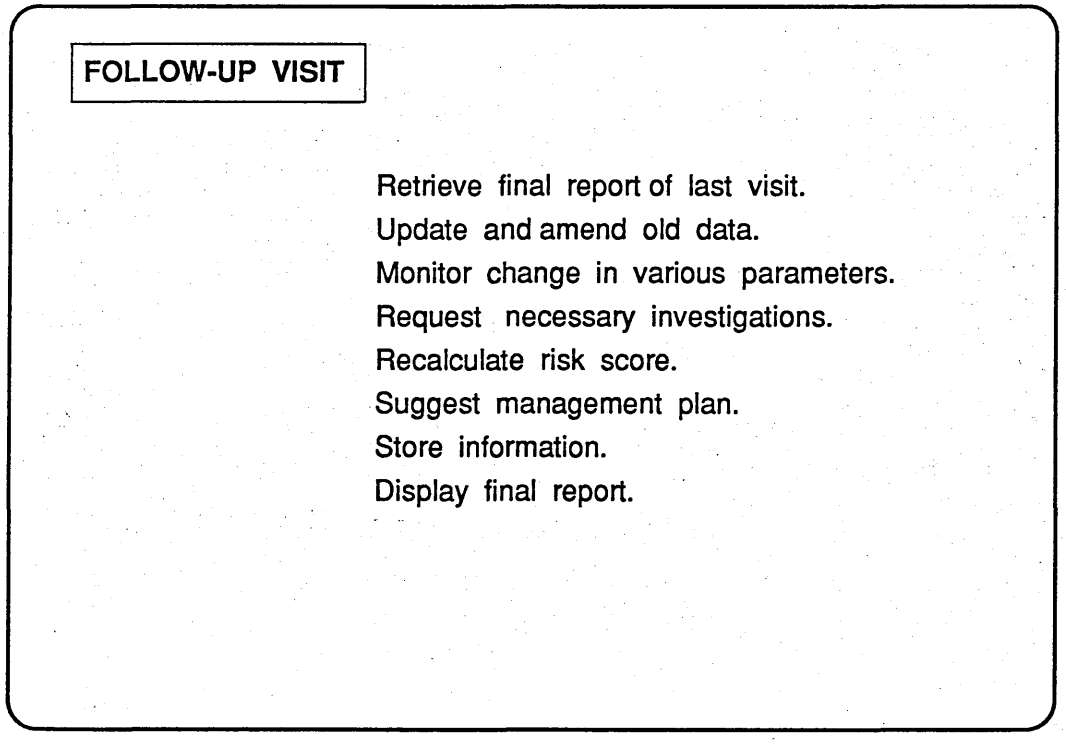


Figure 8.14 Follow-up visit objectives.

Working patterns:

There are two main consultation modes, a 'First visit mode' and a 'Follow up visit mode'. The goals of these modes are shown in Figure 8.13 and Figure 8.14.

At the beginning of a consultation session for a new patient a new file is opened. All the data acquired or the intermediate values (scores) and the conclusions (diagnoses or management plans) generated during the session are automatically saved before ending the consultation.

For a follow up visit, the TEDEX session starts by transferring all the available information from the hard disk into the working memory of the computer. Routine questions about past history are not repeated. The rest of the session is completed in a manner similar to that followed in the first visit. TEDEX compares all the answers and values entered during the current session with those acquired during the previous sessions. The change is evaluated and taken into account with regard to making inferences about the current condition of the patient. Again all the values, variables and conclusions are automatically stored in the data base at the end of the session.

Communication interface:

Throughout a consultation session the user has a dialogue with the communication interface. This interface shows uniform behaviour no matter which of the components the user is using. Possible forms of dialogue include text menus, flashing warning messages, questions and answers or written text. As part of the control mechanism, the communication interface supervises the dialogue and invokes other modules which are appropriate to the state of the consultation. The communication interface itself is an expert system in its own right with knowledge about the hardware, the application, the ergonomic requirements, the user, and the dialogue (Figure 8.15).

The computer keyboard is used to input the data during the dialogue with TEDEX. The output (Figure 8.16) is displayed on the computer screen or sent to a printer if the user wishes.

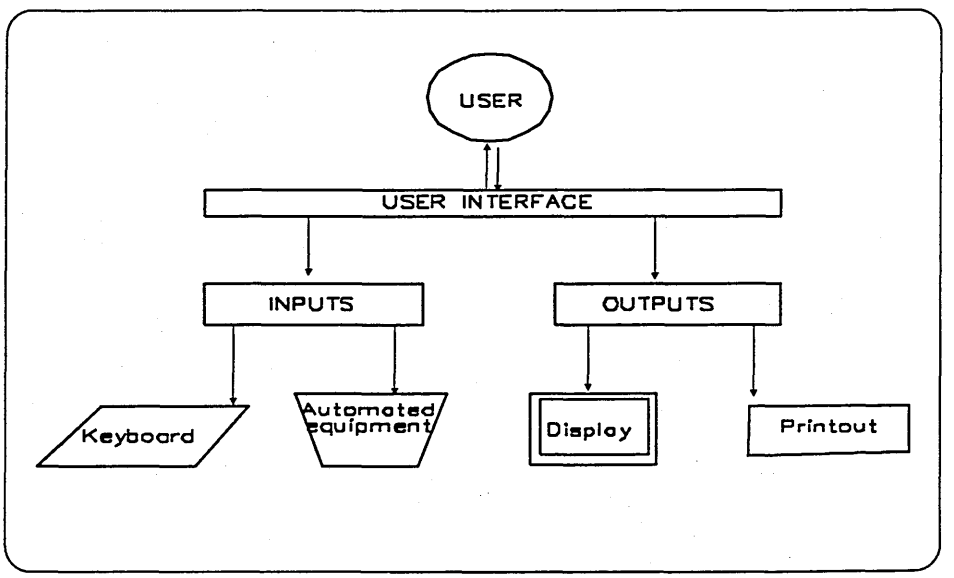


Figure 8.15 User Interface

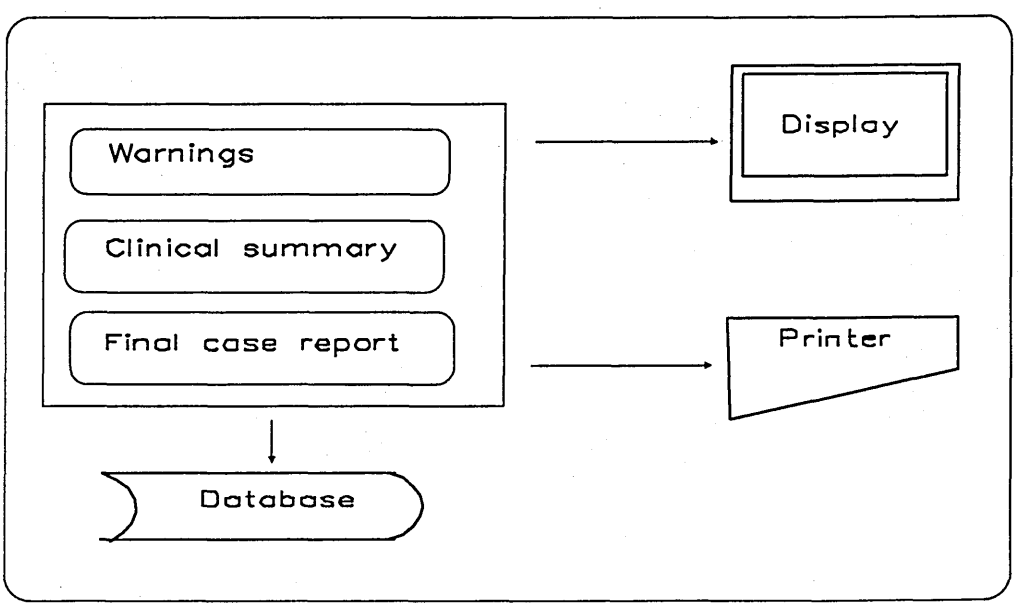


Figure 8.16 System Output

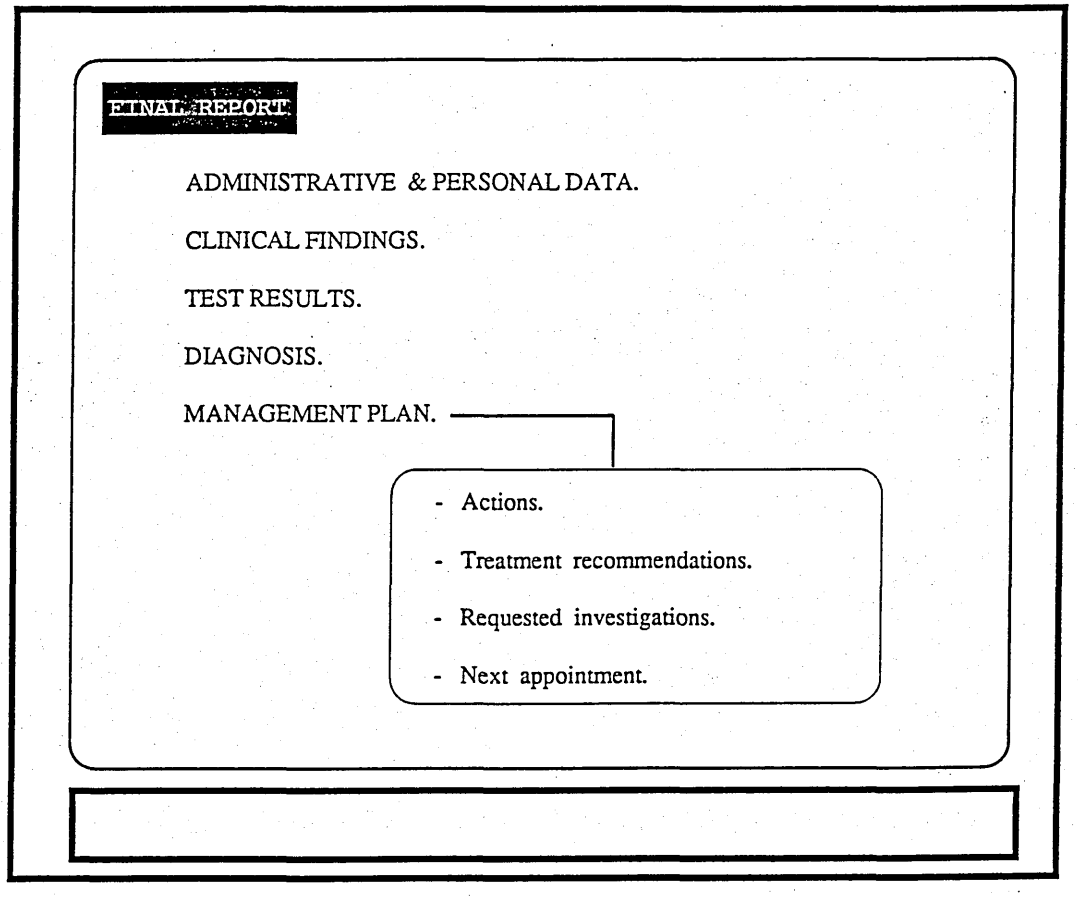


Figure 8.17 Contents of the final report.

Final reporting:

The final report which is displayed at the end of a consultation session contains the items outlined in Figure 8.17. This report is also saved at the conclusion of a consultation session and the user has the choice of displaying or printing it at the outset of the next session. The user might, on some occasions, want to consult TEDEX only to read the displayed or printed most recent report about a particular patient.

File creation and database:

Two files are opened for each new patient at the commencement of a session. The first file contains 181 fields to store all the data acquired during consultation. This file is the first step in establishing the system's data base which is also interfaced with the 'dBase-III+' package which is currently the industry standard data base for IBM and compatible microcomputer. The second file is created to store the final report generated by the system.

8.11. PROTOCOL FOR TESTING AND EVALUATION OF TEDEX:

8.11.1. Rule validation:

After compilation of the system's code, the completeness and correctness of rules were tested using the 'PV' programme which is one of SAVOIR's tools. The task of this programme was to examine every item (variable, question, action and group) in order to assign an initial value to each one. It also performed consistency checks on the model, including searches for circular arguments in the reasoning (e.g., A depends on B which depends on C which depends on A).

8.11.2. Testing - modification cycles:

The system was then tested using exemplary patient data. TEDEX conclusions were compared with the already known correct diagnosis and outcome. Guided by the test results, the system was then modified and adjusted. A loop of 'testing - modification - testing' will continue until the performance of TEDEX is deemed to be satisfactory.

8.11.3. Performance Assessment:

Protocol for performance evaluation:

Testing procedure:

(1) Ten cases representing the whole range of complexity which the system is likely to handle will be used to perform the following tests:

[a] Calculation of the average history taking time:

The time required to complete the history taking part of the user-system dialogue is calculated for each case. The average of the readings is then calculated.

[b] Calculation of the average consultation time:

The average time taken to complete a consultation will be calculated.

[c] Calculation of the average system response time:

The average response time (i.e., the time from the entry of the last question to the display of the final report) is calculated. This average will be calculated using an IBM/AT 6 MHz and a faster computer, AMT/AT 10 MHz, which is an IBM compatible machine.

(2) Evaluation of TEDEX advice accuracy in comparison with historical cases:

50 case histories will be randomly selected from the data base which contains the data of thyroid eye disease study (Chapter 5). The system's diagnosis and management plan will then be compared with the already known diagnoses, management and outcome of each case.

8.12. RESULTS:

One of the chief differences between an expert system model building project and other research projects is that the expert system itself represents the major part of the results. It is also worth mentioning that the only way to dem-

onstrate all the features of the system is by running it. A copy of the programme and an instruction sheet are enclosed for this purpose in Volume 2 pocket, and a copy of the source code of the complete programme files is printed in Appendix D2.

8.12.1. A session with TEDEX:

Case number (074) which has been selected from dysthyroid eye disease study (Chapter 5) is summarised in Table 8.8. Plate 8.2 through 8.10 are screen photographs showing samples of user-system dialogue. Printout of samples of TEDEX menus, questions, messages and reports of the same case are presented in Appendix D3.

8.12.2. Results of testing and validation

Rule validation:

The compiled programme was tested by running the SAVOIR 'PV' testing tool. No errors were found on checking all questions, variables, actions and groups. The complete output of this testing procedure is printed in Appendix D4.

Model statistics:

The complete printed model summary (Appendix D5) is the of source Table 8.9 which shows the number of each of the model items. The programme code occupies about 22 KB and the total number of items is 726.

8.12.3. Performance assessment results:

Table 8.10 shows the average history taking time, the average consultation time and the average system response time for new patients and for follow-up visits when the system was running on the IBM/AT and on the faster AMT machine.

Table 8.11 shows the accuracy of TEDEX in reaching the correct diagnosis and in predicting the 'final' outcome for 50 historical cases whose diagnoses and outcome were already known.

Case summary:

Case No.	074	**Age in years**	50
Sex	F	**Complaint**	Lacrimation, photophobia & cosmetic appearance
Thyroid status			Hyperthyroidism
Duration ophthalmopathy (months)			1
Duration of thyroid dysfunction (months)			48
Treatment of thyroid dysfunction			Carbimazole
Ocular treatment			Artificial tears
Systemic disease			none

Right eye	**First visit**	**Follow-up visit**
Diplopia	None	Mild
Diplopia on examination	On elevation and depression	Combination of restrictions
Exophthalmometry (mm)	25	28
Visual acuity	6/6	6/12
Lid lag	Mild	Mild
Lid retraction	Mild	Mild
Lid œdema	Mild	Moderate
Chemosis	Mild	Moderate
Cornea	S.P.K.	S.P.K.
Intraocular pressure straight	18mm. Hg	20mm. Hg
Intraocular pressure up	24mm. Hg	28mm. Hg
Pupillary reactions	No afferent defect	No afferent defect
Ophthalmoscopy	No papillœdema, No choroidal folds	No papillœdema, No choroidal folds

Table 8.8

Clinical summary of the exemplary case used to demonstrate TEDEX operation.

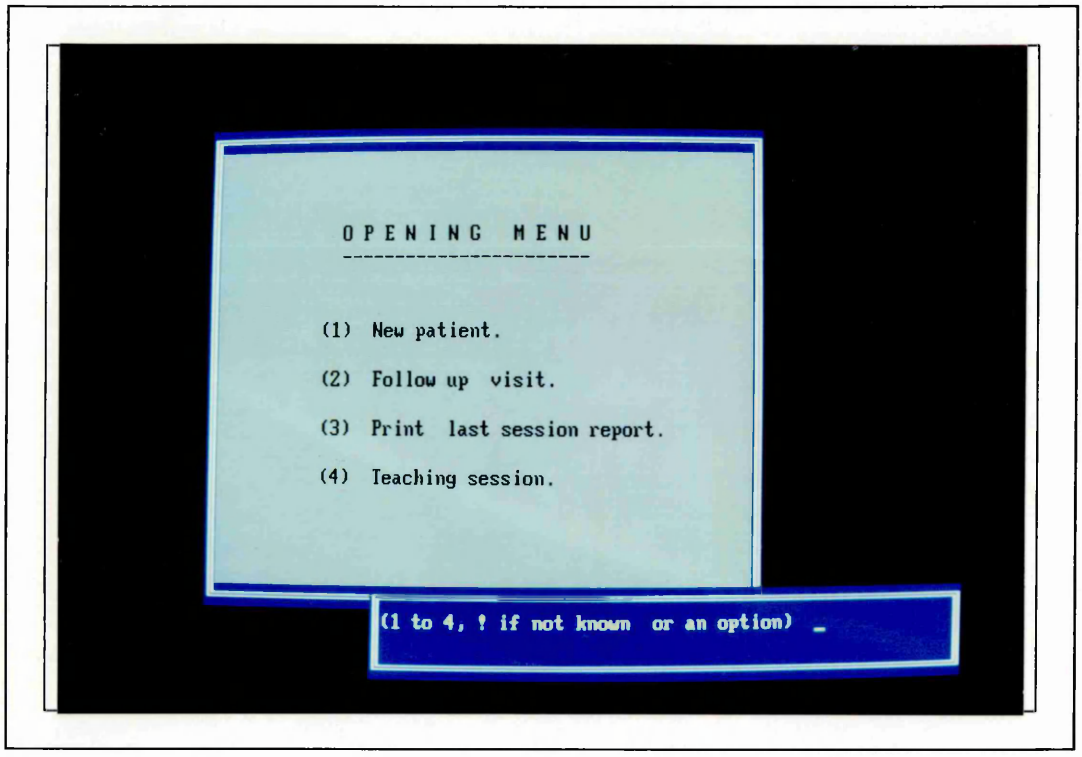


Plate 8.2

Opening menu.

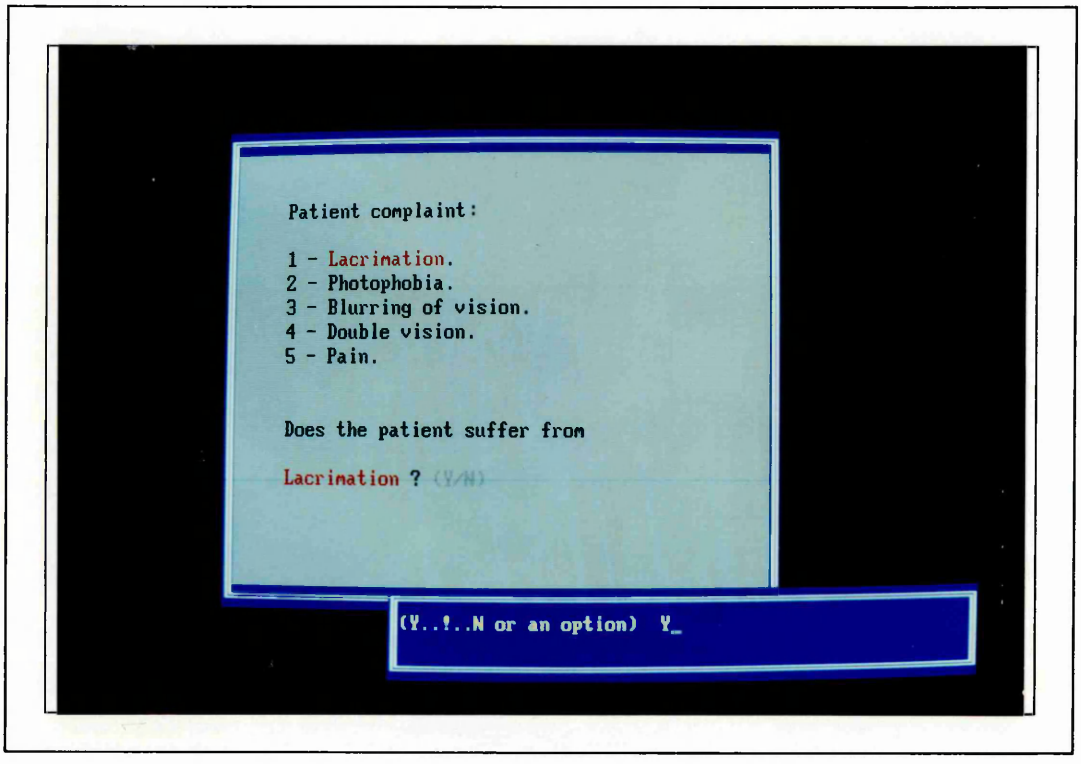


Plate 8.3

History taking.

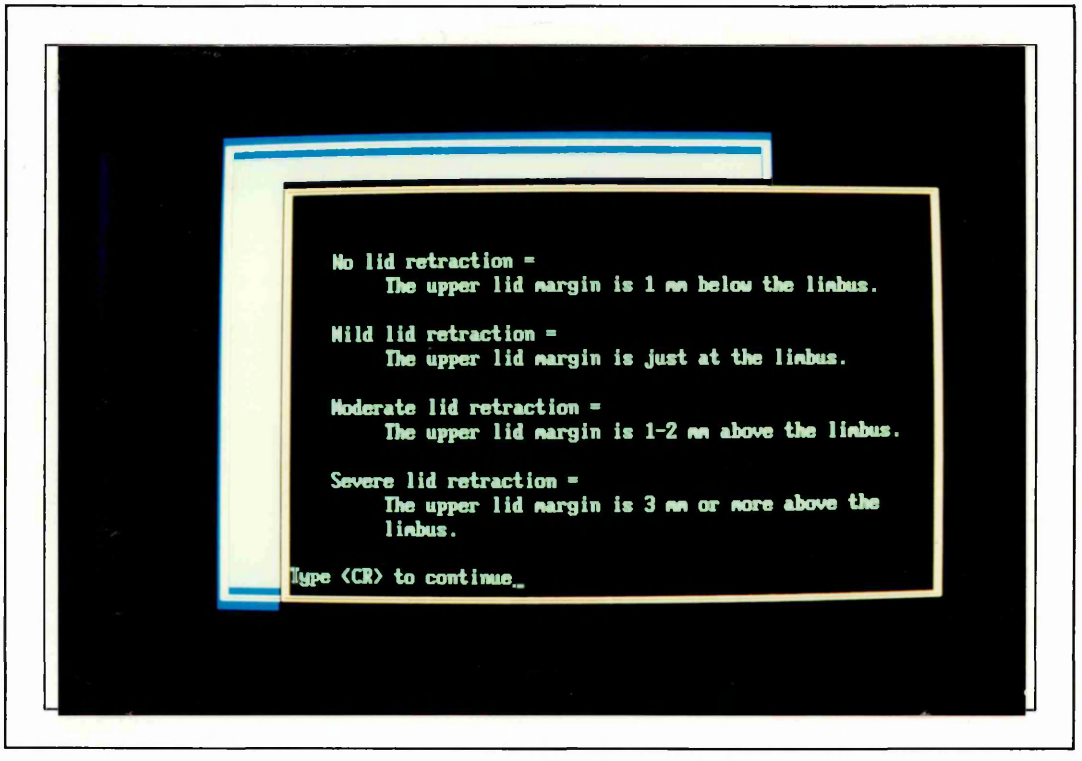


Plate 8.4

Amplification.

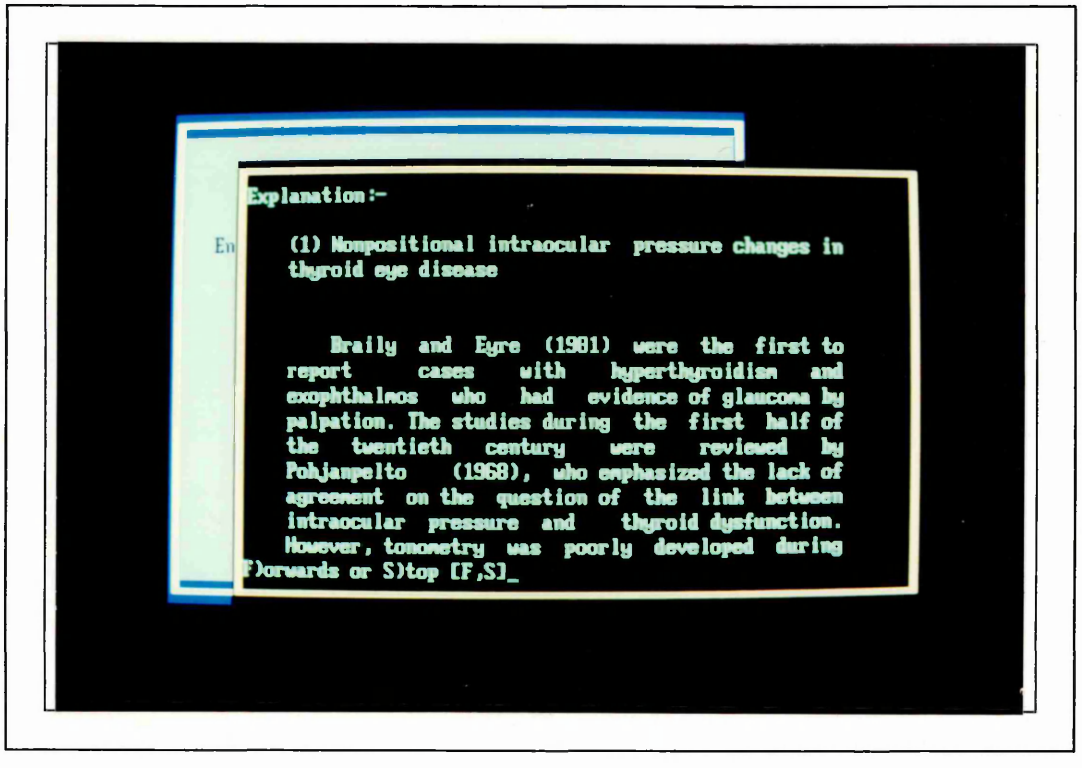


Plate 8.5

Expansion.

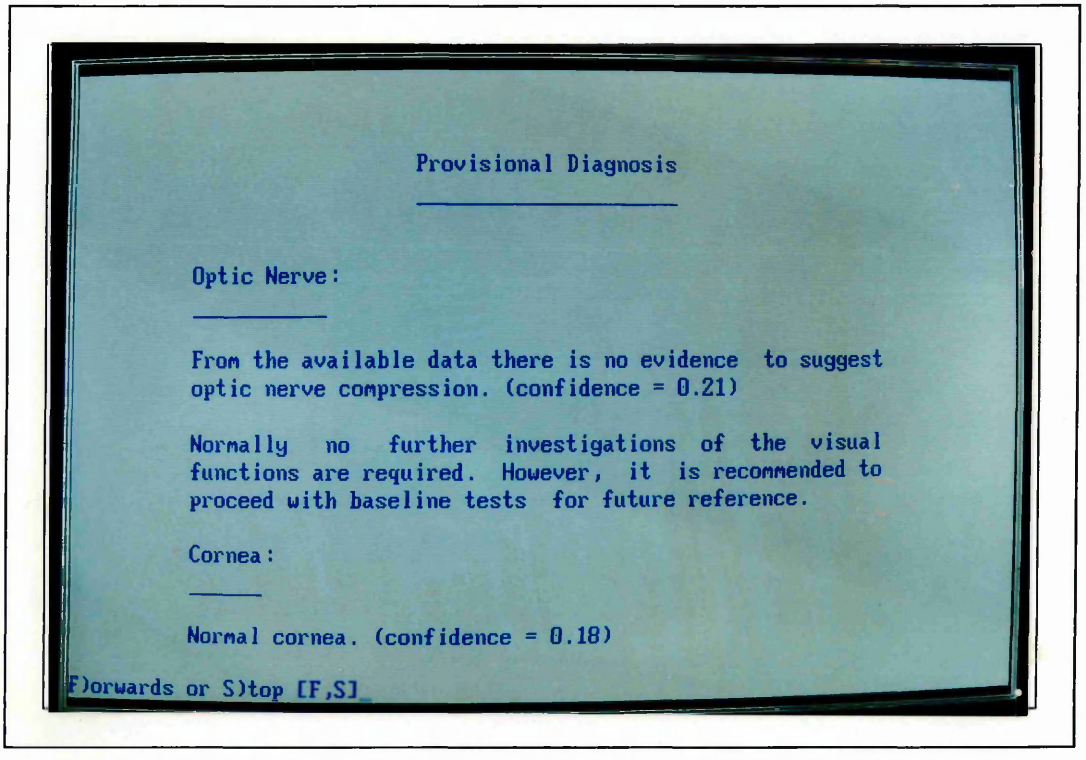


Plate 8.6

Intermediate report.

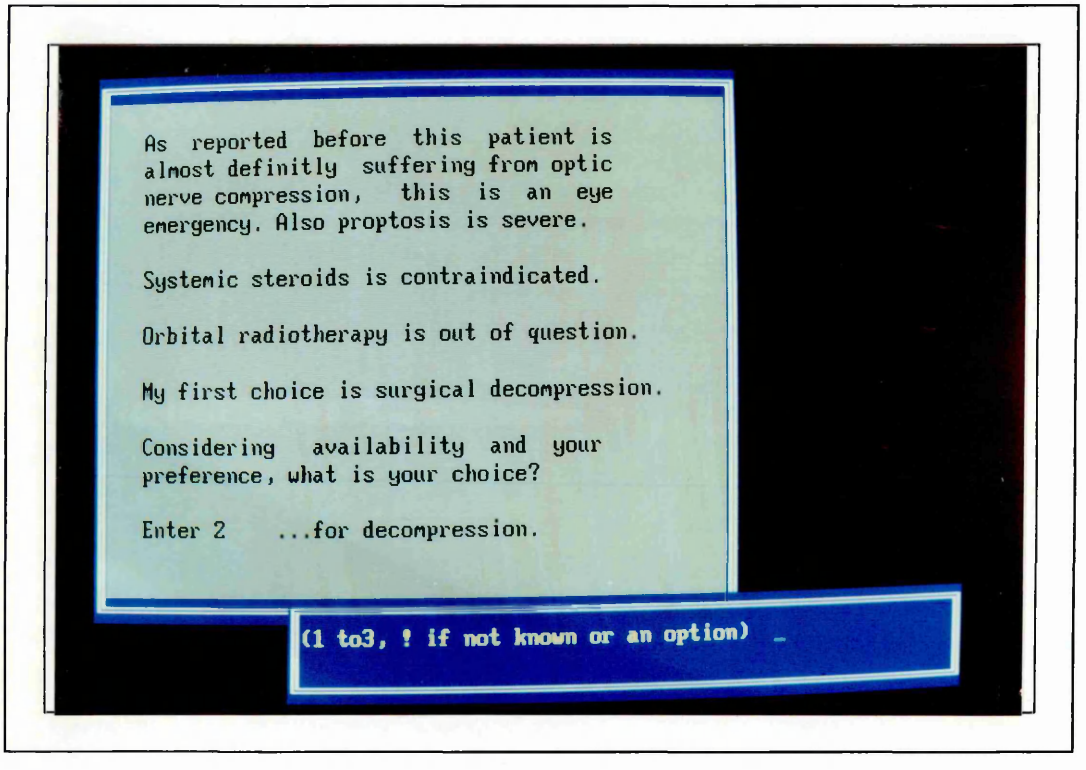


Plate 8.7

System's advice.

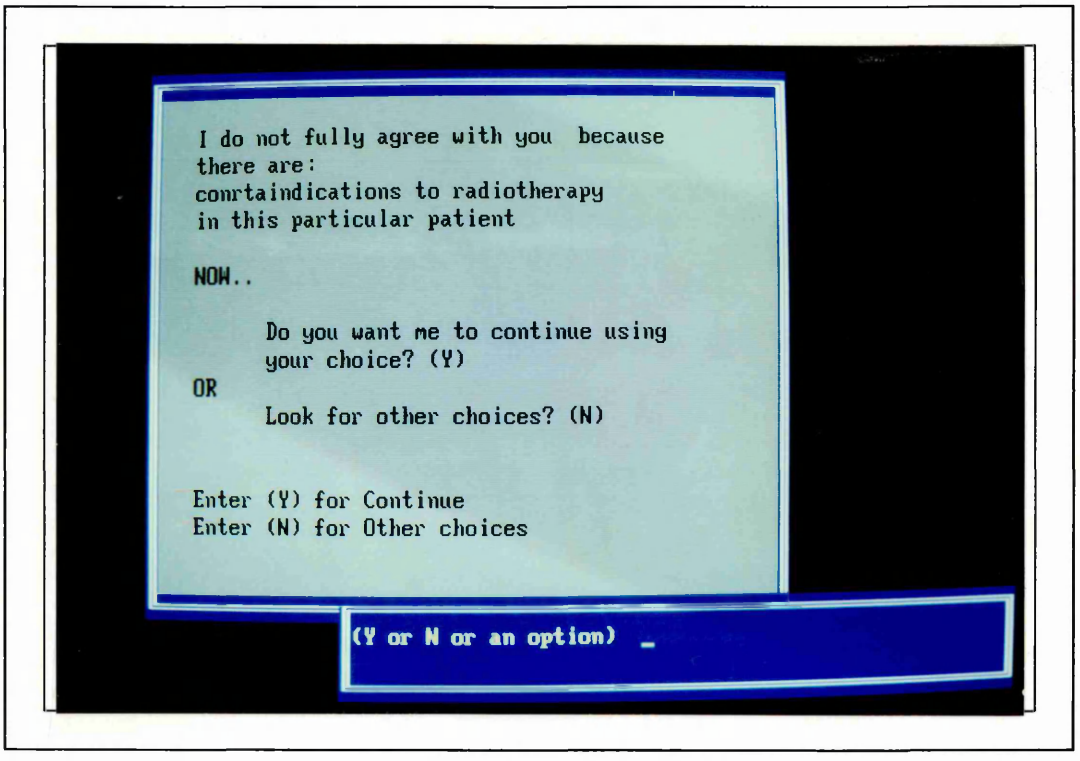


Plate 8.8

User's choice.

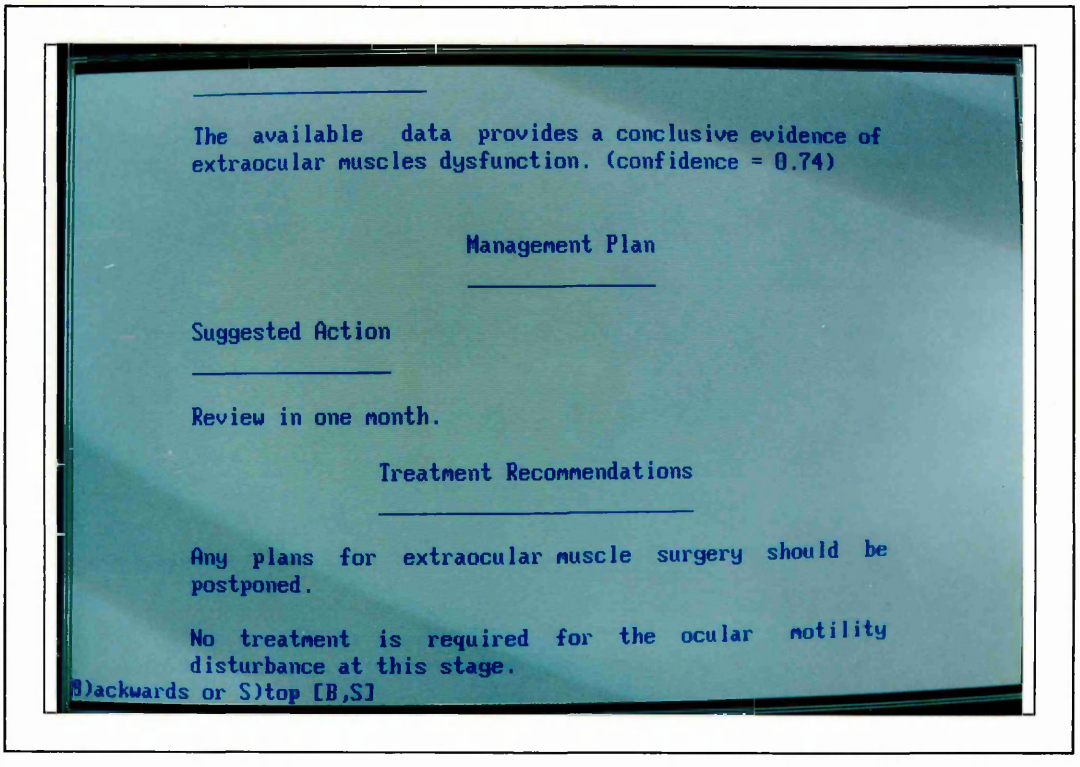


Plate 8.9

Final report.

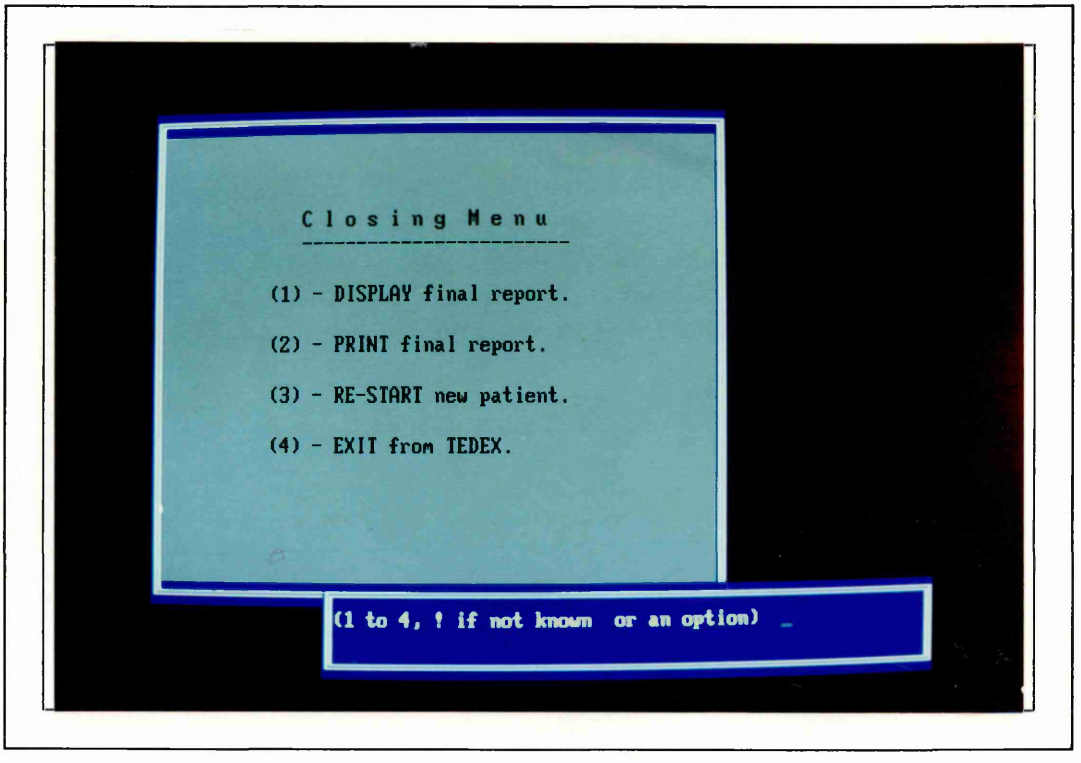


Plate 8.10

Closing menu.

Statistics of the model.	
Questions	121
Variables	414
Actions	178
Database fields	181
Groups	13

Table 8.9

The details of statistics of various components of TEDEX.

Performance evaluation:

	IBM/AT	AMT/AT
History taking in minutes:		
New patients	4.45	3.00
Follow-up visit	2.80	2.30
Mean history taking time	4.23	2.65
System response time in seconds:		
New patients	5.00	3.00
Follow-up visit	5.00	3.00
Mean response time	5.00	3.00
Complete session in minutes:		
New patient	5.45	4.00
Follow-up visit	3.25	2.80
Mean session time	4.35	3.40

Table 8.10

Mean history taking, system response, and complete session times using 10 cases representing various degrees of complexity.

TEDEX Performance:	
Percentage of correct diagnoses	96%
Percentage of correct predictions of outcome	71%

Table 8.11

Assessment of the performance of TEDEX using 50 historical dysthyroid eye disease cases.

8.13. DISCUSSION:

8.13.1. Performance of TEDEX:

No measure or group of values has been universally accepted as a standard to evaluate expert system performance. An expert system can be measured against several criteria for analysis, but the analysis will always be subject to personal interpretation.

From the user point of view the system needs to have a smooth, efficient, and 'natural' interface which is 'user friendly'. An expert system's advice must be useful. Explanations and justifications are needed to explain its decisions in case any questions should arise during the consultation session.

TEDEX takes an average of 5.45 minutes for completion of a session when dealing with a new patient and only 3.00 minutes in subsequent follow-up visits when running on the slow AT machine, which means that in a clinical situation the consultation time will be increased only by this amount of time which includes establishing a complete data base as an added advantage.

The average system response time is 5 seconds when running on the slowest IBM AT personal computer, which is rapid enough to maintain the user's attention. This can be further shortened if the system is run on the faster machines which are currently becoming available. This aspect is important in order to enhance the acceptance of expert systems such as TEDEX by busy clinicians.

TEDEX accuracy in reaching the correct diagnosis was 96% and it was 71% accurate in predicting the 'final' outcome using the exemplary historical cases which are part of the study that constituted the foundations of the system. However, these results can only be interpreted as an indication of the system's integrity and consistency. Evaluation of the performance of the system in general ophthalmic clinics, orbital clinics and in endocrinology clinics needs a separate study and should be carried out using new cases. Such a study should be prospective, long-term, and perhaps multicentric in order to compensate for the rarity of this disorder.

There have been a number of studies in which the accuracy of computer diagnosis has been compared with that of a human presented with the same data (deDombal *et al.*, 1972; Adams *et al.*, 1986; Scherk *et al.*, 1986; Chard, 1987; Barlow *et al.*, 1987). Most of these studies show the computer to be more accurate.

8.13.2. Difficulties:

No established methodology:

No standard methodology for designing and building medical expert system models is available despite more than two decades of research. Most of the published work focuses on presenting the method used in developing a particular system. One of our first tasks was to define the problem and sub-problems and decide on which approach was suitable for each individual sub-problem. Clear set of methodologies was then decided as appropriate.

Software tools for microcomputers:

Few shells for the development of 'real' expert systems are able to run on microcomputers (as opposed to 'toy' expert systems with small number of rules). Moreover, most of the powerful tools have been designed with financial and business applications in mind. A general purpose expert system shell, which had been tried and proved to be sufficiently powerful, was required for the development of TEDEX.

It was decided to use a shell rather than any of the other available tools for several reasons. In general, the expert system building team was immediately able to use a shell for expert system development and is able to describe the knowledge processes using the shell syntax. Prototypes of application programmes can be built and tested when a shell is used. In prototype development the feasibility for a particular application can be tested and the test results used in order to evaluate shell suitability for a particular application. Moreover, a suitable shell offers a considerable increase in programming productivity. Furthermore, new shell architectures can enable one application to run identically in different computer environments. Shells available for IBM personal computers and compatibles are reasonable in price. In addition, developing an expert system application using a shell has a much higher chance of success than build-

ing it from scratch which is, unnecessarily, lengthy and expensive process. These requirements are much reduced if a shell is used.

It was agreed that SAVOIR meets most of the requirements and is the best for our purpose at the present time. Based on the above considerations, the main reasons for selecting SAVOIR were:

1. As a compiler, it has a separate run-time programme with compiled code (as opposed to interpreted) which means that the run time speed will be fast.

2. SAVOIR supports all the data types required.

3. As one of the main features of our system must be a good user interface, it is important that, as developers, we have control over it. SAVOIR allows for this.

4. SAVOIR has good facilities for debugging the knowledge base allowing error capture and fine tuning to be performed rapidly and easily.

5. Explanation and help facilities are essential features of our system. SAVOIR allows for implementation of context sensitive help, general help and justification.

Hardware limitations:

We have committed ourselves to develop the expert system on microcomputers in fulfillment of one of the aims of this study (Chapter 4). Dedicated work stations, such as LISP machines are very powerful, flexible and effective but they are very expensive. Microcomputers have serious limitations regarding speed and graphical capabilities from the developer's point of view. This adds to the development difficulties, although the situation is changing with time.

The TEDEX hardware development system has been configured to minimise the effect of these limitations (Table 8.4). This configuration combined with a powerful and flexible software shell constituted an adequate development system for this particular project.

Expert system application categories:
Interpretation*
Identification*
Prediction*
Diagnosis*
Control*
Design
Planning*
Monitoring*
Debugging and testing
Instruction and training

Table 8.12

Application categories which are suitable for expert system implementation.

**fulfilled by TEDEX*

Transferability:

The deDombal system of abdominal pain has been used in different unites with similar degrees of efficacy (Adams *et al.*, 1986). On the other hand a system for diagnosis of jaundice which was developed at a specialised liver unit in Britain (Knill-Jones *et al.*, 1973) was shown to be inadequate for use in Sweden (Lindberg, 1982), whereas another system developed for use in Sweden was shown, in a later study, to work satisfactorily (Lindberg *et al.*, 1987).

The TEDEX knowledge base has been developed with this potential problem in mind. However, the efficacy of the system elsewhere can be decided only after the system has been evaluated in the new environment. Further adjustment of the knowledge base could become necessary after such tests. It seems that there are two major factors which influence transferability. Firstly, the differences between the population which has been studied to build the expert system (training and testing sets of cases) and the population of patients in the new environment. Secondly, the nature of the knowledge base rules and how much they depend on values which are specific to the population under evaluation.

Further problems can arise if the system has been developed using one class of machine (e.g., IBM microcomputers) while the intended user has a different system (e.g. an Apple MacIntosh). This problem is currently being solved with the introduction of tools which have been written in the C programming language (e.g., NEXPERT, Appendix D6). Such tools enable the developer to use any of several classes of machine for system development and to deliver the finished programme in various formats which ensure compatibility with a wide range of microcomputers. However, TEDEX has been designed to run on the industry standard and the most widely used microcomputer system. The newer transferable development tools have been introduced since the inception of the project and cannot be used for TEDEX.

8.13.3. System features:

Wolfgram *et al.* (1987) discussed various applications categories which are appropriate for expert systems. Table 8.12 lists ten of the major categories. TEDEX has the facility to *control* external data acquisition equipment (e.g., Keyboard, TEMPRAC, Scanner, etc.) to obtain information about a particular patient. It *interprets* and scores the data, *identifies* any error, inconsistency or discrep-

ancy in them and *monitors* the evolution of thyroid ophthalmopathy in time. It suggests a *diagnosis*, *predicts* the prognosis and provides a management *plan*. It therefore fulfils seven of the ten categories listed in Table 8.12.

Domain selection:

Diagnosis, prediction, monitoring and planning the management of a medical disorder are particularly suitable for the application of expert system techniques. The acceptance of such a system by clinicians contributes to the credibility of these techniques and, more importantly, will establish their efficacy and limitations in clinical practice.

The subject of thyroid ophthalmopathy is small enough that an expert system could be developed as a prototype in the designated project time. Furthermore, the amount of domain-specific knowledge involved in the diagnosis and management of this disorder was limited enough to make it possible to acquire, understand and represent that knowledge in the relatively short time available.

Development time:

The development of a functioning prototype of TEDEX required only 18 month (3 man-years) which is considerably shorter than the time taken to develop comparable expert systems such as MYCIN (Section 8.5.5). Although both systems contain approximately 400 rules, MYCIN development required 20 man-years (Engelbrecht and Rothemund, 1987). A number of factors can explain this fact. Firstly, TEDEX has been developed using a shell (Section 8.7.4) whilst MYCIN had been built from scratch; no shells were available at the time of its development. Secondly, enough lessons have been learned form the early work to enable us to avoid many pitfalls which were inevitable in the early nineteen seventies. The growing experience of expert system developers gained during the last two decades is constantly decreasing the development time (Engelbrecht and Rothemund, 1987). Finally, the author as a computer enthusiast and Mr. A. Wail as an artificial intelligence expert (who had just successfully finished a 'Computer fault diagnosis expert system' project for his Master's degree), were able to work in harmony forming a unique expert system building team. This considerably shortened many of the development stages, particularly that of knowledge acquisition which is usually lengthy and difficult.

Large systems running on microcomputers:

TEDEX, which is considered a large system (with a number of rules equivalent to MYCIN) runs on IBM and compatible microcomputers. To the best of our knowledge no such system have hitherto been developed to deal with clinical ophthalmic problems.

Methodology chosen:

The steps outlines in Section 8.10 were chosen as being most appropriate but they should not be considered the only possible course for developing an expert system. However, this project is based on a methodology which led to the achievement of the desired goals in the time available and which could be followed in the development of similar systems for use in other areas. The characterisation of such a methodology in evolving an artificial intelligence system is one of the major aims of this study.

Communicating knowledge:

TEDEX and other medical expert systems exemplify a new concept in communicating and spreading knowledge. They demonstrate that medical expert systems can be used as a medium which contain both the facts and figures (i.e., standard textbook information), in addition to the decision making process itself.

Although textbooks and expert systems are both knowledge repositories, expert systems have some additional potential advantages. A given knowledge base can be used for multiple applications because knowledge can be represented independently from its use. A knowledge base typically contains procedures for making a diagnosis, for teaching and for learning. A textbook generally adopts one view point whilst an expert system can integrate various sources of knowledge and may contain various view points. Textbooks however are more convenient to use and more portable.

The development of an expert system is currently very costly in terms of time needed to build the system, the expertise required and the development tools.

TEDEX versus scoring systems:

Various classifications and scoring systems have been employed to evaluate patients with dysthyroid eye disease (Section 3.5.2). One of the major aims of such systems is to assess disease severity in order to plan management. These systems are generally inflexible and thus inadequate for this purpose.

TEDEX diagnostic and management decisions are based on the structural and functional changes of the individual ocular tissues, and the patterns resulting from the combination of these changes in conjunction with the general condition, and the previous medical and therapeutic history of the patient (Section 8.10.4). In effect, tailor made advice is provided when TEDEX is used which contrasts with the application of a rigid scoring system. Furthermore, computers are superior to human in dealing with situations in which large number of parameters must be simultaneously considered in order to make a decision (Elstein *et al.*, 1972; Macartney, 1987). No scoring system is currently available which gives predictions regarding the course and outcome of the disease.

8.13.4. Similarities and distinctions from other systems:

Knowledge base design:

Part of the routine developed by clinicians is an appropriate order for acquiring clinical information systematically. TEDEX complies with such convention in the history taking part of the data acquisition dialogue. However, the rest of the dialogue is guided by a backward chaining strategy and depends on the line of reasoning selected by the inference engine (Section 8.10.4). Other designers tend to enforce such an order either strictly (e.g., MYCIN, Section 8.5.5) or not at all (e.g., INTERNIST, Section 8.5.3).

Both TEDEX and the deDombal's abdominal pain expert systems (Section 8.5.1) deal with a circumscribed domain. The essential difference between the two systems is that thyroid ophthalmopathy is an uncommon disorder while abdominal pain is very common. Therefore, it was possible to build abdominal pain programme purely on a Bayesian probability approach (Section 8.4.5) which requires a very large number of patients. Bayesian probabilities are used in some parts of the TEDEX knowledge base and represent one of several approaches used (Section 8.10.4).

The ideal expert system:

Expert system should:

(1) Provide the means for efficient transfer of knowledge.†

(2) Have knowledge bases that are expandable & modifiable.†

(3) Show improved competence with addition of new knowledge.†

(4) Interact in a language natural to the expert and user.†

(5) Think in a way that matches the human expert.

(6) Learns from experience.

(7) Insulate the user from the underlying mechanics.†

(8) Have a control strategy that is simple.†

(9) Be computationally fast.†

(10) Be comfortable to use.

(11) Be inexpensive to build and experiment with.†

(12) Have provision for 'help' and dialogue.†

(13) Have displays that are informative to the user.†

(14) Explain reasoning and conclusions.†

(15) Be useful in practice.

Table 8.13

The characteristics of an ideal expert system summarised from Konopasek and Tayramanu (1984). " † *Criteria so far satisfied by* TEDEX. "

TEDEX has some similarities to the frame-based concept of PIP (Section 8.5.4). Each of the diagnosis module components (Figure 8.9) represent one cluster of knowledge with distinct features (i.e., frame-like). However, the TEDEX inference engine manipulates these clusters differently and considers them as one level of abstraction.

The concept of 'multilevel description of states' which is the basis of the CASNET (Section 8.5.2) inference engine design has been modified and used in devising the TEDEX knowledge base. The original CASNET multilevel structure embodied a clinical data level, a pathophysiological level, a diagnosis level and a treatment level. By comparison TEDEX contains a clinical findings level, an intermediate level (data interpreted into scores), a diagnosis level and a treatment level.

Knowledge representation:

A hybrid of three knowledge representation approaches has been used to develop the knowledge base of TEDEX (Section 8.10.4), namely those of semantic network (Plate 8.1), production rules and predicate calculus. Combining such a number of various techniques ensures system flexibility and allows for the implementation of the most appropriate technique for the right situation. TEDEX is unique in making use of this kind of combination but it is in accordance with the concepts of Reggia and Tuhrim (1985) who advised that knowledge representation methods should be chosen according to the specific problem in hand.

8.13.5. How does TEDEX compare to the ideal system:

It can be seen from the above discussion that TEDEX so far embraces 11 of the 15 features of the ideal expert system listed in Table 8.13 (Konopasek and Tayramanu, 1984).

Learning from experience capabilities has yet to be improved and implemented on microcomputers. The usefulness of TEDEX cannot be claimed before the test of time and prospective studies prove it. This is therefore a future research project.

The development of the portable 'laptop' microcomputer effectively negates the argument that computerised systems are impracticable because of their lack of portability.

Perhaps the major hindrance to the potential usage of this system is that it solely deals with one uncommon aspect of ophthalmology. This potentially diminishes the expected level of usage at present. However, as further expert systems are devised and developed and computers become routinely used in the outpatient clinics the use of such system is likely to gain in popularity.

CHAPTER 9.

SUGGESTIONS FOR FURTHER RESEARCH

9.1. INTRODUCTION:

Computer applications to ophthalmic diagnosis and management promise to optimise the existing empirical approaches, and improve patient assessment and clinical data handling. Further research is required to make use of the currently available computer technology in solving clinical ophthalmic problems and to overcome the difficulties and limitations of computing approaches. On the other hand, dysthyroid ophthalmopathy remains to be an enigma. The present work raises new questions and leads to many areas for future research.

9.2. DYSTHYROID OPHTHALMOPATHY:

A long-term study of dysthyroid eye disease using advanced imaging techniques and computerised data collection is required, TEDEX offers a means of starting such a study. Furthermore, the role of advanced and quantitative imaging techniques in the management of ophthalmopathy and in particular their value in determining the appropriate timing of surgical decompression deserve further evaluation.

There is a need for a test which is sensitive and specific enough to detect optic nerve compression at an early stage before irreparable damage occurs. So far, the most sensitive clinical tests for detecting optic nerve compression are the field of vision and the 100-Hue colour vision test. A system for automatic reading and quantification of the charts of these two tests is currently being investigated (Chapter 7) in an effort to improve their sensitivity. The value of this system in increasing the rate of early detection of optic nerve compression has yet to be established.

The safety and effectiveness of orbital radiotherapy and immunosuppressive drugs such as cyclosporin A as a primary and definitive treatment of severe ophthalmopathy need to be investigated using controlled studies which perhaps should be multicentric to compensate for the small number of patients with this disease.

9.3. COMPUTER APPLICATIONS:

9.3.1. Temporal assessment of visual acuity:

Further assessment of the TEMPRAC test is required using larger number of normal individuals in the older age groups.

Evaluation of the usefulness of the test in the diagnosis of optic neuritis patients comparing the results with other visual function test modalities has yet to be carried out. Furthermore, the usefulness of the test in the early detection of optic nerve compression in patients with dysthyroid eye disease requires a separate study.

The value of the test as a screening tool for diseases such as glaucoma, its value in verification of spectacle correction of errors of refraction and the appropriate choice of the optotype to be used in the test, in terms of difficulty of recognition, needs further elucidation.

9.3.2. Automatic chart reading system:

Quantification of other ophthalmic charts and the establishment of an image data base which may include advanced imaging techniques results, photographs, diagrams and histopathology photographs of ophthalmic patients are potential future research projects.

9.3.3. TEDEX

Easy maintenance and updating of an expert system programme can be enhanced by adopting a modular design. However, there is a real need for the development of a user interface with a 'maintenance module' which is intended for the user to readjust his programme by himself according to the changes in investigation techniques, therapeutic procedures, attitudes in social values, working environment or health care cost.

The keyboard is the principal input device of the TEDEX system. Every effort has been made to keep its use as limited and simple as possible. However, the keyboard remains a major barrier to the effective use of microcomputers. The

man-machine interface in the context of medical applications, and voice synthesis and recognition are interesting areas which require active research aimed at providing easier, effective and more natural communication between the user and the computer.

Expert system development requires high software and hardware standards. This is not surprising in view of its attempt to emulate human thought process. Parallel processing is one advance which is well suited to the purpose of expert systems techniques. Neural computing, which is in effect a software emulation of parallel processing has a similar potential. Further research in these aspects of artificial intelligence is needed in order to make the best use of the current technology to solve clinical problems.

One of the features of the ideal expert system (Table 8.13) which is particularly significant for medical applications is its ability to learn from 'experience'. This means that the expert system would be able to extract new rules or modify existing rules in its knowledge base when data of new cases are added to its data base. Unfortunately, the current induction software tools are still very primitive (Clancey, 1983; Ellis, 1987; Chard, 1988). Research is needed to develop such tools and to integrate them into some of the successful expert system building tools. The capability of 'learning from experience' when included in a medical expert system would enhance its acceptance, improve its transferability and ensure that its knowledge base is continuously updated.

The choice of a problem area which is suitable for building a medical expert system is critical. Practical problems for which expertise is in demand are appropriate for expert system applications. Experience has also shown that the domain should be reasonably well circumscribed. Research to define such areas in clinical ophthalmic practice is needed.

Dysthyroid ophthalmopathy and thyroid diseases are interrelated and together form one circumscribed area suitable for development of a comprehensive thyroid expert system. It seems logical to extend the present work to include the systemic aspects of this disorder.

For future expert system building projects, it is recommended that the recently introduced expert systems development tool kits should be used because they are user friendly, powerful and provide transferability across a wide range of available microcomputers in common use. Computerisation of clinical records would guard against the loss of valuable patient data. This gives more accurate statistical results and a better quality of decision rules which in turn enhance the accuracy of future expert systems whose foundations would be based on such data. One of the advantages of using TEDEX is the discipline it imposes on the user which results in establishing a complete patient data base.

Expert systems capabilities open new fields in medical education. Using microcomputers, both interactive problem oriented teaching, and factual knowledge combined with decision making procedures can be handled at the same time. Furthermore, anatomical, physiological, pathophysiological and pathological information can be effectively included in such a system.

The TEDEX development project will have to run for at least one more year during which its intended design features, user interface improvements and further refinements of the knowledge base will be completed. However, the major target during the next year is to link the system into the following equipment:

1- TEMPRAC (Chapter 6)

2- Automatic clinical chart reading equipment (Chapter 7)

3- Microcomputer-based visual field testing.

The completed project aims to act as a model for the demonstration of the concept of clinic automation. One expert system could control and communicate with a wide range of, already computerised, sources of information. Contrast sensitivity testing equipment, visual field testing apparatus, laboratory computer or on-line data bases are but a few examples. Many other potential systems can be integrated in such a clinic automation project, these include charting and graphical representation of knowledge (e.g., displaying chronological data of patients), as part of an advanced reporting capability, simulation of surgical operations and three dimensional imaging of intraocular tumours based on different parameters.

Further research can adapt TEDEX and combine it with other ophthalmic expert systems to constitute a comprehensive ophthalmic advisor for General Practitioners, for the developing countries or for medical teams serving in remote areas.

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